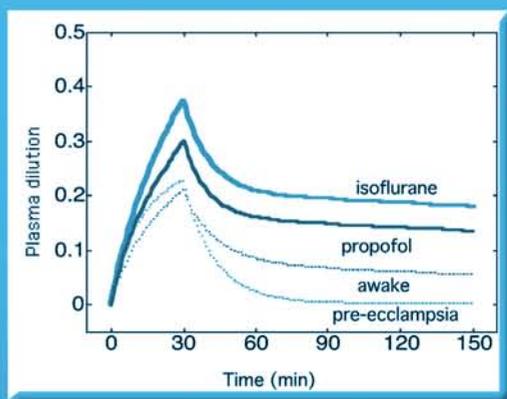
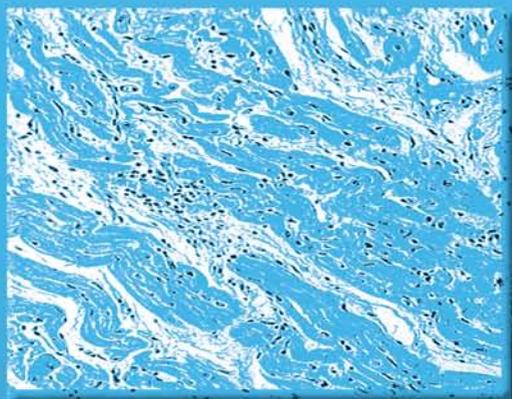
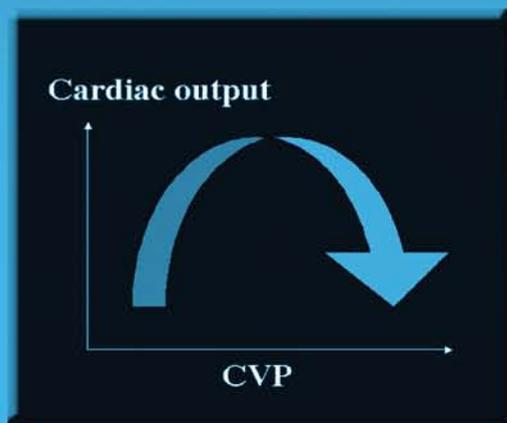


Perioperative Fluid Therapy



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Preface

Intravenous fluid therapy is an essential component of perioperative management. Virtually all surgical patients, ranging from those having brief, minimally invasive outpatient procedures to those having major intracavitary surgery, receive at least preoperative and intraoperative fluids; the majority of surgical inpatients receive postoperative fluids for varying intervals. Perioperative fluid management has historically generated controversy, with little compelling data to address the conflict between the extreme approaches of “keep them dry” and “aggressively hydrate them.” The limited data until now have driven a gradual change toward more liberal fluid administration in recent decades, but, in general, clinicians have used coarse, empirical approaches based on weakly supported rules of thumb. Many clinicians have no doubt concluded that their version of current practice is entirely satisfactory and perhaps have devoted little attention to recent clinical and technological advances in perioperative fluid management.

The scientific literature addressing perioperative fluid therapy is extensive, if somewhat dated and poorly suited to evidence-based management. Within the past 15 years, however, the basic and clinical science of perioperative fluid management has become a vibrant, rapidly advancing discipline. Application of pharmacokinetic principles has clarified the responses to fluid administration of blood volume and fluid excretion in both healthy volunteers and surgical patients. Related studies in experimental animals have explored pharmacologic influences on the kinetics of fluid administration. Well-designed clinical trials have provided important insights into the fluid requirements of patients undergoing specific types of outpatient and inpatient surgery, suggesting that perioperative fluid therapy must be *individualized* and specifically modified based on the type of surgery.

As the dynamic discipline of perioperative fluid management evolves in the years to come, clinicians can anticipate both rapid growth in knowledge and the application of that knowledge to practice. The purpose of this book is to assemble the current knowledge and expertise of international experts on perioperative fluid management. Towards that goal, we have divided the book into seven parts: (I) Basic Science; (II) Methods of Assessing Fluid Balance; (III) Intravenous Fluids; (IV) Intravenous Fluid Therapy in Special Situations; (V) Intravenous Fluid Therapy in Daily Practice; (VI) Adverse Effects of Fluids; and (VII) The Future of Intravenous Fluid Therapy. The chapters within these sections provide a synthesis of fundamental pharmacologic and physiologic issues and an overview of the application of those principles across a broad spectrum of perioperative clinical challenges. We hope to bridge the gap between conventional, crude rules of thumb and current knowledge. To some extent, as this discipline rapidly changes, we must rely on expert opinion. However, the goal of this book is to balance expert opinion with evidence-based recommendations—to emphasize not only *what* to do but, more importantly, *why* to do it.

Robert G. Hahn
Donald S. Prough
Christer H. Svensen

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1 Measurement of Body Fluid Volumes In Vivo

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INTRODUCTION: THE DILUTION PRINCIPLE

The simple relationship, $\text{volume} = \text{mass}/\text{concentration}$, can be used to assess a fluid volume by the dilution principle. A known amount of tracer is diluted and mixed well in a solvent, and the concentration of tracer is determined from a representative sample taken from the fluid. Endogenous compounds can be used as tracers, but the total measurement error is then increased by the measurement error of the baseline concentration (Fig. 1).

An ideal tracer should be distributed exclusively in the volume to be measured and be evenly distributed in that volume, and the rate of equilibration should be rapid to avoid changes in the volume to be measured. Furthermore, the tracer should not undergo metabolism during the time of equilibration. Not many tracers fulfill all these requirements, and adjustments are often needed to correct for distribution outside the volume space being investigated and to compensate for uneven distribution of tracer, changes of volume, or loss of tracer. The time to complete mixing is of crucial importance. A sampling time that is too short will usually indicate falsely high tracer concentrations, with subsequent underestimation of the body fluid volume. If the tracer is eliminated from the fluid volume to be measured, this can be handled by back-extrapolation of the tracer concentration to the time of administration—a procedure that will contribute to the error of the volume estimate. A number of other tracer properties must be considered in the choice of a tracer. These include availability, preparation, purity, sampling procedure, technique of analysis, and cost.

ANTHROPOMETRY

Because all the body fluid volumes relate to the size of the subject, several equations have been developed based on anthropometric data (Table 1). Total body water (TBW) can be predicted from gender, age, weight, and height (1), or derivatives of the body size, such as body surface area or body mass index (2). Skin fold thickness and circumferences are often used to improve estimates of body fat or fat-free mass but not for body fluid volumes. The agreement of the anthropometric prediction of a body fluid volume and an assessment by the reference method for an individual is often in the range of 10% (Table 1). Anthropometric equations always contain errors of the reference method and are only valid for a population that is similar to the reference population—usually healthy Caucasian volunteers. This is in contrast to the clinical interest in body fluid volumes that increase as the subject deviates from the healthy population. Furthermore, ethnicity has rarely been considered (2).

Extracellular water (ECW) is strongly correlated with TBW in healthy subjects (4) but no anthropometric equations have found widespread use. Circulating blood volume (CBV) is often related to body weight (7%). Textbooks refer to red cell volume (RCV) as 30 ± 5 mL/kg in men and postmenopausal women, 25 ± 5 mL/kg in younger women, and plasma volume (PV) as 45 ± 5 mL/kg in all adult subjects. However, because of differences in fat-free mass, these parameters can better be calculated from body surface area (Table 1) (5). A clinical scoring system to improve assessing CBV in intensive care unit (ICU) patients has been proposed (6). No single clinical sign presented a clinically useful predictive value, but a weighted scoring system might be helpful.

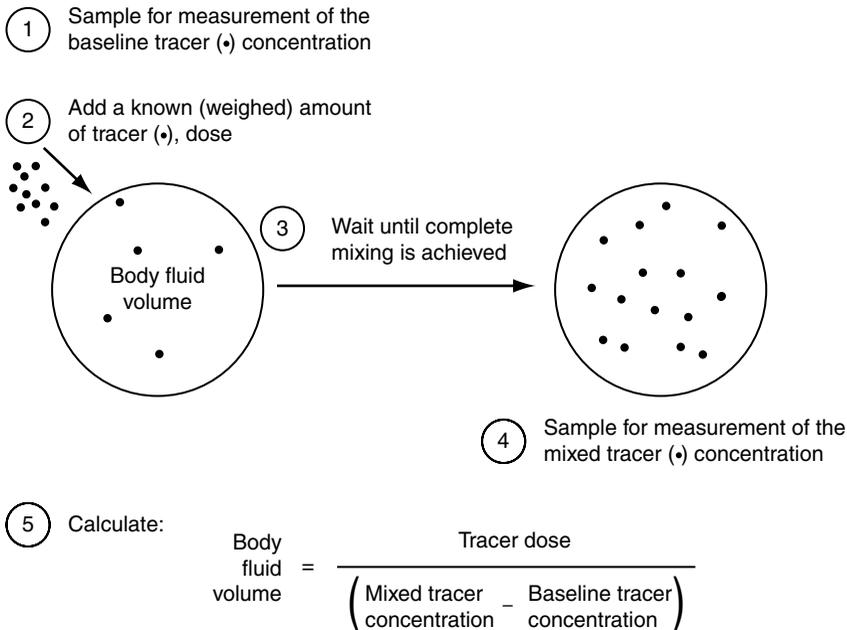


Figure 1 Summary of the dilution principle. If an exogenous compound is used, simply delete step 1 and set baseline level to 0.

THE SETTING OF THE OPERATING ROOM

The setting of the surgical procedure within an operating room may influence the method of measuring a body fluid compartment. The requirement of electrical security prohibits the use of equipment that is not designed and developed for the operating room. Surgery and anesthesia may themselves inflict variations in the studied body fluid volumes by bleeding, volume substitution with intravenous fluids, or redistribution of body fluids. Disease and fluid balance disturbances will make anthropometry or bioimpedance less accurate because these methods are mainly founded on healthy reference subjects.

To improve patient care in the operating room, there is a need for bedside measurements. Procedures should be simple, and complicated preparations of tracers must be avoided. The time of the surgical procedure must exceed the mixing time of the tracer if the dilution principle is to be used. Tracers should have a rapid elimination rate so as to make repeat measurements possible. The ideal tracer should be able to be analyzed within the operating or ICU wards, preferably by already existing equipment.

Table 1 Anthropometric Equations for Body Fluid Volumes

	Equation for females	CV %	Equation for males	CV %
TBW (L) (1)	$-2.097 + 0.1069 \times h + 0.2466 \times bw$	11.2	$2.447 -$	9.0
TBW (L)			$0.09516 \times a + 0.174 \times h + 0.3362 \times bw$	
White subjects	$-10.50 - 0.01 \times a + 0.20 \times bw +$	11.2	$23.04 - 0.03 \times a + 0.50 \times$	11.0
(2)	$0.18 \times h$		$bw - 0.62 \times BMI$	
TBW (L)				
Black subjects	$-16.71 - 0.05 \times a + 0.22 \times bw +$	9.1	$-18.37 - 0.09 \times a + 0.34 \times bw +$	7.9
(2)	$0.24 \times h$		$0.25 \times h$	
RCV (mL) (3)	$1.06 \times a + 822 \times BSA$	9.5	$1486 \times BSA - 825$	10.7
PV (mL) (3)	$1395 \times BSA$	9.7	$1578 \times BSA$	10.3

Note: CV%, precision expressed as the coefficient of variation = $100 \times$ standard deviation for a new individual from the same population/predicted value.

Abbreviations: L, liters; h, height (cm); bw, body weight (kg); a, age (yr); BSA, body surface area (m^2); BMI, body mass index (kg/m^2); RCV, red cell volume; TBW, total body water; PV, plasma volume.

TOTAL BODY WATER

TBW is a dynamic factor that is well regulated in healthy individuals. A decrease of 15% caused by dehydration can be life threatening. The turnover rate of TBW in a temperate environment is about 8% per day (7), but the variation per individual can be huge. Normally, about 2 L of water are lost per day through the urine and 800 mL through the breath, whereas losses through sweat, feces, and transdermal evaporation are negligible in a temperate environment (7). A host of factors influence the state of hydration, such as physical activity, feeding state, meal composition, fluid intake, environmental temperature, and the menstrual cycle. The subjects are assumed to be in a stable state of hydration prior to assessment of TBW.

Weighing organs and chemical analysis of whole human cadavers provide the most accurate measure of body components. Water content could be estimated by desiccation to constant weight. However, the availability of such data is limited to about 10 human cadavers, mostly from severely diseased subjects (8). The applicability of these data to healthy subjects is therefore doubtful.

Water Isotopes

The discovery of deuterium (^2H) and tritium (^3H) in the 1930s was soon followed by reports of isotope dilution analysis to estimate TBW in humans (9). Dilution of water isotopes has emerged as the gold standard for measuring TBW in humans. Three isotopes of water are available for this purpose: $^2\text{H}_2\text{O}$, $^3\text{H}_2\text{O}$, and H_2^{18}O .

The validation of water-isotope dilution methods against desiccation by animal studies has been reviewed (8). Nonaqueous hydrogen atoms in the body, which equilibrate with the tracers, result in an overestimation of TBW. The theoretical maximal size of this hydrogen pool has been estimated as 5.2% of TBW, based on the hydrogen content and turnover rate of different tissues (10). Commonly used figures for the ratios of the water spaces to TBW are 1.041 for $^2\text{H}_2\text{O}$ and 1.007 for H_2^{18}O (11). Isotope fractionation occurs in water vapor relative to water fluid because of different energies or kinetic properties of the water isotopes, which can lead to errors in the ratio of $^2\text{H}/^1\text{H}$ (12). The time to complete mixing of water isotopes into the TBW is about three hours, but can be prolonged up to six hours in patients with expanded extracellular water (ECW) compartments (13).

Tritiated water, $^3\text{H}_2\text{O}$, is easy to measure by scintillation counting and was the most commonly used isotope for several decades. However, the radiation hazard makes it less suitable than the other two water isotopes. Deuterium oxide, D_2O or $^2\text{H}_2\text{O}$, is a nonradioactive isotope of water. Because of the relatively low mass-to-charge ratios, specimens cannot be analyzed directly by mass spectrometry with any acceptable precision. The introduction of gas isotope ratio mass spectrometry for analysis of deuterium decreased the amount of tracer needed to acquire good precision (14), but the analysis requires expensive equipment, sample preparation, and highly skilled operators. Fourier transform infrared spectrometry is another method of analysis that might prove easier to use (15). Because H_2^{18}O is considerably more expensive than $^2\text{H}_2\text{O}$, it is mainly used for energy expenditure studies with double-labeled water.

Potential errors of the water isotope dilution method include errors in the assumptions regarding exchangeable hydrogen, very short equilibration time, residual urine, preparation errors, dosing errors, and error of analysis. If carefully conducted, the precision can be as high as 1%, coefficient of variation (7,16) being among the highest of any body composition measurement method. Dilution of stable water isotopes remains the gold standard for estimating TBW. However, the extended mixing time limits the applicability of the method in the setting of the operating room.

Alternative Tracers—Ethanol

Radiation hazards, expensive equipment and other costs, limited availability, decreased precision in repeat measurements if the dose is not increased, and lack of bedside applicability keep the interest in alternative tracers for TBW alive. Ethanol has been proposed as a suitable tracer of TBW because it has unlimited water solubility, and both the compound and the method of analysis are readily available at most hospitals. Breath ethanol analysis adds to the interest in this tracer because of the possible noninvasive sampling. One major problem is that the rapid elimination of ethanol forces the investigator to make repeat samples and

apply data to some appropriate pharmacokinetic model. Recently, a more thorough investigation of the pharmacokinetics of intravenous ethanol showed that the ethanol volume of distribution is significantly smaller than TBW estimated by D₂O dilution (17). The precision was comparable to that of water isotope dilution, but the bias was variable. The authors speculated that the phenomenon of structured water could explain that not all of the biological water was free to mix with ethanol. If so, this mechanism is likely to constitute a major problem with any small hydrophilic compound that is investigated as a tracer for TBW.

Bioimpedance

Bioelectrical impedance analysis (BIA) is based on the different conductive and dielectric properties of various biological tissues when an electric current is applied. Partly because of the extraordinary simplicity of the method, it has become a very popular study objective with more than 10,000 publications over the last 10 years. Many of these studies were performed in the perioperative period. In BIA, it is assumed that the body behaves as a uniform isotropic conductor of electricity (isotropic means having like properties in all directions), and that the body can be considered as a single cylinder. Both of these assumptions are known to be false. Because the arm and leg are much thinner than the torso, these parts will dominate the obtained estimate, making it impossible to quantify changes in the intraperitoneal fluid (18).

Several instruments are commercially available. By applying a single frequency between surface electrodes at hand and foot, TBW is directly related to the specific resistivity of the tissues and the square of the body stature, and inversely to the body impedance.

The precision of BIA is very good in repeat measurements. However, the ability to quantify TBW change is limited (19). Validity of measurement in the complicated environment of the ICU is doubtful because of stray capacitances (20), and these shortcomings might also apply to the operating room.

BIA is most useful in population studies among healthy individuals. Although cheap and easy to use, there are several issues that must be addressed before BIA can make its way into the operating room. Validity must be improved in that environment. Regional measurements might prove to be more valuable. The more sophisticated concept of bioimpedance spectroscopy (BIS) is discussed in more detail in the section on the extracellular fluid.

Indirect Assessment of Total Body Water from Body Fat or Fat-Free Mass

The hydration of fat-free mass is a constant, about 0.732, over a wide range of species. Therefore, TBW can be calculated from any assessment of the amount of body fat or fat-free mass. The validity of this hydration constant has recently been reviewed (21), and the variability of this figure proved to be a major source of error in such calculations in disease and in states of fluid balance disturbances. Furthermore, many methods to estimate body fat, such as hydro densitometry, air-displacement plethysmography, dual energy X-ray absorptiometry, measurement of total body potassium, computed tomography, magnetic resonance imaging, and in vivo neutron activation analysis lack clinical applicability in the operating room because they require special equipment that is not available in that setting (16).

EXTRACELLULAR AND INTRACELLULAR WATER

ECW normally accounts for about 20% of the body weight or 14 L in a 70 kg standard man. The anatomy of ECW is not as well defined as that of TBW. The two main components, plasma water and interstitial water, separated by the capillary endothelium, are sometimes complemented by connective tissue water, including water in the cartilage and bone. The major draining system of the interstitium is the lymph flow, and when its draining capacity is overcome, edema formation will occur. Critical illness is often associated with such an expansion of ECW, and the degree of edema correlates with clinical outcome. Chloride, sulphate, sodium thiosulphate, insulin, sucrose, and mannitol have all been proposed as markers of ECW. All of these fail to meet the demands of the ideal tracer and have not been widely used. The following discussion will focus on bromide because it is the most widely used tracer for ECW.

Intracellular water (ICW) is difficult to measure directly and is often taken as the difference between TBW and ECW—about 28 L in the standard man. Shrinkage of ICW is associated

with critical illness and might correlate with cell dysfunction. The ratio of ECW to ICW is about 1:2. However, if the body tissues are divided into a high-perfusion (intestines, brain, and blood) and a low-perfusion compartment (skin, muscles, and fat), the volumes for these compartments also form a 1:2 ratio that can lead to misinterpretation of tracer properties.

Bromide Dilution

Bromide is a small, negative ion with chemistry very similar to that of chloride, and it is therefore assumed that bromide is not equally distributed within its volume of distribution. The difference in the concentration of chloride in plasma and in the interstitial fluid is called the Gibbs–Donnan effect (22). It is caused by the combined need to balance osmolality and charge across a membrane that is presented to a membrane-insoluble ionic material on one side. Furthermore, intracellular penetration accounts for about 10% of the fully equilibrated bromide dilution space. In critical illness, the bromide space appears to be further enlarged, possibly due to increased bromide penetration into the ICW (23). Sampling at three and four hours after oral dosing of bromide has been recommended in normal subjects, but when there is an excess of ECW, the sampling period should be prolonged to six hours (7). However, a recent study of bromide kinetics suggested an equilibration time of 8 to 12 hours in normal subjects, defined as the time when the exponential distribution part of the concentration time curve has decreased to less than 5% of its starting value (24). Bromide leaves the body mainly through a first-order renal elimination at a slow rate dependent on water flux.

The procedure for bromide dilution is not well standardized. Either NaBr or ^{82}Br can be used. Several analytical methods exist, such as chromatography, fluorometry, mass spectrometry, and beta counting for radio bromide. Fasting is needed for good precision, and a baseline value, if NaBr is used. An oral dose of 50 mg sodium bromide per kg of body weight can be used. Plasma sampling after six hours appears to be appropriate in most cases. Correction for non-ECW sites of bromide distribution, the Gibbs–Donnan effect, and the water content of plasma must all be applied.

The precision of measuring ECW depends on the bromide dose and the analytical method used and is about half that of TBW, or about 2% (7). The precision of ICW estimates is worse because ICW is calculated from the difference between TBW and ECW, and therefore propagates the errors of both methods. The accuracy of ECW and ICW estimates are unknown because no direct chemical or desiccation method exists.

Bromide is a less ideal tracer for ECW than the water isotopes used for TBW. The main limit of the bromide dilution method in the perioperative setting is the long mixing time that is prolonged by expansion of ECW such as occurs in edema or ascites, and the uncertainty of the assumed relation between the total bromide space and ECW in critical illness.

Bioimpedance Spectroscopy

Bioimpedance spectroscopy (BIS) is a development of the BIA method, where the single frequency is replaced by a multifrequency approach. In BIS, the electrical body model consists of intracellular resistance serial with a cell membrane capacitance, all in parallel with extracellular resistance. Then, low frequency currents will flow mainly through the ECW because of the cell membrane capacitances, whereas at high frequencies, the current can flow freely through all TBW because the cell membranes no longer block the current (4). By using a wide range of frequencies, a Cole–Cole plot of resistance versus reactance is obtained, which will take the form of a semicircle and permit the calculations of the resistances of TBW and ECW, respectively (4). Variation in cell size, cell membrane properties, and geometrical arrangement of cells and organs contribute to the model error. The measurement procedure is very simple, rapid, and similar to that of BIA.

The precision of ECW by BIS is about 1.5% (4). Agreement with bromide dilution can reach 2%, but accuracy is more difficult to establish in the absence of a reference standard and could never exceed that of the bromide dilution method that serves as the internal standard for BIS. In summary, BIS provides estimates for both TBW and ECW and is easy to use, commercial equipment is available, and precision is good. However, like BIA, it is founded on erroneous assumptions and relies on a poor reference method.

BLOOD VOLUME AND ITS COMPONENTS

Red Cell Volume

Isotope-Labeled Erythrocytes

There is no definitive reference method for the RCV. Red cell mass, expressed in mL, is sometimes used instead of RCV, which can be confusing (3). The International Committee for Standardization in Hematology has provided a standard for the measurement of RCV by dilution of isotope-labeled erythrocytes prepared from the subject's own blood (5). The recommended isotopes are ^{51}Cr or $^{99\text{m}}\text{Tc}$, but ^{111}In and $^{113\text{m}}\text{In}$ can also be used. The procedures of isotope labeling of erythrocytes, administration, preparation of standard, measurement of radioactivity, and calculation of results has been covered in detail (5).

Mixing time is often assumed to be 10 to 20 minutes, but is delayed in patients with splenomegaly or in cardiac failure. The half-life of the ^{51}Cr isotope is 27.8 days, whereas the half-life of $^{99\text{m}}\text{Tc}$ is six hours, making the latter more suitable for avoiding residual radioactivity in sequential estimations of RCV.

The recommended sampling schedule varies from 10 to 60 minutes, depending on the chosen isotope and known factors that delay mixing time. It is often the radioactivity in whole blood that is measured for calculating RCV. Therefore, packed cell volume (PCV) corrected for trapped plasma between the packed cells must also be estimated in the same sample to get the activity in the red cells.

The large number of steps needed for the preparation and measuring procedures creates the possibility of many errors. The precision of the method is seldom reported but reaches 3% to 5% in an experienced laboratory (25). Accuracy cannot be determined because no definitive reference method exists. However, dilution of isotope-labeled erythrocytes remains the standard method for measuring RCV.

Carbon Monoxide

Inhaled carbon monoxide (CO) has been used as a tracer for RCV for more than 100 years. This nonradioactive tracer impairs oxygen delivery by binding to the hemoglobin molecule. Binding of the tracer to other heme proteins is likely to cause a small overestimation of the volume of distribution by about 2.2%. Mixing time is probably similar to that of the isotope tracers.

One issue that must be addressed is the safety and efficacy of the delivery system because CO is potentially harmful to the environment and dosing must be exact to avoid serious impairment of oxygen transport in the patient. A closed rebreathing system for delivery of the tracer has recently been developed (26), whereas others apply a method of in vitro labeling of erythrocytes (27).

A bias between CO and ^{51}Cr dilution of about 10% was reported in 19 ICU patients, which is similar to the precision reported in pigs (26). However, the agreement between CO and ^{51}Cr -labeled erythrocytes was better in 18 thoracic surgery patients (27). Whether these discrepancies depend on errors in the ^{51}Cr method or in the CO dilution method remains to be explored.

New techniques for the administration of the CO tracer together with a high availability of CO oximeters in many ICUs and operating wards offer a potential bedside method to estimate RCV.

Sodium Fluorescein-Labeled Erythrocytes

Sodium fluorescein, a dye mostly used in ophthalmology, is nontoxic and has a low allergic risk. Preparation of sodium fluorescein-labeled erythrocytes is not as complicated, and the measurement is easier than for ^{51}Cr -labeled erythrocytes. When the two labels were compared in 35 patients, the mean bias was less than 1%, and standard deviation of the difference between the methods was 5.6% (28). Elimination is rapid, permitting determinations at short intervals, but the impact of this rapidity on the estimates has not been investigated. In summary, this is an interesting, nonradioactive method that will need more investigation before entering routine patient care.

Plasma Volume

Isotope-Labeled Albumin

Radio iodine-labeled human serum albumin (HSA) is the recommended tracer for the PV, and the procedure has been thoroughly described (5). Albumin is not the ideal tracer of PV because

it also equilibrates with interstitial water, which contains about 40% of the total body albumin but at a much lower concentration than in plasma. However, it is possible to compensate for the loss of tracer if the escape rate from plasma is low compared with adequate mixing time, and if sequential measurements are performed. Albumin dilution overestimates PV, but the size of this bias will remain unknown as long as there is no standard reference method. The bias is likely to increase in sepsis and other diseases with impaired endothelial integrity. Another argument supporting the idea that albumin dilution overestimates PV is the inverse relationship between molecular weight and volume of distribution for a number of macromolecules (29).

After the injection of isotope-labeled albumin, samples are taken at 10, 20, and 30 minutes; a linear regression is performed in a semilog paper to the time of injection to compensate for the loss of tracer. Alternatively, only a single specimen is taken at 10 minutes, and the loss of tracer is ignored. ^{125}I has a half-life of 60 days compared with eight days for ^{131}I and has therefore replaced the latter in many laboratories.

The precision of the determination of PV by dilution of ^{125}I -HSA is probably better than 3% (25). The albumin volume of distribution has a large between-subject variability. Accuracy could not be estimated, but many agree that PV is overestimated.

Evans Blue

Evans Blue is a dye that is thought to bind to albumin and indirectly serve as a tracer for PV. It can be analyzed by absorption of light at 620 nm. It has a widespread use, especially in pediatrics and in fertile women, because it does not involve the use of radioactive isotopes. The shortcomings of albumin as a tracer for PV also apply to Evans Blue, such as an overestimation of PV.

Indocyanine Green

Indocyanine green (ICG) is an ionic dye that binds to plasma proteins, mainly globulins. It has a rapid hepatic elimination, resulting in a half-life of about three minutes (30). Because of the albumin binding, some of the errors of the albumin dilution method might apply to the ICG method. The solution must be protected from light. The rapid elimination necessitates an even more rapid distribution, because the two cannot be separated by a simple pharmacokinetic analysis. It has been suggested that the mixing time is less than one minute after injection by a central venous catheter (30), but this is in contrast to all other mixing procedures of body fluids. The rapid elimination makes the method sensitive to sampling errors in time and to the choice of time "zero." Hepatic blood flow is closely related to the rate of ICG elimination, and any change in this flow during the sampling procedure is likely to impair the precision of the PV estimate.

ICG can be analyzed by spectrophotometry at 805 nm in plasma or in hemolyzed blood. After rapid injection by a central venous line, sampling is performed every 30 seconds in arterial blood, starting at one minute after injection and continuing for another six minutes; the concentration at the time of injection can be calculated in a semilogarithmic plot.

The precision of the method is good (2%), and results compare favorably with ^{131}I -HSA. The need for invasive catheters is a serious disadvantage in most clinical settings but not so much in the perioperative situation where the rapid procedure could be of great benefit to the patient.

Hydroxyethyl Starch and Hemoglobin-Based Oxygen Carriers

Macromolecules larger than albumin are likely to remain longer within the circulating blood, and might therefore provide important improvement of the dilution techniques for PV. One consideration is that the infused tracer volume should lack significant effect on the PV. Therefore, only small tracer doses could be given to dismiss the oncotic effect of the tracer as negligible.

Hydroxyethyl starch (HES) has been used as a tracer for PV, and the calculated CBV compared favorably with values from CO dilution method (31). Blood volume was calculated from the difference between glucose concentrations measured after hydrolysis in the plasma before and after the addition of HES. Twelve patients and 50 volunteers participated in that investigation. In another study, fluorescent-labeled HES was diluted in 25 patients, and compared with dilution of ^{131}I -HSA and ^{51}Cr -labeled erythrocytes (32). The volume of distribution

was smaller than for ^{131}I -HSA, but the calculated CBV was greater for ^{51}Cr -labeled erythrocytes. The fluorescent label was stable and analysis was easy and precise.

Hemoglobin-based oxygen carriers (HBOC) are also interesting as tracers for PV (33). After injection of the tracer into 19 anesthetized rabbits, hemoglobin was measured in the supernatant plasma harvested from hematocrit tubes by a commercial photometric method. The agreement between HBOC and Evans Blue methods was very good, with a bias of about 2% and a precision of about 5%.

Circulating Blood Volume

CBV can be determined directly by exsanguinations of small animals, but for obvious reasons there is no such standard reference method for humans. CBV can be estimated indirectly as the sum of independent measurements of RCV and PV (5). The physiological control mechanisms seem to be designed to maintain CBV through independent control of these two components. Many investigators focus on the CBV because it is relevant for oxygen transport and organ perfusion. Some methods that are claimed to measure CBV have been discussed under PV as appropriate. This enables a focused discussion of the transformation of PV or RCV to CBV.

Calculation from Red Cell Volume or Plasma Volume with the Aid of Packed Cell Volume

CBV can be calculated from PCV, corrected for trapped plasma, with the aid of one further measurement of either PV by dilution of ^{125}I -HSA or RCV by dilution of ^{51}Cr -labeled erythrocytes (5). The error of the PCV measurement will be added to the error of the other method. One problem with this transformation is that the PCV varies in different parts of the vascular system.

$$\text{CBV} = \frac{\text{PV}}{1 - f \times \text{PCV}} = \frac{\text{RCV}}{f \times \text{PCV}} \quad (1)$$

f is the supposed ratio between the whole body hematocrit and PCV in venous blood. This ratio has been reported to vary between 0.75 and 0.97, and a recommended mean value of 0.9 has been suggested (5). The variation of f is large in both normal and diseased subjects. However, an f value of 0.9 cannot emanate solely from the variation of PCV in different vascular segments because less than 10% of the blood is found in small vessels and capillaries, and the difference in PCV must then be unrealistically large. If f is solved from Eq. (1), it becomes easier to understand how f depends on errors in RCV, PCV, or PV.

$$f = \frac{\text{RCV}}{\text{PCV} \times (\text{RCV} + \text{PV})} \quad (2)$$

Either dilution of ^{51}Cr -labeled erythrocytes underestimate RCV by some unknown mechanism, or ^{125}I -HSA has a larger volume of distribution than PV. As stated above, albumin is not a good marker for PV because it escapes into perivascular fluid compartments. The overestimation of PV by HSA might be the main reason for the reported f values, and even an f value of 1.0 has been suggested as the most reasonable figure (29). The value of f is also applied to alternative PV tracers that bind to plasma proteins such as ICG or Evans Blue for calculation of CBV. In contrast, the presumably more ideal plasma tracers (HBOC or HES) might not need a factor f different from 1.

Some authors advocate ^{125}I -HSA over ^{51}Cr labeled erythrocytes, even for the determination of red cell mass (25). Both methods have a CV <5%, but ^{125}I -HSA is much simpler and less expensive. Furthermore, the calculation of trapped plasma in PCV determinations could be faulty, and very little evidence that the bias between the volumes of distribution for the two tracers depends solely on albumin has been presented. A calculated f value of 0.864, with a coefficient of variation of 4%, was reported (25).

In summary, different opinions regarding the use of PV to calculate CBV exist, and independent measures of RCV and PV remain the main alternative. In the perioperative setting, however, new tracers that need little preparation and could be estimated at the bedside, such as CO and HBOC, are more interesting.

Pulse Dye Densitometry

It has recently been made possible to analyze ICG noninvasively using pulse spectrophotometry, which is based on the same principles as pulse oximetry—the ratio between pulsatile changes in tissue optical density of two infrared wavelengths at 805 and 890 nm (34). This technique is also called pulse dye densitometry (PDD) (35).

After baseline registration, a bolus injection of ICG is given via a central venous catheter. The optical density is measured continuously at the nostril or fingertip for each heartbeat, and the values are transformed to ICG concentrations in whole blood. Mixing with whole blood is considered to be complete within 2.5 minutes, and the logarithmic values from 2.5 to 5.5 minutes are used for back-extrapolation to time “zero” (34). Note that these authors use the mean transit time as “zero,” because hepatic elimination could not start until the compound is presented to the hepatocytes. The two-compartment model of ICG disposition is neglected by this method, which raises a question regarding the volume that is being measured.

The precision of the PDD method is about 6% (36). CBV by PDD shows good agreement with calculations from dilution of ^{131}I -HAS (35). When compared with a dilution of ^{51}Cr -labeled erythrocytes, a mean bias of 10% was obtained and the standard deviation for differences was rather large (15%) (36).

In summary, PDD is a promising method that could provide bedside measurements of CBV. The lack of standard reference method contributes to the difficulties of validation, as does the complicated procedure involving ^{51}Cr -labeled erythrocytes. The impact of PCV variability in different vascular segments and the multicompartment nature of ICG disposition have not been thoroughly investigated.

OTHER FLUID VOLUME MEASUREMENTS

Peripheral Tissue Thickness by Ultrasound

Peripheral tissue thickness by ultrasound does not measure ECW, but might serve as an online, noninvasive assessment of fluid balance in the operating room (37). A handheld ultrasound device was used to determine forehead tissue thickness in routine surgical procedures. Fasting and standardized hydration with Ringer’s solution were closely related to changes in tissue thickness and interpreted as changes in connective tissue hydration. Different body positions (supine, head-up, or head-down tilt) did not influence changes in tissue thickness.

Global End-Diastolic Blood Volume

Extravascular lung water can be assessed by single- or double-tracer dilution. These methods are covered in detail in the chapter on assessment of pulmonary edema. However, the same methods can also be used to measure or calculate global end-diastolic volume, total intrathoracic thermal volume, and intrathoracic blood volume (38). Commercial equipment is available for online monitoring of these volumes by the combined use of the dilution technique and pulse contour analysis.

Conductance Volumetry

Conductance volumetry is an invasive method of estimating blood volumes within the heart. A volume catheter is inserted and advanced to the left ventricular apex. It operates by the principle of segmental volume measurements by electrical resistivity of the blood to yield total chamber volume. Furthermore, calibration is necessary to eliminate the conductance of the left ventricular muscle wall. The method has been applied to patients in a research setting (39) but is unlikely to reach a widespread use because of the risks associated with the manipulating of catheters on the left side of the heart.

SUMMARY AND CONCLUSIONS

Clinical applications of the dilution technique to determine body fluid compartments in the operating theater are limited by the tracer equilibration time, which often exceeds the time of the surgical procedure, especially for TBW and ECW. Mixing times and some other properties for the main tracers are listed in Table 2. BIS is a feasible method but is based on erroneous assumptions that contribute to a great uncertainty in assessing the magnitude of body fluid

Table 2 Summary of Tracer Properties for Different Body Fluid Volumes

Fluid volume	Tracer	Half-life or turnover rate	Mixing time	Precision %	Bias %	Comments
TBW	$^2\text{H}_2\text{O}$	7 days	3–4 hr	1	+4.1	No radiation (7,11,16)
	H_2^{18}O	7 days	3–4 hr	1	+0.7	No radiation (7,11,16)
	Ethanol	0.1 g/kg/hr ^a	—	2 ^b	-14 ^b	Rapid elimination (17)
ECW	Br	7 days	8–10 hr	2	Unknown	(24)
RCV	^{51}Cr	28 days	30–60 min	5	Unknown	Complicated method (5)
	CO	5.5 hr ^c	15 min ^b	10 ^b	+10 ^d	Bedside analysis (26,27)
PV	^{125}I -HSA	60 days	15–30 min	3	Unknown	Positive bias (5,25,29)
	HES	0.5 hr ^b	Unknown	3 ^b	+2 ^{b,e}	(31,32)
	HBOC	20 hr	Unknown	5 ^b	-2 ^{b,e}	Bedside analysis (33)
	ICG	3 min	1 min ^b	2	+10 ^{b,e}	Bedside method (30,34)

^aNonlinear kinetics resulting in zero-order elimination rate.

^bFigure based on reports that are very limited in number or size.

^cBreathing room air. When breathing 100% oxygen, elimination half-life is 40–80 min.

^dCompared with ^{51}Cr -labeled erythrocytes.

^eCompared with ^{125}I -HSA or Evans Blue.

Abbreviations: TBW, total body water; ECW, extracellular water; RCV, red cell volume; CO, carbon monoxide; PV, plasma volume; HSA, human serum albumin; HES, hydroxyethyl starch; HBOC, hemoglobin-based oxygen carriers; ICG, indocyanine green.

volume changes. CBV can be estimated from the sum of RCV and PV, or the sum of either RCV or PV, and PCV. Even here, mixing times of 10 to 60 minutes have been proposed. The accuracy of PV determinations by dilution of isotope-labeled HSA has been proposed to lack credit. There is a great need for method development, and the new tracers include CO and sodium fluorescein for RCV, and the macromolecules HBOC and HES for PV. ICG is an interesting tracer, with the prospect of repeated measurements because of its rapid elimination. The analytical availability of ICG, HBOC, and CO makes them especially relevant and interesting for use in the perioperative setting. However, further investigations are necessary to determine their precision in repeat experiments, to define the applicability in different groups of patients, to take several samples from each dilution experiment to analyze models of distribution and correct mixing times, and to compare costs with other methods. Skepticism is advocated until proper validation of the new methods is achieved.

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2 | Microvascular Fluid Exchange

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INTRODUCTION

Fluid comprises approximately 60% of total body volume with some variations with age and sex (1). The intracellular volume is about twice as large as the extracellular volume. About three-fourths of the extracellular volume comprises the interstitial space and the rest is plasma volume. The red blood cells belong to the intracellular compartment. Blood (intravascular volume) contributes to about 7% of body weight or 4 to 6L in the adult man. At a normal hematocrit of about 40%, plasma volume in a 70 kg adult is about 3L, but at lower hematocrit values, the plasma volume must be correspondingly larger to maintain normovolemia. In most organs of the body, the interstitial volume comprises 25% to 30% of total extravascular fluid volume of the tissue and the rest is intracellular volume. The relative interstitial volume is somewhat smaller in the brain (2).

Under normal physiological circumstances, variations in total body volume are small, as well as the relative size of the volumes of the various compartments of the body. A therapeutic goal in different pathophysiological conditions is to preserve an adequate relation between the interstitial and the intravascular volume. If this relation is grossly disturbed with fluid passing from the intravascular to the interstitial space, the situation is consistent with hypovolemia and edema, but total extracellular volume is unchanged. If there is a redistribution caused by net filtration in one or just a few organs of the body, this will have a minor effect on total plasma volume, but the adverse effects of local edema development in these organs may be significant. The former condition can be exemplified by a sepsis or systemic inflammatory response syndrome (SIRS) situation, where there may be a general transcapillary leakage of fluid and proteins from the intra- to the extravascular space in most organs of the body (3,4). The subsequent interstitial tissue edema may have adverse effects by increasing the diffusion distances between capillaries, although the main pathophysiological impact of such a situation can be referred more to the loss of plasma volume than to the edema development. The latter condition can be exemplified by brain edema or pulmonary edema and, perhaps, renal edema, conditions that per se often have only minor effects on total plasma volume, but exert significant local adverse effects.

This chapter makes an attempt to describe basic physiological hemodynamic mechanisms controlling fluid exchange across microvascular membranes and possible pathophysiological consequences of disturbances in these systems. Even though the clinical situation often is more complex than that described by known and often simplified physiological principles and models, these may still help in understanding events that otherwise are difficult to explain. Because mechanisms controlling microvascular fluid exchange in the brain differ extensively from those in the rest of the body, and disturbances in brain volume control may have a significant effect on outcome, the brain will be discussed separately. Specific comments will be given on mechanisms controlling transvascular fluid exchange in the lung due to the profound adverse effects of pulmonary edema on gas exchange in all organs of the body. We will also give some comments on distribution and effectiveness of various types of blood volume-expanding solutions, based on the described physiological and pathophysiological principles for transvascular fluid exchange.

MICROVESSELS FOR FLUID EXCHANGE

Due to the large number of capillaries and the design of the microvascular network which is responsible for the exchange, between blood and tissues, of fluid, nutrients, and waste products (Fig. 1), total surface area for exchange in the adult is as large as about 700m² in the

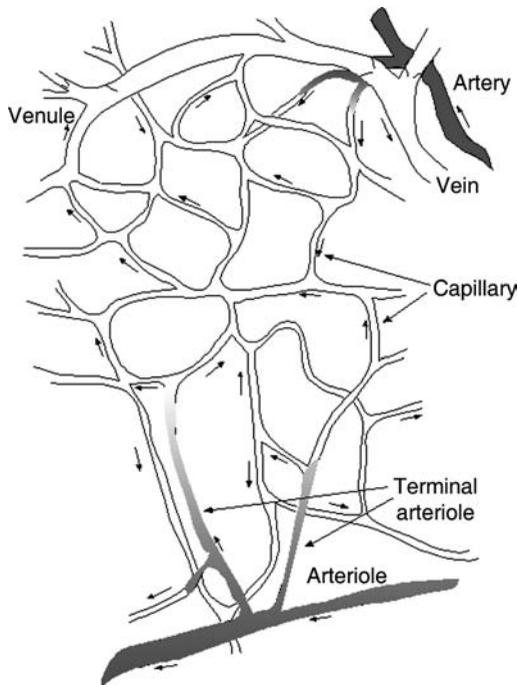


Figure 1 Schematic illustration of the microvascular network. Arrows indicate direction of blood flow.

systemic circulation and about 90 m^2 in the lung (1). The capillary membrane consists of a single layer of endothelial cells. Like other endothelial cells covering the inside of all vessels of the body, these cells have endocrine functions by producing substances such as nitric oxide, prostacyclin, and endothelin. As the capillaries lack smooth muscle cells, and flow resistance in the capillary vascular bed is low, they do not contribute to normal variations in total blood flow to an organ. Transvascular fluid exchange occurs along the capillaries as well as in the most proximal part of the venules, these together comprising "the exchange vessels." The degree of permeability for solutes of the microvascular membrane in these vessels constitutes the essential morphological and physiological basis for transvascular fluid exchange in an organ.

The capillaries (including exchange venules) are grossly divided into sinusoidal capillaries, fenestrated capillaries, and continuous capillaries (1,5). The sinusoidal capillaries are freely permeable to all solutes including proteins, and are present in liver, spleen, and bone marrow. Fenestrated capillaries can be found in glands, glomeruli, and part of the gastrointestinal tract and are characterized by transendothelial fenestrae with a high permeability for fluid and small solutes, but with restricted macromolecular permeability. The continuous capillaries are dominant in the rest of the organs such as the skeletal muscle, heart, lung, cutis, mesenterium, and central nervous system. Except in the brain, the continuous capillaries are characterized by high permeability for small solutes via interendothelial gaps, but they have restricted protein permeability. The three-dimensional organization of the interendothelial junctions in continuous capillaries, as indicated from serial section electron microscopy (6), is shown in Figure 2. In the brain, the interendothelial junctions are tighter, which results in low permeability to all solutes, including small solutes such as sodium and chloride ions, but permeability for water is still relatively high.

The mechanisms involved in the establishment of both the macromolecular and the fluid permeability are still not fully clarified. Factors discussed in this respect are the contractile state of intraendothelial filaments controlling intercellular pore size; electrical charge of the endothelial cell in relation to the charge of various blood elements; the presence of certain plasma proteins such as albumin, fibronectin, and orosomucoid; the erythrocyte concentration in plasma; and the chemical and electrical status of glycoproteins of the endothelial surface (glycocalyx) (7-9).

It has been postulated that proteins may be transported actively via energy-dependent mechanisms in vesicles across the capillary membrane by a process called transcytosis (7,8).

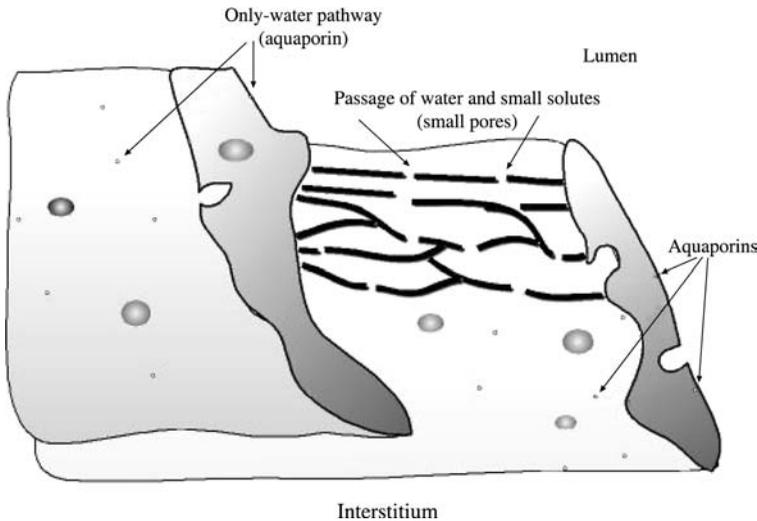


Figure 2 Three-dimensional drawing of an interendothelial junction in a continuous capillary as deduced from Ref. 6. Discontinuous adhesion lines on the surface of an endothelial cell allowing passage of small solutes are shown, as well as the only-water passage membrane channels, aquaporins.

Several recent functional studies, however, indicate that transcytosis plays only a minor role in the overall transport of macromolecules between blood and tissue, and the protein transport is mainly passive (9–11). In the present chapter, therefore, only passive mechanisms for transvascular exchange of fluid and solutes, including macromolecules, will be described.

STARLING EQUATION FOR TRANSVASCULAR FLUID EXCHANGE

In continuous capillaries where permeability for water and small solutes is high and permeability for proteins is low, transvascular fluid exchange (J_v) is normally described by the Starling formula (7,8)

$$J_v = L_p S (\Delta P - \sigma \Delta \Pi) \quad (1)$$

in which L_p represents hydraulic permeability (fluid conductivity), S is surface area available for fluid exchange reflecting the number of perfused capillaries, ΔP is the net transcapillary hydrostatic pressure force for filtration, σ is the reflection coefficient for macromolecules (plasma proteins), and $\Delta \Pi$ is the transcapillary colloid osmotic absorbing pressure force. The reflection coefficient for plasma proteins describes the effective part of the transcapillary colloid osmotic pressure counteracting fluid filtration, and represents the difficulty with which a macromolecule passes the exchange vessels relative to water. The reflection coefficient, therefore, is a crucial factor affecting the amount of proteins and fluid transferred from the intra- to the extravascular space. It is 1.0 when the membrane is impermeable to the molecules, and 0 when the molecules pass through the membrane without limitation. The reflection coefficient for plasma protein molecules given in the literature represents average microvascular permeability for these molecules, and provides an estimate of the effectiveness of a colloid osmotic force to exert absorption across the capillary membranes for a whole organ. The reflection coefficient for proteins is below 1.0 in all organs of the body except in the brain. Albumin is the dominating protein for producing colloid osmotic pressure in plasma, and the reflection coefficients for albumin for various organs are given in Table 1. Skeletal muscle comprises as much as about 40% of the body weight, and reduction in the reflection coefficient in this organ from its normal value of 0.90 to 0.95 therefore has substantial effects on plasma volume. The reflection coefficient for albumin is approximately 0.9 in the intestine and 0.5 to 0.6 in the lung.

Thus, in spite of a low macromolecular permeability, there is a continuous leakage of proteins into the interstitial space even under normal circumstances (transcapillary escape rate of 5–7% per hr), resulting in an interstitial colloid osmotic pressure of about one-fourth

Table 1 Normal Reflection Coefficient Values for Albumin in Man

Skeletal muscle	0.9–0.95
Lung	0.50–0.65
Intestine	0.80
Subcutis	0.80
Liver	0.0–0.05
Spleen	0
Brain	1.0

to one-third of that in plasma. The maintenance of a constant difference in colloid osmotic pressure between the intravascular and the interstitial space of an organ is determined by the sophisticated balance between the rate of protein leakage into the interstitium and the rate with which the interstitial proteins are drained back to the circulation via the lymphatic system. A system with recirculation of proteins between plasma and tissue and back to the plasma is essential in allowing access to the interstitial space of antibodies, protein-bound hormones, cytokines, and a large number of macromolecules. Maintenance of a colloid osmotic pressure in the interstitium also allows a self-limiting system for filtration and absorption (see below).

In normal conditions, the volume of an organ shows minor variations. This implies that the net effect on tissue volume of transcapillary filtration and absorption in combination with the lymphatic drainage is close to zero. Absence of large tissue volume variations can be referred to mechanisms like autoregulation of hydrostatic capillary pressure (12) (see under "Autoregulation" below), and the self-limitation for transcapillary filtration or absorption inherent in the fact that filtration will dilute and absorption concentrate the interstitial colloid osmotic force (7). In all organs of the body with continuous capillaries, except in the brain and the kidney, the interstitial colloid osmotic pressure is high and approximately one-fourth to one-third of that in plasma. Thus, fluid filtration will gradually be reduced, and cease when the new Starling equilibrium is achieved. Similarly, fluid absorption will successively increase the interstitial colloid osmotic pressure and the absorption will cease at a somewhat reduced tissue volume when the new Starling equilibrium is achieved. Filtration-induced increase in interstitial hydrostatic pressure may also counteract filtration, but this effect is weak except in organs enclosed in a rigid shell, such as the brain and the kidney.

THE THREE-PORE MODEL

The Starling equation [Eq. 1] can be used to describe how hydrostatic and colloid osmotic forces control net fluid fluxes across the capillary network in a tissue, but it gives no information on the mechanisms by which proteins are transferred from the intra- to the extra-vascular space. From the specific pore characteristics of the capillary bed, a theoretical pore model has been presented, which may be used to explain transvascular exchange of proteins (9,10). This model and its application to clinical practice will be presented below.

The capillary wall behaves functionally as a membrane containing pores of three different sizes. It contains a high number of small interendothelial pores of 4 to 6 nm radius, which are distributed along the entire capillary wall and permeable to small solutes and water. These small pores are 10,000 to 30,000 times more frequent than the large interendothelial pores with a radius of 20 to 30 nm located mainly on the venular side of the capillary network and on proximal venules and permeable to proteins as well. The capillary membrane includes also very small endothelial transmembranous pores only permeable to water (aquaporins) (8–10). The existence of small pores in the continuous capillaries is confirmed by electron microscopic and other microscopic techniques as schematically illustrated in Figure 2 (6). The chances of visualizing the much less frequent large pores are slight (9), but such visualization has been done under conditions of inflammation (11). Aquaporins are also shown in Figure 2. The total pore area comprises less than 0.1% of the total capillary surface area (1,8,10). The three-pore characteristics of the capillary membrane are described as the three-pore model of microvascular permeability which is explained schematically in Figure 3. To get a quantitative description of the transport of macromolecules, fluid, and small solutes under normal circumstances, the aquaporins can be neglected and the model can be simplified to a two-pore model including only the small pores and the large pores. In combination with

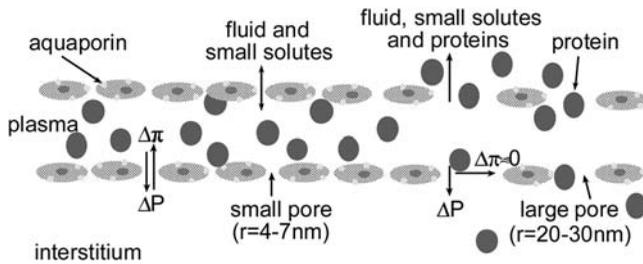


Figure 3 Principles of the three-pore model for controlling transvascular exchange of fluid and macromolecules. Note that there is no colloid osmotic absorbing force across the large pores ($\Delta\pi \approx 0$), which means that there is a “jet” stream of convective protein-rich volume flow through each large pore induced by the hydrostatic transcapillary force ΔP . An increase in the number of large pores will increase the loss of proteins correspondingly even though large-pore areas in relation to total pore area increase only marginally. The only-water pathway transmembrane pores, the aquaporins, are shown.

the Starling formula, this model can be used to better understand events of transvascular fluid exchange under normal physiological and pathophysiological conditions, as will be discussed.

The colloid osmotic pressure gradient can be developed fully across small pores (and aquaporins), counteracting the hydrostatic force for filtration. Because the protein molecule can pass the large pore rather easily, the protein concentrations will be approximately equal on the luminal and interstitial (abluminal) side of the pore opening, resulting in a very low colloid osmotic pressure gradient across each large pore. This means that there is no, or just a small, colloid osmotic transcapillary pressure across the large pore ($\Delta\pi \approx 0$) opposing the hydrostatic pressure force (Fig. 3), and a continuous protein-rich filtration of plasma in terms of a “jet” stream through each large pore, regardless of the direction or magnitude of the total volume flow across the small pores (10). Thus, there is a net flux of proteins even in the absence of net fluid filtration. Under normal conditions, approximately two-thirds of the protein loss is an effect of convection and one-third of diffusion (5), but the relative effect of convection is increased in pathophysiological situations with increased permeability.

The number and size of pores available for protein passage is described by the reflection coefficient for proteins. The large pores only comprise 0.2% to 0.4% of total pore area under normal circumstances (9), but are still essential for plasma protein leakage from the intravascular to the interstitial space. Even a moderate increase in large-pore areas relative to small-pore areas (Fig. 3), which occurs in various pathophysiological clinical settings, in time will cause a large increase in protein leakage due to increase in fluid filtration through the large pores. Only 5% of the net fluid flux from blood to the interstitium passes via the large pores under normal conditions, whereas up to 40% to 45% may pass via the large pores when there is a significantly reduced reflection coefficient for proteins (9).

Disturbances of mechanisms controlling the fluid balance may cause an increase or decrease in tissue volume. It may be due to interference with mechanisms controlling microvascular permeability, changes in transcapillary hydrostatic and colloid osmotic pressures, insufficient lymphatic drainage, or altered surface area for fluid exchange.

AUTOREGULATION

As shown by the Starling fluid formula [Eq. (1)], the hydrostatic transcapillary pressure is a major factor controlling transvascular fluid exchange. An increase in hydrostatic pressure will favor fluid filtration and decrease fluid absorption. In most organs of the body, however, variations of the hydrostatic microvascular pressure are restricted during normal circumstances due to a local autoregulatory mechanism, implying that an increase in arterial pressure induces vasoconstriction and a decrease vasodilatation (12). Autoregulation also means that the variations in blood flow to an organ during variations in arterial pressure are relatively smaller than variations in arterial blood pressure. While autoregulation of blood flow is a consequence of compensatory variations in total vascular resistance of the organ, autoregulation of hydrostatic capillary pressure can be explained by variations in the post-precapillary resistance ratio. The degree of autoregulation varies between organs. It is lacking in the lung and is more effective in

the brain, the skeletal muscle, and the kidney, and in the intestinal circulation. It is believed that autoregulation of hydrostatic capillary pressure is more effective than autoregulation of blood flow (12). The basal circulatory mechanisms behind the autoregulatory phenomena have not been fully clarified, but the main factors can be referred to modulation of the myogenic reactivity by a metabolic feedback mechanism (12).

Autoregulation, however, is a vulnerable system and can be significantly depressed under pathophysiological conditions such as those following surgical or accidental trauma and during SIRS/sepsis (13). A depressed autoregulation implies a higher basal hydrostatic capillary pressure, and there will be an increase from this raised level when arterial pressure rises, and a decrease in capillary pressure when arterial pressure falls. This means that increased arterial pressure during depressed autoregulation will favor filtration, resulting in increased tissue edema and reduced plasma volume, while the filtration will be counteracted by a decrease in arterial pressure. According to the three-pore theory, the increased filtration through large pores induced by an increase in hydrostatic capillary pressure will increase the loss of proteins via convection, especially under conditions of a reduced reflection coefficient (increased permeability) for proteins. Consequently, leakage of plasma fluid and proteins to the interstitium will increase with an increased arterial pressure. It is also suggested that under conditions of increased inflammation of the tissue (e.g., burn injury), there may be alterations in the interstitial matrix, with reduction in interstitial pressure (14). Such factors may also increase the transcapillary protein leakage.

From a physiological point of view, it is obvious that the loss of autoregulation as a consequence of relaxation of the vascular smooth muscle cells does not reduce perfusion of an organ; instead it improves perfusion. Still, loss of autoregulation is often associated with compromised perfusion in the clinical literature. The reason for this is that the compromised perfusion of an organ can be explained by other pathophysiological alterations that occur simultaneously with inhibition of myogenic reactivity of the smooth muscle cells. For example, reduced perfusion of an organ simultaneously with depressed autoregulation following trauma or during SIRS can be explained by disturbed perfusion due to blood cell adhesion/aggregation-induced microvascular occlusion, local vasoconstriction, and endothelial cell swelling. This can be exemplified by a rightward shift of the autoregulatory curve in the brain following a brain trauma (15), which can be explained entirely by the reduced perfusion in and around the contusion areas. Thus, depressed autoregulation per se does not reduce perfusion, but may be a symptom related to compromised perfusion.

HEMODYNAMIC EFFECTS OF INCREASED PERMEABILITY

Increased permeability for proteins (reduced reflection coefficient) is mainly due to an increase in the number of large pores. It reduces the transcapillary colloid osmotic absorbing force, resulting in increased filtration and edema. This is an effect of both the reduced reflection coefficient per se, and the subsequent increase in leakage of proteins into the interstitial space, resulting in a smaller colloid osmotic absorbing force. The protein leakage may have some positive effects on host defense by facilitating the transfer of immunologically active cells and molecules from blood to tissue, but the integrated adverse impact related to the induced hypovolemia, tissue edema, increased tissue pressure, and compromised microcirculation may be deleterious. During a general permeability-increasing process in the body, such as during sepsis or SIRS, the plasma protein concentrations may be considerably decreased and interstitial protein concentrations increased, resulting in a significantly reduced transcapillary absorbing osmotic force. The pathophysiological impact of this process is also dependent on the effectiveness of the lymphatic system to drain the interstitium from protein-rich fluid.

A change in hydrostatic capillary pressure may occur in response to a change in arterial pressure, especially during depressed autoregulation, or in response to precapillary vasodilation/vasoconstriction. The transcapillary fluid filtration rate is mainly related to the fluid conductance ($L_p S$ in the Starling formula). According to the Starling formula, an increased fluid permeability, L_p (mainly in the small pores), or increased surface area (S) available for fluid exchange will not directly influence the direction of the fluid movement or the final magnitude of the tissue volume change when the new steady state is reached. The only consequence of an increased $L_p S$ is an increase in the rate by which the fluid is transported

across the capillary membrane, and thus only influences the time needed to achieve the new steady state (Starling fluid equilibrium) in tissue volume.

A moderate increase in the rate of fluid filtration or an increase in the transfer of proteins may be compensated by the lymphatic system. Under conditions of significantly reduced reflection coefficient for proteins (increased number of large pores), however, the larger volume of filtered fluid will increase the convective leakage of proteins and reduce the transcapillary colloid osmotic absorbing force, resulting in the loss of plasma volume and the development of tissue edema. Increased protein permeability may also influence the effectiveness of various plasma volume expanders (see under "Crystalloid Infusion" and "Colloid Infusion" below).

MICROVASCULAR FLUID EXCHANGE IN THE LUNG

The exchange characteristics of pulmonary microvessels principally do not differ from those in most other continuous capillaries. Thus from a functional point of view, the Starling formula is valid also in the lung. The pulmonary capillaries contain small pores, large pores, and aquaporins, and the pulmonary fluid exchange and endothelial permeability characteristics can be described by the three-pore model (16). The microvessels are, however, adapted to their part in the gas exchange process with a denser microvascular network than in other organs, and they accommodate to large variations in cardiac output and function to "clean" the blood from various immunological and other undesired components.

The pulmonary vascular bed includes smooth muscle cells but lacks autoregulation, and the hydrostatic capillary pressure is lower than in most other organs of the body. Vascular tone is low, and vascular resistance variations occur mainly passively because the sympathetic influence on the pulmonary vessels is weak and they lack myogenic reactivity. The smooth muscle cells constrict when exposed to hypoxia (hypoxic pulmonary vasoconstriction), especially to hypoxia from the alveolar side (1). Under pathophysiological conditions such as during acute respiratory distress syndrome and during primary pulmonary hypertension, the raised pulmonary vascular resistance can be ascribed to hypoxic vasoconstriction, to structural alterations of the vascular wall, and to microvessel occlusion due to blood cell aggregation and wall adhesion (17). So far, only nitric oxide (NO) and prostacyclin (or prostacyclin analogue) inhalation as treatment have been shown to be effective in reducing raised pulmonary vascular resistance in clinical practice, but other potential pulmonary vasodilator substances such as endothelin-1 antagonists are under evaluation.

Fluid accumulation in the lung is minimized by adjustments of lymph flow and by changes in interstitial hydrostatic and colloid osmotic pressures (5,7). It has been suggested that significant edema cannot develop in the normal lung (normal permeability) during increased hydrostatic capillary pressure as long as it is below a critical level of 25 mmHg, when the lymphatic system is utilized at its maximum capacity. Above the critical hydrostatic capillary pressure, which appears to equal the colloid osmotic pressure, there is a linear increase in the fluid content of the lung with an increase in hydrostatic capillary pressure. It has also been suggested that a further increase in hydrostatic pressure may cause distension of the capillary wall with increase in pore size, resulting in a larger number of large pores ("stretch pore phenomenon") (5). The existence of such a mechanism is not fully clarified, but if present, it may favor fluid filtration and convective transport of proteins into the lung interstitium (16). During pathophysiological conditions, lung edema may appear also at lower values of hydrostatic capillary pressure due to reduced reflection coefficient for proteins by analogy with most other organs of the body. Also the airway pressure in the lung may influence fluid flux across the capillary membranes and counteract pulmonary edema (18).

Both small- and large-pore permeability are larger in the lung than in most other organs with continuous capillaries. The effective small pore radius is calculated to average 7.5 to 8 nm compared to 4 to 6 nm in skeletal muscle, and the normal reflection coefficient for proteins is lower in the lung (Table 1). Under normal circumstances, the lymphatic system is, however, effective enough to drain the great leakage of proteins from the lung interstitium (5,7). This pronounced turnover of proteins means that the lung capillary membrane is adapted to a process of blood clearance by the immune system of immunoglobulins, antibodies, complement factors, cytokines, and other macromolecular substances.

MICROVASCULAR FLUID EXCHANGE IN THE BRAIN

Even though the cerebral capillaries are of the continuous type, the mechanisms controlling transvascular fluid exchange in the brain differ markedly from those of other organs with continuous capillaries. The fluid exchange across cerebral capillaries is based on the tight interendothelial junctions. Other factors such as the size and electrical charge of the solute and the composition of the endothelial glycocalyx/basement membrane are probably also involved (2). Altogether this results in a highly sophisticated semipermeable capillary membrane as a part of the blood–brain barrier (BBB) function. This implies impermeability for passive exchange not only for macromolecules, but also for small solutes such as sodium and chloride ions, while permeability for water is rather high. In the brain, net permeability of a solute is also dependent on active transport via energy-dependent pumps in the endothelial membrane (2,19), but their capacity for fluid and molecular transfer is too low for a significant impact on brain volume regulation.

The brain behaves functionally like a one-pore model for fluid exchange, lacking small and large pores but with pores permeable to water. The brain also differs from other organs by including a cerebrospinal fluid (CSF) system and by its lack of a lymphatic drainage system (2). Effective control of brain volume is of great importance for proper functioning of the brain as the brain is enclosed in a rigid cranium, with limited space for volume expansion. Disturbances in mechanisms controlling transvascular fluid exchange in the brain may result in brain edema and increased intracranial pressure, which will reduce the cerebral perfusion pressure and, as a final scenario, cause fatal herniation of the brain stem.

Because cerebral capillary membranes have limited permeability, not only for proteins but also for small solutes, the Starling formula as formulated above [Eq. (1)] cannot be used. A more correct description of volume flow (J_v) across the cerebral microvascular bed is

$$J_v = L_p S [\Delta P - \Delta \Pi_p - \sum \sigma_s \Delta \Pi_s] \quad (2)$$

L_p reflects the specific permeability component for water, S is the surface area available for fluid exchange, and $L_p S$ is the hydraulic conductance of the tissue reflecting the total capacity for fluid exchange, including the number of capillaries in the tissue. ΔP is the transcapillary hydrostatic pressure. $\Delta \Pi_p$ is the effective transcapillary colloid osmotic pressure for proteins, as the reflection coefficient for proteins is 1.0. $\Delta \Pi_s$ is the transcapillary osmotic pressure for a small solute and σ_s , the reflection coefficient of that solute (2,7). The last part of Eq. (2) represents the sum of the effective transcapillary osmotic pressures for all solutes except for proteins, and is zero at steady state, as a change in $\Delta \Pi_s$ will immediately be compensated for by transcapillary water flux. For sodium and chloride ions, which have low lipid solubility, the surface area available for filtration (S) does not differ greatly from the surface area available for diffusion, which is easier to determine in the brain. The diffusion area is therefore often used when comparing available fluid exchange surface areas for various substances in the brain and is expressed as the permeability surface area product (PS-product) (2).

Basic differences regarding the leakage of solutes across brain capillaries at normal and disrupted BBB on one hand, and in the skeletal muscle with normal and increased permeability (representing the main part of the body) on the other hand, are summarized in Figure 4 and will be further discussed below.

Volume Control of the Normal Brain

The effective osmotic force of a solute developed across the BBB is determined by the difference between the intracapillary and the interstitial perivascular osmotic pressure, and the difficulty with which the substance can pass the capillary membrane in relation to water. This latter factor is described by the reflection coefficient (σ_s) for the substance [Eq. (2)] by analogy with the situation for macromolecules in the rest of the body [Eq. (1)]. Sodium and chloride ions are the dominating solutes behind total extracellular osmolality of 5600 mmHg. Under normal circumstances, the reflection coefficient in brain capillaries for these and most other small solutes is 1.0, compared with the rest of the body, where corresponding reflection coefficients are much lower and, in most cases, close to zero. A change in the balance between the colloid osmotic (oncotic) and hydrostatic pressures will induce a passive driving force for filtration or absorption in the brain. However, as will be discussed below, while the induced

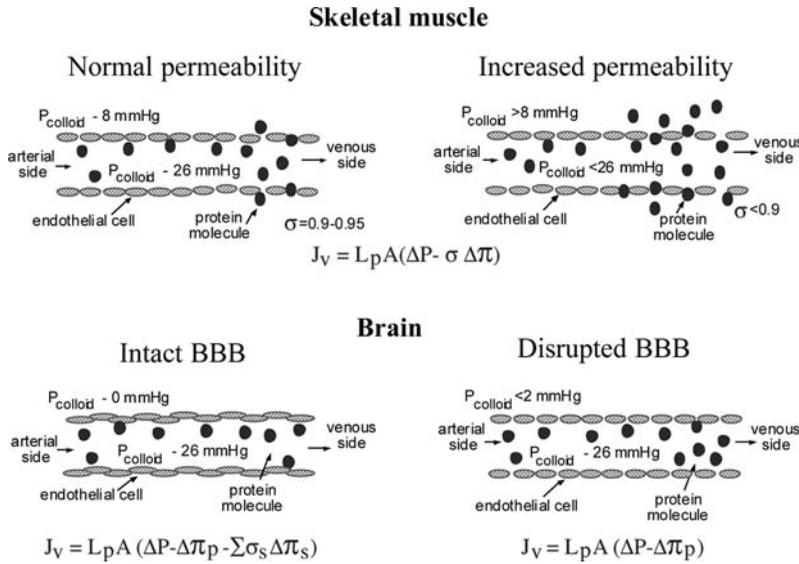


Figure 4 Schematic illustration of principles for protein leakage across the capillary wall in the normal skeletal muscle and brain compared with a state in which there is an increased permeability in these organs. In this respect, the skeletal muscle may be a model organ for other organs of the body in which transvascular fluid exchange follows the principles described by the Starling formula. Note that the interstitial protein concentration is very low not only in the brain with intact BBB but also with opened BBB. Difference in colloid osmotic pressure between the intra- and extravascular space is denoted ($\Delta\pi$) in the skeletal muscle and ($\Delta\pi_p$) in the brain. *Abbreviation:* BBB, blood–brain barrier.

volume flow across the capillary membrane will be small in a brain with intact BBB due to the compensatory effect mentioned above [illustrated by the last part of Eq. (2)], it may be large in a brain with disrupted BBB.

The fact that the reflection coefficient for small solutes such as sodium and chloride ions is close to 1.0 in the normal brain means that water passing the BBB in any direction will be virtually devoid of these ions and fluid entering the brain will induce dilution. Even a small dilution of the interstitial space will cause a clear decrease in the osmotic pressure across the membrane, as the dilution occurs from an osmotic basal level as high as 5600 mmHg, inducing a powerful self-limiting effect on the filtration. This also means that even a minor reduction in the reflection coefficient for sodium and chloride may disturb normal brain volume regulation and induce brain edema following imbalance between the hydrostatic and colloid osmotic pressures (see below).

A difference in hydraulic conductivity (L_p) or available surface area for fluid exchange (S) between different parts of the brain will not influence the total amount of volume flow, but only influence the rate by which the fluid is transferred due to the imbalance between the hydrostatic and osmotic transcapillary pressures. A difference in the hydraulic conductance ($L_p S$) can be illustrated by the two to three times higher capillary fluid conductance (mainly an effect of larger surface area) in the gray matter compared to the white matter of the brain. Differences in hydraulic conductance will be of minor importance for normal brain volume regulation as the net volume flows across the intact BBB are very small due to the strong counteracting effect developed by dilution/concentration of the interstitial space as described above.

Even though both sodium and chloride ions on one hand, and plasma proteins on the other, all have a reflection coefficient in the brain of 1.0, the PS product (reflecting exchange area for diffusion) is 700 to 1400 times smaller for albumin than for sodium and chloride ions (2). Still, the difference in net permeability across the intact BBB between sodium/chloride ions and proteins is insignificant regarding functional brain volume regulation, even when a possible active transport mechanism of inorganic ions, proteins, and amino acids from the perivascular interstitial space is included. Very few protein molecules are transferred to the interstitial space, even though the driving force for diffusion of protein molecules across the capillary membrane is relatively large. Proteins in plasma create a colloid osmotic pressure of about 26 mmHg, while

the cerebral interstitial protein concentration is close to zero. An approximate value of the overall interstitial protein concentration in the brain can be obtained by measuring the protein concentration in the cerebrospinal fluid (CSF), because the interstitial fluid shows continuous communication with the CSF (2). CSF protein measurements reveal that the overall protein concentration is low not only in the normal brain but also in the injured brain, indicating no or just minor leakage of proteins also after brain injury (Fig. 4).

Volume Control of the Injured Brain

According to the principles discussed above for control of microvascular fluid exchange in the normal brain, it is apparent that damage to the BBB in terms of passive permeability for small solutes such as sodium and chloride ions will influence the normal brain volume regulation. This means that fluid exchange due to an imbalance between the hydrostatic and colloid osmotic transcapillary pressures will be less damped, as the filtrate is not devoid of small solutes and therefore will have smaller influence on interstitial osmolarity compared to the situation when BBB is intact. Quite simply, fluid filtration and absorption will be much less counteracted by interstitial dilution and concentration compared with the normal brain. After a severe brain trauma or during meningitis, there may be a disruption of the BBB in terms of passive permeability for sodium and chloride ions and other small solutes, and the concentrations of these ions in the filtrate of the most injured areas may even approach those in plasma. The situation will show some similarity to the normal state in the rest of the body, where effects on microvascular fluid exchange caused by variation in the hydrostatic and colloid osmotic pressures can develop without being counteracted by strong self-limiting mechanisms. There will not even be dilution of interstitial proteins counteracting filtration due to the low interstitial protein concentration in the brain (Fig. 4). This means that an increase in the capillary hydrostatic pressure or a decrease in plasma colloid osmotic pressure can induce interstitial edema. The lack of a strong self-limiting mechanism for fluid exchange as that inherent in the intact BBB may be one factor behind brain edema development following disruption of the BBB. While fluid exchange in the normal brain can be described by a "one-pore model" with pores permeable to water only, the injured brain may be described by a two-pore model including small pores and pores only permeable to water, but no large pores (Fig. 4).

Transcapillary filtration through the disrupted BBB in time will increase intracranial pressure, and the reduced transcapillary hydrostatic pressure will gradually counteract the filtration. The filtration will cease when the transcapillary hydrostatic pressure gradient balances the transcapillary plasma colloid osmotic pressure gradient. As will be explained below, the fact that the brain is enclosed in a rigid shell means that the induced increase in intracranial pressure is much larger than the initial increase in transcapillary hydrostatic pressure or the initial decrease in colloid osmotic pressure, triggering the filtration (20). This fact is of great importance for understanding the physiological mechanisms responsible for transvascular fluid exchange in a brain with disrupted BBB.

Figure 5 shows a schematic illustration of a brain with a disrupted BBB enclosed in its rigid cranium/dura. The normal intracranial pressure (ICP) of approximately 10 mmHg

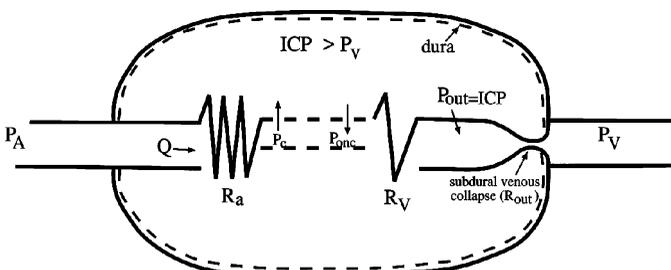


Figure 5 Schematic illustration of a brain with capillaries permeable to small solutes (disrupted blood–brain barrier) enclosed in the rigid cranium/dura. When tissue pressure exceeds the venous pressure (P_V) outside the dura there is a passive collapse of the outflow veins (Starling resistor, R_{out}). P_A is arterial inflow pressure, Q is blood flow, P_c is intracapillary pressure, R_a and R_v are pre- and postcapillary resistances. For the physiological consequences of the subdural venous collapse (R_{out}) for transvascular fluid exchange and intracranial pressure, see text.

always exceeds venous outflow pressure (P_v). This means that there is a passive venous collapse (sometimes called the Starling resistor) just subdurally. If intracranial pressure is increased further (e.g., by edema development), there will be more collapse of the subdural veins, and the venous pressure immediately retrograde to the collapse (P_{out} in Fig. 5) will increase in parallel. This increase will be transferred to the capillaries, but only to a degree of 80% to 85% due to the pressure fall in the venules. Therefore, the increase in intracranial pressure will cause further increase in hydrostatic capillary pressure, causing further increase in intracranial pressure and so on. Finally a new steady state in intracranial pressure will be reached, and theoretically intracranial pressure can increase up to eight times more than the initial increase in hydrostatic pressure (20,21), if 80% of the filtration-induced increase in intracranial pressure is transferred in a retrograde manner to the capillaries. Similarly, a decrease in the colloid osmotic pressure will induce filtration, and the filtration will not cease until the intracranial pressure is increased and by up to eight times more than the decrease in colloid osmotic pressure triggering the filtration (20).

The physical phenomenon of a decrease in perfusion pressure with increase in tissue pressure, providing that the tissue pressure is higher than the venous pressure, is general and may occur not only in the brain, but also in other organs of the body such as abdominal organs at increased intra-abdominal pressure. For example, a reduced perfusion pressure in the kidney because of this mechanism may be a most reasonable explanation behind the well-known reduction in urine production observed in patients with increased intra-abdominal pressure.

These principles indicate that a raised hydrostatic and/or a lowered colloid osmotic pressure may trigger vasogenic brain edema in a state of disrupted BBB. If so, a therapy of brain edema may benefit by including antihypertensive treatment and restitution of a decreased colloid osmotic pressure by infusion of a colloid solution (21,22). Physiological principles of brain volume regulation have been guiding tools in the "Lund Concept" for the treatment of brain edema, so far showing most favorable outcome results (22).

Brain edema, however, also may be of intracellular nature (23) due to the damage of cell membranes and cell dysfunction via cytotoxic and ischemic effects. It may also be a consequence of increased osmolarity in the interstitium following disintegration of various molecules and cell elements. Large efforts have been made to reduce intracellular edema by various types of cell-protecting substances, but all have failed when applied to man. Reduction in intracellular edema has mainly been achieved by measures that improve circulation in the brain, preserve a normal sodium concentration in plasma, or reduce the increased cellular volume by infusion of hypertonic solutions. Treatment with hypertonic solutions to reduce a brain edema is discussed further below.

INTRAVASCULAR VOLUME SUBSTITUTION

Hypovolemia induces peripheral vasoconstriction and a compromised microcirculation due to a baroreceptor reflex-induced increase in sympathetic discharge and release of catecholamines, and is an important factor contributing to multiple organ failure in the intensive care unit. Avoidance of hypovolemia, therefore, is a main goal in the treatment of critically ill patients and patients undergoing surgery. There is a continuing debate regarding which solutions to use regarding colloids and crystalloids, as well as which colloid to use. The use of erythrocyte transfusion for volume substitution in the absence of bleeding is controversial (24,25). Crystalloids are solutions composed of solutes with a molecular weight below 30 kDa, whereas colloid solutions contain also molecules larger than 30 kDa (26).

There is a general consensus that for some critically ill patients (e.g., patients with septic shock or multitrauma), it may be difficult to maintain normovolemia. Physiological aspects on the use of colloid and crystalloid solutions may explain why these solutions are not as effective as expected in restituting normovolemia in the critically ill patient (see under crystalloid infusion and colloid infusion below).

CRYSTALLOID INFUSION

Crystalloid solutions alone or in combination with colloids are widely used as plasma volume expanders. The infused volume of an isotonic crystalloid solution will be evenly distributed to

the whole extracellular space because small solutes pass the capillary membrane freely. Such distribution will not occur in the normal brain due to the intact BBB, but it may occur in the injured brain with a BBB permeable to small solutes. For ions and molecules below 5 kDa molecular weight, the capillary membranes in most organs of the body (not the normal brain) exert no limitation for transfer of the solute across the membrane (the reflection coefficient is close to zero). The diffusion of sodium and chloride ions, for example (<5 kDa), is so fast that blood flow to the organ is the only limitation (flow limited transfer) for equilibration of the transvascular concentration gradients. Thus not more than about one-fourth of the infused volume will stay intravascularly, and the major part of the infused volume passes to the interstitium within minutes. The use of crystalloid solutions to restore a lowered plasma volume therefore always means a simultaneous increase in water content of most tissues of the body. Within reasonable limits of tissue edema, this is of minor importance for most organs of the body. For the lung and the brain, however, an increase in water content of the tissue may have greater pathophysiological significance, the former by reducing oxygenation of blood and the latter by inducing brain edema and increased intracranial pressure.

However, there is a risk that the plasma-expanding effect of a crystalloid infusion will not even be as effective as mentioned above in patients with increased permeability. First, patients with increased permeability may have lost plasma to the interstitium resulting in a lower plasma volume relative to the interstitial volume than the normal relation of about one-fourth. Second, in absolute figures the infusion of crystalloids will cause a somewhat smaller dilution of the interstitium than of plasma, which may result in a decreased colloid-absorbing driving force. It can be calculated that the colloid osmotic pressure in plasma and in the interstitial space will be reduced by about 7% following infusion of 1 L of an isotonic crystalloid solution to a patient with a plasma volume of 3 L and an interstitial volume of 11 L. This means that the normal plasma colloid osmotic pressure of about 26 mmHg is reduced by about 2 mmHg, and the normal interstitial colloid osmotic pressure of about 8 mmHg is reduced by about 0.5 mmHg. The reduced transcapillary absorbing colloid osmotic pressure of about 1.5 mmHg will induce filtration until a new steady state (Starling fluid equilibrium) is reached. This effect, however, is smaller in patients with reduced transcapillary colloid osmotic pressure. Thirdly, in patients with decreased reflection coefficient for macromolecules such as in sepsis/SIRS or after trauma, the transfer of the large volumes of fluid from the intravascular to the interstitial space following the crystalloid infusion will induce a convective loss of proteins when there is an increased fluid volume passing through the large pores. Finally, there may also be an increase in hydrostatic capillary pressure due to the increased arterial pressure resulting from volume expansion (especially at depressed autoregulation), which will also increase the loss of proteins through the large pores via convection.

COLLOID INFUSION

Infusions of colloid solutions are used with the main purpose of restoring a low plasma volume, but sometimes also to restore a low colloid osmotic pressure. The relative distribution of a colloid infusion between the intra- and extravascular space is dependent on the permeability for macromolecules of the capillary membrane. This means that the brain with its low permeability for macromolecules in this respect behaves differently from the rest of the body.

Tissues with Capillaries Permeable to Proteins

The increase in plasma colloid osmotic pressure resulting from a hyperoncotic colloid infusion will initially induce absorption across the capillaries with a further increase in plasma volume added to the initial infusion volume. There is a general experience that the plasma volume-expanding effect of colloids in critically ill patients often is only transient, and therefore the infusion of colloids must be repeated to preserve normovolemia. This behavior can be explained by the three-pore model for transvascular fluid exchange described above (Fig. 3). In short, regardless of the direction or magnitude of the net fluid flux across the capillary membrane, water filtration is forming a "jet" stream through each large pore as there is no colloid absorbing luminal force in these pores, resulting in a continuous, mainly convective leakage of macromolecules through the pore (9,10). The volume of protein leakage, therefore, is dependent on the size and number of large pores (reflecting the reflection coefficient of

macromolecules) and the transcapillary hydrostatic pressure. This means that the loss of macromolecules to the interstitium is much larger at a high macromolecular permeability than in a state with normal permeability, and the macromolecular loss increases with increases in hydrostatic capillary pressure. The increased hydrostatic capillary pressure induced by the vasodilation and the increased arterial pressure following infusion of a colloid solution, therefore, will increase the convective macromolecular leakage. The long-term effectiveness of a colloid solution to restore a low plasma volume in critically ill patients thus seems to be dependent on the degree of reduction of the reflection coefficient for macromolecules, on the autoregulatory capacity, and on arterial pressure. This means that avoidance of hypertension can be a therapeutic measure to counteract hypovolemia and edema in states with increased permeability.

The Brain

There is no transcapillary leakage of proteins and other macromolecules in the normal brain. Even though there is leakage of proteins in the limited areas with mechanically disrupted microvessels (contusion areas) of the injured brain, net leakage of macromolecules for the whole brain is too small to produce any significant colloid osmotic pressure in the brain interstitium (Fig. 4). This means that both with intact and with disrupted BBB, the effective colloid-absorbing force across brain capillaries is of about the same magnitude as the plasma colloid osmotic pressure. An increase in colloid osmotic pressure by colloid infusions will have no influence on transvascular fluid exchange in the normal brain due to the impermeability for sodium and chloride of the intact BBB, as described previously (see under micro-vascular fluid exchange in the brain). The situation is different in a brain with disrupted BBB with increased permeability to small solutes. An increase in plasma colloid osmotic pressure by colloid infusions will induce absorption and reduce the interstitial brain volume until counteracted by the induced decrease in ICP. It must be noted, however, that this is a very slow process due to the low hydraulic conductance of the brain (2).

As mentioned previously in this chapter, the self-limiting mechanism for filtration and absorption, present in most other organs of the body due to the induced dilution or concentration of the relatively high interstitial protein concentration, is lacking in the brain (Fig. 4). Altogether, from a physiological point of view, colloid infusion is of value to the brain-injured patient with a disrupted BBB not only to prevent hypovolemia, but also to reduce or prevent brain edema. These arguments and the fact that crystalloid solutions may be distributed to the interstitium of the injured brain favor colloids over crystalloids for plasma volume expansion to patients suffering from a brain injury with disrupted BBB (21,22).

ERYTHROCYTE TRANSFUSION

Some comments will also be made on the use of erythrocyte infusion to preserve normovolemia. At lowered hematocrit, the relative plasma volume must be correspondingly larger to prevent hypovolemia, which may be difficult to achieve by infusion of crystalloids and colloids in a state of increased protein permeability (reduced reflection coefficient for proteins) as discussed above. The red blood cells do not pass the capillary membrane and will remain intravascularly for a long time and thereby contribute to preservation of the blood volume. Further, it is suggested from experimental studies on dogs (27) and rats (28) that the transcapillary leakage of plasma proteins is smaller with a high than a low hematocrit and, if so, this mechanism also helps to preserve plasma volume.

There is, however, always a risk with blood transfusions such as transfusion reactions, transfer of infectious agents, and immunological reactions, which may explain why we still lack reliable clinical studies supporting liberal use of blood transfusions in nonbleeding patients (24,25). Better tests to exclude infection and a better handling of blood by using leukocyte-depleted blood and blood stored for a shorter time may reduce the adverse effects of blood transfusion (29,30). If so, the deduced beneficial physiological effects of using transfusions with erythrocytes to preserve normovolemia may be of great value in patients where normovolemia is of special importance, such as in patients suffering a severe brain trauma (21,22) or SIRS.

HYPERTONIC SOLUTIONS

Hypertonic solutions are used clinically with the purpose of expanding the plasma volume or to reduce a brain edema (26,31,32). Hypertonic solutions contain small molecules, and in all organs, except the normal brain, they pass the capillary membrane freely. This means an even distribution of the substance in the whole extravascular space. Except in the very short-term perspective, the osmotic pressure force from the substance can therefore be developed only across the cell membrane and not across the vascular membrane. This means that the hypertonic solutions exert their plasma-expanding effect mainly by inducing fluid transfer from the intra- to the extracellular space. The magnitude of the osmotic force developed across the cell membrane and thus the amount of fluid absorbed from the intracellular compartment depends on the osmolality of the solution in combination with the membrane permeability for the infused molecules. Furthermore, hypertonic solutions may cause shrinkage of the vascular endothelial cells and blood cells, thereby improving the microcirculation.

The most common hypertonic solutions in clinical use are mannitol, urea, and hypertonic saline, where mannitol and urea are used mainly to reduce brain edema, whereas hypertonic saline is used both to reduce brain edema and to expand the plasma volume. Urea is an endogenous substance produced in the metabolically active cells and normally penetrating the cell membrane via diffusion. Also mannitol in time penetrates the cell membrane as shown in a glial cell culture (33). This means that the plasma-expanding effect of urea and mannitol is short lasting and rather ineffective in increasing a lowered plasma volume. Further, it has been discussed whether there may be an adverse transient rebound cell volume increase due to intracellular accumulation of mannitol as shown experimentally in glial cells (33) and in cat skeletal muscle (34). The situation may be different for hypertonic saline as sodium pumps in the cellular membrane will prevent intracellular accumulation of sodium and chloride. The absorbing effect of hypertonic saline therefore can be expected to be more long lasting than that of mannitol and urea, with less risk for rebound effects (34).

In the brain, mannitol and hypertonic saline create an absorbing force across the cerebral capillary membrane as the BBB has limited permeability for these substances. This means that there will be a reduction in the volume of the interstitial space, but also of the intracellular space due to the secondary increase in interstitial osmolality. Urea slowly penetrates the cerebral capillaries as well as the brain cell membranes, and therefore, in time, is less effective in reducing the brain volume than mannitol and hypertonic saline. After a brain injury, the situation is dependent on the degree of disruption of the BBB, with regard to the difficulty with which the molecules of the hypertonic solution pass the cerebral capillary membrane. The more the BBB is opened for passage of small solutes, the less fluid will be absorbed over the capillary membrane, and fluid absorption will occur more from the intracellular space. If opening of the BBB is significant, the situation will equal that in the rest of the body with interstitial and intravascular volume expansion after infusion of hypertonic solutions.

PERMEABILITY-REDUCING THERAPY

A pharmacological therapy that reduces increased protein permeability might be an attractive measure to preserve plasma volume by reducing plasma leakage to the interstitium. There is still no permeability-reducing substance shown to be effective in clinical practice, but terbutaline, aminophylline, and prostacyclin are all substances that have been evaluated in experimental studies regarding their permeability-reducing effects (35). The substances analyzed so far have all been suggested to act via an increase in intracellular cyclic adenosine monophosphate, thereby influencing the contractile state of the intraendothelial filaments and the width of the interendothelial pores (8). So far prostacyclin seems to be the most promising alternative because it reduces both protein and fluid permeability in relatively low doses as tested experimentally in a trauma model on cats (36).

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3 Invasive Hemodynamic Monitoring

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PRACTICAL CONSIDERATIONS OF FLUID MANAGEMENT

An accurate method of assessing intravascular volume and preload of the heart is an essential component in the successful management of patients in the operating room and intensive care unit. Left ventricular (LV) preload represents the force or load acting to stretch ventricular muscle fibers at end-diastole. As sarcomeres in the mid-wall of the myocardium are stretched from 1.8 to 2.25 μm , the ascending limb of Starling's law of the heart is defined. This relationship cannot be adequately explained as originally thought by a sliding filament theory with corresponding changes in actin and myosin overlap at greater sarcomere lengths. Rather, the steepness of the ascending limb appears secondary to length-dependent activation of myofibrils (1), perhaps from greater calcium affinity by troponin C or from enhanced release of calcium from the sarcoplasmic reticulum at greater sarcomere lengths (2). In the intact heart, sarcomere length and end-diastolic volume are closely related. As end-diastolic volume is increased, stroke volume is augmented in a linear manner (3).

However, a reliable technique to accurately and repeatedly quantitate LV and right ventricular (RV) volumes has been difficult to find for clinical use. For years, pressure measurements have represented the only estimation of the volume status in the heart, which, of course, depends on myocardial compliance. Low values of filling pressures typically indicate ventricular underfilling; volume expansion would increase both end-diastolic volume as well as stroke volume (4). However, elevated pressures are less specific and may indicate a wide range of ventricular end-diastolic volumes ranging from overfilled in a compliant heart to underfilled in a noncompliant ventricle. To optimize patient care and improve survival, it is essential to correct ongoing fluid deficits and restore cardiac output (CO) and perfusion pressure without evoking compensatory mechanisms that alter systemic and regional vascular resistances (5). A recent meta-analysis of hemodynamic optimization in high-risk patients reports a significant improvement in patient mortality when acute disturbances are aggressively managed early to achieve optimal end points before the onset of organ failure (6). Early optimization reduces mortality by 23% ($p < 0.05$), whereas optimization after the development of organ failure shows no improvement in patient survival. Similarly, therapy that fails to increase oxygen delivery does not alter survival. The key issue is whether optimal hemodynamic parameters are reached either by specific treatment or spontaneously and not necessarily the manner by which these changes are induced (7). Optimization of hemodynamic parameters in critically ill patients should be regarded as an appropriate therapy to prevent rather than to manage organ failure from shock and hypotension. Consequently, an accurate and clinically applicable method to assess plasma volume status and ventricular filling is needed.

Once the decision has been made that aggressive fluid management is indicated, a question arises as to what type of fluids should be used. In terms of plasma volume expansion, the end point of resuscitation is important—whether an improvement in stroke volume by preload-recruitable cardiac function or an increase in tissue oxygen delivery. For stroke volume improvement, the type of infused fluid becomes influential because crystalloids are relatively poor volume expanders due to their rapid redistribution throughout the entire extracellular space (8). In experimental animals, 25 mL/kg of lactated Ringer's infusion produces a peak intravascular fluid expansion of 7 ± 1 mL/kg, which rapidly declines over 30 minutes to only 2 ± 1 mL/kg (9). Resuscitation from hemorrhage by using non-blood-containing solutions may

increase stroke volume and CO, but any overall improvement in tissue oxygen delivery can be proportionately offset by the ensuing dilutional anemia (10). Blood transfusions can enhance tissue oxygen delivery by increasing arterial oxygen content as well as by improving stroke volume from preload recruitability. When nonblood fluids are used, a combination of colloid and crystalloid fluids may be superior to monotherapy alone (11).

However, there can be a significant downside to volume expansion by fluid administration. Edema formation secondary to crystalloid resuscitation can occur in both injured as well as noninjured tissues (12) and potentially can compromise end-organ perfusion by small vessel compression as well as by increasing the diffusion distance for oxygen (11). Interstitial fluid accumulation in the lungs worsens gas exchange. Edema formation and reduced urinary excretion of infused fluid occur more frequently in anesthetized and mechanically ventilated animals than in conscious subjects (13). Myocardial edema may result from isotonic fluid resuscitation, which can reduce myocardial compliance, causing overestimation of cardiac volumes using pressure monitoring (14). Further, any improvement in filling pressure, stroke volume, and systemic perfusion pressure secondary to fluid administration may not necessarily translate to improved end-organ perfusion. For example, with septic shock, an increase in CO secondary to volume expansion does not necessarily improve regional splanchnic perfusion in patients (15). Lastly, the timing of fluid resuscitation warrants consideration because rapid resuscitation of severe, uncontrolled hemorrhage can promote subsequent bleeding and a greater mortality than comparable hemodynamic improvement later during the course of resuscitation (16). Thus, there are multiple, interacting factors to consider when evaluating a patient's volume status and how and when to proceed with fluid therapy.

In terms of the clinical assessment of volume status and circulating preload, physical examination and the vital signs of a patient are often misleading. Bedside patient assessment using clinical indicators of fluid volume status from physical examination alone has an accuracy of only 30% to 50% (17). All clinical tests for assessing hypovolemia suffer from excessive observer bias and variability as well as poor reproducibility, interobserver agreement, and sensitivity (18). In fact, supine hypotension and tachycardia may be absent despite blood loss exceeding 1 L (18). Consequently, invasive hemodynamic monitoring is frequently indicated to allow a more accurate assessment of intravascular fluid status, CO, and systemic perfusion pressure.

PULMONARY ARTERY CATHETERIZATION

Standard pulmonary artery catheters provide hemodynamic data relating to filling pressures [pulmonary artery wedge pressure or (PAWP)] and CO by thermodilution. Relying on right-side pressures such as central venous pressure (CVP) to reflect filling pressure of the left side of the heart are misleading and less sensitive to acute changes (19). Consequently, a more direct assessment of left-side heart pressure is required, which prompted the introduction and widespread clinical use of pulmonary artery catheters.

Pulmonary Artery Wedge Pressure

Pulmonary artery catheters provide hemodynamic data that would otherwise be inaccessible to the clinician. Estimates of LV filling pressures and CO based on physical examination and bedside assessment of the patient alone are accurate in the 30% to 50% range (20). Insertion of a pulmonary artery catheter can provide hemodynamic data and alter subsequent therapy in 60% of cases (20), although not without substantial morbidity (21) as well as a persistent inability of clinicians to accurately interpret waveform data (22). Practice guidelines published by the American Society of Anesthesiologists conclude that pulmonary artery catheter monitoring of selected surgical patients can reduce the overall incidence of perioperative complications, primarily by providing quick access to hemodynamic data (23). However, the clinical significance and benefit of generating these data still remain uncertain.

For PAWP to accurately reflect LV end-diastolic volume several assumptions are required. The first assumption involves whether end-diastolic volume and end-diastolic pressure directly correlate. This relationship describes myocardial compliance, which unfortunately is not linear but curvilinear with left- or right-sided shifts of the curve depending on varying patient pathology and illness such as sepsis, shock, myocardial ischemia, altered capillary permeability, vasoactive drugs, and positive-pressure ventilation (24). Due to the

curvilinear relationship between end-diastolic pressure and volume coupled with potential bidirectional shifts, an accurate assessment of LV end-diastolic volume using a pressure measurement is frequently not feasible. In fact, studies of patients in the intensive care unit fail to document a significant correlation between LV end-diastolic volume and PAWP (25). In nearly 50% of patients, normal intracardiac volumes are found despite elevated values of PAWP. In another study of critically ill and cardiac surgical patients, volume expansion increases PAWP by 30% without significantly improving LV end-diastolic area as assessed by transesophageal echocardiography (TEE) (4). Similar results are reported by others studying patients with cardiomyopathy (26) and reflect the finding that volume expansion in a noncompliant heart is limited by the ensuing increase in filling pressure. Although PAWP may not correlate with LV end-diastolic volume, this pressure represents a real physical force that can have detrimental effects on fluid filtration in the pulmonary parenchyma and on LV coronary perfusion pressure.

Another basic requirement for PAWP to accurately reflect LV end-diastolic pressure is that a continuous column of fluid (blood) must exist between the catheter tip and left ventricle; any interruption of this fluid column can cause overestimation of left heart pressures (24). Such interruption may occur with disseminated intravascular coagulopathy secondary to thrombotic occlusions throughout the pulmonary capillary bed, or, more commonly, with the use of positive end-expiratory pressure if alveolar pressure exceeds pulmonary venous pressure (zone 2 lung condition).

Due to these influences, an accurate reflection of LV filling volume by PAWP remains problematic. In fact, no significant relationship can be found between PAWP and LV end-diastolic area assessed by TEE in cardiac surgery patients ($r = 0.35$; $p = \text{NS}$) or in critically ill patients ($r = 0.21$; $p = \text{NS}$) (4). A low pressure reading may reflect reduced LV preload, but normal or high values do not necessarily imply that the heart is maximally filled. Intermediate readings provide little useful information about the adequacy of cardiac filling (5).

Thermodilution Cardiac Output

Thermodilution CO uses the Stewart-Hamilton equation, where a known amount of cold solution is injected into the right atrium and detected by a thermistor located 4 cm from the tip of the pulmonary artery catheter. The ensuing change in the thermistor temperature allows calculation of the area under the thermodilution curve (27). CO is calculated as:

$$\text{CO} = [V_1(T_B - T_1)K_1K_2] / \int_0^{\infty} \Delta T_B(t) dt$$

where V_1 = injectate volume; T_B = blood temperature; T_1 = injectate temperature; K_1 = density factor defined as the product of the specific heat and specific gravity of the injectate divided by the product of the specific heat and gravity of blood; K_2 is a computation constant reflecting catheter dead space, heat exchange during transit, and injection rate. The denominator of this equation is the change in blood temperature detected by the thermistor as a function of time, which represents the area under the thermodilution curve. From this CO value, stroke volume can be calculated as stroke volume = $(\text{CO} \times 1000) / \text{heart rate}$. Any error that causes less cold solution to be injected, such as injecting less than the prescribed fluid volume, will falsely reduce the area under the curve, causing overestimation of CO. In contrast, any factor that increases the amount of negative thermal energy injected, such as a simultaneous fluid infusion with the cold injectate solution, will falsely increase the area under the curve, causing underestimation of CO (27,28).

Proper coordination of the timing for injection during the ventilator cycle is essential and can introduce significant variability especially in mechanically ventilated patients. Due to the effects of intrapleural pressure on RV filling, these influences can be anticipated, and CO measurements should be taken either at the same point in the ventilator cycle, or by averaging multiple injections made at evenly spaced intervals of the ventilator cycle (27). Another factor introducing variability in CO measurements is tricuspid valvular regurgitation. Tricuspid regurgitation can increase the incidence of unacceptable thermodilution curves and prevent complete and uniform passage of the negative thermal bolus out of the right ventricle past the thermistor. Using an *in vitro* flow system, Spinale et al. compared actual and thermodilution ejection fraction measurements with a volumetric catheter over a wide range of tricuspid

regurgitant fractions (29). Thermodilution values consistently and progressively underestimate actual ejection fraction values as the amount of tricuspid regurgitation increases from 2% to 21%. In a clinical study of patients with varying degrees of tricuspid regurgitation where thermodilution CO is compared with Doppler measurements by TEE, tricuspid regurgitation causes significant underestimation of CO values quantified by thermodilution (30). Comparing thermodilution and Doppler techniques, the difference in CO measurement is 0.5 ± 1.1 L/min with little or no regurgitation, but increases to 0.8 ± 2.0 L/min with moderate tricuspid regurgitation and 1.9 ± 2.3 L/min with severe tricuspid regurgitation.

Another cause of CO underestimation by thermodilution is a rapid change in baseline body temperature, such as the case following rewarming and termination of hypothermic cardiopulmonary bypass. During the initial 10 to 20 minutes after bypass, temperature equilibration lowers baseline pulmonary artery temperature so that falsely lower values of CO by 10% to 15% are obtained (31). Newer models of CO computers can account for the underlying drift in basal temperature and reduce this error. In practical terms, most of the variability in CO measurements using thermodilution results from injecting the cold solution at varying times during the respiratory cycle and from simultaneous fluid administration. In fact, due to the development of other techniques, the placement of pulmonary artery catheters solely for the measurement of CO may be no longer justified (32). Recently, a reliable technique of determining CO by a peripheral venous injection of lithium chloride was introduced, which completely obviates the need for central venous catheterization (33).

Continuous Cardiac Output

Newer technology has been introduced that allows continuous, on-line CO measurement. A thermal filament wrapped on the pulmonary artery catheter measures the amount of energy necessary to keep the filament at a constant temperature. The required heating energy correlates directly with CO. The effects of other thermal noise such as respiration, drug or fluid infusions, or gradual body temperature changes are minimized (34). Clinical studies over a wide range of heart rate and CO values show close correlation with the traditional thermodilution technique (35,36), although a more recent study has questioned the reliability of continuous CO measurements under conditions of markedly elevated (more than 10 L/min) values (34). Intrinsic errors may be introduced immediately after termination of hypothermic cardiopulmonary bypass due to a shift of cold blood from the gastrointestinal tract (37).

Continuous CO can also be determined using beat-to-beat pulse contour analysis (38). This technique requires an initial single calibration with thermodilution using cold injectate or lithium chloride solution and can reliably track CO using radial artery pressure monitoring (39). Different concerns regarding the reliability and accuracy of quantitating CO from a peripheral pulse wave have been recently reviewed (40). Comparing the technique of continuous CO from beat-to-beat pulse contour analysis with transthoracic thermodilution reveals a significant correlation between the two methods ($r = 0.88$; $p < 0.001$; bias 0.2 L/min; SD of 1.2 L/min) (38). The authors conclude that pulse contour CO measurements are reliable even in the face of hemodynamic instability. Using pressure measurements in a peripheral artery, stroke volume of the left ventricle can be calculated by the area under the systolic portion of the arterial pressure wave, as described by Wesseling et al. (41). Following termination of hypothermic cardiopulmonary bypass, pulse contour CO measurements correlate with the thermodilution technique significantly better than continuous CO (37). A newer algorithm that takes into account an individual patient's aortic compliance can improve accuracy, especially, during periods of hemodynamic instability (42). More research in this area is needed but reliable techniques that accurately calculate CO are available for use in the clinical arena other than thermodilution by pulmonary artery catheters.

Indirect Measure of Cardiac Output Using End-Tidal Carbon Dioxide Tension

Under conditions where minute ventilation and carbon dioxide production from metabolism are maintained relatively constant, acute changes in CO are reliably reflected by proportionate changes in the end-tidal carbon dioxide tension or $P_{ET}CO_2$. This finding reflects the fact that an acute reduction in blood flow to the lung from a decrease in CO causes less carbon dioxide to be delivered to the alveoli as well as a change in alveolar dead space (43). The slope of this relationship between the change in CO and the change in $P_{ET}CO_2$ in experimental animals

is 0.73 over a wide range of CO values, indicating a direct linear relationship between the two parameters. In the operating room, $P_{ET}CO_2$ can provide a useful monitor to reflect alterations in CO. If blood pressure decreases but $P_{ET}CO_2$ remains constant, hypotension is likely due to an acute reduction in systemic vascular resistance. If, on the other hand, arterial blood pressure and $P_{ET}CO_2$ decrease simultaneously, a drop in CO, which may or may not be coupled with a decrease in systemic vascular resistance, appears causative.

INTRATHORACIC BLOOD VOLUME MEASUREMENT

Intrathoracic blood volume (ITBV) represents the sum of end-diastolic volumes of all heart chambers plus the blood volume in the pulmonary circulation and thoracic aorta (44). Using a transpulmonary indicator dilution technique, ITBV, CO, extravascular lung water (EVLW), and total end-diastolic volume of the heart (TEDV) can be derived in patients. EVLW represents a sensitive indicator for the development of pulmonary edema, while ITBV and TEDV are suitable guides to determine circulating blood volume and preload to the heart.

Originally, a transpulmonary double-indicator technique was employed, which used simultaneous injections of two separate indicators into the right atrium. These indicators have different physical properties—a thermal dye (usually 0–4°C cold solution) that is freely diffusible and a plasma-bound indicator, which typically is indocyanine green dye. A catheter equipped with a fiberoptic sensor and thermistor inserted into the femoral artery provides arterial sampling of both indicators. More recently, a single-indicator technique using femoral arterial thermodilution has been introduced (44,45). ITBV and the other parameters are calculated based on the passage time of indicator particles between injection and detection points; CO is calculated from the thermodilution curve, using the Stewart-Hamilton formula. Excellent correlation comparing thermodilution CO measured by a pulmonary artery thermistor with that measured by a femoral artery thermistor has been established ($r = 0.96$; $p < 0.01$) (44).

Several studies report that ITBV more accurately reflects preload and blood volume status than the measurement of filling pressures. In patients with acute respiratory failure, changes in cardiac index and tissue oxygen delivery correlate closely with corresponding changes in ITBV ($r = 0.71$; $p = 0.001$ and $r = 0.70$; $p = 0.001$, respectively) but not with CVP or PAWP (46). In septic patients, EVLW correlates significantly with ITBV and TEDV but poorly with various pressure measurements (CVP and PAWP) as well as daily fluid balance (47). In patients with preserved ventricular function undergoing volume expansion, changes in stroke volume and CO correlate significantly with ITBV ($r = 0.62$; $p < 0.01$ and $r = 0.55$, $p < 0.05$, respectively) but not with PAWP (44). In patients undergoing lung transplantation, a linear correlation exists between stroke volume and ITBV ($r = 0.64$; $p < 0.0001$), whereas stroke volume and PAWP correlate extremely poorly ($r = 0.01$; $p = ns$) (48). Whereas pressure measurements are adversely affected by multiple factors (vascular volume, vascular tone, myocardial function and compliance, intrathoracic pressure, etc.), the determination of ITBV tends to be influenced primarily by vascular volume and less so by underlying myocardial function. Mundigler et al. report that volume expansion in patients with normal LV ejection fraction values ($58 \pm 13\%$) increases ITBV significantly, whereas ITBV fails to improve with a similar volume load in patients having poorer ejection fractions ($25 \pm 8\%$) (49). Filling pressures increase in both groups of patients but correlate with directionally similar changes in ventricular volume only in patients having preserved ventricular function. In hypovolemic patients following resuscitation with volume expansion, CVP and PAWP measurements decrease significantly over time, while stroke volume and ITBV remain unchanged (50). In that study, the trend in pressure measurements indicates the need for further volume resuscitation, whereas ITBV measurements reveal status quo with no need for further volume administration. These studies underscore the accuracy of assessing intravascular volume using the transpulmonary indicator dilution technique over conventional monitoring with pressure measurements from a pulmonary artery catheter. In fact, the use of filling pressure measurements alone to guide volume therapy is often misleading and can lead to greater net fluid administration with concomitant morbidity (51).

There are several studies comparing intravascular volume measurements with other techniques that evaluate fluid status. Dye dilution volumetric measurements correlate well with LV end-diastolic area as quantitated by TEE ($r = 0.76$; $p < 0.001$) (52). In anesthetized

animals undergoing hemorrhage and volume resuscitation, ITBV measurements and systolic pressure variability (SPV) prove equally sensitive in reflecting volume status and cardiac preload (53). The potential for mathematical coupling between CO and ITBV exists because CO is used in the calculation of ITBV. However, independent depression of CO by beta-adrenergic blockage does not alter ITBV measurements (52), which indicates that changes in CO per se do not influence the thermodilution assessment of ITBV. Although ITBV measurements require the insertion of a femoral arterial sampling catheter or thermistor in addition to a central venous catheter, the data gained by this technology appears worthwhile to accurately reflect intravascular volume and cardiac preload. Another advantage is that ITBV can be repeatedly determined in spontaneously breathing patients as well as in patients receiving positive-pressure mechanical ventilation.

SYSTOLIC ARTERIAL PRESSURE WAVEFORM VARIABILITY

Another technique to assess intravascular volume status involves the changes induced by positive-pressure ventilation on the arterial pressure waveform. It has long been recognized that hypovolemia in mechanically ventilated experimental animals as well as in patients causes large swings in the arterial blood pressure (54). Presumably, these cyclical blood pressure swings relate to the function of the heart on the steep portion of the Starling curve, where any acute reduction in preload with positive pleural pressure causes a large change in stroke volume. As blood volume is restored or increased, the magnitude of blood pressure changes with mechanical breathing is reduced. Studies by Pizov and Perel in experimental animals and patients have revitalized clinical interest in this area (55–57). This technique is applicable only to subjects receiving mechanical ventilation because the magnitude of the changes in systolic blood pressure occurring during the inspiratory and expiratory phases of the respiratory cycle is quantitated.

Positive-pressure breathing causes cyclical changes in arterial blood pressure due to acute changes in RV and LV loading conditions, which involve both preload and afterload. During early positive-pressure inspiration, systolic blood pressure transiently increases, followed four to five beats later in early expiration by a decrease in blood pressure. These changes in loading conditions occur secondary to the alterations in intrapleural pressure and consequently transmural filling pressures of the right and left sides of the heart (Table 1). Positive-pressure inspiration acutely reduces RV stroke volume by reduced filling secondary to an inspiratory decrease in venous return either from an increase in intrathoracic pressure (reduced RV transmural filling pressure) or direct compression of the inferior vena cava during lung inflation (58). At the same time, impedance to RV ejection (afterload) acutely increases with lung inflation, particularly, if lung volume exceeds functional residual capacity (59). The additive effects of these factors cause a reduction in RV stroke volume during early positive-pressure inspiration. Simultaneously, positive-pressure inspiration increases LV stroke volume by augmenting LV preload as LV afterload is reduced. Lung inflation compresses the alveolar capillary bed, forcing blood back toward the left atrium (60), so that filling of the left heart is maintained or augmented (61). In addition, compliance of the left ventricle may improve during positive-pressure inspiration via interventricular interaction as RV filling decreases (62). As a result, LV stroke volume increases secondary to an overall improvement in end-diastolic volume. At the same time, LV afterload decreases from a reduction in LV transmural pressure, which represents the difference between LV-developed pressure and intrathoracic pressure (63,64). Positive intrathoracic pressure (mechanical inspiration) decreases LV transmural pressure and afterload, while negative intrathoracic pressure (spontaneous breathing) produces the opposite effect.

Table 1 Effect of Mechanical Breathing Using Positive-Pressure Ventilation on Right and Left Ventricular Loading Conditions

Early inspiration	Early expiration
↓ RV preload	↓ LV preload
↑ RV afterload	↑ RV preload
↑ LV preload	
↓ LV afterload	

Abbreviations: RV, right ventricular; LV, left ventricular.

The net effect on the arterial system from these factors is shown in Table 1. During early inspiration, LV stroke volume transiently increases, which is seen on the arterial waveform as an acute increase in systolic blood pressure and pulse pressure. This increment is followed four to five beats later by a decline in blood pressure during early expiration. This latter blood pressure reduction reflects an acute decrease in LV preload secondary to the earlier reduction in RV stroke volume coupled with the time delay for pulmonary passage of blood from one side of the heart to the other. Various mathematical formulas that incorporate these respiration-induced changes in systolic arterial blood pressure and pulse pressure have been derived as indices of intravascular volume and preload, and include systolic pressure variability (SPV), the respiratory systolic variation test, respiratory changes in arterial pulse pressure, and stroke volume variability. Each of these tests will be defined and discussed further.

Systolic Pressure Variability

The biphasic difference in systolic arterial pressure is termed SPV and represents the difference between maximal and minimal values of systolic blood pressure during a single positive-pressure breath. SPV is composed of two components: a delta-up component and a delta-down component (55). Using a short period of apnea to define baseline systolic pressure, the difference between the phasic maximal systolic pressure and baseline systolic pressure is the delta-up component; the difference between the baseline systolic pressure and phasic minimal systolic pressure is the delta-down component (Fig. 1A). SPV represents the magnitude of both of those components where $SPV = \text{delta-up} + \text{delta-down}$ components.

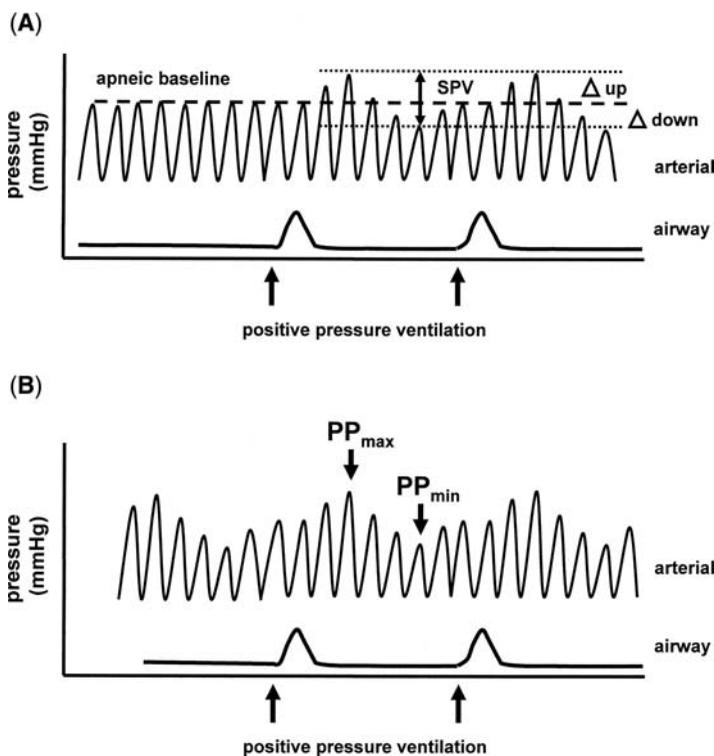


Figure 1 (A) Systolic pressure variability (SPV) is calculated as the maximal excursion of systolic blood pressures during a single positive pressure ventilation. SPV is composed of two components with the delta up component representing the difference between maximal systolic blood pressure and apneic blood pressure while the delta down component is the difference between apneic and minimal blood pressure values. In practicality, SPV can be determined without discontinuing ventilation by calculating the difference between maximal and minimal systolic blood pressures during the ventilatory cycle. (B) Pulse pressure (PP) variability measures the difference in arterial pulse pressure over one respiratory cycle where the respiratory change in pulse pressure (mmHg) = maximal arterial pulse pressure or PP_{max} -minimal arterial pulse pressure or PP_{min} . This difference is divided by the mean of the two values of PP_{max} and PP_{min} and expressed as a percentage.

The delta-up and delta-down components of SPV are affected by several factors. These include intravascular volume status as well as lung and chest wall compliance, tidal volume, method of ventilation (spontaneous or mechanical), abdominal pressure, arrhythmias, and underlying myocardial function (56,57,62,65). If all of these factors that independently affect SPV are maintained relatively constant in a patient, an acute change in SPV will inversely reflect fluid status and intravascular volume. Any factor that increases the magnitude of intrapleural pressure change with positive-pressure breathing, such as an increase in tidal volume or a reduction in chest wall or abdominal compliance will independently produce greater variability in arterial blood pressure and a larger SPV value (60,62). The underlying status of myocardial function is also influential. With normal myocardial function that is preload sensitive and operating on the steep portion of the Starling curve, the marked reductions in biventricular filling from positive-pressure ventilation cause greater SPV due to a larger contribution from the delta-down component and the disappearance of the delta-up component (57). In contrast, with a failing heart having less preload dependence and greater sensitivity to changes in afterload, the degree of SPV is secondary to a larger contribution from the delta-up component with less effect from the delta-down component (66).

Experimental Studies of Systolic Pressure Variability

The concept of SPV as an indicator of vascular volume status has been verified in experimental animals subjected to hemorrhage (55,56). During a steady progression from hypervolemia to hypovolemia, a proportionately greater amount of blood is shifted from the pulmonary circulation into the systemic circulatory system during each positive-pressure inflation (67). Consequently, the progressive reduction in vascular volume results in wider swings in arterial blood pressure, reflected as an increase in SPV. SPV and specifically the delta-down component steadily increase in dogs subjected to 10%, 20%, and 30% blood volume hemorrhage (55). With subsequent volume infusion, both the delta-down component and the degree of SPV decrease. Overall, significant correlations are found between the changes in blood volume and SPV ($r = 0.96; p < 0.05$) as well as the delta-down component ($r = 0.93; p < 0.05$). In fact, the changes in stroke volume correlate best with the corresponding percent changes in SPV and the delta-down component more so than right- or left-side filling pressures. In other studies comparing SPV with ITBV, both appear sensitive to changes in cardiac preload associated with blood loss and replacement, although the magnitude of change is greater with SPV than ITBV (53). SPV and the delta-down component represent specific indicators of intravascular volume status because both increase more with hemorrhage than with an infusion of sodium nitroprusside despite similar reductions in arterial blood pressure (56).

Changes in SPV also reflect the level of underlying myocardial contractile function. In an experimental model of heart failure, SPV morphology changed with the loss of the delta-down component and a significant increase in the delta-up component (57,62,66). It is thought that the failing heart is less preload sensitive (i.e., less delta-down component) but more sensitive to the LV afterload reduction associated with positive intrapleural pressure (i.e., greater delta-up component). Overall, these experimental studies suggest that the degree of SPV can be a useful indicator of cardiovascular derangement during mechanical ventilation—a large contribution from the delta-down component reflects hypovolemia whereas a large contribution from the delta-up component may reflect underlying myocardial contractile dysfunction.

Clinical Studies of Systolic Pressure Variability

SPV represents a better predictor of preload recruitable cardiac function than single-point estimations of LV end-diastolic volume using filling pressures or echocardiographic area measurements (68). In mechanically ventilated patients, the magnitude of SPV appears inversely related to intravascular volume (69). A similar degree of hemorrhage in spontaneously breathing patients does not affect SPV as much due to the uncontrollable variability in tidal volume and consequently intrapleural pressure. However, an exact determination of the threshold value of SPV that reflects hypovolemia in patients has been difficult to establish. In one study, adequate volume status with absence of hypovolemia is confirmed by a SPV value less than 5 mmHg and, specifically, a delta-down component below 2 mmHg (69). SPV values and delta-down components that exceed these values indicate hypovolemia. However, in another

study, although SPV and delta-down could predict a positive response to a fluid challenge, no threshold value could be identified (70).

When comparing SPV with real-time measurements of LV stroke volume variability using continuous arterial pulse contour analysis, both appear well correlated ($r=0.89$; $p<0.001$) (71). In patients having normal ejection fractions undergoing acute blood sequestration prior to cardiopulmonary bypass, SPV provides a superior dynamic measure of LV preload than filling pressures (72). Relative to the changes in CO, SPV shows greater correlation ($r=0.85$; $p<0.001$) than CVP ($r=0.31$; $p=ns$) or PAWP ($r=0.61$; $p=0.02$). In another study of septic patients, the magnitude of the delta-down component provides a superior assessment of the stroke volume response to fluid resuscitation than measurements of end-diastolic area using TEE or PAWP (73). A delta-down component greater than 5 mmHg uniformly indicates a positive response to subsequent volume therapy, with an improvement in stroke volume exceeding 15%. In fact, in ventilated patients in the intensive care unit, the amount of SPV can reliably predict PAWP (74). Using the following equation, where $PAWP=20-(0.7)(SPV)$, one could accurately predict PAWP values from SPV data ($r=0.87$; $p<0.001$).

These studies indicate that SPV is easy to use and provides a clinically relevant monitoring tool that accurately assesses the presence of hypovolemia in patients. Whether this technique is equally sensitive to diagnose hypovolemia in patients with poor LV contractile function has not been verified. In practical terms, SPV is easier to follow than determining the delta-down component because an intervening period of apnea to acquire baseline systolic pressure is not necessary.

Respiratory Systolic Variation Test

The respiratory systolic variation test examines the line of best fit drawn between minimal systolic blood pressures obtained at four successive pressure-controlled breaths of increasing magnitude (5, 10, 15, 20 cmH₂O) (75). This test also alleviates the need for an apneic period. The downslope (mmHg/cmH₂O) is calculated as the decrease in systolic blood pressure at each increment in airway pressure. In experimental studies of animals (75) as well as patients (76), the downslope accurately measures the degree of hemorrhage and resuscitation after volume expansion. The respiratory systolic variation test shows more negative values of the downslope with progressive amounts of hemorrhage, and becomes less negative with fluid resuscitation, thereby, providing a dynamic index measuring fluid responsiveness of the left ventricle.

Respiratory Changes in Arterial Pulse Pressure

Because aortic pulse pressure is directly proportionate to LV stroke volume, the respiratory changes in pulse pressure during mechanical ventilation closely reflect variations in stroke volume. Another technique, termed the respiratory change in arterial pulse pressure, measures the differences in arterial pulse pressure over one respiratory cycle, where

$$\begin{aligned} &\text{respiratory change in pulse pressure (mmHg)} \\ &= (\text{max pulse pressure} - \text{min pulse pressure})/\text{mean of two values.} \end{aligned}$$

An example of this calculation is shown in Figure 1B. A change in arterial pulse pressure exceeding 12% can accurately predict a positive benefit from subsequent volume expansion in patients with a sensitivity of 94% and specificity of 96% (77,78). In one study, the respiratory change in arterial pulse pressure could provide greater accuracy to the response of subsequent fluid administration than SPV alone (78). In critically ill patients, it is suggested that the respiratory change in pulse pressure can be used in place of pulmonary artery catheters (76).

Stroke Volume Variability

Using arterial pulse contour CO, the variations in beat-to-beat stroke volume throughout a respiratory cycle can be calculated. With an algorithm that continuously updates 7.5-second time windows to calculate mean stroke volume, the highest and lowest values of stroke volume during ventilation derive stroke volume variability (71). In postoperative cardiac surgical patients, volume expansion significantly improves stroke volume as SPV and stroke volume

variability proportionately decreases. Both of the latter measures provide greater sensitivity than filling pressures in reflecting any improvement in plasma volume status.

Echocardiographic Measurements

The introduction of echocardiographic methods for measuring preload and CO now permits a less invasive means for assessing these vital measures of intravascular volume and oxygen delivery. TEE and esophageal Doppler monitoring (EDM) were introduced into the perioperative setting, in part, to provide clinicians a less invasive alternative to the pulmonary artery catheter. Unlike the pulmonary artery catheter, TEE does not rely on "pressure" measurements to make volume determinations and as such is not subject to the confounding influence of changes in ventricular compliance, positive-pressure ventilation, or valvular abnormalities (79,80). Indeed several studies have demonstrated that the use of PAWP can be quite insensitive to alterations in preload (4,25,26,81–85). This should not be surprising given that the etiology of hypotension in the perioperative period is frequently due to multiple factors that may have opposing effects on pressure measurements obtained with a pulmonary artery catheter (86).

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

TEE was introduced to the operating room in the early 1980s and found rapid acceptance, particularly in the cardiac surgical suites (87). Current adult TEE probes are approximately 15 mm in diameter and have multiplane transducers that are capable of generating two dimensional (2-D) scan planes around a 180° axis. In addition to 2D images, these transducers also have Doppler capability, which can provide quantitative measurements of blood flow. The probe is connected to a monitor that displays real-time images of cardiac structures and blood velocity profiles. The placement of the TEE probe in the esophagus provides a muscular sleeve to stabilize the probe and an excellent acoustic window given the heart's immediate anterior location to the esophagus. Optimal 2D imaging requires that the scan beam be perpendicular to the reflected surface; these acquired images permit assessment of the changes in LV cavity size (diameter and area) throughout the cardiac cycle. Measurement of LV end-diastole area is the primary method for assessing preload with this technology. Blood velocity is measured by using the Doppler-shift effect from echoes reflected by blood cells moving either toward or away from the TEE probe. A flow velocity profile is generated using a continuous-wave Doppler transducer with fast Fourier transformation signal processing during each ventricular systole. The method for determining CO using Doppler signals will be discussed later in this section.

The assessment of LV preload can be achieved using a single TEE view. The probe is advanced approximately 45 cm past the incisors to achieve a mid-transgastric view at the level of the papillary muscles (88). This image requires a basic TEE skill level and acceptable images can be achieved in more than 85% to 90% of cases (88–90). The LV end-diastolic area is evaluated either qualitatively or traced for quantitative assessment (88). Determination of CO requires a minimum of at least two views, one view permitting alignment of a continuous wave Doppler beam parallel to the flow of blood and the other to calculate the area of the LVOT. These images require an intermediate TEE skill level, and acquisition of necessary images to compute CO can usually be achieved in more than 90% of cases (87–89).

Preload Measurement Using Transesophageal Echocardiography Left Ventricular End-Diastolic Area

The ideal assessment of LV preload would be a three-dimensional assessment of end-diastolic volume (in cm³). Although several studies have demonstrated satisfactory agreement, using geometric models to estimate LV end-diastolic volume by multiple 2-D measures (diameter; area; length), this technique is clearly not practical in an operating room setting (91). A more practical approach takes advantage of the fact that 90% of stroke volume is derived from shortening of the ventricular short axis (92). Several investigators have shown that the LV end-diastolic *area* (using a single mid-transgastric short-axis view) can provide an acceptable estimate of LV end-diastolic *volume*. Studies by Clements et al. (93) and Ryan et al. (94) have both demonstrated that good correlation ($r=0.87-0.92$; $p<0.001$) exists between LV end-diastolic area measured by TEE and volume measured by radionuclide angiography in patients with normal ventricular function. In contrast, such correlations are much weaker in

patients having regional wall motion abnormalities and markedly depressed LV dysfunction (95,96). More recently, Cheung et al. (97) report that *serial* measurements of LV end-diastolic area in patients with wall motion abnormalities still demonstrate a linear decrease when circulating blood volume is decreased by 15% of baseline. The correlations between LV end-diastolic area and stroke volume (or cardiac index) are also acceptable ($r = 0.90$; $p < 0.001$), while correlation with PAWP is poor, especially in the presence of impaired LV contractile function (4,25,84,97).

The reproducibility (or precision) of TEE LV end-diastolic area measured quantitatively is quite reasonable, with coefficients of variability ranging between 4% and 9% (97,98). The lack of a bedside “gold standard” for measuring of LV volume has made it difficult to determine whether TEE LV end-diastolic area is a clinically acceptable alternative measurement of LV end-diastolic volume. The responsiveness of the TEE LV end-diastolic area measurement with interventions that alter preload (blood loss, volume expansion, acute decrease in venous return, etc.) appears good and universally superior to PAWP measurement (97–99).

In practical terms, most clinicians use a qualitative rather than a quantitative assessment of LV end-diastolic area because tracing the borders of the LV endocardial cavity is time consuming and subject to frequent changes in the perioperative setting (100). Some proponents of intraoperative echocardiography argue that the most clinically significant changes seen on TEE are readily apparent, whether systolic cavity obliteration (with hypovolemia) or marked LV dilation (with severe ventricular dysfunction). Indeed, Leung and Levine (101) report that systolic cavity obliteration is associated with a significant decrease in LV end-diastolic area in 80% of cases and can detect hypovolemia with a sensitivity of 100%. In addition, it has been shown in multiple studies that qualitative assessment of TEE LV end-diastolic area is superior to the pulmonary artery catheter at differentiating between decreased preload and ventricular failure in hemodynamically unstable surgical patients (4,26,81,86,102).

Measurement of Transesophageal Echocardiography Cardiac Output

The emergence of the multiplane probe in the 1990s has made periodic determination of CO using TEE feasible. The ability to steer a continuous-wave Doppler beam parallel to the direction of blood flow now makes TEE CO measurement possible in more than 95% of patients (103,104). The aortic valve is imaged at the mid-esophageal level and the Doppler measurements are performed from either the transgastric long axis or deep apical transgastric views (103,104). A second 2-D image of the aortic valve is needed because it has been shown to provide the most accurate view for determining the diameter of the LVOT (103,105,106). Parallel alignment of a continuous-wave Doppler beam with blood flow permits the generation of a spectral velocity profile for each cardiac systole; the area under this curve represents the maximal velocity–time integral or stroke distance along the beam of interrogation during each systole. The CO is then calculated using the velocity–time integral measure along a line crossing the aortic valve, cross-sectional area of the aortic valve, and heart rate as follows:

$$\text{CO (mL/min)} = [\text{velocity – time integral (cm)}] \\ \times [\text{cross – sectional area (cm}^2\text{)}][\text{heart rate (bts/min)}]$$

Several authors have shown that CO can be accurately measured using continuous-wave Doppler across the aortic valve (103,104,107). The time required to make *repeat* CO measurements is usually less than one minute for individuals having intermediate TEE skills. The precision of TEE CO measurement appears acceptable with intraobserver coefficients of variation between 3% and 6% (103,104,107). Three studies have demonstrated a good correlation between TEE and thermodilution CO measurements ($r = 0.90$ – 0.98) (103,104,107). The accuracy of the TEE CO also appears acceptable given its small bias (0.01–0.17 L/min) and reasonable level of agreement (–1.0 to 1.0 L/min). Finally, the concordance between *changes* in TEE and thermodilution CO measurements further suggests that this new method is an acceptable alternative to the thermodilution method for quantitating CO.

Impact of Transesophageal Echocardiography on Clinical Outcome

Data supporting a positive impact of TEE on clinical outcome is somewhat limited. The strongest evidence for its potential benefits lies in its superiority to the pulmonary artery catheter in rapidly diagnosing the etiology of hemodynamic instability. Studies in critically ill patients

demonstrate that the ability to accurately diagnose hypovolemia by a single clinician or achieve concordance among several clinicians is significantly greater using TEE than a pulmonary artery catheter alone (4,25,85,86,108). The ability to directly visualize the relative size of cardiac chambers is particularly useful in patients having valvular abnormalities, poor LV function, or right heart failure (25,83,109). The cumulative effect of multiple pathologic changes occurring simultaneously can obscure an accurate assessment of preload on using pulmonary artery pressures alone (86). Current expert opinion is that the speed and accuracy of assessing preload and cardiac performance with TEE in hemodynamically unstable patients is a Class I indication (high probability to improve outcome) for its use (87).

The TEE assessment of LV end-diastolic area can also be used to optimize preload-recruitable cardiac performance (98,108). Several related studies show that maintenance of normal preload and normal-to-supranormal cardiac indexes can improve clinical outcome in moderate- and high-risk surgical populations (6,7). Whether a TEE-guided treatment algorithm using LV end-diastolic area or CO could be used to guide fluid management for this purpose has yet to be determined. Beyond fluid management, TEE use has been shown to decrease unnecessary return to the operating room following cardiac surgery, which by itself reduces morbidity. Finally, the availability of TEE in the operating room and intensive care unit could reduce both the expense and known complications associated with the use of pulmonary artery catheters in the perioperative period (21,24).

The primary limitations of using TEE perioperatively for fluid management are expense (fixed cost of machine and probe purchase), the training requirement of the operator, and the fact that a qualified person must remain in attendance for serial measurements. Additional technical factors include the presence of significant aortic valve disease, lack of probe tolerance in awake patients, poor image quality (5–10%), and lack of ready access in most postanesthesia or intensive care units. The inability of TEE to provide a continuous, quantitative assessment of preload and CO is another potential criticism. The advent of automated border detection will hopefully provide an acceptable solution to this problem (110,111). Finally, contraindications for TEE use include anatomical abnormalities (malformations, tumors, strictures, etc.), esophageal varices, recent esophageal or upper airway surgery, and acute esophagitis; relative contraindications include known esophageal dysfunction and awake patients. Fortunately, the risk of major adverse events from TEE appears very low (less than 0.05%) (112).

ESOPHAGEAL DOPPLER MONITORING

EDM was initially conceived in the mid-1970s and introduced into clinical medicine in 1989 (113,114). This monitor was designed to fill the need for a less or minimally invasive, technically feasible method for *continuously* assessing preload and CO. The Doppler transducer is located on the tip of a probe that is placed either orally or more preferably nasally, and then advanced to approximately 35 cm before rotating to align the echo beam with the descending aorta posterior to the esophagus. The probe is stabilized using an adhesive nose bridge. The degree of discomfort in the awake patient is analogous to that of a nasogastric tube. The ability to achieve acceptable images is high (95–97%) and the ability to efficiently (less than 5 minutes) obtain accurate measurements of preload and CO occurs usually after 10 to 12 examinations have been completed (115–117).

Similar to TEE, the EDM uses a continuous-wave Doppler beam to generate flow velocity profiles from processed echo signals reflected from red blood cells during each ventricular systole. Unlike TEE, the EDM uses a smaller (8 mm) disposable probe, which derives its measurements from blood flow in the descending (rather than ascending) aorta. The probe is connected to a monitor that instantaneously displays the flow velocity profile and allows for probe adjustment to optimize the quality of the signal. Preload and CO measurements are calculated using the flow velocity profile. Unlike TEE, EDM monitors use either a nomogram (based on patient height and weight) or more recently an M-mode signal from the probe tip to determine the cross-sectional area of the descending aorta (116,118). A correction factor of 1.4 adjusts for blood flow that is lost to the coronary arteries, head, neck, and upper extremities (118).

Measurement of Preload Using Esophageal Doppler Monitoring—Corrected Flow Time

The EDM assesses preload using a parameter derived from the flow velocity profile termed “corrected flow time” or (FT_c). This flow time represents the time needed for the left ventricle

to eject the stroke volume, with the presumption that the larger the LV end-diastolic volume or preload, the longer the flow time. Blood flow time is calculated from the start of waveform upstroke to its return to baseline. Because flow time is also dependent on the cycle time or heart rate, a corrected flow time (flow time/square root of the cycle time) is calculated to adjust for this factor. The range of normal values for the corrected flow time ranges between 330 and 360 msec (118,119). The reproducibility (precision) of the corrected flow time is demonstrated in several studies to be between 4% and 6% (118).

The ability to validate the accuracy of the EDM- FT_c as a measurement of preload has been difficult. The absence of an easily accessible bedside monitor to serve as a "gold standard" measure of LV end-diastolic volume (or preload) as well as the difficulties and expense associated with performing studies using radionuclide angiography, ventriculography, or TEE contribute to the lack of data. The EDM FT_c has a modest correlation with preload when PAWP is low, yet this relationship is lost when PAWP is normal or elevated, especially, in patients with poor LV function (80,120,121). Singer and Bennett (120) report that the concordance between changes in FT_c and PAWP is best when fluid boluses are given to hypovolemic subjects (PAWP < 8 mmHg) or when nitroglycerin is administered to normovolemic subjects (PAWP 8–20 mmHg). DiCorte et al. (99) evaluated the association between FT_c and TEE LV end-diastolic area in patients undergoing cardiac surgery. Measurements in this study taken prior to and immediately following cardiopulmonary bypass show a modest correlation ($r = 0.50$) between EDM FT_c and TEE LV end-diastolic area. Although existing data suggest that use of the FT_c can identify patients who would benefit from subsequent volume expansion, additional studies are clearly needed to validate this concept over a wide range of preload values and degrees of ventricular dysfunction.

Measurement of Cardiac Output Using Esophageal Doppler Monitor

EDM is a much less invasive method than inserting a pulmonary artery catheter for monitoring CO and as such avoids many of the risks associated with the latter (23,24,80). The spectral display on the monitor provides a continuous, real-time assessment of each stroke volume as well as information regarding signal quality. The reproducibility (precision) of the EDM CO ranges between 4% and 8% and compares favorably with that of the pulmonary artery catheter measurement of CO (5–18%) (114,116,118).

A recent review of the literature demonstrates that the EDM could be used in a variety of clinical settings (operating room, intensive care unit, obstetrical suites, etc.) to measure CO with clinically acceptable accuracy and precision (115). In several studies, the overall correlation between the EDM and thermodilution CO measurements has been shown to be acceptable ($r = 0.89$ – 0.95) (99,114–116,122,123). These correlations remain high even when more robust reference standards such as direct Fick equation or electromagnetic flow probe are utilized (99,116).

Determining the accuracy of the EDM CO measurement is complicated by the fact that the coefficient of variability of the reference method using thermodilution can be quite high (15–20%) (124,125). Although the median reported bias in six studies is only -0.01 L/min (range: -1.4 to 2 L/min) (115), the level of agreement (bias \pm 2SD) between these two methods remains quite modest [-2.21 to 2.22 L/min ($\pm 20\%$)] (113,115,122). The relatively large scatter of differences between the two methods primarily reflects the fact that the variability of the thermodilution technique is greater than that of the newer EDM method (124,125). As such, the level of agreement between EDM and thermodilution CO is considered to be acceptable because it does not exceed the maximum variability of the reference measurement, in this case approximately 20% (124). Several studies also demonstrate that the concordance between changes in EDM and thermodilution CO following intervention (fluid bolus, changes in preload, etc.) is acceptable (116,122,123). Sufficient evidence now suggests that the EDM provides a clinically useful alternative measurement of CO.

Impact of Esophageal Doppler Monitoring on Clinical Outcome

The use of EDM measurements to guide fluid management can improve clinical outcome. Several lines of investigation suggest that perioperative hypovolemia is common and may lead to splanchnic hypoperfusion, prolonged hospital stay, and decreased survival in patients undergoing

moderate- to high-risk surgery (126–129). The use of EDM-driven protocols in several studies takes advantage of this monitor's ability to continuously assess preload (FT_c) and stroke volume simultaneously in the perioperative period even in awake patients (118). The treatment algorithm utilizes the ability of the FT_c to detect hypovolemia and to administer fluid boluses until stroke volume no longer increases or until the FT_c exceeds 400 msec (120,127,130). In essence, the EDM-driven protocol utilizes Starling's law of the heart to determine whether preload recruitable cardiac performance has been optimized.

Protocol-driven fluid management has been tested in the perioperative care of several different patient populations (cardiac, general surgical, orthopedic, urologic, gynecologic, etc.) (126–130). Mythen and colleagues (128) in an initial study of 20 cardiac surgery patients report significant decreases in length of stay ($p < 0.02$) and major complications ($p < 0.01$) when fluid therapy is based on the EDM protocol. Studies by Sinclair (129) and Venn (126) in patients undergoing major orthopedic surgery found that the length of stay and the "time to home" readiness are significantly lower in the EDM protocol group. More recently, Gan and colleagues (130) extended these findings in a study of 100 patients undergoing major general surgery, where potential blood loss is estimated to be greater than 500 mL. Patients in the EDM-protocol group have significant reductions in the time to solid food intake (three days vs. five days) and length of stay (five days vs. seven days) compared to the control group. Increases in stroke volume, CO, and crystalloid/colloid administration are noted in most of these studies (126,127,129,130) and are consistent with the concept that suboptimal preload and CO may lead to splanchnic hypoperfusion, with greater postoperative complications.

Limitations of EDM are similar to those of TEE. The contraindications of EDM placement are primarily those that would preclude insertion of a nasogastric tube. The presence of severe lung disease, high airway pressures, thoracic flow disturbances, severe aortic valve disease, and intraaortic balloon pump placement can interfere with EDM accuracy (118). Unlike TEE, the EDM probe is small enough to be tolerated in the awake patient. There have been no reported major complications associated with the use of the EDM.

Other Indicators of Blood Volume Status

There are other experimental and invasive indicators that accurately reflect the relative loss of plasma volume. One method is the continuous on-line measurement of oxygen and carbon dioxide tensions and pH in skeletal muscle (131). In a porcine model of graded hemorrhage and volume resuscitation, persistent skeletal muscle acidosis with $pH < 7.2$ reflects incomplete resuscitation despite complete normalization of hemodynamic parameters. Although a reduction in oxygen tension and increase in carbon dioxide tension are rapid indicators of hypoperfusion, both show wide variability and may not reflect the adequacy of resuscitation. In contrast, the onset of skeletal muscle acidosis precedes the development of systemic acidosis. Newer technology may allow introduction and clinical use of continuous on-line muscle pH as an early warning indicator of the adequacy of systemic and tissue perfusion.

CONCLUSION

This chapter explores a variety of methods currently available for assessing intravascular volume status and insuring optimal preload recruitable cardiac performance. Although, for years, invasive techniques have used pressure measurements to gauge the amount of parenteral volume resuscitation, newer modalities have been introduced which overcome problems associated with the diastolic pressure-volume relationship by directly measuring ventricular volumes and cardiac performance. These less invasive methods (systolic pressure variation, esophageal echocardiography, etc.) for determining the adequacy of preload and CO may permit the selective use of more invasive techniques (such as pulmonary artery catheters), which are associated with increased morbidity. Given the inherent limitations of each of the methods discussed, the most prudent monitoring approach may be to begin with a less invasive method familiar to all those involved in a particular clinical setting and add more invasive methods as the patient condition dictates. The most effective approach to monitor fluid management is just beginning to emerge as these monitors are now being used in protocol-driven, evidence-based clinical outcome studies in a variety of perioperative settings. Anesthesiologists will need to play an active role in this process if questions regarding the best monitoring practice are to be established in a timely fashion.

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4 Oxygen Delivery as a Goal for Fluid Therapy in Surgical Patients

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INTRODUCTION

The conventional perioperative fluid management of patients who have undergone elective or emergency surgical procedures is aimed at maintaining vital signs within the normal range and at assuring a urine output of at least 0.5 mL/kg/hr. This approach to fluid therapy is based on the tacit assumption that the maintenance of hemodynamic stability in conjunction with a satisfactory urinary output is universally predictive of a satisfactory postoperative outcome from the standpoint of perioperative morbidity and mortality. However, this approach does not take into consideration the impact of the severity of the injury (how complicated was the procedure, whether the patient suffered a period of hypoperfusion with a consequent period of ischemia-reperfusion, the extent of a preoperative or intraoperative septic insult, the duration and depth of the anesthesia, as well as the duration of the procedure itself), and other factors commonly encountered during surgical procedures. Furthermore, it disregards the concomitant effect of the anesthetic management on the relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2) during the procedure itself, and in the immediate postoperative period (1,2). Additionally, this approach to perioperative fluid therapy is not tailored to the patient's risk for perioperative complications based on American Society of Anesthesiologists score, preoperative risk evaluation by validated predictive models such as the physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM) model (3), or the amount of oxygen debt incurred during the procedure by the individual patient (2,4).

Are normal vital signs in conjunction with a satisfactory urinary output valid and, more importantly, predictive end points of perioperative fluid therapy in all patients? Should we instead target perioperative fluid therapy to alternate end points, such as a specific DO_2 , and/or VO_2 , or even to normalization of serum lactate levels by individualizing fluid therapy, after having stratified our patients in specific risk categories (low and high) from the standpoint of morbidity and mortality? Surgical patients should be stratified into two groups from the standpoint of risk for the development of complications and mortality. A low-risk group, characterized by the absence of incremental comorbid risk factors and with an expected perioperative mortality following major operative procedures between 2% and 8%, and a high-risk group, characterized by an expected mortality greater than 8% for the same procedures. Patients may be identified as high-risk surgical patients if they have preoperatively or intraoperatively one or more of the risk factors shown in Table 1. A more accurate scoring system to identify high-risk surgical patients is the POSSUM System of Surgical Audit. It uses 12 physiological and six operative variables to determine the risk of morbidity and mortality (Table 2).

CONVENTIONAL APPROACH TO PERIOPERATIVE FLUID THERAPY

The conventional approach to fluid therapy is based on the assumption that the most important goal is to maintain hemodynamic stability and to protect the vital organs namely heart, liver, brain, and kidneys from hypoperfusion. It uses vital signs and urine output as the ultimate end points of therapy; however, the conventional approach to fluid therapy is not

Table 1 Preoperative and Postoperative Risk Factors Used to Identify High-Risk Patients*Preoperative risk factors*

1. Previous severe cardiorespiratory disease (COPD with $PCO_2 > 50$ mmHg and $PaO_2 \leq 50$ mmHg; acute myocardial infarction; congestive heart failure with ejection fraction $\leq 30\%$)
2. Extensive surgery for carcinoma (esophagectomy, total gastrectomy, exenteration)
3. Multiple trauma involving more than three organs or opening of two body cavities (abdomen, chest)
4. Shock (MAP ≤ 60 mmHg)
5. Acute abdominal catastrophe (perforated viscus > 24 hr, gangrenous bowel, extensive peritonitis)
6. Massive blood loss (> 8 units, blood volume < 1.5 L/m², Hct $< 20\%$)
7. Acute renal failure (creatinine > 3 mg/dL)
8. Septicemia (positive blood cultures)

Postoperative risk factors

1. Sustained intraoperative hypotension (MAP < 70 mmHg) with massive fluid shift (> 8 L)
2. Operative blood loss greater than eight units associated with intraoperative hypotension
3. Massive fecal spillage secondary to perforation of viscus

Abbreviations: COPD, chronic obstructive pulmonary disease; PCO_2 , partial pressure of carbon dioxide; PaO_2 , partial pressure of oxygen; MAP, mean arterial pressure; Hct, hematocrit.

supported by scientific evidence linking perioperative hemodynamic stability to the absence of postoperative complications. Furthermore, it assumes that in the presence of normal vital signs and urinary perfusion, as documented by an adequate urine output, there is an absence of subclinical unrecognized tissue hypoperfusion, which may prime the patient to an inflammatory response leading to the development of end organ dysfunction. Should DO_2 instead be the goal of fluid therapy in the perioperative period because it has been shown to correlate with the development of postoperative complications (5).

BASIC CONCEPTS

It was not until the mid-1960s that a clear understanding of body composition with respect to body cell mass and total body water was attained following extensive work by Moore (6). The

Table 2 Physiological and Operative Severity Assessment for the POSSUM System

Score	1	2	4	8
<i>Physiological</i>				
Age (yr)	≤ 60	61–70	≥ 71	–
Cardiac signs	Normal	Cardiac drugs	Edema; warfarin	JVP
CXR	Normal	–	Borderline cardiomegaly	Cardiomegaly
Respiratory signs	Normal	SOB exertion	SOB stairs	SOB rest
CXR	Normal	Mild COPD	Moderate COPD	Any other change
Systolic BP (mmHg)	110–130	131–170 or 100–109	≥ 171 or 90–99	≤ 89
Heart rate (beats/min)	50–80	81–100 or 40–49	101–120	≥ 121 or ≤ 39
Coma score	15	12–14	9–11	≤ 8
Urea nitrogen (mmol/L)	≤ 7.5	7.6–10	10.1–15	15.1
Na (mEq/L)	> 136	131–135	126–130	≤ 125
K (mEq/L)	3.5–5	3.2–3.4	2.9–3.1	≤ 2.8
Hb (g/dL)	13–16	11.5–12.9	10–11.4	≤ 8.9
WBC $\times 10^{12}/L$	4–10	10.1–20	≥ 20.1	–
ECG	Normal	–	Afib	Any other change
<i>Operative severity</i>				
Operative magnitude	Minor	Intermediate	Major	Major+
Number of operations within 30 days	1	–	2	≥ 2
Blood loss (mL)	< 100	101–500	501–999	> 1000
Peritoneal contamination	None	Serious	Local pus	Massive
Presence of malignancy	No	Primary cancer only	Node metastases	Distant metastases
Timing of operation	Elective	–	Emergency < 24 hr	Emergency < 2 hr

Abbreviations: CXR, chest X ray; JVP, jugular venous pulse; SOB, shortness of breath; COPD, chronic obstructive pulmonary disease; BP, blood pressure; Na, sodium; K, potassium; Hb, hemoglobin; WBC, white blood cell count; ECG, electrocardiogram; Afib, atrial fibrillation; POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity.

impact of injury, surgery, and shock on intra- and extracellular fluid dynamics and the role of balanced solutions were elucidated in the late 1960s following the work of Shires, Carrico, and Cunningham (7–12). The understanding of the physiologic response to injury led to the present perioperative fluid therapy of surgical patients aimed at maintenance of normovolemia in conjunction with hemodynamic stability with isotonic and/or colloid solutions. However, this approach has completely ignored the impact of injury and anesthesia on tissue oxygen utilization, and the potential role of an intraoperative oxygen debt, which can occur during prolonged and complicated procedures associated with massive blood loss and fluid shifts, on the development of organ dysfunction/failure in high-risk surgical patients (4).

THE RELATIONSHIP BETWEEN OXYGEN DELIVERY AND OXYGEN CONSUMPTION

Under normal physiologic conditions, VO_2 at the cellular level is maintained constant by a balance between oxygen supply and demand at the organ level through complex autoregulatory mechanisms directed at matching oxygen supply to local metabolic demands. It is noteworthy that autoregulation of blood flow (Q_B) at organ level (increased Q_B relative to increased local metabolism) and local control of Q_B through changes in capillary density were originally defined in relation to the regulation of Q_B and not to regulation of tissue oxygenation. Under normal physiological conditions, high-demand regions receive increased DO_2 , whereas low-demand organs receive decreased delivery. Typically, a DO_2 of approximately 1000 mL/min/m² will provide an intracytosolic oxygen tension of 6 mmHg, which in turn will result in a mitochondrial oxygen tension of 1.5 mmHg. This very limited amount of partial pressure of oxygen within the mitochondrion will assure oxidative phosphorylation, namely, a series of oxidation–reduction reactions where oxygen serves as the terminal electron acceptor, and the production of high-energy phosphate. Under aerobic conditions, the hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP), inorganic phosphate (P_i), and H^+ is not associated with an increased concentration of cytosolic H^+ because these metabolites are reutilized by the mitochondria to regenerate ATP. In this setting, the normal cellular redox potential is maintained and the lactate/pyruvate ratio, which is the mirror image of the reduced nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide ratio, is 20:1 or lower. If there is a decrease in DO_2 and/or a compromise in oxygen extraction (ERO_2) at cellular level, the decrease in cytosolic oxygen tension is associated with an increase in lactate, typically in excess of the pyruvate production; hence, the hydrolysis of the cytosolic ATP to ADP, P_i , and H^+ without reutilization of these metabolites by the mitochondria is associated with an increase in cytosolic hydrogen ion concentration (cellular acidosis).

The oxygen delivered to an organ is equal to the Q_B to the organ, indexed to the weight of the organ or body times the arterial oxygen content (CaO_2) times a factor of 10 used to transform the units in mL/min/m² where

$$DO_2 = Q_B \times CaO_2 \times 10 \quad (1)$$

$$CaO_2 = (Hb \times 1.34 \times SaO_2) + PaO_2 \times 0.003 \quad (2)$$

where Hb is the hemoglobin concentration (g/dL), SaO_2 is the arterial oxygen saturation (%), and PaO_2 is the partial pressure of oxygen (mmHg) in arterial blood.

Total DO_2 is the product of cardiac index (CI) times CaO_2 times 10:

$$DO_2 = CI \times CaO_2 \times 10 \quad (3)$$

Equation (2) shows that the CaO_2 depends heavily on hemoglobin (1 g of Hb can carry 1.34 mL of oxygen) and arterial oxygen saturation and, to a much lesser degree, on the oxygen in solution ($PaO_2 \times 0.003$). Oxygen in solution plays a significant role in increasing DO_2 only in patients who have maximized their CI in response to anemia and refuse transfusions of red blood cells (Jehovah Witnesses). The oxygen content of venous blood (CvO_2) is obtained in a similar way as for arterial blood, except that the oxygen saturation of Hb and the partial pressure of oxygen is measured in venous blood. Hence:

$$CvO_2 = (Hb \times 1.34 \times SvO_2) + (PvO_2 \times 0.003) \quad (4)$$

where SvO_2 is venous oxygen saturation and PvO_2 is the venous oxygen pressure. The oxygen consumed by an organ VO_2 is equal to Q_B to the organ times the difference in arteriovenous oxygen content ($CaO_2 - CvO_2$) where:

$$VO_2 = Q_B \times (CaO_2 - CvO_2) \quad (5)$$

Equation (5) is extremely important because it indicates that VO_2 is a function of Q_B to the specific organ and ERO_2 (the arteriovenous oxygen difference). To maintain VO_2 constant in the setting of decreased Q_B , the organ must extract more oxygen (13). The mechanisms implemented at tissue level to extract more oxygen in relation to local VO_2 include regional redistribution of Q_B and increased capillary density. The first mechanism provides increased Q_B to tissues with a high metabolic rate by diverting blood from low-extraction tissues. The latter mechanism increases capillary density of perfused capillaries within tissues and optimized transit time and diffusion distance, therefore preventing molecular diffusion limitations in the unloading of oxygen. The ability to extract oxygen differs significantly among organs. Organs that function at maximal extraction, such as the heart, cannot increase extraction, and therefore are at high risk of lactate production when metabolic demand is increased and flow cannot be increased. Conversely, low-extraction organs such as the kidneys (9% ERO_2 under normal conditions) can easily maintain VO_2 constant, following a decrease in DO_2 by increasing the extraction of oxygen. Obviously, alterations in the distribution of blood from high-extraction to low-extraction tissues in the surgical patient may contribute to the development of tissue oxygen debt. In the setting of increased oxygen demand, consumption can be kept constant by an increase in delivery. The ability of tissues and the body, as a whole, to extract oxygen to maintain VO_2 constant and to prevent lactate production from the tissues in the setting of decreasing delivery is limited to an extraction ratio of 60% (anaerobic threshold). Under conditions of increasing metabolic demands, the diffusion reserve for O_2 is not sufficient to meet cellular demands when extraction of more than 60% is required. However, the anaerobic extraction threshold is not the maximal extraction, which can reach a value of 80% at maximal exercise (14), and, interestingly, even in dying patients, as shown by Ronco et al. (15). Granger et al. was among the first researchers to evaluate the role of Q_B and ERO_2 in resting and active muscles (16,17).

CRITICAL OXYGEN DELIVERY DURING SURGERY

A clear understanding of the relationship between DO_2 , VO_2 , and ERO_2 in healthy human beings as well as in patients undergoing surgical procedures is essential to be able to understand the mechanisms underlying the development of oxygen debt when perioperative fluid therapy is targeted to the maintenance of vital signs and urine output instead of DO_2 . The idealized relationship between DO_2 and VO_2 is shown in Figure 1. DO_2 , the independent

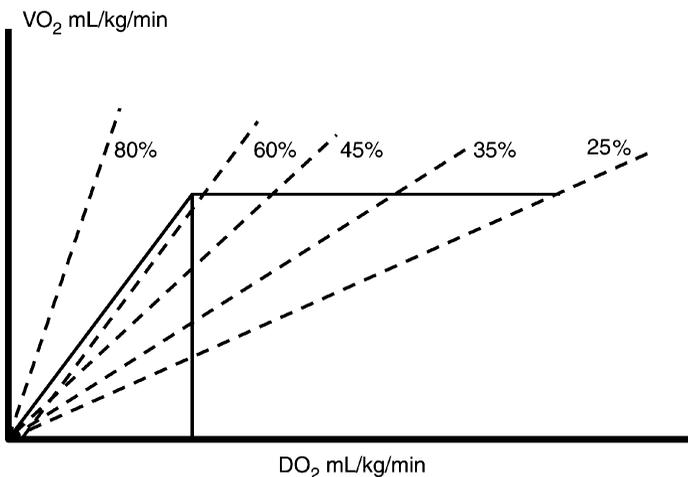


Figure 1 The relationship between oxygen delivery, consumption, and extraction. As oxygen delivery decreases, oxygen consumption is kept constant by an increase in oxygen extraction until the extraction ratio achieves a value between 60% and 80%. At this point, the increase in oxygen extraction is unable to compensate for the decrease in oxygen delivery, hence oxygen consumption decreases, becoming supply dependent.

variable, is expressed on the x-axis, whereas VO_2 , the dependent variable, is shown on the y-axis. The relationship is biphasic. VO_2 is independent of the delivery until a critical level of delivery is reached; below this level (DO_2 crit), VO_2 becomes supply dependent, and anaerobic metabolism ensues. The critical DO_2 , therefore, divides the DO_2 - VO_2 relationship into a supply-independent and supply-dependent region. Because any decrease in DO_2 is immediately compensated by an increase in ERO_2 , it is understandable that any condition that causes a fixed ERO_2 (inability of tissues to extract O_2) may cause a supply-dependent state at a higher level of DO_2 . Published values of DO_2 crit vary from 3.5 to 21 mL/kg/min depending on disease states (15,18–22). Information on the critical DO_2 in relatively healthy subjects comes from observations made in 58 patients undergoing coronary artery bypass, but before the institution of cardiopulmonary bypass. Analysis of the observations made in this series of patients shows that VO_2 remains constant over a range of DO_2 from 700 to 330 mL/min/m². Below a DO_2 of 330 mL/min/m², which corresponded to 8.2 mL/kg/min, VO_2 decreases linearly with decreasing DO_2 in these relatively healthy subjects with coronary artery disease. Danek identified a much higher critical DO_2 , namely 21 mL/kg/min, in 20 patients with adult respiratory distress syndrome (ARDS) subjected to incrementally higher levels of positive end-expiratory pressure, indicating that the critical DO_2 and the slope of DO_2 - VO_2 relationship can change dramatically with different disease states. In contrast, Ronco et al. identified a DO_2 of 3.5 mL/kg/min as the critical level of DO_2 , and additionally, challenged the contention that sepsis raises the critical DO_2 by failing to identify a difference in critical DO_2 and ERO_2 between nine septic and nine nonseptic patients in a well-designed study (15).

Recent evidence suggests that the intraoperative critical DO_2 and ERO_2 values in high-risk surgical patients differ significantly from the values measured preoperatively (1). High-risk surgical patients have a significantly higher critical DO_2 intraoperatively, as compared to their preoperative critical DO_2 . This indicates that these patients have a fixed ERO_2 as a result of a deficit in ERO_2 at cellular level. This deficit is evidenced by a significantly lower ERO_2 reached at the critical level of DO_2 during the intraoperative period when compared to the preoperative ERO_2 ($31 \pm 4.5\%$ vs. $18 \pm 2.3\%$ preoperative and intraoperative ERO_2 , respectively). The mechanisms responsible for the compromised ability of tissues to extract oxygen include local conditions of oxygen transfer at the microcirculatory level, alterations in peripheral autoregulation of Q_B leading to a failure of flow redistribution in the face of decreased DO_2 , a decrease in hemoglobin P_{50} , and rheological changes at microcirculatory level due to hypothermia (increased capillary blood viscosity). Additionally, the hypothermia associated with anesthesia can in itself cause a reduction in tissue efficiency to extract oxygen (23). Furthermore, halogenated anesthetics increase, in a dose-dependent fashion, critical DO_2 and compromise the ability of the tissue to extract oxygen in experimental models; therefore, they contribute to the development of an intraoperative oxygen debt (24). Consequently, the intraoperative period appears to be characterized by an alteration in the ability of tissues to extract oxygen that is proportionally higher than the decrease in tissue metabolic demands produced by a combination of anesthesia and hypothermia. Because the reduction in ERO_2 is proportionately higher than the reduction in metabolic rate, the critical value for DO_2 may be similar to, or higher than, that value in the preoperative period. Thus, the intraoperative period represents for high-risk surgical patients, a condition for the development of a tissue oxygenation debt in the presence of a limitation in DO_2 . Consequently, a fluid therapy not targeted to early optimization of the DO_2/VO_2 relationship may predispose these patients to the development of end-organ dysfunction and possibly, to increased perioperative morbidity and mortality.

Clinical evidence shows that the contraction of a substantial intraoperative oxygen debt, measured as the difference between the actual measured rate of oxygen consumed and the preoperative baseline rate of VO_2 corrected for anesthesia and temperature, is causally related to the subsequent development of multiple-organ dysfunction and death, if fluid therapy is not targeted to optimization of DO_2 , and early repayment of the oxygen debt. In a study conducted by Shoemaker et al. the cumulative average oxygen debt was significantly higher at 33.5 ± 36.9 L/m² in postoperative patients who did not survive, as opposed to 26.8 ± 10.9 and 8.0 ± 10.9 L/m², respectively, in surviving patients with and without organ failure (4). Additional clinical work done by the same group shows that the magnitude and duration of the oxygen debt are causally related to the development of organ failure and death, suggesting that a reduced tissue oxygenation is the priming event of the subsequent development of

organ failure (25). In high-risk surgical patients, a fluid strategy targeted to maintain DO_2 and VO_2 greater than 600 and 170 mL/m²/min, respectively, reduces the intraoperative oxygen debt and decreases the duration of the oxygen deficit. This approach is associated with decreased morbidity and mortality, and is not associated with increased complications as a result of the strategy itself. A fluid strategy aimed at maintaining hemodynamic stability rather than the hemodynamic profile displayed by survivors is associated with a significantly higher mortality in high-risk surgical patients.

The traditional approach to fluid therapy in the surgical patient, with and without preoperative circulatory problems, has been based on an etiologic classification of shock syndromes defined by clinical symptoms, laboratory findings, and pathophysiology. The variables monitored during traditional fluid therapy (hemodynamic stability and urinary perfusion) were selected on a simplistic approach, accepted by the majority of physicians, leading to a one-dimensional therapeutic modality. This approach does not take into consideration the impact of the injury on the body's interactive compensatory responses affecting volume and oxygen transport variables, and separating patients into survivors and nonsurvivors. The most commonly monitored variables such as blood pressure, heart rate, respiratory rate, central venous pressure, arterial PaO₂, hematocrit, and urine output, selected as end points of fluid therapy, have no discriminant power from the standpoint of outcome; therefore, they have a very limited value as end points of therapy (26–32).

High-risk surgical patients have very well-defined temporal patterns of physiological responses to surgery. The temporal patterns of hemodynamic and oxygen transport variable responses differ depending on whether patients start with normal baseline values in the absence of comorbid conditions, or they have abnormal baseline values as a result of associated preoperative conditions. The intraoperative and postoperative response of the hemodynamic and oxygen transport variables of high-risk surgical patients with normal preoperative cardiac profile can be analyzed from the standpoint of survival status, namely, the responses of survivors versus nonsurvivors (33–35). Vital signs including mean arterial blood pressure, heart, and respiratory rate as well as temperature do not differ significantly either intraoperatively or in the immediate postoperative period (up to 96 hours postoperatively) in survivors and nonsurvivors. Nonsurvivors become hypotensive very late in the postoperative course, and typically, at this point they already have developed signs of multiple-organ dysfunction/failure syndrome, which ultimately is the cause of their death. CI, DO_2 , VO_2 , and ERO_2 decrease intraoperatively and start to increase in both groups in the immediate postoperative period; however, while survivors achieve supranormal values (values 25% or more in excess of their normal values), nonsurvivors, at most, return to their preoperative baseline values. The physiological responses of high-risk surgical patients with compromised cardiorespiratory status, as a result of increased age and/or significant cardiac disease, are similar to those of the preoperatively normal patients, but the magnitude of the response of the hemodynamic and oxygen transport variables is less pronounced. In particular, nonsurvivors are unable to raise their DO_2 to the level necessary to prevent supply-dependent VO_2 . Variables reflecting oxygen transport and cellular metabolism, such as DO_2 , VO_2 , ERO_2 , and serum lactate clearance time have been shown to be much better predictors of outcome than the traditional historical variables (36–41). Obviously, the relationship of any given variable to outcome (survival or death) predicts whether the variable should be used to make clinical decisions. Consequently, it is intuitive that the fluid therapy in the high-risk surgical patients should be targeted to the median values of the CI, DO_2 , VO_2 , and ERO_2 that separate survivors from nonsurvivors, and that have been identified in a multivariate stepwise logistic regression analysis as highly predictive variables of outcome (42).

OXYGEN DELIVERY AND INFUSION FLUIDS

Is there good evidence to support such variables as therapeutic end points of fluid therapy? Have the retrospective observations leading to the identification of these variables, as predictors of outcome, been validated in properly designed prospective studies? A recent meta-analysis of randomized studies of hemodynamic optimization in high-risk surgical patients showed that early (within 8–12 hours after the end of the operation) or prophylactically goal-directed therapy aimed at increasing DO_2 to supranormal values with a pulmonary artery catheter improves outcome when the hemodynamic optimization is maintained in the

intraoperative and immediate postoperative period (43). This meta-analysis shows clearly the importance of implementing optimal therapy before the onset of organ failure. Of the studies analyzed in the meta-analysis, seven studies whose optimal therapy was completed before the development of organ dysfunction showed a statistically significant reduction in the mortality rate compared with the conventional therapy aimed at maintaining normal hemodynamic values. In contrast, the seven studies in which optimization was initiated after the onset of organ failure failed to show an outcome benefit of a goal of therapy aimed at supranormal values of the oxygen transport variables. Table 3 shows the randomized controlled trials that have tested the effect of perioperative optimization of the oxygen transport variables on mortality and morbidity. These studies include high-risk surgical patients as well as trauma patients (5,44–47, 49,50). Shoemaker et al. used fluids, inotropes, and vasodilators to achieve supranormal values of DO_2 and VO_2 , above 600 and 170 mL/min/m², respectively, in high-risk surgical patients (42). The mortality in the two control groups randomized to receive perioperative treatment aimed at maintaining conventional hemodynamic end points with either a central venous line or a pulmonary artery catheter averaged 28.3% compared with a mortality of only 3.6% in the protocol group. The more important findings of this study concern the prevalence of organ failures among the groups; there were 31 cases of organ failures in the control groups in contrast to one event of organ failure in the protocol group. The conclusions of this study, however, have been criticized for several reasons, including the randomization process, absence of blinding of the investigators, and a difference in the case-mix of the two groups, which could have accounted for the observed difference in mortality. Boyd et al. tested the value and limitations of a strategy aimed at increasing DO_2 above 600 mL/min/m² with fluids and dopexamine in the perioperative period in high-risk surgical patients in a well-designed prospective randomized controlled trial with an adequate number of patients randomized into two groups. They showed a statistically significant reduction in mortality from 22.2% in the control group to 5.7% in the protocol group. Additionally, the number of complications in the protocol group was reduced by 50% (45). A more in depth analysis of this paper shows a much more pronounced effect on survival in patients allocated preoperatively to the protocol group, thus emphasizing the possible beneficial effect of a deliberate preoperative increase of DO_2 on a reduction of the intraoperative oxygen debt that is typically associated with complex procedures in high-risk surgical patients. It is of note that the two groups in this study did not differ with respect to VO_2 , isolating the beneficial effect of increasing DO_2 to a possible repayment of the intraoperative oxygen debt incurred by high-risk surgical patients undergoing abdominal surgery.

The effects of an increase in DO_2 above 600 mL/min/m², using dopexamine, on mortality and morbidity of high-risk surgical patients undergoing major elective surgical procedures, were corroborated by Wilson et al. in a study that randomized 138 high-risk surgical patients into three groups, namely a conventional treatment group and two protocol groups (49). The two protocol groups were admitted to the intensive care unit a minimum of four hours preoperatively, and after undergoing placement of an arterial and pulmonary artery catheter, were treated with a protocol aimed at achieving a $DO_2 \geq 600$ mL/min/m² with either fluid and dopexamine, or fluid and epinephrine. This end point was maintained in the two protocol groups for 12 to 24 hours postoperatively. In contrast, the control group was treated either in the intensive care unit or on a floor with standard perioperative care aimed at maintaining normal hemodynamic values and adequate urinary output. The control group had a mortality of 17%, slightly higher than 13% predicted by the POSSUM model, in comparison to an overall mortality of 3% in the two protocol groups. It is noteworthy that while there was no difference in mortality between the dopexamine and epinephrine groups, there was a higher morbidity, in the form of infectious complications, in the epinephrine group. The reduced number of infectious complications in the protocol group optimized with dopexamine can be attributed to the well-known anti-inflammatory properties of dopexamine and to the splanchnic vasodilatation caused by this drug, which in turn can reduce bacterial translocation from the gut and potentially the development of the multiple dysfunction organ syndrome (51). Despite the increased use of hospital resources needed to achieve the specific end points of therapy, optimization of the oxygen transport variables of the high-risk surgical patient scheduled to undergo elective major procedures has been shown to be cost effective when compared with the standard perioperative care (52,53). Increasing CI, DO_2 , and VO_2 above predetermined values with fluids and dobutamine (3–15 µg/kg/min) has also been

Table 3 Prospective Trials Testing the Effect of Perioperative Increase in Oxygen Delivery on Mortality and Morbidity

Author/year	Patients	No. pts	Control intervention	Protocol intervention	Control mortality	Protocol mortality	ARR (%)	NNT	CI
Shoemaker, 1988 (42)	High-risk surgical	88	Fluid + inotropes $\text{DO}_2 > 600 \text{ mL/min/m}^2$	Conventional	17/60 (28.3%)	1/28 (3.6%)	24.7	4	3–9
Fleming, 1992 (44)	Trauma	77	$\text{DO}_2 > 600 \text{ mL/min/m}^2$; $\text{VO}_2 > 166 \text{ mL/min/m}^2$	Conventional	15/34 (44%)	8/33 (24%)	20	5	2–43
Boyd, 1993 (45)	High-risk surgical	197	Dopexamine $\text{DO}_2 > 600 \text{ mL/min/m}^2$	Conventional	12/54 (22.2%)	3/53 (5.7%)	16.6	6	3–26
Bishop, 1995 (46)	Trauma	115	$\text{DO}_2 > 600 \text{ mL/min/m}^2$; $\text{VO}_2 > 166 \text{ mL/min/m}^2$	Conventional	24/65 (37%)	9/50 (18%)	19	5	3–32
Yu, 1998 (47)	High-risk surgical	66	Fluid/inotropes	Same	12/23 (52%)	9/23 (21%)	31	3	2–13
Ueno, 1998 (48)	Hepatectomy	34	$\text{DO}_2 > 600 \text{ mL/min/m}^2$ CI > 4.5 L/min/m ²	Conventional	2/18 (11%)	0/16 (0%)	11	10	4–14
Wilson, 1999 (49)	High-risk surgical	138	Dopexamine/ epinephrine $\text{DO}_2 > 600 \text{ mL/min/m}^2$	Conventional	8/46 (17%)	3/92 (3%)	14	7	4–38
Lobo, et al. 2000 (5)	High-risk surgical	37	Fluid/dobutamine $\text{DO}_2 > 600 \text{ mL/min/m}^2$	DO_2 500–600 mL/min/m ²	9/18 (50%)	3/19 (15.7%)	34.3	3	2–17
Sandham, 2003 (50)	High-risk surgical	1994	DO_2 550–600 mL/min/m ²	Conventional	77/997 (7.7%)	78/997 (7.8%)	0.1	–	–

Abbreviations: ARR, absolute risk reduction; CI, cardiac index; NNT, number needed to treat; DO_2 , oxygen delivery; VO_2 , oxygen consumption.

shown to reduce the incidence of postoperative liver failure and hyperbilirubinemia in cirrhotic patients undergoing partial hepatectomy (48). Of interest, patients in the protocol group in this study had lower lactate levels in the immediate postoperative period when compared to the standard therapy group; this suggests that maintenance of a hyperdynamic circulation in cirrhotic patients reduces the systemic oxygen debt incurred during hepatectomy.

Additional studies have proven that increasing DO_2 to a supranormal level decreases mortality in trauma patients. Fleming et al. confirmed, in separate studies, the beneficial effect on morbidity and mortality of increasing DO_2 to supranormal values within 24 hours of the injury in trauma patients. Fleming et al. reported that a therapy targeted to increase DO_2 and VO_2 above 600 and 166 mL/min/m², respectively, decreased mortality from 44% to 24% in a series of trauma patients (44). Bishop reported that the achievement of supranormal DO_2 within 24 hours of injury decreased mortality from 37% to 18%, and also decreased the incidence of ARDS and organ failure in trauma patients (46). The ideal cutoff times to achieve the specific end points are arbitrary; however, from the many studies analyzed, it appears that the achievement of the designated end points of DO_2 and VO_2 differs between high-risk patients undergoing major elective procedures and trauma patients. Ideally, the targeted DO_2 should be reached within the 12 hours, and maintained for 12 to 24 hours after major elective surgery. In contrast, the same end point should be reached within 24 hours of injury in trauma patients, and definitely, before the onset of organ failure, and maintained until normalization of lactate levels. Further support to target perioperative fluid therapy in conjunction with inotropic drugs such as dobutamine, dopexamine, or epinephrine to a value of DO_2 greater than 600 mL/min/m², in high-risk surgical patients, comes from work published by Lobo et al. in 2000 (5). These authors showed that the therapy aimed at increasing DO_2 above 600 mL/min/m² with volume loading with dobutamine and dopamine decreased mortality from 50% in the control group to 15.7% in the protocol group. This study was interrupted because of the significant difference in 60-day mortality between the control and protocol groups. Because there are no trials adequately powered that have investigated the effect of fluids alone on the optimization of DO_2 and mortality, it is impossible to draw any conclusion on whether the effects of fluid therapy and inotropes are synergistic, or to the potential beneficial effect of inotropes on mortality, totally independent of their effect on oxygen transport.

Major surgery and trauma produce an increase in the level of proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6; the increase in these cytokines has been causally associated with the development of multiple-system organ failure and death (54–56). Catecholamines and dopexamine have anti-inflammatory properties not related to their effect on oxygen transport variables; they decrease the hematic level of TNF and increase the level of the anti-inflammatory cytokine IL-10 (54–57). It is possible that the mechanisms explaining the beneficial effect of supranormal DO_2 on mortality in high-risk surgical patients include the prevention of tissue hypoxia by the increased availability of oxygen at cellular level, coupled with the induction of an anti-inflammatory response produced by the use of inotropes.

While there are many papers that support supranormal DO_2 as a perioperative goal to reduce morbidity and mortality in high-risk patients undergoing major elective surgery, there are others that have failed to show the superiority of increasing DO_2 to a predetermined level over the more conventional approach aimed at maintaining hemodynamic stability. A recent multicenter study by Sandham et al. showed no improvement in outcome, in high-risk surgical patients, resulting from a goal-directed therapy aimed at increasing DO_2 between 550 and 600 mL/min/m² and CI between 3.5 and 4.5 L/min/m² with a pulmonary artery catheter (50). Many physicians could use the results of this study as the ultimate proof that a strategy aimed at increasing DO_2 above normal levels is not warranted. However, an in-depth analysis of this study shows that the conclusions reached by the authors are not valid for several reasons, including the fact that only 20% of their patients were optimized preoperatively, in contrast to previous trials which have shown that hemodynamic optimization should be achieved before surgery, and also because they accepted the possibility of a type II error, in addition to using eligibility criteria that identified as high-risk surgical patients, patients who would be considered at most to be at intermediate risk by most surgeons, based on a mortality rate of only 7.7% in the control group. Furthermore, based on a control event rate of 7.7%, assuming the same treatment effect postulated in the study design, they would have required

1488 patients instead of 997 in each group, to identify with a power of 90% and a two-tailed P value less than 0.05%, a difference between the two groups; however, the authors accepted a reduction in the power to identify a difference from 90% in the initial study design to 78%, once the data were analyzed.

CONCLUSIONS ABOUT OPTIMAL PERIOPERATIVE FLUID THERAPY

An unbiased approach to the literature surrounding the role of goal-directed therapy aimed at increasing DO_2 to supranormal values in surgical patients leads to the following conclusions. First, the amount and quality of the evidence supporting early goal-directed hemodynamic management to attain supranormal DO_2 in high-risk surgical patients is greater and better than that supporting commonly accepted interventions aimed only at maintaining hemodynamic stability and urinary perfusion. Second, the application of the same management protocols to surgical patients, either late in their postoperative course or in the presence of established critical illness or organ failure, is less successful because when oxygen debt is not reversible, increased oxygen transport is not effective (58,59). Finally, despite the presence of Level I evidence supporting early cardiovascular optimization to specific end points of DO_2 , of high-risk surgical patients with fluid, inotropes, and vasodilators to decrease mortality and morbidity, this practice is rarely followed because it requires a significant investment in time and resources.

RECOMMENDATIONS

Based on the best evidence available to date, we believe that the following patient groups should undergo cardiovascular optimization with a pulmonary artery catheter to a $DO_2 > 600 \text{ mL/min/m}^2$ either preoperatively or immediately following an emergency major surgical procedure or following major trauma:

1. Patients scheduled to undergo major elective procedures deemed to be at high risk by the presence of two or more of the preoperative risk factors shown in Table 1.
2. Patients who have undergone emergency operations and have two or more of the risk factors described by Shoemaker et al. (25).
3. Trauma patients who have sustained severe trauma.

On identification of a patient who may benefit from cardiovascular optimization, we follow the following protocol to achieve a $DO_2 > 600 \text{ mL/min/m}^2$ as soon as possible, but not later than 24 hours, if the patient has undergone emergency surgery or surgery for trauma. We insert an arterial catheter to monitor arterial blood pressure and an oximetric pulmonary artery catheter (Oximetrix, Baxter Edwards Critical Care, Irvine, California, U.S.A.) to monitor pulmonary artery, right atrial and pulmonary artery occlusion pressures (PAOP), and mixed venous oxygen saturation, and to measure cardiac output, and calculate DO_2 and VO_2 . Our protocol includes therapeutic measures in the following sequence until the specific clinical goals have been achieved: (i) infusion of 250 to 500 mL aliquots of crystalloids over 20 minutes if the hemoglobin level is 10 g/dL or more, to achieve a pulmonary artery occlusion pressure (PAOP) between 15 and 18 mmHg, measured at end-expiration if the patient is intubated on mechanical ventilation; (ii) afterload reduction with sodium nitroprusside, starting at $0.5 \mu\text{g/kg/min}$, if there is an increase in systemic vascular resistance index ($> 28 \text{ mmHg/L/min/m}^2$), measured as the difference between mean arterial pressure and right atrial pressure over CI, and systolic blood pressure is stable and greater than 110 mmHg and CI is low; (iii) dobutamine starting at $7.5 \mu\text{g/kg/min}$ if the systolic blood pressure is higher than 100 mmHg and if CI is less than 3.5 L/min/m^2 ; (iv) epinephrine starting at $1 \mu\text{g/min}$ if systolic blood pressure and CI are low in the setting of a PAOP $> 18 \text{ mmHg}$; (v) norepinephrine starting at $1 \mu\text{g/min}$ if systolic blood pressure is low in the presence of normal or increased CI and decreased systemic vascular resistance index; and (iv) transfusion of red blood cells to a hematocrit of 33% to 35%, but not greater than 35%, if the desired DO_2 has not been achieved with all previous therapeutic measures. We believe that transfusion of red blood cells to a higher hematocrit is not beneficial, and it may actually impair the transfer of oxygen at the microcirculatory level because of the effect of increased blood viscosity at the

low-shear rates found at the level of the microcirculation (60). Additionally, it is important to note that while the transfusion of old blood (three weeks or older) will increase systemic DO_2 , it may actually compromise oxygen uptake at the level of the splanchnic circulation, as documented by a decreased gastric intramucosal pH, due to the inability of stored red blood cells deprived of 2, 3-diphosphoglycerate to unload oxygen at cellular level, and to negotiate the splanchnic microcirculation without sludging and obstruction of the capillaries (61). The target end point of DO_2 is maintained perioperatively using the same protocol until two arterial lactate levels obtained at an eight-hour intervals are normal.

In conclusion, we believe that based on the evidence available, in order to decrease mortality and morbidity in high-risk surgical patients, perioperative fluid therapy should be targeted to achieve a $\text{DO}_2 > 600 \text{ mL/min/m}^2$ until arterial lactate levels are within normal.

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5 | Volume Kinetics

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“EFFECTIVENESS” OF AN INFUSION FLUID

The volume effect of an infusion fluid is a central issue in fluid therapy. This usually implies how much of the infused fluid is retained in the bloodstream or, expressed in another way, how much the blood volume (BV) is increased in response to the infusion. The BV-expanding properties are very important to the capacity of the fluid to restore an impaired hemodynamic situation, and an understanding of this is of crucial importance for the clinician.

Many methods have been used to quantify the volume effect of an infused fluid. One possible approach is to use an isotope such as radioiodine-labeled human serum albumin to measure the BV before and after the infusion (1). The difference in BV before and after the infusion is then divided by the amount of infused fluid to indicate the “efficiency” of the infusion. One problem with such calculations is that the distribution of a crystalloid fluid changes quite rapidly and isotopes require approximately 15 to 30 minutes of stable fluid distribution to correctly reflect the BV. Furthermore, when measuring before and after infusion, only two points of measurement are obtained, which do not give a sufficiently dynamic profile of how the fluid is distributed in the BV. More sophisticated methods for measuring BV now exist, such as the use of indocyanine green, in which the mixing time is claimed to be much shorter (see Chapter 1 by Norberg in this book). This method has a better capacity to capture the volume effect in response to a crystalloid fluid infusion when distribution conditions are rapidly changing.

Another way to assess the efficiency of fluid therapy is to use physiological end points. When blood loss can be assessed, the amount of fluid required to restore impaired physiological parameters to a normal state represents the efficacy of the fluid. Examples of such parameters are cardiac output and pulmonary artery pressure (2). Physiological end points provide data on the effectiveness of one fluid versus another, but only a single figure for each fluid to restore an altered hemodynamic situation is normally obtained.

ANALYZING HEMOGLOBIN CHANGES

A third method to quantify the volume effect of an infused fluid is to measure the corresponding change in blood hemoglobin (Hb) concentration during and after infusion. A glance at this approach would suggest that it is more simplistic than the other methods. The strength of analyzing Hb, however, is that it can be elaborated upon. The following presentation describes how data on Hb can be handled to answer questions about the efficiency of fluid therapy. The most sophisticated of these approaches is *volume kinetics* in which a series of Hb values are interpreted according to a theory of how the body handles infusion fluids.

When starting to analyze Hb changes, the baseline BV is preset at baseline (time 0), by using a multiple regression equation based on the weight and height of a subject. Several such equations have been published and are derived from analyses of the BV by isotopes in a large number of individuals. They all yield quite similar results. One such equation is the one by Nadler et al. (3):

$$BV_0 \text{ (liters)} = 0.03219 \text{ weight (kg)} + 0.3669 \text{ height}^3 \text{ (m)} + 0.6041 \quad (1)$$

The BV change to any time (*t*) can then be obtained as

$$\Delta BV(t) = BV_0 (Hb_0/Hb(t)) - BV_0 \tag{2}$$

The amount of fluid retained in the blood (efficacy of the fluid) is given by

$$\text{Fluid retained (\%)} = 100 * \Delta BV(t) / \text{infused volume} \tag{3}$$

Duplicate samples for Hb analysis should be withdrawn to reduce variability due to the assay. This approach, which has been used in many studies, gives the Hb changes induced by infusion fluids—a simplistic but robust physiological interpretation (4,5). If the urinary output is known, the difference between the infused fluid volume and the sum of the urine and BVs can even be claimed to represent the hydration of the interstitial fluid space (6). This simple way of handling Hb data is not perfect, however, which is evidenced by the fact that more than 100% of a crystalloid fluid load is often “retained” in the bloodstream early during an infusion experiment.

HEMOGLOBIN DILUTION DURING SURGERY

The Hb dilution concept can be developed to yield the efficacy of infusion fluids in maintaining the BV during complex surgical operations. One approach is to estimate the BV change during bleeding by first estimating the total Hb mass in the circulation from which the blood loss is subtracted (7):

$$\text{Hb mass}_0 = BV_0 * Hb_0 \tag{4}$$

$$BV(t) = \frac{\text{Hb mass}_0 - \text{loss of mass}(t-0)}{Hb(t)} \tag{5}$$

$$\Delta BV(t) = BV(t) - BV_0 \tag{6}$$

Thus, the change in BV can be estimated from the Hb level in whole blood provided that the loss of Hb by bleeding is known. These simple equations can easily be entered into a pocket calculator and to help the clinician when assessing whether a patient is hypovolemic or hypovolemic. The equation can also be applied repeatedly during surgery to study, for example, under which circumstances hypovolemic hypotension or tachycardia develops (8). From a theoretical point of view, frequent application of the equation is a strong approach because it is easier to assume Hb to be equally distributed in the blood *on the average* during an operation than it is to assume equal distribution at any single point in time.

The next step is to apply a multiple regression equation to separate the effect of various factors that determine the BV. The tendency for a fluid to increase the BV can be regarded as a vector, and blood loss can be regarded as another vector that acts to reduce it (Fig. 1). This can be expressed as

$$BV(t) = A * (\text{infused fluid volume}) - B * (\text{blood loss}) \tag{7}$$

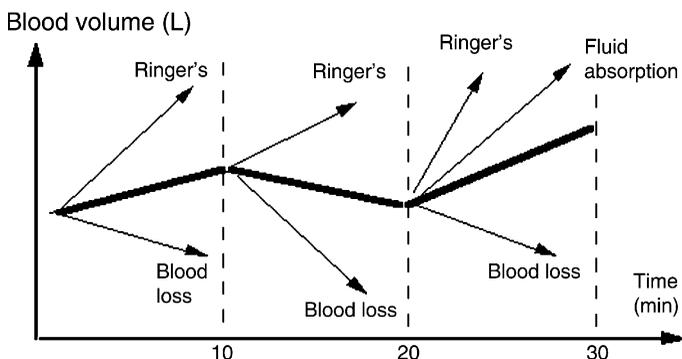


Figure 1 Schematic illustration of how fluid added to and lost from the body during transurethral prostatic resection can be regarded as vectors, which yield a strength to change the blood volume. The strength of each predictor (intentional and accidental fluid infusions and blood loss) can be calculated by multiple regression analysis. *Source:* From Ref. 9.

Data may be assessed separately for each 10-minute period of an operation, otherwise cumulative data are entered. The multiple regression analysis, which can be expanded by introducing other factors also affecting the BV, yields vectors A and B. These represent the "efficiency" of the infused fluid during surgery and the hypovolemic effect of blood loss, respectively. Naturally, when short intervals are assessed, B should be close to 1.0. Over longer periods, capillary refill will reduce the value.

This approach has been used to estimate that Ringer's solution expands the BV by as much as 60% of the infused amount during transurethral resection of the prostate performed under general anesthesia (9). The hemodilution and blood loss were then measured at short intervals, but the procedure in the study did reflect a true clinical situation. During epidural anesthesia, the short-term volume effect (10 minutes) of Ringer's solution was between 48% and 75%, while the cumulative volume effect during the entire operation varied between 30% and 40% (10).

The strong BV-expanding effect of Ringer's solution and also the apparent time dependency were difficult to understand in the 1990s, when it was only acknowledged that between 20% and 25% of the infused crystalloid fluid remained in the blood (1). This view was based on the belief that isotonic crystalloid fluid is evenly distributed between the physiological plasma and interstitial fluid volumes, with little concern for distribution and elimination effects. The difficulties also reflect a shortcoming of the "Hb dilution method," namely its limited potential for ascribing the results to a specific mechanism (Figs. 2 and 3).

DRAWBACKS OF USING HEMOGLOBIN DILUTION

The Hb dilution method has been criticized because isotopes for measuring BV may not behave in the same way as Hb during volume loading. Part of this discrepancy has been accounted for by introducing the hematocrit factor, which is approximately 0.9 at baseline and corrects for anticipated differences in Hb between large and small vessels (13). The hematocrit factor should not be confused with the lower Hb concentration present in the capillaries; the effect of the capillaries on the Hb dilution is very small because only 1% of the BV resides there. Furthermore, Hb may be raised by stress due to the release of erythrocytes stored in the spleen. This effect makes splenectomy necessary before studying fluid balance changes by Hb dilution in animals such as cats and sheep, but in humans, the role of the spleen in temporarily raising the Hb level is very small or even absent (14).

A more recent view of why Hb dilution does not always correspond precisely to the results of tracer dilution techniques is that they are based on different assumptions. External tracers are believed to be evenly distributed in the plasma volume in both well-perfused areas and poorly perfused areas. Another assumption must be added when studying fluids having a rapid turnover. Calculation of the plasma volume by means of a regression equation based on several sampling points of a tracer requires that the fluid distribution is in steady state. This does not occur until quite late in the time course of a crystalloid infusion experiment, and never during a surgical operation. In contrast, the Hb dilution is the reciprocal of the increase in blood water concentration due to the infused fluid. This is a measure of the fraction of the

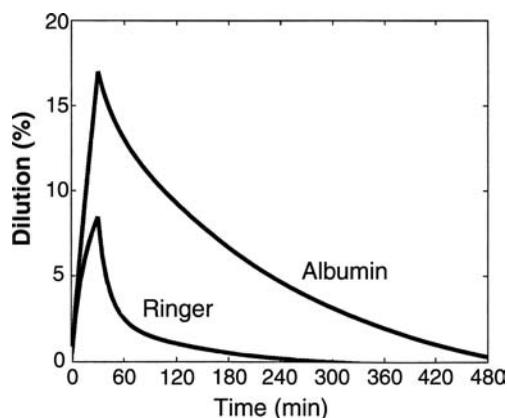


Figure 2 The expected plasma dilution resulting from intravenous infusion of 10 mL/kg of albumin 5% and acetated Ringer's solution in volunteers. The degree of the plasma dilution, the time course, and the shape of the curves differ markedly between the infusions, suggesting the need for kinetic analysis of how the fluids are being distributed and eliminated. *Source:* From Refs. 11 and 12.

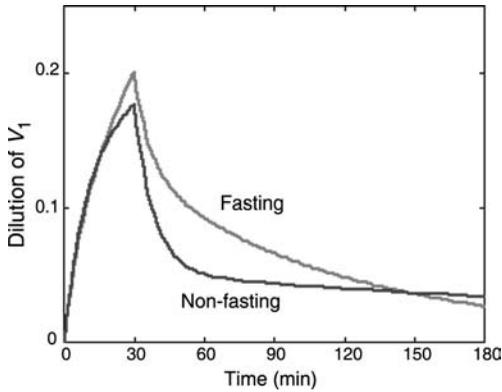


Figure 3 The plasma dilution following infusion of 25 mL/kg of normal saline over 30 minutes in seven sheep in the fasting and in the nonfasting state. The animals tend to retain more fluid in plasma in the fasting state, and this primarily changes the shape of the dilution–time curve *after* the infusion. *Source:* Courtesy of Dr. Cara Connolly and Professor George Kramer, University of Texas Medical Branch, Galveston, Texas, U.S.A.

fluid volume that readily equilibrates with the sampling site, which is normally a well-perfused area of the body. Therefore, the tracer and Hb will yield different results if the distribution of an infusion fluid is governed not only by transcapillary exchange but also by differences in perfusion between capillary beds.

VOLUME KINETICS

The obvious need for a more dynamic model to interpret data on hemodilution and to overcome the uncertainty of how well Hb changes reflect the BV encouraged the development of *volume kinetics* in 1997 (15) and has since been the subject of approximately 30 original publications. Volume kinetics represents an adaptation of pharmacokinetic theory that allows the outcome of the volume administered during intravenous therapy to be analyzed and simulated. Data on dilution of blood can be used to assess the volume of distribution and the subsequent rate of distribution and elimination for any fluid. The results are used to simulate plasma dilution during any infusion regimens the examiner wants to carry out.

One difference from earlier approaches is that the volume kinetic method does not require an assessment of the initial BV. The calculations can be done without it. An estimation of BV is still made to allow a minor correction of the hemodilution due to blood sampling, but this can be overlooked if the sampled BV is small. Moreover, errors in the assumed BV at baseline have only a very limited effect on further calculations. More importantly, infused fluid is said to expand one or several *functional* body fluid spaces instead of being distributed between *physiological* fluid spaces. These functional spaces have a baseline “target volume” that compensatory mechanisms in the body strive to regain after the fluid has been administered.

Pharmacokinetics Applied to Fluids

Drug regimens are commonly based on pharmacokinetic analysis. For this purpose, it is necessary to measure the concentration of the drug in the blood during and after administration. These data are then fitted to the solutions of differential equations describing the situation in a kinetic model created by the investigator, which should reflect reasonably well what happens in the body. The parameters in the model, such as the volume of distribution and the rate of elimination, are then estimated by a mathematical process called nonlinear least-squares regression. This minimizes the difference between the experimental concentration–time data and theoretical values generated by a computer. When the parameters in the kinetic model have been estimated, optimal doses and intervals between doses can be calculated by a computer simulation.

Volume kinetics uses *dilution* instead of concentration as input data because the concentration of a fluid, such as isotonic saline, is difficult to measure. The infused fluid is dissolved in the blood, which is already 80% water. We advocate careful repeated measurements of the blood Hb concentration because this marker remains in a reasonably well-defined space,

namely the BV. However, the volume of distribution for Hb has little to do with the volume in which the infusion fluid is distributed, which might be smaller or larger than the BV. Before being used in further calculations, the hemodilution must be transformed to the corresponding plasma dilution because it is the plasma volume that equilibrates with other fluid spaces in the body. It is also the plasma volume from which urine is excreted. From baseline at time 0 to time t , the dilution of the plasma, which equals the dilution of V and V_1 , can be expressed as

$$\text{Plasma dilution}(t) = [(\text{Hb}_0 - \text{Hb}_t) / \text{Hb}_t] / (1 - \text{baseline hematocrit}) \tag{8}$$

Two-Volume Kinetic Models

The infused fluid is thought to expand a single body fluid space called v , which the body strives to maintain at the target volume V (one-volume model, Fig. 4A). Elimination of fluid occurs by baseline urinary excretion and evaporation (k_b , "basal," set to ≈ 0.5 mL/min) and by a dilution-dependent mechanism governed by a constant (k_r , "renal"). The volume changes in the one-volume model are given by the following differential equation:

$$\frac{dv}{dt} = k_i - k_b - k_r \frac{(v - V)}{V} \tag{9}$$

The parameters used in the one-volume model sometimes have a slightly different meaning than in drug pharmacokinetics (Table 1). For example, the volume of distribution changes continuously during an experiment and is thus represented by v instead of V . The infused fluid may also be thought to expand both a single central and a more peripheral body fluid space called v_1 and v_2 , respectively (*two-volume model*). These body fluid spaces strive to be maintained at the target volumes V_1 and V_2 in a way similar to the inflation of elastic balloons (Fig. 4B). As for the one-volume model, elimination of fluid occurs from v_1 by two mechanisms, k_b and k_r . The expanded space v_1 communicates with v_2 , and the net rate of volume equilibration between them is proportional by a constant (k_t) to the relative difference in dilution between them. Hence, the dilution will be different in v_1 and v_2 (Fig. 5). The volume

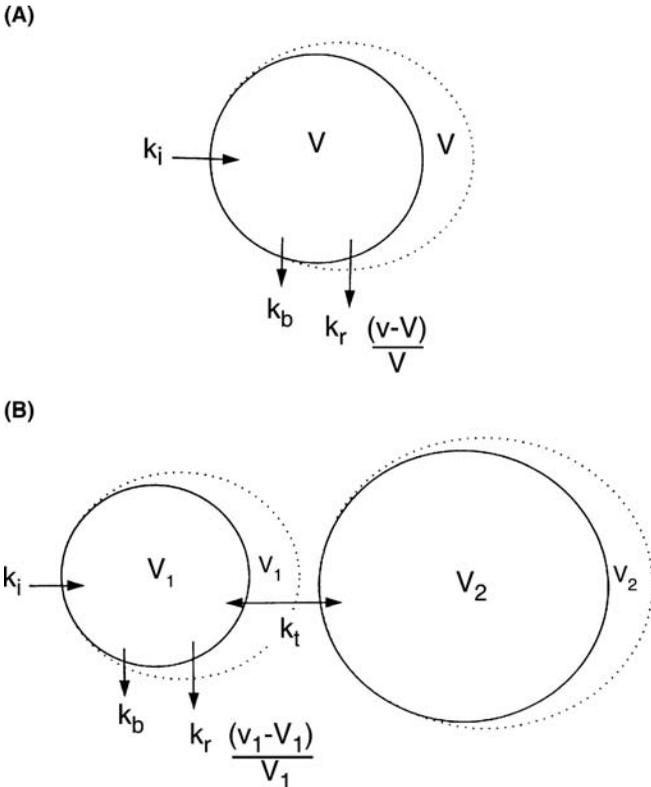


Figure 4 Diagrammatic representation of the one-volume fluid-space model (A) and the two-volume fluid-space model (B).

Table 1 Parameters that Are Comparable in Traditional Drug Kinetics, Based on a Concentration–Time Curve and a Dilution–Time Curve in Volume Kinetics (One-Volume Model)

	Drug pharmacokinetics	Volume kinetics
Input variable	Concentration	Dilution
Unit	mg/mL	No unit
Volume of distribution	Dose/ C_0	v
Elimination	Clearance (CL)	k_r
Elimination rate constant	K	k_r/V
Rate of elimination	$CL * C$	$\frac{k_r(v-V)}{V}$
Half-life	$\frac{\ln 2}{K}$	$\frac{\ln 2 * V}{k_r}$
Steady state	$k_i = CL$	$k_i = k_r$

Note: The baseline fluid losses k_b , which have no relation to other parameters, have been omitted.

k_i = rate of infusion, C_0 = concentration at time zero.

V = baseline size of expanded body fluid space.

Source: Courtesy of Dr. Dan Drobin, South Hospital, Stockholm, Sweden.

changes in the two-volume model are given by the following differential equations:

$$\frac{dv_1}{dt} = k_i - k_b - k_r \frac{(v_1 - V_1)}{V_1} - k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right] \quad (10)$$

$$\frac{dv_2}{dt} = k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right] \quad (11)$$

The dilution-time profiles, sometimes augmented by the urinary excretion, are entered into a computer, which fits the solutions to the differential equations describing the fluid shifts in these kinetic models to the data (11). The output consists of the optimal values for the unknown parameters in the models together with their standard errors, which represent the uncertainties of each estimate. The unknown parameters in the one-volume model are V and k_r , while, in the two-volume model, the corresponding unknown parameters are V_1 , V_2 , k_t , and k_r .

There are several ways to examine the quality of performance of the models. One way is to look at the standard error for each parameter, because this error should ideally be less than 10% of the best estimate. If the error is higher than its corresponding parameter, one may question whether the information given by the parameter is important. Residual plots also indicate whether the one- or two-volume model is the best (Fig. 6). A good curve fit is indicated by random distribution of the residuals around zero. Of the two models presented, the one with the simplest solution should be chosen, and the selection is made by using a statistical test (Boxenbaum's F test) (16,17).

The computer gives partial derivatives for the parameters, which show during which part of the experiment their respective values are generated (Fig. 7). Partial derivatives are helpful when planning the length of new experiments.

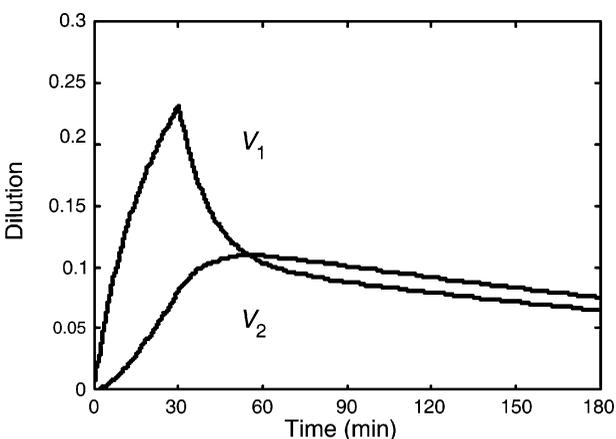


Figure 5 Dilution of the central (V_1) and peripheral (V_2) body fluid spaces during and after a 30-minute infusion of 25 mL/kg of Ringer's acetate solution in volunteers just after 900 mL of fluid was withdrawn. Computer simulation based on the average two-volume kinetic parameters from 10 male volunteers. Source: From Ref. 16.

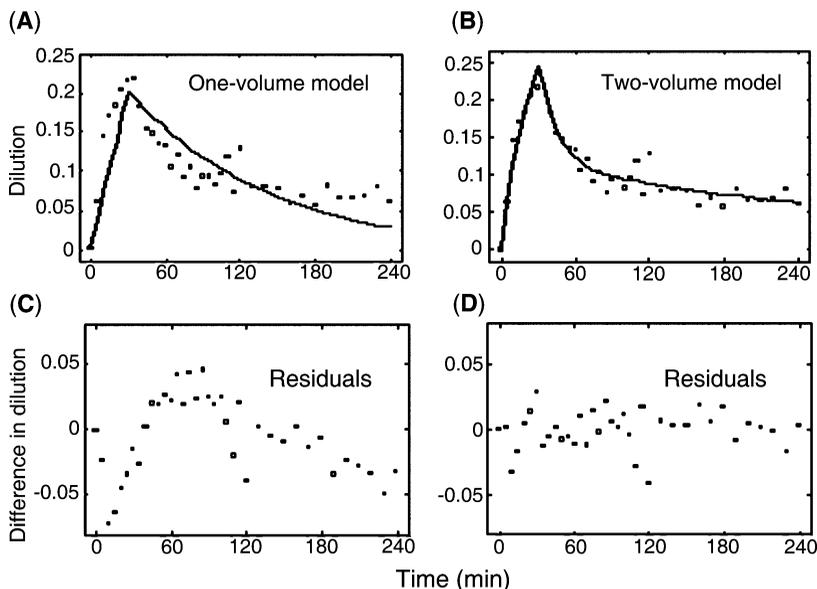


Figure 6 (A) Optimal curve fitting when fitting the one-volume and (B) the two-volume model to the same data in one normovolemic male volunteer who received 25 mL/kg of Ringer’s acetate solution over 30 minutes. (C) and (D) highlight the corresponding residuals, that is, the difference between the model-predicted and the measured data. The random scatter of the residuals around zero in (D) suggests that the two-volume model best describes the data.

The volumes reported in volume kinetics may not have actual resemblance to known physiological volumes, but they may have greater predictive value than the analysis of traditional physiological spaces. It would be tempting to address V_1 as the plasma volume and V_2 as the interstitial volume, and we have made some reflections of this kind in this chapter. The parameters may reflect the sensitivity of volume kinetic analysis to the rate of mixing in the vascular and extravascular spaces. An alternate V_1 represents the well-perfused and

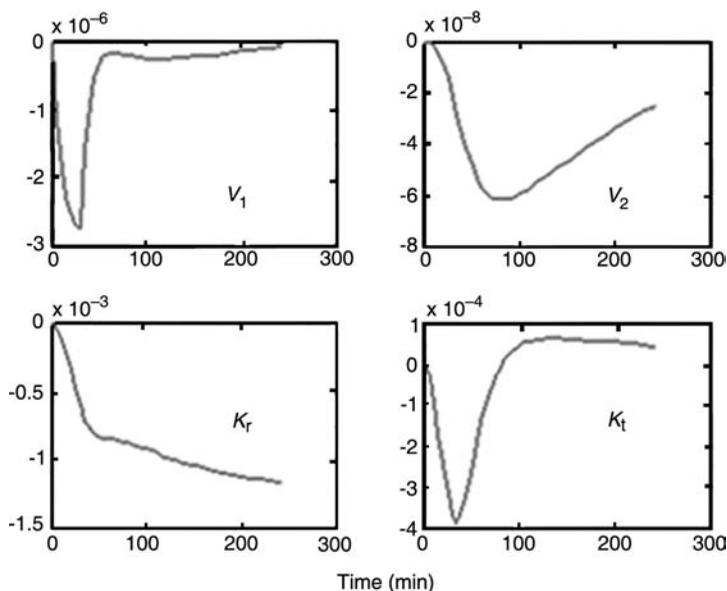


Figure 7 Partial derivatives for the kinetic analysis according to the two-volume model shown in Figure 5. A longer distance from zero shows that data more strongly contribute to the estimated parameters. V_1 and k_t are derived at the end of and shortly after the infusion, whereas data obtained later contribute most to V_2 and k_r .

well-mixed components of the circulation, whereas V_2 represents the remainder of the circulation and the part of the interstitial space that mixes with an infused fluid.

Basic Findings

Analysis of the dilution–time profile according to the volume kinetic models is a useful tool in the study of the effects of fluid therapy. The one-volume model usually applies to colloidal fluids. In one study, the size of V for 6% dextran 70 was 2.8 L, which may be used to imply a small initial withdrawal of interstitial fluid into the plasma when this fluid is infused (11).

For a crystalloid fluid like Ringer's solution, the one-volume model typically applies when the urinary excretion is prompt. Because distribution between V_1 and V_2 requires as much as 30 minutes to be completed (Fig. 5), peripheral edema does not develop (i.e., fluid does not translocate to V_2) if the renal excretion is effective (k_r is high). In contrast, the two-volume model normally applies in dehydrated subjects and during surgery when the body strives to conserve fluid.

While V for the one-volume model is usually 4.5 L, typical sizes of V_1 and V_2 for Ringer's solution are 3.5 and 6 to 7 L, respectively. This means that V_1 has a volume similar to the plasma volume, while V_2 occupies two-thirds of the expected size of the interstitial fluid space (11,16,17). This discrepancy is probably due to the fact that the interstitial space of bone and brain tissue is not normally expanded by isotonic crystalloid fluid. The size of V_1 is reduced in proportion to the amount of blood lost during hypovolemia (16). A recent study suggests that the flow of fluid indicated by k_t correlates quite well with the net filtration from the capillaries.

Optimal analysis of volume kinetic parameters requires that the dilution is measured over a period of three to four hours. Shorter experiments might result in a high degree of covariance between V_2 and k_r , because these parameters are both generated late during an experiment (Fig. 6). More rarely, a very slow elimination of infused fluid (low k_r) causes the same covariance problem, although the experiment is of "normal" length. If that problem arises, the urinary excretion might be helpful in estimating k_r , because this parameter is in fact the renal clearance for the infused water volume, provided that no third-space losses occur (18). With this approach, the experiments may be kept as short as 90 minutes if the studied fluid is infused over 15 to 30 minutes (11). While this practice might be useful for laboratory experiments, third-space losses do occur during anesthesia and surgery, and the model-predicted k_r then exceeds the renal clearance. Indeed, the difference between k_r and the renal clearance for infused fluid may be perceived to represent third-space losses of fluid (19). To obtain data on such losses, Hb must be monitored with good precision over 3–4 hours and analysed together with the excreted urine volume.

Volume Kinetics at Work

Ringer's acetate solution has been administered repeatedly in male volunteers in order to determine whether the size of V is changed by a previous fluid challenge (17). In these studies, the investigators believed there was a possibility that V_2 would increase as a result of hydrostatic pressure-induced breaks in the interstitial matrix. However, no evidence of such damage by a rapid infusion (2 L over 15 minutes) of Ringer's solution was found. The only difference occurring when the crystalloid fluid was given repeatedly was an increase in k_r , which indicated a more efficient elimination of the second infused fluid. Hence, the sizes of V_1 and V_2 seem to be very robust in healthy volunteers.

In another study, blood was withdrawn in two volumes (450 and 900 mL) from healthy volunteers (16). Volume kinetics was analyzed and compared to control experiments performed when the same volunteers were normovolemic. Again, the main difference seen was that hypovolemia changed k_r , but in this study the constant was decreased by approximately two-thirds. In part, this reduction represents a change of baseline, because the body strives to restore the BV after a blood loss. This means that a residual plasma dilution is to be expected.

Induction of anesthesia is a special situation with respect to the body's handling of infusion fluids. Here, the urinary excretion in response to a fluid load is very small, corresponding to a k_r of only 10 to 15 mL/min (20,21), as opposed to 70 to 100 mL/min in volunteers. This rate corresponds to a half-life of crystalloid fluid of several hundred minutes (Fig. 8). Both for spinal and for general anesthesia, the vasodilation associated with the induction creates a small V_1 of approximately 1.6 L, and reduces k_t . This probably implies that, in the standard patient,

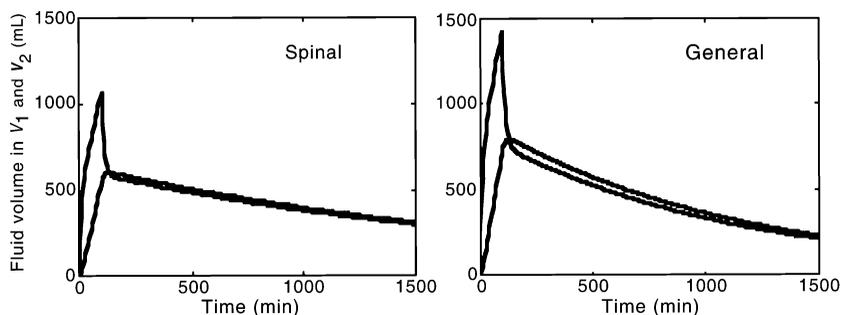


Figure 8 Predicted dilution of v_1 (upper curve) and v_2 (lower curve) over time after infusing crystalloid fluid during induction of two forms of anesthesia. Here, the half-life of infused fluid is much longer than it is in volunteers. Computer simulation based on kinetic data. *Source:* From Ref. 20.

infused fluid is being maintained in the central circulation to compensate for a circulatory stress response.

Marked conservation of fluid is characteristic also for the perioperative period. The rate of elimination of fluid was markedly reduced (k_r is 5–15 mL/min) during cholecystectomy (22) and during thyroid surgery (23) even to the extent that the plasma volume expansion in response to crystalloid fluid would be similar to that of a colloid fluid (Fig. 9). In contrast, V_1 , V_2 , and k_r obtain values quite similar to those reported in volunteer experiments. Fluid also escapes from the kinetic system at a rate of 2 to 3 mL/min (23). This might represent “third-space” losses of fluid, or simply a lack of free equilibration of fluid.

The effect of trauma on the postoperative handling of Ringer’s solution has been studied after hip surgery. The results show that k_r was reduced by 50%, whereas the size of V changed very little (25). In another study, a small trauma seemed to have a very limited effect on the volume kinetics of isotonic and hypertonic fluid given during transport to the hospital (26). Similarly, one day after hysterectomy, the elimination of glucose 2.5% with electrolytes was similar to that of volunteers, although a slight reduction of the uptake of the glucose to the cells still remained (27). This type of quantification of the impact of trauma on the diuretic response to volume loading had been difficult to achieve previously.

Osmotic Fluid Shifts

Kinetic analysis of infusion fluids that redistribute volume between cells and noncells prompts the mathematical handling of a cellular fluid space denoted by V_3 . For hyperosmotic saline, the translocation of fluid from V_3 during infusion can be calculated from the difference in osmolality between the infused fluid and the body fluids (28). However, the model must be able to assess the rate of reflow of translocated fluid to V_3 .

When glucose solution is analyzed, the uptake of glucose into the cells brings along large amounts of fluid by virtue of osmosis (3.6 mL/mmol of glucose). The uptake can be calculated

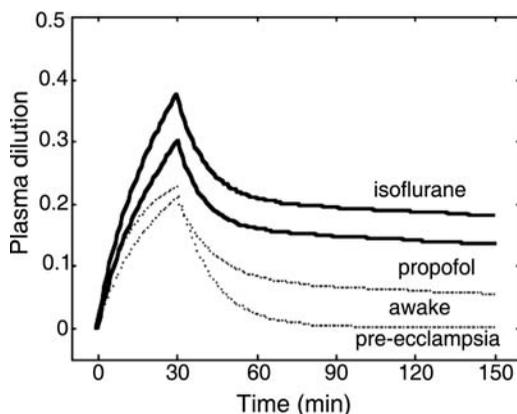


Figure 9 Different plasma dilution responses to 1.7 L acetated Ringer’s solution administered over 30 minutes. Predicted dilution of v_1 (same as the plasma) in hospitalized patients undergoing thyroid surgery under isoflurane or propofol anesthesia, in awake male volunteers, and in awake females with pre-eclampsia. *Source:* From Refs. 11, 23, and 24.

by first analyzing the kinetics of the glucose added to the system. Such analyses show that glucose solution expands a fairly small V_1 , amounting to approximately 3 to 4 L (27,29). The fluid apparently hydrates V_3 but does not expand the intermediate space V_2 . The potential V_2 simply becomes too effectively drained by the fluid uptake to V_3 to become expanded and, consequently, cannot be kinetically determined. For V_2 to become expandable, it requires a low glucose clearance and/or a low k_r .

Presenting Kinetic Results

The results of volume kinetic analyses can be illustrated in many ways. The parameter estimates should be reported but are difficult to evaluate without a computer. Simulations may be presented to show the outcome of a kinetic analysis more clearly (Fig. 8). The disposition of infused fluid in patients and controls can be compared by entering the kinetic parameters into a simulation program that overlays the curves (Fig. 9). Various possible combinations of infusion rates and infusion times required to obtain a predetermined dilution in any specified clinical situation may be indicated by a nomogram (Fig. 10). The rates at which the fluids should be infused in order to maintain steady state can also be shown in a nomogram (16,27). For such predictions, it does not matter much whether the one-volume model or the two-volume model is used to analyze the underlying experiments. The simulation is based on the sum of all dilution–time profiles for the individual underlying experiments. The sum of all dilutions divided by the number of experiments represents the expected overall dilution response to the infusion of the fluid.

The volume changes of V_1 and V_2 over time may also be shown after multiplying the dilution–time plot by the computer-estimated size of the corresponding body fluid space at baseline (16). Such plots allow us to examine how much of the infused fluid is retained in V_1 in the example shown in Figure 3. At the end of the infusion, 47% of the infused fluid is located in V_1 , while, after equilibration with V_2 has been completed at 60 minutes, only 20% remains. This illustrates that the volume effect of Ringer's solution may be quite good during an infusion, but it soon wears off when the infusion is ended.

The efficiency of one infusion fluid can be compared to that of another by simulating how much volume is needed to dilute the plasma in a predetermined way, such as to create a dilution of 20% within 30 minutes ("target dilution method") (28). After assigning isotonic saline to the equivalent efficiency of 1.0, the efficiency of other infusion fluids in male volunteers has been calculated as follows: Ringer's lactate 0.94, Ringer's acetate 0.97, 7.5% saline 4.44, and 7.5% saline in 6% dextran 6.15. Such data are of value for the planning of fluid therapy.

FUTURE CHALLENGES

Scientific studies aimed at comparing the effects of various infusion fluids should be more ambitious than in the past. Such efforts should include careful standardization of the volume

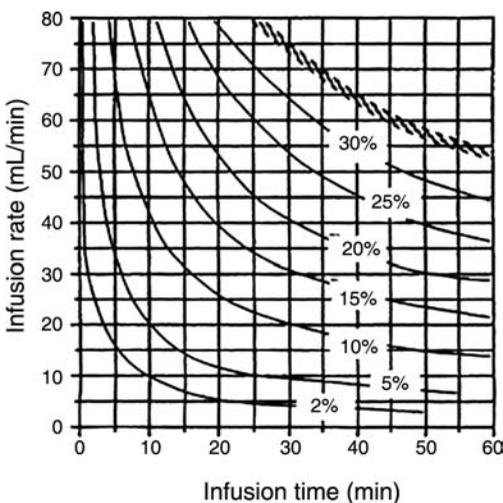


Figure 10 Combinations between infusion rates and infusion times, which yield different degrees of plasma dilution on infusion of Ringer's solution. Based on kinetic data from 10 volunteers from whom 900 mL of blood has just been removed. The thick irregular line shows the isobar for normovolemia. *Source:* From Ref. 16.

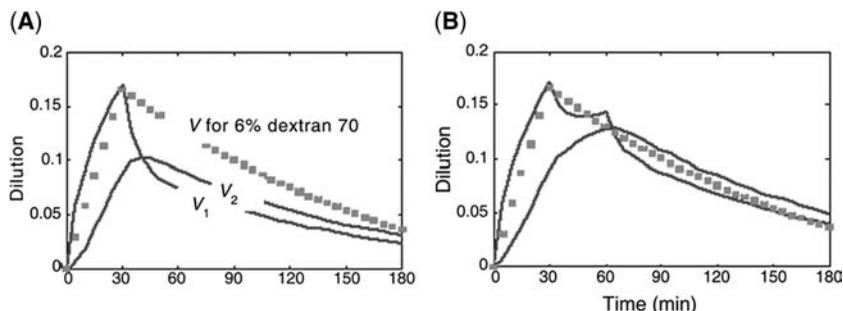


Figure 11 (A) The use of volume kinetics to calibrate volume effects between infusion fluids. Simulation shows that 50 mL/min of Ringer's acetate over 30 minutes reaches the same dilution of V_1 during infusion as that of 16 mL/min of 6% dextran 70%. (B) To also correspond to the dilution from dextran after the infusion, however, Ringer's acetate needs to be maintained at a rate of 20 mL/min between 30 and 60 minutes. Simulations are based on kinetic data. Source: From Ref. 11.

effects (dilution) in the central fluid space, which is the key target for most hemodynamic and hormonal adjustments, during the entire experiment. When using volume kinetics, this is a relatively simple task, but virtually no studies on the differences between various infusion fluids are adjusted for standardization of the volume effects. An example of such standardization is given in Figure 11. One specific area in which a lack of standardization of volume effects is a frequent problem is the evaluation of artificial oxygen carriers, where adequate hydration has effects that, in many respects, such as oxygenation and hemodynamic status, overlap those of the product. Furthermore, many comparisons of the outcome of surgery using various fluid regimens lack adequate control of the volume effects associated with the fluid therapy, leaving the reader in doubt as to whether the volume effects, instead of the quality of the fluid, are responsible for reported differences between fluids.

The most important challenge in the future for volume kinetics is to tailor fluid programs for anesthesia. By using nomograms of the kind shown in Fig. 10, the clinician may plan fluid administration to reach and maintain any predetermined volume expansion during surgery. If the elimination of fluid is slow, as it is during surgery, the expected development will be that volume expansion increases progressively with time, which puts an undue burden on the hemodynamic system. For such programs, the blood loss needs to be considered and, potentially, also the choice of anesthesia. Work on these issues is in progress.

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6 Pulmonary Edema: Etiology and Measurement

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BACKGROUND

The lung may react with edema and consolidation in response to various insults. The morphological changes are accompanied by functional disturbances signified by impaired ventilation-perfusion matching and shunt, with subsequent impediment to oxygenation of blood and carbon dioxide removal. This chapter will review clinical and theoretical aspects of pulmonary edema formation and treatment, as well as techniques for the assessment of edema formation.

CLINICAL ASPECTS OF PULMONARY EDEMA

As a clinician, the prime question arising in facing pulmonary edema patients is “what is the rational approach that gives a patient optimum chances to heal?” First of all, a probable cause needs to be established. It is practical and traditional (1) to divide pulmonary edema (PE) into at least two main groups: hydrostatic (cardiac) pulmonary edema (HPE) and high-permeability (noncardiac) pulmonary edema (HPPE).

Hydrostatic Pulmonary Edema

The division into two main types of edema rests upon the knowledge that even a perfectly healthy lung may react with a rapid and dangerous increase in extravascular lung water (EVLW) if pulmonary capillary pressure is elevated and maintained above 25 mmHg (2). However, if pressure is reduced, reabsorption will take place and we will see rapid clearing of the fluid from lung parenchyma. The main safety factor involved is lymphatic drainage. Any process that retards or obstructs lung lymph flow will thus predispose for pulmonary edema formation and slow down reabsorption. In addition, patients with reduced plasma oncotic pressure will react with edema formation at a lower threshold hydrostatic pressure.

From this introduction, it is obvious that effective therapy should focus on a reduction of hydrostatic pressure as soon as HPE is suspected. Pain and anxiety relief (IV administration of morphine) reduces vascular pressures by bringing down sympathetic nervous system drive; oxygen supplementation releases hypoxic pulmonary vasoconstriction, which adds to a reduction in pulmonary artery pressure; frusemide redistributes intravascular fluid to the periphery even before enhancing diuresis, all of which reduce filling pressures. Venesection or a form of phlebotomy can be achieved by occluding venous return from the legs, thus reducing central venous pressure and favoring reabsorption of lung fluid. Breathing a continuous positive airway pressure (CPAP) on a tight-fitting face mask should offer immediate improvement in arterial oxygen saturation. This can be explained by a reduction in shunting through redistribution of edema in the lung at the same level of EVLW, similar to applying positive end-expiratory pressure (PEEP) during mechanical ventilation (MV) (3).

High-Permeability Pulmonary Edema

HPPE is the hallmark of acute lung injury (ALI) and its severe form, acute respiratory distress syndrome (ARDS) (4). Volumes of literature have flooded the intensive care unit meetings for

years on etiology, therapeutic approaches, and treatment strategies. We have seen expensive molecular targeted therapies yield disappointing efficacy results in one randomized study after another. The crucial point to consider is that the barrier function of the vasculature to larger molecules and cells is no longer intact in HPPE. This permeability increase leads to a rapid and profound fluid leakage followed by inflammation and destruction of lung parenchymal structure over a period of a few weeks. Furthermore, it must be clearly recognized that the process is not completely irreversible, and patients displaying even the most severe forms of disease are known to have pulled through and progressed to an impressive recovery of lung function, as tested up to a year after the acute illness (5). Thus, there is little room for therapeutic nihilism even in life-threatening circumstances.

An important part of therapy in HPPE is fluid restriction while maintaining adequate organ perfusion. A recent study of patients treated with extracorporeal membrane oxygenation (ECMO) reported a fairly good outcome (6). A combined approach was used, aiming at a strongly negative fluid balance, by applying continuous venovenous hemofiltration when necessary, as well as early reestablishment of spontaneous-breathing (SB) efforts on continuing ECMO support of gas exchange (Dr Palmér, personal communication). Their overall aim is to optimize pulmonary edema resolution capacity where SB is thought to pump out extravasated fluid through the lymphatic system. A further advantage of ECMO is the low central venous pressure that does not oppose lymph drainage. This clinical hypothesis is based, among other observations, upon animal studies discussed earlier (7). Therapy of HPPE threatens to fail if the primary etiology of ALI/ARDS is not treated adequately, such as correct antibiotics in sepsis, surgery for an abdominal compartment syndrome, drainage of septic foci, stabilization of fractures, administration of steroids if a rheumatoid-type cause is suspected, and much more.

The importance of maintaining SB, we think, cannot be overemphasized. In addition to the above, SB at CPAP may both counteract atelectasis formation basally in the lung and facilitate the ability to clear secretions with the reemergence of cough. Restricted use of sedatives brings a more awake patient, who can move around in the bed a little, and allows the patient to participate in physiotherapy. It should be mentioned that PE might be seen in a few additional and more unusual circumstances. Among them, we recognize PE due to extreme negative intrapleural pressures (occluded upper airway and breathing efforts), PE after reexpansion of a collapsed lung, and high altitude PE.

THEORETICAL ASPECTS OF PULMONARY EDEMA

Basic Principles of Edema Formation

About a century has passed since Starling presented experiments demonstrating that hydrostatic and oncotic factors balanced each other over the capillary membrane, determining the rate of fluid moving from the circulation to an extravascular region. A later modification of his work led to the equation now named after him (8):

$$Q = K_f[(P_{mv} - P_{pmv}) - \delta(\pi_c - \pi_t)]$$

where Q is the net fluid filtration from the pulmonary microvascular (intravascular) capillary system to the perimicrovascular (extravascular) pulmonary tissue, K_f is the capillary filtration coefficient, P is the hydrostatic pressure, given as P_{mv} and P_{pmv} in the microvascular and perimicrovascular compartments, respectively, δ is the protein reflection coefficient [varying between 0 (freely permeable to proteins) and 1.0 (impermeable to proteins)] and π is the protein colloid osmotic pressure in the microvascular (π_c) and perimicrovascular (π_t) tissue. The expression K_f reflects the surface area available for fluid flux and the hydraulic conductance for fluid.

It is obvious from this expression that edema may form in a tissue for a variety of reasons or combination of factors. In the lung, we recognize HPE as opposed to "high-permeability" pulmonary edema (HPPE). The idea here is that the former may be a result of mainly extrapulmonary factors such as left heart failure. In contrast, the latter type of edema is mainly caused by an alteration of the permeability of the capillary membranes in the lung, permitting fluid and large molecules to extravasate even at normal vascular pressures. Naturally, the therapeutic approach, apart from symptomatic support, differs according to the etiology of edema formation.

Furthermore, edema may accumulate due to a combination of altered hydrostatic and permeability factors. This can, for example, be seen in early experimental septicemia caused by injecting live bacteria or lipopolysaccharides. Sheep typically react with both a sharp increase in pulmonary artery pressure and an increased permeability in lung capillaries (9). Both these factors, therefore, contribute to edema formation in the lung.

Effects of Airway Pressure or High Capillary Pressure

To what degree the maintenance of a high airway pressure is detrimental or not has been the subject of considerable debate. We have experienced an era where the idea of "super PEEP" was advocated by some groups in the treatment of ALI. Because mechanical ventilation (MV) was introduced in the treatment of ALI, it was obvious that barotrauma, with or without pneumothorax, was an adverse effect to consider when using intermittent positive pressure ventilation (10). The Kolobow group studied sheep treated with MV that had their lungs over-expanded by the application of peak airway pressures at 50 cmH₂O (11). With this ventilator setting, the clinical picture of ARDS could be produced by MV alone. Webb and Tierny created impressive alveolar edema in rats by ventilating with high airway pressures for only 20 minutes (12). This work was recently confirmed and extended by Dreyfuss and Saumon (13), suggesting the term "volotrauma" as opposed to "barotrauma." This latter study offered evidence that overexpansion of the lung tissue by volume alterations is more damaging than overexpansion by pressure alterations. We can conclude that severe lung damage with edema can be caused by airway-mediated mechanical factors, resulting in repeated tearing of tissue due to overexpansion by volume. West et al. have published impressive electron microscopic evidence of how "overexpansion by pressure increase" of either the airway or the capillary vessels (increased blood pressure) will result in "stress failure" of these structures (14). The damaged structures allow fluid, larger molecules, and sometimes whole blood corpuscular elements to exit the circulation and participate in edema formation.

Our group measured lung lymph flow in anesthetized dogs ventilated with or without PEEP (7). During MV with PEEP 10 cmH₂O, the lymphatic flow from the lung was reduced almost 50% compared to that occurring with zero end-expiratory pressure. On the other hand, during SB, lung lymph flow was markedly elevated (Fig. 1) (7). This indicates that intrapulmonary pressure can influence lung fluid balance and that SB considered in relation to lung lymph flow might have an advantage when compared with MV.

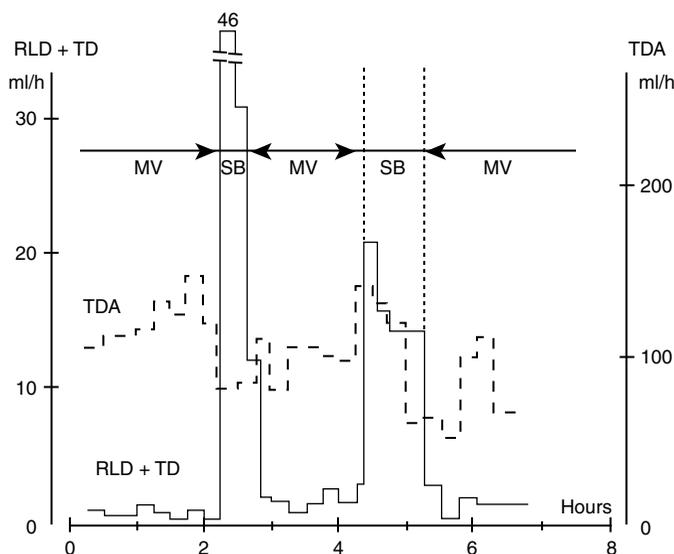


Figure 1 Pulmonary lymph flow (RLD + TD) and abdominal lymph flow (TDA) during mechanical ventilation and spontaneous breathing (SB) in a 30-kg anesthetized dog. Note the dramatic increase in lung lymph flow during SB, suggestive of impeded lymph drainage during mechanical ventilation. Note also the decrease in abdominal lymph flow during spontaneous breathing. Whether this reflects decreased capillary leakage remains to be shown. *Abbreviation:* MV, mechanical ventilation. *Source:* From Ref. 7.

It can be summarized that in the early stages of lung injury a number of factors contribute to edema formation:

1. Increased capillary pressure (fluid overloading, left heart failure)
2. Elevated airway pressure causing barotrauma (MV, PEEP, and need for higher tidal volumes due to intrapulmonary shunting)
3. Elevated airway pressure impeding lymphatic drainage of lung tissue and possibly pleural cavities
4. Increased permeability of the capillary or alveolocapillary membranes
5. Impeded active transport of water from the alveoli back to the interstitium and circulation
6. Extravasation of activated neutrophils and macrophages, which further lowers permeability after releasing inflammatory mediators locally and into the bloodstream
7. Microthrombotization of lung blood or lymph capillaries by local activation of platelets, reducing the functional area of the lung capillary bed, which contributes to an elevated microvascular (hydrostatic) pressure (flow limitation) and possibly impedes lymphatic flow

Clearance of Pulmonary Edema

When discussing clearance of extravasated fluid from the lung, the situation becomes very complex. From a clinical point of view, it seems advisable on the basis of the above discussion to keep vascular pressures low (pulmonary artery pressure and central venous pressure). We attempted to optimize Starling factors by using a hyperoncotic, hypertonic infusion during pulmonary edema in dogs, but found to our surprise that this manipulation did not increase the rate of reduction of EVLW (15). Obviously, other factors limited the maximum rate of reabsorption of fluid. At this point, we consider the Starling equation unable to alone express all relevant factors that determine lung fluid balance. An illustration of the need to take additional factors into account is the demonstration that the pleural cavities may act as safety factors delaying and minimizing edema formation. It is now known that a significant portion of interstitial fluid during edema formation is excreted into the pleural cavities and cleared from the parietal pleura (16). Experiments on dogs demonstrate to what extent this animal is dependent upon an intact lymphatic system to clear the pleural cavity from protein-rich, extravasated fluid. This was shown by ligating the lymphatic vessels draining the pleural cavity, measuring the rate of removal of indicator-labeled protein from a pleural effusion (17). The dog could not remove such an effusion after lymphatic ligation. Our conclusion must be that a number of factors concerning clearance of edema, and safety factors against edema formation, have to be taken into consideration when discussing the fluid balance of lung tissue. We have previously suggested the calculation of "net fluid leakage" per time unit as a more relevant parameter to use for such an analysis (18).

Our understanding today is that there exist several ways by which the lung can rid itself of edema. Fluid can be

1. Locally reabsorbed through the capillary membrane by Starling-type mechanisms, or actively pumped out of the alveoli (19)
2. Cleared through the lymphatic system as lymph and returned to the circulation (8)
3. Excreted to the pleural space directly from the lung tissue (16) and from there taken up into parietal pleural lymphatics for return to the circulation
4. Transported to the lung hilus interstitially and from there migrate into the mediastinum and be absorbed (20)
5. Cleared through the airway

Different pathways of fluid transport in the lung are shown schematically in Figure 2 (21).

GAS EXCHANGE IN PULMONARY EDEMA

If severe enough, edema formation in the lung progresses from interstitial edema to alveolar edema. It has been stated that alveolar edema starts to form at or above a value of EVLW of 12 mL/kg (22). In early pulmonary edema up to this point, little or no disturbance of gas

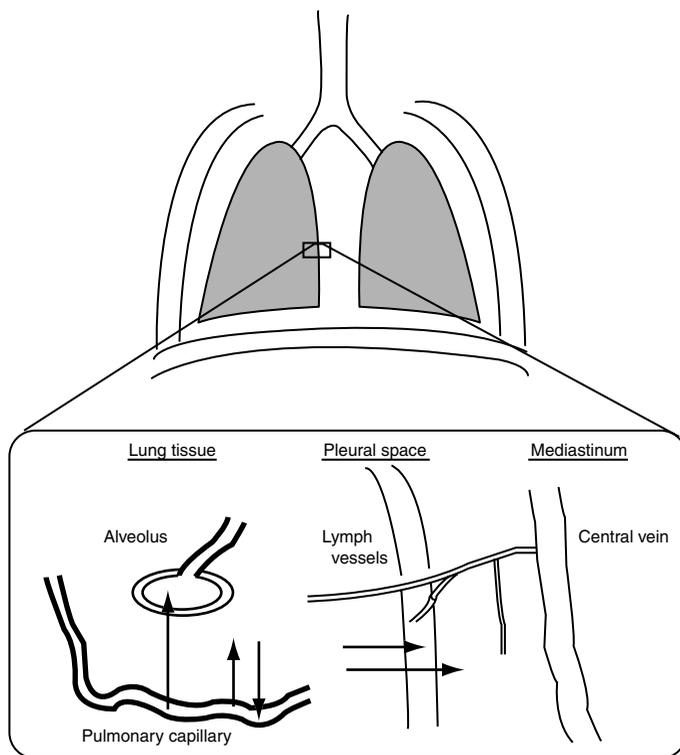


Figure 2 Pathways of filtered fluid from the intravascular to the extravascular spaces in the lung. *Source:* From Ref. 21.

exchange is to be expected. The lung is a little stiffer (or less compliant) as the interstitium becomes more and more filled with fluid. After this point, gas exchange is progressively impaired as EVLW is elevated. Clinically, the patient displays increased frequency of breathing and some degree of hypoxemia. Retention of carbon dioxide is a late phenomenon. Blomqvist attempted to correlate physiologic changes with the level of EVLW determined by indicator dilution in anesthetized dogs during the formation of HPE (23). No parameter closely reflected the level of EVLW. Even the degree of hypoxemia could vary greatly, depending upon the level of PEEP administered. Thus intrapulmonary shunting could be almost abolished by PEEP without a reduction in EVLW (3).

MEASUREMENT OF PULMONARY EDEMA

The amount of edema formed in the lung can be measured as the content of blood-free water outside the circulation (=EVLW). This way of defining EVLW does not permit a distinction between alveolar, interstitial, or intracellular water. EVLW can be estimated in several ways.

Gravimetry

The “gold standard” has traditionally been determined postmortem by gravimetric technique, gravimetric EVLW. Obviously, this can only be done once. Excised lung tissue is homogenized after adding water, causing total hemolysis. Residual blood content is estimated by determining the fraction of hemoglobin in the homogenate. Fractional water content is measured by drying the samples to constant weight, and in the end, EVLW can be calculated (24). Normal values obtained for healthy lung tissue are around 4 mL/kg body weight. Interstitial edema develops into alveolar edema in some lung regions at around 12 mL/kg, and values of 20 to 30 mL/kg are typically measured in severe pulmonary edema (22).

A more simple way of estimating edema of excised lung tissue is just to weigh the tissue sample promptly when it has been excised, and then again, when it has dried to constant weight. The wet weight/dry weight ratio will then give an indication of the degree of edema. However, blood leak and pooling are confounding factors.

Indicator Dilution Techniques

Typically, two indicators are administered in a central vein, which get mixed with the blood when passing through the heart, and then are detected on the arterial side, after they pass through the pulmonary circulation. In this way, the "mean transit time" for each indicator can be determined. For further details, see Ref. (25). A source of error with this technique is occlusion of pulmonary vessels, which leads to an underestimation of EVLW (26).

In systems using the so-called thermal-/dye-dilution technique, indocyanine green (ICG) is typically used as the intravascular marker. ICG binds to albumin and, therefore, remains in blood even during lung injury with increased permeability. It will mix with the blood in the pulmonary vessels, in the heart, and in the vessels between the lung and the sampling site. It thus gives an estimate of the "central blood volume," and part of it is pulmonary blood volume. Important information on the vascular filling can be obtained from this marker. It appears to be more valuable in determining whether the patient is hypo-, normo-, or hypervolemic than any vascular pressure recording (27), e.g., the recording of wedge pressure. Near ice-cold isotonic saline or glucose is used as a "negative heat" indicator that is not limited to the circulating blood but also penetrates the surrounding tissue. The "negative heat" or "cold" diffuses more rapidly into the lung tissue than any other potential marker of the extravascular space (Fig. 3) (28). These indicators have been either measured intravascularly in the arterial system with catheter-placed sensors, or withdrawn into an extracorporeally placed cuvette and then detected (29). If the indicators are measured at different sites, e.g., the heat intravascularly and the green dye in a cuvette, it is important that the delay of the green dye signal is corrected for. Another potential source of error is inability to correctly detect the onset of the dilution curve. Because the curves have less amplitude at high cardiac output because of greater dilution, such an error may become more prominent at high flow than at low. A combination of these sources of error may be the explanation for the cardiac output dependency that has been reported for a frequently used commercial system (30). A later system employs a fiberoptic thermistor-tipped arterial catheter, detecting both indicators intravascularly. This system does not display the same cardiac output dependency (30).

In a system using deuterium and dye, arterial blood is withdrawn into an extracorporeal cuvette, which allows for real-time detection of both indicators (31). A possible source of error in any thermistor-based system is the response time characteristics of the thermistor probe, which does not allow for real-time measurements and instead requires assumptions or mathematical corrections. This has been suggested as an obstacle for obtaining reliable EVLW measurements with a thermistor-based technique (32).

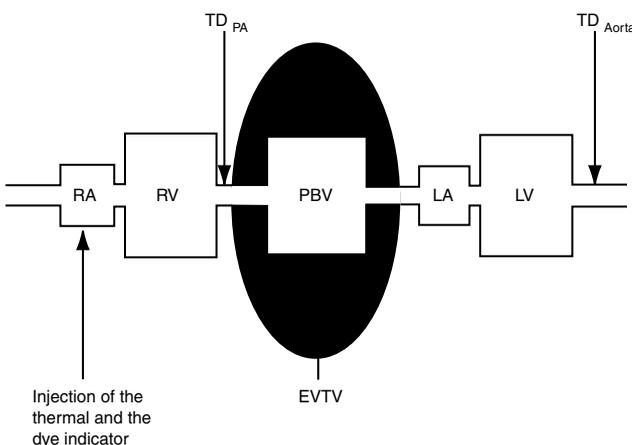


Figure 3 Schematic drawing of the cardio-pulmonary system in the recording of central blood volume and extravascular lung water. The indicator dye is determined simultaneously at the corresponding point in the descending aorta. *Abbreviations:* RA, right atrium; RV, right ventricle; PBV, pulmonary blood volume; EVTV, extravascular thermal volume; LA, left atrium; LV, left ventricle; TD_{PA}, thermodilution measurement in the pulmonary artery; TD_{aorta}, thermodilution measurement in the aorta. *Source:* From Ref. 29.

Radiological Techniques

Conventional X Ray

The radiological features on plain chest film permit a relatively early detection of edema and a certain quantification (33). By using a "reading table," an increased level of objectivity can be produced (34). Experienced radiologists may be able to differentiate between different causes of edema by looking at the (i) distribution of edema, (ii) peribronchial cuffing, (iii) air bronchograms, (iv) septal lines, (v) vascular pedicle width, (vi) azygos vein width, (vii) pulmonary blood volume, (viii) pleural effusions, (ix) blood flow distribution, (x) soft tissue thickness, (xi) cardiac size, and (xii) lung volume (34). However, the correlation between edema evaluation from plain chest radiographs and that from other techniques such as indicator dilution has not always been good.

Computed Tomography

Computed tomography (CT) of the lungs allows a further analysis of the distribution of pulmonary edema and also a global quantification if the CT covers the whole lung. The basic principle is that the X-ray tube rotates around the body during a continuous exposure. A transverse image can then be reconstructed usually in a 512×512 matrix. Each picture element (pixel) in the matrix will receive an attenuation number on a scale that ranges from -1000 Hounsfield units (HU) (air) via 0 HU (water) to $+1000$ (bone). Collapsed lung tissue or flooded alveoli with no remaining air will thus have an attenuation number of approximately 0 HU. Poorly aerated tissue with, e.g., 20% air at 80% tissue corresponds to -200 HU. Well-aerated tissues will be found in the range of -500 to -900 HU (a lung region with 70% air corresponds to -700 HU) and overexpanded or hyperinflated lung regions have an attenuation value of -900 HU or lower. Aeration decreases down the lung such that the uppermost regions may have 90% air and the lowermost, barely 50% . By knowing the volume of a single pixel (normally a few milliliters) and summing up the gas and tissue volume of each pixel, the gas volume (FRC, if measured after a normal expiration) and tissue volume can be estimated. The tissue volume will thus comprise blood, dry tissue, and extravascular fluid. By comparing the tissue volume in a patient with suspected pulmonary edema with normal values, the excess tissue or edema can be determined (Fig. 4) (35,36).

It has been assumed that the sequence of fluid accumulation during acute pulmonary edema is quantal, i.e., an alveolus can exist only in one state of being, either air filled and expanded or fluid filled and collapsed (37). Wegenius et al. tested this assumption by analyzing CT scans of the chest in pigs on inspiratory and expiratory breath-holding at various degrees of oleic acid pulmonary edema (38). The ratio of the mean attenuation on inspiration to that of expiration was calculated and defined as an alveolar instability index. This index correlated well with EVLW measured by double indicator dilution technique ($r=0.98$). The technique may be cumbersome in clinical practice, but the good correlation with indicator technique supports the hypothesis of quantal behavior of the lung.

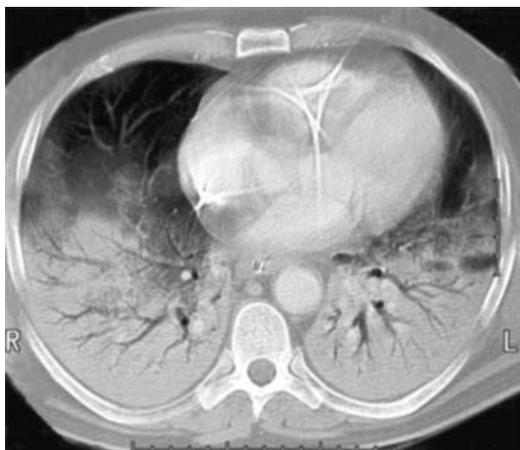


Figure 4 Computed tomography scan of the chest in a patient with acute respiratory distress syndrome. Note the densities in dependent parts of the lungs, indicating edema and consolidation. The larger airways are visualized by their aeration as compared to the surrounding collapsed and fluid-filled tissue ("air bronchogram"). Middle regions show "ground glass opacification."

Ground glass opacification has frequently been used as a sign of early pulmonary edema. Morphologically, ground glass opacification corresponds to alterations in lung parenchyma that are below the spatial resolution of a CT scanner. In pulmonary edema, it is caused by increased fluid volume in either the interstitial or the alveolar compartment of the lung parenchyma, or in both. A close correlation between the appearance of ground glass opacification on thin-slice high resolution CT and a rise of pulmonary capillary pressure above the critical pulmonary capillary pressure has been demonstrated (39). The critical pulmonary capillary pressure was calculated from the colloidal osmotic pressure [critical pulmonary capillary pressure = $1.55 \times$ colloidal osmotic pressure -6.8 (pressure expressed in mmHg)].

It may thus be concluded that CT strengthens the subjective evaluation of the pulmonary edema as compared to conventional chest X ray. More importantly, it enables a quantitative evaluation of excess tissue that in most cases will reflect edema.

Magnetic Resonance Technique

Magnetic resonance imaging (MRI) can be used to evaluate the lung water content qualitatively and quantitatively. However, the application of MRI to the lung parenchyma has been hampered mainly by three factors: (i) low proton density resulting in a low signal-to-noise ratio, (ii) signal loss due to physiologic motion (cardiac and respiratory movement), and (iii) susceptibility artifacts because of multiple air-tissue interfaces. However, there is also the advantage of different spin and relaxation characteristics of different edemas. Thus, the so-called T1 relaxation time was significantly longer in HPE than in controls, whereas the T2 relaxation time was not different. This differs from the permeability pulmonary edema, where both T1 and T2 relaxation times were significantly longer. Good correlations between T1 and T2 and the EVLW in rats as well as in isolated human lungs have been demonstrated. It may thus be concluded that MRI offers unique possibilities to study the distribution of edema, to quantify the amount of edema, and even analyze causes of the edema. However, at present, the availability of the technique is limited [for a review, see Ref. (40)].

Isotope Techniques

Various markers have been labeled with isotopes to quantitate the severity and cause of pulmonary edema. The difference in the distribution volumes between one marker that can diffuse from the vascular into the extravascular space and another marker bound to the vascular space will yield the EVLW. The measurement is thus based on the same principle as for thermal dilution. 125 Iodine-antipyrine or 125 iodine has been used to estimate the total EVLW, and 99 technetium-labeled red cells or 125 iodine-albumin have been used to evaluate pulmonary blood volume. These isotopes can be detected by a standard gamma camera, and correction for uneven attenuation by body tissue and varying distance to the radiosensitive crystal can be made by an external ring of radioactive source that produces a transmission scan (41).

Even more advanced and accurate measurements can be made by positron emission tomography (PET) that allows measurements of the regions blood volume, blood flow, and EVLW by using intravenous H_2^{15}O and inhaled CO^{15}O (42). However, complicated and expensive technique and limited availability make isotope measurements for the assessment of lung water of limited interest.

The strength of isotope techniques may rather be the possibility to detect changes in pulmonary microvascular permeability. This can be achieved by labeling small proteins with an isotope and measuring the accumulation of intravenously injected substances in the lung tissue by external counters or a gamma camera. $^{99\text{m}}$ Technetium-labeled albumin or $^{113\text{m}}$ indium-labeled transferrin have been used in different studies. Interested readers can refer to a comprehensive review by Groeneveld (41).

Impedance Measurements

Transthoracic monitoring of the impedance of the thorax is a technique that may detect an accumulation of fluid in the lung, whether the fluid is intra- or extravascular (43). A drawback with this technique has been large variations already at baseline and a dependence on the distribution of edema (28). The impedance will also depend on the gas volume in the lung so that any change in FRC, e.g., by the application of PEEP, will change the impedance. Another problem with the technique is a zero drift that is, at least in part, due to variation

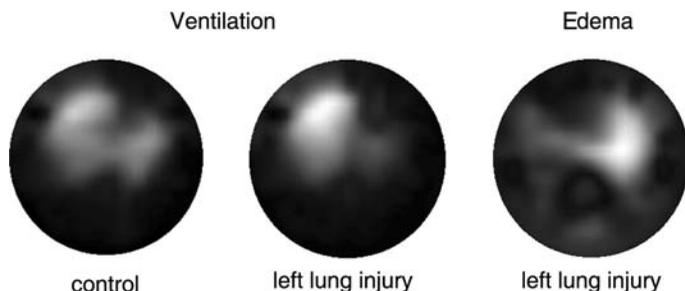


Figure 5 Functional electrical impedance tomography images of regional lung ventilation, before and after oleic acid–induced left lung injury (*left and middle panels*), and the distribution of edema between the right, “healthy,” and the left, injured, lung (*right panel*). The pig was mechanically ventilated, tidal volume was 500 mL, and a positive end-expiratory pressure of 5 cmH₂O had been applied. *Source:* Based on material presented in Ref. 45. Photos courtesy of Mr. Inez Frorich, University of Göttingen, Göttingen, Germany.

in the skin-to-electrode impedance. This has been claimed to be overcome by applying an algorithm that subtracts the skin-to-electrode impedance from the remaining impedance that is called the internal thoracic impedance. Commercial equipment that includes this algorithm has been developed (44). It may be concluded that the recording of changes in fluid accumulation in the lung by thoracic impedance measurements rests on a rather simple and sound principle. The use of the same equipment for assessing stroke volume and cardiac output requires many more assumptions that will render the result much less reliable.

The thoracic impedance can be measured with a few electrodes applied to the chest in order to give a single-value impedance value. The technique has been developed further, and transverse images of the thorax can be reconstructed by applying a number of electrodes around the chest. Thus, Hellige and coworkers have developed an electrical impedance tomography (EIT), and the method has been used to monitor experimental as well as clinical lung injury (45). The technique is based on the application of 16 electrodes attached on the thoracic circumference and applying a current to varying pairs of electrodes and using the other ones for voltage measurements, a cross-sectional reconstruction of the distribution of the impedance can be made. The distribution of fluid can thus be assessed. Moreover, by repeating the measurements rapidly over a breath, the distribution of the tidal volume can be evaluated. This enables the detection of nonaerated consolidated lung regions, which makes the EIT an interesting technique with potential clinical value (Fig. 5).

CONCLUSION

Development of pulmonary edema continues to be an important and life-threatening clinical condition. The resolution of HPE is often rapid but to some extent dependent upon extrapulmonary factors such as heart and kidney functions. High-permeability-type pulmonary edema resolves more slowly and is characterized by a complex inflammatory process in the lung. The prognosis is less favorable, and the syndrome requires the application of an array of diagnostic and therapeutic resources. It is obvious that understanding of the mechanisms of edema formation and the resolution of edema is a prerequisite for successful treatment. Moreover, knowledge of available techniques for diagnosis and quantification of edema is mandatory for the institution and monitoring of such treatment.

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7 Intravascular Volume Assessment in the Critically Ill Patient

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INTRODUCTION

Clinical assessment of intravascular volume is of paramount importance in the management of critically ill patients. Intravascular volume assessment relies on physical examination findings, weight measurements, and urine output as a means of determining a patient's fluid status. While this approach provides a global evaluation of intravascular volume, overreliance on physical examination findings in a critically ill patient may be misleading (1,2). Furthermore, lack of data regarding individual organ perfusion and function limits the use of the physical examination as an accurate assessment of a patient's volume status. Consequently, invasive hemodynamic monitoring using pulmonary artery catheters has been incorporated and accepted as an integral part of intensive care medicine. While pulmonary artery catheters are being widely used in many intensive care units (ICUs), concern has been raised regarding the lack of improvement in patient outcomes (3–5). An observational study involving over 5700 critically ill medical and surgical patients raised issues related to use of the pulmonary artery catheter and patient safety (6). Various reports have indicated that potential problems with the use of the pulmonary artery catheter may be related to patient selection and data interpretation (7–11). Furthermore, a recent, prospective randomized trial reported no benefit to therapy directed by the pulmonary artery catheter compared with standard care of elderly, high-risk surgical patients (12). Therefore, there is a need for novel, alternative techniques that will complement bedside findings and thereby provide an improved means of assessing intravascular fluid in critically ill patients (13). The following review will examine currently available devices and techniques to directly or indirectly determine intravascular volume status in critically ill patients.

TRANSESOPHAGEAL DOPPLER ECHOCARDIOGRAPHY

Echocardiography is a promising, noninvasive method of assessing left ventricular performance in critically ill patients (14). Transthoracic echocardiography has been commonly employed as an initial imaging modality, given its noninvasive nature. Yet, there are limitations to the use of transthoracic echocardiography, including a limited role as an intraoperative monitor during cardiothoracic surgery and suboptimal views in patients with obesity, chronic lung disease, bandages, or extensive burn injuries. Therefore, transesophageal echocardiography has become a popular intraoperative method of evaluating cardiac function, particularly during cardiac surgery and lung transplantation (15,16). First described in 1971, the transesophageal Doppler has undergone modifications, allowing it to be used as a continuous monitor of cardiac function (15). Use of the Doppler technique depends on measuring changes in reflected sound waves directed at blood flowing through the descending aorta. Given that aortic blood flow is pulsatile, changes in blood velocity from the onset of flow to the termination of flow over time may be calculated as the area under the velocity–time curve. Subsequently, stroke volume may be calculated as the product of average blood velocity, ejection time, and the cross-sectional area of the aorta. With this information, cardiac output may be calculated by multiplying stroke volume and heart rate. Consequently, stroke volume may be monitored continuously during the course of several hours, thereby providing instantaneous information regarding left ventricular preload. Stroke volume measurements may be obtained at the mitral or aortic valve or left ventricular outflow tract. Transesophageal

probes may be placed both through the oral or nasal route, and in the adult, the ideal location is between the fifth and sixth rib or 30 to 40 cm from the incisors. At this level, the esophagus is parallel to the aorta and the proximity of the esophagus to the aorta provides a good imaging window. Placement of the esophageal probe is reported to be safe and easy. However, there are contraindications to placement of an esophageal probe, which include the presence of esophageal varices, stricture or tumor, acute esophagitis, and recent esophageal or upper airway surgery.

A good correlation has been established between cardiac output measured by esophageal Doppler compared with pulmonary artery catheter thermodilution and Fick techniques (17–23). Doppler echocardiography has been described to assess left ventricular filling and estimate left ventricular preload (17,20,24). Doppler waveform analysis involves measurement of the peak-flow velocity signal that reflects myocardial contractility. Furthermore, measurement of flow-time or left ventricular ejection time corrected for heart rate provides an estimate of preload, and has been reported by several investigators (17,20,24). Recently, a study in a small group of critically ill surgical patients reported a better correlation between the flow-time method and cardiac output compared with measurement of pulmonary artery occlusion pressure (25). Clinical application of the esophageal Doppler technique as a means of assessing patient outcomes have reported favorable results in elderly patients undergoing hip surgery (25) and in cardiac surgery patients (26). A randomized trial involving 40 elderly patients undergoing hip surgery compared intravascular fluid administration using an esophageal Doppler-directed protocol and standard care (25). Patients randomized to the esophageal Doppler-directed protocol received more intravenous fluid and demonstrated higher cardiac outputs, yet exhibited similar blood pressure and heart rate. In addition, the median length of hospitalization was less for the esophageal Doppler-directed treatment group, suggesting an advantage to this technique. However, the findings of this investigation need to be confirmed, given the concern that the treating physicians were not blinded to the groups with respect to the amount of fluid administration. Feissel et al. evaluated esophageal Doppler measurements of stroke volume in 19 mechanically ventilated patients with sepsis and reported that respiration-induced fluctuations in stroke volume followed a similar response to pulse pressure variation following intravenous fluid administration (27). These reports provide support for clinical application of this monitoring device in fluid management.

Limitations to this technology have been reported and one potential source of error concerns Doppler estimation of cardiac output. Stroke volume calculations account only for the blood in the descending aorta and do not take into account blood distributed through the branches of the aorta. Approximately 70% of the measured stroke volume travels through the descending aorta, therefore this technique serves to estimate cardiac output (28). Although a correction factor may be added to address this discrepancy, the assumption of a constant proportion of blood flow to the descending aorta may not be valid during pregnancy, acute hemorrhage, aortic cross clamping, or lumbar epidural anesthesia (29–32). Another potential source for error lies with probe placement. Placement in the suprasternal, transesophageal, and transgastric regions has been described; however, to obtain an optimal signal, it has been recommended that the probe be placed 20 degrees to the axial flow (13). In addition, appropriate probe placement and interpretation of the Doppler signal requires training (33). Several authors have examined the role of intensivists and anesthesiologists in the use of Doppler echocardiography in the care of critically ill patients. These reports indicate that intensivists may acquire accurate and efficient skills required to use this technique (34–37). Finally, concerns have risen regarding the accuracy of stroke volume measurements, given that the aortic cross-sectional area used to calculate stroke volume may vary among patients and even within the same patient during different stages of an acute illness (28). Esophageal Doppler models measure cross-sectional aortic area by obtaining a single image at the commencement of the study, or by using a nomogram based on gender, age, and body surface area. However, use of a nomogram-based estimate may lead to an error, given the biological variation in the size of the aorta. Furthermore, changes in the tone and caliber of the aorta, which arise from volume infusion, the use of vasoactive agents, or aortic cross clamping, may lead to an error (21,38). This concern has been addressed with the development of a model containing a Doppler and an ultrasound probe that allows repeated measurements of aortic cross-sectional area and continuous assessment of aortic blood flow (22).

PULSE CONTOUR ANALYSIS

Initially described by Wesseling, arterial pulse contour analysis is a technique designed to continuously monitor left ventricular stroke volume (39). Pulse contour analysis is based on the assumption that assessment of the arterial pressure profile can be related to stroke volume. This technique estimates left ventricular stroke volume by taking into account the impedance of the aorta, which is reflected in the shape of the arterial pressure waveform. Pulse contour analysis uses an algorithm to compute the integral of the change in pressure from end-diastole to end-systole over time, divided by the systemic vascular resistance (Fig. 1). Systemic vascular resistance or aortic impedance is calculated using a transpulmonary thermodilution technique that has been validated as being comparable to pulmonary artery catheter thermodilution (40,41). The pulse contour analysis technique considers the shape of the systolic portion of the arterial waveform to be comprised of an interaction between cardiac contraction, blood flow, and the mechanical properties of the vascular tree (42). Furthermore, the vascular system may be viewed as a series of compliance and resistance vessels, and the impedance of the vascular tree may be expressed as a lumped variable describing the mechanical properties of various arterial beds. Thus, changes in the contour of the arterial waveform are a reflection of a change in cardiac contractility in relation to the changes in vascular impedance. In effect, pulse contour analysis provides continuous cardiac output monitoring using a properly placed arterial catheter. Importantly, the shape of the arterial waveform is dependent on the site of measurement, with the preferred site being the femoral arterial site. Another advantage of this technique concerns the ability to estimate intrathoracic blood volume and extravascular lung water as a surrogate of cardiac preload (13). Yet, concern regarding the utility of this methodology for daily use in critically ill patients has been raised (42). One concern surrounds the need for recalibration of the device following repeated thermodilution measurements, especially during episodes of hemodynamic instability (43,44). Yet, a recent report by Godge described the application of a pulse contour device containing a new algorithm in post-cardiac surgery patients requiring vasopressors to be reliable during changes in cardiac output (41). Another concern involves the concept that vascular impedance is not constant and is dependent on pressure and vascular tone (42). As such, the contour of the pressure waveform and cardiac output measurements may change with rapid changes in hemodynamics, as in patients with septic shock requiring vasoactive agents. Lastly, pulse contour analysis is semi-invasive, requiring the placement of a 4-French catheter in the femoral or axillary artery. These sites are preferable to more distal sites, because of diminished accuracy of the measurement obtained in peripheral arteries. While the conventional site for arterial catheter placement is the radial artery, measurements obtained at this site are unreliable, particularly in patients requiring vasopressors (41). Therefore, to maintain accuracy and precision, the manufacturer-recommended sites for arterial catheter placement are the femoral, axillary, or brachial sites. Presently, there is one commercially available pulse contour device that

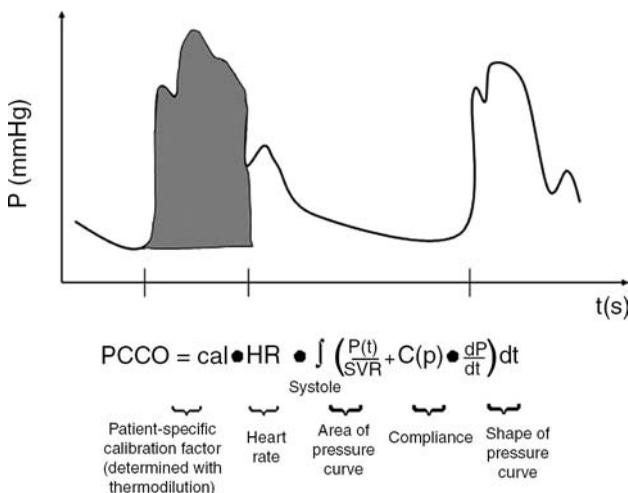


Figure 1 Graphical display using the shape of the pressure waveform and the area under the systolic portion of the pressure wave area. Below the graphical display is the mathematical formula for determination of PCCO. *Abbreviation:* PCCO, pulse contour cardiac output. *Source:* From Ref. 41.

measures cardiac output and intrathoracic blood volume (PCCO, Pulsion Medical Systems, Munich, Germany).

Pulse pressure contour analysis has been primarily evaluated in patients undergoing cardiac surgery (43–49). Comparison studies of pulse contour analysis and pulmonary artery catheter measurements of cardiac output have reported a good correlation between both techniques. A retrospective study of patients with ARDS compared pulse contour and pulmonary artery catheter measurements of cardiac output to be well correlated (48). Another study also demonstrated a close correlation with cardiac output obtained using pulmonary artery catheter and continuous pulse contour analysis (43,46). Concern about the diminished accuracy of pulse contour analysis with administration of vasoactive agents has been voiced, given that they may alter arterial vascular tone (49). A report by Godge evaluated a pulse contour device in 24 postoperative cardiac surgery patients receiving intravenous vasoactive agents and displaying large swings (greater than 20%) in cardiac output. In this report, they found the pulse contour analysis to be reliable during profound changes in cardiac output (41). However, further investigational studies are required to address the role of pulse contour analysis as a monitoring tool in patients with sepsis receiving vasopressors.

RESPIRATION-INDUCED CHANGES

Heart–lung interactions during the respiratory cycle produce phasic changes in left ventricular stroke volume such that the amplitude of the arterial waveform is diminished during inspiration and returns to baseline on expiration (50). These cyclic changes in stroke volume during mechanical ventilation are a function of the inspired tidal volume and intrathoracic pressure and have been recognized to produce fluctuations in vascular pressure measurements. The phasic changes in vascular pressures during the respiratory cycle are readily detected in central venous, pulmonary artery, and pulmonary capillary wedge waveform tracings. The mechanisms describing the heart–lung interactions occurring during mechanical ventilation are complex and have been reviewed elsewhere (51,52). Yet, in simple terms, mechanical insufflation and exhalation of the lungs have been noted to produce cyclic variation in left ventricular stroke volume and venous return, as observed in central venous and arterial pressure tracings. Consequently, the variation in the amplitude of the arterial pressure waveform is greater in volume-depleted patients and is reduced following intravascular fluid administration. Assessment of the respiration-induced changes in arterial pressure has been recognized as a dynamic measure of ventricular preload.

RIGHT ATRIAL PRESSURE

Measurement of right atrial pressure is frequently taken as a surrogate of right ventricular preload and used to monitor fluid resuscitation (53). Following a fluid bolus, changes in right atrial pressure are expected to reflect changes in left ventricular preload and function. The initial right atrial pressure is used to monitor intravenous fluid administration to hypotensive patients, with the expectation that this will reflect systemic hemodynamics. Unfortunately, this is frequently not the case. Although volume administration is expected to increase right atrial pressure, right ventricular end-diastolic volume, left end-diastolic volume, stroke volume, and cardiac output, the relationship between the right atrial pressure and the other variables is not linear. Furthermore, in critically ill patients, ventricular compliance may be altered by ventricular mass, cardiac ischemia, or ventricular stiffness (54,55). A recent review described results of several studies in which right atrial pressure was measured prior to and after intravenous fluid administration (56). Responders and nonresponders were defined as patients demonstrating an improvement in cardiac performance following intravenous volume expansion. Prior to volume expansion, right atrial pressure was lower in responders and nonresponders in two reports (57,58). However, other investigators reported right atrial pressures to be similar between responders and nonresponders prior to fluid administration (59,60). These contradictory findings may be attributable to differences in the type of fluid administered as well as the rate of volume expansion. Nonetheless, static right atrial pressure measurements do not appear to be discriminant of a patient's response to fluid administration. In contrast, dynamic or respiration-induced changes in right atrial pressure have been reported to predict the response to a fluid bolus (61,62). In spontaneously breathing patients,

Magder and colleagues reported that an inspiratory decline in right atrial pressure was predictive of the response to volume expansion. They reported an inspiratory decrease in right atrial pressure of 1 mmHg or greater to be predictive of an improvement in cardiac output following fluid challenge (61). Their findings were noted to have a positive predictive value of 77% or more and a negative predictive value of 84% or more. While promising, further investigation is required to determine the role of inspiration-induced changes in right atrial pressure as a means of determining fluid responsiveness.

SYSTEMIC ARTERIAL BLOOD PRESSURE

Respiration-induced variation in the arterial pressure has been reported as a clinical sign of a low intravascular volume (63). Subsequently, Perel et al. reported a close correlation between respiration-induced changes in systolic blood pressure and intravascular volume in mechanically ventilated animals undergoing graded hemorrhage (64). In this report, they also observed that the variation in systolic blood pressure could be minimized through fluid administration. More recently, respiration-induced variations in arterial blood pressure have been examined as a means of determining intravascular volume and thereby predicting the response to fluid administration (56). Accordingly, the variation in the arterial pressure has been separated into various components. Because systolic pressure variation is negligible during end-expiration, this is used as a reference point. With the end-expiratory systolic blood pressure as a reference point, the increase in systolic pressure (Δ up) and the maximal decrease in systolic blood pressure (Δ down) have been evaluated (Fig. 2). The total variation in systolic blood pressure is the sum of Δ down and Δ up, and the individual contribution during the respiratory cycle has been recently reported (50). In mechanically ventilated patients with septic shock, Tavernier et al. demonstrated a Δ down threshold value of 5 mmHg or more to significantly discriminate volume expansion responders and nonresponders (65a). Furthermore, a positive correlation ($r^2 = 0.58$) between baseline Δ down and the proportional increase in stroke volume following volume expansion was reported. Other investigators identified Δ down in mechanically ventilated patients undergoing aortic surgery or prostatectomy and reported a significant decline following fluid administration (66,67). Another variable is the pulse pressure variation, and several investigators have reported the changes in pulse pressure during mechanical ventilation (64,68). One report examined the utility of monitoring

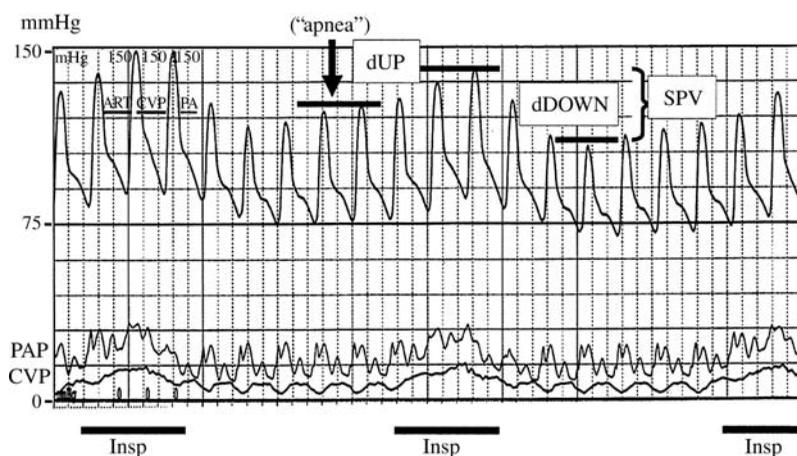


Figure 2 Arterial pressure changes due to respiratory variation. Systemic arterial blood pressure, pulmonary artery pressure and central venous pressure rise during inspiration and return to baseline during expiration. Systolic pressure variation (SPV) is the difference between maximum and minimum systolic arterial pressure during the respiratory cycle. The inspiratory rise in pressure relative to the value at end-expiration is dUp, and the fall in pressure relative to the end-expiratory value is dDown. The arrow indicating “apnea” represents the end-expiration value for determining dUp and dDown. The greater the dDown and SPV, the greater the predicted increase in cardiac output with volume loading. *Abbreviations:* PAP, pulmonary artery pressure; CVP, central venous pressure; SPV, systolic pressure variation. *Source:* From Ref. 65.

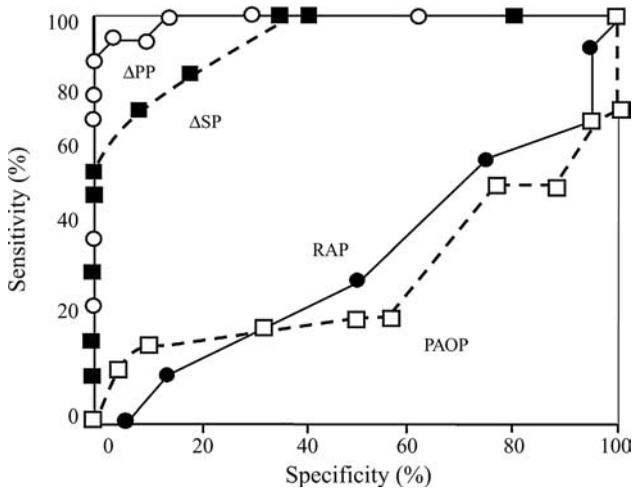


Figure 3 Receiver operating curve (ROC) comparing respiratory changes in pulse pressure (ΔPp), respiratory changes in systolic pressure (ΔPS), right atrial pressure (RAP), and pulmonary artery opening pressure (PAOP) after administration of intravascular colloid solution in 40 mechanically ventilated patients. Hemodynamic measurements following volume expansion were used to discriminate responders (CI increase $\geq 15\%$) and nonresponders. The area under the ROC curve for ΔPp was greater compared to ΔPS , RAP, and PAOP ($p < 0.01$). *Abbreviations:* ROC, receiver operating curves; ΔPp , pulse pressure; ΔPS , systolic pressure; RAP, right atrial pressure; PAOP, pulmonary artery opening pressure. *Source:* From Ref. 69.

the hemodynamic effects of positive end-expiratory pressure (PEEP) by measuring pulse pressure tracings obtained with an arterial catheter (68). They found that application of increasing levels of PEEP produced a decrease in cardiac output and greater pulse pressure variation. Moreover, the pulse pressure variation was diminished following intravenous fluid administration. Recently, the same group compared right atrial pressure, pulmonary artery opening pressure, and pulse pressure variation as a means of predicting the response to a trial of volume expansion in mechanically ventilated patients with sepsis (69). For the purposes of this study, a pulse pressure variation was defined as $\Delta Pp(\%) = 100 \times (Pp_{\max} - Pp_{\min}) / [(Pp_{\max} + Pp_{\min}) / 2]$. Michard and colleagues reported the changes in pulse pressure before volume expansion accurately predicted the effects of fluid administration. Furthermore, the changes in pulse pressure were more reliable indicators of fluid responsiveness than changes in right atrial pressure, pulmonary artery opening pressure, or systolic pressure (Fig. 3). Pulse pressure variation of greater than 13% discriminated between responders and nonresponders, with a positive predictive value of 94% and negative predictive value of 96%. An important point in measuring respiration-induced changes in systemic blood pressure concerns the need for deep sedation or temporary neuromuscular paralysis. Attempts to obtain these measurements in spontaneously breathing subjects have been reported to lead to inaccurate results (66). During spontaneous ventilation, variability in tidal volume, respiratory rate, and inspiratory and expiratory flow rates influences pulse pressure variation independently of the intravascular volume status. The magnitude of changes observed in Δ down, systolic pressure, or pulse pressure variation is affected by chest wall and pulmonary compliance, tidal volume, cardiac function, and intravascular volume status (70,71). In patients with cardiac arrhythmias, measurement of pulse pressure variations will not be accurate due to changes in stroke volume unrelated to the respiratory cycle. With these caveats in mind, this is an attractive method of indirectly assessing preload, as well as assessing cardiac performance following volume expansion (71).

CHEST RADIOGRAPHY

Portable ICU chest X rays account for a significant proportion of radiographic examinations in many U.S. hospitals. Furthermore, there is much information to be gleaned from serial examination of chest radiographs, and daily viewing has become an essential component of intensive care medicine (72–75). However, chest radiographs have been primarily employed to evaluate for placement of catheters and monitoring devices, as well as to assess for complications. Yet it was Milne et al. who described a novel application of the chest radiograph as a means of estimating intravascular volume. They reported that increases in intrathoracic blood volume correlated with widening of the vascular pedicle as a result of engorgement of the azygous vein and/or superior vena cava (76). Subsequently, they described the vascular pedicle to be the silhouette of the azygous vein, superior vena cava, subclavian artery, and aorta (77)

(Fig. 4). Application of this knowledge to the ICU led a group of investigators to describe an increase in the vascular pedicle width as a useful means of assessing intravascular fluid status in patients with extensive burn injuries (78). Other investigators have found changes in the vascular pedicle width to correlate with changes in intravascular volume status. After examining radiographic features and hemodynamic data in 100 critically ill patients, they reported that a vascular pedicle width greater than 72 mm improved their ability to interpret volume status in a given patient (Fig. 5) (79). More recently, a report described decline in vascular pedicle width to be associated with net fluid and weight loss in mechanically ventilated patients (80).

The vascular pedicle width is measured by dropping a perpendicular line from the point at which the left subclavian artery branches off the aortic arch (Fig. 4). A line is then drawn across the cardiac silhouette to the point at which the superior vena cava crosses the right mainstem bronchus. This horizontal distance is the vascular pedicle width. If the right border of the pedicle is difficult to visualize, the vertical lateral border of the superior vena cava or right brachiocephalic vein may be used to assess the vascular pedicle width (76). Although values for the vascular pedicle width have been reported, it should be stressed that use of absolute values may be misleading, and monitoring changes in the vascular pedicle width over time may be more useful (76,79,80).

Although this noninvasive technique is attractive, it has limitations. One limit concerns the method used to obtain the radiographic image and raises issues about technique standardization. Although much attention has been focused on technologic aspects, body position and mode of ventilation have been reported to alter appearance of the vascular pedicle and lung parenchyma. For example, the vascular pedicle width may increase when moving from upright to supine position, as well as during patient rotation to the right. To obtain comparable images, body position and mechanical ventilator parameters should remain constant at least at the time of obtaining the radiograph (81). Other clinical situations that may widen the vascular pedicle include recent cardiac surgery, prior mediastinal irradiation, obesity, and application of PEEP (82). Therefore, measurement of the vascular pedicle may not be feasible in these patients. A concern regarding this technique has centered on the issue that it does not directly measure intravascular volume, but rather indirectly determines blood volume. However, a good correlation has been reported between blood volume and vascular pedicle width (77). Measurement of the vascular pedicle as a means of estimating intravascular volume is promising, especially, given the wide availability and frequent use of the chest radiograph.

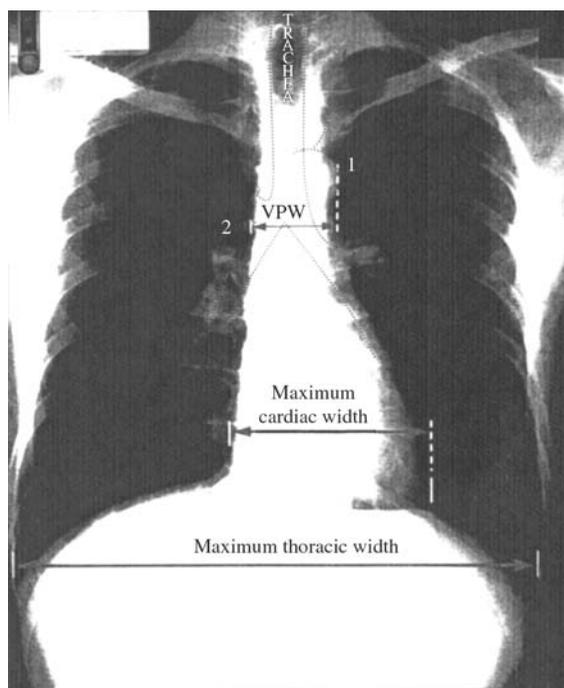


Figure 4 Representative image demonstrating landmarks by which to measure vascular pedicle width (VPW) on a chest radiograph. Point 1 represents the origin of the left subclavian artery as it exits the aortic arch. Point 2 indicates the superior vena cava crossing the right mainstem bronchus. VPW is determined as the distance between the perpendicular lines separating the two points. *Abbreviation:* VPW, vascular pedicle width. *Source:* From Ref. 80.

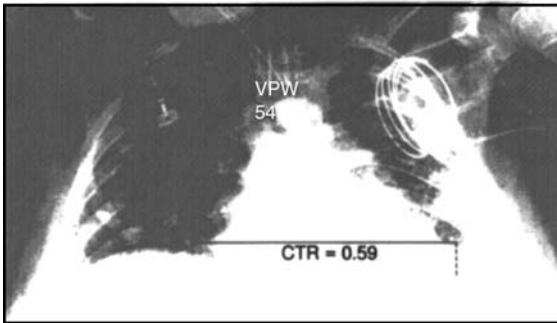
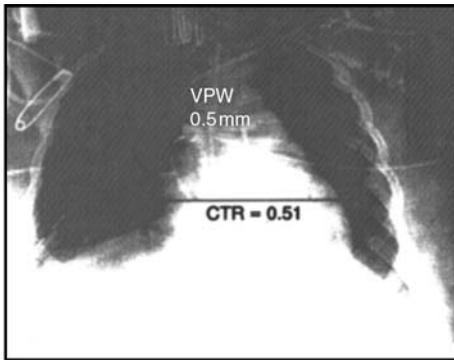


Figure 5 Representative portable, supine chest radiograph from a patient with acute lung injury. Vascular pedicle width (VPW) and cardiothoracic ratios (CTR) are depicted at presentation in the top figure. The bottom figure reveals a portable, supine chest radiograph from the same patient demonstrating a significant decrease in VPW and mild decline in CTR at day 5 after diuresis of 6.5 liters. *Abbreviations:* VPW, vascular pedicle width; CTR, cardiothoracic ratios. *Source:* From Ref. 80.

An algorithm has been proposed to apply measurements of the vascular pedicle width in the care of critically ill patients (82). An understanding of the simplicity of this technique and its limitations may provide information that can be incorporated into the daily care of critically ill patients. Finally, this technique is not meant to substitute for other methods of intravascular volume assessment, and only further study will determine its role in the ICU setting.

CLINICAL EVALUATION

Initial bedside approach to critically ill patients frequently requires incorporation of the medical history, physical examination, radiographic findings, and laboratory data to determine a patient's intravascular volume status. Physical examination should be the foundation, with focus being placed on general appearance, mentation, weight, heart rate, blood pressure, and urine output. Assessment of urine output and presence of edema and vital signs provides a platform for further decision-making. Unfortunately, many times, the amount of data to make a sound decision is insufficient. The clinician is faced with administering a fluid bolus or diuretic and waiting for the response to this therapy. As pointed out in a recent review, 40% to 72% of critically ill patients have demonstrated a significant improvement in stroke volume or cardiac output following a trial of volume administration (56). This range of uncertainty points out the need to predict which patients will benefit from a trial of volume expansion. This can be readily assessed with the use of an arterial catheter and sedatives to limit or prevent spontaneous respiration. Using the method described by Michard and others, respiration-induced changes in arterial blood pressure provide a reasonable estimation of left ventricular preload and stroke volume. One must be cognizant of the fact that large tidal volumes will produce greater swings in pulse pressure or Δ down variation. In addition, the change in pulse pressure variation may be related to the volume of fluid, rate of infusion, and type of fluid administered, and may likely influence the response. Atrial arrhythmias or frequent ventricular ectopy will make measurement of pulse pressure variation difficult. Echocardiography provides useful data regarding stroke volume and is more amenable to use in the operating suite where the device can be used continuously. Postoperative use of echocardiography may be limited by proper replacement of the probe and need for a qualified physician to interpret the images and be able to troubleshoot if any dilemmas arise. Unfortunately, many ICUs are not

equipped with personnel to place and interpret these images, and proper training is required. In the ICU, this technique becomes less attractive, given the need for operator expertise regarding interpretation and placement. Pulse contour analysis is not widely used in the United States, thereby limiting its utility. This method is appealing and may serve as an alternative technique to pulmonary artery catheter placement. Chest radiography, a well-established part of daily ICU management, might provide complementary information to the intensivist. The noninvasive nature and relative ease of measurement of the vascular pedicle width with current digital radiograph view monitors is complementary to contemporary critical care practice. Taking notice of a widening vascular pedicle over time, or measurement of a width greater than 70 mm in the absence of parenchymal infiltrates, may represent an increase in intravascular volume, thereby pointing out the need to evaluate fluid intake and output (82). Development of reliable, safe techniques to assess intravascular volume in critically ill patients will continue to be sought. However, application of new techniques such as chest radiography and pulse pressure variation may be quickly incorporated with current practice standards.

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8 Intravenous Access in Adults

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PERIPHERAL VENOUS ACCESS

Indications

Establishing and maintaining vascular access is one of the most common problems encountered in hospitalized patients and in patients presenting to physician offices, emergency departments, operating rooms, and procedure suites. While the use of central venous catheters has become more frequent, peripherally inserted intravenous lines (PIVs) remain the safest, easiest, and most common means of establishing vascular access. Vascular access is indicated for blood sampling, intravenous (IV) fluid administration, transfusion of blood products, and drug delivery, including glucose and electrolyte replacement (1,2).

Sites

Many factors affect the choice of sites for venous cannulation. The operative site may contraindicate the placement of venous cannula in one or more extremities. Patient factors, including patient preferences, may direct catheter placement. Ultimately, the availability of superficial veins is the most obvious and important factor dictating catheter placement (3).

Veins of the upper extremity, including those on the dorsum of the hand, the lateral forearm, and the antecubital space, remain the most common sites of cannulation. Occasionally, veins on the dorsum of the foot and saphenous veins can be used when upper extremity sites are unusable (3).

Most practitioners prefer to attempt cannulation at more distal sites and make subsequent attempts in more proximal sites if necessary. Antecubital veins and veins of the upper arm may be chosen initially if large bore access is required, especially during emergencies and rapid resuscitation. Peripherally inserted venous catheters may also be placed in the external jugular vein, veins of the upper chest wall, and veins of the scalp when no other sites are utilizable.

Catheters

The smallest device possible should be used to deliver IV therapy (4). Manufacturers market a number of peripheral devices, and clinicians should consider factors such as type and duration of therapy when making a selection. Currently, over-the-needle PIVs are the type most commonly used in clinical practice. These devices consist of a catheter over an internal stylet. The original catheters were made of Teflon, a stiff, fluorine-based plastic that can kink. Improvements in the quality and properties of polyurethane have resulted in a softer, high-strength material that becomes pliable once inside the vein (4). Additionally, smaller catheters will limit the contact between the catheter itself and the vessel wall. However, changes in the lumen size and catheter length can affect the flow rate. Thin-walled catheters can allow greater flow rates than thick-walled catheters of equal gauge. Therefore, smaller gauge thin-walled catheters are preferred. Flow rates greater than 1400 mL/hr can be allowed by 24-gauge thin-walled catheters or 22-gauge non-thin-walled catheters. These smaller catheters are usable in most clinical situations; however, they may not be adequate for perioperative care or resuscitative efforts when large volumes or high flow rates are necessary (4).

Techniques

Various techniques have been employed to facilitate IV insertion including the use of tourniquets, transillumination, and vasodilation. Tourniquets placed on extremities should be fitted tight enough to occlude venous return without jeopardizing arterial inflow. Transillumination of the palm of the hand has shown promising results in neonates and infants but has no demonstrable benefit in adolescents or adults. Vasodilation by application of topical nitroglycerin or warm compresses often aids in placement of IV catheters (5).

Complications

Peripherally inserted IV catheters may be used in more than 60% of hospitalized patients, and many patients develop complications associated with their use (6). Loss of patency secondary to clot formation, dislodgment with tissue infiltration, infection, and phlebitis are the most frequently encountered problems (1).

Loss of Patency

Currently, no consensus of opinion exists on how to best maintain catheter patency to minimize patient discomfort and limit costs associated with catheter replacement (1). Both heparin and normal saline have been employed as IV irrigants. While heparin has more benefit as an antithrombotic agent, its use has been linked to thrombocytopenia, hemorrhage, and development of phlebitis (2). Research suggests that flushing catheters with normal saline can reduce the cost of maintaining IV catheters and is not associated with thrombocytopenia, hemorrhage, or tissue damage. In randomized clinical trials, normal saline has been equally effective in maintaining catheter patency (7).

While literature provides substantial evidence regarding the type of irrigant solution that should be used, little information exists regarding the frequency of flushing or the volume of irrigant solution that is optimal to prevent complications. Most reviews suggest that the volume should be between 5 and 10 mL of irrigant solution, or a volume equal to twice the capacity of the cannula and add-on devices (8).

Additionally, no coherent recommendations exist on the frequency with which IV cannulas should be flushed. Most research recommend that catheters should be flushed after insertion, before and after administration of medications, and at least every eight hours if not in use (7). According to some reviews, catheters should be flushed a minimum of once every four hours for optimal care. In summary, no well-designed clinical trials exist to compare the effectiveness of the frequency of flushing catheters on common complications, particularly catheter patency and phlebitis (9).

Dislodgment

Infiltration or extravasation of fluids and drugs into subcutaneous tissues is a common problem with dislodgment of peripheral IV catheters (10). The dorsum of the hand has a subcutaneous space and a subaponeurotic space separated by an aponeurosis. Lymphatic drainage from this space can be compromised by extravasation of fluid into this space resulting in vascular compression and nerve injury, which ultimately require surgical decompression (3). Osmolarity can affect fluid extravasation because solutions with high osmolarity can damage capillary endothelium and cause increased permeability (11). Likewise, large volume resuscitation has been cited as a frequent cause of infiltration and compartment syndrome, especially in patients with a depressed level of consciousness. Certain medications, particularly phenytoin and chemotherapeutic agents, can cause severe complications such as necrosis and ulceration if extravasation occurs (3). Finally, delivery of IV fluids and medications through IV pumps is more likely to cause infiltration because the pumps will continue to deliver fluids even after catheter rupture or dislodgment (12,13). For this reason, a gravity drip is generally preferred in emergency departments or operating rooms.

Infection

Systemic infections occur primarily with the use of central venous catheters, but local-site infections occur much more commonly with peripherally inserted IV catheters (14). Patients who appear to be most likely to develop local infections include those at the extremes of age, patients who are immune suppressed, patients with ongoing infections from other

sources and receiving antibiotics, and those who have multiple invasive procedures or poor nutrition (14).

Infections around peripherally inserted venous cannula are associated with commensal skin flora. The most common organisms causing catheter-related infections are those that exist naturally on the skin, especially coagulase-negative staphylococci. Patients may infect themselves with their own flora or with a hospital strain. Health-care workers may also serve as a mode of transmission by passing organisms from other patients or staff in a process known as cross-infection or cross-contamination (15). In a susceptible host, the peripheral cannula serves as a portal of entry and an infection begins.

Apparently, different catheter materials have different susceptibilities to adherence and colonization by microbes. Polyurethane catheters seem to be associated with a lower risk of infection than Teflon catheters. After a catheter has been placed, the outer surface becomes coated with fibrinogen, collagen, and other glycoproteins (16). *Staphylococcus aureus* also adheres strongly to host proteins, after which it is shed into the blood as infective emboli.

Recent evidence shows that the hands of health-care workers are the most significant mode of transmission for infective organisms. Regular hand washing by all involved clinical personnel remains essential to preventing catheter-related infections (15). Despite the substantial body of evidence, noncompliance on the part of health-care workers with these recommendations persists. Published guidelines state that hand washing with a liquid soap is sufficient for most clinical activities. Wearing gloves will protect both patients and health-care workers themselves from cross-infection but should not be an alternative to hand washing.

Patients' commensal flora is also a significant source of infection. Some authors suggest that insertion of peripheral IVs should be considered a minor surgical procedure in the sense that hand hygiene and aseptic technique should be employed. Disinfection of the site with antiseptic solution is an imperative measure. Among antiseptic solutions, 2% chlorhexidine appears to be the most effective for immediately reducing transient flora and for long-term bacterial suppression (15).

Other ways to reduce infectious risk include selecting sites less associated with phlebitis, such as the antecubital fossa, and minimizing the number of skin punctures. Other guidelines recommend that infusion sets be changed every 72 hours when giving crystalloid and colloid solutions, but should be changed every 24 hours when administering blood, blood products, and lipid emulsions.

Dressing the IV site should allow for visual inspection of the site while minimizing the accumulation of moisture. Transparent polyurethane dressings have become the safest and most effective method for protecting catheter sites and minimizing infection. These dressings should be semipermeable to water, allowing patients to bathe without saturating the dressing. Gauze should not be used because it is not waterproof and does not allow for routine visual inspection of the site (6). Dressings should not be replaced unless they become soiled or loose allowing exposure to contamination.

Phlebitis

Up to 70% of patients with indwelling IV cannula develop inflammatory changes in the vein, a condition known as phlebitis. This condition may result from mechanical trauma, chemical irritation, or bacterial colonization. Regardless of the etiology, phlebitis can cause permanent damage to veins and incur significant morbidity while raising costs of one's hospitalization (4).

Phlebitis is an inflammatory condition of veins characterized by pain, edema, and erythema, which often appears as a red streak along the course of the vein. Injury to the endothelium of the veins causes release of inflammatory mediators such as histamines, bradykinin, and serotonin. These substances cause vasodilation and increased capillary permeability resulting in increased blood flow and leakage of protein and fluid from the intravascular space into the interstitial space. Simultaneously, inflammation triggers the coagulation cascade leading to thrombus formation and induration. Lastly, leukocyte activation causes pyrogenes to stimulate the hypothalamus, creating fever (4).

Many factors have been associated with an increased risk of phlebitis, such as increasing age, female gender, immunosuppression, neuropathy, peripheral vascular disease, larger and longer catheters, Teflon catheters, and catheters placed in veins in areas of flexion or over bony prominences (4,17).

Phlebitis secondary to mechanical trauma occurs when an intravascular cannula injures the vessel wall it is in contact with. Catheter size, material, location, and duration can all affect the development of phlebitis. To minimize the contact between catheter and vessel wall, the smallest acceptable catheter should be used. However, small changes in the lumen size and catheter length can greatly change the flow rate as governed by Poiseuille's Law of flow through a tube, i.e., doubling the internal radius increases the flow rate by a factor of 16, whereas doubling the length cuts the flow rate in half. Also, thin-walled catheters can allow greater flow rates than thick-walled catheters of equal gauge. Therefore, smaller gauge thin-walled catheters are preferred. Flow rates greater than 1400 mL/hr can be allowed by 24-gauge thin-walled catheters or 22-gauge non-thin-walled catheters (4). While these catheters are not appropriate for intraoperative use or use in trauma resuscitation, they can be used in most clinical situations. Other studies have reported that polyurethane catheters create less friction and therefore are less likely to cause phlebitis than polytetrafluoroethylene catheters and are also more resistant to infection (4).

Many recommendations exist to reduce the likelihood of developing phlebitis. Catheters should not be placed over bony prominences, in veins that feel hardened, at points of flexion, or at points of bifurcation or valves. New lines should not be placed within 3 in. of previous insertion sites, and should always be started more proximally. According to the Centers for Disease Control and Prevention, peripheral IVs should be replaced at least every 96 hours, even if no problems exist, and if mechanical complications do exist, then the catheter should be removed followed by application of warm, moist compresses to the site (18).

Chemical phlebitis is caused by infusion of agents that injure the vascular endothelium. In this situation, the inflammation occurs along the course of the vein beyond the tip of the catheter. Vascular damage usually occurs due to infusion of substances whose pH or osmolality varies significantly from that of blood. With slower flow rates, mixing takes place more slowly and neutralization by blood buffering systems takes longer, making the chances of phlebitis greater. Substances with osmolalities less than 450 mOsm/kg pose the lowest risk of phlebitis, with substantially higher risk occurring as the osmolality increases to greater than 600 mOsm/kg. Infusion Nursing Society recommendations state that central lines should be placed for infusions with osmolalities greater than 500 mOsm/kg (19). Finally, many drugs are associated with chemical phlebitis, including the cephalosporins, erythromycin, nafcillin, oxacillin, acyclovir, and amphotericin (4). If chemical phlebitis is suspected, the cannula should be removed and warm compresses should be applied. The infusion should be restarted in another site if possible, and the solution can be diluted to minimize the risk.

Bacterial phlebitis occurs when microorganisms are introduced at the insertion site or through the IV tubing or catheter itself. In addition to pain, erythema, and edema, bacterial phlebitis may present with expression of purulent exudates or with fever and leukocytosis. Prevention of infection requires strict adherence to aseptic techniques during venous cannulation, proper hand washing and no disruption of the integrity of the IV solution or infusate (4,6). Should bacterial phlebitis be suspected, the catheter should be completely removed and a new one replaced in the contralateral extremity if possible.

CENTRAL VENOUS CATHETERS

Indications

Peripherally inserted venous lines are the most common form of intravascular access devices used in hospitalized patients. However, an increasing number of patients require placement of central venous catheters for their clinical management. Indications for central venous lines include administration of specific drugs such as antibiotics and vasoactive infusions, delivery of parenteral nutrition, hemodialysis, hemodynamic monitoring, and the inability to attain peripheral IV access (20). Certainly, the most common sites of placement for central venous lines are the internal jugular (IJ) vein and the subclavian vein; yet placement of central lines in the femoral vein remains a popular choice in other circumstances.

Internal Jugular Vein

Successful cannulation of the IJ vein relies on an understanding of the neck anatomy and familiarity with the multiple described approaches to catheterization. The IJ vein lies lateral to the

carotid artery at the level of the thyroid and cricoid cartilage. From there, it passes beneath the sternocleidomastoid muscle and through the apex of the triangle formed by the heads of the sternocleidomastoid muscle and the clavicle, then passes posterior to the clavicle to join the superior vena cava (SVC) at the junction of the SVC and subclavian vein. IJ vein catheterization may be difficult in obese patients with poorly defined landmarks. Numerous approaches to cannulation of the IJ vein have been described, but the three used most commonly in clinical practice are the high anterior, low anterior (apical), and posterior approach. In the high anterior approach, a needle is introduced at the level of the thyroid or cricoid cartilage immediately lateral to the carotid pulse and medial to the medial border of the sternomastoid muscle. The needle is held at a 30° angle to the skin and directed toward the ipsilateral axilla or ipsilateral nipple. If the vein is not encountered, subsequent attempts should be made using the same entry point but directing the needle more medially. In the apical or low anterior approach, a needle is introduced lateral to the carotid pulse and just superior to the apex of the triangle formed by the medial and lateral heads of the sternocleidomastoid muscle and the clavicle. The needle is directed at a 30° angle with the skin and toward the ipsilateral nipple, with subsequent attempts made with the needle directed more medially. In the posterior approach, the needle is introduced at the level of the cricoid cartilage and below the sternocleidomastoid muscle, and is then directed toward the sternal notch. No method has proven more successful than another, and the choice of insertion technique depends more on operator experience than the method of cannulation.

Subclavian Vein

The subclavian vein is almost always catheterized using an infraclavicular approach. The subclavian vein originates from the axillary vein where it crosses the lateral border of the first rib and is situated just below the clavicle. For catheterization, a shoulder roll is placed longitudinally between the scapulae and the patient is placed in slight Trendelenburg position. A needle is inserted approximately 2 cm caudal to the clavicle in the deltopectoral groove or at the junction of the middle and medial thirds of the clavicle. The needle is maintained parallel to the ground and directed toward the sternal notch with the bevel up. Once the clavicle is encountered, the needle is withdrawn slightly and passed just below the edge of the clavicle and advanced toward the sternal notch while gently aspirating. If the vein is not encountered, the needle should be directed slightly more cephalad on subsequent attempts.

Femoral Vein

Cannulation of the femoral vein is a useful alternative to IJ or subclavian vein catheterization when these sites are unavailable or difficult. The femoral vein lies approximately 1 cm medial to the femoral artery in the inguinal region. For catheterization of the femoral vein, the patient is placed in the supine position. The femoral artery is palpated 1 to 2 cm caudal to the inguinal ligament. A needle is inserted 1 cm medial to the femoral artery, held at 30° to the plane of the skin, and directed toward the umbilicus. Subsequent attempts should be made by fanning the needle slightly medially, and then laterally, until the vein is encountered.

Ultrasonic Locating Devices

Central venous catheters are traditionally placed using anatomic landmarks as described in the previous discussion. The variable rates of failure and complications from central venous line placement are still a significant source of morbidity, increased costs, and patient discomfort. Anatomic anomalies may make cannulation difficult, and vessel thrombosis can preclude cannulation regardless of anatomy. Additionally, patients with concomitant disease, especially the critically ill, can have dire consequences from failed attempts at central line placement. Therefore, successful cannulation of the vein on the first attempt is ideal.

Ultrasound devices that are operator friendly and readily transportable for bedside use have been developed. The devices can be used to locate veins in two ways. Real-time ultrasonography generates a two-dimensional image of the vein and surrounding structures, while continuous wave Doppler ultrasound generates audible sounds from blood flow within the vein (21). Recent clinical trials have compared the success of central venous catheterization using ultrasound-guided techniques versus traditional landmark methods. A systematic review of these trials has shown a clear benefit for using these ultrasound-guided techniques.

The important benefits are a lower failure rate overall, more first attempt success, and fewer complications. The ultrasound device defines the position of the vein with respect to the surrounding structures. Additionally, the device can assess the patency of the vein or the presence of a thrombosis, which would make cannulation potentially difficult or impossible. The ultrasound device showed the greatest benefit in IJ vein cannulation, followed by subclavian vein and then femoral vein (21). Certainly, practitioners need to familiarize themselves with these ultrasound devices because they have become more inexpensive and more available, and liability associated with complications from central line placement is costly and becoming unjustifiable. Nonetheless, landmark methods need to be well understood for use in emergencies and circumstances where ultrasound guidance is unavailable (22).

Choice of Sites

Many factors affect the decision of where to place a central venous catheter. The experience of the practitioner, patient preference, anatomic landmarks, operative site, availability of central veins, and other patient comorbidities may dictate the site of central line placement. Accessing the IJ vein may be difficult in patients who are obese or in those who have difficult anatomic landmarks. The IJ vein may not be available for access in trauma patients or in patients in cervical collars where manipulation of the cervical spine is not warranted. IJ catheters are more likely to become infected in patients with a tracheotomy. Placement of IJ catheters may not be advisable in some neurosurgical patients where venous outflow may be compromised or when neck exploration may become necessary, such as during aneurysm clipping. The IJ vein may be the best choice in coagulopathic patients, because the vessels of the neck are the most compressible in the event of arterial puncture or hematoma formation (23,24).

The subclavian vein is the site with the lowest infectious rate and is generally considered the most comfortable for patients; therefore, it is the best choice for long-term use or administration of parenteral nutrition. The subclavian vein should be avoided in patients with severe hypoxemia, when pneumothorax may be fatal. Additionally, the subclavian vein is usually spared in dialysis-dependent patients because thrombosis in this area may compromise future dialysis access. The femoral vein is often chosen for initial resuscitation of trauma patients because of the speed with which it can be placed, and the site is generally free while advanced cardiac life support maneuvers are being performed in the head, neck, and chest area. Femoral cannulation can be complicated by retroperitoneal hematoma and should be avoided if possible in coagulopathic patients; patients with contaminated inguinal regions are at high risk for catheter-related bloodstream infections (24).

Complications

Mechanical

The majority of mechanical complications occur during placement of central venous catheters, while infectious and thrombotic complications occur with indwelling lines. The most common mechanical complications upon insertion of central venous catheters include arterial puncture, hematoma, pneumothorax, hemothorax, and nerve injury (20). The overall risk of mechanical complications is the same in IJ catheterization and subclavian catheterization. Many large-scale retrospective analyses have shown the risk of pneumothorax to be equal in IJ and subclavian catheterization (20). Mechanical complications, especially arterial puncture and hematoma formation, are most common during femoral cannulation. Most arterial punctures can be recognized by the aspiration of bright red blood in the syringe. In patients with hypoxemia or hypotension, where color changes and pulsatile flow may not be obvious, connection of the catheter to a pressure transducer can confirm venous cannulation (24). The use of ultrasonic locating devices has been shown to reduce the frequency of mechanical complications from central line placement.

Infection

The rate of suspected or confirmed catheter-related bloodstream infections is highest for femoral catheters and lowest for subclavian lines. Clinical trials have shown a lower rate of catheter-related bloodstream infections with the use of antimicrobial-impregnated catheters. Among them, catheters impregnated with chlorhexidine and silver sulfadiazine and catheters impregnated with minocycline and rifampin are the most frequently used (24).

The development of resistant microorganisms from the use of these types of catheters has yet to be elucidated. Prevention of infection begins with full barrier precautions upon insertion, which include mask, cap, gown, gloves, and a full sterile drape. Skin preparation with chlorhexidine solutions as opposed to iodine solutions may be more efficacious at preventing catheter-related infections. The routine use of prophylactic antibiotics for line insertion cannot be justified secondary to concerns about the proliferation of antibiotic-resistant organisms. Despite these precautions, catheter-related infections still occur. If catheter-related infections are suspected, blood samples for culture should be drawn to assess for the presence of bacteremia. Purulence or erythema at the insertion site necessitates that the catheter be removed. Signs or symptoms of systemic sepsis are an indication for empiric antibiotic therapy for treatment of infection caused by *Staphylococcus epidermidis* or *S. aureus*. Gram-negative coverage should be included in immune-suppressed patients and in those with neutropenia. Once antibiotic therapy has begun, the catheter can be changed over a wire. In patients with septic shock and no other infectious etiology, the catheter should be removed and replaced at another site. If a culture from a catheter tip that has been changed over a wire is positive, then the catheter should be pulled and a new one replaced at another site. If the catheter-tip cultures are negative, then another source of infection is more likely (24).

Thrombosis

Patients with indwelling catheters are at high risk for thrombotic complications, many of which are directly attributable to the catheter itself. The risk of catheter-related thrombosis is correlated with the insertion site. The highest percentage occurs in femoral catheters and the fewest occur in subclavian lines (25). With all catheters, these thromboses have the potential to embolize, the more frequent complication is the inability to cannulate these vessels in subsequent attempts.

Care

Proper maintenance of central venous catheters and insertion sites may minimize the risk of catheter-related complications. Routine application of topical antibiotics to insertion sites has not been shown to reduce the rate of bloodstream infections and may promote the growth of resistant bacteria and fungi (26). Currently, no strong evidence favors the use of gauze versus transparent dressings, nor can any recommendations be made regarding the frequency of routine dressing changes. Regardless, routine visual inspection for the presence of erythema or pus, and palpation for insertion site tenderness should be the standard care for any indwelling catheters. The catheter hub is a common source of infection. These catheter hubs should be changed routinely, probably at least every three days, to reduce the incidence of catheter-related bloodstream infections. The risk of catheter-related infections goes up substantially after five to seven days of catheterization. However, trials requiring the routine exchange of catheters over wire have not shown a decrease in catheter-related infections, while replacement of catheters at new insertion sites is likely to result in increased numbers of mechanical complications. Catheters should be removed after they are no longer needed to reduce the likelihood of catheter-related infections, which increases over time.

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9 Vascular Access in Children

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INTRODUCTION

Vascular access is indicated in most infants and children undergoing anesthesia. A common exception is the well-hydrated child undergoing a very brief procedure (e.g., myringotomy). In general, vascular access is used to administer fluids and drugs in the perioperative period when the oral route is unsuitable or contraindicated. A vascular cannula also can be used for blood sampling and pressure monitoring. In healthy children undergoing inhalation anesthesia, it is customary to obtain vascular access after induction. However, vascular access should be obtained prior to induction in children requiring fluid resuscitation, when rapid-sequence induction is planned, and in children who prefer intravenous induction of anesthesia.

The ability to establish vascular access in infants and small children is one of the important skills that distinguish the pediatric anesthesiologist. Even with recent improvements in catheter design and the availability of small-size catheters, some patients may still be very challenging.

PERIPHERAL VENOUS ACCESS

Indications

Peripherally inserted intravenous (IV) catheters are most commonly used for short-term needs, such as during routine surgical procedures. IV lines provide access for administering fluids, drugs, electrolytes, glucose, blood products, and pain medications in the perioperative period. In the child who has a full stomach necessitating a rapid sequence induction and the child who refuses mask induction, IV placement is performed before induction of anesthesia. Children who require sedation for radiologic procedures with injected contrast, or minimally painful procedures, often require IV placement to allow administration of sedatives and analgesics.

Percutaneous

The fastest and safest approach for routine IV access in children undergoing surgery is to introduce the catheter percutaneously after inhalational induction of anesthesia. Direct visualization or palpation of veins and adjacent landmarks are common techniques used in children to identify appropriate sites for peripheral venous access. Veins on the dorsum of the hand and feet are often used in infants and small children for percutaneous venous cannulation. There are some sites in infants and chubby children that can be accessed blindly by palpating a vein even though the veins may not be visible. The saphenous vein lying superficial and anterior to the medial malleolus, and the wrist vein on the radial bone proximal to the anatomic snuffbox are two examples of these sites.

Choice of Sites

The sites chosen for venous cannulation depend on the site of the operation and the availability of the superficial veins. Prior to venous cannulation, it is helpful to determine which hand, the left or the right, the child prefers to have free in the immediate postoperative period. This allows one to avoid placing the IV in the favored hand, which the child uses for thumb sucking, drawing, or playing. Children who require long-term IV lines for alimentation and the administration of antibiotics, chemotherapy, or other medications require central lines.

Veins on the dorsum of the hand or the outside surface of the foot are usually visible, and are most commonly used for routine cases. Gentle stretching of the skin by flexion of the wrist



Figure 1 Venous cannulation in infant—tightening the skin over the dorsum of the hand.

helps stabilize the vein and improves the chances of success (Fig. 1). The greater saphenous vein is a popular site when a large IV line is needed. This vein has a consistent anatomical location anterior to the medial malleolus of the tibia, and is usually visible even in neonates and premature infants. In chubby toddlers, it can be cannulated successfully by palpation and aiming the catheter toward the back of the knee in a medial direction (blind saphenous) (Fig. 2). Holding the foot in extreme plantar flexion and external rotation helps to straighten and stabilize the vein for cannulation. Ambulating children who require an IV for more than 24 to 48 hours may prefer the nondominant upper limb rather than the lower limbs. The lower extremity sites are also not appropriate for infusing fluid replacement when blood loss is proximal to the IV site (e.g., during resection of a large abdominal tumor).

Despite the larger size and the superficial position of the median, antecubital, basilic, and median cephalic veins, they are not ideal for peripheral IV access. They are often reserved for central access from a peripheral site and for blood drawing. These veins, however, are frequently selected by emergency room personnel for insertion of large-bore IV lines for resuscitation. Percutaneous IV placement in the femoral vein is used if other sites are difficult to access.

Risk of infection in the groin location in infants and young children makes IV placement in the femoral vein less desirable. Recognizing the medial location of the femoral vein in relation to the femoral artery and the femoral nerve is necessary to avoid injury to these structures. In newborn infants, superficial scalp veins can be used if other peripheral veins are not accessible. Use of a thin rubber band instead of a tourniquet and carefully shaving the hair around the vein is often necessary to cannulate these scalp veins and stabilize the catheters. Care must be taken to avoid cannulating branches of the temporal artery in this location.



Figure 2 “Blind” saphenous vein cannulation by palpation of the vein and medial malleolus.

External jugular veins (EJVs) may be used in children if there is difficulty with peripheral IV access, despite problems of dislodgement and intermittent cessation of IV fluid flow due to positional changes. In addition, there is significant difficulty in stabilizing short catheters in these veins over a long period of time. Other sites for peripheral vein access are limited only by the attendant's skill and imagination. It is not unusual to see IV lines placed in the toe or thumb veins, shoulders, or abdominal wall when there is only a short-term need.

Choice of Catheters

Well-secured, nonrigid, indwelling catheter-over-needle devices made of Teflon, Silastic, polyurethane, and other flexible, less-thrombogenic materials allow patient movement without fear of dislodgement and infiltration. A catheter-over-needle device consists of a low-friction catheter ranging in diameter from 10 to 24 gauge, and from 0.75 to 3 inch long, enclosing an introducer needle. A 22-gauge cannula is sufficient for fluid and drug administration in most children. A 24-gauge catheter is adequate in infants. A common cause for unsuccessful cannulation is an attempt to insert a cannula that is too large for the size of the vein. If massive fluid or blood replacement is anticipated, it is acceptable to place two separate lines. A skin "nick" with a large needle may be necessary if the skin is tough to make a small puncture to enable the small catheter to pass without folding. It is imperative that the catheter and the needle enter within the vessel lumen together before the catheter is advanced further. If venous cannulation is unsuccessful, both catheter and needle should be removed together. Attempting to retract the catheter over the needle, or replacing the needle within the catheter, can potentially cause shearing of the catheter. If a vessel is transfixated, the needle can be withdrawn gently from the cannula until there is free flow of blood. The cannula alone can be advanced into the vessel with a slight rotatory movement or with the help of a flush. A short extension tube is often attached to the venous cannula in children to minimize interference with the cannulation site.

Recent government regulations have mandated the availability of retractable needle systems for IV catheters, to reduce the incidence of accidental needle-stick injuries (1). A limited variety of these catheters are now available. Initial experience suggests that some of these catheters may be more difficult to use in small children, particularly those with difficult IV access. Some brands of retractable IV catheters allow more splattering and spilling of blood compared with traditional catheters (2). In any event, wearing gloves and goggles is still recommended to reduce exposure of operating room personnel to spilled or splattered blood.

Techniques to Facilitate Intravenous Insertion

IV insertion may be facilitated when the veins are enlarged by using tourniquets. Tourniquets should be just tight enough to obstruct venous return, but still allow arterial flow to continue. Fixation of the site is essential. Even the most skilled practitioner will have less chance of success working with a moving target. In awake children, it is important to obscure the cannulation process from their view, even when eutectic mixture of local anesthetics (EMLA[®]) has been applied, and have an experienced assistant to hold the limb to immobilize it.

Transillumination

Transillumination is a method by which deep tissues are illuminated with a cold, high-powered source of light. Transilluminating the palm of the hand in small infants has been shown to be very effective in visualizing veins before establishing venous access. In one study, venous access was successfully obtained in 39 of 40 children, with a single venipuncture following transillumination (3).

Vasodilation

Vasodilation by the application of a warm, wet cloth or local application of nitroglycerin has been shown to increase the success rate of IV cannulation in infants.

Minimizing Pain of Venipuncture

Children hate needles. Minimizing the pain of venipuncture is not only a humane and right thing to do, but it actually increases the chance of a successful outcome by inducing the child's cooperation and preventing movement.

Dermal Analgesia in Children

Traditionally, intracutaneous injection of lidocaine has been the anesthetic of choice for providing a “numbing” effect prior to venipuncture. However, patients undergoing these procedures are often afraid of needles and the discomfort associated with injections. As a result, topical anesthetic agents using creams for topical percutaneous local anesthesia [EMLA, ELA-Max[®], Synera[®] (S-Caine patch)] have been explored and developed as painless alternatives to injected intradermal anesthesia.

EMLA is a topical emulsion of lidocaine (2.5%) and prilocaine (2.5%) in a 1:1 ratio, which produces anesthesia of the intact skin after application. For optimal effect, EMLA cream must be applied and covered with an occlusive dressing for 60 minutes before venipuncture. A thick deposit is more effective than a thin layer. EMLA cream can significantly decrease venipuncture and IV insertion pain in 85% of the patient population (4). However, it can also result in skin blanching and vasoconstriction, which can make IV cannulation difficult. The application of glyceryl trinitrate ointment after EMLA removal promotes vasodilatation and increases the ease of cannulation after EMLA application in school-age children (5). Because small children tend to rub and occasionally swallow the cream and the dressing, it is advisable to place a bandage over the occlusive dressing to minimize that risk.

ELA-Max (4% lidocaine delivered in a liposomal vehicle) is a more recent addition to topical anesthetics. It provides a longer duration of analgesia because the lipid carrier prolongs the localization of the lidocaine anesthetic. Advantages of ELA-Max over EMLA include a shorter time for analgesic effect and the lack of need for an occlusive dressing (6).

The S-Caine[®] patch (Synera[®], Endo pharmaceuticals, Chadds Ford, Pennsylvania, U.S.A.) is a new system of anesthetic delivery, which comprises a eutectic mixture of lidocaine and tetracaine that is used in conjunction with a disposable, single-use heating system. Studies in the pediatric population showed it to be safe and effective in lessening pain associated with venipuncture procedures (7).

Iontophoresis is a technique that uses an electric current to facilitate movement of solute ions across the stratum corneum to provide dermal analgesia. Lidocaine iontophoresis [Numby Stuff (IOMED, Inc., Salt Lake City, Utah, U.S.A.)] uses a low-level electric current to deliver an ionized form of 2% lidocaine with epinephrine into the skin. It is a quick, non-invasive alternative that has been shown to provide pain relief similar to EMLA (8). An additional injection of lidocaine using a very small, 25- or 30-gauge needle subcutaneously may be needed especially if surface analgesia is inadequate.

Nitrous Oxide Analgesia

The use of nitrous oxide analgesia to facilitate IV access has been found to be just as effective as EMLA cream in providing effective analgesia, with an added benefit of anxiolysis (9). Although both 50% and 75% concentrations of nitrous oxide are effective, the higher inspired concentration can be associated with more dysphoria and inhibition than the 50% concentration (10).

Complications

The major disadvantage of peripheral venous access is the potential of acquiring an infection, dislodgement, and leakage of fluids into the extravascular tissues. Tissue necrosis and compartment syndrome from extravasation of hypertonic solution limits the use of peripheral IV lines, when solutions of high osmolarity must be infused. Subcutaneous infiltration of calcium, potassium, or hypertonic solutions can result in skin sloughing and a need for skin grafting. Frequent inspections of the vein site and the surrounding area will enable detection of this serious problem.

Attention to prevent air from forming in IV lines is important. Air bubbles may cause systemic embolization in infants with patent foramen ovale or other types of right-to-left shunting.

Kinking

Kinking is a major problem when small catheters, especially 24-gauge, are used. Unfortunately, the use of EMLA cream makes the skin “greasy” and allows the catheter to move under the dressing. Meticulous attention to drying the skin and taping the cannula with the metal

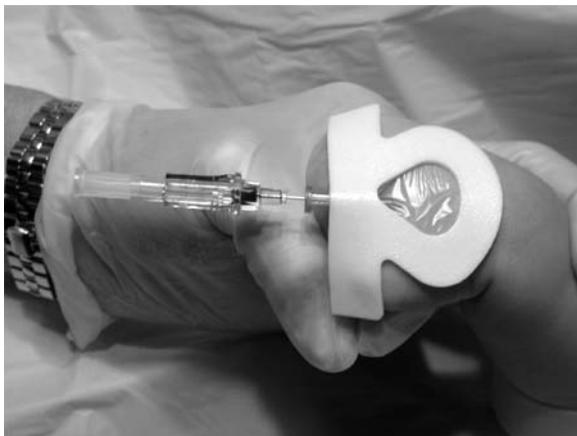


Figure 3 Inner needle “splinting” the catheter while taping to prevent kinking.

needle still in place to “splint” the catheter will minimize this risk (Fig. 3) (Kester Brown, personal communication, 2001). Kinking should be suspected if the catheter is difficult to flush.

Accidental Dislodgement

Accidental dislodgement of IV lines is a constant concern in awake children. In addition to very careful fixation, the use of a padded arm-board is extremely effective in minimizing dislodgement (Fig. 4). Care must be taken to prevent the child from using the board to scratch the eyes.

Infiltration

Infiltration is less likely with modern catheters than it used to be with metal-type scalp vein needles. Still, frequent inspection of the catheter site is essential. The use of transparent dressings (e.g., Veni-gard Jr., ConMed Corporation, Utica, New York, U.S.A.) will facilitate this task (Fig. 4).

Phlebitis

A prospective study of peripheral IV catheters inserted into neonates, infants, and children admitted to a pediatric unit over a five-month period showed a 6.6% incidence of phlebitis. In general, peripheral IV cannulae can remain in situ for up to six days if carefully handled. The risk of phlebitis is higher in neonates and when the catheter is required to remain for a longer duration (11).

Surgical Cutdown

Venous cutdowns are less commonly used because of technical difficulty, morbidity, and ease of dislodgement compared with the ease of inserting peripherally inserted central catheter



Figure 4 Ideal taping of IV catheter in an infant with short extension tubing: Veni-gard[®] and padded arm-board.

(PICC) lines. In emergent situations, however, this technique still offers an alternative means of venous access, when inserting a percutaneous line is not possible. Saphenous, antecubital, and femoral veins can be cut for vascular access if percutaneous access is difficult or impossible to obtain. Patient sedation and lidocaine infiltration of subcutaneous tissue around the vein is often necessary in the awake child.

To perform a saphenous vein cutdown, the child's leg is immobilized with the foot turned to expose the medial malleolus with the saphenous vein lying anterior and lateral to it. The site is prepped, made sterile, and draped. If the patient is not anesthetized, 1% lidocaine is injected subcutaneously over the vein. An incision is made perpendicular to the vein 1 cm anterior to the medial malleolus, and with the help of a curved hemostat, the vein is isolated and two sutures are looped around the vein. The proximal suture is held taut and a small incision is made with a No. 11 blade on the saphenous vein, taking care not to transect the vessel. A Seldinger technique, or direct entry with a catheter-over-a-needle device, is also possible instead of a venotomy. The catheter is inserted and advanced with ease into the vein lumen prior to securing it in place by tying the proximal suture loop. The skin edges are approximated with simple nylon sutures and a sterile dressing is applied.

CENTRAL VENOUS ACCESS

The ability to cannulate a small vascular structure with a very small needle, through which a guidewire can be passed into the vessel lumen (Seldinger technique), is a unique technique that has advanced the safety and ease of vascular access even in preterm infants.

The Seldinger technique has largely replaced the older "catheter through a needle" approach. The technique is also useful for exchanging catheters at the same venous site should the catheter become damaged (12). Peripheral IV catheters, central venous catheters, pulmonary artery catheters, and arterial catheters can be inserted using the Seldinger technique. An appropriate sized single-, double-, or triple-lumen catheter can be advanced over the guidewire, often with the help of a dilator, to be threaded into the desired location within the vessel.

Indications

Central venous catheters provide a secure means for monitoring cardiac filling pressures and for administration of vasoactive drugs in infants and children undergoing cardiopulmonary bypass or other major surgeries with large fluid shifts. In pediatric cardiac patients, measurement of central venous pressure and mixed venous acid-base balance is possible, especially in the intra- and postoperative periods. Central line placement is often indicated through the femoral route when aspiration of air emboli is anticipated in children undergoing craniotomy in the sitting position. Prolonged infusion of hyperosmolar fluids that are sclerosing to the peripheral veins (hyperlimentation, antibiotics, and vasopressors) requires central line placement.

Peripherally Inserted Central Catheters

Peripherally inserted central catheters (PICC) lines have become the most popular method of vascular access in newborns and in older children who require intermediate or long-term IV therapy. PICC insertion shares the attributes of both peripheral and central venous access because of its insertion from the periphery into a central location. Percutaneously inserted central catheter lines are silastic, of very small caliber, soft, thin, flexible, and long. They are placed via the basilic or cephalic veins into the central veins and are much more durable and reliable than a standard peripheral IV line. PICCs are quick and easy to place under fluoroscopy, with very few complications in most children (13). A recent survey of PICCs used in our institution showed that the majority could be inserted under local anesthesia and moderate sedation. The indication for general anesthesia was in children who were sicker, with American Society of Anesthesiologists physical status III or higher (14).

PICCs are usually placed by invasive radiologists under local or topical anesthesia with minimal to no sedation. A needle is inserted percutaneously under ultrasound guidance, using a small hockey stick-shaped linear array probe into the peripheral vein in the upper arm. A temporary tourniquet is applied above, and a guidewire is inserted through it into the vessel lumen under C-Arm guidance followed by a dilator. A peel-away sheath is then

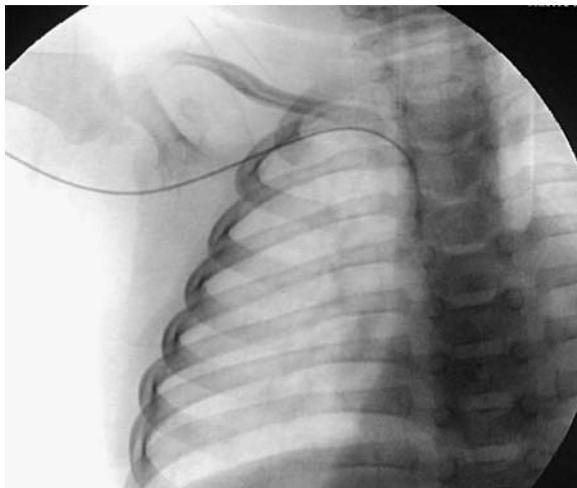


Figure 5 C-arm confirmation of peripherally inserted central catheter's line tip position.

inserted over this guidewire to allow the introduction of the soft PICC. The most common site used is the basilic vein, 3 cm above the elbow. Under C-Arm guidance, the catheter is advanced until it is at the junction of superior vena cava and the right atrium (Fig. 5). Natural flow turbulence occurs in the cavoatrial junction, which decreases fibrin sheath and thrombus formation. The catheter is then affixed to the skin, usually with an adhesive fixation device or sutures. A dressing is applied and the arm is loosely wrapped with a protective elastic Ace bandage to prevent the PICC from being pulled out.

The PICC is made of a biocompatible material and has a special hub attached to it. The CLC2000 needle-less hub is recommended by radiologists, because it is easy to use and specially designed to prevent backup of blood into the PICC line tubing after infusions and flushes. The hub is placed at the end of a short, clear plastic extension tube that is attached to the PICC line (Fig. 6). These catheters are currently used in any situation where long-term vascular access is indicated for hyperalimentation, infusion of other hyperosmolar solutions, frequent blood sampling, and long-term antibiotic therapy. Several sizes are available ranging from 1-French to larger multilumen catheters. Infusing blood through PICCs is not recommended because of a high incidence of occlusion. In newborns and small infants with very small veins, a 1.9- to 2-French catheter less than 1 mm in diameter is placed for IV medications.

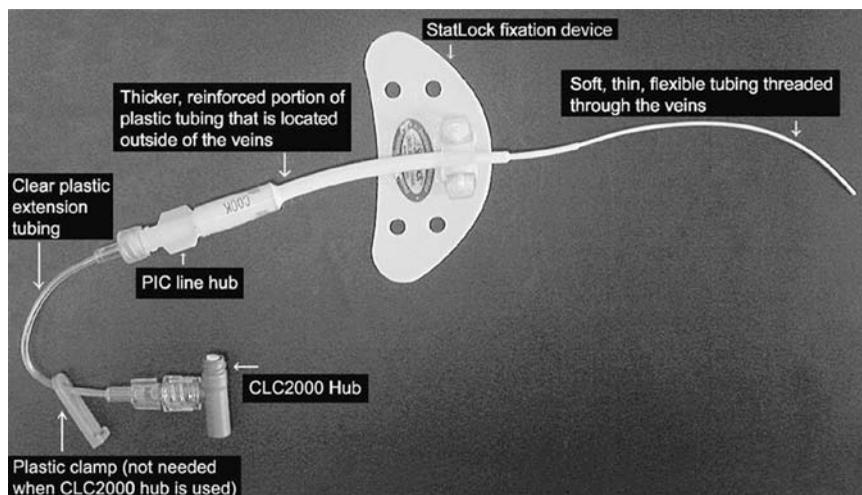


Figure 6 PICCs. Catheter with CLC2000 needle-less hub and extension tubing. *Abbreviation:* PICC, peripherally inserted central catheter.

These thin catheters should not be used for drawing blood for laboratory work because they are prone to clogging easily with backed-up blood. Drawing blood is possible from PICC lines of at least 1 mm diameter (3- or 4-French), which should be followed by immediate flushing with 3 mL of heparinized saline (10 units/mL) to prevent clogging after each use. It is important that this concentrated heparin solution be aspirated and discarded before any drugs or solutions are injected through these, or through other heparinized central lines. This is particularly important when wide-bore implanted catheters are accessed for dialysis, because the volume of concentrated heparin they contain may be enough to fully anticoagulate a small child. The dressing should be inspected daily by unwrapping the Ace bandage without actually removing the gauze and adhesive dressing.

Patients are usually sent home with PICCs for prolonged antibiotic therapy after perforated appendicitis, empyema, meningitis, osteomyelitis, and immunodeficiency virus infection. The central location of a catheter inserted under sterile conditions from a percutaneous site minimizes the infection rate and incidence of dislodgement of the PICCs. PICCs are well tolerated by children, and the success rate by fluoroscopy ranges from 96% in infants to 98% in the older children. Complications include infection, thrombosis, line occlusion, fracture, and tip perforation. The incidences of infection and pericatheter venous thrombosis, the two main complications, were 6% and 0.3%, respectively, in infants and children (15). Personnel who handle these catheters must be aware of this fact, and pay careful attention to sterile technique and cleaning the catheter hub prior to use.

There are several advantages for using PICCs instead of tunneled subclavian central venous catheters and other vascular access devices in children. Risk of pneumothorax with subclavian puncture, need for greater sedation or general anesthesia for tunneling, device placement and removal are some of the disadvantages of vascular access devices (16). However, the choice of vascular access device (tunneled external catheters and completely covered ports) should be reserved for children who require central venous access for prolonged periods of time instead of for those who require short or intermediate time period cannulation.

Internal Jugular Vein Cannulation

Central venous cannulation is routinely performed to permit monitoring of central venous pressure and for infusion of vasoactive drugs in infants undergoing open-heart surgery and other major thoracoabdominal cases. Internal jugular vein (IJV) cannulation is preferred to accessing the subclavian vein (SCV) as a route to achieve this end because of a higher incidence of pneumothorax and subclavian artery puncture with the latter (17). Right IJV is preferred over left IJV because of its straight course into the right atrium and the absence of the thoracic duct. Studies of autopsy specimens of infants less than 6 kg have shown a different central venous anatomy, because the right and left SCVs enter at an acute angle compared with those in the older child and the adult (18). In contrast, the EJVs and IJVs entered centrally in almost a straight line even in the infant. Results of this study point to the safety and the reliability of these neck vessels as portals for the percutaneous entry of catheters into the central location, especially in critically ill infants with coagulopathy or pulmonary problems. In infants, percutaneous entry of IJVs guided by palpation of anatomical landmarks is often difficult and carries a higher incidence of carotid artery (CA) puncture. By using ultrasonography in children, the anatomical position of the IJV has been shown to be highly variable (19). Anomalous venous anatomy has been reported to be as high as 18% in children, with a 10% incidence of posteriorly positioned CA in another study of pediatric patients. Several authors have noted a decrease in the complication rate from 60% to 20% when an ultrasound scanner was used to guide cannulation instead of relying on the traditional method of external landmarks (20). A review of IJV cannulation in over 1000 infants and in children under 10 years of age showed an increased difficulty and incidence of CA puncture, with a lower success rate in infants compared with that in the older children (21). An analysis of factors that influenced successful IJV cannulation in children by using the landmarks showed an inverse correlation of success with age (22).

The patient is placed in a Trendelenburg position during insertion. The traditional approach to IJV cannulation is by observing and palpating the following external landmarks: sternocleidomastoid muscle, clavicle, sternal notch, cricoid ring, and the CA pulsation. At the level of the cricoid ring and at the apex of the triangle formed by the division of sternocleidomastoid muscle and the base of the clavicle, a 21-gauge, 4.0-cm long needle is inserted at a 30°

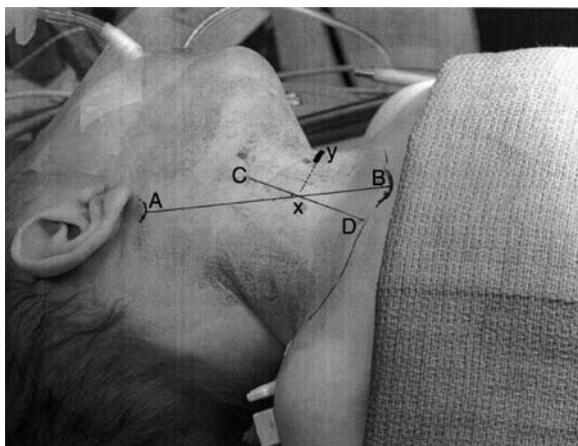


Figure 7 Landmarks for internal jugular vein cannulation in a child: (A), mastoid process; (B), sternal notch; (C), (D), carotid artery; (Y), cricoid; (X), point of needle insertion.

angle lateral to the CA and directed toward the ipsilateral nipple. This point lies roughly lateral to the intersection of the CA with a line between the mastoid process and the suprasternal notch (Fig. 7). The pulsating CA can be retracted gently medially by the left index and middle fingers. IJV puncture is identified by the easy aspiration of dark venous blood from the vein. Using a standard Seldinger technique, a guidewire is passed through the needle, followed by tissue dilation with a dilator and advancement of a heparin-coated, polyurethane, double-lumen catheter (Cook Central Venous Catheter; Cook Critical Care, Bloomington, Indiana, U.S.A.) appropriate for the child's age. In our own experience, we have reported an increased success rate of IJV cannulation in infants when the straight end of the catheter was used as opposed to the curved end (23).

Successful intraluminal catheter placement is confirmed by the easy aspiration of dark blood from both the lumens of the catheter and by observing the transduced atrial waveform on the monitor. Detecting atrial signals by using the guidewire as an internal electrode in children is another method of confirming the correct location of a central venous catheter in children (24). The absolute confirmation of the position of the central line is obtained by a chest X ray taken at the conclusion of the surgery.

The Site Rite ultrasound scanner (SITE RITE[®], Dymax Corp., Pittsburgh, Pennsylvania, U.S.A.) has been used for IJV cannulation in infants successfully. This technique was shown to be superior to the landmark technique in terms of success, speed, and decreased incidence of CA puncture by our own study in infants (25). This high-resolution, computerized ultrasound unit is a portable, lightweight, real-time ultrasound imaging system especially designed for viewing the IJV and CA. The probe uses a frequency of 7.5 MHz, a sector angle of 25°, with the focal length positioned 1.5 cm from the cap. The skin surface imaged superiorly with the vessel images below can be visualized on a screen as a two-dimensional image display. The probe is covered by an elongated sterile sheath containing Aquasonic gel to maintain a sterile field.

After antiseptic prepping and draping of the right neck, the sterile sheath-covered ultrasound probe is placed on the right neck, and vessels are identified (Fig. 8). The CA and IJV can be identified by their relative positions, compressibility of the vein, and the enlargement of the vein by liver compression or Valsalva maneuver (Fig. 9). Other methods used to locate the position of the IJV include the smart needle and the audio Doppler (26,27). There are several maneuvers (Trendelenburg position, applying pressure on the underside of the liver, and applying positive-end expiratory pressure) that can be used to increase the size of the IJV (28). Whether this enlargement of the target vessel will improve the success of cannulation remains to be studied.

External Jugular Vein Cannulation

Central venous cannulation via the EJV, although easy and associated with minimal complications, carries a high failure rate compared with cannulation of the IJVs or SCVs. The use of the Seldinger J-wire increased the success rate of cannulation from 50% to 79% and even to 90% in



Figure 8 Using an ultrasound probe to guide the needle for internal jugular vein cannulation. Note the side drapes placed to intersect at the nipple.

adults (29). Catheters do not pass beyond the clavicle or sometimes pass into the axillary vein or face toward the opposite side. In adults, shoulder manipulations have shown facilitation of central vein catheterization from the EJV (30). Circumventing the plexus of veins at the clavicle can be performed by the J-end of the guidewire (31,32). In children, despite the avoidance of complications that usually accompany cannulation of IJV and SCV, the EJV is not used often for central venous cannulation because of a higher frequency of failure. The disadvantage of using EJV catheterization is the difficulty encountered often in advancing the catheter into the central circulation, especially in smaller children. Our study comparing the technique of inserting central venous catheters through the EJV and the IJV showed the difficulty in reaching the central circulation through the EJV in children under two years of age (33).

Difficulty in reaching the central circulation is often due to difficulty in maneuvering the J-wire through the EJV-SCV junction. A study in children undergoing cardiac surgery, where central venous catheterization was attempted through the EJV, showed a success rate of 54%, with a greater efficacy in older children (34).

To perform the procedure, the table is tilted to a 30° Trendelenburg position and the child is positioned with three or four towels under the shoulders to extend the head and allow full access to the neck. The neck is prepped and draped under aseptic conditions and venipuncture of the EJV is performed with a 20 or 22 Jelco Angiocath (Fig. 10). The needle is removed from the catheter and the curved end of the guidewire (J-wire) is inserted into the vessel and

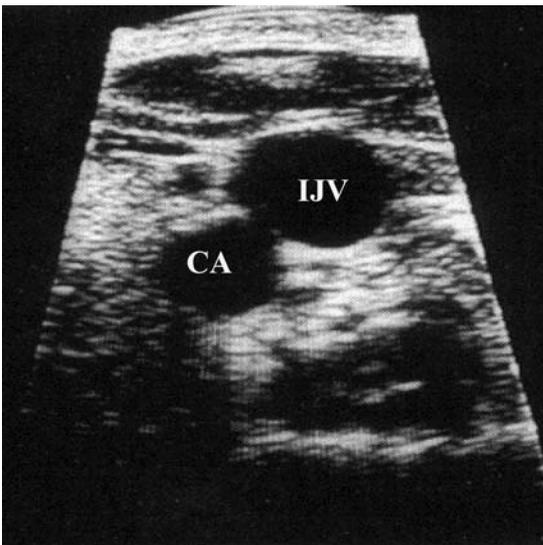


Figure 9 Ultrasound image of CA and IJV. *Abbreviations:* CA, carotid artery; IJV, internal jugular vein.



Figure 10 External jugular vein cannulation. Note stretching of skin and occlusion at the clavicle to enlarge the vein.

advanced into the superior vena cava. After dilatation at the skin and subcutaneous tissue, the catheter is advanced over the guidewire into the circulation and the guidewire is removed. Easy aspiration of venous blood and observing a venous pressure tracing on the screen indicate IV placement. Absolute confirmation of the catheter location is by a chest X-ray.

Subclavian Vein Cannulation

The SCV is frequently used for central venous cannulation because of patient comfort, fixed landmarks, and the ease of securing the catheter to the patient for a prolonged period. The success rate for percutaneous SCV catheterization in children younger than six months of age is lower (78.8%) than in those over six months of age (96%) (35). The SCV approach is considered as the first approach in critically ill patients in some pediatric emergency rooms and pediatric intensive care units compared with peripheral venous cutdowns, due to a higher success rate and lower complications (36,37). The success rate of SCV cannulation in infants and children can be increased from 71% to 86% with fluoroscopy. The serious complication of arterial puncture (8%) is similar in right- and left-sided SCV insertion, with more right-sided attempts resulting in abnormal positions than the left (38).

The SCV is accessed with the infraclavicular approach. The patient is positioned in the head-down position with a shoulder roll placed between the shoulder blades. The needle enters the area just inferior to the mid-clavicle where the clavicle bends posteriorly and the needle tip is directed toward the suprasternal notch in a slightly cephalad direction, advancing first posteriorly to the clavicle, then parallel to the frontal plane. Elevation of the ipsilateral shoulder assists passage of the catheter from the sheath to the SCV and then into the superior vena cava in children older than one year (39). In a recent pediatric study utilizing ultrasonography, SCV size was found to be optimal without a shoulder roll placement, while maintaining the head in a normal position with the chin in the midline (40).

Life-threatening complications can result from SCV cannulation and include pneumothorax, hemothorax, and pneumomediastinum. Hence, a postprocedure chest X-ray is routinely required. Avoiding ventilation when needle probing during SCV catheter insertion can decrease the incidence of pneumothorax. A direct cutdown of the IJV should be attempted instead of a percutaneous SCV puncture in children with coagulopathy.

Axillary Vein

The axillary vein is an alternate access site for central venous catheterization in critically ill infants and children (41). With the patient placed in the Trendelenburg position and the arm abducted to 100° to 130°, the axillary vein is entered parallel and inferior to the axillary artery after a sterile "prep and drape." The axillary block can be used to facilitate axillary vein catheterization (42). Catheter-related infections following axillary vein catheterization have been found to be similar to those observed after IJV catheterization (43). Studies have shown a frequency of 11.65% of upper extremity deep-vein thrombosis with this technique, especially if the catheters were left in place for more than six days (44).

Antecubital Veins (Basilic and Cephalic) Cannulation

The antecubital veins offer the advantage of being superficial and away from the intrathoracic vital structures. Percutaneous deep-brachial or basilica vein cannulation is often attempted in the emergency department in patients with difficult IV access. Use of a 7.5-MHz ultrasound probe can enable quicker identification of these vessels and a safer successful cannulation in adult patients (45). The basilic vein is preferable to the cephalic vein due to its straighter course and easier passage into the SCV. Achieving central location is often difficult with catheters introduced from the brachiocephalic vein. Arm motion may affect the central vein catheter position when antecubital veins are used, resulting in catheter migration. Phlebitis is a common complication with the use of antecubital veins.

Femoral Vein Cannulation

Central venous catheterization using the femoral approach appears to be a safe method of obtaining central venous access in critically ill infants, children, or young adults, especially in the pediatric emergency department setting. Femoral veins are often cannulated during cardiac catheterizations, and hence, should not be used for routine IV catheter placement in children with congenital cardiac disease. In children under two years, the insertion site for the femoral vein lies approximately 4 to 5 mm medial to the femoral artery pulse and 2 to 3 cm below the inguinal crease. Proper positioning entails placing the child's leg slightly abducted and externally rotated, with a towel positioned beneath the buttocks. A palpable pulse is found halfway between the pubic tubercle and the anterior superior iliac spine. The vessel is entered at a 15° to 30° angle from the horizontal with the needle pointed cephalad and parallel to the vein. The Seldinger technique is used to cannulate the vein and to place the catheter. The desired location for the femoral vein catheter tip is at the junction of the inferior vena cava and the right atrium. The advantages of femoral vein cannulation are the availability of good landmarks, the ability to apply pressure over a hematoma from an accidental femoral artery puncture, and the peripheral location of the target vessel, which lessen the likelihood of pneumothorax and hemothorax. During cardiopulmonary resuscitation and attempts to establish and maintain airway in an emergency in a critically ill child, access via the femoral venous route is preferred to the internal jugular and SCV routes. A review of central venous catheters placed in a pediatric emergency department showed the femoral vein to be the preferred route of choice compared to either SCV or IJV (83% vs. 10% and 6%, respectively) (46). If lower limb fractures or major abdominal emergency or trauma are suspected, the femoral vein access is avoided. Studies of children with femoral cannulations compared with those with nonfemoral catheters have not shown a significant increase in the incidence of infections (47). Subcutaneous tunneling of central venous catheters in the femoral site is a safe procedure and significantly decreases the rate of central venous catheter colonization in critically ill children (48). Ultrasonic imaging is an adjunct to femoral vein catheterization in children with massive soft tissue edema as in burn patients (49). Even in the setting of stem cell transplantation, long-term venous access by inserting tunneled femoral catheters is safe and feasible when the superior vena cava is obstructed (50).

Implantable Silastic Catheters: Broviac and Hickman Catheters

Chemotherapy produces intestinal mucosal damage by inhibition of its stem cell division. Parenteral nutrition is therefore essential because of chemotherapy-induced malabsorption, anorexia, and nausea. Safe, reliable venous access is a crucial part of the overall management of children with a malignancy. Vascular access is used for chemotherapy, parenteral nutrition, blood drawing, antibiotic therapy, and transfusion of blood and its components. Episodes of thrombophlebitis from frequent venipuncture can result in calcification of veins. In a retrospective review of vascular access by means of central venous catheters, those inserted via a tunnel lasted four times longer than those inserted directly into a vein (51).

The Broviac catheter was developed for providing long-term parenteral nutrition in patients with chronic intestinal disease. It is a small-lumen, silastic catheter tunneled subcutaneously from the chest to the subclavian, internal jugular, and facial veins, entered either percutaneously or by the cutdown method. The Hickman catheter is also a single or double-lumen silastic catheter developed to provide reliable IV access in bone marrow transplant recipients who need repeated blood drawings, chemotherapy, transfusion, and parenteral nutrition. The extravascular catheter segments of both these catheters are anchored in place by

a subcutaneous Dacron cuff, which serves as a barrier to infection. Due to their floppy nature and narrow lumens, these catheters cannot be used for central venous pressure measurements. Both catheters must be clamped when not in use.

Implantable MediPort

Totally implantable venous access devices (TIVADs) are very valuable when prolonged intermittent IV therapy or access is required. This is the only system that is totally internal and, hence, least susceptible to infection compared with external central catheters. A significant problem of altered body image with visible external catheters in young children and adolescents is avoided by having a catheter and port totally hidden under the skin. TIVADs or "ports" are particularly useful in children with cancer and leukemia, who require intermittent vascular access for a long duration. The injection port has a hard, durable protective shell made of hard plastic, titanium, or stainless steel with a silastic diaphragm overlying it to allow for access into the reservoir. A special noncoring needle with a side hole (Huber needle) is utilized for this purpose. Preprocedure antibiotics and coagulation status are optimized. A subcutaneous pocket is created in the upper chest wall in the pectoral fascia. A tunneling device is used to pull the catheter into the access site and carefully introduce it into the vein. This device must be placed surgically, under general anesthesia, often in the anterior chest wall but always in the subcutaneous tissue. The hidden nature of this port preserves the body image and decreases the rate of infection in children while placing no restriction on their activities. After applying EMLA or ELA-Max to produce cutaneous anesthesia, the "port" may be accessed often without producing any damage to the diaphragm and eventually removed under general anesthesia when not needed. The need for general anesthesia for both its placement and removal appears to be the only disadvantage in this technique. Several studies in children have shown a significantly lower infection rate with this device when compared with external central venous catheters (52,53).

Alternate Sites

Other "high-risk" sites have been considered when the usual sites are thrombosed, infected, or otherwise unavailable. One such alternative is surgical cutdown directly into the lumbar veins through a flank incision below the 12th rib, or into the deep inferior epigastric veins. In the past, children with superior and inferior vena caval thrombosis required a thoracotomy to directly cannulate the hemiazygous, intercostal, or azygos veins, or the right atrium. Advances in imaging have now enabled tunneled silastic catheters to be placed in the inferior vena cava percutaneously via the translumbar or transhepatic route by ultrasonic guidance with minimal complications (54).

Umbilical Vein Cannulation

The umbilical vessels are accessible during the first one week of life and may be cannulated directly or indirectly by a cutdown, even at two weeks of age. The umbilical cord contains two umbilical arteries (UAs) and a single umbilical vein (UV). They can be used for blood sampling, infusion of drugs and fluids, and for direct intravascular blood pressure (UA) and central venous pressure (UV) measurements.

To cannulate the UV, it is important to identify it by its anatomic position and characteristic appearance. The UV has a thinner wall and a wider lumen compared to the UA and is found at the 12 o'clock position at the level of the skin. In the first few days of life, the UV in the neonate can be cannulated directly and easily without requiring a surgical cutdown. The UV provides access to the central circulation in the newborn infant and allows the infusion of vasoactive drugs and hyperalimentation and a route for exchange transfusion and blood sampling. If the neonate is older than a few days, then a sterile cutdown is necessary to cannulate the vein.

For the actual procedure, the neonate is restrained and maintained in a warm, comfortable position. The field around the umbilicus is prepped and draped, and a silk suture is looped around the base of the umbilical stump. While keeping tension on the base to prevent blood loss, the umbilical cord is cut 1 to 2 cm above the umbilicus, the patulous UV is identified and held open with a smooth forceps and cannulated directly with a round-tipped transparent nonthrombogenic catheter filled with heparinized saline. The tip of the UV catheter is advanced while maintaining caudal traction on the umbilical stump to facilitate catheter

advancement. The desired position of the UV catheter tip is at the junction of the inferior vena cava and the right atrium. Radiographic confirmation is necessary after placement of the UV catheter, to avoid its tip being placed in the liver. Injection of sclerosing and hyperosmolar solutions (calcium chloride, sodium bicarbonate, 25% glucose, etc.) into the liver can produce portal necrosis and subsequent cirrhosis. After covering the site with an antibiotic ointment, the UV catheter is sutured in place, and marked as UV prior to taping it to the abdominal wall. The catheter is connected to a constant heparin containing infusion system (1 unit heparin/mL) and removed as soon as its use is no longer indicated. Studies in neonates have shown that umbilical venous catheterization in the first two weeks of life is a relatively safe, less stressful, cost-effective means of providing IV therapy (55). Complications after UV catheter insertion are infection, thrombosis of portal or mesenteric veins, portal cirrhosis, endocarditis, cardiac tamponade, and rarely pulmonary infarction.

Complications of Central Lines

Complications of CV catheterizations include bleeding and hematomas from unsuccessful venous puncture as well as unanticipated arterial puncture. Vessel and heart perforation, cardiac tamponade, arrhythmias, catheter discontinuity, venous thrombosis, and infection can occur with central venous catheter placement. Heparin-bonded, antibiotic-impregnated catheters have been used to decrease the incidence of thrombosis. Pneumothorax and air embolism are two other significant complications of central venous access at the SCV, IJV, and EJV sites.

The choice of a central venous line (CVL) in any child depends on vessel patency, duration of time needed, underlying illness, age, size, and maturity of the patient, and the family requirements. PICC lines are usually placed for one to six weeks or more. Temporary or non-tunneled CVLs are indicated in patients who need rapid venous access, and may have single or double lumens. For long-term need, tunneled CVL or a subcutaneously implanted port is often ideal, with the latter being the optimal choice if long-term intermittent access is indicated. There are some scenarios where IJV and SCV cannulation should be avoided. These include children with a single ventricle where SCV flow should be left intact, children with hydrocephalus who may be relying on a ventricular-atrial shunt for CSF drainage, and children who require repeat endocardial biopsies after heart transplantation.

Femoral vessels should be used with caution in children with congenital heart disease, who may need these vessels set aside for diagnostic or interventional catheterization.

Intraosseous Venous Access

Intraosseous access to the circulation was used for several decades after its introduction in 1922 and once again became popular in the mid-1980s. The bone marrow is essentially a non-collapsible venous reservoir that empties into the central venous circulation via emissary and nutrient veins. The intraosseous route, therefore, provides rapid and effective access to the circulation for the administration of drugs and fluids.

This technique is used in emergency situations if attempts to establish an IV route both peripherally and centrally have failed. This method of administering IV fluid into the medullary cavity of long bones was commonly used in the past. To use this technique properly, one should be careful in palpating the correct landmarks. As soon as a stable IV infusion site is obtained, the intraosseous infusions should be discontinued to prevent complications and clotting of the intraosseous needle. Due to the absence of adjacent critical organs, the proximal tibia is commonly used in infants and children under six years of age (56).

To perform the procedure, palpate the tibial tuberosity and select a point on the medial surface of the tibia 1 to 2 cm below and medial to the tibial tuberosity, where the mantle of the tibia is thin. This area is prepped and local anesthetic injected to lessen the pain of entry of a large needle. With the proximal end held in the palm of the operator's hand, the distal needle end is rotated or screwed into the bone at a 10° to 15° angle from the perpendicular toward the feet, away from the epiphyseal or growth plate (Fig. 11). Several types of needles, including a stylet spinal needle or a special short needle with a stylet, may be used to puncture this thin area until a "give" is sensed. When a loss of resistance is felt, indicating the entry of the needle into the marrow, the advancing needle is stopped; bone marrow is aspirated after removal of the stylet. One should be able to flush in a syringe of saline easily prior to attaching the standard IV infusion equipment. If the needle is in the intraosseous space, the fluid should

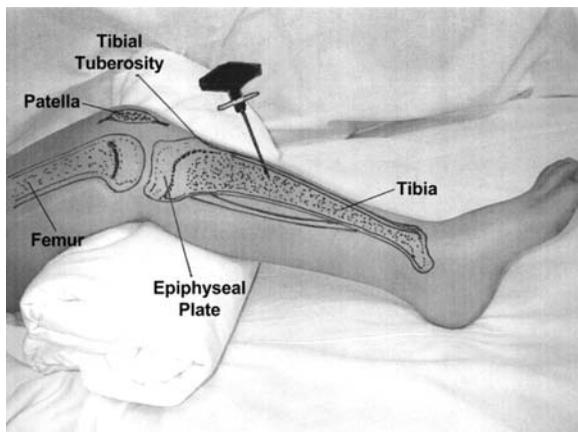


Figure 11 Direction of the intraosseous needle away from the growth plate.

flow freely without any sign of extravasation. There are several types of intraosseous devices with different needle sizes with more than one opening. A needle with a stylet is recommended to avoid plugging the needle. When a Jamshidi device is used to puncture, the stylet is first removed and the adjustable sleeve is twisted down to skin level to secure the needle. Blood samples for laboratory analysis can be obtained and the infusion rate can be increased with the use of a pressure bag around the IV bag. Complications reported with this technique are less than 1% and include extravasation, skin necrosis, compartment syndrome, bone fracture, cellulitis, abscess, and osteomyelitis. Prospective radiographic analysis of tibial growth after intraosseous infusion has not shown any problems.

Emergency Vascular Access Protocol

Although the usual methods of access in the perioperative child are by peripheral and central venous access, other methods are often needed to gain access to the circulation in an emergency situation. Kanter et al. evaluated the use of an emergency vascular access protocol in children (57). Their protocol involved rapid sequential attempts at percutaneous femoral vein catheterization, saphenous vein cutdown, and intraosseous infusion if initial percutaneous peripheral IV insertion failed. While no single technique provided completely reliable and rapid IV access, utilization of all techniques per protocol significantly improved IV access time. When initial percutaneous peripheral IV attempts failed, resuscitations in compliance with the protocol achieved IV access more rapidly (median 4.5 minutes) than those deviating from the protocol (median 10.0 minutes). Even with incomplete compliance, 66% of resuscitations achieved IV access within the first five minutes. Their recommendation based on their experience indicates that IV access during pediatric resuscitation should rarely be delayed beyond the fifth minute if all available IV techniques have been used.

PEDIATRIC INTRAVENOUS EQUIPMENT

One of the essential requirements in pediatric IV therapy is to guarantee accurate delivery of the prescribed volume of IV solutions and medications. It is imperative that age and size-appropriate equipment be available for every child.

Control of Volume

Most children require an hourly volume of fluids far less than the contents of the usual 500-mL or 1-L bag used for adults. Calibrated chambers (e.g., Buretrol solution set, Baxter Healthcare Corporation, Deerfield, Illinois, U.S.A.) will allow the practitioner to limit the maximum volume of IV fluid that can be delivered, even if the IV infusion is accidentally left wide open (Fig. 12). These chambers also contain either a ball-valve combination or a flap mechanism to prevent air from entering the tubing when the infused volume is completed.



Figure 12 Buretrol with microdrip chamber to limit volume administration.

Control of Flow Rate

Most pediatric IV sets have microdrip chambers that allow a flow of approximately 60 drops per mL. Calculating the flow rate can then be easily figured by counting the number of drops per minute. For cases that require IV infusion for a longer time, or when extreme accuracy is needed in neonates and small children, the use of volumetric or syringe pumps is recommended.

Injection Ports

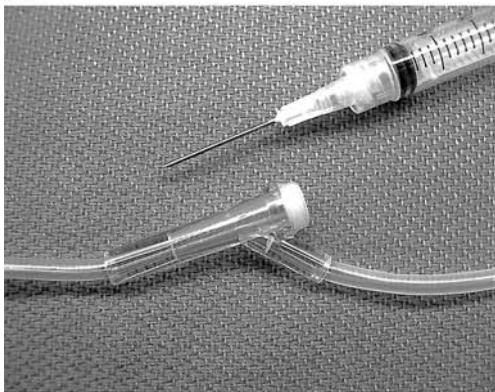
Once an IV line is established, it is frequently needed to add medications to the infused fluids. Traditionally, this required the use of needles in side-port. Although syringe/needle/tubing technology has been touted as simple and intuitive, it is a known cause of personnel and sometimes patient injury (1). Health care workers sustain 600,000 to 1,000,000 needle-stick injuries per year, resulting in at least 1000 new cases of HIV, hepatitis C, or hepatitis B. More than 80% of needle-stick injuries can be prevented through the use of safe devices. These include the use of stopcocks or valved injection ports (e.g., the Clave or SmartSite systems) for IV drug injections. Although the internal dead space of these devices is small, it can result in major inaccuracies when small volumes of drugs are injected, as typically happens in infants and small children (Fig 13-A, 13-B, 13-C). A recent study showed that when very small volumes (0.1 and 0.25 mL) of drugs were injected, the needle system is consistently accurate. Injection through a stopcock is the least accurate, especially when no flushing is employed (58). The valved needle-less Clave system delivers accuracy close to that of a needle, especially with flushing. The technique of flushing has a considerable effect on the ultimate amount of drug injected. If flushing is performed using the same syringe that delivered the drug, the additional trace of drug that is contained in the dead space significantly increases the actual delivered dose. It is therefore recommended that a separate syringe, not containing traces of the injected drug, be used for flushing. When using a stopcock for bolus dosing, a dilution of the intended dose to a minimal volume of 0.5 mL, followed by flushing, will ensure accurate dosing.

ARTERIAL CANNULATION

Radial Artery Cannulation

Radial artery cannulation is frequently used in children other than newborns for monitoring arterial blood pressure, blood gases, and pH. The right radial artery, which is preductal in position, is selectively cannulated in newborns if preductal measurement of blood pressure and saturation is desired. In children with coarctation of aorta, it is clearly the site of choice because of the need to clamp the left subclavian artery during the repair of the coarcted

(A)



(B)



(C)



Figure 13 (A) Injection side port; no dead space. (B) Three-way stopcock; dead space up to 0.15 mL. (C) Clave[®] connector; dead space = 0.06 mL.

segment. A modified Allen's test may be performed as a method to ascertain collateral flow to the ulnar artery prior to radial artery cannulation. The ideal way to cannulate these tiny arteries begins with proper positioning. The hand is well extended on a short hand-board with the help of folded four by four (inches) sponges prior to a sterile "prep and drape." Several methods can aid in identifying the radial artery. The most common method is by palpation of the vessel by the operator's index and middle fingers. Visual and audible Doppler devices have been used to locate the radial artery in children (59). The artery is palpated, and a 24- to 22-gauge needle is positioned over the maximal pulsation of the artery at a 20° or 30° angle. Cannulation can be achieved by direct entry into the lumen as the catheter advances into the artery or by allowing the needle to transfix the artery and gain entry during withdrawal of the cannula. When there is free flow of bright blood from the catheter, the needle is withdrawn and a guidewire is threaded in smoothly through the lumen of the 24-gauge catheter into the radial artery without encountering any resistance. The catheter is then removed and replaced by the winged 2.5 Cook catheter. The catheter is firmly attached to a

T-connector to permit continuous infusion (1–2 mL/hr) of heparinized saline (1 unit/mL) via a constant infusion pump. A pressure transducer is attached to display and monitor the arterial pressure continuously. The transducer is calibrated with mercury to the patient's heart level after meticulously removing all the air bubbles, to provide an accurate measurement of arterial blood pressure. The radial artery entry site is covered with Betadine after securing the catheter. Sampling of blood is performed with minimal blood loss and avoidance of bolus flushes that might result in retrograde blood flow to the brain. A study of the factors affecting the success of peripheral arterial cannulation in infants and children undergoing cardiac surgery found that percutaneous cannulation in infants is technically more difficult than in the older child, but is still more efficient than cutdown (60). Interestingly, in another study, it was evident that polycythemia adversely affects cannulation success in infants and children (61). In infants we found that the use of the Percutaneous Doppler Access (PDA) system reduced the need for surgical cut down when percutaneous arterial cannulation by palpation was unsuccessful (62).

Umbilical Artery Cannulation

Cannulation of this vessel is undertaken in the newborn when monitoring of continuous arterial pressure, blood gases, and pH is indicated. In emergency situations, fluids, glucose, and drugs can be infused through the arterial line. There are two UAs, which appear smaller with muscular walls, lying below the single patent UV at the 12 o'clock position. They are accessed in a similar fashion as the UV, taking extreme care to occlude the vessels to prevent blood loss during cannulation. Unlike the caudal traction necessary for advancing the catheter during UV cannulation, a cephalad traction on the umbilical stump is desirable to facilitate umbilical arterial cannulation. The optimal position of the tip of the arterial cannula is at a point just above the aortic bifurcation, which usually corresponds to L3–L4 vertebrae. Care must be taken to confirm the position of the catheter tip and to prevent its entry into the smaller iliac vessels, which results in ischemia and necrosis. Catheter placement in the proximal aorta at or just below the diaphragm, although easier to maintain, predisposes the infant to increased risk of ischemic and embolic phenomena in the renal and mesenteric vessels. Once the ideal position of the catheter is confirmed radiologically, a constant infusion of heparinized saline is maintained in the system. Prolonged placement of catheters in the UA can produce bowel ischemia in premature neonates (63). Complications from UA cannulation include vascular spasm, sepsis, embolization of air and blood clots, and accidental disconnection and exsanguination.

Caring for Central Lines

Guidelines for the prevention of intravascular catheter-related infections by the Centers for Disease Control and Prevention have emphasized five specific areas (64): (i) educating and training health care providers who insert and maintain catheters; (ii) using maximal sterile barrier precautions during central venous catheter insertion; (iii) using a 2% chlorhexidine preparation for skin antiseptics; (iv) avoiding routine replacement of central venous catheters as a strategy to prevent infection; and (v) using antiseptic/antibiotic impregnated, short-term central venous catheters if the rate of infection is high despite adherence to other strategies (i.e., education and training, maximal sterile barrier precautions, and 2% chlorhexidine for skin antiseptics).

These guidelines also identify performance indicators that can be used locally by health care institutions or organizations to monitor their success in implementing these evidence-based recommendations.

SUMMARY

Pediatric vascular access techniques have evolved significantly with the availability of new and improved vascular catheters and advances in imaging modalities. The use of real-time fluoroscopy during catheter and guidewire insertion by trained interventional radiologists has increased the speed, safety, and reliability of placing CVLs in neonates and small infants, thus decreasing the complications. The infusion needs, patient size, weight, and underlying disease must guide the choice of a CVL or device as well as the approach to the target vessel.

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10 | Glucose Solutions

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INTRODUCTION

Solutions with a low or moderately low content of glucose are widely used in the treatment of debilitated hospital patients. Although glucose solutions are indicated for hydration when there is simultaneous starvation, their use during and immediately after surgery is quite controversial. In these situations, glucose is usually infused in an isotonic 5% solution without electrolytes. Alternatively, the glucose 5% solution is buffered and then contains small amounts of sodium, chloride, and acetate (or lactate) to limit the risks of hyponatremia and acidosis when the glucose has been metabolized. To allow more rapid administration, the bag sometimes contains only 2.5% glucose together with ions and buffer. For postoperative use, the infused fluid might contain as much as 10% of glucose.

At present, administering glucose in the perioperative setting is probably most widely practiced in Scandinavia. This chapter will review the pros and cons of doing so.

BASIC NEEDS FOR GLUCOSE

Glucose is the principal source of energy in the cellular metabolism. The central nervous system has only small stores of glycogen and therefore needs glucose continuously. In the fasting condition, this glucose is mainly provided by the liver, from which it is delivered throughout the body by the bloodstream. However, patients who have very low glycogen stores in the liver after fasting overnight might, in theory, be at risk of developing hypoglycemia, and this risk is more real if alcohol has been part of the diet (1,2). Indeed, low blood glucose is a frequent observation in patients arriving in the operating room (3). When surgery starts, however, the hormonal changes associated with surgery act to raise the blood glucose level by stimulating glycogenolysis and gluconeogenesis. The incidence of blunt hypoglycemia in nondiabetic patients undergoing surgery is not known, but this complication is probably very rare. In diabetics, it is more evident that glucose should be infused and combined with perioperative measurements of plasma glucose. Preoperative patients are not allowed to eat and an erroneous balance between insulin injections and food intake might therefore be at hand.

Other functions than those of the central nervous system also require a continuous supply of glucose. The needs of the brain, red blood cells, adrenal medulla, and wound healing may be estimated to be 120 mg/kg/hr. In an adult male, this corresponds to infusing one liter of glucose 5% every six hours. The normal volume infused in the diseased patient is usually only two to three liters per 24 hours, however. Three liters of buffered glucose 5% provides 600 kcal of energy, but although this is too little for the basic needs, the glucose supplementation still reduces the muscle-wasting characteristic of starvation ("nitrogen-sparing effect") (4). Thus, administration of glucose inhibits gluconeogenesis and makes nitrogen available for incorporation in proteins. On the other hand, the nitrogen-sparing effect of exogenous glucose is less pronounced under stressful conditions than in the nonstressed state, and the "sparing" is therefore quite limited.

Providing "Free" Water

Some anesthesiologists emphasize that infusing glucose is their only way to provide "free" water to compensate the body for evaporation losses from the airways and from open wounds (5). The main or only source of osmolality in the solution is the glucose itself, but all osmotic strength disappears after metabolism to water and carbon dioxide (the latter being eliminated

by breathing). This fact should be considered to indicate that glucose solutions should always contain electrolytes when evaporation losses are *not* greatly increased. Otherwise, repeated administration of glucose without electrolytes increases the risk of subacute hyponatremia, which typically develops two to three days after surgery (6).

GLUCOSE AND THE “STRESS RESPONSE”

Patients who undergo surgery are usually in the fasting state because anesthesia impairs or abolishes the swallowing reflexes and the induction is associated with an increased risk of vomiting. However, starting surgery with relatively empty glycogen stores increases the insulin resistance that develops as part of the “stress” response to surgery. In a series of studies, Ljungqvist et al. have shown that supplying a fairly large dose of glucose (300 g) by infusion (7) or ingesting a meal rich in carbohydrates (8) *before* a medium-sized operation starts abolishes the surgery-induced insulin resistance. The same effect is obtained by administering glucose and insulin before and during an operation (9). However, these studies do not demonstrate any value of infusing glucose alone during surgery.

Reducing insulin resistance reduces the time in hospital, but a lower incidence of complications has not yet been demonstrated (10). However, the degree of insulin resistance after hysterectomy is related to muscle breakdown and to the reduction of the intracellular fluid volume that develops from the second postoperative day (11).

GLUCOSE AND INSULIN

The interest in supplying glucose together with insulin after surgery was boosted in the fall of 2001 when Van der Berghe et al. (12) demonstrated a reduction of the mortality in intensive care patients from 8.0% to 4.6% by keeping the blood glucose level within normal levels by supplying insulin to nondiabetic patients. The daily dose of glucose was 3 L of glucose 10%. The most apparent reduction of mortality was seen among those who spent more than five days in the intensive care unit and in those suffering from multiorgan failure. A closer look at the study showed that 70% of the patients had just undergone cardiac or thoracic surgery. The most pronounced differences between hyperglycemia and normoglycemia were also seen in these postoperative patients.

The practice of administering glucose and insulin, usually together with potassium, is fairly well established in cardiothoracic anesthesia where it is claimed to improve survival by improving cardiac output in severe cardiac insufficiency (13–15). In a small-sized study, glucose–insulin has also reduced the overall rate of complications after acute myocardial infarction (16). These studies rest on substantial experience from animal experiments showing that a heart under the stress of trauma or surgery fares better if glucose–insulin is provided (17–19). The mechanism probably involved is that insulin forces the myocardium to use glucose instead of free fatty acids for its metabolism, which is supposedly more suitable for a heart under stress.

GLUCOSE LEVELS DURING SURGERY

In the laboratory setting, an intravenous infusion of glucose is followed by a prompt increase in insulin secretion, which restores the plasma glucose to baseline approximately 30 minutes after the end of the infusion (Fig. 1). The volume of distribution (V_d) for the exogenous glucose can be estimated to be 10 to 12 L and the clearance (CL) 0.6 L/min, which corresponds to a half-life of 12 to 16 minutes (20). During laparoscopy, measurements in my hospital show that V_d is approximately the same while CL is only one-third of the value obtained in the laboratory, with the half-life being extended to approximately 35 minutes (21). This huge difference shifts the glucose–time curve for buffered glucose 2.5% shown in Figure 1 upwards so as to agree quite well with the glucose–time curve for glucose 5% obtained in the laboratory.

The difference in the body’s handling of an exogenous load of glucose under surgery and nonsurgery is due to insulin resistance and to endogenous glucose production. For a more detailed analysis, insulin resistance needs to be quantified by an insulin clamp and the endogenous glucose production by comparing the disappearance curves of glucose and a dose of radioactive glucose. Plotting the expected plasma glucose concentration over time, based on

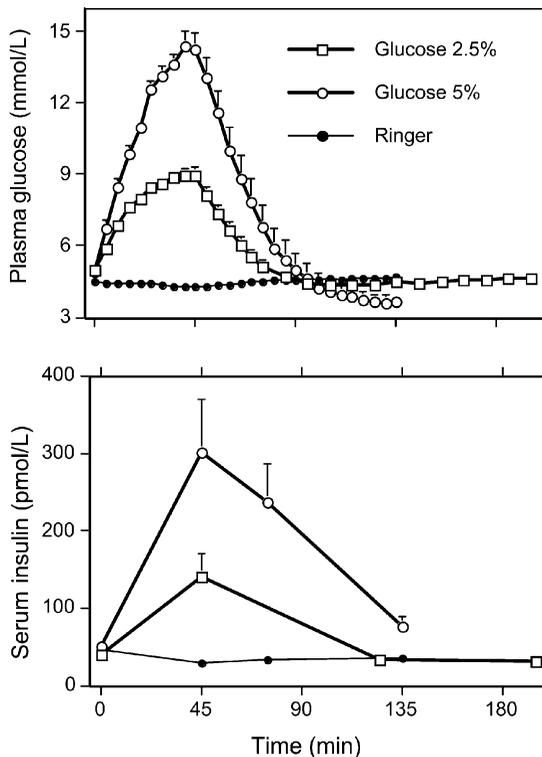


Figure 1 The plasma glucose and serum insulin concentrations in response to an intravenous infusion of 1 L of glucose 5%, buffered glucose 2.5%, and Ringer's acetate solution over 45 minutes in 12 healthy volunteers. Data are the mean and standard error of the mean. *Source:* From Ref. 20.

kinetic modeling, shows that supplying even the basal requirements of glucose (120 mg/kg body weight per hour) leads to hyperglycemia during surgery but not in the laboratory setting; the baseline level is likely to reach a steady state approximately 50% over the upper limit for the normal range (Fig. 2).

With due precaution regarding the recent data obtained when combining glucose and insulin (12), elevation of the plasma glucose level alone is not believed to cause adverse effects. However, the fluid and electrolyte balance might be disturbed by promoting osmotic diuresis if the renal threshold for the reabsorption of glucose from plasma is exceeded (>12–15 mmol/L, the normal concentration in plasma being 4–5 mmol/L). In diabetics, however, prolonged hyperglycemia has long-term toxic effects, in particular, through accelerated atherosclerosis and degeneration of small blood vessels. In these patients, uncontrolled hyperglycemia may lead to diabetic ketoacidosis.

The presence of insulin resistance and the rate of infusion are crucial to the incidence of glycosuria during minor gynecological operations in nondiabetic patients. Doze and White (3) recorded an 88% incidence of glycosuria in fasting female patients who received glucose 5% during surgery. The rate of infusion was as high as 5 to 10 mL/min, however, which is

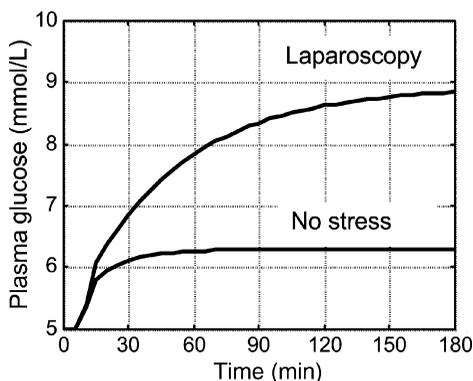


Figure 2 Computer-derived simulation of the plasma glucose concentration following an intravenous infusion of 1 L of glucose 5% over six hours in a human subject weighing 75 kg in the laboratory setting and during moderate-sized surgery (laparoscopy). This rate is said to represent the basic needs of glucose. Each line is based on the mean kinetic data from 12 individuals.

comparable to infusing 1 L over 45 minutes. This is the same dose as the highest one given to volunteers in Figure 1. In contrast, infusing glucose 2.5% did not result in glycosuria.

Plasma Volume Expansion

Glucose solution should not be used as a plasma volume expander because there are firm limitations as to how fast the fluid can be administered. These limits are set by how effectively the patient clears glucose from plasma. After metabolism of the glucose, the fluid distributes over the total body water, which suggests weak plasma volume–expanding properties. However, the plasma volume increase during and for the first 30 minutes after the infusion of isotonic glucose in the laboratory setting is similar to that obtained with Ringer’s solution (20) and 0.9% saline (22). A comparison of two studies of the plasma volume expansion of glucose 2.5% with electrolytes and acetated Ringer’s solution during laparoscopic cholecystectomy suggests that the plasma volume–expanding properties of these two fluids are also quite similar in the perioperative setting (21,23).

Although the plasma volume expansion during infusion is quite good, it soon levels off as glucose is taken up into the cells and water moves along with it by virtue of osmosis (Fig. 3). A prompt glucose uptake following brisk volume loading with glucose 5% even results in a modest hypovolemia (20). This complication is unlikely to occur during and after surgery due to the longer half-life of exogenous glucose and a markedly reduced rate of elimination of infused fluid (20,21,23–25).

Rebound Hypoglycemia

The prompt release of insulin when glucose is infused intravenously at a high rate poses a problem if the administration of glucose is brought to an abrupt stop. Although the plasma glucose concentration might be in the range of causing osmotic diuresis, the series of infusions with glucose 5% in volunteers illustrated in Figure 1 shows that hypoglycemia might develop just 45 minutes after glucose administration is discontinued.

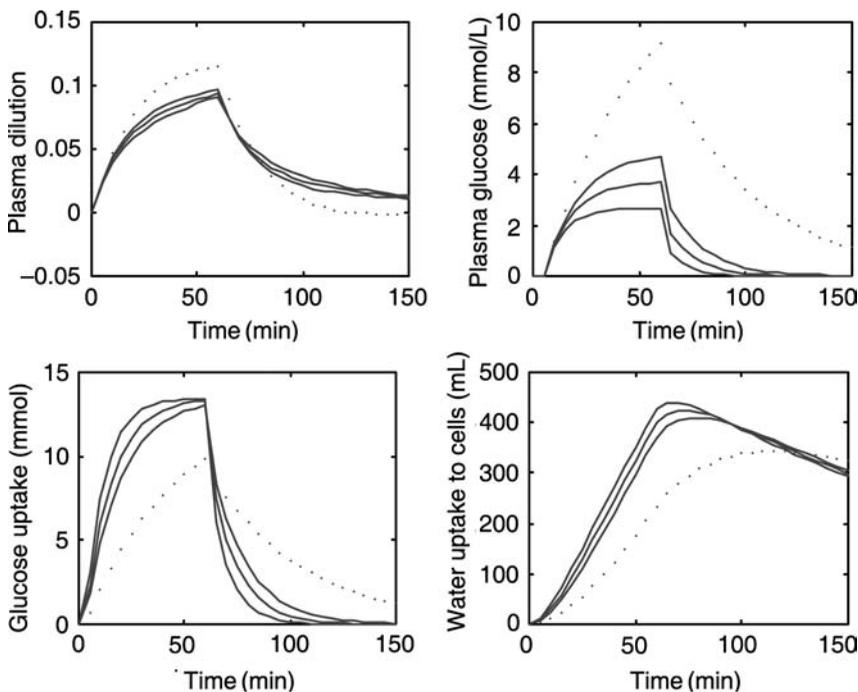


Figure 3 Consequence of a changed glucose clearance alone on the plasma glucose and fluid distribution during and after an infusion of 1 L of glucose 2.5% over one hour in healthy adults. Computer-derived simulation of data from in successive order, from firemen ($CL = 1.0$ L/min), medical students (0.72), and patients one day after hysterectomy (0.42) and during laparoscopic cholecystectomy (0.2, dotted line). Those who undergo surgery have a clearly altered disposition of glucose solution. *Source:* From Refs. 11, 20, and 21.

The "rebound hypoglycemia" is a potential problem if parenteral nutrition is turned off when the patient arrives in the operating room. It is then recommended to start a slow glucose drip and monitor the blood glucose level. Another potentially risky situation is when glucose is infused during labor. The glucose is passively transported across the placenta to the fetus which produces insulin in response to this supplementation. When the fetus is separated from the mother, a strong insulin effect remains while the newborn has little chance to counteract hypoglycemia by endogenous glucose production (26,27). A dangerous situation develops, which might result in convulsions and brain damage.

This problem can be avoided by infusing the glucose no faster than 10 g/hr for no more than four hours before delivery (4). This rate is not exceeded by supplementing the basic needs of glucose (1 L glucose 5% over six hours). Nevertheless, a useful rule would still be to slow down the rate of infusion of the glucose solution at the end of delivery. If these precautions are forgotten, a glucose drip should be administered into the newborn during the first hours after delivery, and the rate of infusion should be gradually reduced.

Serious "rebound hypoglycemia" might occur in the newborn if glucose 5% is used for volume loading in the mother before Cesarean section. This iatrogenic complication is then associated with convulsions and brain damage (27).

Brain Damage

An important reason why glucose is banned by many anesthesiologists is that cerebral damage will be more widespread if cardiac arrest occurs during hyperglycemia than during normoglycemia. Myers and Yamaguchi (28) reported, in 1977, that monkeys developed myotonic seizures and had a worse neurological outcome if glucose 5% in saline was given just before cerebral ischemia was induced. However, between 100 and 200 mL of the fluid was infused rapidly in the monkeys weighing between 2.5 and 3.5 kg, which must have resulted in very severe hyperglycemia. Siemkowicz (29) found that recovery was the same in rats subjected to cerebral ischemia when the plasma glucose level varied between 2 and 22 mmol/L, while recovery was impaired and combined with seizures if hyperglycemia was even more pronounced. Interestingly, fasting for three days prior to the ischemia increased mortality from 0% to 14% although plasma glucose was normal (6.6 mmol/L). In another study, rats having their hyperglycemia lowered from 28 to 12 mmol/L by insulin just prior to cerebral ischemia had a normal recovery (30). The cerebral damage in hyperglycemic rats can be limited by treatment with pentobarbital or diazepam after the ischemia (31).

Courten-Myers et al. (32) studied hypoxia in cats and found that brain damage developed if the hypoxia resulted in arterial hypotension. When hypotension had developed, the extent of the brain damage was more severe if the hypoxia-induced stress had resulted in a sevenfold elevation of the plasma glucose level (fed animals) as compared to the cats that had a doubling of plasma glucose (two days of starvation). Hence, stress-induced elevation of the plasma glucose level does not seem to be a beneficial response in neurological emergencies. In contrast, a benefit is apparent in hypovolemic emergencies because the associated elevation of the extracellular osmolality attracts water from the cells.

It should be emphasized that the plasma glucose level had to be substantially raised (to well above the limit for osmotic diuresis) in these animal experiments before the neurological outcome was impaired.

INDICATIONS AND CONTRAINDICATIONS FOR GLUCOSE

There are subgroups of patients for which glucose 2.5% or 5% should be provided during surgery due to an inherent risk of hypoglycemia. In addition to alcohol addicts and patients on parenteral nutrition treated with highly concentrated glucose solutions, these groups comprise patients with rare diseases such as pancreatic islet cell tumors and hepatomas. Due to more widespread cerebral damage associated with severe hyperglycemia, liberal administration of glucose solution is contraindicated in acute stroke and during operations with a high risk of cerebral ischemia, such as surgery on the carotid artery and cardiopulmonary bypass. For other patients, providing glucose during surgery is a matter of judgment and tradition. In patients with impaired lung function, one should consider that carbon dioxide production from glucose metabolism might impose a burden on the ventilation.

Little is known about what glucose formulation is optimal. Plain glucose 5% might be preferred in operations with large evaporation losses. With a more modest degree of evaporation, buffered glucose 2.5% is probably more suitable. During the postoperative follow-up, buffered glucose 2.5% (which is half-isotonic with respect to electrolytes) is better to use than Ringer's solution or plain glucose 5% due to smaller disturbances of the water and electrolyte content of muscle cells (33). This fluid and glucose 5% with electrolytes are unlikely to cause subacute hyponatremia alone. However, this complication might occur if the fluids are combined with a liberal intake of cold drinks. If several liters of the fluid are infused daily for several days, the serum sodium concentration should be measured (34).

Glucose infusion might also decrease the serum phosphate concentration. This level should be controlled when intravenous glucose is infused during prolonged periods of time.

Glucose should not be administered through the same infusion equipment as whole blood because hemolysis and clumping can occur.

CONCLUSION

Buffered glucose 2.5% and 5% is indicated for hydration of both the extra- and intracellular body fluid spaces and also provides a baseline energy supply of glucose. The fluid is widely used in medical and surgical patients while, in some countries, its value is questioned in routine surgery. The risk profile of this fluid is primarily associated with too fast administration and abrupt discontinuation of the infusion. The fluid should be used with caution in operations with an increased risk of cerebral ischemia.

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11 Crystalloid Solutions

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INTRODUCTION

The first use of an intravenous crystalloid solution was during the cholera epidemic in the 1830s in Great Britain. The pathophysiology of cholera was not known and there was no current treatment. William Brooke O'Shaughnessy, a young doctor of 22, was the first to publish guidelines in the *Lancet* in December 1831. He observed that the blood from patients in the late stages of cholera was thick and black, and drew the conclusion that the "blood had lost a large proportion of water" (1). Thomas Latta, subsequently following these observations, became the first to administer intravenous injections of salt and water to the dying patients.

Although most of the reports showed improvement, this was only a temporary treatment and the true origin of the disease was still not yet fully understood.

Despite further pandemics, the treatment did not prosper because the patients to whom it was applied were mostly moribund, and the amount of fluid given was not enough to maintain the fluid balance. Furthermore, the fluids were chemically impure and carried the risk of bacteremia with pyrogen reactions and hemolysis (1). Interest in these treatments diminished and blood transfusions attracted more attention.

Surgeons in the mid-19th century understood the necessity of both transfusion and replacement with saline when hemorrhaging from injured blood vessels, but firm indications for fluid therapy were not developed until much later (2). Sydney Ringer's observations in the 1880s that salts of sodium, potassium, calcium, and chloride in certain concentrations and in precise proportions necessary for protoplasmic activity led to the invention of a well-known intravenous salt solution (3). During the Spanish-American War in 1898, saline therapies were given rectally or subcutaneously but the interest in blood transfusions still attracted more attention.

George Crile resuscitated animals subjected to hemorrhagic shock in 1899 and further developed the shock concept that had been expressed earlier in the mid-1800s (4,5). He used warm intravenous infusions of saline.

During the first World War, casualties were treated with colloid and salt solutions. The work of Walter B. Cannon was especially important to treating shock (6,7). Cannon recommended gum acacia, an early colloid, for fluid replacement. In rare situations, saline infusions were advocated but their effects were thought to be only temporary. Alfred Blalock categorized the shock concept after the war (8) into the well-known distinctions of hemorrhagic, cardiogenic, neurogenic, and septic shock. He could further demonstrate that tissue trauma resulted in the loss of extracellular fluid (9). Hartmann and Senna, in the early 1930s, treated children with infantile diarrhea and found that they developed hyperchloremic acidosis. To overcome the inevitable acidosis caused by saline, he added sodium lactate and allowed the sodium to bind with the excess chloride after the lactate was metabolized. This modification later became lactated Ringer's (LR) solution also called—Hartmann's solution—now widely used for fluid management (10,11).

The Second World War brought renewed insights into hypovolemic shock, and due to improved logistics, plasma and blood were given (12) in the field. Parallel with these wartime experiences, peri- and postoperative fluid management were considered "salt-restrictive" due to the correct conclusion that most patients lose very little fluid during normal elective surgery and the stress response results in water and salt retention (13–15). In 1945, Collier and Moyer described fluid translocations produced by the administration of saline to postoperative patients (16), and later Tom Shires and coworkers (17–20) documented the necessity of adding large volumes of crystalloids to whole blood and plasma for successful resuscitation during

hemorrhagic shock. The extracellular loss was estimated to be at least 5L in hemorrhagic shock (21). Shires and other researchers further extended their ideas that extracellular fluid volume decreased also during major surgeries (19). This concept of redistribution to a "third space" was based on elegant studies using fixed pressure Wiggers models (22,23) and simultaneous triple isotopes for estimating fluid spaces (19). Both Fogelman and Shires showed that the mortality rate in their experimental animals was lower if lactated Ringer's was added to reinfuse the shed blood. This was convincing, but later studies have been unable to confirm these findings in postoperative patients (24–30) due to differences in measurement techniques, timing of observations, and surgical stress. The problem has been, and still is, to accurately measure the extracellular volume, and critique against Shires has been that the single-sample radioactive sulfate technique he used could give different results when used before and after shock (31,32). Shires later confirmed his findings in major elective surgery (19) by using multiple blood sampling and other methods to look at alterations in cellular membranes (33). A potential functional deficit may be discovered because the use of radioactive ions may, through their distribution into the gastrointestinal tract, help measure both functional and sequestered fluid. Volume kinetics (34) could be a useful tool in fluid measurement. Nevertheless, on the basis of the work described above and related supported work, the treatment with addition of large amounts of crystalloids, became the standard of care in the Vietnam Conflict and resulted in a significant reduction in the rate of renal failure. Extremely high volumes were used in the Navy hospital in Da Nang and thus highlighted the pulmonary problems commonly referred to as the "Da Nang lung," "wet lung syndrome," or "shock lung," now recognized as the adult respiratory lung syndrome (ARDS) (35,36). Despite the lessons learned in Vietnam, with increased incidence of pulmonary failure and ARDS, aggressive fluid resuscitation with crystalloids gained increasing acceptance.

The fluid regimes for treating battle victims also became accepted routine for the management of civilian trauma and undoubtedly led to an overuse of fluids for elective surgical procedures as well. In 1967, Moore and Shires presented a moderation to the earlier findings and clearly drew a line between the extensive trauma and elective procedures (37).

The purpose of this chapter is to describe some basic understanding of fluid distribution with emphasis on the behavior of crystalloid fluids. General properties of crystalloids will be addressed together with the adverse effects of infusing these solutions.

PHYSIOLOGICAL PRINCIPLES

The activity (concentration) of particles in a solution is inversely related to the activity of water molecules in the solution. This is called the osmotic activity and is expressed in osmoles (osm). For monovalent ions, the osmotic activity in milliosmoles (mOsm) per unit volume is equivalent to the concentration of the ions in milliequivalents (mEq) per unit volume. For instance, the osmotic activity of isotonic saline (9 mg/mL sodium chloride) is:

$$\begin{aligned} 0.9\% \text{ NaCl} &= 154 \text{ mEq Na/L} + 154 \text{ mEq Cl/L} \\ &= 154 \text{ mOsm/L} + 154 \text{ mOsm Cl/L} \\ &= 308 \text{ mOsm/L} \end{aligned}$$

Intravenous fluids differ in osmolarity and tonicity. "Osmolarity" quantifies the forces the osmotically active particles in a solution (solutes plus water) have on the distribution of water and refers to the number of particles per liter solution. It is expressed in mOsm/L. In contrast, "osmolality," is a measurement of the number of osmotically active particles per kg solution. "Osmolality" in serum is defined by the equation:

$$\begin{aligned} \text{Osmolality (mOsm kg/L)} &= ([\text{Na}^+] \times 2 + \text{glucose}/18) + (\text{BUN}/2.8) \\ &= (2 \times 140) + 90/18 + 14/2.8 \\ &= 290 \text{ mOsm/kg H}_2\text{O} \end{aligned}$$

where Na^+ is expressed in $\text{mEq} \cdot \text{L}^{-1}$, serum glucose is expressed in $\text{mEq} \cdot \text{dL}^{-1}$, and blood urea is expressed in $\text{mEq} \cdot \text{dL}^{-1}$. The plasma sodium concentration is the principal determinant of the relative volumes of the intracellular and extracellular fluids.

Osmotic activity can also be expressed in terms of "osmotic pressure," which means the attraction the solution has over a semipermeable membrane like the endothelium. The changes in osmotic pressure produced by a change in osmolality can be expressed as:

$$\Delta \text{Osmotic pressure (mm Hg)} = 19.3 \times \Delta \text{osmolality (mOsm} \bullet \text{kg}^{-1}\text{)}$$

When two solutions are separated by a membrane that allows the passage of water but not solutes, the water passes from the solution with the lower osmotic activity to the solution with the higher osmotic activity. The relative osmotic activity in the two solutions is called effective osmolality, or "tonicity." Hyperosmolarity is said to exist when the number of osmotically active particles is high. This condition can occur during a raised level of urea, hyperglycemia, and hyponatremia. When the hyperosmolarity causes a redistribution of water from the intracellular to the extracellular volume, there is a condition of "hypertonicity." An isotonic solution is a solution in which the osmotic pressure is similar to that of plasma. A solution with lower osmolality is described as "hypotonic."

CONVENTIONAL DISTRIBUTION OF FLUID VOLUMES

Water accounts for 60% of body weight in a normal person and is contained in three compartments: intracellular (40%), interstitial (16%), and intravascular (4%). The latter two form the extracellular space. Therefore, in a 70-kg adult, total body water = 42 L, intracellular volume = 28 L, and extracellular volume = 14 L of which four-fifths (approximately 11.2 L) is interstitial and one-fifth (approximately 2.8 L) is plasma volume (red cell volume is part of the intracellular volume). The ionic composition of intra- and extracellular compartments varies. Sodium is dominant extracellularly, 140 mEq/L, whereas the concentration of potassium is the dominant ion intracellularly, 150 mEq/L. Potassium concentration averages 4.0 mEq/L extracellularly and sodium concentration averages 10 to 15 mEq/L intracellularly. Starling's equation summarizes the forces governing the flow of fluid out of blood vessels into surrounding tissues. The Starling equation states that:

$$Q_f = K_f[(P_c - P_i) - \sigma_d(\pi_c - \pi_i)]$$

where Q_f is the total fluid flow and K_f is the filtration coefficient (the product of the membrane conductance and the membrane surface area). P represents the hydrostatic pressure, $(P_c - P_i)$ is the hydrostatic pressure across the vessel wall ($P_{\text{capillary}} - P_{\text{interstitial}}$), π is the oncotic pressure, $(\pi_c - \pi_i)$ is the oncotic pressure gradient across the vessel wall, and σ_d is the oncotic reflection coefficient, the tendency of a membrane to impede the passage of oncotically active particles across it (38). Microvascular hydrostatic pressure is the major driving force responsible for fluid extravasation. The filtration coefficient K_f is the rate of fluid transfer per unit of driving pressure. This pressure decreases because blood flows along the vessel from the artery, through the capillary, to the vein. The oncotic pressure gradient ($p_c - p_s$) is the other major component in the Starling equation. The oncotic pressure depends much on the ratio of lymph protein to plasma protein, normally a ratio of 0.65 to 0.75 (39). Fluid movement between the vessel and the interstitium is impeded by membranes. The prevention by the vascular wall of the passage of proteins into the interstitium can be reflected by the reflection coefficient σ_d . A reflection coefficient of 0 indicates a membrane completely permeable to protein while a reflection coefficient of 1 indicates a membrane that completely prevents protein diffusion. The reflection coefficient in the lung is normally quite high (0.8–1.0) (40) but can vary in other tissues with higher compliances such as the skin and connective tissues.

During normal conditions, sodium-free water will be distributed across the total body water. Solutions containing sodium in physiologic concentrations will be distributed almost exclusively within the extracellular space. Solutions in which colloid osmotic pressure is equal to or above plasma oncotic pressure will remain in the vascular space. Based on this, less than 1/14 of a sodium-free infusion will remain in the plasma volume in a 70-kg adult. If an isotonic solution would be given, slightly less than 3/14 (20–25%) of the fluid should remain in the plasma volume. If an iso-oncotic infusion was to be given, plasma volume would expand by an amount similar to the infused volume (41). These estimates are, at best, static perceptions that do not consider the changing conditions in a clinical setting.

Several methods have been used to quantify the volume effect of an infused fluid. One approach is to use an isotope such as radioiodine-labeled human serum albumin (42). The difference in blood volume before and after the infusion is then divided by the amount of infused fluid to indicate the "efficacy" of the infusion. One problem with such calculations is that the distribution of a crystalloid fluid changes quite rapidly and that isotopes require approximately 15 to 30 minutes of stable fluid distribution to correctly reflect the blood volume. Furthermore, when measuring before and after infusion, only two points of measurement are obtained. This does not give a sufficiently dynamic profile of how the fluid is distributed in the blood volume. More sophisticated methods for measuring blood volume now exist such as the use of indocyanine green, a method in which the mixing time is claimed to be much shorter (43) (see Chapter by Norberg). Such a method would more accurately describe the volume effect for an infusion when distribution conditions are rapidly changing. Also, in a clinical setting there is never an ideal situation that can be fully assessed when urinary losses, or other physiologic or pharmacological perturbations such as the effects of fluid deprivation, hypoproteinemia, anesthesia and surgery (44–46), hemorrhage, or septicemia (47–49) occur. When protein concentration decreases in the plasma or rises in the interstitium, the Starling equilibrium will change. If the membranes are injured, permeability increases to water, crystalloids, and colloids, and the oncotic gradient is less able to restrict fluid extravasation (39). It is important to understand that the distribution of fluids in the body is a continuously changing phenomenon that depends not only on compartmental differences in oncotic and hydrostatic pressures, but also on differences in perfusion of the whole of the body and its organs.

KINETIC DISTRIBUTION OF FLUID VOLUMES

One method of quantifying the volume effect of an infused fluid is to measure the corresponding change in blood hemoglobin (Hb) concentration following infusion.

When starting to analyze Hb changes, the baseline blood volume is preset at baseline (time 0) by using a multiple regression equation based on the weight and height of a subject (50).

$$BV_0(\text{liters}) = 0.03219 \text{ weight (kg)} + 0.3669 \text{ height}^3(\text{m}) + 0.6041$$

The blood volume change at any time (t) can then be obtained as:

$$BV(t) = BV_0(\text{Hb}_0/\text{Hb}(t)) - BV_0$$

The amount of fluid retained in the blood (efficacy of the fluid) is given by:

$$\text{Fluid retained (\%)} = 100 * BV(t)/\text{infused volume}$$

This approach, which has been used in studies by Hahn, gives the Hb changes induced by infusion fluids a simplistic but robust physiological interpretation (51,52). If the urinary output is known, the difference between the infused fluid volume and the sum of the urine and blood volumes can even be claimed to represent the hydration of the interstitial fluid space (53). In a more developed way, this approach can be used to estimate the efficacy of an infused fluid during surgery. Such an approach has been used by Hahn in a near continuous way to estimate the blood volume change during transurethral resection of prostate surgery with concomitant bleeding (54). By using this method, it could be shown that Ringer's solution expands the blood volume by as much as 60% of the infused amount during transurethral resection of the prostate performed under general anesthesia (9). During epidural anesthesia, the "short-term" volume effect (10 minutes) of Ringer's solution was between 48% and 75%, while the cumulative volume effect during the entire operation varied between 30% and 40% (10).

The strong but short-acting blood volume expanding effect of Ringer's solution and also the apparent time dependency were difficult to understand in the 1990s, when it was acknowledged that between 20% and 25% of the infused crystalloid fluid remained in the blood (42). This view was based on the belief that isotonic crystalloid fluid is evenly distributed between the physiological plasma and interstitial fluid volumes with little concern for distribution and elimination effects.

The Hb dilution method has been criticized because isotopes for measuring blood volume may not behave in the same way as Hb does during volume loading. Part of this discrepancy has been accounted for by introducing the hematocrit factor, which is approximately 0.9 at

baseline and corrects for anticipated differences in Hb between large and small vessels (55). The hematocrit factor should not be confused with the lower Hb concentration present in the capillaries; the effect of the capillaries on the Hb dilution is very small because only 1% of the blood volume resides there. Furthermore, Hb may be raised by stress due to the release of erythrocytes stored in the spleen. This effect makes splenectomy necessary before studying fluid balance changes by Hb dilution in animals such as cats and sheep. In contrast, this effect in humans is very small or even absent (56).

A more modern view of why Hb dilution does not always correspond precisely to the results of tracer dilution techniques is that they are based on different assumptions. External tracers are believed to be evenly distributed in the plasma volume in both well-perfused and poorly perfused areas. Furthermore, calculation of the plasma volume using a regression equation based on several sampling points of a tracer requires that the fluid distribution be in a steady state. This does not occur until quite late in the time course of a crystalloid infusion experiment, and seldom during a surgical operation. In contrast, the Hb dilution is the reciprocal of the increase in blood water concentration due to the infused fluid. Thus, it reflects the fraction of the fluid volume that readily equilibrates with the sampling site, which is most likely a well-perfused part of the body. Therefore, there will be different results from using externally administered tracers or Hb tracer if the distribution of an infusion fluid is governed not only by transcapillary exchange but also by differences in perfusion between capillary beds.

One approach to a more accurate understanding of the distribution of fluids and their effects is kinetic analysis. This can potentially serve the same purpose as pharmacokinetic analysis of drug concentrations. A pharmacokinetic curve profile can permit estimation of peak concentration and clearance from the body. An infusion of a crystalloid solution will inevitably mean that a solution, which almost entirely consists of water, will be infused into the plasma volume, which already consists of 80% water. To make calculations feasible, the level of Hb is used as an endogenous tracer. Hemoglobin concentration provides similar estimates of volumes of distribution and clearance rates as the more tedious and nonpractical blood water concentration (34). Because the infused fluid is located in the plasma volume, the hemodilution needs to be transformed to corresponding plasma dilution. The plasma volume equilibrates with other fluid spaces in the body and it is from the plasma volume that urine is secreted. One major advantage with a kinetic approach is that the outcome of the volume administered during intravenous therapy can be analyzed and simulated. Data on dilution of blood can be used to assess the volume of distribution and the subsequent rate of distribution and elimination for any fluid. The results are used to simulate plasma dilution of other infusion regimens that the examiner wants to investigate. Infused fluid is said to expand one or several "functional" body fluid spaces instead of being distributed between "physiological" fluid spaces. These functional spaces have a baseline "target volume" that compensatory mechanisms in the body strive to regain after the fluid has been administered (57).

Subsequently, dilution data are fitted to the solutions of differential equations describing the situation in a kinetic model created by the investigator, which describes reasonably well what happens in the body. The parameters in the model, such as the volume of distribution and the rate of elimination, are then estimated by a mathematical process called nonlinear least-squares regression. This minimizes the difference between the experimental concentration-time data with theoretical values generated by a computer. When the parameters in the kinetic model have been estimated, the infused fluid is thought to expand a single body fluid space called v , which the body strives to maintain at the target volume V (Fig. 1). Elimination of fluid occurs by baseline urinary excretion and evaporation (k_b) and by a dilution-dependent mechanism governed by a constant (k_r). The volume changes in the one-volume model are given by the following differential equation:

$$\frac{dv}{dt} = k_i - k_b - k_r \frac{(v - V)}{V}$$

The infused fluid may also be thought to expand both a single central and a more peripheral body fluid space called v_1 and v_2 , respectively ("two-volume model") (Fig. 1).

These body fluid spaces strive to be maintained at the target volumes V_1 and V_2 in a way similar to the inflation of elastic balloons. As for the one-volume model, elimination of fluid occurs from v_1 by two mechanisms, k_b and k_r . The expanded space v_1 communicates with v_2

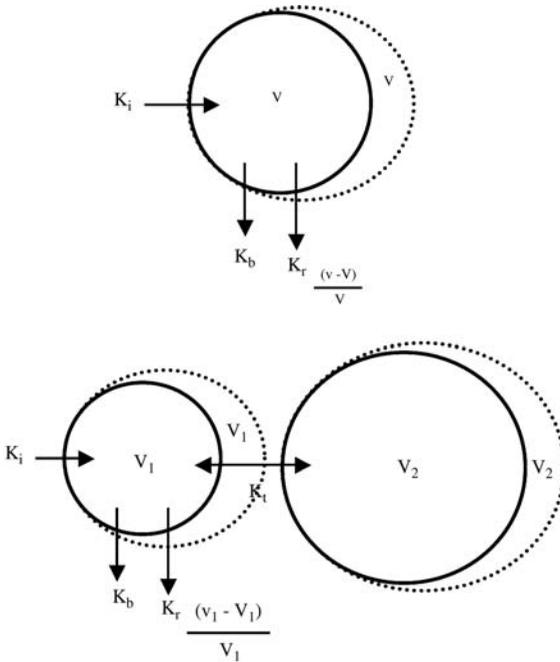


Figure 1 Schematic drawing of the kinetic model used to calculate the size of the body fluid space expanded by intravenous of fluid in humans. *Source:* From Ref. 34.

and the net rate of volume equilibration between them is proportional by a constant (k_t) to the relative difference in dilution between them. Hence, the dilution will be different in v_1 and v_2 . The volume changes in the two-volume model are given by the following differential equations:

$$\frac{dv_1}{dt} = k_i - k_b - k_r \frac{(v_1 - V_1)}{V_1} - k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right]$$

$$\frac{dv_2}{dt} = k_t \left[\frac{(v_1 - V_1)}{V_1} - \frac{(v_2 - V_2)}{V_2} \right]$$

The dilution-time profiles, sometimes augmented by the urinary excretion, are entered into a computer, which fits the solutions to the differential equations describing the fluid shifts in these kinetic models to the data (34). Results are the optimal values for the unknown parameters in the models, together with the uncertainties of each estimate. The unknown parameters in the one-volume model are V and k_r , while in the two-volume model, the corresponding unknown parameters are V_1 , V_2 , k_t , and k_r .

The volume kinetic approach is more fully discussed elsewhere in this book (see chapter on Volume Kinetics).

CRYSTALLOID SOLUTIONS

A crystalloid is a solution of small particles. They are composed of low molecular weight solutes ($MW < 30,000$ D) either ionic (e.g., Na^+ and Cl^-) or nonionic (e.g., mannitol). The colloid osmotic pressure is by definition zero. They are inexpensive compared to blood products and artificial colloids. The contents of a number of commonly used crystalloids are listed in Table 1.

These solutions do not contain larger, oncotic particles and will therefore pass freely across the microvascular membrane. The distribution will be determined by the amount of sodium in the solution. Solutions that contain isotonic concentrations (e.g., 0.9% saline, Hartmann's solution or Ringer's solutions) will, according to traditional view, distribute across the extracellular fluid space.

Table 1 Composition of Different Crystalloids

Fluid	Physicochemical properties of common crystalloids							
	Osmolality (mosmol/kg)	pH	Na ⁺ (mEq/L)	K ⁺ (mEq/L)	HCO ₃ ⁻	Cl ⁻	Ca ⁺⁺	Dextrose
0.9% saline	308	5	154	0	0	154	0	
Hartmann's solution	280	6.5	131	5	29	111	2	
Ringer's lactate	273	6.5	130	4	28	109	3	
Ringer's acetate	270	6	130	4	30	110	2	
5% dextrose in water	253	4	0	0	0	0	0	50
5% dextrose in 0.45% saline	505	4	77	0	0	77	0	
2.5% dextrose in saline	270	6	70	0	25	45	0	25
5% glucose buffered	440	6	70	0	25	45	0	
Plasmalyte A	294	7.4	140	5	50	98	0	
3% saline	1026		513			513	0	
7.5% saline	2400		1250			1250		

Hypotonic Crystalloid Solutions

Hypotonic solutions (e.g., 0.45% saline and 5% dextrose in water) contain free water, which, when infused rapidly in large volumes, can lower plasma osmolality. These solutions are indicated during hypertonic dehydration. Dextrose solutions are not used for perioperative management but more for maintenance. When the glucose is metabolized, the solutions become hypotonic. They should also be used with caution in patients with traumatic brain injury because they can increase cerebral water and raise intracranial pressure (ICP).

Isotonic Crystalloid Solutions

The most commonly used isotonic fluid is Ringer's solution (lactated or acetated) or 0.9% saline. The latter is often confusingly referred to as "normal" saline although there is little normal about it. Lactated Ringer's or acetated Ringer's is mildly hypotonic when compared to plasma but still regarded as isotonic. Sydney Ringer was the first to come up with the idea of saline solutions in the 1880s (3). Hartmann and Senna improved it by adding lactate in the 1930s (10). Acetate-containing solutions seem to have at least a theoretical advantage over lactated solutions because the capacity to metabolize lactate is mainly dependent on the functional capacity of the kidney and the liver. Acetate can be metabolized by all tissue cells, which could be beneficial if the patient is hypovolemic or in shock. It is doubtful whether this has a general clinical significance (58).

Hypertonic Solutions

These solutions are described elsewhere in this book (see chapter on Hypertonic Solutions). They have not yet found their way into common perioperative fluid management although there are many promising studies addressing their volume effects and anti-inflammatory properties during surgical procedures (59–61). The procedures have been introduced in the prehospital and the military settings (62) and are in common practice in many countries except in the United States (63,64).

Volume Effect of Crystalloid Solutions

In their work with experimental animals subjected to hemorrhagic shock, Shires and coworkers described a decrease in the functional extracellular volume to 28% correlating to the degree of trauma (65). Shires explained the decrease by sequestration within the traumatized

tissue area (called the “third space”) and fluid translocating to bowel and peritoneum, and recommended replacement of these losses with crystalloids (65,19). This work was extended to trauma patients, in whom he described similar losses in extracellular fluid volume (19,20). Fluid was now directed to replace not only intravascular but also extravascular deficits. Dillon et al. showed that lactated Ringer’s, given in a volume two to three times the shed blood volume, was as efficacious as 6% dextran in saline given in volume equal to the shed blood volume (66). These results led to a more extensive use of salt-containing solutions not only for fluid replacement during hemorrhagic shock, but also for elective surgical procedures way in excess of actual losses (37,67–70).

Traditionally, infused crystalloids have been said to remain 20% to 25% in the vascular space. The estimates, based on a strict compartmental distribution of crystalloid fluids, are not sufficient. To more closely analyze the volume effect of different plasma expanders, Lamke and Liljedahl measured plasma volumes after surgery infused different plasma expanders and then measured plasma volumes again. The average loss of plasma volume during surgery was 250 mL. When replacing the lost plasma with 0.9% saline during 1½ hours, they found that the “volume effect” of saline infusion was only 180 mL (71). Shoemaker and Monson found that volume expansion was dependent on the primary deficit (72). Similarly, Hauser et al. showed that infusion of 1 L of lactated Ringer’s in critically ill surgical patients expanded the plasma 190 mL (73).

Analysis of the dilution-time profile according to the volume kinetic models has proven to be a useful tool in the study of the effects of fluid therapy. For a crystalloid fluid like Ringer’s solution, the one-volume model typically applies when the urinary excretion is prompt. Because distribution between V_1 and V_2 requires as much as 30 minutes to be completed, peripheral edema does not develop (i.e., fluid does not translocate to V_2) if the renal excretion is effective (k_r is high). In contrast, the two-volume model normally applies in dehydrated subjects and during surgery when the body strives to conserve fluid.

While V for the one-volume model is usually 4.5 L, typical sizes of V_1 and V_2 for Ringer’s solution in a two-volume model are 3.5 L and 6 to 7 L, respectively (Table 2).

It would be tempting to look at these functional volumes as physiological volumes. During normal hydration and healthy conditions, V_1 has a volume similar to the plasma volume, while V_2 occupies two-thirds of the expected size of the interstitial fluid space (34,74,75). The functional volumes express how the fluid distributes over time. V_1 could be the plasma volume in easily perfused organs and parts of the extracellular space where infused fluid is easily equilibrated, while V_2 is an area more poorly perfused, taking a longer time for the fluid to allocate.

Table 2 Volume Kinetic Data for an Intravenous Infusion of 25 mL/kg of Ringer Solution Over 30 min in Eight Male Volunteers as Obtained by Analysis of the Plasma Dilution Indicated by the Blood Hemoglobin, Blood Water, and Serum Albumin Concentrations

	Blood hemoglobin	Blood water	Serum albumin
<i>2-volume spaces</i>			
n	4	5	7
V_1 (mL)	3327 (438) 1175 (463)	2769 (445) 569 (130)	3851 (395) 880 (126)
V_2 (mL)	6926 (2594) 1805 (375)	4443 (1054) 1039 (256)	8138 (1271) 2122 (372)
k_t (mL/min)	295 (59) 205 (113)	190 (34) 66 (31)	283 (38) 97 (28)
k_r (mL/min)	91 (15) 11 (2)	110 (28) 9 (1)	81 (22) 15 (3)
<i>1-volume space</i>			
n	4	3	1
V (mL)	4500 (875) 906 (541)	3834 (494) 377 (66)	5729 463
k_r (mL/min)	280 (81) 36 (22)	180 (11) 13 (3)	114 8

Note: The first line for each parameter gives the estimate and second line gives its standard error. The parenthesis after each mean value gives the variability for the group expressed as the standard error of the mean.

Source: From Ref. 34.

Drobin has recently made an effort to apply a kinetic approach to the efficacy or the "volume effect" of different volume expanders in healthy volunteers. He found, not surprisingly, that there was less intravascular retention of common crystalloids. 0.9% saline had a somewhat better efficacy than acetated Ringer's (76). If 0.9% saline was given 1.0 for comparison, lactated Ringer's had a relative value of 0,80 and acetated Ringer's had a value of 0,77. As a comparison, he also investigated both hypertonic saline, which had 3.23 and hypertonic saline with added dextran at 6.25. These values were obtained as areas under the dilution curves for corresponding plasma dilutions. It is obvious that to understand the effects of infusing crystalloids, one needs to understand that it is a dynamic process where the volume effect will depend on primary deficits, ongoing losses, neuroendocrine stress responses, implications of anesthesia and surgery, and concomitant side effects of the infused solutions.

SURGICAL PROCEDURES AND BLOOD LOSS

The strategy of using crystalloids for replacement of fluid losses during elective surgical procedures has been, and still is, in controversy. It is apparent from both clinical observations and experimental studies that a subject better tolerates loss of red cells (Hb) than loss of plasma volume (77). The distribution of crystalloids into the interstitium could hardly be expressed as a leakage, rather than a function of a predictable equilibration across a semipermeable membrane in response to the balance of hydrostatic and oncotic forces. The behavior of extracellular fluid to achieve equilibrium under changing conditions could at least theoretically be predicted. The Starling hypothesis has for a long time been a valid description of the opposing forces that should be balanced. When plasma volume is diluted during infusion of an isotonic crystalloid, plasma oncotic pressure will be diminished and subsequently the interstitial hydrostatic pressure needs to rise to keep the Starling forces balanced. These are forces working under normal conditions. However, during hemorrhage, there are protective forces initiated by the body to increase intravascular volume. During the initial phase of hemorrhage, there is an instant resetting of the pre- to postcapillary sphincters leading to reduced hydrostatic pressure in the vessel. This will diminish outward filtration at the arteriolar end of the capillary and increase the relative importance of the colloid osmotic pressure exerted by the plasma proteins at the venular end. A combined effect of alpha-adrenergic activity and beta-adrenergic activity will augment the resorption flux to about 0.5 L into the vascular system (78). Another important contributing factor seems to be the recirculation of proteins into the vascular space (79). During prolonged and severe hemorrhage, the glucose-osmotic fluid absorption seems to be at least equally important to preserve the increased plasma volume (80-82,78).

Common replacement strategies of the required volume of crystalloid to blood loss ratio have traditionally been 3:1 (83,84) and even higher up to 5:1 (41). To preserve normovolemia with crystalloids, large volumes need to be given to fulfill this requirement during trauma and hemorrhage up to an extreme relation 20:1, or even above that to keep the Starling equilibrium intact with crystalloids (85,86). This clearly indicates that the interstitial compliance is no longer a linear function (Fig. 2) as in dehydration or initial overhydration but has instead reached a point where it is very high or virtually infinite because very large volumes (74) are required to maintain the interstitial hydrostatic pressure (87,88). Furthermore, the capacity of the lymph system becomes inadequate to retransport the interstitial fluid to the vascular space (88).

Difficulty in obtaining accurate measurements of the fluid phases may relate to the use of isotopes with different volumes of distribution, different equilibrium times, and differences in neuroendocrine and inflammatory responses (89). The extreme amount of fluids required to balance capillary fluid forces could be challenged when looking at trials focusing on hemodynamic end points. Considering these studies it seems that in early resuscitation of hemorrhage, much lower volumes are required (90,91). In a kinetic study, Drobin and Hahn found a more profound volume effect of infused crystalloids during hemorrhage (75). The apparent discrepancies in the volumes needed to restore normovolemia with crystalloids during hemorrhage are due to the kinetic performance of the fluids, but also depend on when the fluids are given during the resuscitation process. Current regimes are probably too rigid and need to be adapted to the type of procedure, timing, and the ongoing pathological condition. An instant bolus to a predetermined dilution point, followed by a slower maintenance infusion rate,

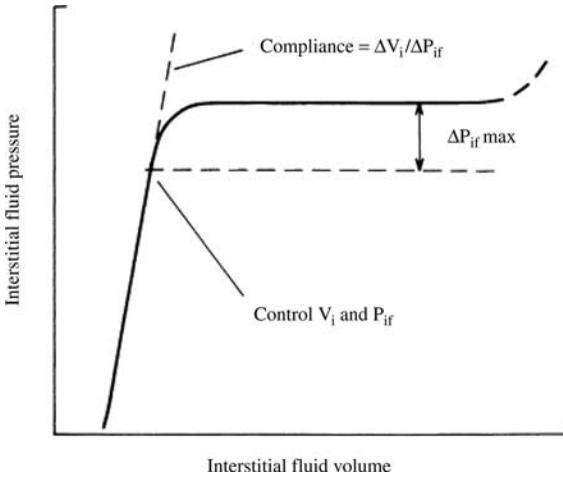


Figure 2 Interstitial fluid volume (V_i)—(P_{if}) pressure in skin and muscle. *Source:* From Ref. 88.

would be more correct to avoid interstitial accumulation. Nomograms for fluid administration in these situations are available (Fig. 3) (75).

ADVERSE EFFECTS OF LARGE-VOLUME CRYSTALLOID INFUSION

There is no doubt that excess fluid accumulation can cause several problems after surgery. The extravascular accumulation of infused crystalloids will mainly occur in tissues with high compliance like skin and connective tissue, but also in vital organs like the lungs and kidney (84). Furthermore, of great concern is inhibition of gastrointestinal motility and delayed healing of anastomoses (73). Based on this, it seems rational to severely restrict or even omit maintenance fluids and just replace upcoming losses during minor elective cases (92). A condition is that the patient arrives for surgery in a normovolemic state, which implies that the patient should be allowed to drink clear fluids up to two hours before surgery.

Fluid accumulation in the lungs may predispose patients to pneumonia, respiratory problems, and delayed ventilatory support withdrawal. Based on a one-year retrospective review of patients undergoing major surgery at two university medical centers in the United States, an annual incidence of 8,000 to 74,000 cases of postoperative pulmonary edema occurred, including a frequency of 2.6% in patients without important comorbidities (93). Another study (94) showed that a significant portion of deaths in surgical service could be attributed to fluid overload on the basis of continuous intravenous infusion, significant acute weight gain, and

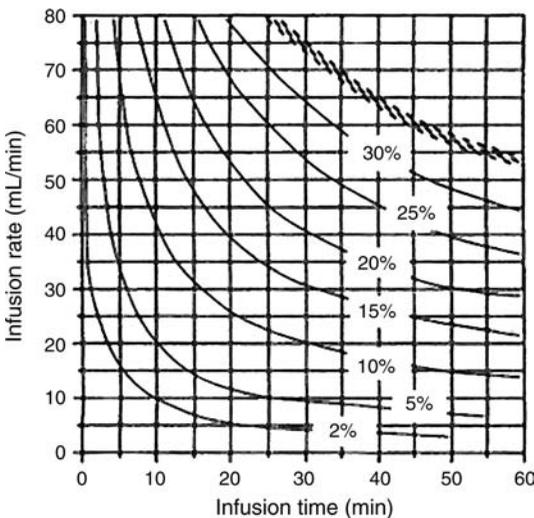


Figure 3 A nomogram showing the relation between infusion rate and infusion time for crystalloid solution when 900 mL of blood has been withdrawn. The dilution required to obtain normovolemia is indicated by the thick irregular line. The % isobars show the predicted dilution of v_1 in a kinetic model. *Source:* From Ref. 75.

clinical evidence of abnormal extracellular fluid volume. The literature on the effects of crystalloid infusion on pulmonary extravascular fluid accumulation is conflicting. It is obvious that the lung lymph flow has a capability to vastly increase when challenged by lower plasma oncotic forces (95–97). These studies demonstrate that in the absence of lung injury, lung lymph flow is directly related to vascular pressure and inversely related to oncotic pressure. Several animal studies where pulmonary endothelial damage was induced showed that when microvascular leak was present, crystalloids may have been a better or at least as good a choice as a solution with larger molecules (98).

Clinical data supporting significant deleterious effects of crystalloid infusions are not supported in large studies of critically ill patients (99–101). However, these data are from meta-analyses that contain a large number of studies that differ in underlying illness and treatment regimes. Brandstrup et al. in a recent randomized study on colorectal surgical patients using restricted versus standard fluid regime showed significantly higher morbidity in the group given larger amounts of fluid (92). Normal control of interstitial fluid volume is obtained via changes in hydrostatic and colloid osmotic pressures and the recirculation via lymph vessels. When significant volume has been given, the interstitial fluid to volume pressure relationship is at some point deranged and the interstitial compliance will become infinite leading to edema (88). The interstitium is likely a future area for pharmacological intervention.

When the endothelium is deranged due to inflammatory response, there is raised capillary filtration combined with lowered interstitial hydrostatic pressure, further enhancing the capillary filtration (102–104).

EFFECTS OF CRYSTALLOID INFUSION ON IMMUNE FUNCTION

Trauma, surgery, and hemorrhage stimulate the immune system. During trauma with significant hemorrhagic shock, there is neutrophil activation, adherence, and emigration into tissues contributing to the systemic inflammatory response, which can lead to ARDS and multiorgan failure. When hemorrhaging experimental animals, lactated Ringer's caused a burst of activity of neutrophils compared to resuscitation with blood or hypertonic saline where no such activity could be found (105,106). These studies suggest that fluid resuscitation from hemorrhagic shock is not innocuous, and that the type of fluid chosen may contribute to the inflammatory syndrome and promote apoptosis in highly vulnerable tissues like the gut (107).

EFFECTS OF CRYSTALLOIDS ON ACID-BASE BALANCE

Cushing described in 1901 deleterious effects of crystalloids in muscle preparations (108). Much interest has been shown in the electrolyte composition of crystalloids. During shock and ischemic conditions, there is loss of intracellular potassium and an increase in intracellular sodium due to malfunction of the sodium–potassium pump. This can be exacerbated by sodium chloride causing hyperchloremic acidosis. Most crystalloid solutions are acidotic and have high chloride content. Traditionally, the saline-induced acidosis has been explained by the dilution of bicarbonate in plasma. However, studies have shown high chloride levels in spite of unchanged plasma volume (109). A more extended explanation is that the addition of saline is altering the dissociation of water, leading to more free hydrogen, which is measured as a fall in pH (110,111). Because of this, hyperchloremic acidosis may be an issue even with perioperative fluid management during stable conditions when large amounts of saline 0.9% are given (109,112,113). In a study by Wilkes et al., patients were randomized to the colloid Hextend, which contains 6% hetastarch in a solution like Ringer's lactate but with magnesium and lactate and lactated Ringer's, or the 6% hetastarch in saline, and the crystalloid saline. No patient developed hyperchloremic acidosis in the group with lactated Ringer's (114). There has been a debate on whether the acidosis caused by hyperchloremia actually has clinical relevance (115) and although there is conflicting evidence, it has been shown that hemostatic defects, impaired urinary output, (116) and changes of the central nervous system occur both objectively and subjectively (117). There is furthermore a raised level of abdominal discomfort when patients are given 0.9% saline instead of lactated Ringer's (117). Lactated Ringer's is a racemic mixture containing two stereoisomers of lactate: D(–) lactate and L(+) lactate. Metabolism of D-lactate and L-lactate occurs via different pathways and produces distinct metabolic consequences. A rise in serum D-lactate alters neurologic function, producing encephalopathy

and also possibly various degrees of cardiac arrhythmogenicity in animal studies (118). Current regimes of Ringer's use racemic mixtures of lactate or acetate and show no signs of toxicity when administered in large volumes during resuscitation. The significant advantage of using lactated or acetated Ringer's is that it provides a source of bicarbonate as a result of the metabolism of CO₂ and H₂O and unlike bicarbonate, lactated or acetated Ringer's do not precipitate calcium when added to intravenous fluids. Acetate-containing Ringer's seems at least theoretically more advantageous because acetate can be metabolized by all tissue cells. Lactate can only be metabolized by the liver or kidney. It is doubtful whether this has any clinical relevance except when severe shock is at hand.

EFFECTS ON COAGULATION

Several studies have shown that both in vitro and in vivo crystalloids cause a hypercoagulability (119–122). The probable cause for this is an imbalance between naturally occurring anticoagulants and activated procoagulants with a reduction in antithrombin III being the most important. This occurs when infusion is rapid (122,123) and may have some consequences for patients with vascular diseases (124).

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12 Colloid Fluids

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INTRODUCTION

The purpose of this chapter is to compare colloid solutions based on their different characteristics. The results of outcome studies comparing fluids will be covered elsewhere. We will first discuss basic notions; thereafter, general properties of colloids will be addressed, before finishing with a review of each available solution. It is noteworthy that the availability of solutions in North America and in Europe is not the same and we will, therefore, try to limit discussion to general aspects rather than going into the specifics of individual fluids.

To correctly understand and define what a colloid is, it is useful to review two basic physiological concepts: body fluid compartments and Starling's law. The total body water is divided into body fluid compartments, namely the intracellular and extracellular spaces, which are separated by the cell membrane (Fig. 1). The extracellular space is further divided into intravascular and interstitial compartments separated by the capillary membrane. Water can freely pass from one space to another, but electrolytes can move freely only between the two extracellular components. Larger molecules such as proteins are not readily exchanged between those spaces in health individuals.

Another concept of prime importance when discussing colloids is the simplified Starling's law that rules the fluid exchange between intravascular and interstitial compartments. This equation states that fluid movement depends on two gradients: the gradient between intravascular and interstitial hydrostatic pressures ($P_{iv} - P_{it}$) that tends to move fluid outwards from the intravascular space, and the gradient between oncotic pressures in those two compartments ($\pi_{iv} - \pi_{it}$) favoring the retention of fluid inside the intravascular space. The reflection coefficient, illustrated by σ , is a measure of permeability of the membrane to the passage of proteins. The lower the σ value, the greater the passage of proteins and the less the influence of oncotic pressure gradient on transmembrane exchange. In health, passage of proteins is relatively unimportant.

Those two concepts help us to define what a colloid is, namely a high molecular weight (MW) substance that largely remains in the intravascular compartment, thereby generating an oncotic pressure. Colloids are considered to have a greater intravascular persistence when compared to crystalloids, based on these facts. This property is lost, however, when capillary membranes are altered.

Human albumin, hydroxyethyl starch (HES), gelatins, and dextran solutions are the main colloids. Other substances are considered colloids but are restricted to specific indications and will be discussed elsewhere. Fresh frozen plasma is one such solution; its administration should be restricted to specific indications including the need to provide coagulation factors.

COMPARATIVE DISCUSSION OF THE PRINCIPAL COLLOIDS

Table 1 describes the major characteristics of the different colloids. We will discuss these in general before reviewing individual solutions.

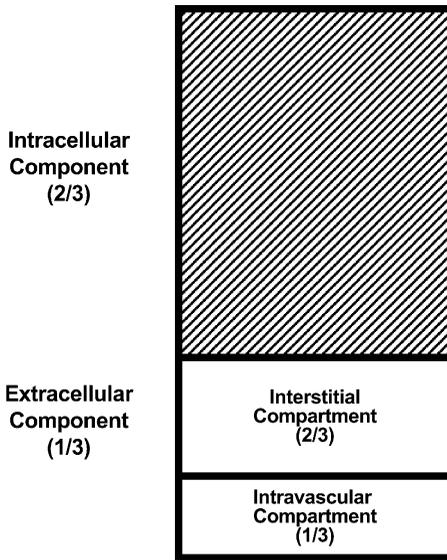


Figure 1 Schematic representation of division of body fluid compartments.

Molecular Weight

The MW of a colloid directly influences its intravascular persistence. However, artificial colloids are polymers containing molecules with a wide range of MW. Thus, it is better to speak in terms of the number average MW to describe each substance, because this figure accurately describes the colloid and is linked to intravascular persistence. Gelatins have the smallest MW, whereas HES solutions have the highest, accounting for their different intravascular persistence (1).

Osmolality and Oncotic Pressure

Almost all colloid solutions have a normal osmolality. The oncocity of the solution will influence the vascular expansion, as predicted by Starling's law. The higher the oncotic pressure, the greater the initial volume expansion.

Plasma Half-Life

The plasma half-life of a colloid depends on its MW, the elimination route, and, of course, the involved organ function (mainly eliminated by the renal route). Half-lives of colloids vary greatly and will be discussed when reviewing individual solutions.

Plasma Volume Expansion

The degree of volume expansion is mainly determined by the MW, whereas the intravascular persistence is also determined by the elimination of the colloid. When compared to crystalloids, colloids induce a greater plasma volume expansion for the same administered volume. Thus, all colloids are good volume expanders. The duration of volume expansion varies, however, among the different colloids. Gelatins have the shortest duration of volume expansion.

Acid-Base Composition

Albumin and gelatin solutions have physiological pH, while other solutions tend to have acidic pH. The clinical relevance of this observation is, however, far from elucidated and probably negligible.

Electrolyte Content

With crystalloids, effective volume replacement requires sodium administration, so colloid solutions have been proposed as salt-free preparations. For example, the sodium concentration is been kept low in "salt-poor albumin". However, the sodium content of other commercially

Table 1 Properties of Colloid Fluids that Are Commercially Available

	Albumin solutions			Starches		Dextrans		Gelatins
	4%, 5%	20%, 25%	6% or 10% pentastarch	6% hetastarches	10% dextran	3% dextran 60 and 6% dextran 70	Succinylated and cross-linked: 2.5%, 3%, 4%; urea-linked: 3.5%	
Available solutions					40		30–35 300–350	
Molecular weight (kDa)	69		100–450		40–70			
Osmolality (mOsm/L)	300	1500	300–326		280–324			
Oncotic pressure (mmHg)	19–30	74–120	23–82		20–60		25–42	
Initial volume expansion (%)	70–100	200–300	100–160		100–200	80–140	70–100	
Duration of volume expansion (hrs)	≤24		≤12	≤4–36	≤4–6	≤8–24	≤4–6	
Plasma half-life (hrs)	16–24		2–12		2	~24	~2–9	
Possible side effects			Alteration of coagulation Pruritus Possible renal dysfunction Anaphylactoid reactions (rare)	Alteration of coagulation	Alteration of blood viscosity Alteration of coagulation Alteration of renal function Anaphylactoid reactions Allergic reactions		High calcium content (for urea-linked) Anaphylactoid reactions	

available colloid solutions is similar to that of crystalloid solutions, while the potassium concentration differs. Urea-linked gelatin solutions contain a small, but not negligible, concentration of potassium. Calcium, similarly, is also present in these gelatin solutions.

Pharmacoeconomic Dimension

Colloids are considered expensive compared to crystalloids. Albumin, the sole natural colloid, is the most costly on a per liter basis in Europe. However, if cost were the only factor in reaching a hemodynamic target, the situation would be simple, but other aspects must be taken into consideration. For example, what about the edema that develops when large volume of crystalloids is infused? What about other possible beneficial effects on organ function? What about effects on length of stay, need for mechanical ventilation, and tolerance to enteral feeding? Even a minor effect on organ function may result in a lesser need for expensive technology and thus be cost-effective. Unfortunately, data on those questions are lacking, and rigorous trials are needed (2).

SPECIFIC PROPERTIES OF COLLOIDS

Human Albumin Solutions

Albumin, the principal natural colloid, possesses unique properties. It contributes to about 80% of the normal oncotic pressure (3,4), but in states of increased capillary permeability, this relationship is not so clear, because other substances can contribute to the oncotic pressure (5).

Albumin has a long half-life (exceeding 16 hours). When administered, two phases are observed. The first depends on the transcapillary exchange rate that corresponds to the passage of albumin from the intravascular to the extravascular compartments. The mechanism by which it occurs is incompletely defined, but albumin passes through pores in the capillary membrane and also makes use of a transporter called albondin (6). The second phase is a function of the fractional degradation rate.

The increase in intravascular volume is about 500 mL following administration of 100 mL of 25% albumin solution (7), mainly due to the passage of fluid from the interstitial space into the plasma as a result of the increase in oncotic pressure (8).

Albumin is the principal binding protein of endogenous or exogenous substances (9). For drugs that are strongly linked to albumin, and those with narrow therapeutic ranges and in states of hypoalbuminemia, this will increase the free fraction of the drug. For some drugs, this could lead to toxicity. Phenytoin is a good example of this situation (10,11). For other drugs, this could lead to beneficial effects, as has been described with ceftriaxone (12).

Albumin has also been shown to possess antioxidant and scavenger effects. Albumin binds free oxygen radicals (13), exchanges thiol groups (14), and plays a role in the modulation of other substances involved in oxidation reactions (15).

Albumin influences coagulation (16,17). It decreases platelet aggregation (16) and possesses heparin-like activity, being able to potentialize antithrombin (17).

Albumin, a negatively charged protein, contributes to the formation of the normal anion gap, influencing the acid–base status (18).

Although controversial, there is evidence that albumin might influence the microcirculation by modifying capillary permeability (19). The protein, due to its high MW, is thought to be able to block leaks present in the capillary membrane.

Finally, studies support a role of albumin in the modulation of apoptosis in humans (20,21). With modern processing techniques, transmission of infectious disease is rare, and albumin solutions have a long profile of safety (22). Anaphylaxis induced by administration of albumin has been reported in about 1.5% of cases (23).

Hydroxyethyl Starch Solutions

Starches are derived from glycopectins that have been modified by the addition of hydroxyethyl groups, preventing them from degradation by endogenous amylase. The heterogeneity of HES solutions makes a classification difficult. HES are characterized by the following properties (24):

- Concentration: low (6%) or high (10%)
- Average MW: low (~70 kDa), medium (~200 kDa), or high (~450 kDa)

- Degree of substitution: low (0.45–0.58) or high (0.62–0.70)
- C2/C6 ratio: low (< 8) or high (> 8)

The degree of substitution refers to the modification of the original substance by the addition of hydroxyethyl groups. The higher the degree of substitution, the greater the resistance to degradation, and consequently, the longer its intravascular persistence.

The C2/C6 ratio refers to the site where substitution has occurred on the initial glucose molecule and, similarly, the higher the C2/C6 ratio, the longer the half-life and, thus, the persistence in the blood.

Like albumin solutions, the expanded volume is generally higher than the infused one, especially for more concentrated solutions (25–30). Such an intravascular expansion has been considered to be equal to or greater than that obtained with dextrans (28,29,31,32). The increase in colloid osmotic pressure obtained with HES is considered equivalent to that obtained with albumin (33).

The half-life depends, of course, on the MW, but also on accumulation in the tissues. Kidneys eliminate HES, although some of them must be broken down by endogenous enzymes, with about 70% of the administered substance eliminated in eight days and about 90% in 42 days (34). HES have also been shown to accumulate in the reticuloendothelial system, including the subcutaneous tissue, accounting for some cases of prolonged pruritus in patients who have received these solutions (35), although this finding has been challenged (36).

A new generation of low MW substances has been developed and has been shown to possess similar properties regarding volume expansion, but with fewer side effects (see sections on “Gelatin Solutions” and “Dextran Solutions” below) (37–39).

HES solutions can alter the coagulation system in a dose-related manner. These effects are also directly related to the MW of the HES. Apart from the MW, it appears that the degree of substitution is of importance in these findings (40). Whether or not low MW HES have the same effects on coagulation is doubtful (41). Such alterations have long been attributed to a dilution, but it is now clear that other effects are implicated. HES solutions decrease platelet aggregation, von Willebrand factor, factor VIII, and clot strength, and increase prothrombin and partial thromboplastin times (24,42–44).

Effects of HES on renal function are also a concern. One study by Schortgen et al. (45) has shown an increased incidence of renal failure in septic patients when they were transfused with a 6% HES solution. Again, it is questionable whether this result can be applied to lower MW solutions. Other studies on the renal effects of HES have shown conflicting results (46–50).

Anaphylactoid reactions have been reported in a low percentage of cases (less than 0.1%) (51,52).

Pentastarch solutions have a lower MW than HES and they possess fewer substituted hydroxyethyl groups (53,54). These solutions are available as 6% or 10% solutions with a mean average MW of about 264,000 kDa. Their tissue retention is not so pronounced and their half-life is about five hours (55). Just like the other colloids, they are able to expand the intravascular volume by more than the infused volume.

Gelatin Solutions

Gelatin solutions are derived from bovine collagen and are not available in North America. There are two types of gelatin solutions, the urea-bridged and the succinylated forms.

The relatively low MW of these substances makes them good, but transient, volume expanders. Gelatin solutions are rapidly excreted by the kidneys.

Although gelatins are usually considered free of effects on the coagulation system, some have demonstrated an influence on clotting (56).

Gelatin solutions can generate more allergic reactions than other solutions. Anaphylactoid reactions occur in 0.345% of patients (52), but true anaphylactic reactions are rare.

Dextran Solutions

Dextran solutions result from the hydroxylation of polysaccharides by a bacterial source, resulting in substances with various MWs. Two main types of dextran solution exist, dextran-40 and 70, referring to the average MW.

The administration of 500 mL of dextran-40 can increase intravascular volume by 750 mL at one hour (57).

The kidneys primarily excrete dextran solutions, although a non-negligible portion is cleared endogenously. Smaller molecules (14,000–18,000 kDa) can be readily excreted in 15 minutes, whereas larger molecules (55,000 kDa) stay in the circulation for several days (58). As a rule of thumb, up to 40% of dextran-40 and 70% of dextran-70 remains in the circulation at 12 hours (59,60).

Dextrans can influence the coagulation system in various ways. They can decrease platelet adhesion (61), induce fibrinolysis (62), decrease fibrinogen (63), and also lower blood viscosity (64). These effects explain why dextran solutions have been used by some as an anticoagulant drug in the prevention of thromboembolism phenomenon. However, the use of heparin has replaced dextrans for most anticoagulation indications (65). These effects also explain why, when administered in quantity, a bleeding tendency can be observed.

Dextran solutions have been linked to the development of renal failure, especially in hypovolemic patients (66–70).

Anaphylactoid reactions remain the major risk with dextran solutions (described in 0.273% of patients with dextran-70) (51,52). They are, however, preventable.

CONCLUSION

Complex issues exist when discussing colloid solutions (Fig. 2). Compared to crystalloids, colloid solutions generally remain longer in the intravascular space, resulting in less edema. With regard to colloids, making a choice requires the clinician to have a thorough knowledge of the different properties and side effects of available preparations, and results from outcome studies.

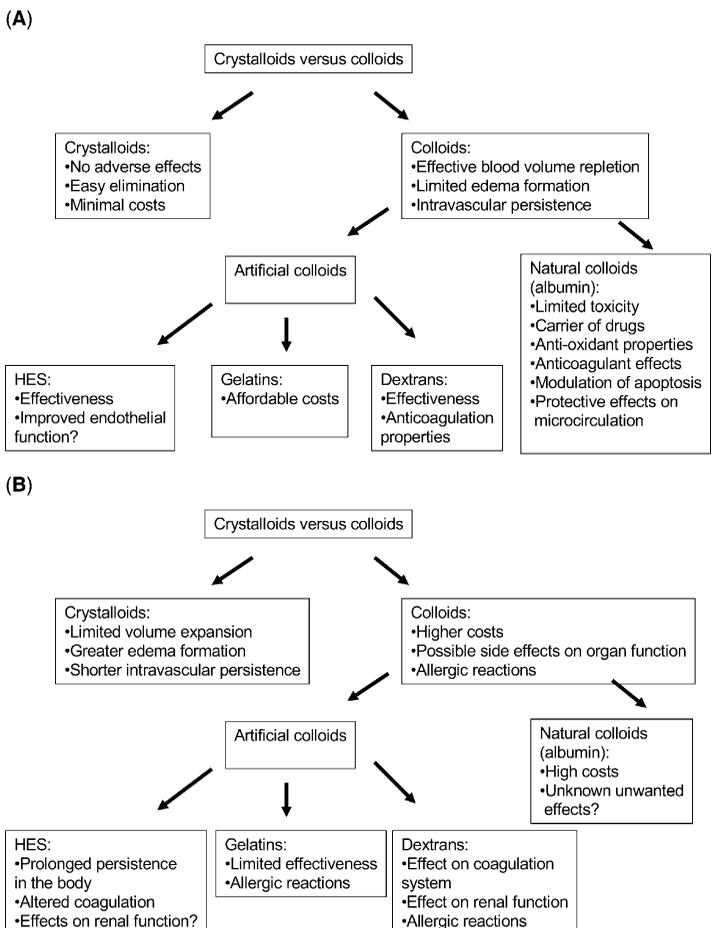


Figure 2 Some of the advantages (A) and disadvantages (B) of various colloid solutions.

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13 | Hypertonic Solutions

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HISTORY AND BACKGROUND

In the military setting, where longer transport times and logistical concerns present more difficult problems than in the civilian setting, there is a need for small-volume resuscitation fluids (1). In the past two decades, the answer to this requirement has been the administration of hypertonic saline (HS) solutions with and without the addition of colloids. In 1999, the Committee on Fluid Resuscitation for Combat Casualties for the U.S. Army recommended the use of HS for the treatment of combat casualties (2). The concept behind this treatment strategy is, however, by no means new. During World War I, physicians fully recognized the importance of intravascular volume replacement in hemorrhage. George Crile, who was working in a field hospital in France in 1917, experimented with the infusion of seawater (with a salinity of approximately 35%) diluted in sterile water to treat a pulseless soldier with a gunshot wound (3). The treatment was successful for this particular soldier, but it was not put into general practice. In 1926, however, Silbert used 5% saline to treat Burger's disease (4). Moderately hypertonic solutions of 1.5% to 3% have been used to treat patients with burn shock and hypovolemia since the 1970s (5). There was a renewed interest in hypertonic solutions in 1980, when researchers in São Paulo, Brazil reported using 2400 mOsm HS (7.5%) to treat severe hemorrhagic shock in animals successfully (6,7). Numerous studies over the past two decades have established that HS infusions promote diuresis/natriuresis, augment cardiac output, increase cardiac contractility, and directly vasodilate the peripheral vasculature. Adding a colloid can transiently (depending on the type added) expand and preserve plasma volume (8). Several experimental and clinical studies have investigated the efficacy, dosages, and infusion times of different hyperosmotic solutions—primarily 7.5% HS administered solely or in combination with dextran or hetastarch (9–11). The focus now is on 7.5% HS, 7.5% HS/6% dextran 70 (HSD), and 7.2% or 7.5% HS/6% hetastarch (HHS). Although originally developed for hypovolemic resuscitation in the prehospital setting, these solutions have also been used to treat burns, sepsis, nontraumatic hemorrhages, and vascular and cerebral injuries.

MECHANISMS OF HYPERTONIC SOLUTIONS

Volume Expansion

The initial incentive for the clinical study of HS solutions was the early work on survival of animals (6,12,13). Velasco et al. could show that in dogs that were lightly anesthetized and hemorrhaged to a blood pressure of 40 mmHg and sustained for 30 minutes, the administration of 4 mL/kg (10% of the blood lost) of a 7.5% HS solution rapidly restored blood pressure and improved survival (6). One of the most striking features of infusing hypertonic solutions is the rapid onset of plasma volume expansion (8,14,15). This is accomplished by the mobilization of fluid from the extravascular into the vascular space, because of the concentration difference created by the infusion of the hypertonic solution (8,16,17). An analysis of transcapillary-driving forces shows a nearly immediate vascular expansion after HS infusion. This effect is even greater and more prolonged if a colloid (dextran or starch) is added (6,8,13,18–28). On the basis of field studies of resuscitation with hypertonic solutions, it was estimated that administration of 250 mL HSD to a 70-kg patient who had suffered a 2-L blood loss would result in plasma volume expansion of at least 700 mL (or, in other words, a three- to fourfold increase to the infused volume). To achieve at least momentarily the equivalent plasma volume expansion with lactated Ringer's, the solution mostly advocated for resuscitation of trauma, it has been estimated that nearly 3 L would be necessary (29). Crystalloids will quickly

redistribute into the interstitial space and will have poor sustained volume effect. Other concerns are postresuscitation edema from infusing large amounts of crystalloids. Recent kinetic studies have further shown that the volume effect, or "efficacy," is about four times as high for HS and seven times as high for HSD compared with the equivalent amount of 0.9% saline or lactated Ringer's (27,30).

Cardiac Effects and Vascular Effects

Several reasons for the instant volume expansion have been suggested. One theory postulating a vagus-mediated pulmonary reflex, which dilates peripheral resistance vessels while constricting venous capacitance vessels (31) has been ruled out (32). Instead, some investigators have suggested that the instant volume expansion is, at least in part, centrally mediated (33,34). A more recent explanation is that the rapid onset of cardiovascular response to HS infusion is explained by the mobilization of endothelial cell water, the reduction of hydraulic resistance, and the restoration of the sodium/potassium pump, which in turn restores intracellular pH, adenosine triphosphate, and Ca^{2+} levels (9). There is an enhancement of left ventricular contractile force by the increase in plasma osmolality and a greater preload due to the expansion of blood volume. Due to the decreased resistance caused by arteriolar vasodilatation, afterload is reduced. The increase in the cardiac output is proportionally more than the decrease in the oxygen-carrying capacity caused by blood volume expansion and hemodilution (8,19–26,35,36). Early in the course of hypovolemia and shock, the lumen of the capillaries become narrower as a result of swelling of hypoxic endothelial cells (37,38) and adhesion of activated polymorphonuclear leukocytes to the endothelium of postcapillary venules (39), which may block local flow. This is followed by the release of vasoactive mediators and free radicals that promote macromolecular leakage, interstitial edema, and redistribution of tissue perfusion, which results in compromised oxygen transport to tissues. When administering hypertonic solutions, endogenous fluid is mobilized first from the microvascular endothelium and the red blood cells, with the most pronounced effect taking place in those capillaries that have a swollen endothelium (38). Increasing concentrations of sodium have a positive inotropic effect (40) at an osmolality range of 240 to 320 mOsm, whereas concentrations higher than 320 mOsm have a negative effect. This could possibly explain why too rapid infusion of HS could lead to a decrease in blood pressure.

Renal Effects

Renal physiologists have infused 5% to 10% salt solutions to determine how the kidneys handle an acute salt load and increased serum osmolality (41).

Administration of hypertonic solutions is associated with an increased urine output, which is in turn associated with a natriuresis, to which, in hypovolemic conditions, rectification of renal blood flow and glomerular filtration are contributing factors (40,42). The improvement in diuresis, which occurs even during hypovolemia, is the result of an osmotic diuresis.

Coagulation Effects

The administration of hypertonic solutions affects coagulation by the extent of hemodilution (43). The slight effect of prolongation of prothrombin and decreased human platelet aggregation when diluting human blood with HSD is attributed to the HS component (40). Because dextran 70 is a part of HSD, there have been concerns about combined causes of impaired hemostasis (44). In fact, the doses of dextran needed to impair hemostasis must be much higher (45), and there is no interaction between the HS component and the dextran component. Furthermore, there are no effects on typing or cross-matching when using clinical doses of HSD (46).

Immunologic Effects

The physiologic responses to trauma and hemorrhage are manifestations of complex cellular and molecular events. Inflammatory cells, including macrophages, polymorphonuclear cells, and lymphocytes are recruited to the site of injury and secrete inflammatory mediators. In response to hypoperfusion and subsequent reperfusion, there is an activation of leukocytes

with release of cytotoxic substances and reactive oxygen species that damage the endothelial barrier. The inflammatory response to injury involves an interplay between hormones (e.g., catecholamines, adrenocorticotrophic hormone, cortisol, and glucagon), cytokines [e.g., tumor necrosis factor- α , interleukin (IL) -6, IL-8, IL-10, and IL-1 β], and other cellular products such as proteases, free radicals, eicosanoids, acute-phase reactants, and growth factors (47,48). The individual response is, however, determined by many factors, including the virulence of the organism, the size of the inoculum, and the patient's coexisting conditions, age, and polymorphisms in genes for cytokines (49).

Posttraumatic immunosuppression is a well-documented phenomenon that has been implicated in the pathogenesis of complications such as adult respiratory distress syndrome, sepsis, and multiple organ failure. Therapeutic approaches to counter these threats have been the focus of numerous investigations for many years. Traditional therapies have concentrated on antibiotics, mechanical ventilation, and fluid therapy guided by target endpoints such as oxygenation, blood pressure, and urine output (50). Current fluid regimens use large volumes of both crystalloids and colloids (50). Many studies have shown the detrimental effect of aggressive crystalloid treatment causing overload (51). The infusion of 0.9% saline causes hyperchloremia, and recent research has shown that lactated Ringer's solution itself has inflammatory properties (52,53).

Efforts to use hypertonic solutions in animal models as a volume expander have shown some promising results (i.e., less volume used and improved cardiac support) (54,55). In addition, HS has been shown to enhance T-cell function *in vitro* and cell-mediated immune function *in vivo* (54). It has been suggested that these capabilities of HS are the result of the ability of the fluid's hypertonicity to costimulate activated T-cells in proliferation and also restore the function of suppressed T-cells. Thus, HS replaces the abundant signal pathway for activating T-cells in immune-compromised patients (54,56). Furthermore, it has been shown that hypertonicity reversibly suppresses several neutrophil functions particularly the neutrophil-endothelial interaction (55,57)—this is a concept that researchers have suggested might protect patients from septic challenge (58), improve intestinal mucosal blood flow (23), and reduce the onset of late complications in trauma patients (1). As in the prehospital scenario (1), animal investigations have shown that HSD should be given as early as possible if it is to be used to enhance the immune response (1,59,60). It has also been shown that hypertonic solutions are associated with the attenuation of the neuroendocrine response to surgery and hemorrhage (23,61). Although it is evident that hypertonicity affects many parts of the immune system *in vivo*, there are few clinical studies addressing the immune effect of HS that show any effect on markers of immune function in humans (57). A study performed on normovolemic women (62) showed no significant changes in the immune response. This may, however, be different in a trauma setting.

CLINICAL USE

Prehospital Use

Instant and safe resuscitation of the patient suffering from hemorrhagic hypotension is attractive to both military and civilian health-care professionals. In warfare, wounds from bullets and shrapnel cause bleeding, hypotension, and, ultimately, hemorrhagic shock (63). Often, the battlefield setting is plagued by long transport times and difficult logistics. Added to these problems is the fact that medics can carry only a limited amount of fluids. From the civilian perspective, conditions are quite different. Typically, transport times are much shorter, and logistical preparations allow ambulances and rescue personnel to carry substantial amounts of fluids.

The types of trauma encountered in each setting also differ. While military medical personnel most often have to deal with penetrating trauma, civilian health-care professionals encounter both penetrating and blunt trauma. The importance of early intervention has been debated (63–68), but there is now widespread consensus to initially stabilize a traumatized victim by securing the airway, stabilizing the neck, and stopping external bleeding. Present prehospital guidelines state that 1 to 2L of lactated Ringer's should be infused rapidly in shock if the insertion of an intravenous (IV) cannula will not delay the transportation of the patient to definitive care (69). These guidelines follow traditional recommendations to immediately replace the lost intravascular volume (70). The principle of massive and aggressive infusion of crystalloids comes from recommendations by Shires et al. (71–73)

who advocated the replacement of extracellular deficits in addition to the lost intravascular volume. These principles were successfully implemented in the Vietnam War. With the advent of rapid transportation systems and trauma centers, however, the type, volume, time of initiation, and even the value of prehospital fluid resuscitation have been challenged over the past 20 years (68,74). The reluctance of certain providers to start IV fluid therapy in the field has been associated primarily with the lack of sufficient education among rescue personnel, the lack of benefit of such administration (68), the risk of rebleeding (68,75,76), and the delay of transportation to definitive care sites (68). Since the development of new technologies, no firm consensus has been reached as to how to initially treat trauma patients, and different trauma protocols have been launched, depending on the different types of trauma and the different settings in which they occur (69,70).

Hypertonic solutions have been used in double-blind studies of patients who are hypotensive and have traumatic injuries (1,18,77–83). A large number of patients have been included in these studies, and criteria for entry have employed measurements that can be attained in the initial minutes of treatment, such as the determination of traumatic injuries, hypotension, and a trauma score (assessment of respiratory rate, blood pressure, and cognitive function) (84,85). Efficacy end point in the studies has been survival. The studies have contained patients with traumatic injuries and hypotension, consequently involving an extremely heterogeneous trauma population with a low probability of survival. Although promising, these clinical trials have not provided definitive data as to the efficacy of hypertonic solutions (86–88). This has been in part due to the limited numbers of enrolled patients and the diversity of the underlying trauma responsible for the injuries. Wade et al. in 1997 conducted an extensive meta-analysis of all randomized prospective clinical trials using hypertonic 7.5% saline solutions to determine whether hypertonic solutions improved survival in patients with hypotension associated with traumatic injury (86). They separated the analysis into the effects of a 250-mL bolus of HS alone and in combination with HSD. The two hypertonic groups were compared with matched groups receiving a 250-mL bolus of isotonic solution. In all cases, additional isotonic solution was administered to continue the hypertonic solution started. After a meticulous search for available studies, the authors found six eligible studies using HS and eight studies using HSD. A total of 615 patients were treated with HSD, and 340 patients were treated with HS. All individual studies were randomized, included a control group, and had as end points survival at discharge or after 30 days. In the meta-analysis for studies using HS, no difference in outcome was found. In the HSD group, all studies (1,18,77–82) except one showed an improvement in survival, but again, differences reached statistical significance in only one of the individual studies (82) and only in specific subpopulations—patients with head injuries (79) and those with penetrating injuries requiring surgery (1). The mean difference of survival calculated for all studies favoring treatment with HSD over controls was 3.5% ($p = 0.07$, one-tailed). The conclusion was that HSD might be beneficial in improving survival in patients with hypotension associated with traumatic injury. Subsequently, a meta-analysis using individual data from six of the eight studies containing data with HSD was performed (83), which showed a significantly lowered mortality for HSD in patients in whom HSD was infused as the first fluid (in contrast to isotonic therapy).

The lesson to be learned from these studies is that the number of patients in individual trauma trials generally has been insufficient to establish statistically significant improved survival, and that aggregate data from these trials are encouraging but not fully significant. Moreover, meta-analysis studies can be criticized (89), because there are difficulties associated with comparing the underlying studies. Because meta-analyses are not generally considered sufficient evidence for regulatory approval, HSD has not been approved for use in the United States. Interestingly, no other currently used IV fluid or volume expander has been required to improve survival in order to be used in the clinical setting. Current fluids are used mainly because they have shown volume-expansion properties. The lack of definitive proof of lowered mortality, coupled with concerns raised among surgeons when Bickell et al. (68) reported that conventional fluid therapy might be inferior to delayed prehospital fluid resuscitation in hypotensive and penetrating trauma patients, has resulted in a general reduction of interest in prehospital resuscitation with hypertonic solutions in the United States.

In Europe and other countries, however, the situation is different. In Austria, HS colloid solution has been in use since 1991. Austria and Brazil were the first countries in which this type of solution was used routinely for resuscitation from severe trauma and shock. In Austria,

HS is mixed with hetastarch (Osmohes—7.2% sodium chloride + 10% hetastarch 200/0.5—now replaced by Hyperhes—7.2% sodium chloride + 6% hydroxyethyl starch 200/0.62). In the past decade, more than 50,000 units have been administered safely. Sweden was the first country to register Rescueflow[®], (7.5% sodium chloride + 6% dextran 70) in 1998 (90). Rescueflow is currently registered in several countries in Europe. Finally, Germany in 2000 approved HyperHAES[®] (7.2% sodium chloride + 6% hetastarch 200/0.5). In the majority of these cases, the standard amount of hypertonic solutions given was 250 mL. The introduction of these solutions in prehospital protocols has encouraged new studies of the possible benefits in different settings and for targeted populations, but currently no new studies have been published that convincingly change the conclusions drawn so far.

Head Trauma

Closed head injury is a common feature of severe blunt trauma. The outcome of closed head injury is determined primarily by the severity of the injury and the age of the patient. Additional important factors are the presence of hypoxia and hypotension (91,92), making the brain vulnerable to secondary brain injury. Because the normal blood–brain barrier is highly impermeable to sodium, small changes in serum sodium exert greater osmotic pressure gradients across the cerebral capillary bed than do relatively large changes in serum protein concentrations (93). Consequently, hypotonic solutions, including lactated Ringer's, are likely to increase brain water. Hypertonic solutions acutely reduce brain water, and therefore tend to reduce intracranial pressure (ICP). In a double-blind, cross-over study in head-injured children, 3% saline decreased ICP significantly, whereas 0.9% saline had no effect (94). Prehospital care of patients should focus on minimizing the effects of secondary insults to the brain (92). Many patients with severe head injury have hypoxemia upon arrival at the hospital, with partial pressure of oxygen values less than 60 mmHg or pulse oximeter saturation readings less than 90% (95,96). Hypoxemia may be caused by direct injuries to the brain as occurs when a driver's head hits the windshield of a car during a crash, or by associated injuries to the chest or major hemorrhage. Considering this, it must be understood that in head injury, hypotension combined with hypoxemia is a severe condition that will increase morbidity and mortality. Studies have highlighted the importance of maintaining the cerebral perfusion pressure (CPP) (91), which is defined as a difference between the mean arterial pressure (MAP) and the ICP:

$$\text{CPP} = \text{MAP} - \text{ICP}$$

MAP could be measured fairly accurately in the field by using noninvasive devices, but it is not possible to measure ICP. However, when the Glasgow Coma Scale Score is 8 or less, the prehospital rescue team should be able to assume that ICP is elevated unless there is substantial evidence to suspect that the low level of consciousness is related to reasons other than trauma or hypoxemia (97). To reach a perfusion higher than the necessary 70 mmHg, the MAP would need to be maintained in the range of 90 to 105 mmHg (assuming an ICP of 20 to 25 mmHg) (98). During the initial management of combined head injury and uncontrolled bleeding in a highly reproductive model, Stern et al. could show that the highest survival was obtained when target MAP was set at 60 mmHg with hypertonic fluid (99). Conventional fluid therapy for head trauma patients or multiple injury patients with head trauma consists of crystalloids, preferably normal saline and a combination of crystalloids and colloids (100,101). Early fluid resuscitation with crystalloid solutions after head injury worsens cerebral hemodynamics (102). Mannitol has conventionally been used to treat increased cerebral pressure (103). Despite some conflicting evidence in animal models showing improved perfusion pressure, but worsened oxygen delivery because of hemodilution (104–106), there may be clinical evidence that HS in combination with colloids could be the fluid of choice for head trauma patients (79,86,92,97,107). However, a large randomized study in Australia that focused on patients with hypotension and severe traumatic brain injury, who also received prehospital resuscitation with HS without added colloid, demonstrated that these patients had almost identical neurological function, six months after injury, as did patients who received conventional fluids (88).

Vascular Surgery

Elective aortic surgery with clamping of the artery is associated with major blood volume shifts and hemodynamic changes when the clamp is removed. 7.2% and 7.5% HS in combination

with hetastarch and dextran have been used to attenuate the hemodynamic responses as well as in the support of intravascular volume during surgery. There are several studies in humans showing improved fluid balance, pulmonary capillary wedge pressure (PCWP), pulmonary arterial pressure, improved cardiac index, better maintenance of blood pressure, improved oxygen delivery, and decreased peripheral resistance (108–111). The most advisable method seems to be to give the fluid bolus of hypertonic solution titrated toward an end point. A feasible end point seems to be PCWP between 13 and 18 mmHg before declamping (112,113). The hypertonic solution is given over a period of 20 minutes via a central venous catheter, so that the infusion is ended just before declamping (111). There are, however, concerns raised about the inaccuracy and raised morbidity with pulmonary artery–guided therapy (114,115). While not neglecting the benefit of hypertonic solutions in these patients, it may be necessary to use other end points.

Coronary Surgery

In patients requiring cardiac surgery, the use of hypertonic solutions appears to be beneficial as an alternative volume therapy to improve fluid balance and cardiac performance pre-, intra-, and postoperatively. This has been established by several researchers using 1.8% NaCl (61,116), 7.5% NaCl in 6% dextran 70 (117–119), 7.2% NaCl in 6% hetastarch (120–123). It seems important to infuse hypertonic solutions in these settings to an end point and not to a fixed dose. The reasons are that hypertonic solutions are the most powerful volume expanders in clinical practice, and consequently titration should be the method of choice toward a feasible end point. It has been suggested to use left ventricular filling pressure (118,119) or highest cardiac index at the lowest possible PCWP (118).

Burn Injury

In the military setting, burn injury remains a constant source of morbidity and mortality. Unlike penetrating trauma, the immediate and sustained fluid requirements necessary for resuscitation of burn injuries preclude the use of limited or hypotensive resuscitation. If the Parkland formula (124) should be followed during prolonged evacuation, this could inevitably mean that a 70-kg soldier with a 40% total body surface area burn would need 11,200 mL of fluid over the first 24 hours and half of that needs to be given over the first eight hours. Hypertonic resuscitation could be an alternative for the cause of limiting the infused volume. A 250-mL HS with or without colloid could be administered over two to four hours to maintain initial plasma volume expansion (125).

ADVERSE EFFECTS

Dose and Rate of Administration

Hypertonic solutions were originally developed for prehospital use and designed to replace larger volumes of isotonic solutions. The reasons for using a standard dose of 4 mL/kg or 250 mL of HS, HSD, or HHS seem to be based more on practicality due to the limited weight a military medic can carry. Although it may be reasonable even in the prehospital area to titrate the solutions toward an end point (75,126), there is still support among some clinicians for using a standard dose for reasons of simplicity. Recent conclusions by Wade et al. from animal data have found prolonged survival time when administering 4 to 11.5 mL/kg of HSD compared to lower doses (127). Although the dose of 4 mL/kg was originally chosen arbitrarily, it seems to avoid peripheral vascular irritation, excessive hypernatremia, and potential neurological sequelae (128). The infusion can be given rapidly in a peripheral vein in order to establish the desired effects. Rapid infusion in two minutes of HS and HSD was initially recommended, but more recent data suggest that slower infusions are equally or more advantageous (129). The greatest concern, apart from accidental perivascular infusion, has been derived from the hypothesis that fluid resuscitation of prehospital trauma can exacerbate uncontrolled internal hemorrhage (75,76,126,130,131). A controlled bleed (less than 1 L) is normally treated adequately by the internal redistribution of fluids and thus does not need IV fluid support. Controlled bleeding greater than 1 L implies a situation in which fluids need to be given, but if IV line insertion will be difficult and transport time will be short, it is recommended to transport to the hospital immediately. In the scenario in which major penetrating

injury to the heart or large vessels has created an uncontrolled bleeding that has not stopped, immediate transport to the proper surgical center is the only thing that will save the patient.

Uncontrolled bleeding that has stopped is seen in some victims of penetrating trauma, but also at times in cases of blunt trauma (132). In such cases, when IV fluid is started before surgical hemostasis, an increased risk of rebleeding should be considered. Because hypertonic solutions tend to increase blood pressure more than isotonic solutions, this could be a potential risk. Consequently, decreasing the rate of infusion and reducing the infused volume to patients with presumptive "uncontrolled bleeding" is recommended (126). However, this recommendation is disputed because the clinical data do not show that the administration of hypertonic solutions increases mortality in the clinical setting (80). Also, the monitoring of "permissive hypotension" or "end-point resuscitation" could be difficult in the field. The results of experimental studies suggesting that administration of HS exacerbates bleeding from injured vessels and leads to early death in anesthetized animals with lacerations in the aorta or cut tails are probably not relevant to the clinical setting in most patients (79,80). Nevertheless, it seems reasonable to slow the infusion time from the originally recommended two to five minutes to 5 to 10 minutes. Furthermore, the timing of the infusion must be considered. In an urban setting with short transport times, it is best to transfer the patient to an emergency department immediately and withhold prehospital fluid unless indicated in severe head trauma. In a longer transport scenario, it is unlikely that health-care providers will start IV infusion earlier than 15 minutes after trauma, and because it takes 15 to 20 minutes for a clot to get organized, the risk of rebleeding should be less likely. During a longer transport, it is the close monitoring of the provider that finally will determine the type and rate of infusion.

The intraosseous route (IO) for the administration of hypertonic solutions has been recommended for combat casualty care (2). Animal research has suggested acute resuscitation efficacy with IO delivery of HS dextran; however, a recent report suggests that soft tissue and bone necrosis can occur hours after treatment (133).

Hypernatremia

Hypernatremia is common with the infusion of hypertonic solutions. Levels of hypernatremia in excess of 165 mmol have been reported without any adverse effects (1). The levels of sodium and raised osmolality usually go up 9 to 12 mmol and return to baseline within four to six hours. The infusion of hypertonic solutions causes an increased diuresis, increased natriuresis, and subsequent kaluresis. As a result, it is recommended that clinicians monitor electrolytes closely. There have been no adverse neurological or neuropathological abnormalities found at autopsy that could be explained by the increase in sodium concentration (81). Furthermore, patients who died had no incidence of central pontine myelinolysis (80,81). However, there is little information as to the use of HS solutions in children who may be more susceptible to the adverse effects of hypernatremia.

Anaphylaxis

It has been suggested that HSD can cause anaphylactic reactions because of the dextran contained in the solution. Patients with hypersensitivity have high plasma titers of dextran-reactive antibodies, particularly, of the immunoglobulin G-class. Infusion of dextran in a patient with such antibodies may cause formation of large immune complexes with ensuing activation of plasma enzyme cascades and anaphylactic reaction. HSD contains a small amount of dextran. Nevertheless, only a few drops of dextran can cause an adverse reaction, and pretreatment with hapten dextran is normally necessary. Trauma patients, however, seem to be more protected with regard to reactions of this type compared to other patients. This may be due to the large amount of circulating catecholamines. Hapten dextran (Promit[®]) normally administered prophylactically against anaphylactics before dextran infusion, was not given in any of the prehospital studies (1,18,77–82). There were no anaphylactic reactions in any of these clinical studies. Similar to dextran, previous exposure to hetastarch can trigger reactive antibodies that cause anaphylactoid or anaphylactic reactions. Clinical experience, however, demonstrates that the administration of HHS to trauma patients is safe (10).

Other Adverse Effects

HS 7.5%, used for acute fluid resuscitation in trauma situations or preoperatively in the management of surgical patients, has a high osmolality of about 2400 mOsm/kg H₂O and may

consequently induce local inflammatory responses. Therefore, it is not surprising that this type of hyperosmolar fluid has been reported to cause sensations of heat and compression around the arm at the infusion. These sensations seem to be transient and will disappear immediately after the completion of the infusion. Because usually a small volume (about 4 mL/kg BW) of HS is infused, it appears that these local adverse effects of HS fluid therapy are rather mild and seem well tolerated (134).

Rapid IV infusion of HS (or 7.5% NaCl + 6% dextran 70) at a dosage of 4 mL/kg BW within 10 minutes has, in addition to previously mentioned local sensations, been reported also to cause a sensation of heat starting in the upper part of the thorax and spreading upward to the throat, face, and head. Slight headache for a few minutes or euphoric feelings may ensue. Such unpleasant transitory sensations of headache and/or heat in the thorax following infusion of HSD seem more pronounced in normovolemic than in hypovolemic individuals (28). It was shown that hypertonic sodium solution, containing either chloride or lactate anions, could induce panic in patients with panic disorders but not in normal healthy subjects (135). These adverse effects must of course be weighed against the benefit of infusing the solution. Also, these side effects are most likely not noticed by trauma patients with lowered level of consciousness.

SUMMARY

The voluminous amount of work reported on hypertonic solutions shows that it is very safe to give them. In 35 clinical trials, more than 1400 patients have received HSD or HSS without any complications (10,136). There are several centers in Europe that use hypertonic solutions mainly for prehospital purposes, but also for in-hospital treatment of severely compromised patients. In the prehospital scenario, patients suffering from severe head trauma seem to be the group that benefits most from receiving hypertonic solutions.

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14 Oxygen-Carrying Plasma Expanders: A New Class of Fluids for Perioperative Support

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INTRODUCTION

Immense scientific and commercial efforts continue toward the development of a safe and effective, synthetic, oxygen-carrying solution that could be used in place of blood or packed red blood cells (pRBCs). The term “blood substitute” is traditionally used to describe such solutions, but most solutions in development provide only two blood functions, oxygen delivery and volume expansion. Hemostasis, humoral and cellular immune defense, and drug and metabolic transport by protein binding are important functions of blood that are not imparted to currently developed blood substitutes. The term “RBC substitute” is more appropriate. However, because the plasma volume (PV) expansion of RBC substitutes is much greater than pRBCs and often greater than clinical colloids, we suggest that this new class of fluids may best be referred to as oxygen-carrying plasma expanders. Hemoglobin (Hb)-based oxygen carriers (HBOCs) will be the major focus of this review, because they have received greater research focus and commercialization, and are farther along in the regulatory process. However, a short discussion on perfluorocarbon solutions will also be presented.

The goal is to produce a safe and effective RBC substitute with the functionality of pRBCs and without the significant limitations of blood, i.e., immune suppression, loss of efficacy with storage, and risk of viral contaminants. Such a product would have a huge market for preoperative and critical care medicine, as a replacement for the current blood supply. Furthermore, the hope is that an easily storable product could be used effectively for prehospital and battlefield trauma where current fluid resuscitation strategies are lacking in efficacy.

BACKGROUND

There are perhaps three main evolutionary advantages for Hb to be contained in RBCs: (i) If RBC Hb was free in plasma, it would generate a plasma colloid osmotic (oncotic) pressure (COP) equal to two to three times that of normal plasma or three to five times that of normal plasma if added on top of the other plasma proteins. This would drastically alter the micro-circulatory Starling forces that determine the balance and partitioning of vascular and extravascular water. (ii) The O₂ dissociation curve of Hb is altered by changes in its immediate chemical environment. Changes in intracellular phosphate allow adaptation to changes in altitude and pulmonary function without requiring alteration of the extracellular milieu. (iii) The Hb molecule is highly unstable in plasma, but chemically stabilized by unique and protected composition of the RBC cytosol. The synthesis and, particularly, the degradation of Hb are biologically costly in that the heme molecule and its iron are toxic and require special enzymatic processing and handling by a family of transport proteins.

The quest for an effective and safe RBC substitute is one of modern medicines most costly and complex undertakings. While some efforts have focused on the development of a completely synthetic RBC substitute, most have focused on modifications to the Hb molecule to impart increased structural stability, normalize oxygen unloading, and induce polymerization and other physical-chemical changes that may or may not have benefit.

The complex challenge of developing an oxygen carrier and the relative availability and familiarity with plasma expanders have focused the development of RBC substitutes almost exclusively on their ability to load and unload oxygen. This is unfortunate because HBOCs

have unique pharmacologic and physiologic properties in solution, which can impart unexpected effects on COP and volume expansion as well as associated hemodynamic responses. The goal of this review is to present and compare the available knowledge on volume expansion effects of RBC substitutes. Several recent reviews have focused on the oxygen carrier properties of RBC substitutes or on their clinical utility (1–3).

SCIENTIFIC AND CLINICAL CHALLENGES

The primary challenges of and progress in the development of RBC substitutes have been discussed in several reviews since the first studies conducted over 30 years ago (3–5). The predominant indications for using pRBCs are anemia, trauma and hemorrhage resuscitation, and replacement of perioperative blood loss. The clinical need and physical characteristic of RBC substitutes suggest two different roles for RBCs—(i) correction of anemia and (ii) resuscitation of hypovolemic blood loss. Formulations of free Hb tetramers made up to the concentration of blood (12–18 g/dL) or the pRBCs (20–25 g/dL) would be excessively hyperoncotic. While normal COP for humans is 28 mmHg, most surgical and anemic patients have some level of hemodilution and substantially lower COP. Polymerization is a strategy used to increase Hb concentration, while minimizing increases in COP.

All HBOCs in advanced clinical testing have Hb concentrations of 13 g/dL or less, and all have a COP greater than that of a typical patient. Hyperoncotic solutions can be effective for correction of hypovolemia, because they are efficient volume expanders. However, pRBCs are rarely administered to correct volume, but are rather used to correct anemia. Anemic patients are typically normovolemic or even hypovolemic, and thus, in order to deliver an effective Hb dose, hypervolemia may be induced. Hypervolemia is often not well tolerated in patients with cardiac dysfunction attributable to heart disease or acute traumatic insult.

The other potential role for a hyperoncotic HBOC is as a resuscitative fluid in patients with hemorrhagic shock in which hypovolemia and not anemia is the primary deficit. Standard-of-care treatment of hemorrhage and trauma is to administer crystalloid solutions to restore volume. Although traditional volume expanders cause some level of anemia, hematocrit (Hct) levels as low as 25 to 30 are tolerated in most patients.

PRODUCTS IN DEVELOPMENT

RBC substitutes under development fall into two general categories—HBOCs and perfluorocarbon-based oxygen carriers.

Table 1 lists most of the RBC substitutes that are or have been in clinical trials as a part of the U.S. Food and Drug Administration's (FDA) regulatory process. Most of the current products are HBOCs, although one perfluorocarbon oxygen carrier (PFOCs) has also progressed to advanced clinical trials.

Table 1 Hb- and Perfluorocarbon-Based RBC Substitutes with Advanced Clinical Testing

Company	HBOC name	Source	Clinical testing
Baxter	HemAssist ^a	Human RBC	Phase III, adverse outcomes, ↑ mortality in trauma
Northfield Labs	Polyheme	Human RBC	Phase II, completed trauma trials Phase III, intraop ongoing
Hemosol	Hemolink	Human RBC	Phase II, adverse events stopped cardiothoracic surgery trials
Biopure	Hemapure	Bovine Hb	Phase III, orthopedic and general surgery ongoing
Curacyte, Inc.	PHP	Human RBC	Phase II, sepsis, cancer
Sangart	Hemospan	Human RBC	Phase II, elective surgery
Somatogen	Optro ^a	Recombinant Hb	Phase II, cardiac surgery excessive vasoconstriction, poor clinical results
Alliance Pharmaceutical	Oxygent ^a	Perfluorocarbon	Phase II, adverse outcome in orthopedic patients—strokes

^aDevelopment cancelled or trials stopped due to adverse outcomes.

Abbreviations: Hb, hemoglobin; RBC, red blood cell; HBOC, hemoglobin-based oxygen carrier; PHP, pyridoxylated hemoglobin polyoxyethylene conjugate.

Table 2 Physical and Chemical Properties of Red Blood Cell Substitutes

HBOC	Chemistry	Hb or PF concentration (g/dL)	COP (g/100 mL) (mmHg)
HemAssist	Diaspirin cross-linked tetramer	10	34
Polyheme	Pyridoxylated tetramers and glutaraldehyde-polymerized	10	
Hemolink	<i>o</i> -Raffinose-polymerized	10	26
Hemopure	Glutaraldehyde-polymerized	13	21
PHP	Pyridoxylated tetramers conjugated with polyoxyethylene	8	46
Hemospan	Tetramers conjugated with polyethylene glycol	4.4	46
Optro	Cross-linked by generic mutation	5	≈15
Oxygent	Perflubron	60%	0

Abbreviations: HBOC, hemoglobin-based oxygen carrier; Hb, hemoglobin; PF, perfluorocarbon; COP, colloid osmotic pressure; PHP, pyridoxylated hemoglobin polyoxyethylene conjugate.

Eight RBC substitutes (Table 2) have advanced to FDA-sanctioned trials. Perhaps the most extensively studied and financed HBOC was HemAssistTM or diaspirin cross-linked hemoglobin (DCLHb), which ultimately failed dramatically. Over 100 animal studies and several trials in volunteers and elective surgery patients suggested that DCLHb had acceptable safety and efficacy. However, when used as an early emergency room treatment of severely traumatized patients, a significantly increased mortality was observed (6,7). Subsequent animal studies that mimicked severe trauma and hemorrhage also showed an increase in mortality with DCLHb versus pRBCs, particularly, when DCLHb was infused along with large-volume crystalloid infusions (8–10). The take-home message may be that most animal models and even clinical trials do not have the sensitivity to fully evaluate the safety or efficacy of HBOCs in severely injured patients. Prehospital or emergency room use of HBOC may be more challenging than intraoperative use, where skilled anesthesiologists can pharmacologically titrate the infusion rate and administer drugs to prevent extreme hemodynamic alterations.

The conventional wisdom is that, to be effective, a HBOC must be able to increase the Hb concentration in blood, have an O₂ dissociation curve similar to red cell Hb, be devoid of severe vasoconstrictive effects, and be iso-oncotic or slightly hyperoncotic with a high Hb concentration. An added, perceived HBOC benefit is that such solutions have low viscosity, thus augmenting cardiac output (CO) while reducing cardiac work. The Hb substrate used by the different pharmaceutical companies comes from outdated human and bovine blood or human Hb variants produced by genetically altered *Escherichia coli*. Several products including Baxter HealthCare's HemAssistTM, Northfield Laboratories' PolyhemeTM, Biopure's HemopureTM, Hemosol's Hemolink, and Alliance's Oxygent have advanced to large scale FDA Phase III trials (Table 1) (11,12). However, research setbacks and disappointing trials have occurred more often than not. DCLHb, developed by the U.S. Army and Baxter's Hemoglobin Therapeutics, is the best-studied RBC substitute. DCLHb's development was cancelled after it exhibited a high mortality rate in trauma trials (6). Somatogen cancelled the development of Optro after cardiac surgery trials of its product produced adverse events. Hemosol's development was terminated as a phase III trial of Hemolink had an imbalance in adverse events. The PFOC that had advanced the farthest toward regulatory approval is Alliance's Oxygent, whose development was terminated due to a higher incidence of strokes in the Oxygent-treated patients (13). Both Northfield's Polyheme and Biopure's Hemopure continue with their phase III clinical research. Because of the dramatic failures in safety issues, the FDA is likely to be cautious and conservative before granting marketing approval to an RBC substitute. A commercially available blood substitute may be a matter of a few months or many years away.

Perfluorocarbon-Based Oxygen Carriers

Perfluorocarbons are hydrophobic liquids with a high solubility for oxygen (14,15). It is necessary to emulsify perfluorocarbons with phospholipids in a crystalloid solution for intravenous use. These emulsions generate no oncotic pressure unless a colloid solution is part of the formulation; in general, they are made up in buffered electrolyte solutions. Typically, they consist of a high-volume content of perfluorocarbon emulsion, e.g., 40% to 60% perfluorocarbon,

and when spun in an Hct tube, the white emulsion is visible and the % content of PFOC in blood (F-crit) can be measured.

The milky white perfluorocarbon emulsions are considered candidates for increasing oxygen delivery during the hemodilution of cardiopulmonary bypass and other major operations with expected blood loss and/or hemodilution. Another potential value of perfluorocarbon emulsions in bypass surgery is a high gas solubility of perfluorocarbon that allows rapid absorption and elimination of gaseous emboli generated during extracorporeal circulation. On the other hand, the emulsion particles can stimulate host defense mechanisms, activate the complement system, and depress the reticuloendothelial system. Such side effects may be of minor consequence and easily treatable, or if severe enough, they would prevent regulatory approval. A high incidence of stroke was evident in the recent Oxygent trial; this outcome may reflect an unfortunate design of protocol or a real and serious side effect (5).

We are unaware of any definitive data on volume expansion properties of PFOCs. Presumably, the perfluorocarbon component would expand PV equal to its infused volume and the crystalloid component would expand PV equal to 20% to 30% of its infused volume. Thus, a 1-L infusion of PFOC with 60% perfluorocarbon and 40% crystalloid might expand blood volume to approximately 700 mL, a volume similar to most clinical colloids. The time course of the volume expansion would be dependent on the vascular retention of perfluorocarbon emulsion and that of its diluent. A potential advantage of expansion using either pRBCs or emulsion is that there is limited dilution of plasma components (proteins, hormones, and nutrients) compared with classic plasma expanders, which dilute in proportion to their expanded volume. It must be stressed that this discussion is only a theoretical estimate of vascular expansion; to our knowledge, there are no reports on vascular volume expansion after the infusion of a PFOC.

TIME COURSES OF VOLUME EXPANSION WITH FLUID INFUSIONS

Fluid infused directly into circulation is distributed over time into the vascular space or extravascular space (intestinal and cellular) or is lost via urine output. Figure 1 shows the time course of these compartments during and following a 24-mL/kg 20-minute bolus infusion of 0.9% NaCl into a conscious sheep (16). Vascular volume expansion was calculated from serial blood sampling and the dilution of the Hct or blood Hb concentration after using indocyanine green measurement of baseline PV (16,17). The relatively low vascular expansion efficacy (vascular expansion/infused volume) of isotonic crystalloid shown in Figure 1 is well described, although the fact that most of the crystalloid leaves the vascular space even as it is infused is generally not appreciated. In practice, two to five times greater volumes of crystalloid are infused to obtain the same expansion as that obtained by an equivalent volume of blood or colloid, particularly albumin, the most abundant plasma protein.

COLLOIDS AND COP

Osmotic pressures are generated by the molar concentration differences of impermeable solute across a semipermeable membrane. In a dilute solution, the osmotic pressure (Π) can be

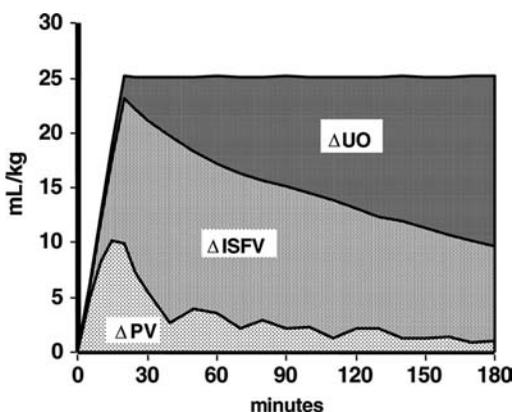


Figure 1 Time course of partitioning of a 24-mL/kg 20-minute bolus of 0.9% NaCl IV infusion into a healthy, conscious sheep with ΔPV , change in plasma volume; $\Delta ISFV$, change in interstitial volume; ΔUO , cumulative urine output. *Source:* Adapted from Ref. 16.

calculated from the concentration in g/L (C), absolute temperature degrees Kelvin (T), the gram molecular weight (M), and the molar gas constant (R) from van't Hoff's law.

$$\Pi = CRT/M$$

This relationship shows that the osmotic pressure is directly proportional to the molar and osmolar concentration of the solute, i.e., the number of free particles. Figure 2 plots the calculated osmotic pressure for human serum albumin (MW = 68,000) from van't Hoff's law and compares it to the actual colloid oncotic pressure of plasma, as defined by the equations of Nita, derived from measured data (18). The large discrepancy and nonlinearity is believed to be due to steric macromolecule-to-macromolecule interactions that occur with significant concentrations of colloid molecules (19,20). The large size of these molecules sterically excludes the spatial distribution of other macromolecules and effectively concentrates their chemical activity in solution. Simply stated, the position of a macromolecule is excluded from a space equal to the molecular diameter of other macromolecules in solution. Thus, the effective concentration and COP in the free solution is essentially enhanced in a nonlinear fashion as molecular size and concentration increases.

In general, these noncolligative properties of colloidal solutions are not easily predictable. Figure 3 compares the oncotic pressure of three molecules with similar molecular weights, human serum albumin, dextran 70, and diaspirin cross-linked albumin. The greater oncotic pressure of albumin versus Hb is partly due to the greater negative charge of the albumin molecule, which causes a Donnan disequilibrium and transmembrane partitioning of cation sodium, which augments the solute difference and oncotic pressure across the capillary wall. The greater oncotic pressure of dextran versus albumin or Hb is caused by the larger molecular size of the less dense dextran molecule and its greater volume exclusion when compared with the two denser proteins. Also plotted is the high COP of Hb decorated with polyethylene glycol that greatly increases the molecular size. Such pegylation is a strategy for stabilizing and imparting unique characteristics to the Hb molecule (21).

The transient expansion with crystalloid results from the near immediate distribution throughout the extracellular space and an induced diuresis, whereas the higher volume expansion efficiency (VEE), expressed as mL expansion per mL infused, of colloids is due to the COP, which maintains infused volume in the circulation. Figure 4 compares data of vascular expansion calculated from dilution measurements of a two-minute bolus infusion of normal saline and 6% dextran 70 in sheep (22). Similar results have been reported for infusion of normal saline and dextran 70 in human volunteers (23). PV is normally maintained by colloid osmotic or oncotic pressure generated by plasma proteins. Normal concentration of plasma proteins produces only 1 to 2 mmol concentration and exerts a force of 1 to 2 mOsm or about 28 mmHg in the plasma of a healthy normal human. The transcappillary gradient is only 5 to 10 mmHg or less than 1 mOsm because the interstitial concentration of plasma proteins and interstitial matrix produces an oncotic pressure equal to about half that of plasma.

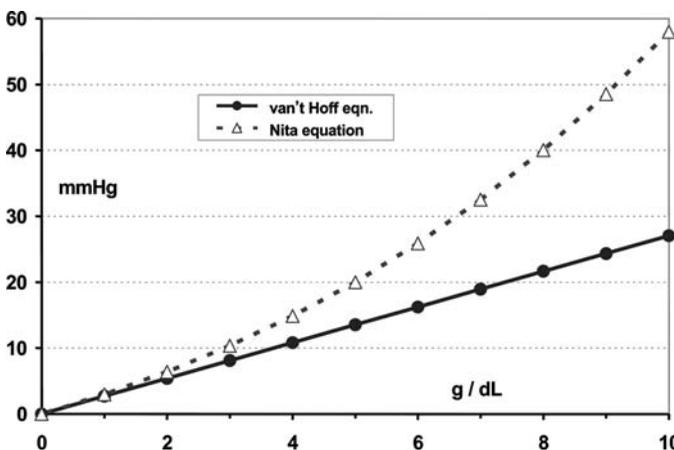


Figure 2 Colloid osmotic pressure of human serum albumin versus concentration plotted from van't Hoff's law for an ideal solution and from Nita's equation determined from measured values. Source: From Ref. 18.

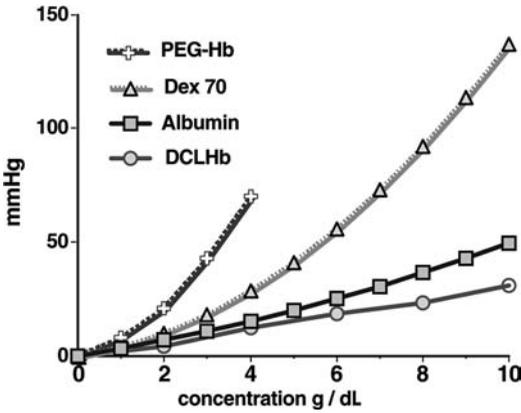


Figure 3 The colloid osmotic pressure (COP) of human albumin, DCLHb and dextran 70 molecules of similar molecular weight. The greater COP of dextran is due to the larger molecular size and excluded volume compared to albumin. The slightly greater COP of albumin versus Hb tetramer is due to a Donnan equilibrium and higher anionic charge of albumin. The much greater oncotc pressure of PEG-Hb is due to its greater molecular size and excluded volume. *Abbreviations:* PEG, polyethylene glycol; Dex70, dextran 70; DCLHb, diaspirin cross-linked hemoglobin. *Source:* From Refs. 20, 43.

PV expansion and VEE are generally found to be proportional to the COP of the infused solution, but can also be influenced by such factors as the vascular halftime of the solute and its hemodynamic and renal effects, which can alter the volume retention concentration. Furthermore, from the observations made in Figures 1 and 2, it can be seen that the relative COPs of two colloids in the blood after dilution may vary from the full strength “in the bag” concentration of the infused solutions due to the nonlinear relationship between COP and concentration. Furthermore, volume expansion changes with different physiologic states such as hydration or when stress hormones alter VEE. For example, hypovolemia due to hemorrhage or burn shock enhances VEE compared to normovolemia (24,25).

Infusion of an HBOC cannot increase the Hb concentration of plasma or blood above the iso-oncotic concentration of the HBOC solution, because water is pulled into the circulation to dilute the infused concentration. This is relatively anemic, 6 to 8 g/dL, for most monomer Hb formulations. Polymerized Hb is one strategy for increasing the Hb concentration without causing excessive increases in COP. Polymerization decreases the number of free molecules, but increases the molecular size and augments the nonlinear increase in COP with concentration. The net result is not easily determined from theory, and direct measurements of COP as well as measurements of plasma expansion and VEE are needed.

The most useful and accurate measure of the volume expansion effects of an RBC substitute would be direct comparisons with other volume expanders in the same animal model

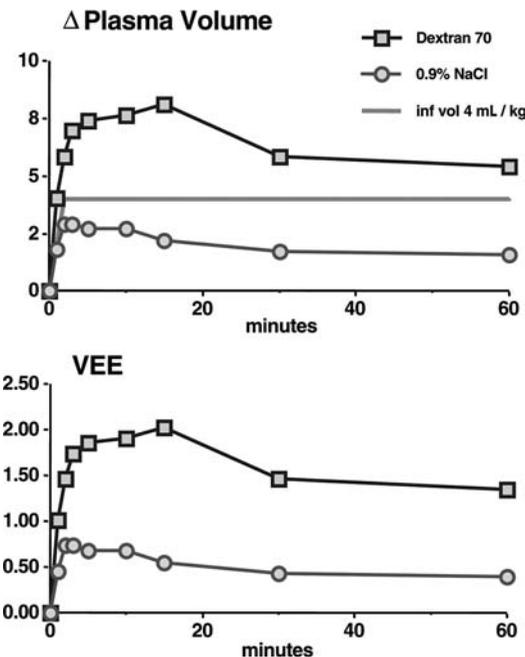


Figure 4 Volume expansion of crystalloids and colloids. This figure shows plasma volume (mL/kg) after a two-minute bolus infusion of 4 mL/kg of 0.9% NaCl and 6% dextran 70 in 0.9% NaCl, in conscious sheep. VEE is defined as mL expansion per mL infused. *Abbreviation:* VEE, volume expansion efficiency. *Source:* From Ref. 22.

or clinical condition using identical infused volumes and infusion rates. Fischer et al. compared PV expansion after a 30-minute infusion of 20 mL/kg 6% DCLHb, iso-oncotic 7.8% human albumin versus 60 mL/kg of lactated Ringer's (LR) solution in a conscious sheep under conditions of normovolemia and hemorrhagic hypovolemia (26). Figure 5 shows Δ PV calculated from Evans blue indicator dilution and Hct dilution as well as the calculated VEE.

The relatively increased expansion of 10% DCLHb versus 7.8% human albumin is quite surprising as the albumin was made up to be an iso-oncotic control to the DCLHb. The explanation for the enhanced volume expansion of DCLHb is unknown, but several mechanisms can be hypothesized. PV enhancement could be due to a reduction in capillary pressure due to arteriolar vasoconstriction. Alternatively, increased lymphatic pumping could return interstitial protein into the circulation and augment the plasma COP and expansion. Indeed, Fischer et al. did report an increased plasma protein concentration and COP in the DCLHb group despite the albumin and DCLHb being matched for the volume infused and the COP (26).

Vane et al. measured how vasoconstriction with phenylephrine infusion altered volume expansion of a bolus infusion on normal saline (27). As opposed to the vasoconstriction and augmented PV expansion with DCLHb, phenylephrine greatly reduced volume expansion. It should be noted that capillary pressure is dependent on the ratio of arteriolar to venular resistance. If DCLHb primarily vasoconstricts precapillary vessels, while phenylephrine vasoconstricts both, then it is still possible to explain the results of DCLHb's PV augmentation and phenylephrine's PV loss caused by a change in capillary pressure. We must await data on the other HBOCs as to their effectiveness as volume expanders. Oxyglobin (13 g/dL and a COP of 31 mmHg), an FDA-approved HBOC for veterinary use is a potent volume expander (28). Hypervolemia and circulatory overload are listed as a potential adverse reaction when used with other fluids. We know of no reports of the measured PV effects of either Hemopure or Polyheme, which are the only two HBOCs continuing in advanced phase III clinical trials for human use.

Nearly all preclinical research has compared the efficacy and safety of an HBOC versus a control solution such as LR or albumin, for example, in the treatment of shock. On the other

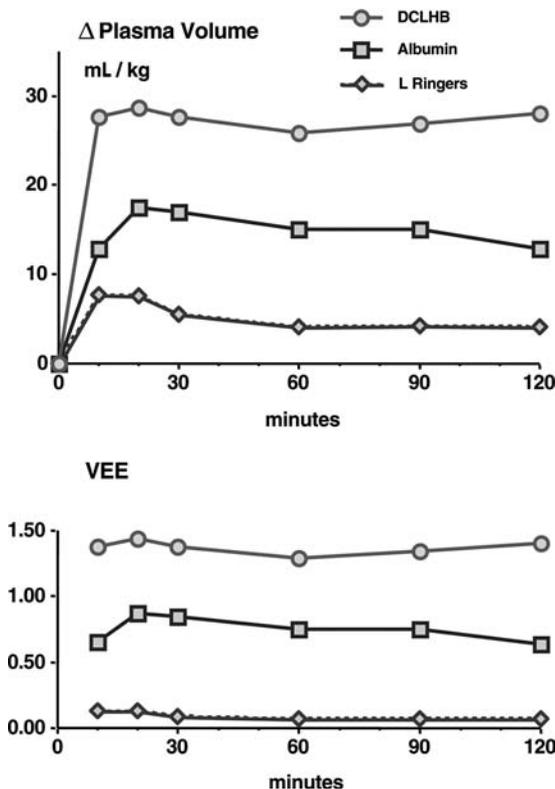


Figure 5 The figure shows plasma volume expansion and VEE in conscious sheep after a hemorrhage (40 to 44 mL/kg) over two hours and then resuscitated with 30-minute infusion of 20 mL/kg of 10% DCLHb, 7.8% human serum albumin, or 60-mL/kg L Ringer's. *Abbreviations:* VEE, volume expansion efficiency; DCLHb, diaspirin cross-linked hemoglobin; L Ringer's, lactated Ringer's. *Source:* From Ref. 26.

hand, the clinical use of HBOCs will likely be after asanguineous volume expanders are infused. Brauer et al. evaluated the volume expansion and hemodynamic effects of a 20-minute infusion of DCLHb before and after a large-volume infusion of LR in conscious sheep hemorrhaged as previously described by Fischer—two-hour hypotension to 50 mmHg, as maintained by bleeding (26,29). Thereafter, animals were infused with a 30-minute 60-mL/kg infusion of LR followed by 20 minutes of monitoring and a second 30-minute infusion of 20 mL/kg of DCLHb. A crossover group received the two solutions in reverse order. Figure 6 shows the Δ PV of DCLHb, before and after LR, as well as the Δ PV of LR, before and after DCLHb. The reduced volume expansion of LR when infused after DCLHb is an expected finding because preexisting or antecedent hypovolemia augments volume expansion, and preexisting hypervolemia would be expected to oppose volume expansion due to normal mechanisms of volume regulation (24,25). However, the sustained or slightly enhanced volume expansion of DCLHb after a large volume of LR is an unexpected finding, and suggests that at least some HBOCs can cause fluid overload when used after other fluids.

RELATIONSHIPS BETWEEN HBOC VOLUME EXPANSION AND CO

The goal of volume expansion is almost always to increase CO. Interestingly, reports of HBOC infusion have no effect or cause only modest increases in CO (26,30). Figure 7 shows CO plotted against right arterial pressure for LR, albumin, and DCLHb, as calculated from data of Fischer et al. and Brauer et al. (26,29). A suggested hypothesis is that the HBOCs do not increase CO because of the greater O₂ delivery. However, this is not satisfying, because all other volume expanders increase O₂ delivery, and O₂ therapy alone does not reduce CO. Vane et al. found some deaths in animals treated with DCLHb after a large-volume LR treatment of hemorrhage in an anesthetized model of a major abdominal surgical procedure (31). These authors concluded that the combination of vasoconstriction, hypervolemia, and cardiac depression likely contributed to the poor outcomes. These data suggest that some level of cardiac dysfunction or impairment can occur with some HBOCs. Clinical data comparing how infusion of HBOCs and traditional plasma expanders alter the CO, right atrial pressure, and blood volume are not available.

HBOCs' potent volume expansion properties may limit their ability to increase the Hb concentration of blood after infusion. Volume expansion dilutes RBCs, and if the oncotic pressure of HBOCs is greater than that of the patient's plasma, the HBOC-free Hb is also diluted.

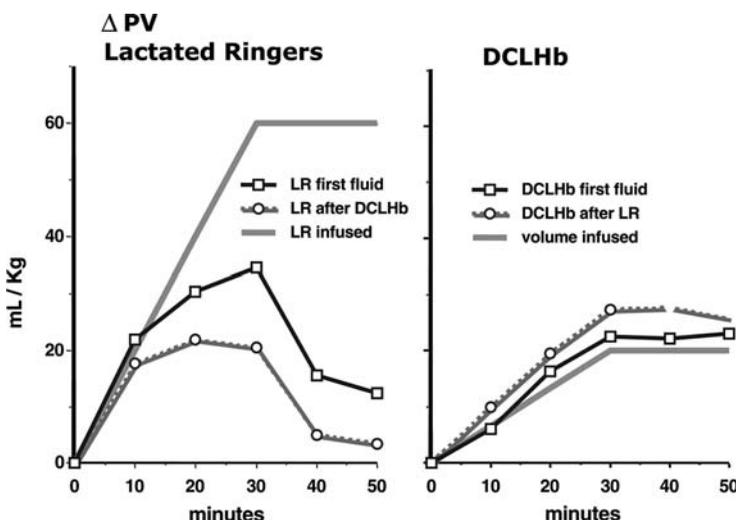


Figure 6 The figure shows a change in PV expansion of a 30-minute infusion of 20 mL/kg DCLHb and 60 mL/kg LR, infused in sheep hemorrhaged 40 to 45 mL/kg. Data is shown for LR and DCLHb when infused as first fluid and when infused as second fluid 20 minute after the end of the first infusion. *Abbreviations:* PV, plasma volume; DCLHb, dextran cross-linked hemoglobin; LR, lactated Ringer's. *Source:* From Ref. 29.

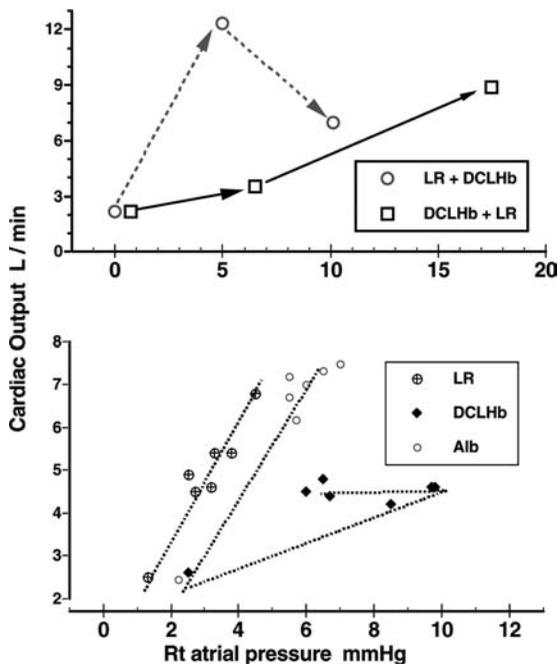


Figure 7 Increased cardiac output (CO) plotted versus Rt atrial pressure after vascular expansion using albumin, LR, and DCLHb in hemorrhaged sheep. Vascular expansion with LR or albumin increases Rt atrial filling pressure and CO and defines normal contractility. An altered filling pressure and CO relationship with DCLHb suggest depressed cardiac contractility. *Abbreviations:* LR, lactated Ringer's; DCLHb, diaspirin cross-linked hemoglobin; Rt, right. *Source:* From Refs. 26, 29.

For example, infusion of DCLHb, an Hb tetramer, with a concentration of 10g/dL is effectively reduced by volume expansion to a concentration of approximately 7.2g/dL, a value not too far above the transfusion trigger for patients. Figure 8 compares the effects of transfusion with RBCs and DCLHb solution, expressed as the Hb infused versus total blood concentration of Hb due to RBC Hb and plasma Hb, as determined from a model in which the VEE of DCLHb is 1.3 as determined from experimental measurements (26). Data on the volume expansion properties of other HBOCs is needed to determine how effectively they increase Hb content of blood versus pRBCs.

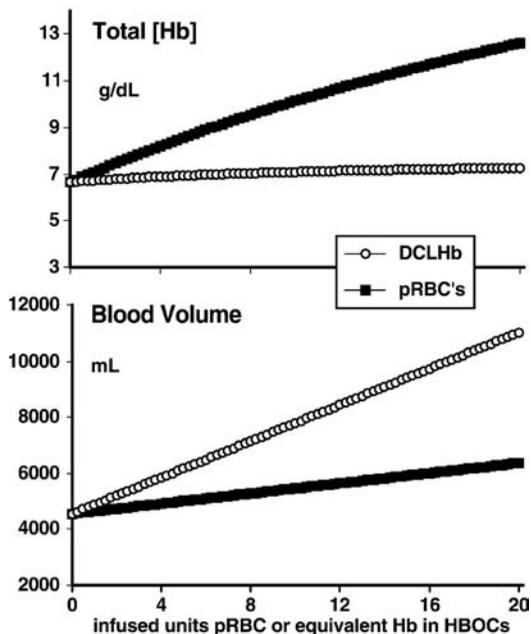


Figure 8 The figure shows a comparison of transfusion of pRBC and a 10-g/dL HBOC shown to expand plasma volume (PV) equal to 1.3 times the infused volume. Data from a model suggest that initial conditions of anemia (Hb=7g/dL) and normovolemia (PV=45 mL/kg) can occur with either chronic anemia or hemorrhage and on resuscitation with asanguineous fluid. *Abbreviations:* Hb, hemoglobin; DCLHb, diaspirin cross-linked hemoglobin; pRBC, packed red blood cell; HBOC, hemoglobin-based oxygen carrier. *Source:* Authors' unpublished data.

HBOCs AS RESUSCITATIVE FLUIDS

All HBOCs or oxygen-carrying plasma expanders have the potential to be an effective resuscitation solution. Indeed, the high oncotic pressure and augmented VEE of the HBOCs makes them attractive for the treatment of hypovolemia. Asanguineous fluids expand vascular volume and increase CO, but dilute RBCs and oxygen content. However, increased CO may effectively increase oxygen delivery several fold from the depressed levels associated with shock to normal or even supranormal levels. Augmentation of supranormal levels of CO with fluid resuscitation often occurs without full restoration of blood pressure, presumably due to lowered viscosity and widespread vasodilation from local autoregulatory mechanisms. Many, if not all, HBOCs appear to impair CO enough such that oxygen delivery is not increased above that reported for conventional volume expanders. Recent comparison of the use of Polyheme versus that of Hextend in hemorrhaged anesthetized swine and conscious rats, when both solutions were infused to maintain a systolic blood pressure to approximately 70 mmHg for limited "hypotensive" resuscitation, showed no oxygenation or hemodynamic advantage (rat and pig) and an increased incidence of mortality (rat) (32,33). It may be that the oxygen-carrying plasma expanders offer minimal advantage in limited resuscitation regimens due to the small dose of Hb administered.

Similar conclusions on ineffectiveness of HBOCs in small volumes can be reached studying the combination of hypertonic 7.5% saline plus HBOC. Such mixtures were suggested as an improvement over a small increase in oxygen delivery attributable to replacing dextran with an HBOC and assuming CO is increased equally. However, an analysis of experimental data suggests that hypertonic saline dextran (34) is more effective than hypertonic saline-HBOC (35) due to the HBOC's apparent depression of CO.

A novel approach to HBOC development has been the development of a counterintuitive formulation of polyethylene glycol-modified human Hb (MalPEG-Hb). MalPEG-Hb is an anemic (4 g/dL), viscous, hyperoncotic formulation with a P50 of 5.5 mmHg. Data suggests that the free Hb in plasma unloads oxygen more efficiently when compared to RBC Hb due to the removal of the microcirculatory spatial heterogeneity imposed by cellular Hb (36-38). Enhanced O₂ unloading might increase arteriolar O₂ tension and induce arteriolar vasoconstriction (20,21,39). This opposes the conventional, well-researched view that Hb's affinity for nitric oxide, (NO) is responsible for the vasoconstriction (40). In theory, the elevated O₂ affinity (low P50) of MalPEG-Hb delays the early release and prevents vasoconstriction. Furthermore, vasodilation may be induced by MalPEG-Hb's high viscosity, increasing blood-endothelial shear forces and thus enhancing NO release (41).

The vision is that MalPEG-Hb's other unique features might increase its effectiveness enough to compensate for its diluted concentration. Data of microcirculatory function in a skin window suggests enhanced O₂ delivery (42), but such an enhancement may not take place in more critical tissue with higher O₂ demands and life-sustaining function. Still, the concept that a Hb solution with high oncotic pressures and high viscosity has enhanced efficacy is intriguing and deserves evaluation in clinically relevant models.

CONCLUSION AND RECOMMENDATIONS

HBOCs are potent plasma expanders. Such volume expansion may be a limitation for their use as a blood substitute, but may have utility and advantages as a resuscitative fluid. The limited amount of independent experience with the HBOC solutions currently under development makes conclusions difficult. We recommend that all HBOCs have their COP as well as data on comparative volume expansion versus standard crystalloid and colloid formulations published. Such information will allow physicians to better plan utility and allow researchers to evaluate experimental regimens designed to make the best use of HBOCs' often unique volume expansion properties.

Infusion regimens for HBOCs will likely be different than that for pRBCs or asanguineous fluids due to the unique physical properties and physiological effects of HBOCs. At present, it is not clear if such solutions will offer an improvement in the standard of care. Despite the authors' caution, developing a safe and effective oxygen-carrying plasma expander remains an attractive goal. It is likely that an effective Hb molecular structure, optimal concentrations, and carrier solutions will be developed. Such development and clinical

utility will take substantial preclinical and clinical study to define the safety and efficacy and the optimal therapeutic regimens of such formulations.

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15 Hypovolemic Shock

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INTRODUCTION

“A renewed interest in shock is always manifested in time of war.” (1). The step-wise increases in the clinical understanding and treatment of hypovolemic shock owe their origins, in part, to the battlefields of the 20th century. The two World Wars, the Korean war, the Vietnam war, and the Arab–Israeli conflicts and inner city violence in the latter part of the 20th century have all given rise to changes in the treatment of hemorrhagic hypovolemia, which include correction of the circulating volume with blood, early fluid resuscitation in the “golden hour,” and bleeding control prior to aggressive resuscitation to limit fluid-induced coagulopathy. Concepts learned from the management of hemorrhagic hypovolemia have been applied to the diagnosis, monitoring, and treatment of other causes of hypovolemia, as our knowledge of the underlying pathophysiology has improved.

Hypovolemia implies a reduced circulating volume. Shock implies that the body’s metabolic requirements of supply and removal are not being met by the reduced cardiac output. A large number of etiologies can be listed according to the predominant fluid lost (Table 1). These etiologies unfortunately often overlap, which means that the clinical situation is not so clearly demarcated. Treatment continues to be dogged by the crystalloid-versus-colloid debate, which remains unresolved. Other issues to be resolved are which crystalloid or colloid to use, early versus delayed resuscitation, how much fluid to infuse, and what means to use for the monitoring of fluid resuscitation.

ETIOLOGY

Hemorrhage remains the most studied model of hypovolemic shock because compensatory mechanisms remain intact. However, other forms of fluid loss can result in hypovolemic shock as is evident from Table 1. Patients whose compensatory mechanisms are compromised by the precipitating process or from concurrent comorbidity are particularly at risk.

Hemorrhage remains an important cause of hypovolemic shock because this may be due to trauma in the young where intact physiological responses limit the changes in standard monitored variables until later on. As a result, it continues to be underdiagnosed and undertreated. Trauma remains the leading cause of death in the United States in patients under the age of 40 (4). In addition, the projected figures for worldwide deaths from the global epidemic of injury are 8.4 million by the year 2020 (2), with about a third of these deaths due to hemorrhagic shock (3–5). External blood loss is usually easy to see but difficult to quantify, whereas concealed hemorrhage needs to be at the forefront of an attending physician’s mind. This particularly applies in cases of trauma where long bone fractures, pelvic fractures, and hemorrhage into a body cavity can lead to an underassessment of blood loss and hence appropriate fluid resuscitation.

The relevance of etiology comes second to initial, basic resuscitative measures along the lines of ABC (see section on treatment). However, the importance of etiology lies in gaining an assessment of the duration of hypovolemia as it relates to the degree of total body fluid depletion and the type of fluid lost, as this will influence fluid replacement. Ongoing fluid therapy should address total body fluid depletion and treatment of the underlying cause. For example, in a patient presenting with hyperosmolar nonketotic hyperglycemia, the insidious nature of the presentation often results in profound total body water depletion due to the

Table 1 Causes of Hypovolemia

Blood loss	Revealed Concealed	Intrathoracic Intra-abdominal Retroperitoneal Fractures Soft tissues
Plasma loss	Burns Peritonitis Ascites Pleural effusions Intestinal obstruction Pancreatitis	
Salt and water loss	Hyperglycemia Excess diuresis Diarrhea and vomiting Fistula Dehydration/exercise Addisonian crisis	Diabetic ketoacidosis Hyperosmolar nonketosis
Redistribution	Sepsis Hyperpyrexia Drugs/anesthesia Spinal anesthesia Spinal cord injury Anaphylaxis/anaphylactoid reaction Toxic shock Thyroid storm	

osmotic diuresis consequent upon grossly elevated serum glucose. Treatment aimed only at restoring the circulatory volume will therefore fail.

PHYSIOLOGICAL RESPONSE TO HYPOVOLEMIA

In a simplified model, a fall in circulating volume is detected as a reduction in the degree of stretch in receptors in the central veins and right atrium. On the systemic side of the circulation, the reduction in stretch in baroreceptors in the carotid sinus and in the aortic arch leads to an increase in sympathetically mediated vasomotor tone in the venous system, via the vasomotor center in the medulla. This attempts to restore stroke volume and, therefore, systemic pressure.

Further hemorrhage results in arteriolar constriction mediated via further sympathetic activity as cardiac output starts to fall. This arterial constriction is selective and acts to maintain perfusion to the vital organs resulting in hypoperfusion in regional beds (i.e., splanchnic, skin, and muscle). These tissue beds essentially act as a volume reservoir from which the body can draw upon in moments of hypovolemic stress.

Further hemorrhage leads to changes in commonly measured variables such as heart rate, which increases to maintain blood pressure, and then finally, blood pressure starts to fall. Heart rate increases as a result of direct sympathetic stimulation, and via an increase in circulating adrenaline secreted by the adrenal glands. Increases in circulating noradrenaline, released from synaptic clefts and the adrenal gland, increase and maintain vasoconstriction aided by vasopressin and neuropeptide Y. Increases in heart rate increase contractility via the Bowditch effect to try and maintain blood pressure for a given stroke volume. Venos constriction acts to maintain stroke volume and, hence, systemic blood pressure. These changes are shown in Figure 1.

Respiratory rate increases during progressive hypovolemia as a result of increased activity in the carotid bodies, which respond to falls in pH and PaO₂, BP < 70 mmHg, and increased PaCO₂.

With further hemorrhage, shock is decompensated and cardiovascular responses start to fail, leading to bradycardia, profound hypotension, coma, and death.

Longer-term mechanisms to restore the circulatory volume act to increase fluid intake, conserve fluid losses from the kidneys, and redistribute fluid from the interstitium to the circulation via changes in the equilibrium of Starling forces (Figure 2).

Changes in renal blood flow result in constriction of both efferent and, to a lesser extent, afferent vessels. Increases in renin secretion from the juxta glomerular apparatus increase

Venoconstriction acts to maintain stroke volume and, hence, systemic blood pressure:

$$BP = CO \times SVR = (SV \times HR) \times SVR$$

Arteriolar constriction and rise in SVR maintain blood pressure:

$$BP = CO \times SVR$$

HR rises to maintain CO as SV falls. With progressive hemorrhage when SVR and HR reach critical level BP will fall with any further reduction in SV

$$BP = (SV \times HR) \times SVR$$

where BP = blood pressure, CO = cardiac output, SVR = systemic vascular resistance, SV = stroke volume, and HR = heart rate.

Figure 1 Measures to maintain blood pressure during progressive hypovolemia.

levels of angiotensin, which acts to maintain vasoconstriction, whereas antidiuretic hormone secretion increases thirst and salt and water retention, aided by a fall in atrial natriuretic factor resulting from the fall in preload. Urine is therefore concentrated with a high specific gravity and low urinary sodium.

Classical teaching divides these physiologic responses to hemorrhagic hypovolemia into four stages or classes. These stages correspond to the percentage of normal circulating volume lost and equate to less than 15% in Stage 1, 15% to 30% in Stage 2, 30% to 40% in Stage 3, and greater than 40% in Stage 4 (6). These stages of percentage volume loss have been assigned clinical signs and symptoms by which the clinician can theoretically determine volume replacement (Fig. 3). There are, however, confounding variables related to the patient, the treatment already administered, and the environment, which make using this classical framework difficult in the clinical situation. Factors related to the patient include age, injury type, comorbidities with their drug treatments, and recreational drugs, including alcohol. Treatments already administered include intubation and ventilation, analgesia, and intravenous fluids, while environmental factors may influence the degree of pain, fear, and temperature loss. All of these have a bearing on the sympathetic response of the individual and the individual's physiological response to hypovolemia. In turn, this can lead to errors in the assessment of volemic status and volume replacement.

We know that some patients do not respond classically. Barriot and Riou (7) found that in approximately 7% of patients, a tachycardic response was not found to hypovolemia, and Sander-Jensen et al. (4,8,9) demonstrated vagal slowing of the heart during hemorrhage. This vagal slowing has been viewed as a protective mechanism to limit further blood loss and has been linked to improved survival (10).

$$\text{Fluid Movement} = K[(P_c + \Pi_i) - (P_i + \Pi_c)]$$

Where K = capillary filtration coefficient.

P_c = capillary hydrostatic pressure.

P_i = interstitial hydrostatic pressure.

Π_c = capillary colloid osmotic pressure.

Π_i = interstitial colloid osmotic pressure.

Figure 2 Starling forces governing net fluid movement.

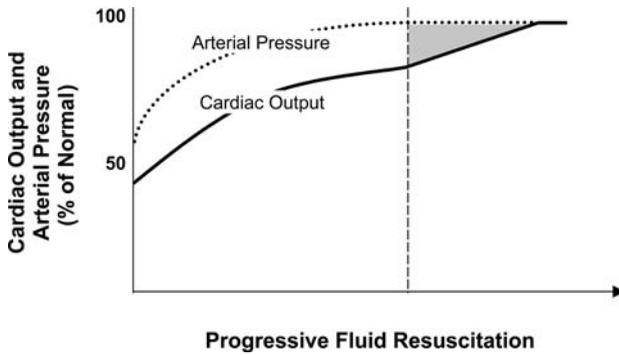


Figure 3 Schematic representation of cardiac output lagging behind arterial pressure during resuscitation. The shaded area represents potential continuing regional-bed hypoperfusion, despite seemingly adequate volume resuscitation based on arterial blood pressure.

An alternative to this classical system is to divide the hypovolemic shock into covert-compensated hypovolemia, overt-compensated hypovolemia, and overt-decompensated hypovolemia (Table 2). These do not correspond directly to percentage volume lost, but to the changing interactions between the volume lost, volume replaced, pharmacologic treatment, and the ventilatory status of the patient.

Covert-Compensated Hypovolemia

This is the most common, yet the least often diagnosed form of hypovolemia. As a result, covert-compensated hypovolemia is probably associated with the greatest morbidity. It refers to the presence of a reduced circulating blood volume associated with no demonstrable physical signs. Price found that healthy volunteers could have 10% to 15% of their blood volume removed, with no significant change in heart rate, blood pressure, cardiac output, or blood flow to the splanchnic bed (gut, etc.). However, splanchnic blood volume was reduced by 40%. The subjects in his study had essentially autotransfused and were maintaining the systemic circulating volume at the expense of the splanchnic circulating volume (11). More recently, Hamilton-Davies et al. (12) performed a similar experiment on healthy volunteers. They found that approximately 25% of the blood volume could be removed, with no effect on the commonly measured cardiovascular variables, but consistent with Price’s findings, the gastric mucosal PCO₂ rose immediately followed by a fall in cardiac stroke volume (12). The same process happens when we donate a unit of blood with no obvious adverse effects. Over the course of the next few hours, we feel thirsty and therefore drink more; we also ingest salt and, at the same time, reduce urine output of salt and water. We synthesize new proteins and blood cells and, very soon, everything has returned to normal with no sequelae. In hospitalized patients, however, many of the natural compensating mechanisms malfunction and this, coupled with the fact that fluid replacement is being determined by a second party, namely the physician, makes hypovolemia common.

Covert-compensated hypovolemia is extremely difficult to diagnose. In the conscious patient, central nervous system (CNS) symptoms are the best guide. In the two experiments cited above, all the subjects developed CNS symptoms such as drowsiness, nausea, or hiccoughs. Any thirsty patient should be assumed to be hypovolemic. Urinalysis showing an increased urinary osmolality and decreased sodium concentration is the most useful laboratory investigation.

Table 2 Clinical Signs and Monitorable Changes in Covert-Compensated, Overt-Compensated, and Overt-Decompensated Hypovolemia

Hypovolemia	Clinical signs	Monitored changes
Covert compensated	Difficult Thirst, agitation, drowsiness, hiccups	↑ Urinary osmolality ↓ Urinary sodium ↑ Gastric mucosal PCO ₂
Overt compensated	Tachycardia, tachypnea, cool peripheries, narrow pulse pressure	As above Reduced stroke volume Oliguric
Overt decompensated	Hypotension Tachycardia, sometimes bradycardia Coma	Not required to make diagnosis and commence immediate volume replacement

Although covert-compensated hypovolemia is common and probably contributes significantly to morbidity, the majority of patients withstand the insult. If hypovolemia persists, consequent end-organ hypoperfusion may be present for many days before it manifests itself as organ dysfunction. By this time, the patient is usually in a state of overt-compensated hypovolemia.

Overt-Compensated Hypovolemia

Here, hypovolemia worsens to an extent where reflex mechanisms that are required to maintain perfusion to vital organs are obvious on clinical examination, but blood pressure is maintained. The patient will demonstrate the manifestations of increased sympathetic drive with tachycardia, i.e., wide arterial pulse pressure, typically increased systolic blood pressure, and cool, clammy skin, particularly, at the hands and feet. There may be other evidence of inadequate cardiac output such as drowsiness, confusion, and increased respiratory rate.

Decompensated Hypovolemia

Decompensated hypovolemia is what many people refer to as shock. The degree of hypovolemia is such that reflex redistribution of blood flow is insufficient to compensate, and vital organs are no longer adequately perfused. If untreated, this clinical state rapidly progresses to total circulatory arrest. No special equipment or investigations are needed to make the diagnosis of decompensated hypovolemia and to start aggressive volume replacement therapy. Inaccurate diagnosis and inappropriate colloid administration are an overrated problem. Delay in the treatment of hypovolemic shock greatly reduces the chances of successful resuscitation. Most causes of hypovolemic shock carry a far better prognosis than any condition that presents in a similar fashion, but would be made worse by a fluid challenge.

PATHOPHYSIOLOGIC RESPONSE TO HYPOVOLEMIA AND REPERFUSION INJURY

As stated earlier, physiological measures to restore circulating volume in hypovolemia result in regional hypoperfusion to the nonvital organs such as skin, gut, and muscle. Should regional hypoperfusion continue, a chain of reactions may be initiated which results in multiple-organ dysfunction. At the worst, this may culminate in organ failure and late death despite restoration of an adequate circulating volume. At the least, it results in major morbidity and therefore financial implications. Heckbert et al., in an inception cohort study conducted at a Level 1 trauma center, found that of the 208 patients identified with hemorrhagic shock (BP < 90 mmHg), 54% died (13). Of those who survived the first 24 hours, 19% subsequently died. Some late deaths are avoidable, but they only represent the tip of the iceberg of the increased morbidity of those inadequately resuscitated.

Regional bed hypoperfusion results in a build up of metabolites, oxidants (for example, proteases), and other inflammatory mediators. These may initially be concealed until either flow is restored or sufficient time has elapsed for these metabolites to be washed back into the general circulation. This explains why base excess and lactate are poor markers of hypovolemia in its early stages. Selective blood sampling from regional beds confirms higher oxygen extraction and build up of metabolites (14). When these inflammatory mediators are released into the general circulation, they may initiate a systemic reperfusion injury, possibly converting resuscitated hypovolemic shock into septic shock, because the induction and release of nitric oxide results in vasodilation. A by-product of excess nitric oxide metabolism is peroxynitrite, which is cytotoxic (15–17). Activation of neutrophils and macrophages at distant sites results in further release of inflammatory cytokines and further endothelial injury. The free radicals that are generated tip the balance of oxidant–antioxidant in favor of oxidant-mediated tissue injury and subsequent multiple-organ dysfunction.

Splanchnic Hypoperfusion

The splanchnic circulation is an early casualty of selective vasoconstriction, and as a result has been targeted as the engine of subsequent multiorgan failure (18), via translocation of bacteria, endotoxin, and cytokine release (9,19), and as a site for monitoring ongoing occult

hypovolemia using a gastric tonometer (see Section "Monitoring and Treatment"). At a gross level, gut failure may be manifest as failure of enteral feeding, or shock liver may occur with hyperbilirubinemia, high transaminases, and failure of synthetic function, which may compound the coagulopathy resulting from massive transfusion of blood, crystalloids, and colloids.

Renal Hypoperfusion

There is a reduction in total renal blood flow and regional changes mediated via prostaglandins. If prolonged, despite resuscitation, this will result in renal tubular ischemia leading to acute renal failure, which may last for weeks before recovery.

Myocardial Function

Cardiac blood flow is well maintained until late in hypovolemia. The physical demands made upon it rapidly escalate as afterload, and then the heart rate increases. Myocardial oxygen and nutritional requirements, therefore, increase at a time when coronary perfusion pressure and flow are falling. Left in this state, cardiac function will begin to deteriorate such that, even if volume resuscitated, cardiac function will not immediately return to normal (6). Furthermore, reperfusion injury and endotoxemia will depress cardiac function (20), which, if volume resuscitation occurs, may reveal a cardiogenic component of shock.

Lung Hypoperfusion

Finally, in patients who go on to develop organ failure following hemorrhagic shock, the lung is the most frequently affected (21). Shock lung is due to a combination of poor perfusion during the low output state, and then to reperfusion-induced injury. The end result is leaky capillaries that impair compliance and gas transfer. The lungs are thus a marker of a global injury, manifest by our ability to monitor lung dysfunction more easily than that of other organs. The lung injury may be compounded by lung contusion and fat embolism syndrome. The treatments administered may also be implicated in the form of excess fluid therapy, massive blood transfusion, and transfusion-related acute lung injury, and lastly ventilator-associated injury.

Similar to the gut, the lung is implicated as a cytokine-generating organ, which may drive the systemic inflammatory response leading to multiple-organ failure. With this comes the recognition that excess ventilation not only damages the lung but also contributes to morbidity and mortality (22).

Monitoring and Treatment

The diagnosis, treatment, and monitoring of acute hypovolemic shock go hand in hand and follow the basic resuscitation model of airway, breathing, and circulation. The aim is to establish maximal oxygen delivery while the circulation is being assessed, establish venous access, and institute measures to restore circulatory volume with fluid.

As alluded to earlier, studies examining the physiological responses to varying degrees of hypovolemia confirm that the commonly measured variables of heart rate, blood pressure, base excess, and lactate are all late markers in hypovolemia, because the compensatory measures maintain pressure at the expense of flow. Central venous pressure (CVP) may be misleading in the presence of pulmonary vascular disease, right ventricular impairment, and valvular disorders, and will not accurately predict left ventricular end-diastolic pressure in isolated left ventricular failure. Also, isolated values are difficult to interpret in the presence of profound venoconstriction as CVP may be high or normal in the presence of hypovolemia and may in this instance actually fall during fluid resuscitation. Use of these variables alone may result in a patient being seemingly adequately resuscitated (i.e., covert-compensated hypovolemia). Regional bed hypoperfusion continues, thereby inadvertently fueling a systemic inflammatory response.

The fluid challenge, at present, remains the tool of choice in both the diagnosis and the treatment of hypovolemia. Changes in physiological variables before and after a given fluid volume challenge can be used to assess volume status. In overt-decompensated hypovolemia this may be large volume resuscitation with heart rate and blood pressure as the variables used, whereas in covert- and overt-compensated hypovolemia, lower volume challenges may be given to restore adequate urine output. Flow variables provide a better means of assessing

adequate resuscitation than pressure variables alone, and these may be used in conjunction with CVP in the algorithm. The clinician then waits till the stroke volume rises to its maximum and a plateau is reached. This provides a more accurate measure of movement along a curve of pressure (preload) against stroke volume, i.e., a modified Starling curve. In cardiac surgical patients and in those undergoing surgery for fractured neck of femur, where achievement of optimal circulatory volume may be difficult to ascertain or invasive monitoring is not routine, there is evidence that flow variable-guided resuscitation improves outcome (13,23,24). There is also evidence that attainment of the supranormal circulatory values of cardiac index, oxygen delivery, and oxygen consumption improves both morbidity and mortality, following trauma with a blood loss of approximately 2000 mL (25). Outcome has also been improved by rapid aggressive resuscitation in sepsis and septic shock using fluids, vasopressors, and dobutamine to achieve a mixed venous oxygen of 70% (26). These studies may demonstrate that attainment of full resuscitation of the circulation puts a brake on a systemic inflammatory response by reversing ongoing regional hypoperfusion. Those patients who subsequently go on to develop septic shock do not appear to benefit from efforts to achieve these values (Fig. 4) (27).

Continuing controversy regarding pulmonary artery catheters in terms of morbidity and mortality surrounding their insertion, removal, and therapeutic interventions based upon the measurements has led to interest in monitors that are less invasive. Systolic pressure variability and pulse pressure variability provide a means to assess volume expansion in a hypovolemic state (28). This is the application of science to the commonly applied adage that a large swing

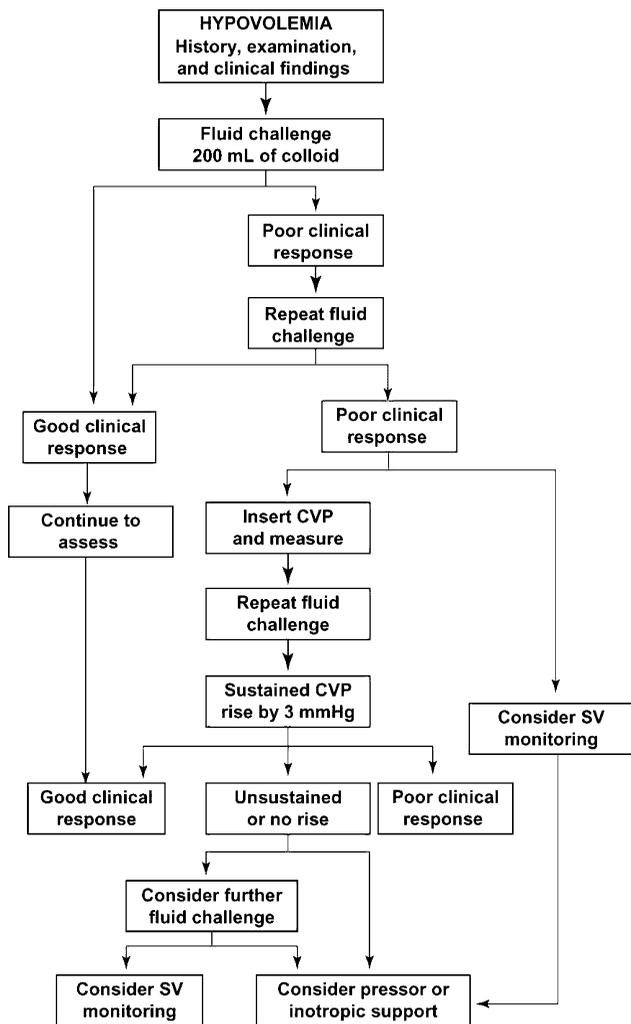


Figure 4 Algorithm for fluid challenge. Stroke volume measurements may be used instead of, or in conjunction with, central venous pressure to reach plateau of Starling curve. *Abbreviations:* CVP, central venous pressure; SV, stroke volume.

on the arterial pressure trace suggests that the circulation is underfilled. Thus when venous return is low, exaggerated changes in right ventricular preload result from intermittent positive pressure ventilation. This leads to an intermittent reduction in left ventricular preload and hence systemic blood pressure. The greater the degree of preload reduction from hypovolemia, the greater the intermittent reduction in blood pressure from positive pressure ventilation. In the nonventilated patient, although the basis for intermittent preload reduction is reversed in terms of venous return and inspiration and expiration, this does occur but appears to be less predictable, probably due to changes in respiratory rate and depth. Michard et al., in a study conducted on patients with acute circulatory failure due to sepsis, found that pulse pressure and systolic pressure variability over one respiratory cycle were better indicators of fluid responsiveness than CVP and pulmonary artery occlusion pressure (29).

Changes in vascular tone have also been studied as a possibly less invasive measure of resuscitation in hemorrhagic shock (30).

All these methods of monitoring and attempting to optimize volume status do not deal directly with end-organ perfusion but presume that end-organ perfusion will follow from achieving a "well-filled" circulation. Resuscitation measures may restore systemic pressure and cardiac output to normal parameters while still leaving a patient in covert-compensated hypovolemia. This has led to a search for markers, other than urine output, of reduced end-organ perfusion in covert-compensated hypovolemia.

As stated earlier, Price et al. showed that a 15% reduction in total blood volume resulted in a reduction of approximately 40% in splanchnic blood volume, with no change in any of the commonly measured cardiovascular variables (11). Hamilton-Davies et al. (12), in a two-staged hemorrhagic model of hypovolemia with a total reduction of 25% of circulating blood volume in awake subjects, monitored heart rate, blood pressure, stroke volume with suprasternal doppler, base excess, lactate, and $\text{PiCO}_2\text{-PaCO}_2$ with a gastric tonometer. $\text{PiCO}_2\text{-PaCO}_2$ is the gap between gastrointestinal CO_2 , and arterial CO_2 , which is thought to aid in avoiding some of the pitfalls involved in the previously measured gastric pH_i . During the first stage they found no consistent change in any of the hemodynamic variables other than $\text{PiCO}_2\text{-PaCO}_2$. During the second stage, $\text{PiCO}_2\text{-PaCO}_2$ continued to worsen, with the stroke volume also showing a marked fall. All other variables did not alter consistently or to such a degree as to elicit clinical suspicion of a hypovolemic state.

In the clinical setting, tonometric measurements have been shown to be a sensitive but not specific predictor of perfusion failure and adverse outcome in sepsis, trauma, general surgical, and cardiac surgical patients (31). Other sites in the body in which interest has been shown to monitor end-organ perfusion include the esophagus, colon, bladder, submucosal capnography, and skeletal muscle pH, PCO_2 , and PO_2 . SVO_2 meanwhile provides a global measure of oxygen extraction but does not reflect regional bed perfusion.

CONCLUSION AND FUTURE DEVELOPMENTS

In conclusion, hypovolemic shock is an increasingly common medical problem and accounts for a highly significant worldwide mortality. More importantly it accounts for an even higher morbidity, something that we may potentially be able to do more about with prompt detection and early adequate restoration of circulating volume. This may prevent the later complications of the systemic inflammatory response syndrome and sepsis caused by ongoing regional hypoperfusion, which arises as a consequence of the body's attempt to maintain pressure at the expense of regional flow. Evidence in favor of preoptimization of the circulation with fluids and inotropes before major surgery (15,24,32) points to the importance of avoiding regional hypoperfusion and initiation of an inflammatory response. Further potential evidence is provided by Rivers et al. (26), who demonstrated improved outcome from aggressive early resuscitation in sepsis-induced hypovolemia. Dividing hypovolemia into covert compensated, overt compensated, and overt decompensated may help in the diagnosis and treatment of hypovolemia rather than relying on the classical teaching of percentage volume lost. Covert-compensated hypovolemia may be treated, and its complications avoided, by focusing the physician's attention to the importance of the interactions between volume lost, volume replaced, drug treatment, and ventilatory status.

Conclusive evidence from large, sufficiently powered randomized controlled studies of interventions based upon measurements using end-organ perfusion is lacking.

The ideal monitoring method should provide dynamic evidence of full restoration of circulating volume and end-organ perfusion, while limiting iatrogenic injury from overadministration of fluids. Rapid full resuscitation should limit reperfusion injury, while interest has also centered on antioxidants in fluids used in resuscitation to aid this (3).

The natural variability in the general population's distribution of endotoxin antibodies and, therefore, an individual's response to translocation of endotoxin also point the way to treatments based on identification of genetic factors that influence the response to hypovolemic shock.

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16 Septic Shock

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INTRODUCTION

Sepsis is a systemic inflammatory response syndrome (SIRS) associated with an infection. It is currently the 13th leading cause of death in the United States, and despite advances in modern medicine, the mortality from sepsis has not changed (1). Patients may present with tachycardia, tachypnea, fever, and leukocytosis, or may be in shock with multiple organ failure. Like SIRS, the release of systemic inflammatory mediators in sepsis results in perturbations in the microcirculation, venodilation, and renal and myocardial dysfunction. Fluid therapy is necessary in the treatment of sepsis because of the relative hypovolemia and continued extravasation of fluid from the vascular compartment. The goal of fluid resuscitation in sepsis is to restore arterial and filling pressures to improve end-organ perfusion and oxidative metabolism, while minimizing excessive overhydration, which can lead to pulmonary edema, paralytic ileus, and compartment syndromes. To attain this goal, physicians use several different indices to guide fluid and other therapies. Intensive efforts are made to avoid overhydration. However, to maintain intravascular hydration, fluid therapy in sepsis, nonetheless, results in a large positive fluid balance. Although necessary, fluid therapy alone is rarely enough to maintain physiologic homeostasis, and adjunctive therapies such as pressors or even inotropes are often needed.

The pathophysiology of sepsis involves the release of inflammatory mediators from neutrophils, macrophages, T-lymphocytes, and endothelial cells, or in the case of gram-positive and gram-negative organisms, endotoxins and exotoxins. The cellular targets of these mediators further stimulate the release of cytokines, eicosanoids, proteases, oxygen radicals, and nitric oxide (NO) and its catabolites. The cytokines cause the differentiation of T-cells, B-cells, and natural killer cells, which can lead to direct tissue injury. This activation of the inflammatory cascade also results in hypercatabolism and fever. Injury to the cardiovascular system results in myocardial dysfunction and a loss of microvascular integrity. The transvascular fluid flux that occurs in the microcirculation can be summarized by the Starling–Landis equation (2):

$$J_v = K_f[(P_c - P_i) - \sigma(\pi_p - \pi_i)]$$

in which J_v is the transvascular fluid flux, K_f is the filtration coefficient (hydraulic conductance \times surface area of exchange—an index of microvascular permeability to small molecules, P_c is the capillary hydrostatic pressure, P_i is the interstitial hydrostatic pressure, σ is the reflection coefficient to protein—an index of the microvascular permeability to large molecules, π_p is the plasma oncotic pressure, and π_i is the interstitial oncotic pressure. Under normal physiologic conditions, the equation is nearly balanced and net transvascular fluid flux is close to zero. Thus, the fluid that is filtered by the difference in capillary and interstitial hydrostatic forces is restored by the difference in oncotic forces. Many disease states, including sepsis, alter these forces in favor of fluid filtration, resulting in intravascular volume loss and edema formation.

Microvascular permeability, especially to large molecules, increases during sepsis due to endotoxin and the release of other inflammatory mediators (3,4). Proteins and other large molecules that are normally contained within the capillaries "leak out," and water osmotically follows. The restoring oncotic gradient becomes less effective as microvascular permeability increases. Although the exact mechanism for microvascular permeability has not been completely delineated, endothelial contraction may play an important role. Increases in capillary pressure by systemic mediators, such as histamine and bradykinin, and myocardial dysfunction further enhance fluid extravasation. Finally, large volume fluid administration that replaces vascular volume loss contributes to the dilution of plasma proteins, thereby decreasing plasma oncotic pressure. The net result of these alterations in the microcirculation leads to fluid extravasation and edema formation.

Venodilation, resulting from the release of inflammatory mediators such as nitric oxide (NO), reduces ventricular filling and thereby decreases cardiac output and arterial pressure. Normally, the cardiovascular system compensates for the reduced preload by increasing systemic vascular resistance and myocardial contractility and heart rate, but in sepsis, these mechanisms are ineffective due to a poorly responsive circulation. The lack of responsiveness is partially the result of the formation of NO. Fluid is administered to augment venous return and increase cardiac output. In patients who initially respond to fluid boluses, cardiac output, hypotension, and organ perfusion can be restored. However, in a large subset of patients, larger amounts of fluid with or without inotropic and vasopressor agents are required to maintain venous return and adequate perfusion to vital tissues.

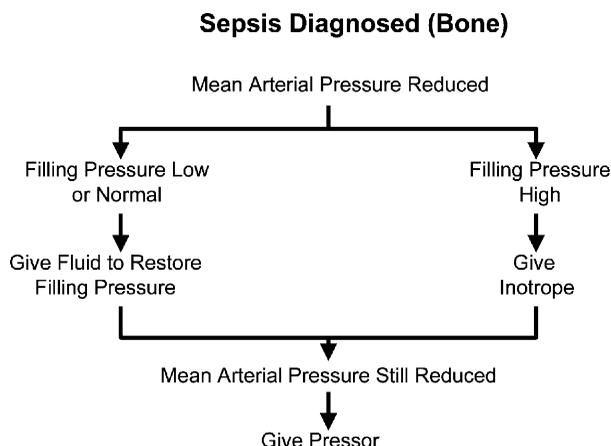
Although cardiac output increases during resuscitation of patients with septic shock, reduced ventricular compliance, decreased contractility, and dysrhythmias occur during sepsis. Tumor necrosis factor- α and other cytokines can cause the formation and release of NO by myocytes, which results in myocardial depression (5). Systolic function, measured by echocardiography, is reduced by 20% to 30% during sepsis (6). Intravascular volume may be lost secondary to increased capillary pressure, because patients with reduced ventricular compliance and reduced myocardial contractility require higher filling pressures to maintain adequate stroke volume. Therefore, fluid resuscitation is a necessary attempt to maintain hemodynamic stability.

END POINTS OF RESUSCITATION

Once fluid resuscitation has begun, clinicians use several end points for guiding fluid administration. Initially, urinary output, mean arterial pressure, and heart rate may be chosen to guide fluid therapy. Although these end points can predict intravascular volume in the non-septic hypovolemic patient, they fall short of predicting global perfusion during sepsis. More invasive monitors such as the pulmonary artery catheter are associated with higher risks of causing injury including pneumothorax, infection, pulmonary artery rupture, and dysrhythmias. While newer techniques are being increasingly tested and show potential promise as better indices of fluid resuscitation, hemodynamic monitoring and urine output measurement are the most common and are available to most clinicians. In this section, we will discuss the advantages and limitations of each monitoring technique.

Mean Arterial Pressure

Arterial hypotension is used to gauge the severity of septic shock. Although a mean arterial pressure less than 60 mmHg is a criterion of septic shock (7), values greater than 60 mmHg in patients with chronic hypertension can also be considered as septic shock. Rarely does fluid resuscitation alone restore mean arterial pressure to normotensive levels. In fact, the risk of overhydration such as pulmonary edema, intestinal edema, and abdominal compartment syndromes will likely result if this sole end point is used to guide fluid therapy. Arterial pressure serves as a measure of the extent of shock, rather than an end point of resuscitation. In addition, mean arterial pressure must be closely followed as part of any paradigm of resuscitation to ensure adequate perfusion of the cerebral and coronary vasculatures. If hypotension is still present and other indices of intravascular volume are normal or higher than normal, consideration must be given for administration of an inotrope in such a moribund situation. If the inotrope is not effective, a pressor agent should be considered.



Heart Rate

Tachycardia (heart rate > 90) is present during sepsis. This can occur in the presence or absence of low intravascular volume. Patients with sepsis exhibit hypermetabolic states, increased heart rate with fever, catabolism, and low systemic vascular resistance. Even after fluid challenges, tachycardia typically does not resolve. Bradycardia can also be present in some septic patients.

Urinary Output

Urinary output greater than 0.5 mL/kg/hr is often used to guide fluid therapy. Specifically, this number represents the minimum clearance of nitrogenous metabolic waste and metabolic acid produced by the body, and the maximal concentration ability of the kidney to excrete the metabolic load. Although urinary output may be a reasonable predictor of renal perfusion in the nonseptic patient, there are limitations with using it as an index of either global or regional perfusion. We have reported that glomerular filtration rate is reduced in sepsis as a result of reduced glomerular filtration pressure (8). Thus, urinary output may not be a reliable index of the adequacy of resuscitation. Urinary output can be normal or increased despite reduced renal blood flow, because levels of atrial natriuretic factor are elevated in sepsis (8,9). Hyperosmotic states such as hyperglycemia, or diuretic therapy such as furosemide, will augment urine production even in the presence of a reduced glomerular filtration rate. These confounding factors are common in septic patients. Hypoproteinemia, which is also present in the majority of septic patients, promotes urine formation despite a potential reduction in renal blood flow, because the low plasma colloid osmotic pressure is less able to facilitate oncotic reabsorption.

Cardiac Filling Pressures

Right atrial pressure (RAP) and pulmonary artery occlusive pressure (PAOP) are common end points used by clinicians to estimate preload in patients who respond poorly to fluid challenges. Under normal physiologic conditions, RAP and PAOP correlate with left ventricular end-diastolic volume or preload of the heart. Thus, volume and pressure are linked. To maximize cardiac output, filling pressures are typically increased to 12 to 15 mmHg. However, in sepsis, filling pressures may not reflect end-diastolic volume. Decreased ventricular compliance, increased airway pressure from ventilation, tricuspid regurgitation, pulmonary hypertension, and ventilation/perfusion abnormalities in the lung occur, making the relationships between filling pressure and end-diastolic volume difficult to interpret. Caution should be exercised when using absolute numbers to guide fluid therapy. Rather, trends in filling pressure may be more reliable indices of preload. These measurements, although invasive, are usually immediately available and are familiar to most clinicians.

Oxygen Delivery and Oxygen Consumption

Oxygen delivery and oxygen consumption are obtainable from the pulmonary artery catheter.

$$\text{Oxygen delivery (mL/min)} = \text{cardiac output (L/min)} \times \text{hemoglobin concentration (g/dL)} \times 1.34 \text{ (mL O}_2\text{/g hemoglobin)} \times \% \text{ O}_2 \text{ arterial saturation}$$

$$\text{Oxygen consumption} = \text{cardiac output} \times (\text{O}_2 \text{ saturation arterial} - \text{O}_2 \text{ saturation mixed venous blood}) \times 1.34 \text{ (hemoglobin concentration)}$$

There is lack of consensus in using oxygen delivery or oxygen consumption as end points for guiding fluid therapy in sepsis. This may be due to the perturbation in cellular metabolism, leading to inadequate utilization of oxygen and nutrients despite "adequate perfusion." Decreases in mixed venous oxygen saturation (S_vO_2) can reflect a reduction in cardiac output and oxygen delivery. An S_vO_2 less than 50% is highly suggestive of decreased perfusion. Augmenting cardiac output or administering packed red blood cells may be necessary to increase oxygen delivery. However, septic patients often exhibit increases in S_vO_2 . This results from increases in blood flow to nonmetabolically active tissues. In fact, if blood flow to nonmetabolically active tissues is greater than blood flow to metabolically active tissues, the S_vO_2 will be higher than normal.

Lactate/Base Excess

Serial blood gas determination, including serum lactate concentration, is a reasonable prognostic indicator of tissue hypoperfusion in sepsis (10). However, the laboratory feedback from these measurements is not rapid, and may incur expense if serial measurements are made. In addition, Wolfe's group (11) has reported that glycolysis is greatly accelerated during trauma and sepsis. The accelerated activity of this pathway in the absence of increased energy utilization causes an elevation of pyruvate and thus lactate. Apparatus for rapid determination of lactate is becoming more and more common in stat laboratories. However, to interpret the changes in lactate, it is advisable to know the lactate/pyruvate ratio.

Echocardiography and Doppler

Echocardiography is also able to gauge ventricular contractility and competency of heart valves, both of which may be abnormal in septic patients. More and more intensive care units are getting these devices, and critical care physicians are being trained to use them. However, echocardiography is not a continuous monitor of resuscitation. Fluid responsiveness in sepsis has been evaluated using Doppler. Recently, Fissel et al. have demonstrated that changes in aortic blood flow velocity during respiration, measured by either Doppler or transesophageal echocardiography, can accurately reflect fluid responsiveness in septic patients with preserved systolic function (12).

Intrathoracic Blood Volume

Measurement of intrathoracic blood volume utilizes the principle of transpulmonary thermal dilution by venous-arterial transit time. Intrathoracic blood volume can be calculated if the cardiac output (L/min) and transit time (min) are known. A device marketed by Pulsion (Pulsion Medical Inc., Cornelius, North Carolina, U.S.A.) measures cardiac output, systolic and diastolic arterial pressures, heart rate, stroke volume, and stroke volume variation and calculates systemic vascular resistance, continuous cardiac output, and intrathoracic blood volume. The system requires peripheral arterial and central venous catheters. It is not as invasive as a pulmonary artery catheter, because the catheter is not placed in the heart or pulmonary artery. Intrathoracic blood volume has been shown to have a much higher correlation as an index of preload than central venous pressure or PAOP (13,14). In fact, central venous pressure and PAOP may not bear any relationship to stroke volume in critically ill patients (15).

Blood Pressure Variation

Techniques utilizing dynamic indices of preload are now being increasingly tested and potentially show the most promise in predicting fluid responsiveness. Systolic blood pressure variation and pulse pressure are closely linked to the amount of preload in the heart, because they take into account the dynamics of cardiac cycle during respiration (16). Although systolic blood pressure variation may not account for changes in pleural pressures, pulse pressure variation does and may be an advantageous measurement. However, measurements must be made by a skilled operator.

Gastric Tonometry

Regional indices of end-organ perfusion have gained increasing attention, with a particular focus on gut perfusion. Gastric tonometry involves the placing of a saline-filled balloon into the stomach or proximal portion of the gastrointestinal tract. After 30 to 60 minutes of contact with the mucosal wall, the saline-filled balloon equilibrates with the mucosal wall tissue CO_2 . Intramucosal pH is then calculated by measuring the pCO_2 from the saline-filled balloon and simultaneous serum bicarbonate sample. The few randomized, controlled trials utilizing this method as an effective end point for resuscitation have shown mixed results (17,18). Further studies are needed to validate the utility of gastric tonometry in guiding resuscitation.

CHOICE OF FLUIDS

The debate over the choice of fluids in the treatment of sepsis is ongoing. Whether crystalloid, colloid, or hypertonic fluids are used in the resuscitation of septic shock seems to be more a matter of personal practice than a standard of care. Although total fluid balance can be reduced if colloid solutions are administered, there has been no conclusive evidence demonstrating that any specific type of fluid reduces overall morbidity or mortality. Rather, it appears that the extent of fluid resuscitation is more indicative of outcome.

Crystalloids

Crystalloids such as 0.9% NaCl or lactated Ringer's (LR) are the most common, most available, least antigenic, and least expensive of the resuscitation fluids. However, greater amounts of crystalloid infusion are required to maintain vascular volume. There is no doubt that infusing crystalloid solutions for fluid resuscitation of sepsis results in an obligatory edema and the potential for metabolic disturbances. The large fluid load further dilutes plasma protein and decreases plasma colloid osmotic pressure.

One liter of 0.9% NaCl (normal saline) contains 154 mEq sodium and 154 mEq chloride and has an osmolarity of 308 mOsm/L. Large volume 0.9% NaCl infusion will result in hyperchloremic metabolic acidosis, which may worsen an existing metabolic acidosis. Similarly, there have been reports of gastrointestinal discomfort and central nervous system problems with the administration of large volumes of 0.9% NaCl. LR is slightly hypotonic (273 mOsm/L) and has less sodium and chloride than 0.9% NaCl. One liter of LR contains 130 mEq sodium, 109 mEq chloride, 28 mEq lactate, 3 mEq potassium, and 3 mEq calcium. The lack of suprphysiologic chloride levels in LR and the presence of lactate for the remainder of its anion component make it a more physiologically balanced solution than 0.9% NaCl, especially if large volumes are administered. Lactate eventually undergoes metabolism to bicarbonate after conversion in the liver. Liver dysfunction or a severe metabolic lactic acidosis is a contraindication for using LR, and these abnormalities occur in septic shock. Additionally, caution must be used in infusing LR in head-injured patients, because cerebral edema may be exacerbated by LR hyposmolarity.

Colloids

Colloid solutions such as albumin, fresh frozen plasma, hetastarch, dextran, or gelatins generate an increase in plasma colloid osmotic pressure. The volume-sparing effect of colloids is due to the osmotic retention of fluid in the vascular space. During sepsis, microvascular permeability is increased, leading to the extravasation of protein and water into the interstitial space and thereby reducing the effective plasma-interstitial oncotic gradient. In particular,

lung fluid balance has been the focus of many clinical and experimental studies comparing crystalloid and colloid administration. It appears that there is either no difference or even less pulmonary edema, when colloids are used for resuscitation (19,20).

Albumin is a naturally occurring 69 kD protein. It generates the majority of the oncotic pressure in the plasma and is used either as a primary resuscitation regimen or as an adjunctive fluid. A recent review by the Cochrane injury group suggested an increased mortality in patients treated with albumin (21). There have been a number of articles critical of this review. Formerly, most biologicals were permitted to contain as much as 1 $\mu\text{g}/\text{mL}$ of endotoxin. Unfortunately, many of the papers used for the Cochrane review came from that era. Albumin also carries little risk of disease and virus transmission compared to plasma; however, it is more costly than crystalloid solution or artificial colloid solutions. Most patients who are under stress demonstrate the acute phase protein response. A major consequence of this protein reaction to stress is a reduction of constitutive proteins such as albumin. Given its importance in oncotic pressure and as a carrier protein, some clinical groups try to maintain albumin levels above 2 g/L in trauma patients.

Although fresh frozen plasma may have been used in the past for resuscitation of shock, cost and availability prohibit its use for fluid resuscitation of hypovolemia. Conditional uses for administering plasma to septic patients include disseminated intravascular coagulopathy, severe liver insufficiency, and reversal of coumadin effect, and in patients who have received massive blood transfusions.

Hydroxyethyl starch solutions are polysaccharide molecules that are larger than albumin. The commercial brand Hespan[®] is the most common formula in the United States. It is a mixture of 6% hetastarch in 0.9% NaCl. Hespan has a similar oncotic pressure compared to albumin, but is six times larger with an average molecular weight of 450 kD. Hespan costs less than albumin and has similar physiologic effects. Although Hespan has an average molecular weight of 450 kD, it is a mixture of many different-sized materials from as small as 5000 D to as large as several million. There has been concern that the infusion of Hespan can result in a coagulopathy, and it is generally recommended that no more than 15 mL/kg of Hespan be administered to a patient in a 24-hour period. This typically means administering no more than one liter of Hespan to a septic patient, and supplemental fluids are needed to maintain vascular volume. The coagulopathy is the result of the high-molecular-weight materials inhibiting factor VIII and von Willebrand's factor (22).

Another concern with Hespan administration is the development of renal failure. A recent study by Schortgen et al. concluded that there was a twofold increase in the risk of developing acute renal failure in severe septic patients treated with Hespan compared with other colloids (23). The mechanism of renal insufficiency with Hespan is not clear. Hextend is a newer hydroxyethyl starch formula that is more physiologically balanced than Hespan and can be administered in larger doses. In an experimental sepsis model, Hextend showed an increase in survival when compared to saline (24). Other hydroxyethyl starch formulas with different branch-chain substitutions are less likely to induce a coagulopathy. There has also been an effort to produce compounds with molecular weights that would prevent them from leaking from the circulation, even when there is a permeability change, but not large enough to affect factor VIII. This led to the development of pentafraction colloids. We have used high molecular weight (pentafraction) colloids for resuscitation in experimental sepsis and burn injury (25). The advantage of this material is due to its high molecular weight (100,000–250,000). It does not leak from the circulation even when permeability is increased. We found it to be very effective. It has been a hope of many that such a compound may be approved for use in the United States. Unfortunately, the Food and Drug Administration demands that the compounds be proven to be superior to Ringer's in clinical trials. Clinical trials being so expensive, no company has been willing to undertake them.

Dextran is another branched-chain polysaccharide with a higher oncotic pressure per concentration than either albumin or hetastarch. Six percent dextran 70, a 70 kD molecule, has an oncotic pressure twice that of albumin. Resuscitation with dextran restores vascular volume and requires less fluid than either Hespan or albumin. Dextran, like hetastarch, is eventually metabolized and eliminated by the kidneys. However, dextran is reportedly more antigenic than either hetastarch or albumin. Anaphylaxis or anaphylactoid reactions occur in approximately 1 in 400 patients (26). Therefore, the use of a Hapten competitor Dextran 1 (Promit) is recommended prior to infusion to reduce the risk of anaphylaxis or

anaphylactoid reactions. Dextran may also interfere with platelet function that can exacerbate an underlying coagulopathy.

Gelatins are not commonly administered in the United States, but are common in Europe and other countries. Like hydroxyethyl starches and dextrans, these artificial colloids have been demonstrated to be retained in the vascular space despite increases in capillary permeability (27). These solutions are also less expensive than albumin.

Hypertonic Saline

Both experimental and clinical data demonstrate that hypertonic saline can restore central hemodynamics, normalize injured microcirculation, reduce fluid needs, and offer protection to the myocardium following trauma and burn injury (28–31). Hypertonic solutions work by osmotically drawing water, primarily cellular water, from the extravascular space into the vascular space. Despite the high concentration of sodium, no adverse effects of hypernatremia were demonstrated in trauma patients resuscitated with 4 mL/kg of 7.5% NaCl. The combination of dextran 70, which is a hyperoncotic colloid, with 7.5% NaCl (HSD) may further sustain vascular volume. In addition to physiological effects, hypertonic saline has been shown to have a favorable immunomodulatory profile, and at least experimentally decreases susceptibility to sepsis (32–35).

Although septic shock is more complicated than hypovolemic shock, some of the attributes of hypertonic saline resuscitation, such as preservation of myocardial function and maintenance of a more competent immune system, are attractive. Experimental studies in treating sepsis have shown a potential role for hypertonic saline (36,37). The major interest in hypertonic saline as a resuscitation fluid is shifting away from its volume-sparing effect to its protective effects on immune system and myocardium. These solutions are unique among the fluid regimens, but will need further evaluation in treating sepsis.

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17 Prehospital Fluid Therapy

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INTRODUCTION

History

Even the most primitive humans were aware of the importance of blood. Greek mythology is full of tales of transfusion to replace lost youth. The Egyptians used blood to soak their bodies for treatment of filariasis while some Romans are said to have been drinking blood from gladiators as a therapy for epilepsy (1). The first known transfusion is said to have been in 1492 when the terminally ill pope Innocentius VIII received blood from three young boys and the pontiff gave some of his blood to the youngsters. The attempt ended with the death of all three donors and the pope. The whole story is probably a fable and if transfusion had occurred, although it is said to have been vein-to-vein, blood may have been ingested by mouth (2,3). The perception of blood circulation was not clarified until William Harvey published his dissertation in 1628 (4). Harvey could not, however, fully explain how blood could pass from the arterial to the venous system. The discovery of this connection was made possible by the invention of the microscope and the works of Marcello Malpighi. The architect of St. Paul's Cathedral in London, Sir Christopher Wren, in 1658, fashioned a quill and a pig's bladder to instill wine, ale, opium, and liver of antimony into the veins of dogs (1). Lower publicly demonstrated transfusion between two dogs in 1666 (1). The first successful blood transfusion to a human was performed in Paris 1667 by Jean Baptiste Denis, physician to Louis XIV, who transfused blood directly from the carotid artery of a sheep to a hypovolemic young man. Repeated transfusions between animal to man, however, mostly led to disasters that forced the Royal Society of London, the French Parliament, and the Church of Rome to prohibit further experiments of this kind.

CONTINUED EFFORTS

The transfusion of blood fell into oblivion for the next 150 years. However, during the first quarter of the 19th century, James Blundell at the Thomas' and Guy's Hospital in London was appalled by the bleeding postpartum in women and saw the necessity of returning lost blood to the circulation. Blundell invented the precursor of the syringe and transfused 10 patients, of whom five survived (1,5). Wartime has always led to efforts to develop new medical treatments to save the lives of soldiers. During the American Civil War, U.S. Army physicians are said to have performed transfusions on rare occasions (6). While transfusion was recognized as beneficial in blood loss, the complexity of the procedure and the high morbidity and mortality made it impossible to use in clinical practice in those days.

In 1831, William Brooke O'Shaughnessy published outlines in the *Lancet* on how to treat cholera victims. Although he never treated any patients, O'Shaughnessy was the first to understand the composition of the blood volume when patients became dehydrated. Thomas Latta, following the principles of O'Shaughnessy, was the first to clinically administer saline infusions in human beings in 1832 (7). These early infusions were hypotonic and chemically impure and carried the risk of bacteremia, pyrogen reactions, and hemolysis. Surgeons in the 19th century were very well aware of the necessity of both transfusion and replacement with saline for hemorrhaging from injured blood vessels (8). Ringer's observation in 1882 that salts of sodium, potassium, calcium, and chloride in definite concentrations and in precise proportions were necessary for protoplasmic activity eventually led to the introduction of a solution similar to the one that now carries his name (9). Hartmann, when treating

children suffering from diarrhea, would in the 1930s add sodium lactate to overcome the acidosis that inevitably followed saline infusion. The solution was later named lactated Ringer's (LR) or Hartmann's solution (10). During the Spanish–American War in 1898, surgeons gave salt infusion therapies both rectally and subcutaneously (11). Furthermore, Crile, at the turn of the previous century, developed special cannulas that permitted easier infusion of blood and other fluids (12). In 1900, Landsteiner described red blood cell isoagglutinins, thereby facilitating blood typing and cross matching (13), which revolutionized blood transfusion.

Walter B. Cannon, a captain in the U.S. Army during the First World War, was assigned to the Harvard University Hospital Unit and served in the British Expeditionary Force. He understood the critical level of blood pressure required to perfuse vital tissues (14,15) but pointed out the danger of raising such pressure before surgical hemostasis had occurred. He also concluded that the body cells most vulnerable to lack of oxygen were in the central nervous system and that severe shock was associated with hemodilution. He described phenomena such as "deliberate hypotension" and "capillary refill." He also pointed to the fact that "toxic material is given off by smashed and dying tissue and affects the circulation in such a way as to cause a lowering of the blood pressure." We now call this ischemic-reperfusion damage (16). Cannon favored gum acacia (gum salt), the early polysaccharide equivalent to present-day dextran and starch. This was 6% to 7% acacia in 0.19% saline sodium chloride. Although used by a great many hospitals, the incidence of fever and other adverse reactions was high. Considerably safer was normal saline or Ringer's solution, but this was thought to be temporary in its effectiveness (11). Consequently, colloid and whole blood were recommended if intravenous (IV) therapy was needed to restore circulation (Fig. 1).

Blalock in the 1930s was the first to outline protocols for the administration of blood and colloid (17). The colloid recommended was pooled plasma. After an initial lack of both supply and organization, plasma and later blood transfusion therapies were made available to wounded soldiers in World War II, beginning in the Pacific and continuing during the North African campaign (11,18). Hypotensive patients were, however, not aggressively treated until



Figure 1 Walter B. Cannon.

surgical hemostasis had been achieved (19). Because patients suffering from trauma and surgery were thought to be "salt resistant" and not able to eliminate the salt load, physicians were restrictive with salt solutions. This concept, however, was to change by the findings of Moyer, Jenkins, and Shires.

The Korean War, like World War II, began quite unexpectedly for the United States. The medical capabilities, however, were quickly organized and (11) new medical resources included helicopter evacuation to effective mobile army surgical hospitals (MASHs). Also, more advanced vascular repair techniques were used. Pulmonary edema and respiratory failure were not commonly seen because this still was a "colloid era" (20,21). The colloid was initially plasma but the incidence of hepatitis increased and so albumin and artificial colloids, followed by whole blood, were given instead. Renal failure was, however, a problem. The renal failure was prerenal in origin and could be prevented by infusing even larger volumes of fluid during resuscitation. In Vietnam, things changed drastically when the principle of massive transfusion was advocated by the aggressive use of crystalloid solutions together with packed red blood cells (PRBCs). Together with improvements in field resuscitation and quick transportation, this normally led to successful resuscitation and a lower frequency of renal failure. Unfortunately, this treatment regime also led to a new shock lesion first observed in the army hospitals in Da Nang in South Vietnam. To the clinicians, it was obvious that the pulmonary problems were due to over-resuscitation with IV fluids and the lesion was called the "wet lung syndrome" or the "Da Nang lung." Today we recognize this as the adult respiratory distress syndrome (ARDS) (20). The aggressive resuscitation with crystalloids and PRBCs was a consequence of the new ideas of Shires et al. who used simultaneous triple-isotopes to study fluid distribution in hemorrhagic shock (22–24). They found there was a contraction of the extracellular fluid space in humans, up to 5 L (25). Because the lost fluid could not be accounted for, it was speculated that it was lost intracellularly or to "third spacing." This was so convincing and could thoroughly explain why so much fluid was necessary that all that had been learned in hospitals, laboratories and battlefields during the last 50 years was forgotten. The elegant studies by Shires et al. were performed based on the Wiggers model (26), which may not truly reflect a clinical situation. Other researchers have had difficulties in finding similar extracellular deficits mainly due to differences in the choice of tracers, differences in timing of measurements, and differences in underlying trauma (27–34). The new fluid regimes together with the poor intravascular persistence of crystalloids (35–39) inevitably led to an extensive use of new fluids for resuscitation.

CIVILIAN PRACTICE

Somehow the guidelines and practice for the military setting in the Vietnam War found its way into the civilian setting. Mobile coronary care units in Belfast, Northern Ireland, were supplied with IV 5% dextrose solutions, and in 1972, ambulances in Miami were equipped with LR (40). Shires also later confirmed his findings with regard to surgical patients, using more frequent sampling (23). The prehospital use of IV fluids, however, still remains a particularly controversial issue that causes lots of discussion. In fact, the whole prehospital concept of advanced life support has been challenged (41–47) because it has never been validated as beneficial by a prospective, randomized trial including all areas of prehospital trauma.

Many trauma surgeons and emergency physicians in the United States do not recommend prehospital fluid resuscitation. They argue that it is detrimental (48–54) and does not improve the outcome. It takes too long a time to establish an IV line in severely traumatized victims and the volume expansion of a hemorrhaging patient would just exacerbate the patient and delay the only curative treatment, which is surgical access to the damaged organs (43,55,56). Others argue IV resuscitation that is properly performed in a prehospital setting is necessary to restore and preserve circulation to the brain (57) and other tissues that would otherwise succumb. In the current Prehospital Trauma Life Support (PHTLS) Program, there is still a recommendation to start with the insertion of two large-bore IV catheters when shock is present and to rapidly administer 1 to 2 L of warmed crystalloid solution, preferably LR (58). This is based on the current Advanced Trauma Life Support (ATLS) program for in-hospital resuscitation (59). Although there is a recognition of different "responses" to these regimes (58), there are currently no firm guidelines on how to titrate or withhold the fluids.

Animal Trials

Fluid resuscitation of the patient with hypotension and severe traumatic injuries has acute effects on immediate survival, as well as on the occurrence of later complications which ultimately affect quality of life and long-term survival. Hemorrhage is a major contributor to injury-related morbidity and mortality and, therefore, the goal of fluid resuscitation would be to immediately restore blood volume and reestablish blood flow to critical organs, with the definitive outcome being survival (60). This "immediate" resuscitation was the standard goal until challenged more than a decade ago. Much of the initial work of understanding shock in trauma patients originates from the work on "controlled bleeding" animal models by Wiggers, where a standardized amount of blood is removed from the circulation to produce shock (24,26,61,62). Shires et al. demonstrated that after removal of sufficient blood, improved recovery required reinfusion of not only the shed blood but also large quantities of crystalloid solutions (20,24,63). On the other hand, animal studies of "uncontrolled hemorrhage" have demonstrated that aggressive fluid resuscitation will not only increase blood pressure but also reverse vasoconstriction, dislodge early thrombus, increase blood loss, cause a dilutional coagulopathy, reduce oxygen delivery, and cause a metabolic acidosis (14,52,64–69). Mostly, the hemorrhage was induced by tears in the aorta or sharp resection of rat tails (70,71), but there are also blunt models with similar findings (72). Animals that were resuscitated with fluids had a poorer outcome compared to nonresuscitated animals. If the intervention, however, was converted to a controlled bleeding or the blood pressure was allowed to stay low ("permissive" or "deliberate hypotension"), survival was significantly improved (73,74). Timing of the infusion is probably also important because organization of clots is important for hemostasis. These models, however, do not fully reproduce the pathophysiology of fluid resuscitation in the presence of an ongoing hemorrhage following trauma (75). Real trauma patients are nonanesthetized, and usually suffering from a complex pattern of trauma triggering several reactions that are not reproduced in research animals models.

In the clinical area, both controlled and uncontrolled bleeding situations are common. Patients with an isolated fracture such as a closed femur fracture have usually lost less than 20% of their blood volume and would respond to an initial fluid bolus and remain hemodynamically stable. Examples of uncontrolled bleeding are more common in penetrating injury scenarios or when the subject has multiple lacerations of internal organs or a multifractured pelvis (73). Organs and organ systems with a high incidence of exsanguination include the heart, thoracic and abdominal vascular systems, and the liver. Cervical and extremity vascular injuries are also sites where large amounts of uncontrolled blood loss can occur (54).

Clinical Trials

Clinical trials with available conventional solutions tend to support the animal studies that recommend withholding prehospital fluid therapy (53). Further, concerns have been raised as to the efficacy of most available solutions (76–81). The ideal resuscitation fluid should expand vascular volume, be able to transport oxygen or reduce oxygen demand, not increase bleeding, and be able to be administered and handled rapidly. No such solutions exist, although there have been several attempts to find the optimal fluid for resuscitation.

Consequently, there is much debate on whether IV cannulation should be attempted at the scene of the incident. In studies, time varies from 90 seconds to 12 minutes for IV cannulation (43,82–86). The time for this procedure could sometimes very well exceed the transport time to a hospital in an urban setting (43). The speed with which IV access can be gained is related to the competence of the practitioner (87,88). The volume of infused fluid prior to arrival at the hospital is often too small and subtherapeutic because of slow infusion rates, low suspension height in the ambulance, and other logistical problems (84,86). Computerized modeling of IV fluid therapy has suggested that potential benefits of crystalloid infusion will only occur if there is a bleeding rate of initially 25 to 100 mL/min and the rate of fluid infusion is at least equal to the bleeding rate, and if the prehospital time exceeds 30 minutes (89). In practice, these conditions would seldom be met. This should be contrasted with newer views of "hypotensive resuscitation" or "permissive hypotension," which clearly would require less volume. The problem with permissive hypotensive regimes is that they may very well work in a monitored setting but can be very difficult to perform in the field. Current consensus today is to try to secure an IV cannula at the scene provided it would not delay transportation.

In several reports, cannulation en route is advocated and in one study was actually found to be as successful as when attempted at the scene (41). Current prehospital protocols in the United States advocate the insertion of two large-bore catheters (14 or 16 gauge) en route (58). By personal experience the author would like to point out that there is certainly a challenge to try to insert a large catheter in a patient in a moving ambulance or an airborne helicopter; consequently it may be better to secure the IV before transportation (Fig. 2).

When establishment of an effective vascular access is imperative, the intraosseous route could be indicated. Intraosseous infusion ports are as efficient as IV infusion ports. This is especially recommended in children under the age of six, but can be used in other patients from neonates to adults; however, it would be more difficult to properly insert them in adults (90–96). The preferred insertion site is 1 to 2 cm medial and 0.5 cm above the tibial tuberosity. Sternal infusion ports are being introduced in some prehospital protocols but are still under trial. In prehospital systems where physicians are working, there is a possibility of using central access. This could anecdotally be used as a last resort in a situation where the patient is entrapped. The high risk of infection and of causing further damage to underlying organs should be weighed against the possible benefit.

The general recommendation is thus to try to secure one peripheral IV without delaying transport of the patient. However, even if prehospital times were not affected by IV placement, there is currently little evidence to demonstrate that the prehospital administration of IV fluids in urban settings improves patient outcome (53,97). Studies that have attempted to measure the effects of prehospital IV fluids have predominantly used crystalloid infusions and have mainly dealt with penetrating trauma in urban settings (53). There are currently no fluids that have undergone extensive clinical trials and subsequent regulatory approval for prehospital use (98). The majority of the human studies addressing prehospital fluid therapy have assessed the impact of IV fluids as a part of a protocol rather than a single intervention (43,99–101). Most of these studies are severely limited in their ability to show the effects of IV fluid administration alone (84,86,87,102,103). The studies were not randomized and showed a mixed intervention, where IV fluid therapy could not be distinguished from other interventions. This is also complicated by the fact that in these studies pneumatic antishock garment (or Military Anti Shock Trousers (MAST)) suits were also used and consequently the results in altered hemodynamics were not the result of IV fluid therapy alone. The antishock garment still exists in some protocols (58) but has mostly been abandoned as a device for maintaining intravascular circulating volume due to deleterious side effects and the lack of significant



Figure 2 Helicopter EC-135 hovering in the archipelago of Stockholm, Sweden. This helicopter carries one patient and is staffed by an anesthetist, an anesthetic nurse, a navigator with staff nurse competence, and a pilot. The helicopter is fast and quiet.

improved outcome. The study done by Mattox and coworkers showed that MAST application adversely affected the outcome most significantly for patients with cardiac and thoracic vascular injury. The overall mortality of 31% in the MAST group, compared to 25% in the no-MAST group was statistically significant ($p=0.05$) (104–108).

There are, however, studies attempting to more specifically isolate the effects of prehospital IV fluid administration. A large retrospective study of 6855 trauma patients (55) found no differences in mortality, although this was not adjusted for risk factors. In another retrospective study (85), there was an additional mortality risk when administering IV fluids prehospitally, and this risk increased when the prehospital time increased.

Perhaps the most famous and most cited prehospital fluid therapy study is a large, prospective, controlled clinical trial comparing immediate prehospital and emergency department IV fluid resuscitation with fluid resuscitation delayed until arrival in the operating room conducted in Houston (53). In this study, hypotensive patients with penetrating torso injuries received either aggressive isotonic fluid resuscitation preoperatively (immediate group) or were given fluids only on arrival in the operating room (delayed group). Patients in the immediate group had significantly higher mortality rates, along with higher rates of postoperative complications, compared with patients in the delayed resuscitation group (survival 62% vs. 70%). The conclusion was that rapid administration of IV fluids prior to control of hemorrhage resulted in worse outcomes. This is probably the most elegant and robust of all studies addressing the impact of prehospital IV fluids ever performed. Nevertheless, it has not been without criticism. There were some protocol violations with 8% of the delayed-fluids group receiving fluids. Further, the study was limited in its generalizability to an inner-city setting with short transport times. The study was performed on patients with penetrating torso trauma and could not be extrapolated to patients with head trauma or blunt trauma. Most providers would agree that in a longer transport scenario, it would be difficult to withhold fluids in a patient with poor tissue perfusion. The authors of the Houston study, however, argue that the results would have been even more impressive if there had been more time to infuse more fluids (109).

By definition, it is difficult to perform prehospital studies. The logistics and environment create enormous problems for the investigators. In the late 1980s and early 1990s, there were efforts to overcome this, and a large number of double-blind randomized clinical trials with hypertonic solutions were performed mainly in the prehospital area (98,110–122). The pharmacological properties and side effects of these solutions are described elsewhere in this book (Chapter on Hypertonic Solutions) but it could briefly be said that several studies over the past two decades have established that hypertonic saline (HS) infusions promote diuresis/natriuresis, augment cardiac output, increase cardiac contractility, and directly vasodilate the peripheral vasculature (123,124). Adding a colloid can transiently (depending on type added) expand plasma volume and can be used safely for resuscitation of patients with hypovolemia (125–127). The settings have included administration in the field at the site of the accident, in the transport vehicles, and in the emergency room. The efficacy end point of all of the studies of hypertonic solutions has been survival. A number of formulations of hypertonic solutions have been evaluated. The most extensive set of data for the treatment of traumatic injuries is available for the formulations of HS (HS; 7.5% NaCl) and hypertonic saline dextran (HSD; 7.5% NaCl in 6% Dextran 70). The studies were randomized as to treatment with HS and HSD compared to an equal volume of the standard-of-care solutions (normal saline or LR). All solutions have been evaluated at 250 mL, with additional fluids and rescue protocols as necessary.

On the whole the use of HS or HSD in the resuscitation of patients with traumatic injuries has been favorable. Wade et al. performed a meta-analysis on both HS and HSD (128). They found there to be little effect of HS alone on survival until discharge. When the combination solution HSD was evaluated in 615 patients compared to standard-of-care in 618 patients, there was a 3.6% increase in survival. This equates to a 13% reduction in mortality. The odds ratio was 1.20 in favor of the use of HSD, with a 95% confidence interval of 0.94 to 1.57. This was not significant ($p=0.142$ two-tailed, $p=0.07$, one-tailed). However, the results were in favor of HSD and when a meta-analysis on individual data from six of the underlying eight studies in the original meta-analysis was performed, the odds ratio was 1.47 (95% CV 1.04, 2.08, $p < 0.05$) in favor of HSD (98). The randomized studies that were the basis for the meta-analysis (128) were all well done but individually too small to show significant changes

when looking at survival as an end point. The population that can be affected by any treatment in a trauma population is probably very small. Deaths following trauma have a distinct pattern, with 50% occurring at the scene, 30% within a few hours, and the remaining 20% within days or weeks (129). Our immediate fluid intervention could possibly affect a few patients in the surviving groups but there are patients who are going to die whatever the intervention is and there are others who are going to survive regardless of interventions. Therefore, the “therapeutic window” is very small, making an impact of treatment difficult to demonstrate. It is therefore useful to evaluate subgroups of interests. Cautions must, however, be exercised because conclusions are drawn from meta-analysis (130). They can never fully replace single, randomized, controlled studies.

Blood Pressure

When considering subpopulations of interest to assess the advantage of hypertonic solution administration, it appears that patients with initial low blood pressure benefit from administration of HSD (114,116–118). In the majority of the studies of patients who were hypotensive, a systolic blood pressure of less than 90 mmHg was used as an entry criterion (128). It could be argued that patients with a low blood pressure that is sustained for a long period will have a poor outcome (131). The use of HS solutions is beneficial because there is a consistent finding of a greater increase in blood pressure following administration compared to treatment with standard-of-care (110,111,115,117,118). An increase in blood pressure has been said to induce bleeding in the presence of uncontrolled hemorrhage (54,132). In animal models, the increase in blood pressure associated with the administration of fluids leads to increased blood loss and ultimate death (49,67). This has been shown in studies with both HS and HSD (48,71,74,133). Furthermore, if the dose and rate of infusion of HSD are reduced, the mortality is also reduced (74). But again, these are models in which animals are anesthetized. The patients given hypertonic solutions in these studies did not have an increased mortality, which underlines the discrepancy between animal models and real trauma patients. In a study randomizing trauma patients with ongoing bleeding to either a conventional pressure resuscitation protocol (systolic blood pressure >100 mmHg) or target systolic blood pressure (70 mmHg, “permissive hypotension”), there was no benefit in titrating toward a lower end point. Half of these patients suffered from penetrating trauma. The patients stopped bleeding either spontaneously or by surgical hemostasis or radiological embolization (132). Efforts to use blood pressure as a detector of uncontrolled bleeding in blunt trauma have been made (134), but blood pressure measurements are difficult in the prehospital setting.

The concerns associated with uncontrolled bleeding are focused on those patients with penetrating injuries to a major vessel that require surgery. It is interesting that in a number of studies, the patient group that had the greatest improvement in discharge survival were those patients with penetrating injuries requiring surgery (115,117). Ideally, it would have been better to design the studies using hypertonic solutions in the same way as the study by Bickell et al. (53) (consequently HSD vs. no fluid) for comparative reasons. The reason for using the standard dose of 4 mL/kg or 250 mL seem to be based more on practicality rather than on any true physiologic concept. Although it may be better in the prehospital area to titrate the solutions to clinical response, there is still support among some clinicians for using a standard dose for reasons of simplicity. One reason for the more successful outcome with hypertonic solutions compared to standard-of-care fluid regimes in trauma patients could be that hypertonic solutions with the dextran component in animal studies have anti-inflammatory properties (135–137), thereby preventing late sequelae of the trauma.

Head Trauma

In blunt trauma in combination with head injury (the most recognizable severe trauma in motorvehicle accidents), brain swelling can occur and elevated intracranial pressures (ICP) have been reported in 40% of patients with severe traumatic brain injury. These patients are unconscious and regularly score low on the Glasgow Coma Score (GCS) Scale. Conventionally, this has been treated with the insertion of an endotracheal tube (if patients score 8 or below) and hyperventilation. This is considered temporary because vasoconstriction could cause ischemia to parts of the brain and there are concerns of a too vigorous ventilation regime for

trauma patients with hypovolemia (138). Prompt restoration of systolic blood pressure and mean arterial pressure (MAP) is essential especially when ICP is increased. Although restoring circulating blood volume is the mainstay of treatment, temporary use of vasopressors will improve cerebral perfusion pressure (CPP), where $CPP = MAP - ICP$. Because the intact blood-brain barrier enhances the influence of changes in serum sodium on brain water, hypotonic solutions (including LR solution) are more likely to increase brain water content than 0.9% saline or colloids dissolved in 0.9% saline. Although colloid osmotic pressure has been considered less important than serum osmolality, Drummond et al. (139) demonstrated that infusion of colloid solutions after experimental traumatic brain injury was associated with lower brain water accumulation than infusion of crystalloid solutions.

A potential intervention is to administer a dose of mannitol, normally 100 to 150 mL of 150 mg/mL, to reduce the ICP. The effect of mannitol is thought to depend on reduced viscosity and thereby result in increased cerebral blood flow and oxygen delivery (140). Mannitol takes only a few minutes to take effect, an effect that lasts from 90 minutes up to six hours; yet its diuretic effect takes 15 to 30 minutes to establish. The diuretic effect could be less favorable if the patient has both head trauma and hypovolemia. To reach a CPP higher than the necessary 70 mmHg, the MAP would need to be maintained in the range of 90 to 105 mmHg (assuming an ICP of 20–25 mmHg). A possibility would be to use HS, but in a large randomized trial in Australia, not particularly looking at survival but rather at differences in neurological outcome, there were no differences compared to conventional fluids (141). However, evidence points to the fact that the addition of a colloid to the HS such as in HSD treatment improves survival of patients with brain injury and a Glasgow Coma Score 8 or less (98,114,116,117,128,142–144). A delicate situation will of course be if we are dealing with a head trauma, necessitating increased perfusion pressure, in combination with ongoing hemorrhage from other injuries, requiring withholding aggressive fluid resuscitation. A HS colloid solution titrated to response is probably most ideal.

THE CLINICAL USE OF HYPERTONIC SOLUTIONS

The lesson to be learned from available studies with hypertonic solutions is that the number of patients in individual trauma trials generally has been insufficient to establish statistically significantly improved survival and that aggregate data from these same trials are encouraging but not fully significant. Moreover, meta-analyses studies can be criticized (130) because there are difficulties associated with comparing the underlying studies. Because meta-analyses are not generally considered sufficient evidence for regulatory approval, HSD has not been approved for use in the United States. Interestingly, no other IV fluid or volume expander has been required to improve survival in order to be used in the clinical setting. Current fluids are used mainly because they have shown volume-expansion properties. The lack of reduced mortality using hypertonic solutions, coupled with concerns raised among surgeons when Bickell et al. (53) reported that conventional fluid therapy might be inferior to delayed prehospital fluid resuscitation in hypotensive and penetrating trauma patients, resulted in a general reduction of interest in prehospital resuscitation with IV solutions, conventional as well as hypertonic, in the United States. Nevertheless, a recommendation of an early prehospital infusion of crystalloids according to PHTLS and ATLS protocols is still existing in the United States (58,59).

In Europe and other parts of the world, however, the situation is different. Europe is traditionally more orientated to using a mix of crystalloids and a wide variety of colloids. This is reflected in the prehospital care. In Austria, HS together with a colloid has been in use since 1991. Austria and Brazil were the first countries in which this type of solution was used routinely for resuscitation from severe trauma and shock. In Austria, HS is mixed with hetastarch (Osmohes[®]—7.2% sodium chloride + 10% hetastarch 200/0.5—now replaced by Hyperhes—7.2% sodium chloride + 6% hydroxyethyl starch 200/0.62). In the past decade, more than 50,000 units have been administered safely. Germany recently approved HyperHAES[®] (7.2% sodium chloride + 6% hetastarch 200/0.5), and furthermore, with Sweden as the first country in 1998 (125), several countries in Europe have registered Rescueflow[®] (7.5% sodium chloride + 6% dextran 70). In the majority of these cases, the standard amount of solution given was 250 mL.

OTHER ASPECTS

Blood Transfusion

Blood transfusion is a vital component of resuscitation in hemorrhagic shock. It is usually not available in the civilian prehospital environment. There are no prospective, randomized human studies that evaluate the efficacy of transfusion in the prehospital setting, although efforts have been made to study this retrospectively (145). Animal studies show that early blood transfusion results in less acidosis and improved survival (51,146). If available and if logistics permit, blood could be transfused in rare situations where patients are entrapped and cannot be evacuated.

Artificial Blood

As a consequence of the necessity of hemoglobin for oxygen transport and the lack of benefit of most conventional prehospital fluids, there have been efforts to develop an artificial oxygen carrier. Having overcome a number of problems with toxic stroma, short intravascular half-life, and high colloid osmotic pressure, a number of hemoglobin-based oxygen carriers are now under development (147–151). The products currently under investigation come from bovine blood and outdated human blood using biotechnological methods, and do not require cross matching. It has been the purpose that they should have similar oxygen dissociation curves compared to blood. However, many of them have a significant vasopressor effect from scavenging endothelial nitric oxide (149). A diasporin–cross-linked hemoglobin (DCLHb) product (HemAssist, Baxter Healthcare, Round Lake, Illinois, U.S.A.) reached the prehospital field in the form of a randomized clinical trial with an unfortunate negative outcome (151). The commercialization had to be abandoned. The reason for this is unclear but the pressor effect of DCLHb, causing pulmonary and systemic resistance, may be related to the negative outcome (152). A glutaraldehyde-polymerized bovine hemoglobin product (Hemopure or HBOC-201, Biopure Corporation, Cambridge, Massachusetts, U.S.A.) has a reduced O₂ affinity that promotes O₂ loading in the tissues. This product has been shown to be safe and effective for blood replacement in anemic orthopedic surgery patients, according to the first U.S. Phase III clinical trials. This product is approved for perioperative use in South Africa. A closely related product is approved for veterinary use in the United States and the European Union. The U.S. Army is expected to start clinical trials with HBOC-201 in the near future.

Hypothermia

Hypothermia is often present in trauma patients on admission to the hospital, particularly in cold climates, and is related to long extrication times, spinal cord injury, alcohol ingestion, removal of clothing, exposure to wet environments, and rapid volume resuscitation. Accidental hypothermia is associated with increased Injury Severity Scores and mortality in patients with major trauma (153–155). On the other hand, induced hypothermia has been studied with promising results in patients with severe stroke (156) and variable results in patients with severe head injury (157,158). Hypothermia may decrease heart rate, blood pressure, cardiac output, and coronary blood flow, increase systemic vascular resistance, and cause alterations in mental status (159). Postinjury coagulopathy is also affected by hypothermia. The pathophysiology is multifactorial (159) and includes retardation of temperature-dependent enzyme-activated coagulation cascades, platelet dysfunction, endothelial abnormalities and a poorly understood fibrinolytic activity. A limited amount of IV fluids, however, in trauma victims, has been shown to have no effect on core body temperature (159). The core body temperature is mainly determined by the severity of trauma (159). However, it seems advisable to try to give the patients IV fluids that are warm and not cold.

Vasopressors and Hemostasis

The use of vasopressors in hypovolemic shock has been condemned (160). Nevertheless, an approach to the vasopressor phenylephrine in an animal model has been made. In a swine model, animals were randomly assigned to either controls or splenic laceration and cryogenic brain injury. The experimental group received either of three prehospital resuscitation regimens: delayed resuscitation, Ringer's lactate, or phenylephrine to maintain MAP in an effort to treat brain injury. Although it was concluded that phenylephrine increased MAP and CPP, it

did not reduce secondary neuronal ischemia. Furthermore, it was concluded that LR restored cerebral blood pressure earlier and was associated with less secondary ischemia than either phenylephrine or delayed resuscitation. The study is flawed by large variations in hemorrhage volumes and hemodynamic responses and lack of significance (161). That large amounts of LR were necessary to maintain MAP and LR is in itself inflammatory and hypotonic (162). Further, the fluid kinetics when infusing phenylephrine has been found to diminish plasma expansion (163).

The mechanism of action of recombinant activated factor VII suggests the enhancement of hemostasis is limited to the site of injury without systemic activation of the coagulation cascade. Therefore, the use of this drug in trauma patients suffering uncontrolled hemorrhage has been suggested as an added treatment (164).

RECOMMENDATIONS

The scenario facing paramedics, ambulance drivers, rescue personnel, nurses, and doctors when they arrive at the scene of the accident can sometimes be very cumbersome and chaotic (Fig. 3). It is mandatory that the personnel have specific training to be able to work in this environment. Many Emergency Medical Services (EMS) systems develop protocols for the initial assessment of the patients. These protocols exist in different forms and have been outlined in certain guidelines and handbooks in the United States (58,59). These protocols were by intention designed so that rescue workers should work in a uniform and consistent manner. It is, however, tempting to say that the traditional management of trauma has been complicated by attempts to simplify it (138). Most EMS systems try to develop treatment algorithms, especially when it comes to fluid therapy, which do not delineate between the different mechanisms of injury or anatomic locations of wounds (138). Trauma patients are by definition complex, with a variety of wounds that poorly fit into a protocol and there is no gold standard on how to handle them. Debate still occurs as to whether to give just basic life support or to give more advanced treatment on scene (47).

The concept of "permissive hypotension," which has been suggested for prehospital infusion protocols has several pitfalls. First, it is difficult to perform a physical examination in the prehospital setting, especially when there is foul weather or other severe conditions.



Figure 3 The situation at an emergency can sometimes seem very disorganized. It is important not to stay too long at the scene.

Heart rate is often measured only quantitatively, and blood pressure is seldom or accurately measured. Under these conditions, the diagnosis of shock and uncontrolled bleeding is difficult. Secondly, to perform hypotensive resuscitation, close monitoring of the patient is mandatory. Monitoring of MAP, which is a cornerstone of hypotensive resuscitation, requires at least the application of a continuous noninvasive blood-pressure cuff.

Patients with exsanguinating hemorrhages in the chest or cardiac tamponade require the only lifesaving treatment available: immediate thoracotomy and surgery. Patients with blunt or penetrating abdominal trauma, presenting with severe hemorrhagic shock, require urgent laparotomy (54). Consequently, these patients need immediate support and transportation to a trauma facility. On-scene time should be as short as possible and optimally less than 10 minutes (58). If there is a combined head trauma and short distance immediate transport should be considered, but a hypertonic solution could be life saving. In the intermediate perspective, an IV should be started, if possible en route (138). If the patient cannot be evacuated and there is a long distance to the hospital, line placement and circulatory support with careful attention to the patient's response is needed (75,165). Fluid resuscitation must here be considered because patients may succumb before reaching the trauma center. Patients should be assessed and their treatment priorities established based on their injuries, their vital signs, and the injury mechanism. Patient management must consist of a rapid primary evaluation, resuscitation of vital functions, and immediate transportation to definitive care.

PHTLS guideline (166) must be looked upon as recommendations and will eventually be a judicious mix of interventions taken by the provider at the scene or during transport. In an urban setting, proper Basic Life Support interventions and immediate evacuation are advocated. For longer transports in rural areas, more advanced Advanced Life Support interventions must be considered.

Based on the vast and conflicting number of studies and different opinions the following recommendations can be given:

A. *Airway management:*

Maintain patency, adequate oxygenation, and adequate ventilation. Beware of overzealous positive pressure ventilation and its impact on cardiac output (138). Respiratory rate of 8 to 10 breaths/min is generally adequate (138). If life-threatening pneumothorax, immediate decompression.

B. *Circulation with hemorrhage control:*

1. Stop external bleeding.
2. Discriminate between blunt or penetrating trauma. If there are concerns about internal or uncontrollable hemorrhage: immediately evacuate the patient.
3. Insert IV catheter if it will not delay transportation.
4. In patients with controllable bleeding: provide IV fluids for patients with signs of shock.
5. In patients with penetrating trauma with uncontrollable bleeding: infuse IV fluids only if patient is moribund (unconscious, no palpable pulses, MAP < 40 mmHg or not measurable). Otherwise: restrict or withhold fluids.
6. In patients with blunt trauma: restrict or withhold. If administered: titrate to response.
7. Head trauma with GCS < 8: Maintain CPP above 70 mmHg; systolic pressure needs to be maintained at over 90 mmHg. Administer hypertonic-saline dextran 250 cc for 5 to 10 minutes. If not available, give 0.9% saline or a colloid.
8. Combined head and multiple trauma. Treat head trauma as in the case of head trauma with GCS < 8 but with "treatment to response" so as not to cause excessive bleeding.

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18 | Fluid Therapy in Trauma

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INTRODUCTION

Trauma is the number one killer of Westerners aged 40 or younger, exceeding the combined death toll from cancer and cardiovascular disease in this age group (1). Of these deaths, a significant number, if not the majority, are a direct consequence of major hemorrhage and its end result, hemorrhagic shock. Adding to its importance, hemorrhage has been identified as the single most treatable cause of early trauma deaths (2).

Bearing this in mind, it is hardly surprising that the subject of fluid therapy in trauma is dominated by the acute resuscitation of shocked trauma patients. Yet, at the dawn of the new millennium, despite extensive research into the subject, controversies still remain over seemingly basic issues such as which fluid to use, how much to give, and when to give it. The age-old crystalloid-versus-colloid debate continues, hypertonic solutions struggle to find their place, and hypotensive (delayed) resuscitation competes with conventional resuscitation protocols. Autologous blood transfusions become increasingly attractive, while researchers race to find the perfect red cell substitute.

What follows is a brief account of the currently accepted principles of shock management in trauma, wherein some of the more recent advances and controversies regarding fluid therapy will be discussed.

ETIOLOGY OF SHOCK IN ACUTE TRAUMA

Shock is a state of circulatory insufficiency resulting in inadequate organ perfusion and tissue oxygenation. Hemorrhage is the most common cause of shock in the injured patient (3). The causes of shock in trauma are therefore conveniently divided into two groups, namely hemorrhagic shock and nonhemorrhagic shock.

Hemorrhagic Shock

Hemorrhage, defined as the acute loss of circulating-blood volume, depletes the intravascular fluid compartment, resulting in a reduced venous return to the heart. Decreased venous return leads to reduced cardiac filling with a resultant decrease in end-diastolic volume. Because the end-diastolic volume determines the end-diastolic myocardial muscle fiber length or preload, which in turn is related to the force of myocardial contractility (Starling's law), the end result is a reduced force of myocardial contraction leading to a smaller stroke volume and ultimately a drop in cardiac output. Hemorrhage is invariably a component of all major injuries and may occur in two forms: external (overt) or internal (occult). For the most important sites of internal hemorrhage and their diagnoses, see Table 1.

Importantly, most nonhemorrhagic-shock states will respond, at least partially, to volume restoration. Therefore, current Advanced Trauma Life Support (ATLS[®]) guidelines call for all shock states to receive fluid resuscitation during the initial assessment and management phase (4).

Nonhemorrhagic Shock

This group of causes collectively is less common than hemorrhage alone in trauma-related shock. Nevertheless, they form an important group because they require different treatment

Table 1 Major Sites of Internal Hemorrhage and Their Diagnoses

Sites	Diagnostic tools
Chest (hemothorax)	Chest X ray
Abdomen (hemoperitoneum)	FAST/DPL/CT
Pelvis (retroperitoneum)	Pelvic X ray
Long bones (femurs)	Clinical± X ray

Abbreviations: FAST, focused abdominal sonography in trauma; DPL, diagnostic peritoneal lavage; CT, computed tomography.

strategies and generally are rapidly correctable with appropriate therapy. Equally important, they may be rapidly fatal if overlooked or incorrectly treated. Because this group of causes may be difficult to remember in the highly stressed environs of the casualty area, a real “test of one’s central nervous system (C.N.S.),” a mnemonic may be helpful:

T(est) C.N.S.S.

where, T = tension pneumothorax; C = cardiac tamponade, cardiac contusion, air embolus, acute myocardial infarction, or valvular rupture; N = neurogenic shock (spinal cord injuries); and S = septic shock (delayed presentation); S = supine hypotension syndrome (second and third trimester of pregnancy).

A brief overview of diagnostic measures and emergency treatment of these nonhemorrhagic causes of shock is presented in Table 2. For a more detailed account of these conditions, please refer to the recommended text (5).

Table 2 Common Nonhemorrhagic Causes of Shock, Their Diagnoses and Emergency Management

Causes	Diagnoses	Treatment
T-tension pneumothorax	Respiratory distress Tracheal deviation to contralateral side ↓ Breath sounds (ipsilateral) ↑ Resonance (ipsilateral) Hypotension	Immediate needle thoracentesis Chest tube insertion
C-cardiac tamponade	Distended neck veins Distressed patient Hypotension Distended neck veins Muffled heart sounds ↑ Pulsus paradoxus ↑ Central venous pressure Echo: pericardial fluid ECG: electrical alternans	Pericardiocentesis (if immediate surgery is not possible) Urgent thoracotomy or sternotomy
C-cardiac contusion	Compatible injury (blunt chest trauma) Poor response to fluids ↑ Central venous pressure ECG: arrhythmias ↑ Cardiac enzymes	Judicious therapy Early invasive monitoring Inotropic support, e.g., dobutamine
N-neurogenic shock	Weakness Sensory level Relative bradycardia Warm extremities	Judicious fluid therapy Early invasive monitoring Inotropic support, e.g., epinephrine
S-septic shock	Delayed clinical presentation Warm extremities (early phase) Pyrexia Positive blood culture	Control of infective source Appropriate IV antimicrobial therapy Supportive management (ICU)
S-supine hypotensive syndrome	Advanced pregnancy Supine position Poor response to fluid resuscitation	Position patient in 15° left lateral tilt

Abbreviation: ICU, intensive care unit.

MANAGEMENT PRINCIPLES OF TRAUMA-RELATED SHOCK

Resuscitation of the shocked trauma patient, as with severely injured patients, starts with securing the airway, providing supplemental oxygen, and ensuring adequate ventilation. External hemorrhage must be immediately controlled by direct compression over the bleeding site. Current practice guidelines advise that intravascular volume should be restored to normal as rapidly as possible by the rapid infusion of isotonic fluid, most commonly Ringer's lactate solution (4). Acute anemia is better tolerated than hypovolemia. Therefore, volume restoration takes precedence over correction of anemia, though transfusion of red cells will often be necessary to restore oxygen-carrying capacity in more significant bleeds.

Vitally important in the process of resuscitation is early surgical control of active internal hemorrhage. Continued fluid resuscitation in the face of ongoing bleeding will exacerbate dilutional anemia and thrombocytopenia, and worsen hypothermia. The resultant coagulopathy, from hypothermia-induced platelet dysfunction and dilution of platelets and clotting factors, will serve to perpetuate ongoing bleeding and indeed mitigate successful surgical hemostasis. A "bloody vicious cycle" of hypothermia coagulopathy and acidosis may result in a situation where it would be increasingly difficult to control hemorrhage and restore effective circulation. The resulting mortality is understandably high (6).

To summarize, the current approach to trauma-related shock can be broken down into a number of steps. Having secured the airway and ensured adequate ventilation, the subsequent steps can be easily remembered using the "SHOTS" approach.

S—Stop

H—Hemorrhage

O—Optimize intravascular volume

T—Transfuse

S—Search for (i) internal bleeding (Table 1) and (ii) nonhemorrhagic causes of shock (Table 2); surgery for hemostasis.

Stop the hemorrhage by applying direct pressure over sites of external bleeding. Bleeding from distal limb sites may be temporarily controlled by inflating a proximally positioned blood pressure cuff above systolic pressure. Splinting long bone and "open book" pelvic fractures may limit further blood loss.

Optimize intravascular volume by rapidly infusing warm isotonic fluids to correct any deficit. ATLS protocols recommend an initial bolus of 2 L in an adult and 20 mL/kg in a pediatric patient, using a Ringer's lactate solution.

Transfuse red blood cells to restore oxygen-carrying capacity if necessary, and consider the need for platelets and clotting factors (*vide infra*).

Search actively for nonhemorrhagic causes of shock and for possible sites of internal bleeding. Early surgical control of internal hemorrhage is crucial.

All seriously injured patients are at a risk of developing hypothermia, defined as a core temperature of less than 36°C in the trauma setting (7). This may have several adverse effects, which are summarized in Table 3. Consequently, it is important to prewarm all intravenous fluids prior to administration. Various methods of fluid warming are available, from simple immersion of fluids in warm water baths to inline countercurrent exchange systems that add heat to fluids during infusion. Even microwaving of crystalloids has been used safely, though complications may result from overheating or hemolysis if used on packed red cells (8).

Table 3 Complications of Hypothermia

Complication	Mechanism
Increased bleeding	Reversible platelet and clotting-factor dysfunction
Decreased oxygen delivery	Left-shifted oxyhemoglobin dissociation curve
Increased septic risk	Immunosuppressant effect
Increased cardiac morbid events	Increased catecholamine levels Increased oxygen demand during shivering
Increased acute mortality	Hypothermia-induced arrhythmias Multifactorial (see above)

Table 4 Infusion Rate vs. Cannula Size

Cannula size	Flow rate (mL/min)	
	Crystalloid	Colloid
8.5FG	1000	600
14G	125	90
16G	85	65
18G	60	35
20G	40	17

Specialized rapid infusion systems such as the Level 1™ have made it possible to rapidly warm the large volumes of fluid required in trauma resuscitation.

VASCULAR ACCESS AND FLOW RATES

To meet the rapid infusion rates needed to restore intravascular volume and keep up with ongoing losses, special attention must be given to vascular access and administration sets. Flow rate is proportional to the pressure gradient across the system and inversely proportional to the resistance of the circuit. Consequently, increased flow rates may be achieved by increasing the driving pressure (e.g., increasing the height of the drip bag above the patient or using pressure bags) or by reducing the resistance of the circuit. Circuit resistance, according to Poiseuille's Law, is inversely related to the radius of the conduit raised to the fourth power while only directly proportional to the length of the tubing and fluid viscosity, i.e.,

$$\text{Resistance} = \frac{(\text{Length} \times \text{Viscosity})}{\text{Radius}^4}$$

Hence, the caliber of the tubing is the single most important factor determining maximum flow rate. More specifically, the narrowest part of the circuit, usually the intravenous cannula, becomes the rate-limiting factor. This problem is overcome by using at least two large-bore, intravenous cannulae, ideally 16 gauge or larger. In principle, with all intravenous cannulae and administration sets, the shorter the line, and the wider the tubing, the faster the flow will be. For the estimated maximum achievable flow rates through cannulae of different diameters, please refer to Table 4. The recommended sites of intravenous access are listed in Table 5.

Generally speaking, peripheral intravenous access is the safest, fastest, and most widely available route in most hands. However, in the hypovolemic, "shut-down" patient, central venous access may be easier due to intense peripheral vasoconstriction. The level of skill and the experience of the attending doctor are important factors in the decision-making process.

HYPOTENSIVE RESUSCITATION AND PREHOSPITAL FLUIDS

Hypotensive Resuscitation

Whether in the field or at a level-1 trauma center, there is no argument that initial stabilization of airway and breathing and control of external hemorrhage are absolute requirements. From this point, opinions vary over the rate and type (if any) of fluid that should be given in cases where ongoing internal bleeding is likely. Current practice calls for attempted rapid volume restoration with infusion of large volumes of isotonic fluid, usually crystalloid, in an attempt to restore effective circulation and reverse tissue ischemia. Many authorities argue that aggressive fluid therapy prior to surgical hemostasis increases bleeding and worsens outcome (9).

Table 5 Recommended Sites of Intravenous Access

Peripheral veins	Forearm and antecubital veins
Central veins	Internal jugular veins Subclavian veins Femoral veins
Cut-down sites	Greater saphenous veins (ankle) Medial basilic veins (antecubital fossa)
Intraosseous sites	Proximal tibia (children less than 6 yr of age)

Conventional wisdom regarding prompt fluid resuscitation of hypovolemic shock is based largely on animal studies conducted in the 1950s and 1960s, which utilized controlled hemorrhage models where bleeding was stopped prior to fluid resuscitation (10). Results of these animal studies concluded that early fluid resuscitation was life saving. Unfortunately, these controlled hemorrhage models failed to consider the impact of fluid resuscitation in the presence of active bleeding. Subsequently, uncontrolled hemorrhage models have shown that early fluid resuscitation, although elevating blood pressure, dislodges early thrombus, increases blood loss, causes a dilutional coagulopathy, and worsens the survival rate (11,12).

These results suggest that maintaining low blood pressure until surgical hemostasis is established improves survival.

Bickell et al. conducted the first prospective randomized human trial (13). They confined their study to patients with penetrating torso trauma and hypotension (prehospital systolic pressure <90 mmHg). Study-group patients were cannulated but received no intravenous fluids prior to their arrival in the operating room. The control group received standard fluid resuscitation. The results showed a significant improvement in survival (70% vs. 62%) as well as significantly fewer postoperative complications (30% vs. 23%) in the study group compared with the control group. These results should be interpreted with caution. Only patients with penetrating torso trauma were included, and prehospital times were very short (mean prehospital time of 30 minutes). This implies that the time to definitive surgical hemostasis was also very short. The time issue is critically important because duration of hypotension correlates closely with the later onset of multiple organ failure (14,15). The findings of this study should not be extrapolated to include patients with blunt trauma, elderly patients with chronic illness, patients with head injuries, or to other emergency medical services (EMSs), where prehospital times may not be as short (16).

To summarize, maintenance of a low blood pressure preoperatively in the setting of penetrating torso trauma has been shown to be beneficial, provided early surgical hemostasis can be achieved. The beneficial effect of permissive hypotension in this setting is less clear if there is concomitant head injury or systemic illness.

Prehospital Fluids

Along similar lines, the practice of prehospital fluid administration is being increasingly challenged (9). There are two important reasons for this. First, prehospital transfer times may be significantly lengthened by attempts at intravenous cannulation on the scene (17,18). The resultant delay in reaching definitive treatment negatively impacts patient outcome (19,20). Second, the average volumes of fluid administered prior to arriving at the hospital are commonly too small to exert any real therapeutic effect (21–23). Therefore, in many circumstances, the disadvantage of prolonging the transfer time outweighs any small therapeutic effect gained from the infusion of fluids (24).

An interesting retrospective study conducted by Demetriades et al. showed that severely injured patients had a greater chance of survival when transported to the hospital by private car (25).

In the setting of penetrating trauma, where transfer times are 30 minutes or less, current evidence favors a policy of “scoop and run” over “field stabilization” (26). Once again, however, caution must be taken not to extend this policy to include all injured patients. In particular, cases of head injury or those with prolonged prehospital times benefit from prehospital fluid administration. Hypotension is the most important cause of secondary brain injury, and attempts to restore cerebral perfusion pressure must be immediately instituted (27).

The Joint Royal Colleges Ambulance Service Liaison Committee has suggested guidelines that limit prehospital intravenous cannulation to those instances where on-scene entrapment or transfer times are likely to exceed 20 minutes. It is further recommended that intravenous cannulation be attempted en route, not at the scene.

CRYSTALLOIDS AND COLLOIDS: ISOTONIC SOLUTIONS

Although controversy exists over the optimal time to initiate fluid replacement, there is no argument that once hemorrhage has been controlled, intravascular volume should be restored as quickly as possible to restore effective circulation and reverse tissue ischemia. Failure to

adequately resuscitate patients at this stage is associated with the later onset of multiple organ failure, with increased morbidity and mortality (14).

The ideal resuscitation fluid, if it existed, would restore and maintain intravascular volume; restore oxygen delivery; minimize postresuscitation edema; lack unwanted side effects such as coagulation disturbances, metabolic disturbances (pH and electrolytes), organ dysfunction (cardiac, pulmonary, renal, and central nervous system), disease transmission, cytokine response (systemic inflammatory response), and allergic reactions; be suited to all types of patients and injuries; be readily available with no specific storage or administration requirements; and be cost effective.

Clearly, no single fluid meets all these requirements at present. One fluid may be superior to another in one area, but inferior in another. Much controversy has arisen over which fluid to use in trauma resuscitation.

Crystalloids

A crystalloid is a solution of small ionic or nonionic particles that pass freely across the capillary membrane and so do not contribute to plasma oncotic pressure. Crystalloids used for resuscitation are usually isotonic with plasma (hypertonic fluids are considered later). Conventional concept states that isotonic crystalloids are evenly distributed throughout the extracellular fluid compartment, with, therefore, only 20% to 30% remaining intravascular (28). The result of this phenomenon is that approximately three times the blood-loss volume must be administered to restore intravascular volume to normal (known as the "3 to 1" rule). Kinetic studies (29,30), however, show a more flexible volume effect, which means that these rough guidelines, based on Shires' original studies, must be looked upon with caution even more carefully. Although crystalloids effectively resuscitate the extravascular compartment, they tend to do this excessively resulting in tissue edema. Furthermore, due to the considerable volumes of crystalloid that are often required, there is a greater potential to cause hyperthermia and dilutional coagulopathy.

Crystalloid solutions are relatively cheap, do not cause allergic reactions, and apart from dilutional effects, do not directly interfere with coagulation or platelet function. For the composition of the more commonly used crystalloids, please refer to Table 6.

Colloids

A colloid is a solution that contains particles too large to pass freely through the normal capillary membrane, exerting an oncotic effect. To put it simply, they remain, at least initially, within the intravascular compartment. The duration of intravascular persistence depends on both the oncotic particle (size, ionic charge, and rate of biodegradation) as well as the permeability of the capillary membrane. Colloids are a diverse group of fluids ranging from naturally occurring (albumin and dextrans) to semisynthetic substances (gelatins, hydroxyethyl starches, and hemoglobin solutions). Their pharmacological properties vary widely between groups and within groups (31). This fact seems to have been overlooked in most studies comparing crystalloids with colloids.

Considered collectively, colloids are required in smaller volumes, although they remain considerably more expensive than crystalloids. Colloids are associated with a number of

Table 6 Composition of Isotonic Crystalloid Solutions

	Solutions	
	Ringer's lactate	Normal saline
Tonicity (mOsm/L)	273	308
Na ⁺ (mEq/L)	130	154
Cl ⁻ (mEq/L)	109	154
K ⁺ (mEq/L)	4	0
Lactate (mEq/L)	28	0
Acetate (mEq/L)	0	0
Ca ²⁺ (mEq/L)	3	0
Mg ²⁺ (mEq/L)	0	0
Gluconate (mEq/L)	0	0

specific side effects not seen with crystalloids. Anaphylactoid reactions (gelatins, dextrans, hydroxyethyl starches) and coagulopathy (dextrans and high-molecular-weight hydroxyethyl starches) are the most noteworthy. Gelatin-based colloids have recently been shown to have a direct antiplatelet effect (32).

Albumin is physiologically the main provider of capillary oncotic pressure, but there is no evidence that maintaining plasma albumin levels with exogenous albumin, versus artificial colloids, is advantageous. In fact, albumin administration has even been found to worsen pulmonary function and increase mortality in certain studies (33). Adding its considerable expense into the equation makes albumin an unsuitable choice for fluid resuscitation.

Dextrans are polysaccharide molecules derived from bacterial action on a sucrose medium. The most commonly used formulation is a 6% solution of dextran-70, formulated in either a 0.9% saline or a 5% dextrose solution. Dextran's intravascular persistence is generally greater than that of the gelatins, but less than that of the starches.

Dextrans reduce blood viscosity and platelet adhesiveness and enhance fibrinolysis. This effect may lead to clinically significant bleeding, particularly at doses above 1.5 g/kg body weight (31). Although mild anaphylactoid reactions are common, severe anaphylactic reactions are rare and can be prevented by a prior intravenous administration of dextran-1 (monovalent hapten dextran), which blocks the offending antibodies. Modern dextran solutions do not interfere with blood crossmatching (34).

Gelatins are polypeptide molecules derived from bovine collagen. Polygelin (Haemaccel[®]) is a 3.5% solution and contains calcium (6.25 mmol/L). The calcium content prevents the use of the same administration set for blood transfusions and sodium bicarbonate infusions.

Succinylated gelatin (Gelofusine[®]) is a 4.5% solution with improved intravascular persistence and no calcium content, making it a more suitable choice for fluid resuscitation.

Although traditionally believed to have little effect on hemostasis, at least one study has demonstrated that gelatins have a direct antiplatelet effect, which is more pronounced with Haemaccel[®] (32).

Gelatins have been associated with the highest incidence of anaphylactoid reactions (0.146%) and were withdrawn from use by the U.S. Food and Drug Administration in 1978. Although forbidden in the United States, the use of gelatin-based colloids remains high in the United Kingdom, Europe, and South Africa. When compared to other colloids, gelatins are relatively inexpensive but have an effect of shorter duration.

Hydroxyethyl starches are synthetic polymers derived from amylopectin.

Pentastarch (HAES-steril[®] and Pentaspan[®]) in 6% and 10% formulations is most commonly used in fluid resuscitation. In this molecular weight range, there is minimal effect on coagulation.

Hetastarch is a 6% solution with a high degree of protection from metabolism. This is a high-molecular-weight formulation with prolonged intravascular retention even in the setting of capillary leaks. In the acute setting, its usefulness is limited because of its significant effect on coagulation by reducing levels of factor VIII and the Von Willebrand's factor (35).

Anaphylactoid reactions are very uncommonly associated with hydroxyethyl starches.

To date, the three published meta-analyses of crystalloids versus colloids for fluid resuscitation have all shown a survival advantage in favor of crystalloids in trauma patients (36–38). There has been considerable criticism regarding the strength of these conclusions, in particular the failure of these analyses to consider the virtues of each colloid individually (31).

Conceivably, with the later onset of the "capillary leak" syndrome, colloids exhibiting greater intravascular persistence may considerably outperform colloids with lesser persistence. This is an area requiring ongoing study, where the crystalloid-colloid issue will continue to be disputed.

HYPERTONIC SOLUTIONS

Hypertonic solutions are crystalloid fluids that have osmolalities far higher than normal plasma. By virtue of their greater tonicity, these solutions draw fluid from the intracellular compartment and greatly expand intravascular volume. The only hypertonic solution of any practical significance is hypertonic saline, usually formulated as a 7.5% solution (2400 Osm/L), either alone or in combination with 6% dextran-70.

Theoretically, a resuscitation fluid that is effective at very small volumes has many potential benefits. These relate specifically to prehospital fluid therapy, where the absolute volume of fluid is often limited by inadequate venous access and short transfer times. In the military setting, the importance of "traveling light" makes small volume, hypertonic resuscitation attractive.

Initially tested in hemorrhagic animal models, hypertonic fluid infused at volumes around 4 mL/kg (~10% of shed blood volume) showed dramatic improvements in hemodynamics and survival. In addition to volume expansion of three to four times the infused volume, hypertonic saline improved heart rate and contractility and reduced peripheral vascular resistance, thereby greatly enhancing circulation (39). The addition of dextran to hypertonic saline was found to prolong these hemodynamic effects.

To date, there have been a number of prospective human trials comparing small-volume hypertonic fluid resuscitation (250 mL bolus of 7.5% hypertonic saline \pm 6% dextran-70) with standard, large-volume isotonic fluid therapy. Of importance is the fact that the initial bolus of hypertonic fluid was usually followed by standard isotonic fluid therapy, as deemed necessary by the attending medical personnel. This practice may have "diluted" some of the results. A meta-analysis of all these comparative studies resulted in the following conclusions (40). When compared with standard-volume isotonic fluid resuscitation, hypertonic saline dextran, at a dose of 250 mL, resulted in a greater increase in blood pressure; a reduction in early and 24-hour total fluid and blood requirements; a trend toward improved survival overall (not statistically significant); a significant survival benefit in hypotensive, brain-injured patients, and a significant benefit in patients requiring emergency surgery (*vide infra*); and no significant adverse effects (i.e., central neurological dysfunction, coagulopathies, interference with blood crossmatching, and clinically significant electrolyte abnormalities).

Controversy has arisen over the desirability of the greater hemodynamic effects of hypertonic fluid resuscitation, when viewed in the light of hypotensive resuscitation strategies (*vide supra*). It must be noted, however, that there was no increased mortality in these studies when administering the solution. Furthermore, in comparison with isotonic fluid controls, hypertonic fluid-resuscitated patients requiring emergency surgery demonstrated reduced transfusion requirements and improved survival.

In summary, although hypertonic solutions have not demonstrated clear survival benefits in all patients, they have been proven safe at the recommended dose, and particularly beneficial in patients with concomitant traumatic hypotension and brain injury (41).

TRANSFUSIONS: ALLOGENIC

Acute hemorrhage leads to volume depletion and loss of red cell mass. In healthy subjects, losses of up to 30% of blood volume can often be tolerated provided intravascular volume is restored and there is no ongoing hemorrhage. Hemoglobin levels as low as 7 g/dL and a hematocrit as low as 20% to 21% may be well tolerated in this subset of patients (42). More significant blood loss (more than 30% blood volume), ongoing bleeding, or preexistent medical disease (especially ischemic heart disease) may render blood transfusions life saving.

Restoration of oxygen-carrying capacity is the single most important indication for transfusions in trauma. Intravascular volume restoration is an added bonus, because this is achievable with crystalloids, colloids, and hypertonic solutions. Other indications for blood component therapy include correction of coagulation abnormalities and, rarely, correction of granulocyte deficiencies.

The decision to initiate transfusion of blood is based primarily on clinical parameters. Important factors include the estimated volume of blood lost, the patient's hemodynamic status and response to initial fluid therapy, and the likelihood of ongoing bleeding. Patients who display obvious signs of shock (class III and IV shock) secondary to blood loss will usually require transfusion.

Initial hemoglobin or hematocrit values are very poor indicators of the degree of blood loss in acute hemorrhage, particularly prior to fluid resuscitation. "It has been shown that, after a healthy adult male lost approximately 1000 mL of blood rapidly, the venous hematocrit fell only 3% during the first hour, 5% at 24 hour, 6% at 48 hour, and 8% at 72 hour, thus indicating the time required for the body to restore blood volume" (43). Therefore, a normal

hemoglobin or hematocrit level does not exclude major blood loss, while a low level might suggest massive blood loss, aggressive fluid resuscitation, or prior anemia.

Current transfusion practice favors the use of component therapy over whole blood (WB), to maximize the use of a scarce commodity.

While fresh WB is theoretically superior to packed red blood cells (PRBC) due to its greater volume expansion, presence of clotting factors and platelets, and higher levels of 2,3-diphosphoglycerate (DPG), it is impractical for general use. Storage of WB at the required temperature of 1°C to 6°C leads to a rapid decline in levels of platelets (24 hour) and clotting factors (14 days), thereby negating its beneficial effects.

As a result, PRBC are most commonly used to restore hemoglobin levels. An average unit of PRBC has a volume of 250 mL and a hematocrit of 60% to 80%. The small residual amounts of clotting factors and platelets remaining in each unit are rendered nonfunctional by the isolation process.

The urgency of the required transfusion will determine the degree of blood compatibility testing possible prior to administration. Four categories of blood are recognized (44).

Fully Crossmatched Blood

This process takes most blood banks in the order of 45 to 60 minutes to complete, making this unsuitable for the acutely unstable patient. The chance of an incompatible transfusion is around 0.05%.

Type-Specific, Partially Crossmatched Blood

This includes an ABO-Rh typing and an immediate-phase crossmatch. It takes most blood banks one to five minutes to complete, and helps eliminate potential errors in ABO typing, which could result in serious hemolytic reactions.

Type-Specific, Uncrossmatched Blood

The patient's blood group must be determined at the time of hospitalization—a process that usually takes less than a minute. Reliance on medical records or patient histories to determine blood grouping is to be strongly cautioned against.

Approximately 99.8% of these administered units will be completely compatible, but prior pregnancies or blood transfusions do increase the risk of an adverse reaction. In mass casualty settings, there is a significant potential for administering incorrect units to patients.

Type O, Uncrossmatched Blood (“Emergency Blood”)

This blood is immediately available for use in patients who are actively exsanguinating. It is best given in packed red cell form to reduce the amount of plasma that contains anti-A and anti-B immunoglobulins, which may cause lysis of recipient red blood cells. If four or more type O units are administered, it is advisable to continue using type O blood instead of switching to the patient's correct blood type (A, B, or AB), because this may result in lysis of the new donor red cells. Type O, Rh-negative blood is preferred for women of child-bearing age to avoid the possibility of Rh disease in future pregnancies.

An important consideration in trauma resuscitation where it is commonplace to rapidly infuse many units of PRBC is the development of coagulopathy.

Dilution of platelets and clotting factors, hypothermia, and the development of a disseminated intravascular coagulopathy are all potential causes. Thrombocytopenia is cited as the most common disorder resulting from massive transfusion (45).

Correction of platelet and clotting-factor deficiencies may be achieved with the administration of platelet concentrates and fresh frozen plasma (FFP), respectively.

A standard, adult dose of platelets is $\pm 3 \times 10^{11}$ platelets, which will provide a rise in platelet count of 30,000 to 60,000/ μL . This quantity of platelets is found in a 300 mL unit of single-donor platelets or six to eight random-donor platelet concentrates.

FFP should be administered at 10 to 15 mL/kg to correct coagulation abnormalities, which will restore clotting factors to within 25% of normal in most instances. Because the average volume of a unit of FFP is 200 to 225 mL, approximately four units will be required for a 70 kg adult.

Table 7 Complications of Massive Blood Transfusion

Complication	Explanation
Coagulopathy	Dilutional thrombocytopenia Dilution of clotting factors Hypothermia-induced platelet and clotting-factor dysfunction Hypocalcemia, only in cases of extremely rapid transfusion rates or with concomitant liver dysfunction or hypothermia Disseminated intravascular coagulopathy
Hypothermia	Rapid administration of cold fluids
Reduced oxygen delivery	Left-shifted oxyhemoglobin dissociation curve due to: Hypothermia ↓ 2,3-diphosphoglycerate levels Metabolic alkalosis (citrate toxicity)
<i>Potassium disturbances</i>	
Initially ↑ K ⁺	Uncommon (seen with transfusion of “old” blood, hemolytic reactions, and acidosis)
Delayed ↓ K ⁺	Common (due to delayed metabolic alkalosis)
<i>pH disturbances</i>	
Initial metabolic acidosis	Secondary to hypoperfusion-induced lactic acidosis, not the transfusion per sé
Delayed metabolic alkalosis	Common (due to citrate toxicity)
Acute respiratory syndrome	Activation of proinflammatory cytokine responses Accumulation of microaggregates in the pulmonary vasculature
Immunosuppression	Multifactorial Especially affects cell-mediated immunity Dose dependent
Volume overload	Overenthusiastic volume resuscitation Exacerbated by the “capillary leak syndrome”

Some authorities advocate the empirical administration of FFP and platelets based on the number of units of PRBC transfused. While there is no evidence to show benefit from such a policy, they argue that undue delays while awaiting laboratory evidence of coagulopathy may worsen the clinical picture. Arguments against the empirical administration of platelets and FFP include the relative infrequency of documented dilutional thrombocytopenia or coagulopathy, and the increased risk of transfusion without proven benefit. A possible compromise, recommended in a reputable trauma textbook, is the simultaneous performance of platelet counts and coagulation studies along with ordering platelets and FFP. If the laboratory results are not ready by the time the platelets and FFP are available and there is evidence of ongoing nonsurgical bleeding, then the first dose should be given empirically (46).

Massive blood transfusions (more than 10 units in 24 hours) carry with them a number of complications, mostly metabolic in nature, in addition to the usual complications of nonmassive transfusions. A short list of the more important complications is displayed in Table 7.

A further consideration to bear in mind whenever administering blood products is their immunodepressant effect. Blood transfusions have been shown to correlate with postinjury septic complications in a dose-dependent fashion (47).

AUTOTRANSFUSION: AUTOLOGOUS

Autologous blood transfusion (autotransfusion) implies that the patient's own blood is used. Collection of the blood may take place prior to the event (e.g., elective surgery) or at the time of surgery or resuscitation. Clearly, acute trauma falls into the later category.

Beside preserving banked blood stores and reducing incompatible reactions and transfusion-transmitted diseases (TTDs), additional benefits of autotransfusion include the provision of warm blood with normal levels of 2,3-DPG, thereby facilitating oxygen offloading at a tissue level.

Although widely adopted in elective surgery, the practice of autotransfusion has been slow to be accepted in the trauma setting due to a number of concerns (48). Chief among them is the fear of infectious complications by reinfusion of blood from a contaminated field.

Other concerns include the risks of aggravating a consumptive coagulopathy and provoking a systemic inflammatory response by reinfusing activated clotting factors and inflammatory mediators. Finally, the practicalities and cost effectiveness of using this technique in trauma are largely uncertain.

Prior to further discussion of these concerns and the current status of autotransfusion in trauma, a brief overview of the techniques of autotransfusion is in order.

AUTOTRANSFUSION

Essentially, two forms of "onsite" autotransfusions exist. The first, and the simpler of the two forms, involves collection of shed blood, which is anticoagulated and returned to the patient via a filter. This technique is most commonly used for collecting and reinfusing blood from chest tube drains following thoracic trauma (49). Its major advantages are simplicity, speed, and independence from expensive machinery or trained personnel. Important drawbacks include the reinfusion of anticoagulant, activated clotting factors, proinflammatory cytokines, activated platelets, and bacterial contaminants.

The second, more complex, technique incorporates a cell-washing step. This requires specialized machinery and trained personnel, and involves a time delay between collection and reinfusion of red cells (~20 minutes). The cell-washing step removes the anticoagulant as well as the harmful products mentioned previously (*vide supra*). Bacteria can be cleared in up to 85% of units saved by more modern machines (50,51).

Furthermore, the cell-washing process also removes normal plasma and platelets so that only red cells are reinfused. It follows, therefore, that the reinfusion of large numbers of "cell saved" units can contribute to dilutional thrombocytopenia and coagulopathy.

Bacterial contamination (e.g., hollow viscus injury) has traditionally been regarded as a contraindication to the salvage of blood for autotransfusion. There is now mounting evidence that with the use of the more modern cell-washing machines, this concern is unfounded. Several prospective human trials comparing the incidence of postoperative septic complications in patients reinfused with blood from a contaminated field versus patients receiving banked blood have failed to show a difference (50,52). Broad-spectrum antibiotic cover was used in cases of autotransfusion.

Although further studies are required, it would seem appropriate that in the setting of a life-threatening situation and in the absence of available blood, bacterially contaminated blood may be salvaged and reinfused, provided it is adequately washed. A broad-spectrum antimicrobial cover is advisable for at least 24 hours.

Blood contaminated with pancreatic secretions is potentially harmful if reinfused, despite cell-washing steps (53), and requires further investigation.

Reinfusion of activated platelets, clotting factors, and inflammatory mediators may all contribute to the formation of a disseminated intravascular coagulopathy. This, together with the reinfusion of an anticoagulant (used during collection of blood), is more relevant to the autotransfusion method that does not incorporate a cell-washing step.

To help limit the development of coagulopathy, the reinfusion of unwashed WB should be limited to 1.5 L or less (46).

Washed units produce clinically relevant coagulopathy after an average of 15 units (52). Interestingly, bacterial contamination of salvaged blood reduces the number of units required to produce deranged clotting.

The practical application and cost effectiveness of autotransfusion will no doubt continue to improve as both technological advances and a better understanding of its indications are discovered.

RED CELL SUBSTITUTES

The search is still on for a safe and effective blood substitute. The ideal blood substitute would be universally compatible and free from side effects, have a long shelf life, and possess oxygen-carrying characteristics similar to normal blood.

Initially, attention was focused on perfluorochemical emulsions, but these solutions failed to demonstrate clinical benefit (54).

More recent efforts have centered on blood-based substitutes, derived from outdated units of banked blood, bovine, or recombinant Hb. Because the hemoglobin molecules are removed from the red cells, they are referred to as stroma-free.

Normally occurring hemoglobin molecules are intensely nephrotoxic and are rapidly cleared from the bloodstream, making them unsuitable for transfusion. Cross-linking hemoglobin molecules to tetramers by various chemical methods reduces nephrotoxicity and increases intravascular persistence. Unfortunately, unwanted pressor effects, presumably caused by a nitric oxide scavenging effect, result in troublesome systemic and pulmonary hypertension and splanchnic hypoperfusion.

Polymerization of hemoglobin into larger molecules eliminates this pressor effect and further reduces nephrotoxicity (55). Polymerized, pyridoxylated, stroma-free hemoglobin (PolyHeme) is a new generation red cell substitute that has similar oxygen-carrying capacity, oncotic pressure, and volume effect to banked blood.

An unresolved problem is the relatively short duration of action (< 24 hours) of most Hb-based (red cell) substitutes, with the result that blood transfusions are often still necessary at a later stage.

Currently, blood remains the only fluid in common use to restore oxygen-carrying capacity. This situation may change in the near future, with a number of new improved red cell substitutes already undergoing phase III clinical trials.

CONCLUSION

Many unanswered questions still haunt the subject of fluid therapy in trauma. Uncertainty persists regarding which fluid to use, how much to give, and when to give it. Perhaps there is no universal "solution," implying that each patient's fluid requirements are different and must be individualized.

Meanwhile, autotransfusion is on the increase because newer evidence refutes prior concerns, and the advent of a safe, effective hemoglobin substitute is here.

A new and exciting avenue of research is the inflammatory response to resuscitation fluids. Evidence that shows significant differences in cytokine responses to various fluids is already emerging.

The future certainly holds many changes that will shape and reshape our current approach to fluid therapy in trauma.

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19 Fluid Management in the Severely Burned Patient

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INTRODUCTION

The survival rate of patients suffering from large total body surface area (TBSA) burns has improved significantly during the last 30 years. Much of this survival benefit is due to advances in fluid management. Prior to the 1940s, most patients with large TBSA burns died from hypovolemic shock and renal failure. It later became apparent that burn patients develop intravascular hypovolemia in association with generalized interstitial edema. Underhill (1) was one of the first to develop the concept of burn shock through his study of victims from the Rialto Theater fire in 1921. Cope and Moore (2) confirmed and extended these observations through their study of burn patients in the 1940s. They hypothesized that the transfer of fluid from the intravascular compartment to the interstitium was responsible for the development of the edematous state.

Evans first developed a fluid resuscitation protocol based on total body surface burn area in the 1950s. This protocol was modified by physicians at the Brooke Army Hospital and served as the standard for fluid resuscitation in burn patients for nearly 20 years. The work of Baxter and Shires (3,4) in the late 1960s established the Parkland formula for burn resuscitation that continues to serve as a guideline for the resuscitation of most burn patients today.

In this chapter, we will review the pathophysiology of burn shock, discuss protocols for burn resuscitation, and evaluate end points for assessing adequacy of resuscitation in severely burned patients. The goal of this review is to provide a logical framework for executing effective fluid resuscitation in severely burned individuals.

THE PATHOPHYSIOLOGY OF BURN SHOCK

Thermal injury has profound effects on the systemic circulation and hemodynamic management is a major factor of care. After massive thermal injury, a state of burn shock develops due to intravascular hypovolemia and, in most cases, myocardial depression. These alterations lead to decreased cardiac output. The host responds to the fall in cardiac output with a reflex increase in systemic vascular resistance in an attempt to sustain central arterial blood pressure. However, if this state of low cardiac output and high peripheral vascular resistance persists, tissue hypoperfusion will ensue (5,6). This is particularly true of the splanchnic circulation, which is often compromised in an effort to sustain perfusion of vital organs such as the brain and heart.

Although the pathophysiology of burn shock is not completely understood, several important observations have been made. The hallmark of burn shock is a marked increase in vascular permeability in both burned and unburned tissues. The subsequent exudation of protein-rich fluid from the intravascular compartment to the interstitium leads to intravascular hypovolemia and the development of massive interstitial fluid accumulation. Cutaneous lymph flow increases dramatically in the immediate postburn period and remains elevated for approximately 48 hours (7). However, fluid accumulation progresses as the flux of fluid from the intravascular space to the interstitium overwhelms lymphatic outflow. The forces responsible for this massive fluid shift involve all components of the Starling equilibrium (8).

$$Q = kA [(P_c - P_i) + \sigma(\pi_i - \pi_c)]$$

The specific alterations include (i) an increased microvascular permeability coefficient (k) due primarily to the release of local and systemic inflammatory mediators such as bradykinin, histamine, platelet-activating factor, and leukotrienes. The increase in vascular permeability involves not only fluid and electrolytes but also plasma colloids. In directly burned tissues, the increased vascular permeability is also due to direct vascular injury resulting in endothelial disruption; (ii) an increase in intravascular hydrostatic pressure (P_c) due to microvascular dilatation. This is due to production of nitric oxide and vasodilatory prostaglandins that causes increased blood flow at the site of burn injury as well as nonburned areas exposed to inflammatory mediators; (iii) decreased interstitial hydrostatic pressure (P_i). Although the exact process causing negative interstitial pressure in burned tissues is not well understood, this phenomenon has been documented in several investigations (9,10). Lund et al. (9) have proposed that the negative interstitial pressure is caused by collagen degradation in burned skin; (iv) decreased intravascular oncotic pressure (π_c) due to leakage of protein from the intravascular space; and (v) a relative increase in interstitial oncotic pressure (π_i) due to the movement of protein-rich fluid from the intravascular space to the interstitium. The leakage of protein and fluid into the interstitial space often results in a washout of the interstitium and markedly increased lymph flow. The net effect of these changes is the development of massive edema during the first 12 to 24 hours after thermal injury with a concomitant loss of intravascular volume. The progression of interstitial edema is largely dependent on the adequacy of volume resuscitation because administered fluids certainly contribute to the progression of edema formation.

The hypotension associated with burn injury is also due, in part, to myocardial depression. The inflammatory response to thermal injury results in the release of large amounts of tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and prostaglandins. TNF- α and IL-1 are known to have myocardial depressant effects (11,12). These proinflammatory mediators, and other possibly unrecognized factors, are thought to be responsible for the depression in myocardial function resulting from burn injury. The hypotension caused by intravascular volume depletion and myocardial depression induces a reflex increase in systemic vascular resistance. All of these factors lead to a fall in cardiac output and decreased tissue perfusion if the patient is not adequately volume resuscitated.

If the patient survives the initial burn shock and is adequately resuscitated, a state of hyperdynamic circulation develops by approximately three to four days postburn. The hyperdynamic response is driven by systemic inflammation in response to the large-scale tissue injury caused by the burn. This state of massive inflammation has been termed the systemic inflammatory response syndrome (SIRS) and is characterized by tachycardia, a marked decrease in systemic vascular resistance, and increased cardiac output (Fig. 1) (13). SIRS has a continuum of severity ranging from the presence of tachycardia, tachypnea, and fever to refractory hypotension and, in its most severe form, shock and multiple organ system dysfunction (14). In thermally injured patients, the most common cause of SIRS is the burn itself; however sepsis, SIRS with the presence of infection, is also a common occurrence. Delayed or inadequate resuscitation is an independent risk factor for the development of SIRS.

RESUSCITATION OF BURN PATIENTS

Burn patients require large volume fluid resuscitation in the immediate postburn period. Delayed or inadequate fluid resuscitation is an independent risk factor for mortality in severely burn patients (15). The goal of volume resuscitation in burn patients is to sustain tissue perfusion while minimizing interstitial edema. Ideally, the least amount of fluid necessary to maintain organ perfusion should be given. The volume administered should be continually titrated to avoid over- or under-resuscitation. As fluid resuscitation of burn patients advances, larger volumes of fluid have been advocated to sustain tissue perfusion. However, over-resuscitation can exacerbate burn edema and cause compartment syndrome in the extremities and abdomen. To quote Pruitt (16), "The lungs and soft tissue compartments are increasingly sacrificed on the alter of the kidneys, as manifested by postresuscitation edema, the need for tracheostomy in patients with scald burns, the need for fasciotomies in unburned limbs, and the occurrence of abdominal compartment syndrome."

Currently, there is not a clear consensus on the type of fluid that should be used in burn resuscitation. In fact, it is likely that different types of fluids will have advantages and

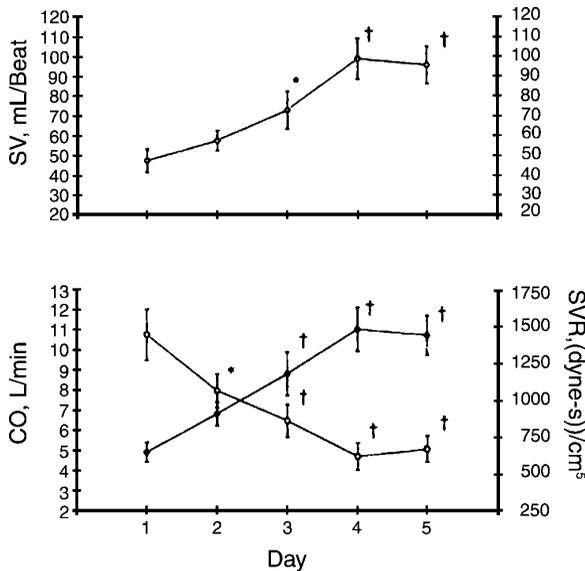


Figure 1 Typical hemodynamic response seen following adequate burn resuscitation. Characteristic findings include increased cardiac output due primarily to increased stroke volume and a fall in peripheral vascular resistance. *Abbreviations:* CD, cardiac output; SV, stroke volume; SVR, systemic vascular resistance. *Source:* From Ref. 13.

disadvantages under varying conditions. However, one fact is clear, no matter which type of fluid is given, adequate volumes of water and salt must be replaced to sustain tissue perfusion and restore homeostasis.

Crystalloids

Several resuscitation protocols that utilize various combinations of crystalloids, colloids, and hypertonic fluids have been developed (Table 1). Isotonic crystalloid resuscitation is employed in most burn centers and generally provides adequate volume resuscitation. Buffered crystalloid solutions such as lactated Ringer’s solution are the most popular resuscitation fluids currently utilized. The classic crystalloid resuscitation formulas are the modified Brooke and Parkland formulas. The modified Brooke formula evolved from the Evans and Brooke formulas and advocates administering 2 mL/kg/% TBSA burned during the first 24 hours following burn injury. The Evans formula was developed in the 1950s and was the first to provide fluid resuscitation based on the percentage of TBSA burned. The Brooke formula was a modification of the Evans formula and advocated a higher percentage of crystalloid relative to

Table 1 Formulas for Estimating Adult Burn Patient Fluid Resuscitation Needs

Formula	Crystalloid	Colloid
Crystalloid formulas		
Modified Brooke	Lactated Ringer’s 2 mL/kg/% burn	
Parkland	Lactated Ringer’s 4 mL/kg/% burn	
Colloid + crystalloid formulas		
Evans	Normal saline 1 mL/kg/% burn	1 mL/kg/% burn
Brooke	Lactated Ringer’s 1.5 mL/kg/% burn	0.5 mL/kg
Slater	Lactated Ringer’s 2 L/24 hr	FFP 75 mL/kg/24 hr
Demling	Dextran 40 in saline 2 mL/kg/hr Lactated Ringer’s, maintain urine output	FFP 0.5–1 mL/kg/% burn
Hypertonic formulas		
Hypertonic saline (Monafo)	250 mEq sodium/L (1–2 mL/kg/% burn)	
Modified hypertonic (Warden)	Lactated Ringer’s + 50 mEq NaHCO ₃ (4 mL/kg/% burn/First 8 hr) Lactated Ringer’s (maintain urine output/second 8 hr) Lactated Ringer’s + albumin (maintain urine output/third 8 hr)	

Abbreviation: FFP, fresh frozen plasma.

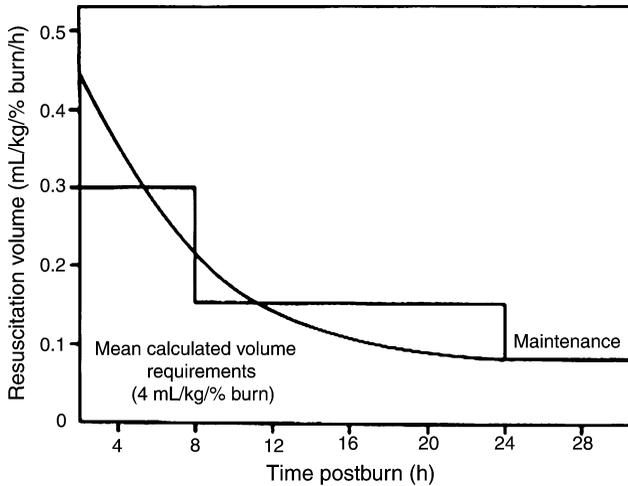


Figure 2 Fluid administration strategy based on the Parkland formula. One half of the calculated fluid volume is given in the first eight hours with the second half administered in the second eight hours. Adapted from Ref. 17.

colloid than the Evans formula. The modified Brooke formula is a purely crystalloid resuscitation protocol. The later work of Baxter (3) and Shires (4) resulted in the development of the Parkland formula that prescribes administering crystalloids in a volume of 4 mL/kg/% TBSA burned. The first half of volume is given in the initial 8 hours and the second half administered in the next 16 hours after injury (Fig. 2) (15,18). However, it should be pointed out that these formulas simply serve as guides for fluid therapy and that the patient must be closely monitored to optimize burn shock resuscitation. Several investigators have shown that actual fluid requirements, particularly for patients with large surface area burns, often exceed those predicted by the Parkland formula (19). The specific end points of resuscitation will be discussed later in this chapter.

Crystalloids are the most commonly utilized fluids for burn shock resuscitation. Currently, there are no prospective studies to show that colloids or hypertonic saline have any added benefit compared to isotonic crystalloids in the resuscitation of most burn patients. Furthermore, isotonic crystalloids are less expensive to administer than colloids. However, the potential disadvantage of crystalloids is the relatively large volumes of fluid needed for burn shock resuscitation and the potential exacerbation of tissue edema that may ensue. There is certainly a risk of over-resuscitation if patients are not closely monitored. The excess fluid collects primarily in the interstitium. Most studies do not show an increased incidence of pulmonary edema in patients receiving crystalloid resuscitation. Holm et al. (20) recently confirmed that most burn patients do not exhibit increased pulmonary vascular permeability after burn injury and pulmonary edema formation is rare as long as intravascular filling pressures are maintained within normal limits. Other potential complications of high-volume crystalloid resuscitation are hypoalbuminemia and electrolyte abnormalities. Whether these alterations are associated with significant morbidity and mortality has not yet been demonstrated.

Colloids

Theoretically, colloids provide the potential advantage of providing better intravascular volume resuscitation in a lesser volume and in a shorter time than crystalloids. In patients with an intact endothelium, colloids are more avidly retained than crystalloid fluids in the intravascular compartment. Plasma proteins play a vital role in maintaining vascular volume by providing colloid osmotic pressure that counteracts the outward intravascular hydrostatic pressure. However, burn patients exhibit increased vascular permeability to solutes, electrolytes, and colloids. This has caused some practitioners to question the use of colloids during the initial 8 to 24 hours after burn injury. Because of the increased vascular permeability observed in burn patients, colloids may not be retained within the circulation any better than crystalloids. In addition, some practitioners fear that colloid flux into the interstitium may worsen burn edema. However, the extent and duration of vascular permeability to plasma proteins are not totally clear and are certainly dependent on the severity of the burn

injury. Subsequently, several empiric approaches to the use of colloids in burn shock resuscitation have been made. Some practitioners advocate avoidance of colloids during the first 24 hours after burn injury. They argue that colloids have not been shown to have any advantage over crystalloids in burn shock resuscitation and may actually worsen burn edema formation. Others advocate the use of protein colloids in the initial 8 to 12 hours after burn injury while a third group advocates the use of protein colloids throughout the resuscitation of burn shock. All of these approaches are anecdotal because there is no hard scientific evidence to strongly support any particular approach. Animal studies have shown that colloids administered within the first eight hours after burn injury significantly decreased total fluid requirements (21). Other investigators have shown that administration of albumin in the first six to eight hours after burn injury does not increase the incidence of pulmonary complications (22). However, colloid resuscitation within the first 24 hours of burn injury has not been shown to improve outcome compared to crystalloid resuscitation (18,23). Furthermore, a recent meta-analysis indicated that mortality is higher in burn patients receiving albumin as part of the initial resuscitation protocol with a 2.4 relative risk of mortality compared to patients receiving crystalloid alone (24). However, this meta-analysis has been criticized for methodological flaws. Overall consensus is that there is insufficient evidence to determine whether albumin administration during burn shock resuscitation is beneficial or deleterious. Because of the added cost with little benefit, colloid solutions have not been used routinely in the United States for initial volume resuscitation in burn patients. However, many centers continue to employ albumin as part of their burn resuscitation protocol. This is particularly true in the pediatric population in which plasma protein levels decrease rapidly after burn injury.

Hypertonic Fluids

The use of hypertonic saline, either alone or in conjunction with colloids, has been advocated by some practitioners for the initial resuscitation of burn patients. Among the potential benefits of hypertonic fluids are reduced volume requirements to attain similar levels of intravascular resuscitation and tissue perfusion compared to isotonic fluids (25). Theoretically, the reduced volume requirements would decrease the incidence of pulmonary and tissue edema thus decreasing the incidence of tracheal intubation, and the need for escharotomy. Hypertonic saline solutions have been shown to expand intravascular volume by mobilizing fluids from intracellular and interstitial fluid compartments (25). However, the expansion of the intravascular space is transient. Some clinical and experimental studies have shown that overall total resuscitation fluid needs are not decreased if hypertonic fluids are used early in burn shock resuscitation (26,27). However, others have demonstrated total fluid sparing when hypertonic resuscitation fluids were given compared to isotonic crystalloids (28).

Although the overall benefits of hypertonic fluids in burn resuscitation need to be fully determined, hypertonic fluids may have benefit in certain situations. Specific scenarios include battlefield conditions where it is difficult to carry large volumes of fluid for resuscitation and also in patients with coexisting disease who are at an increased risk of congestive heart failure. However, there is no consensus on which hypertonic fluid will provide most benefit. Several investigators have studied hypertonic saline and hypertonic lactated saline solutions and reported total volume sparing (29,30). However, one study showed higher mortality in patients receiving hypertonic lactated saline compared to those receiving isotonic salt solutions (31). In some cases, colloid has been combined with hypertonic fluids for burn shock resuscitation. Griswold et al. (32) reported added volume sparing in patients receiving albumin or fresh frozen plasma in conjunction with hypertonic saline solutions, and Jelenko et al. (33) reported fewer escharotomies, decreased ventilator days, and lower fluid requirements in patients receiving albumin and hypertonic saline compared to patients receiving hypertonic saline alone or with isotonic crystalloids. However, Gunn et al. (34) did not observe volume sparing when giving fresh frozen plasma in conjunction with hypertonic saline solutions.

A major concern in the administration of hypertonic saline solutions is the development of hypernatremia. Serum sodium concentrations of greater than 160 mEq/L have been reported to occur in 40% to 50% of patients receiving hypertonic saline for burn shock resuscitation (35). Huang et al. (36) reported a series of deaths associated with this resuscitation approach. Because of the potential for severe electrolyte disorders and lack of evidence to show that hypertonic resuscitation will improve mortality, isotonic salt solutions are utilized

Table 2 Formulas for Estimating Pediatric Resuscitation Needs

Formula	Volume	Timing	Composition
Cincinnati	4 mL/kg/% burn + 1500 mL/m ² burn	First 8 hr Second 8 hr Third 8 hr	Lactated Ringer's + 50 mg NaHCO ₃ Lactated Ringer's Lactated Ringer's + 12.5 g albumin
Galveston	5000 mL/m ² burn 2000 mL/m ² burn	First 24 hr	D ₅ LR 5% albumin

in most centers for resuscitation of patients with major burns. Overall, hypertonic fluids should only be used by physicians who are experienced in their use, due to the risk of associated complications.

Special Considerations

Pediatric Patients

In general, children have higher resuscitation requirements per kg than adults. Studies have documented fluid requirements of 5.8 to 6.3 mL/kg/% TBSA in burned children (37). Overall, burned children require usual maintenance fluids in addition to the volume that is predicted by the Parkland formula. In addition, albumin is commonly added to the resuscitation fluid due to the rapid fall in serum albumin levels that are commonly observed in children. The most widely recognized pediatric resuscitation formulas have been developed at the Shriners Burns Hospitals in Cincinnati and Galveston (Table 2). The Cincinnati formula advocates the addition of sodium bicarbonate to resuscitation fluids during the first eight hours followed by transition to lactated Ringer's during the next eight hours, and the addition of albumin after 16 hours of resuscitation. In Galveston, albumin is added to lactated Ringer's from the beginning. Both formulas utilize body surface area burned in square meters rather than weight to guide overall fluid requirements.

Inhalation Injury

Several studies have shown that fluid resuscitation requirements are increased in patients suffering from combined burn and inhalation injuries compared to burns alone (38,39). Navar et al. (38) showed that fluid requirements are increased by approximately 50% in patients with smoke inhalation injuries. Some investigators propose that the increased fluid requirements are deleterious and increase the incidence of pulmonary complications (39). However, other groups have not shown an association of increased fluid requirements and pulmonary complications. Holm et al. (20) recently assessed extravascular lung water (EVLW) amounts in patients with inhalation injury. They reported that EVLW levels were not elevated in patients suffering combined burn and smoke inhalation injuries following aggressive fluid resuscitation as long as vascular filling pressures were maintained within normal limits. However, these investigators point out that many smoke inhalation victims still exhibited significant alveolar-arterial oxygen gradients and hypoxemia despite normal EVLW measurements. They hypothesize that this is due to small airway closure, ventilation-perfusion abnormalities, and pulmonary shunting independent of pulmonary edema. Still other investigators propose that underresuscitation of patients with inhalation injury will worsen lung injury (40). Therefore, it appears prudent to provide adequate fluid resuscitation to patients with inhalation injury in accordance with their increased fluid requirements.

END POINTS OF RESUSCITATION

Several parameters have been used to assess the adequacy of volume resuscitation in burn patients (Table 3). Regardless of the parameter used, a critical factor is early volume resuscitation and establishment of tissue perfusion. Traditionally, urine output (0.5–1 mL/kg/hr) and normalization of blood pressure (mean arterial blood pressure > 70 mmHg) have been used as end points to indicate adequate volume replacement. However, recent studies indicate that these parameters may be poor predictors of adequate tissue perfusion. Jeng et al. (41) showed that attaining urine outputs of greater than 30 mL/hr and mean blood pressures of greater than 70 mmHg correlated poorly with global indicators of tissue perfusion such as base deficit and blood lactate levels. In order to maintain perfusion of vital organs such as heart and brain,

Table 3 Criteria for Adequate Fluid Resuscitation

Normalization of blood pressure
Urine output (1–2 mL/kg/hr)
Blood lactate (<2 mM/L)
Base deficit (<–5)
Gastric intramucosal pH (>7.32)
Central venous pressure and pulmonary artery occlusion pressure
Intrathoracic blood volume index
Cardiac index (4.5 L/min/m ²)
Oxygen delivery index (600 mL/min/m ²)

blood flow is often redistributed away from splanchnic organs. Persistent hypoperfusion of these tissues ultimately results in organ injury and may be a contributing factor to multisystem organ dysfunction. Holm has advocated that many burn patients who have normal vital signs and adequate urine output are in a state of compensated shock (42). Recent studies have shown that normalization of blood pressure, heart rate, and urine output do not correlate with improved outcome (43,44). Therefore, although vital signs and urine output serve as important targets during early burn resuscitation, these parameters should be used in conjunction with measures of global, and possibly regional, tissue perfusion to guide fluid resuscitation in burn patients.

Pulmonary artery catheters are not used routinely in burn patients in volume resuscitation. Most patients can be adequately resuscitated without using pulmonary artery catheters. However, a small subset of patients such as those with underlying cardiovascular disease or those that do not respond normally to volume resuscitation may benefit from invasive monitoring. Some recent investigations have focused on the use of cardiac index and oxygen delivery as useful end points to guide volume resuscitation (45,46). One way in which shock can be defined is oxygen debt. Therefore, maintaining an adequate cardiac index and oxygen delivery capacity such that oxygen delivery meets oxygen consumption provides useful criteria in guiding volume resuscitation. Bernard et al. (47) have shown that patients surviving large burn injuries had higher cardiac indices and more effective oxygen delivery than nonsurvivors. Some investigators have proposed the use of supranormal oxygen delivery as a means of assuring adequate tissue perfusion (48,49). The preselected goals were a cardiac index of 4.5 L/m² and an oxygen delivery index of 600 mL/min/m². These values represent approximately 150% of normal cardiac index and oxygen delivery values. Attaining supraphysiologic cardiac output and oxygen delivery has been shown to improve outcome in some studies. Schiller et al. (45) demonstrated that maintaining a hyperdynamic hemodynamic state using fluids and inotropes improved survival in burn patients. However, other reports, including a meta-analysis, have shown that achieving supraphysiological levels of cardiac output and oxygen delivery did not improve mortality or decrease the incidence of organ failure in trauma and burn patients (50–52). Using inotropes to attain supraphysiological oxygen transport could be detrimental in some cases. One study that employed dobutamine to increase cardiac output and increase oxygen delivery demonstrated increased mortality (53).

Invasive cardiovascular monitoring also allows for measurement of central venous pressures (CVP) and pulmonary artery occlusion pressures (PAoP). Precise targets for CVP or PAoP in burn resuscitation have not been established and are likely to vary depending on the patient's physiological status. A recent study by Holm et al. (54) showed that CVP and PAoP correlate poorly with cardiac index and oxygen delivery index in burn patients (Fig. 3). However, the correlation of intrathoracic blood volume (ITBV) with cardiac index and oxygen delivery was significantly better than CVP or PAoP. ITBV is measured using the transpulmonary thermodilution technique. The transpulmonary thermodilution requires placement of a central venous line and central arterial catheter, most commonly in the femoral artery. Cold saline is injected into the central venous line and temperature changes are measured by a thermistor present in the arterial line. Cardiac output is calculated using the Stewart–Hamilton equation in a manner identical to calculation of cardiac output using a pulmonary artery catheter. A high degree of correlation has been observed when comparing cardiac output measurements using pulmonary artery catheters and the transpulmonary thermodilution technique, (Fig. 4; 55). Holm et al. (57) recently confirmed a high degree of

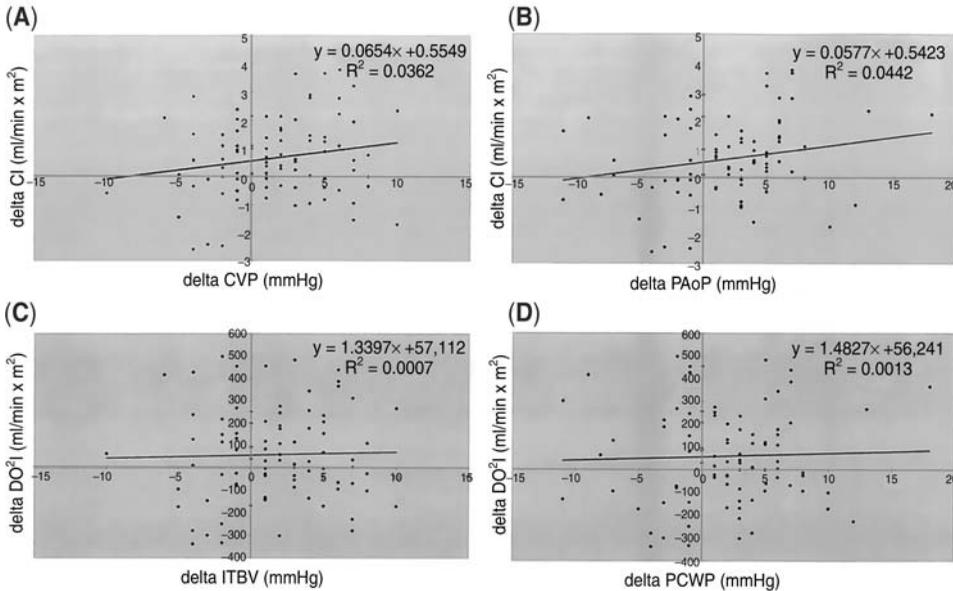


Figure 3 Correlation of preload measurements with cardiac index in severely burned patients. (A) Central venous pressure versus cardiac index; (B) pulmonary artery occlusion pressure versus cardiac index; and (C) intrathoracic blood volume versus oxygen delivery index. (D) Pulmonary artery occlusion pressure versus oxygen delivery index. *Source:* Adapted from Ref. 54.

correlation of cardiac output measurements obtained by pulmonary artery catheters and transpulmonary thermodilution in burn patients.

There are two advantages of the transpulmonary thermodilution technique compared to pulmonary artery catheter placement. Specifically, it is less invasive and allows direct calculation of intravascular volumes rather than inference of vascular volumes from pressure measurements. In addition to cardiac output determinations, two key variables are necessary for calculation of intravascular volumes using the transpulmonary thermodilution technique. These measurements are mean transit time and downslope time (Fig. 5). The product of cardiac output and mean transit time represents the total volume between the site of injection and the site of measurement; in this case, the intrathoracic thermal volume (ITTV). ITTV represents ITBV as well as the interstitial volume in the lung because the lung allows free transit of a

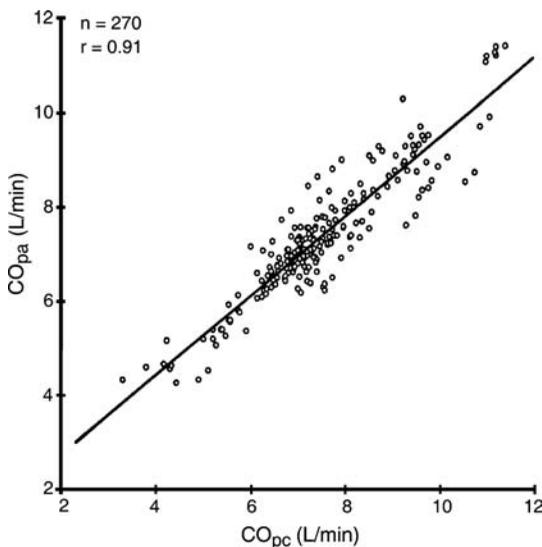


Figure 4 Correlation between cardiac output obtained with pulmonary artery catheter (CO_{pa}) and transpulmonary thermodilution (CO_{pc}). *Source:* Adapted from Ref. 56.

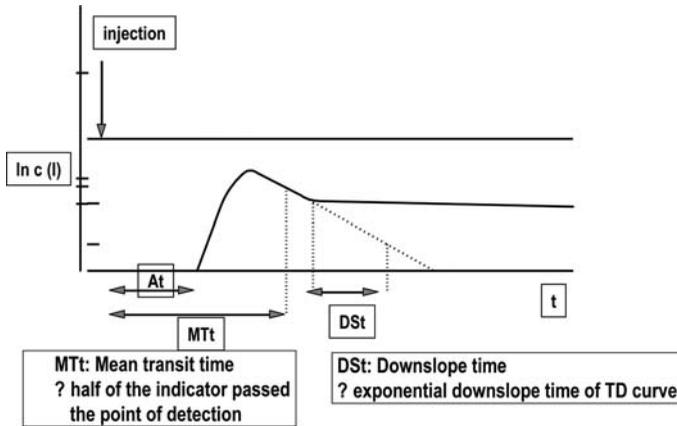


Figure 5 Determination of mean transit time and downslope time. Mean transit time is the time taken for half of cold indicator to pass the point of detection. Downslope time is the exponential downslope of the thermodilution curve. The x-axis represents time and the y-axis temperature. *Abbreviation:* At, appearance time. *Source:* From Ref. 58.

thermal volume into the interstitium (Fig. 6). Multiplication of cardiac output by the downslope time provides the volume of the largest mixing chamber. This volume is representative of the pulmonary thermal volume (PTV), which comprises pulmonary vascular volume, and pulmonary interstitial volume. Global end diastolic volume (GEDV) may be calculated by subtracting PTV from ITTV. Finally, ITBV is determined by multiplying GEDV by 1.25. The latter constant was determined using indocyanin green, an indicator dye that remains in the intravascular space. Because it is not possible to use indocyanin green in the clinical setting practically, a constant was determined that is representative for most patients. The utility of the transpulmonary thermal dilution technique in burn shock resuscitation remains to be evaluated in clinical trials. Numerous questions remain to be answered. Among these are target values for ITBV in burn patients and whether the use of ITBV as an indicator of preload will optimize fluid administration and improve outcomes in patients suffering severe, large body surface area burns. However, early results indicate that this technique may be valuable in monitoring preload in severely burned patients.

Blood lactate and base deficit provide indirect indices of global tissue perfusion. Lactic acid is a byproduct of anaerobic metabolism and is an indicator of either inadequate oxygen delivery or impaired oxygen utilization. In the absence of conditions such as cyanide poisoning or sepsis that alter oxygen utilization at the cellular level, lactate production serves as a useful marker of oxygen balance. Serum lactate levels have served as a useful marker of fluid resuscitation and tissue perfusion in burn patients. A recent study showed serum lactate to be the most predictive index of adequate tissue perfusion, and a lactate level of less than 2 mM/L in the first 24 to 72 hours after burn injury correlated with increased survival (59). Base deficit

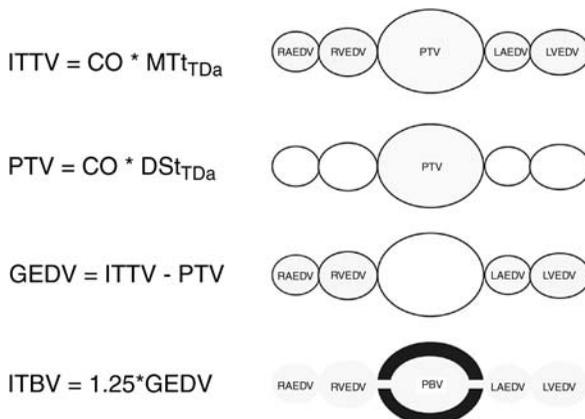


Figure 6 Determination of vascular volumes using transpulmonary thermodilution. *Abbreviations:* ITTV, intrathoracic thermal volume; CO, cardiac output; PTV, pulmonary thermal volume; GEDV, global end diastolic volume; ITBV, intrathoracic blood volume. *Source:* From Ref. 58.

is another indirect indicator of global tissue perfusion. The base deficit is calculated from the arterial blood gas using the Astrup and Siggard-Anderson nomograms. Although it is not directly measured, base deficit provides a readily obtained and widely available indicator of tissue acidosis and shock. Base deficit has been shown to correlate closely with blood lactate and provide a useful indicator of inadequate oxygen delivery. A retrospective study by Kaups et al. (60) showed that base deficit was an accurate predictor of fluid requirements, burn size, and mortality rate.

Lactate and base deficit serve as global markers of tissue perfusion and oxygen delivery. However, in burn patients, tissue perfusion is not uniform. Perfusion of the splanchnic beds is often sacrificed in order to maintain the perfusion of heart, brain, and kidneys. The use of gastric intramucosal pH (pH_i) has been advocated as a measure of splanchnic perfusion. Several studies have shown that measurement of pH_i is useful in guiding resuscitation and that low pH_i is a predictor of organ failure and death (61). pH_i is measured by gastric tonometry and can provide useful information regarding tissue perfusion.

CONCLUSION

Fluid management is a critical part of care for severely burned patients. In the immediate post-burn period, treatment of burn shock is a major priority and, in most cases, is essential for the survival of the burned victim. Isotonic crystalloids are most commonly employed in the treatment of burn shock although some centers utilize colloids and hypertonic crystalloids as part of their resuscitation regimen. Currently, there is no scientific evidence to indicate that colloids or hypertonic fluids have any better overall benefit compared to isotonic crystalloids in the resuscitation of patients with burn shock. The goal of fluid resuscitation is to maintain organ perfusion with the least amount of fluid necessary to achieve this goal. Compartment syndrome caused by excessive fluid resuscitation is a common complication in severely burned patients, which can be avoided in many cases if the patient is closely monitored. Early targets of fluid resuscitation include normalization of systemic blood pressure and maintenance of adequate urine output. However, these parameters should not be used alone to assess adequate resuscitation. Indices such as blood lactate, base deficit, or pH_i are important in providing evidence of adequate global and regional tissue perfusion. Invasive monitoring is not necessary in most burn patients. However, patients who do not respond as predicted to fluid resuscitation or have underlying cardiovascular disease may require placement of invasive monitors. Some practitioners advocate induction of supranormal levels of cardiac output and oxygen delivery in burn patients. However, this approach has not been shown to be beneficial in some studies and remains controversial. Recent studies show that central venous and PAoPs do not correlate well with cardiac output in severely burned patients. Preliminary studies indicate that ITBV measurements may be a better predictor of preload although specific target values and the overall benefit of this approach remain to be established.

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20 Perioperative Fluid Management of the Neurosurgical Patient

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INTRODUCTION

The perioperative fluid management of patients with neurologic disease or cerebrovascular disease presents many challenges. Individual patients may require optimizing intravascular volume, improving cerebral blood flow (CBF), and minimizing cerebral edema. This chapter reviews the basic physiologic principles that determine the movement of water between the intra- and extracellular spaces, both in peripheral tissues and the brain, before addressing specific pathologic conditions.

PHYSICAL PRINCIPLES GOVERNING FLUID MOVEMENT BETWEEN THE INTRA- AND EXTRAVASCULAR SPACES

Total body water (TBW) is partitioned between the intracellular volume (ICV) and extracellular volume (ECV) by cell membranes, which are semipermeable to water but less permeable to most ions and all proteins. Under certain circumstances, water can be redistributed between the ICV and ECV by creating osmotic gradients, usually accomplished by changing the serum sodium concentration $[\text{Na}^+]$. In peripheral tissues, fluid distribution between plasma volume (PV) and interstitial fluid volume is governed by gradients of oncotic pressure, i.e., the proportion of osmotic pressure attributable to protein. With the notable exception of those located in the brain and spinal cord, capillary membranes are highly permeable to water, ions, and other low-molecular-weight (M_W) compounds, but limit the movement of high- M_W substances, including albumin, globulins, and synthetic colloids such as hydroxyethylstarch and dextrans. Impermeability of brain capillary membranes to most hydrophobic solutes is a key characteristic of the blood–brain barrier (BBB).

Osmolality

Osmolality is the term used to quantify the number of particles in a solution. Because of the minimal penetration of most solvents, especially sodium, through the BBB, abrupt changes in osmolality can cause comparably rapid changes in brain water concentration. For physiologic solutions, osmolality is commonly expressed as milliosmoles per kilogram (mOsm/kg) of solvent, whereas the units of measure for osmolarity are milliosmoles per liter (mOsm/L) of solution. For dilute solutions (including most of physiologic importance), the two terms may be used interchangeably. The osmolarities of some commonly used intravenous fluids are shown in Table 1.

Osmolarity can be easily calculated if the M_W of the solute is known. A 0.9% solution of sodium chloride (NaCl) contains 9 mg/mL or 9 g/L. A 1 M solution of NaCl would contain 58.43 g/L, because the gram M_W of NaCl is 58.43. Therefore, a 0.9% NaCl solution would be a 0.154 M or 154 mmol solution. However, at this concentration, each molecule of NaCl dissociates into one Na^+ and one Cl^- ion, i.e., each mmol dissociates into 2 mOsm. Therefore the calculated osmolarity of 0.9% saline is 308 mOsm/L.

Table 1 Osmolarities and Oncotic Pressures of Common Intravenous Fluids

Fluid	Solute(s) primarily responsible for osmolarity	Osmolarity (mOsm/L)	Osmotic pressure (mmHg)	Solutes contributing to oncotic pressure	Oncotic pressure (mmHg) ^a
Lactated Ringer's	Na ⁺ , Cl ⁻ , lactate	273	5,269		0
D5 lactated Ringer's	Glu, Na ⁺ , Cl ⁻ , lactate	525	10,133		0
0.9% Saline	Na ⁺ , Cl ⁻	308	5,944		0
D5 0.45% saline	Glu, Na ⁺ , Cl ⁻	406	7,836		0
0.45% Saline	Na ⁺ , Cl ⁻	154	2,972		0
20% Mannitol	Mannitol	1098	21,191		0
Hydroxyethyl starch (6%) (as Hespan TM)	Na ⁺ , Cl ⁻	310	5,983	HES	312
Hydroxyethyl starch (6%) (as Hextend TM)	Na ⁺ , Cl ⁻ , lactate	310	5,983	HES	312
Dextran 40 (10%) ^b	Na ⁺ , Cl ⁻	0.300	5,790	DEX	1693
Dextran 70 (6%)	Na ⁺ , Cl ⁻	0.300	5,790	DEX	193
Albumin (5%)	Na ⁺ , Cl ⁻	290	5,597	Alb	19
Plasma	Na ⁺ , Cl ⁻	295	5,694	Prot	21

^aColloid osmotic pressure.

^bLow MW dextran.

Abbreviations: D5, 5% dextrose (glucose); glu, glucose; HES, hydroxyethyl starch; DEX, dextran; Alb, albumin; Prot, serum protein.

When solutions of unequal osmolarity are separated by a membrane permeable to water but not to solutes, the difference generates osmotic pressure. Water will move from the solution of lower osmolarity across the membrane, and dilute the solution of higher osmolarity. Movement of water continues until the osmolarities on both sides of the membrane equalize. Each difference of 1 mOsm across a semipermeable membrane generates a pressure of approximately 19.3 mmHg. Thus, osmolar differences can provide a potent driving force for the movement of water between the ICV and ECV, and those differences generate an even greater force across the BBB. Osmolar gradients produced by the administration of hypo- or hypertonic fluids are fleeting; water will move from one compartment until osmolarity is equal in all body compartments.

Whether described in terms of osmolarity or osmolality, the concentrations of solutes are important in determining fluid movement between various physiologic compartments. An important concept related to osmolarity and osmolality is effective osmolality (1). Solutes such as urea, which freely penetrate cell membranes and distribute across TBW, are ineffective osmoles and will not generate fluid shifts; however, solutes that *slowly* penetrate cell membranes are effective osmoles and will generate fluid shifts. Thus, uremia will not change water distribution, but hypernatremia will dehydrate the intracellular space.

Oncotic Pressure vs. Osmotic Pressure

Oncotic pressure, also termed colloid osmotic pressure, is defined as the osmotic pressure generated by solutes larger than an arbitrary limit (usually 30,000 M_w). Albumin ($\sim M_w$ 69,000), hydroxyethyl starch (mean M_w = 480,000), dextran 40 (mean M_w 40,000), and dextran 70 (mean M_w = 70,000) are clinically important compounds that exert oncotic pressure. Osmotic and oncotic pressures of plasma and solutions of mannitol, hydroxyethyl starch, dextran, and albumin are shown in Table 1. Because colloids are particles suspended in solution, they contribute to the total osmolality and osmotic pressure of the fluid. However, because they are present in such small numbers compared to the ionic components of the solution, their contribution to osmolarity and osmotic pressure is small. The oncotic pressure produced by all plasma proteins (albumin, globulins, fibrinogen, etc.) accounts for less than one-half of 1% of total plasma osmotic pressure.

However, because colloids penetrate systemic capillaries slowly, intravascular protein concentrations considerably exceed interstitial protein concentrations. The gradient between intravascular and interstitial oncotic pressure is partially responsible for preservation of intravascular volume, as expressed in the Starling equation:

$$Q_f = K_f A [(P_c - P_i) - \sigma(\pi_c - \pi_i)] \quad (1)$$

Figure 1 The Starling Equation identifies the three forces favoring the movement of water from the intravascular space into the interstitium. These three forces are the capillary hydrostatic pressure (P_c), the interstitial hydrostatic pressure (P_i), and the interstitial oncotic pressure (π_i). The only force acting to maintain water in the capillary lumen is π_c , the plasma oncotic pressure.

$$J_v = K_f [(P_c - P_i) - (\pi_c - \pi_i)]$$

where Q_f represents the net amount of fluid that moves between the capillary lumen and the surrounding interstitial space; K_f is the filtration coefficient for the membrane; A is the surface area of the capillary membrane; P_c is the hydrostatic pressure in the capillary lumen; P_i is interstitial hydrostatic pressure (usually negative); and σ is the reflection coefficient. This number, which can range from 0 (no movement of the solute across the membrane) to 1 (free diffusion of the solute across the membrane), quantifies the "leakiness" of the capillary and will be different for vessels in the brain versus peripheral tissues; π_c is the colloid osmotic pressure in the capillary plasma, and π_i is the colloid osmotic pressure of the fluid in the interstitium.

P_c , which is generally near 20 mmHg; P_i , which is negative in nonedematous tissues; and π_i act together to move fluid from the capillaries into the interstitial space of tissues. The only factor that serves to maintain intravascular volume is π_c , which is produced predominantly by albumin and to a lesser extent by immunoglobulins, fibrinogen, and other high- M_w plasma proteins (Fig. 1). Under most circumstances, the net product of the four variables results in a value for Q_f that slightly exceeds zero, indicating a net outward flux of fluid from the vessels and into the tissue interstitial space, from which it is cleared by the lymphatic system.

Surgical patients frequently illustrate the clinical effects of altering one or more of the variables in the Starling equation. Patients who have received large volumes of crystalloid solutions develop peripheral edema owing to dilution of plasma proteins, resulting in a decrease in π_c , usually associated with a normal or elevated P_c . Therefore, fluid flux from the vasculature into the tissues increases, and, if fluid flux exceeds the drainage capacity of the lymphatics, results in clinically apparent edema. Another example of the Starling equation is facial edema, which is frequently seen in patients who have been placed in the prone, head-down position for extensive lumbar surgery. In these patients, decreases in π_c may contribute to edema formation, but the more important factor may be a regional increase in P_c , which favors increased transudation of fluid into facial tissues. In either case, edema tends to be self-limited because P_i increases and π_i decreases as interstitial fluid accumulates, thereby reducing fluid transudation.

Fluid Movement Between Cerebral Capillaries and Brain Tissue

The Starling equilibrium most accurately describes the factors governing fluid movement between the intravascular and peripheral interstitial spaces (e.g., the interstitium of lung, bowel, or muscle). However, the brain and spinal cord, unlike most other tissues, are isolated from the intravascular compartment by the BBB. In cerebral capillaries, σ for most solutes is nearly 1.0. Morphologically, this barrier is now thought to be composed of endothelial cells that form tight junctions in the capillaries supplying the brain and spinal cord (2). The small pore size of the BBB (7–9 Å) limits movement not only of plasma proteins, but also of sodium, chloride, and potassium ions between the intravascular compartment and the brain's interstitial space. In effect, the BBB functions in a fashion similar to the solute-impermeable membrane of an osmometer, i.e., transmembrane movement of water is determined by the relative concentrations of impermeant solutes.

In contrast, in systemic capillary beds in which endothelial cells do not form tight junctions, the pore sizes may be 1000-fold larger. While larger pores still may preclude free movement of most protein components of plasma, electrolytes pass more easily from the capillary lumen into the interstitial space. Hence, in peripheral tissues, movement of water is governed by the transcapillary concentration difference of large macromolecules ($\pi_c - \pi_i$), as predicted by the Starling equation. In contrast, fluid movement in and out of brain capillaries is primarily determined by the osmolar gradient (which is determined by relative concentrations of all osmotically active particles, including most electrolytes) between the plasma and the interstitium. This difference in the determinants of fluid flux explains why the administration of large volumes of iso-osmolar crystalloid will result in peripheral edema owing to

dilutional reduction of plasma protein content, but does not generally increase brain water content or intracranial pressure (ICP).

Implications for Patient Care

Because osmolality is the primary determinant of water movement across the intact BBB, the administration of excess free water (i.e., in parenteral or enteral fluids in which the $[\text{Na}^+]$ is \leq plasma $[\text{Na}^+]$) can increase ICP and result in an edematous brain (3). Conversely, the intravenous administration of markedly hyperosmolar crystalloids (e.g., mannitol) to increase plasma osmolarity will decrease brain water content and ICP. Use of hyperosmolar solutions, a routine part of neurosurgical practice, represents a standard therapy for the treatment of intracranial hypertension. Increasing plasma osmolality creates an osmotic gradient favoring the movement of water into plasma from both the brain interstitial space and the brain intracellular compartment.

Despite convincing experimental evidence that isotonic crystalloid solutions (those in which $[\text{Na}^+] \sim$ serum $[\text{Na}^+]$) exert minimal effects on brain water or ICP, conventional neurosurgical practice restricted the use of any crystalloids in patients at risk for intracranial hypertension (4). To maintain PV in such patients, infusion of colloids has often been recommended based on the now-discredited inference that maintaining or increasing π_c will decrease cerebral edema. However, if the BBB is intact, neither theory nor experimental evidence suggests that colloids exert this effect on cerebral edema. More recently, the crystalloid–colloid question has been addressed in animal models of cerebral injury with varying and sometimes conflicting results. Warner and Boehland (5) studied the effects of hemodilution with either 0.9% saline or 6% hydroxyethyl starch (dissolved in 0.9% saline) in rats subjected to 10 minutes of severe forebrain ischemia. Despite approximately a 50% reduction in π_c in the saline group (17.2 ± 0.8 – 9.0 ± 0.6 mmHg), hetastarch produced no beneficial effect on cerebral edema formation. Similarly, in a study using cryogenic cerebral injury, Zornow et al. (6) found no differences in regional water content or ICP in animals that received 0.9% saline, 6% hetastarch (in 0.9% saline), or 5% albumin (in 0.9% saline). In contrast, in rats subjected to fluid-percussion traumatic brain injury (TBI), Drummond et al. (7) reported that 6% hydroxyethyl starch limited water accumulation in injured brain in contrast to iso-osmolar or hypo-osmolar solutions. One possible explanation is that TBI modifies the permeability of the BBB so that small solutes can pass easily while proteins pass less readily, i.e., after TBI the BBB may behave similarly to the systemic circulation. However, other experimental models in which the BBB is disrupted failed to show a protective effect of increased oncotic pressure.

In contrast, hyperosmolar (hypertonic) solutions, in circumstances of localized brain injury with disruption of the BBB, appear to readily cause fluid flux out of brain tissue in which the BBB remains intact. In effect, “dehydration” of the normal brain compensates for edema in the injured brain. In experimental cryogenic brain injury, infusion of a hypertonic solution attenuated the increase in ICP associated with the lesion, but did not change the water content of brain tissue at the lesion site or in its immediate vicinity (8). The most likely mechanism for the reduced ICP is a decrease in brain water content in regions remote from the lesion.

CHARACTERISTICS OF INTRAVENOUS FLUIDS

Most solutions used for intravenous administration are categorized as crystalloids or colloids. Crystalloid solutions are subdivided into hypotonic, isotonic, and hypertonic solutions.

Crystalloids

Crystalloids are solutions composed solely of low- M_W solutes ($M_W < 30,000$), which may be charged (e.g., Na^+ , Cl^-) or uncharged (e.g., mannitol). Because these solutions by definition lack high- M_W solutes, the oncotic (colloid osmotic) pressure is zero. Colloquially, the terms “hypotonic,” “isotonic,” and “hypertonic” refer to fluids in which the total osmolality is less than, roughly equal to, or greater than serum osmolality. However, as is evident from the discussion of the impermeability of the BBB to sodium, the more important consideration is whether the fluid has a $[\text{Na}^+]$ less than, approximately equal to, or greater than plasma. Unless another osmole, e.g., dextrose or mannitol, is present in large quantities, the proportion of water in excess of that necessary to provide an isonatremic solution is the variable of greatest interest.

Solutions containing free water ($[Na^+]$ substantially $<$ serum), when infused rapidly in large volumes, reduce plasma osmolality, drive water across the BBB into the brain, and increase cerebral water content and ICP. The dextrose in solutions may temporarily increase serum glucose concentration, holding water intravascularly. However, as the serum glucose concentration decreases, changes in serum $[Na^+]$ induced by the ratio of sodium to water in the infused fluid again become critical.

The most commonly used "isotonic" fluids are lactated Ringer's solution and 0.9% saline. Lactated Ringer's solution actually is mildly hyponatremic when compared to plasma (Table 1). When large volumes of lactated Ringer's solution are infused rapidly, the free water (~ 114 mL/L) may decrease serum $[Na^+]$ and plasma osmolality and increase brain water and ICP. Figure 2 illustrates the influence on plasma $[Na^+]$ of rapid infusion (60 mL/kg over two hours) of lactated Ringer's solution and 0.9% saline in patients undergoing gynecologic surgery. At that rate of infusion, lactated Ringer's solution was associated with a decrease of plasma $[Na^+]$ of nearly 2.0 mEq/L and 0.9% saline was associated with an increase of plasma $[Na^+]$ of nearly 2.0 mEq/L. Converted to differences in osmotic pressure, these changes in plasma $[Na^+]$ are equivalent to decreases and increases in plasma osmotic pressure of approximately 36 mmHg, with the total difference between the two fluids, infused in those volumes over that time interval, of approximately 72 mmHg.

For many years, clinicians have acutely increased plasma osmotic pressure to reduce brain water and ICP. Conventionally, hypertonic mannitol, a six-carbon sugar (M_w 182), has been the primary agent used for therapeutic brain dehydration. Mannitol, which is excreted unchanged in the urine, is available as 20% and 25% solutions (osmolarities of 1098 and 1372 mOsm/L, respectively). Mannitol is usually given in doses of 0.25 to 1.5 g/kg and cannot pass through the intact BBB; hence, intravenous administration acutely increases plasma osmolality and establishes an osmotic gradient favoring the movement of water from the brain's interstitial space into the vasculature. Rapid administration of large doses of mannitol may have a biphasic effect on ICP. Initially, ICP may increase owing to an increased cerebral blood volume as a consequence of the cerebral vasodilatory effects of the acute increase in plasma osmolality. Subsequently, ICP will decrease owing to the movement of water from the brain interstitial space into the vasculature.

Hypertonic saline solutions, loosely defined as any saline solution containing sodium in greater concentrations than that in 0.9% saline, are crystalloid solutions that also have been used for acute brain dehydration as well as for low-volume resuscitation, especially in patients with TBI, and as an alternative to mannitol for osmotic reduction of ICP. Hypertonic saline solutions have been proposed for the treatment of hemorrhagic shock and control of intracranial hypertension. Although Weed and McKibben (10) first suggested nearly 100 years ago that hypertonic saline would reduce brain bulk, current enthusiasm results from the work of Velasco et al. (11), who successfully resuscitated severely hemorrhaged dogs with small volumes (4.0–6.0 mL/kg) of 7.5% hypertonic saline. In patients who have failed to respond to large doses of mannitol, intravenous infusions of small volumes of hypertonic saline solutions have been reported to rapidly restore blood pressure, improve urinary output, and

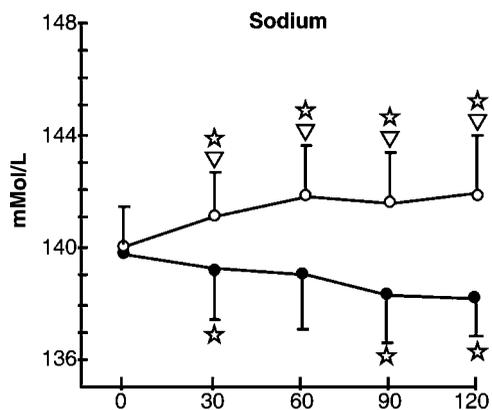


Figure 2 Changes in plasma sodium in gynecologic surgical patients receiving approximately 60 mL/kg of 0.9% saline (open circles) or lactated Ringer's solution (closed circles) over 120 minutes. Saline was associated with a moderate increase in plasma sodium concentration, and lactated Ringer's solution was associated with moderate decrease in plasma sodium concentration. Source: Ref. 9.

Table 2 Advantages and Disadvantages of Hypertonic Resuscitation Fluids

Solution	Advantages	Disadvantages
Hypertonic crystalloid	Inexpensive Promotes urinary flow Small initial volume Improved myocardial contractility? Arteriolar dilation Reduced peripheral edema Lower intracranial pressure	Hypertonicity Subdural hemorrhage Transient effect
Hypertonic crystalloid plus colloid (in comparison to hypertonic crystalloid alone)	Sustained hemodynamic response Reduced subsequent volume requirements	Added expense Coagulopathy (dextran > HES) Osmotic diuresis Impaired crossmatch (dextran)

Abbreviation: HES, hydroxyethyl starch.

Source: From Ref. 14a.

decrease ICP (12). Three percent saline has been used to decrease ICP in hemodynamically stable, head-injured children (13). Hypertonic solutions, often combined with a colloid, have also been used to reduce ICP in adults undergoing neurosurgical intensive care (14). Hypertonic solutions should be administered in judicious amounts and with frequent monitoring of plasma osmolality and sodium concentrations (Table 2). A substantial obstacle to wider clinical application of hypertonic saline solutions is the transient nature of the PV expansion produced by hypertonic saline administration.

Hypertonic saline solutions have approximately the same influence on brain water and ICP as mannitol solutions of similar osmolality. In a recent randomized study comparing the effects on increased ICP of infusions of 7.2% hypertonic saline/hydroxyethyl starch versus 15% mannitol, for hypertonic saline solutions, the effects were slightly superior, but the osmolality was substantially greater (15). Similarly, when equimolar, rapid intravenous infusions of 200 mL of 20% mannitol or 100 mL of 7.5% saline/6% dextran-70 solution were given over five minutes to neurological and neurosurgical patients with increased ICP, hypertonic saline dextran exerted a greater effect; however, an equimolar dose of 7.5% saline, because it is almost completely ionized, contains twice the number of osmoles and would be expected to exert a greater effect than mannitol (16).

Hypertonic saline has been associated, as has high-volume resuscitation using 0.9% saline, with hyperchloremic acidosis (Table 3). The gradual change in neuroanesthesia practice from the use of lactated Ringer's solution to 0.9% saline has resulted in the more common postoperative occurrence of hyperchloremic metabolic acidosis. Metabolic acidosis, usually characterized by a reduced pH (< 7.35) and reduced $[\text{HCO}_3^-]$ (< 21 mEq/L), occurs as a consequence of the buffering by $[\text{HCO}_3^-]$ of endogenous or exogenous acid loads or as a consequence of abnormal external loss of $[\text{HCO}_3^-]$. Two types of metabolic acidosis may be distinguished, based upon whether the calculated anion gap is normal or increased (17). Metabolic acidosis associated with a high anion gap (> 13 mEq/L) occurs due to excess production of lactic acid or ketoacids, increased retention of waste products (such as sulfate and phosphate) that are inadequately excreted in uremic states, and ingestion of toxic quantities of substances such as aspirin, ethylene glycol, and methanol. The anion gap

Table 3 Production of Hyperchloremic Metabolic Acidosis by Rapid Administration of 0.9% Saline or Hypertonic Saline

	0.9% Saline	Hypertonic saline
Blood gases		
pH	7.40	7.29
PaCO ₂ (mmHg)	40	29
$[\text{HCO}_3^-]$ (mEq/L)	24	14
Electrolytes		
Na ⁺ (mEq/L)	140	140
Cl ⁻ (mEq/L)	105	115
CO ₂ (mEq/L)	25	15
Anion gap (mEq/L)	10	10

($\text{Na}^+ - [\text{Cl}^- + [\text{HCO}_3^-]]$) is normal ($< 13 \text{ mEq/L}$) in situations such as diarrhea, biliary drainage, and renal tubular acidosis, in which $[\text{HCO}_3^-]$ is lost externally, or after administration of large volumes of 0.9% saline or hypertonic saline, which effectively dilute serum $[\text{HCO}_3^-]$. Hyperchloremic acidosis associated with infusion of hypertonic saline usually requires no treatment, but does require differentiation from other causes of metabolic acidosis.

Because small volumes (relative to shed blood volume) of hypertonic saline, with or without added colloid, rapidly increase blood pressure and cardiac output, clinical trials have evaluated whether rapid infusion of hypertonic solutions will improve outcome when used for prehospital resuscitation. In the largest clinical study of prehospital hypertonic saline resuscitation, Mattox et al. randomized 422 patients, half of whom required surgery, to receive 250 mL of either conventional crystalloid fluid or 7.5% saline in 6% dextran (18). Although overall survival was unaffected, survival was improved in those patients in the Saline-dextran group who required surgery. In a randomized multicenter study, Vassar et al. (18) evaluated the effects of 250 mL of 7.5% sodium chloride with and without 6% and 12% dextran 70 for the prehospital resuscitation of hypotensive trauma patients. A small subgroup of patients with Glasgow Coma Scale scores below 8, but without severe anatomic injury, seemed to benefit most from resuscitation with one of the hypertonic solutions (19). One might speculate that the hypertonic fluids restored mean arterial pressure (MAP) while reducing ICP, therefore improving cerebral perfusion pressure. However, Cooper et al. (20) subsequently randomized 219 patients with TBI to prehospital resuscitation, beginning with either 250 mL of 7.5% saline or lactated Ringer's solution. Despite differences in serum $[\text{Na}^+]$ and $[\text{Cl}^-]$, there were no differences in outcome assessed using an 8-point extended Glasgow outcome scale (Fig. 3).

To address concerns about central nervous system (CNS) dysfunction due to hypertonicity and hypernatremia associated with hypertonic saline solutions, Wisner et al. demonstrated, using high-energy phosphate nuclear magnetic resonance spectroscopy, a decreased intracellular pH after hypertonic saline resuscitation compared with lactated Ringer's solution. However, this decrease was not attributable to anaerobic glycolysis, but to concentration of intracellular hydrogen ions in volume-contracted cells (21). Rats resuscitated from controlled hemorrhage with 7.5% saline in 10% hetastarch demonstrated a sufficient increase in regional CBF to restore cerebral oxygen delivery (CDO_2) to baseline levels; however, administration of the hypertonic solution had no effect on the cerebral metabolic rate for glucose (22). In humans resuscitated with hypertonic saline, acute increases in serum sodium to 155–160 mEq/L produced no apparent harm (19), specifically no evidence of central pontine myelinolysis, which follows excessively rapid increases of serum $[\text{Na}^+]$ during correction of severe, chronic hyponatremia (23).

Colloids

A variety of colloidal solutions are available for clinical use. Each gram of intravascular colloid holds approximately 20 mL of water in the circulation (21). After equilibration, PV expansion is determined primarily by the number of grams of colloid infused, not by the original volume or concentration of the infusate. Concentrated colloid-containing solutions (e.g., 25% albumin) may exert sufficient oncotic pressure to translocate substantial volumes of interstitial fluid into the PV.

Hydroxyethyl starch or hetastarch (HespanTM) is a 6% solution of hydrolyzed amylopectin dissolved in 0.9% saline (Table 1). Eighty percent of the molecules range in size from 30,000

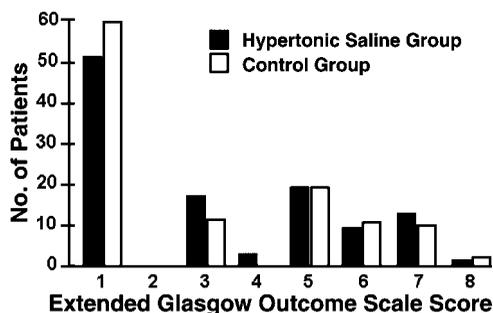


Figure 3 Outcome assessed using the eight-point extended Glasgow Outcome Scale (one point being death, eight points being upper good recovery) of 219 patients with hypotension after traumatic brain injury who were randomized to receive initial resuscitation consisting of 7.5% saline (hypertonic saline group) or lactated Ringer's solution. There were no differences in outcome. *Source:* Ref. 20.

to 2,400,000 Da. The weight average M_W for hetastarch is approximately 480,000 Da. The low- M_W fraction of an administered dose of hetastarch (those hetastarch molecules weighing <50,000 Da) is excreted by renal filtration within 24 hours. The hetastarch influences coagulation by multiple mechanisms, including hemodilution of clotting factors, inhibition of platelet function, and reduction of the activity of factor VIII. Sporadic case reports of prolonged clotting times after administration of hetastarch have prompted many neurosurgeons and neurointensivists to use hetastarch with caution or to avoid it altogether in patients at risk for intracranial hemorrhage. In an uncontrolled series, 14 patients treated with hetastarch for volume expansion to treat cerebral vasospasm developed a significant increase in partial thromboplastin time, and six developed clinically significant bleeding; in contrast, 12 patients receiving plasma protein fraction had no increase in partial thromboplastin time and no clinical coagulopathy (24). Hextend™, a solution of hetastarch that is dissolved in lactated Ringer's solution rather than 0.9% saline, exerts similar effects on intravascular volume and coagulation (25).

Pentastarch (Pentastarch™), a formulation of hydrolyzed amylopectin approved for use during leukapheresis, may have a role as a PV expander. Pentastarch differs from hetastarch in that it has a lower mean weight average M_W (264,000 vs. 480,000 for hetastarch), which results in more rapid and complete renal clearance of the compound. In the urine, 70% of pentastarch versus 30% hetastarch is excreted within 24 hours. Preliminary studies also suggest that pentastarch may have fewer adverse effects on coagulation than hetastarch.

Dextran solutions (dextran 40 and dextran 70) are colloids composed of glucose polymers with mean M_W s, respectively, of 40,000 and 70,000. While the oncotic pressure of dextran 70 approximates that of plasma, resulting in volume-expanding capabilities similar to albumin, dextran 40 is hyperoncotic and can transiently expand PV by more than the amount infused by recruiting interstitial water into the vascular space. About 50% of dextran 40 (low- M_W dextran) and dextran 70 is renally excreted within 24 to 48 hours of administration. A variety of adverse effects have limited the clinical use of dextrans. Occasional anaphylactoid reactions, occurring in approximately 0.032% of patients, can be prevented by the prior administration of 20 mL of very low- M_W dextran (dextran 1) immediately before giving either dextran 40 or 70. Dextran 1 binds to circulating immunoglobulin G, preventing it from cross-linking with larger dextran molecules and activating complement. An additional problem with dextran solutions is that administration of volumes exceeding 20% of blood volume may interfere with blood typing and crossmatching.

Available in either 5% or 25% concentration, human serum albumin is an effective volume expander that has not been associated with allergic-type reactions and has no intrinsic effects on clotting. Because albumin solutions are devoid of clotting factors found in whole blood or fresh plasma, large doses may produce a dilutional coagulopathy. However, rabbits hemodiluted to replace 40% of blood volume with albumin, but not Hextend, actually became hypercoagulable secondary to a loss of antithrombin activity with simultaneous maintenance of Factor VIII complex activity (VIII C) (26). Although derived from pooled human plasma, the risk of disease transmission is nearly eliminated by heat-treating and ultrafiltration of albumin. Albumin can be given without regard to the recipient's blood type because all of the isoagglutinins have been removed during processing. Although safe and effective as a volume expander, albumin solutions, volume for volume, are considerably more expensive than hetastarch.

Fresh frozen plasma (FFP) should be reserved for use only when there is an acute need to replace clotting factors and there is evidence of a dilutional coagulopathy. Volume expansion and nutritional support are no longer considered valid uses for fresh plasma or FFP. Although all plasma is derived from volunteer blood donors, and careful screening procedures have markedly reduced viral transmission, the risk of disease transmission remains a reality (27).

GENERAL PRINCIPLES OF NEUROSURGICAL FLUID ADMINISTRATION

Fluid Compartments

Rational decisions regarding intravenous fluid therapy require an understanding of how TBW is partitioned. Accounting for approximately 60% of body weight (42 L in a 70-kg person), TBW includes ICV (40% of TBW) and ECV (20% of TBW). ECV is further partitioned into PV, which equals about 20% of ECV, and IFV, which accounts for the remaining 80% of

ECV. Red cell volume, approximately 2 L in a 70-kg person, is a subdivision of ICV. Blood volume in lean young individuals can be estimated by adding red cell volume (2 L) to PV (2.8 L) to arrive at 4.8 L, or approximately 7% of adult body weight.

The ECV contains most of total body sodium, with $[\text{Na}^+]$ approximately 140 mEq/L, in both the PV and IFV. Albumin, the most important oncologically active constituent of ECV, is unequally distributed in PV (~ 4 g/dL) and IFV (~ 1 g/dL). The IFV concentration of albumin varies greatly among tissues. ECV is the distribution volume both for most crystalloid solutions, depending on $[\text{Na}^+]$, and colloids, although the final concentrations of infused colloids may vary between PV and IFV.

Distribution of Infused Fluids

The formula describing the effects of the infusion of intravenous fluids on PV is as follows:

$$\text{PVE} = V_i(\text{PV}/V_d) \quad (2)$$

where PVE = PV expansion, V_i = volume infused and V_d = distribution volume of the infused fluid.

By this estimate, to replace a 2-L blood loss using lactated Ringer's solution or 0.9% saline, which distribute throughout ECV, requires the infusion of 10 L:

$$2 \text{ L} = 10 \text{ L} (2.8 \text{ L}/14) \quad (3)$$

where 2.8 L = PV and 14 L = ECV in a 70-kg person.

If 5% albumin, which exerts colloid osmotic pressure similar to plasma, were infused, the infused volume initially would remain in the PV, perhaps attracting additional interstitial fluid intravascularly. However, volume kinetic studies demonstrate that these calculations are at best snapshots of a dynamic process and may overestimate or underestimate the volumes of crystalloid required to increase intravascular volume (28,29).

Maintenance Requirements for Water, Sodium, and Potassium

The predicted daily maintenance fluid requirements for healthy, 70-kg adults is 2500 mL/day of a solution with a $[\text{Na}^+]$ of 30 mEq/L and a $[\text{K}^+]$ of 15 to 20 mEq/L. Intraoperatively, fluids containing sodium-free water (i.e., $[\text{Na}^+] < 130$ mEq/L) are rarely used in adults because of the necessity for replacing isotonic losses.

Dextrose

Traditionally, glucose-containing intravenous fluids have been given in an effort to prevent hypoglycemia and limit protein catabolism. However, due to the hyperglycemic response associated with surgical stress, only infants and patients receiving insulin, oral hypoglycemics, or drugs that interfere with glucose synthesis are at risk for hypoglycemia. Iatrogenic hyperglycemia can limit the effectiveness of fluid resuscitation by inducing an osmotic diuresis in animals, and may aggravate ischemic and traumatic (30) brain injury in humans. Recent studies in critically ill patients and postoperative patients strongly suggest that hyperglycemia should be rigorously avoided. In critically ill patients, tight control of plasma glucose (maintenance of plasma glucose between 80 and 110 mg/dL) was associated with reduced mortality and morbidity (31,32). Evidence also suggests that poor glycemic control is associated with poor outcome in surgical patients (33). As a consequence, patients receiving dextrose-containing solutions should be carefully monitored for development of hyperglycemia.

Fluid Shifts During Surgery

Replacement of intraoperative fluid losses must account for the acute increases in IFV that accompany trauma, hemorrhage, and tissue manipulation and should also take into account changes in serum proteins during resuscitation. In association with reduced colloid osmotic pressure in traumatized patients, the ratio of IFV to blood volume was increased, in some patients exceeding 5:1 (34); therefore, the ratio of IFV to PV could be greater than 8:1 (vs. the normal ratio of 4:1) and the volume of infused fluid necessary to obtain any given increment in PV would be increased. However, these data apply to patients with systemic trauma, with or

without TBI. Patients with isolated cranial trauma or those undergoing only craniotomy do not sequester clinically important quantities of interstitial fluid, and consequently require much less fluid.

MONITORING FLUID ADMINISTRATION

Two contrasting methods are used to assess the adequacy of intravascular volume. The first, conventional clinical assessment, is appropriate for most patients; the second, goal-directed hemodynamic management, may be superior for high-risk surgical patients. Recently, transthoracic echocardiography (TEE) has shown promise as a means of estimating cardiac dimensions and preload.

Conventional Clinical Assessment

Clinical quantification of blood volume and ECV is difficult. The clinician must first recognize settings in which deficits are likely, such as protracted gastrointestinal losses, bowel obstruction, bowel perforation, preoperative bowel preparation, chronic hypertension, chronic diuretic use, sepsis, burns, pancreatitis, and trauma. The physical signs of hypovolemia are insensitive and nonspecific. Suggestive evidence includes oliguria, supine hypotension, tachycardia, and a positive tilt test. Oliguria implies hypovolemia, although hypovolemic patients may be nonoliguric and normovolemic patients may be oliguric, because of renal failure or stress-induced endocrine responses (35). Supine hypotension implies a blood volume deficit exceeding 30%. However, arterial blood pressure within the normal range could represent relative hypotension in an elderly or chronically hypertensive patient. Substantial depletion of blood volume and organ hypoperfusion may occur despite an apparently normal blood pressure and heart rate.

In the tilt test, one of the traditional methods of assessing intravascular volume depletion, a positive response, suggesting a blood volume deficit greater than 20%, is defined as an increase in heart rate by 20 beats/min or more and a decrease in systolic blood pressure of 20 mmHg or more when the subject assumes the upright position. However, young, healthy subjects can withstand acute loss of 20% of blood volume while exhibiting only postural tachycardia and variable postural hypotension. In contrast, elderly patients may demonstrate orthostatic changes in blood pressure despite normal blood volume. In volunteers, withdrawal of 500 mL of blood (36) was associated with a greater increase in heart rate on standing than before blood withdrawal, but no significant difference in the response of blood pressure or cardiac index. Orthostatic changes in filling pressure, assessed before and after fluid infusion, may represent a more sensitive test of the adequacy of circulating blood volume (37). In patients with chronic renal failure, infusion of fluid slightly increased the mean supine central venous pressure (CVP), but eliminated the marked postural decline in CVP (37).

Laboratory evidence that suggests hypovolemia or ECV depletion includes hemoconcentration, azotemia, low urinary sodium, metabolic acidosis, and metabolic alkalosis (Table 4). Hematocrit, a poor indicator of intravascular volume, is virtually unchanged by acute hemorrhage; later, hemodilution occurs as fluids are administered or as fluid shifts from the interstitial to the intravascular space. If intravascular volume has been restored, hematocrit measurement will more accurately reflect current red cell mass and the extent of previous hemorrhage. Measurements of blood urea nitrogen (BUN) and serum creatinine (SCr) require careful interpretation because of multiple confounding variables (Table 4). In prerenal oliguria, enhanced sodium reabsorption should reduce urinary $[Na^+]$ to less than 20 mEq/L, and enhanced water reabsorption should increase urinary concentration (i.e., urinary osmolality > 400 ; urine/plasma creatinine ratio $> 40:1$). However, the sensitivity and specificity of measurements of urinary $[Na^+]$, osmolality, and Cr ratios may be misleading in acute situations. Severe hypovolemia may result in systemic hypoperfusion and lactic acidosis.

Although hypovolemia does not generate metabolic alkalosis, ECV depletion is a potent stimulus for the maintenance of metabolic alkalosis. Metabolic alkalosis, usually characterized by an alkalemic pH (> 7.45) and hyperbicarbonatemia (> 27.0 mEq/L), should be anticipated in neurosurgical patients who have received diuretics or glucocorticoids, who have had prolonged nasogastric suction, or who have been fluid restricted. Metabolic alkalosis is associated with hypokalemia, ionized hypocalcemia, cardiac arrhythmias, and digoxin toxicity. Metabolic

Table 4 Laboratory Evidence of Hypovolemia

Test	Normal range	Suggests hypovolemia	False positives
BUN (mg/dL)	8–20	>20	High protein intake Gastrointestinal bleeding Catabolic state
SCr (mg/dL)	0.5–1.2	>1.2	Renal compromise Advanced age Increased muscle mass Catabolism
BUN:Cr ratio	<20	>20	Renal compromise All of the above
UNA (mEq/L)	>30	<20	Renal compromise
UOSM (mOsm/kg)	<800	>400	Renal compromise
Lactic acidosis (serum lactate; mmol/L)	<2.0	>3.0	Hypoperfusion from any cause
Metabolic alkalosis (serum bicarbonate; mEq/L)	22–26	>26 (pH alkalemic)	

Abbreviations: BUN, blood urea nitrogen; SCr, serum creatinine; UNA, urinary sodium concentration; UOSM, urinary osmolality.

alkalosis may also generate compensatory hypoventilation (hypercarbia). Alkalemia-induced leftward shift of the oxyhemoglobin dissociation curve may make oxygen less available to tissues, as may cardiac output reduction induced by alkalemia.

In addition to recognizing existing volume deficits, perioperative management of neurosurgical patients requires estimation of intraoperative blood loss. Visual estimation, the simplest technique for quantifying intraoperative blood loss, assesses the amount of blood absorbed by gauze sponges and laparotomy pads, collected on the surgical drapes, and accumulated in the suction canisters. Both surgeons and anesthesiologists tend to underestimate losses, the magnitude of the error being directly proportional to the actual blood loss.

The adequacy of intraoperative fluid resuscitation must be ascertained by evaluating multiple clinical variables, including heart rate, arterial blood pressure, urinary output, arterial oxygenation, and pH. Tachycardia is an insensitive, nonspecific indicator of hypovolemia. In patients receiving potent inhalational agents, maintenance of a satisfactory blood pressure implies adequate intravascular volume. Preservation of blood pressure, accompanied by a CVP of 6 to 12 mmHg, more strongly suggests adequate replacement. During profound hypovolemia, indirect measurements of blood pressure may significantly underestimate true blood pressure. In patients undergoing extensive procedures, direct arterial pressure measurements are more accurate than indirect techniques and provide convenient access for obtaining arterial blood samples. An additional advantage of direct arterial pressure monitoring may be recognition of increased systolic blood pressure variation accompanying positive-pressure ventilation in the presence of hypovolemia (38,38).

Urinary output usually declines precipitously during moderate-to-severe hypovolemia. Therefore, in the absence of glycosuria or diuretic administration, a urinary output of 0.5 to 1.0 mL/kg/hr during anesthesia suggests adequate renal perfusion. Arterial pH may decrease only when tissue hypoperfusion becomes severe. Cardiac output can be normal despite severely reduced regional blood flow. Mixed venous hemoglobin (Hgb) desaturation, a specific indicator of poor systemic perfusion, reflects average perfusion in multiple organs and cannot supplant regional monitors such as urinary output.

Echocardiographic Assessment of Intravascular Volume

The limitations of traditional monitoring in estimating ventricular volume have been well documented. Preload can also be estimated with transthoracic echocardiography or by TEE by using two-dimensional (2-D) imaging and Doppler measurement of blood flow velocities.

In general, echocardiography is now considered the monitoring technique of choice for evaluation of preload in patients who have received fluid boluses to treat hypotension and who have failed to respond to apparently adequate volumes of fluids (40). Two methods by which 2-D echo can be used to evaluate ventricular preload are by measurement of left ventricular end-diastolic volume (LVEDV; semiquantitative) and by disappearance of the left ventricular cavity at end-systole (qualitative).

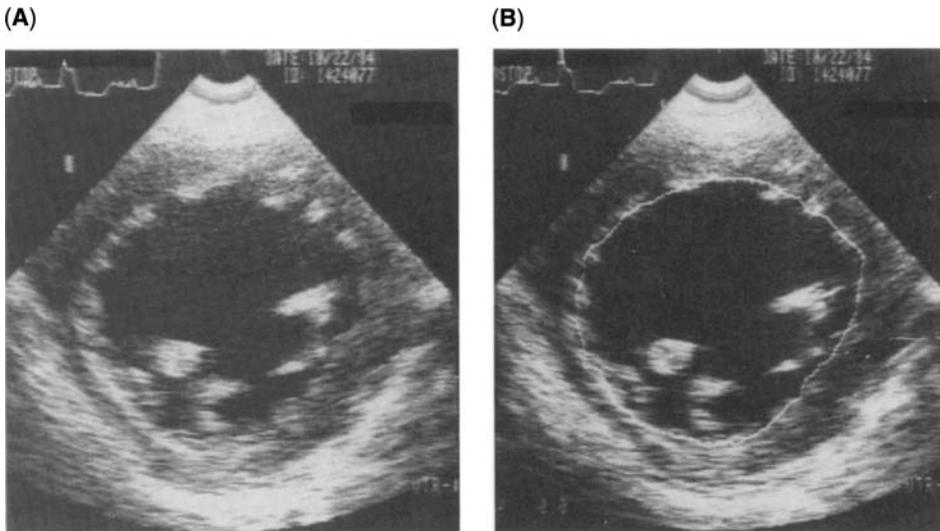


Figure 4 2-D image of a transverse slice of the left ventricle at the midpapillary muscle level demonstrating endocardial tracing used to determine the end-diastolic volume. Measurement of end-diastolic volume at this single level has been shown to accurately reflect acute changes in preload. *Source:* Ref. 41.

2-D echocardiographic measurement of LVEDV measures preload better than traditional hemodynamic measures, but compares less favorably to radionuclide quantitation of LVEDV. Because the most frequently used view for evaluating left ventricular function by TEE is the transgastric view at the midpapillary muscle level, evaluation of LVEDV in this single slice has been compared to evaluation of preload using pulmonary arterial occlusion pressure (PAOP) (Fig. 4). In this study, changes in LVEDV correlated well with changes in cardiac index, whereas changes in PAOP did not (41). End-diastolic volumes obtained at the midpapillary transgastric level have been sensitive enough to detect acute changes in preload, even in patients with ventricular wall-motion abnormalities (42,43).

End-systolic cavity obliteration visualized at the midpapillary transgastric level on TEE has been used clinically as an index of hypovolemia. There are few studies to validate this practice. Leung and Levine (44) compared the presence of end-systolic cavity obliteration to decreases in LVEDV and reported high sensitivity but poor specificity, because of the complex interaction of ventricular contractility and afterload with changes in preload, suggesting that this variable should be correlated with other echocardiographic or hemodynamic measures of preload.

Echocardiographic measures can serve as an important adjunct to traditional hemodynamic measurements, and allow a more accurate clinical assessment of the intravascular volume status. Assessment of left ventricular end-diastolic area has been proven to more accurately measure preload than conventional measurement of transmitted pressures. TEE is also associated with fewer adverse events than placement of a central venous or pulmonary artery catheter. The greatest disadvantages are the cost of the equipment and the need for experienced, well-trained echocardiographers to obtain and interpret the images.

Monitoring the Cerebral Circulation

In patients with acute neurologic disease, fluid resuscitation should maintain or improve cerebral perfusion. Although clinical experience suggests that morbidity and mortality can be altered by therapeutic alteration of CBF and cerebral metabolism in some neurologically injured patients, no data confirm the general clinical utility of neurologic monitoring. The following three questions are central to the utility of monitoring cerebral variables:

1. In what circumstances do blood pressure, PaCO₂, PaO₂, and body temperature provide insufficient information about the adequacy of CDO₂ (CDO₂ = CBF × CaO₂)?

2. In what circumstances does more precise information about the adequacy of CDO₂ permit therapeutic interventions that improve outcome?
3. What the proportion of patients within a specific diagnostic category will develop avoidable injury sufficiently large to justify extensive (and potentially expensive) application of neurologic monitoring devices?

Few data quantify the relationship between monitored cerebrovascular variables and the risk of preventable neurologic injury. Virtually all neurologic monitors are intended to detect actual or possible cerebral ischemia. Cerebral ischemia, defined as CDO₂ insufficient to meet metabolic needs, can result from a critical reduction of any of the components of CDO₂, including CBF, Hgb concentration, and arterial Hgb saturation (SaO₂). The brain constitutes only 2% of total body weight, but receives 15% of cardiac output and accounts for 15% to 20% of total oxygen consumption. Certain regions of the brain, such as the cerebellum, the basal ganglia, the CA-1 layer of the hippocampus, and the arterial boundary zones between major branches of the intracranial vessels, appear to be selectively vulnerable to ischemic injury (45).

Practical use of brain monitors requires definition of critical thresholds at which therapeutic interventions should be undertaken. Thresholds of CBF that correlate with various clinical outcomes, physiologic changes, and changes in monitored variables have been defined based upon animal experiments (46), and to a lesser extent upon clinical data (47). If a monitor of brain function detects cerebral ischemia, the actual severity is not established. All that is known is that cerebral oxygenation in a region of brain that contributes to that function has fallen below a critical threshold. The shortfall could be slight or severe. Because more severe ischemia will produce neurologic injury in less time, it is impossible to predict with certainty if changes in function will be followed by cerebral infarction. In addition, if regional ischemia involves structures that do not participate in the monitored function, infarction could develop without warning. This predictable relationship no doubt explains the failure of monitors to detect cerebral ischemia in patients who subsequently develop clinical evidence of brain infarction, as well as reports of profound changes in monitored variables that are followed by no apparent change in clinical condition. The complexity and heterogeneity of brain tissue virtually preclude development of a single, perfectly predictive brain monitor.

In most patients, arterial flow velocity can be readily measured in intracranial vessels, especially the middle cerebral artery (MCA) using transcranial Doppler (TCD) ultrasonography. Doppler flow velocity uses the frequency shift, proportional to velocity, observed when sound waves are reflected by moving red blood cells. Blood moving toward the transducer shifts the transmitted frequency to higher frequencies; blood moving away, to lower frequencies. Blood flow is a function both of velocity and vessel diameter. If diameter remains constant, changes in velocity are proportional to changes in CBF; however, intersubject differences in flow velocity correlate poorly with intersubject differences in CBF. Being entirely noninvasive, TCD measurements can be repeated at frequent intervals or even applied continuously. TCD has been used to manage volume expansion after subarachnoid hemorrhage (SAH) (48) and in patients with head trauma.

Measurements of jugular venous bulb oxygenation reflect the adequacy of CBF, as systemic "mixed venous" oxygenation reflects the adequacy of cardiac output. CBF, the cerebral metabolic rate for oxygen (CMRO₂), CaO₂, and jugular venous oxygen content (CjvO₂) are related according to the following equation:

$$\text{CMRO}_2 = \text{CBF}(\text{CaO}_2 - \text{CjvO}_2) \quad (4)$$

Mixed cerebral venous blood, like mixed systemic blood, is a global average and may not reflect marked regional hypoperfusion. Therefore, abnormally low jugular venous saturation suggests the possibility of cerebral ischemia; but normal or elevated jugular venous saturation does not indicate adequate cerebral perfusion. The internal jugular vein can be located by external anatomic landmarks and the catheter is directed toward the mastoid process, above which lies the jugular venous bulb. In clinical use (49), jugular venous blood gas sampling or continuous monitoring has detected unexpected cerebral desaturation. Jugular venous saturation has been used as a fundamental component of brain monitoring in patients after TBI (50). In response to jugular venous desaturation, volume expansion is one of the potential techniques that could improve cerebral perfusion.

Ideally, cerebral oxygenation would be assessed noninvasively. Currently, no noninvasive, continuous monitor of cerebral circulatory adequacy is available. Recently, a technique that suggests the possibility of noninvasively monitoring cerebral venous oxygenation has been described, although considerable work remains to be done (49). A brain monitor that could be used for goal-directed therapy would provide the opportunity to manage the cerebral circulation as comprehensively as the systemic circulation can now be managed. The challenge then would be to demonstrate that improved therapy based on enhanced monitoring will improve outcome.

FLUID ADMINISTRATION IN SPECIFIC SITUATIONS

Fluid Administration for Craniotomy

Recommendations for fluid therapy can be formulated based upon the preceding principles. As a general rule, isotonic crystalloid solutions should be used to replace preexisting deficits and blood loss. As the patient's Hgb concentration approaches 8 g/dL, consideration should be given to transfusing red blood cells. Transfusion may be indicated at a higher Hgb concentration if there is evidence of tissue hypoxia or ongoing uncontrolled hemorrhage. Solutions containing dextrose are to be avoided unless there is a specific indication for their use (i.e., hypoglycemia). To reduce brain volume and improve operating conditions, the administration of hypertonic mannitol is considered a standard practice. Hypertonic solutions, by creating osmotic gradients between the intracellular and extracellular spaces, cause fluid to move across the cell membrane and decrease brain tissue volume. Hypertonic saline solutions may prove to be useful in the rapid volume resuscitation of hypovolemic trauma victims with brain injury and intracranial hypertension. FFP may be infused if there is persistent hemorrhage despite adequate surgical hemostasis. There are few indications for the administration of synthetic colloids to neurosurgical patients. Colloids do not prevent the formation of brain edema, and there is some evidence that dextran and hetastarch may be associated with coagulopathies.

Head Injury

Patients who sustain TBI often have multiple concurrent injuries and may hemorrhage substantially before arrival in the operating room or intensive care unit. In the absence of a history of myocardial injury or dysfunction, hypotension in traumatized patients should raise the suspicion of inadequate volume resuscitation, after other treatable causes (e.g., tension pneumothorax and tamponade) have been excluded. Physicians caring for these patients must achieve adequate volume resuscitation while considering intracranial hemodynamics and ICP.

Isotonic crystalloid solutions (preferably 0.9% saline) are often the first solutions to be infused in hypotensive trauma patients, because they are readily available and inexpensive. If the initial evaluation suggests intracranial hypertension, mannitol (0.5 g/kg) may also be appropriate. Fresh whole blood, arguably the ideal fluid for patients in hemorrhagic shock, is not available in most centers, owing to the need to test all donated blood for infectious agents and the commitment that blood banks have made to fractionating donated units into their various components (platelets, plasma, red cells, etc.). Packed red blood cells resuspended in 0.9% saline or thawed FFP are suitable alternatives. Unfortunately, dilution with FFP increases the recipient's exposure to multiple donors and the attendant risks of transfusion reactions and infectious complications.

Although not yet considered a standard of care, hypertonic saline solutions may be useful in certain situations. In the presence of hypovolemia accompanied by intracranial hypertension, or when large volumes of isotonic crystalloid solutions are not available or cannot be rapidly infused, the use of hypertonic saline appears to be an attractive option. Extensive animal experience supports the efficacy of hypertonic solutions in reversing shock and, usually, decreasing ICP. In those few studies in which hypertonic saline did not reduce ICP (51), it is likely that the BBB was diffusely damaged by trauma or ischemia. In such cases, it is also unlikely that mannitol will be efficacious in reducing ICP. Hypertonic saline solutions have been extensively studied for prehospital resuscitation and are currently being used for prehospital resuscitation of hypovolemic, TBI patients in Europe. Whether this approach will gain popularity in the United States remains to be seen.

Diabetes Insipidus

Neurogenic diabetes insipidus may occur in patients with lesions in the vicinity of the hypothalamus, after pituitary surgery, or after TBI. This syndrome is characterized by a failure of the neurons located in the supraoptic nuclei of the hypothalamus to release sufficient quantities of anti-diuretic hormone (ADH) (vasopressin) into the systemic circulation. Diabetes insipidus is characterized by the production of large volumes of dilute urine in the face of a normal or elevated plasma osmolality. In severe cases, urinary output can exceed 1 L/hr. Left untreated or unrecognized, diabetes insipidus can quickly result in severe hypernatremia, hypovolemia, and hypotension. To promptly make the diagnosis of diabetes insipidus, it is important to have a high index of suspicion when dealing with patients at risk. Confirmation may be obtained by documenting elevated serum osmolality and $[Na^+]$ in conjunction with a low urinary specific gravity or osmolality. Vigorous volume expansion should be accomplished. Because of the preexisting hyperosmolar/hypernatremic state, 0.9% saline may actually reduce serum $[Na^+]$. As a caution, rapid increases in serum $[Na^+]$ are quickly compensated for by generation of intracellular idiogenic osmoles that preserve cerebral ICV; therefore, if therapy too rapidly reduces serum $[Na^+]$, cerebral edema will result. Concomitantly, replacement of endogenous ADH should be initiated with either aqueous vasopressin (5–10 units by intravenous or intramuscular injection) or desmopressin (DDAVP) 1 to 4 g subcutaneously or 5 to 20 g intranasally every 12 to 24 hours. DDAVP lacks the vasoconstrictor effects of vasopressin and is less likely to produce abdominal cramping (52). Incomplete ADH deficits (partial diabetes insipidus) often are effectively managed with pharmacological agents that stimulate ADH release or enhance the renal response to ADH. The combination of chlorpropamide (100–250 mg/day) and clofibrate or a thiazide diuretic has proven effective in patients who respond inadequately to either drug alone.

Patients at Risk for Cerebral Ischemia

In patients at risk for cerebral ischemia, the most important concept related to fluid administration is hemodilution. Cerebral perfusion can be improved by reducing blood viscosity with hemodilution. Hypervolemic hemodilution with dextran produces small, statistically insignificant increases in CBF in animals with normal cerebral vasculature (53). Although moderate hemodilution appears to be beneficial, marked decreases in hematocrit may be deleterious. In rabbits hemodiluted to a Hgb of 6 or 11 g/dL after embolization of the MCA, the authors found that profound hemodilution (Hgb of 6 g/dL) resulted in larger infarcts in both the cortex and subcortex (54).

The Scandinavian Stroke Study Group, which randomized 373 patients to receive either conventional therapy or normovolemic hemodilution after stroke, demonstrated an increased incidence of cardiovascular complications and an increased early mortality among hemodiluted patients (55). The Italian Acute Stroke Study Group randomized 1267 patients to receive conventional therapy or normovolemic hemodilution and found no difference in the outcome (56). However, both studies were constrained by the cardiovascular risk of volume expansion. In contrast, the Hemodilution in Stroke Study Group used invasive cardiovascular monitoring to guide hypervolemic hemodilution with pentastarch and increase cardiac output in patients with acute ischemic stroke (57). Although overall mortality and neurologic outcome were not superior in the hemodilution group, neurologic outcome was apparently improved in patients who were entered into the trial within 12 hours of the onset of stroke and in whom cardiac output increased by 10% or more.

Although no firm recommendation can be attached to the use of hemodilution in patients at risk for cerebral ischemia, it is certainly reasonable to avoid hypovolemia and the attendant risks of hypotension and hemoconcentration.

Cerebral Aneurysms and Vasospasm

Patients who present for surgery after rupture of a cerebral aneurysm require careful consideration of fluid management. Cerebral vasospasm is a leading cause of morbidity in these patients, producing death or severe disability in approximately 14% of patients who survive rupture of their aneurysm, and angiographic evidence of vasospasm occurs in as many as

60% to 80% of patients after Subarachnoid hemorrhage (SAH) (58). Arteriography in patients who have vasospasm demonstrates luminal irregularities in large conducting vessels, although these are not the major sites of precapillary resistance. CBF is not reduced until the angiographic diameter of the cerebral arteries is decreased by 50% or more, compared to normal. The intraparenchymal cerebral resistance vessels tend to dilate after the onset of spasm of the larger vessels, thus partially compensating for increased upstream resistance. ICP and cerebral blood volume may actually increase during vasospasm, owing to dilation of cerebral capacitance vessels (veins) and accumulation of tissue edema resulting from cerebral ischemia (59).

The incidence of vasospasm reaches a peak between the 4th and 10th days after SAH. Three to nine days after SAH, the patient with symptomatic vasospasm will characteristically become disoriented and drowsy over a period of hours. Focal deficits may follow. Vasospasm is presumed to be the cause if recurrent hemorrhage, mass lesions, intracranial hypertension, meningitis, or metabolic encephalopathy can be excluded through proper diagnostic studies. The diagnosis may be confirmed by angiography or documentation of high-velocity flow patterns by Doppler examination of the cerebral vessels.

Two currently accepted therapeutic interventions may decrease the incidence or severity of vasospasm. The first of these is hypervolemic-hyperdynamic therapy. Theoretical evidence supporting the need for volume expansion includes the observation that after SAH, 10% to 33% of patients develop hyponatremia, associated with negative sodium balance and intravascular volume contraction (60). Hyponatremic patients are more likely to develop vasospasm.

In patients suffering from neurologic impairment secondary to vasospasm, volume loading in conjunction with inotropic support can reverse or reduce neurologic morbidity. In one series, prophylactic volume expansion was associated with outcomes as good as those achieved with prophylaxis with calcium-channel blockers (61). Although no large clinical trials have used a controlled randomized design to compare volume expansion with other therapies for symptomatic vasospasm, clinical reports provide circumstantial evidence of the efficacy of hypervolemia and induced hypertension in treating vasospasm. One algorithm for producing hypervolemia and increasing cerebral perfusion pressure consists of pulmonary artery catheterization and infusion of fluid, either saline or colloid, to increase the PAOP to approximately 15 mmHg. Associated therapeutic goals include a CVP of approximately 10 mmHg, a systolic blood pressure of approximately 180 mmHg (a MAP \sim 130 mmHg), and adequate CaO_2 , defined as a Hgb concentration of 11 g/dL and an oxyhemoglobin saturation of 95% or more. If volume expansion does not achieve these hemodynamic goals, vasopressors such as phenylephrine or dopamine are added. Using this protocol, most neurologic deficits attributed to vasospasm improve within one to four hours. While the use of pulmonary arterial catheterization permits more precise quantification of systemic responses to hypervolemic therapy, central venous catheterization may provide adequate monitoring information in patients who have normal cardiovascular function. In patients with no history of heart disease, a PAOP of 14 mmHg is associated with maximum cardiac performance (62). Volume expansion beyond this point will increase PAOP, but probably will not increase cardiac index (62).

COMMON PERIOPERATIVE ELECTROLYTE ABNORMALITIES IN NEUROSURGICAL PATIENTS

Neurologic surgery is associated with disorders of both total body sodium and $[\text{Na}^+]$. Increases or decreases in total body sodium, the principal extracellular cation and solute, tend to increase or decrease ECV and PV. Disorders of $[\text{Na}^+]$, i.e., hyponatremia and hypernatremia, usually result from relative excesses or deficits, respectively, of water. This chapter discusses these entities in limited detail. Sodium concentration is primarily regulated by ADH, which is secreted in response to increased osmolality or decreased blood pressure. ADH stimulates renal reabsorption of water, diluting plasma $[\text{Na}^+]$; inadequate ADH secretion results in renal free-water excretion, which, in the absence of adequate water intake, results in hypernatremia. In response to changes in plasma $[\text{Na}^+]$, changes in secretion of ADH can vary urinary osmolality from 50 to 1400 mOsm/kg and urinary volume from 0.4 to 20 L/day.

Hyponatremia

The signs and symptoms of hyponatremia depend on both the rate and severity of the decrease in plasma $[\text{Na}^+]$. Symptoms usually accompany $[\text{Na}^+]$ of 120 mEq/L or less. Because the BBB is poorly permeable to sodium but freely permeable to water, a decrease in plasma $[\text{Na}^+]$ promptly increases both extracellular and intracellular brain water. Acute CNS manifestations relate to increases in brain water content. Compensatory responses to cerebral edema include bulk movement of interstitial fluid into the cerebrospinal fluid and loss of intracellular solutes, including potassium and organic osmolytes (previously termed "idiogenic osmoles") (63). Because the brain rapidly compensates for changes in osmolality, the symptoms are more severe in acute than in chronic hyponatremia. In chronic hyponatremia, rapid correction of plasma $[\text{Na}^+]$ to normal values may lead to abrupt decreases in brain water content and volume.

Hyponatremia ($[\text{Na}^+] < 135 \text{ mEq/L}$) with a normal or high serum osmolality results from the presence of a nonsodium solute, such as glucose or mannitol, which does not diffuse freely across cell membranes. The resulting osmotic gradient results in dilutional hyponatremia. A discrepancy exceeding 10 mOsm/kg between measured and calculated osmolality suggests either factitious hyponatremia or the presence of a nonsodium solute. In the practice of neurosurgical anesthesiology, hyponatremia with a normal osmolality could be seen in patients after administration of mannitol, but before urinary excretion had occurred.

Hyponatremia with hyposmolality, which may occur with high or low total body sodium, is evaluated by assessing BUN, SCr, total body sodium content, urinary osmolality, and urinary $[\text{Na}^+]$. Increased total body sodium characteristically accompanies hyponatremia in edematous states, i.e., congestive heart failure, cirrhosis, nephrosis, and renal failure. Reduced urinary diluting capacity in patients with renal insufficiency can lead to hyponatremia if excess free water is given, as may occur with perioperative administration of hypotonic fluids. In hyponatremia with low total body sodium content (hypovolemia), volume-responsive ADH secretion sacrifices tonicity to preserve intravascular volume.

Euvolemic hyponatremia, associated with a relatively normal total body sodium and ECV, is almost invariably due to the syndrome of inappropriate ADH secretion (SIADH). Euvolemic hyponatremia is usually associated with excessive ectopic ADH secretion (as occurs with certain neoplasms), excessive hypothalamic-pituitary release of ADH (secondary to intracranial pathology, stress, pulmonary disease, or endocrine abnormalities), exogenous ADH administration, pharmacologic potentiation of ADH action, or drugs that mimic the action of ADH in the renal tubules.

Treatment of hyponatremia associated with a normal or high serum osmolality requires reduction of the elevated concentrations of the responsible solute (Figs. 4 and 5). Treatment of edematous (hypervolemic) patients necessitates restriction of sodium and water, and is directed toward improving cardiac output and renal perfusion and using diuretics to inhibit sodium reabsorption. In hypovolemic, hyponatremic patients, blood volume must be restored, usually by infusion of 0.9% saline, and excessive sodium losses must be curtailed. Correction of hypovolemia usually results in removal of the stimulus for ADH release, accompanied by a rapid water diuresis.

The cornerstone of SIADH management is free-water restriction and elimination of precipitating causes. Water restriction, sufficient to decrease TBW by 0.5 to 1.0 L/day, decreases ECV, even if excessive ADH secretion continues. The resultant reduction in glomerular filtration rate (GFR) enhances proximal tubular reabsorption of salt and water, thereby decreasing free-water generation, and stimulates aldosterone secretion. If renal, cutaneous, and gastrointestinal losses exceed free-water intake, serum $[\text{Na}^+]$ will increase. Free-water excretion can be increased by administering furosemide. In patients who have seizures or who acutely develop symptoms of water intoxication, 3% saline can be administered at a rate of 1 to 2 mL/kg/hr, to increase plasma $[\text{Na}^+]$ by 1 to 2 mEq/L/hr; however, this treatment should not continue for more than a few hours. Even symptomatic hyponatremia should be corrected cautiously. Although delayed correction may result in neurologic injury, inappropriately rapid correction may result in abrupt brain dehydration, central pontine myelinolysis, cerebral hemorrhage, or congestive heart failure. To limit the risk of myelinolysis, plasma $[\text{Na}^+]$ may be increased by 1 to 2 mEq/L/hr; however, plasma $[\text{Na}^+]$ should not be increased more than 12 mEq/L in 24 hours or 25 mEq/L in 48 hours (64).

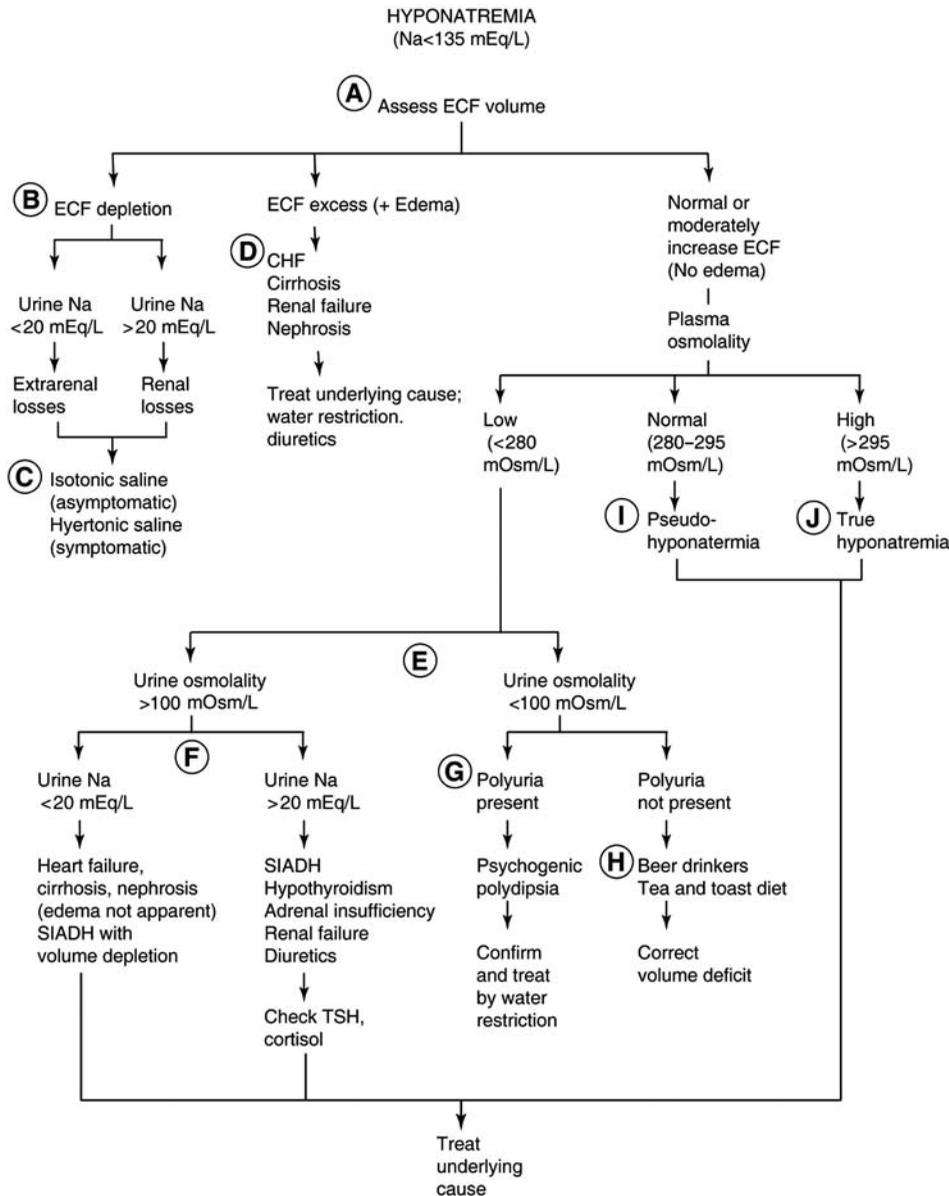


Figure 5 Flow chart for treatment of hyponatremia. *Abbreviations:* CHF, congestive heart failure; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Hypernatremia

Hypernatremia also produces neurologic symptoms (including stupor, coma, and seizures) in addition to hypovolemia, renal insufficiency, and decreased urinary concentrating ability. Because hypernatremia frequently results from diabetes insipidus or osmotically induced losses of sodium and water, many patients are hypovolemic or azotemic. Postoperative neurosurgical patients who have undergone pituitary surgery are at particular risk of developing transient or prolonged diabetes insipidus. Polyuria may be present for only a few days within the first week of surgery, may be permanent, or may demonstrate a triphasic sequence: early diabetes insipidus, return of urinary concentrating ability, then recurrent diabetes insipidus. The clinical consequences of hypernatremia are most serious at the extremes of age and when hypernatremia develops abruptly. Brain shrinkage may damage delicate cerebral vessels, leading to subdural hematoma, subcortical parenchymal hemorrhage, SAH, and venous

thrombosis. Polyuria may cause bladder distention, hydronephrosis, and permanent renal damage. At the cellular level, restoration of cell volume occurs remarkably quickly after tonicity is altered (65).

By definition, hypernatremia ($[\text{Na}^+] > 150 \text{ mEq/L}$) indicates an absolute or relative water deficit and is always associated with hypertonicity. Because hypovolemia accompanies most pathologic water loss, signs of hypoperfusion also may be present. In many patients, before the development of hypernatremia, an increased volume of hypotonic urine suggests an abnormality in water balance (66). The TBW deficit can be estimated from the plasma $[\text{Na}^+]$ using the equation:

$$\text{TBW deficit} = 0.6 (\text{weight in kg}) [(\text{actual } [\text{Na}^+] - 140)/140] \quad (5)$$

Treatment of hypernatremia produced by water loss consists of repletion of water as well as associated deficits in total body sodium and other electrolytes. Hypernatremia must be corrected slowly because of the risk of neurologic sequelae such as seizures or cerebral edema (67). The water deficit should be replaced over 24 to 48 hours, and the plasma $[\text{Na}^+]$ should not be reduced by more than 1 to 2 mEq/L/hr.

The management of hypernatremia secondary to diabetes insipidus varies according to whether the etiology is central or nephrogenic. As noted earlier, the two most suitable agents for correcting central diabetes insipidus (an ADH deficiency syndrome) are DDAVP and aqueous vasopressin.

SUMMARY

Appropriate fluid therapy in patients with neurologic disorders requires an understanding of the basic physical principles that govern the distribution of water between the intracellular and extracellular compartments. In the CNS, unlike peripheral tissues, osmolar gradients are the primary determinants of the movement of water. Changes in serum oncotic pressure have negligible effects on brain water content. In contrast, administration of hypertonic solutions (e.g., 20% mannitol) results in a "dehydration" of normal brain tissue with a concomitant decrease in cerebral volume and ICP. Various monitoring modalities may help the clinician in the assessment of intravascular volume. Fluid administration should never be restricted to the point that cardiac output and blood pressure are compromised. Arterial hypotension after brain injury is an ominous sign that correlates with a marked increase in morbidity and mortality. In addition to management of intravascular volume, fluid therapy often must be modified to account for disturbances of $[\text{Na}^+]$, which are common in patients with neurologic disease.

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21 | Fluid Therapy in the Intensive Care Unit

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INTRODUCTION

Fluid therapy is one of the most important components of supportive care administered in the intensive care unit (ICU). The difference between a routine hospital course and one complicated by organ failure is often determined by decisions related to fluid management. Patients with primarily medical disorders often have the disadvantage of harboring infections or other disease processes for days or more, prior to receiving aggressive therapy in an ICU. Surgical patients often are ambulatory prior to their operations; therefore, while the operations themselves may be sources of considerable stress, an opportunity exists to optimize the patient's physiology closer to the time of injury, and create a better outcome. This chapter will address issues related to fluid therapy in the critically ill, with an emphasis on patients after major surgery. Physiology related to fluid distribution will first be reviewed, and choices of fluid and preoperative and postoperative resuscitation strategies will then be discussed.

PHYSIOLOGY

Fluid Balance

Water comprises 60% of the lean body mass. Behavior, thirst, and neuroendocrine mechanisms attempt to match the loss of fluids to their intake. The normal physiologic economy of fluids readily adapts to a range of conditions, including exercise, variability in water and solute intake, and injury. In the steady state, homeostatic mechanisms achieve a balance of fluids between different aqueous compartments. Of total body water (TBW), two-thirds is intracellular, and the other third is shared between the interstitial (25% of TBW) and intravascular (8% TBW) compartments. The relative representation of these compartments to body water, as well as the percent body mass that is water, can vary dramatically depending on the etiology and chronicity of a disease process. Infused fluids interact with these compartments in a predictable manner. Free water (including 5% dextrose solution) distributes evenly throughout all three compartments. Crystalloids such as "normal" saline (NS) and lactated Ringers (LR) rapidly equilibrate between the interstitial and intravascular compartments, while normal capillary barriers keep red blood cells, exclusively, and colloids, primarily, in the intravascular space.

Restoration of fluid homeostasis requires an understanding of individual sources of fluid loss and a replacement strategy that takes these factors into account. For example, acute hemorrhage causes an immediate depletion of intravascular fluid, red blood cells, and plasma protein. If their replacement is not immediate, interstitial fluids will shift to the intravascular compartment. Intracellular fluid may also increase from isotonic movement of water and solutes from the interstitium.

Critically ill patients typically have an expanded interstitial space, which manifests as dependent edema and anasarca. Cellular injury, infection, and inflammation all increase capillary permeability and the Starling equilibrium of transcapillary fluid flux. Thus, a patient who appears to be "total body" overloaded with fluid may still require continued fluid administration to achieve and maintain adequate intravascular volume until the acute process subsides. Further, positive pressure mechanical ventilation can stimulate the renin-angiotensin-aldosterone system

Table 1 Calculation of Oxygen Transport and Utilization Variables

Variable	Calculation
DO ₂	CO × CaO ₂
VO ₂	CO × (CaO ₂ - CvO ₂)
CaO ₂	(1.34 × Hb × SaO ₂) + 0.0031 PaO ₂
O ₂ ER	VO ₂ /DO ₂ = (CaO ₂ - CvO ₂)/CaO ₂

Note: Indices for cardiac output and oxygen delivery (CI and DO₂I) are calculated by dividing CO and DO₂ by body surface area.

Abbreviations: DO₂, oxygen delivery; CI, cardiac index; CO, cardiac output; CaO₂, arterial oxygen content; VO₂, oxygen utilization; CvO₂, mixed venous oxygen content; Hb, hemoglobin; SaO₂, hemoglobin saturation; DO₂I, DO₂ index.

to retain fluid and sodium, regardless of the underlying pathology. An ideal hospital course may therefore require an initial phase of positive fluid balance to maintain hemodynamic stability, a second stage of even fluid balance, and, finally, a stage with a spontaneous or induced diuresis associated with remobilization of interstitial fluid. However, in critically ill patients, plasma protein levels are often not sufficient for several weeks to allow rapid mobilization of interstitial fluid.

Tissue Oxygen Balance

Tissue oxygen delivery (DO₂) is the product of cardiac output (CO) and arterial oxygen content (Table 1). Under normal conditions, oxygen consumption (VO₂) is relatively independent of DO₂ until DO₂ decreases below a critical value (1). Figure 1 describes this general relationship.

The relationship between VO₂ and DO₂ may be altered in a number of conditions, particularly cellular dysfunction resulting from shock. Blood loss, dehydration, and cardiopulmonary failure can all compromise DO₂. As DO₂ decreases in the supply-independent region (i.e., the flat portion of the curve where VO₂ is not limited by DO₂), the oxygen extraction ratio increases so that VO₂ remains constant (Fig. 1). In general, a decrease in mixed venous oxygen saturation to values less than 70% reflects increases in oxygen extraction. The value of DO₂ that divides the supply-dependent and supply-independent regions is termed the critical DO₂. In normal anesthetized patients, the critical DO₂ is approximately 330 mL/min/m². When DO₂ decreases in the supply-dependent region, it limits mitochondrial respiration so that a transition to anaerobic metabolism occurs and lactic acid is produced, corresponding to a VO₂ of approximately 110 mL/min/m² (2). In general, patients with a DO₂ value in the supply-dependent region have lactic acidosis, while patients with a DO₂ value in the supply-independent region do not (3). Among critically ill patients, there is no easily defined threshold value of DO₂ or VO₂; as stress or sepsis alters VO₂, the critical DO₂ may vary between patients and over time (4). In instances in which the clinician is faced with inadequate oxygen supply due to increased demand, sedation, ventilatory support, and paralysis warrant consideration as means to minimize VO₂.

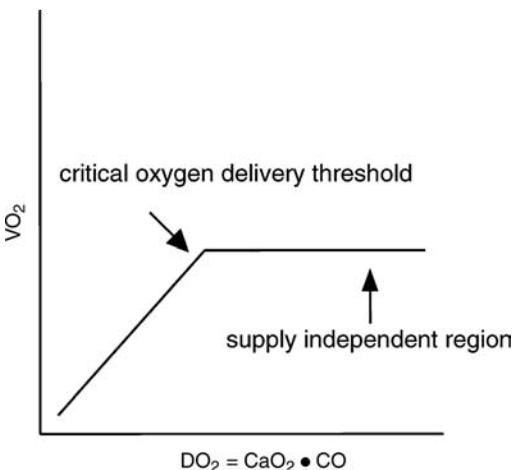


Figure 1 The relationship between oxygen delivery (DO₂) and oxygen consumption (VO₂). Normally, decreases in hemoglobin concentration are compensated by increasing cardiac output and the oxygen extraction ratio without decreasing oxygen consumption. Decreases in cardiac output also are compensated by increasing the oxygen extraction ratio without decreasing oxygen consumption. For example, mild blood loss will cause leftward movement through the supply-independent region, without limiting oxidative metabolism. Decreases in DO₂ below a critical value can create a supply/demand imbalance, leading to anaerobic metabolism and cellular oxygen starvation that will progress to organ dysfunction if not rapidly reversed.

Serum Albumin and the Starling Equilibrium

The Starling equilibrium describes fluid flux across a semipermeable membrane according to the following equation:

$$J_v = K_f [(P_{\text{vas}} - P_{\text{int}}) - \sigma(\pi_{\text{vas}} - \pi_{\text{int}})]$$

where J_v = fluid flux, K_f = capillary filtration coefficient, P_{vas} = vascular hydrostatic pressure, P_{int} = interstitial hydrostatic pressure, σ = Staverman reflection coefficient, π_{vas} = vascular oncotic pressure, and π_{int} = interstitial oncotic pressure.

Predictions of fluid movement based on this equilibrium have been the focal point of arguments regarding the use of crystalloid and colloid solutions to meet resuscitative goals. The Starling equation is often simplified as the difference between the net hydrostatic and the net oncotic pressure, but this does not account for the role of σ (see discussion below). In the normal lung, P_{vas} and π_{int} have positive values and P_{int} is negative, so that π_{vas} is the only force that acts to maintain fluid in the intravascular space. In the normal lung, the net Starling balance is slightly positive so that there is continuing movement of fluid from the intravascular space to the interstitial space where it is drained by lymphatics.

Under normal conditions, albumin is responsible for 60% to 80% of the total colloid osmotic pressure (COP). Forty years ago, Guyton demonstrated that pulmonary edema occurred at lower left atrial pressures when COP was decreased (5). Multiple subsequent studies using plasmapheresis to decrease COP have confirmed this finding (6–8). Observational studies have clearly demonstrated that patients with lower albumin concentrations or COP have an increased incidence of pulmonary edema and lung dysfunction (9). Decreased COP may result not only in pulmonary edema, but also in edema of other organs such as the heart, brain, gut, kidney, and skin, leading to diastolic myocardial dysfunction, altered mental status, decreased bowel motility, increased intestinal permeability, renal dysfunction, and decreased wound healing. Decreased COP is a strong predictor of organ dysfunction, complications, length of stay, and mortality (9). Based on a review of the literature, Goldwasser et al. concluded that the risk of death increased 24% to 56% for each 2.5 g/L (0.25 g/dL) decrease in albumin (10).

Although multiple studies have demonstrated that albumin, COP, and the gradient between pulmonary artery occlusion pressure (PAOP) and COP correlate with the development of pulmonary edema and organ dysfunction, it remains controversial whether the decrease in COP is the major etiologic factor or is simply a marker for severity of illness. Serum albumin concentrations decrease during critical illness due to decreased synthesis of albumin and leakage of albumin across the endothelium (9,11,12). Thus, even if COP itself does not affect outcome, the lowest values would be expected to occur in the sickest patients with the highest mortality. Mangialardi et al. demonstrated that low serum protein levels were highly predictive of the development of the acute respiratory distress syndrome (ARDS) and death among patients with sepsis (13).

FLUID TYPES, CHARACTERISTICS, AND CONTROVERSIES

Characteristics of crystalloid and colloid resuscitative solutions commonly used in the United States are summarized in Table 2. Choices regarding their use are often based on the desire to control the distribution of water and solutes between intravascular and interstitial compartments. As will be shown below, the normal physiology of transcapillary fluid flux often does not predict the accumulation of fluids in critical illness. Fortunately, the results of several outcome studies and meta-analyses have helped guide decision-making with regards to fluid selection and use.

Crystalloid Solutions

Crystalloids are solutions that contain water and simple solutes. Preparations vary according to tonicity and electrolyte concentrations relative to plasma. Crystalloids are universally used either alone or with other solutions to replace loss or redistribution of water, solutes, and blood. The distribution of crystalloids throughout the vascular, interstitial, and intracellular spaces depends on their solution concentration relative to plasma (14). For example, volumes

Table 2 Composition of Fluids for Intravenous Administration

Solution	Composition (mEq/L)					Osmolality	Cautions	Cost ^a (US\$)
	Na	Cl	K	Ca	Buffer/other			
<i>Crystalloids</i>								
LR	130	109	4	3	Lactate	273	Hyperkalemia	0.89
NS (0.9% NaCl)	154	154				308	Metabolic acidosis	0.72
D5W	0	0			Glucose 50 g/L	252	Free water	
D5W 0.45% NaCl	77	77			Glucose 50 g/L	406		
7.5% NaCl	1283	1283				2567	Metabolic acidosis	
<i>Colloids</i>								
Dextran-40 (10%)	154	154				310	Allergy, bleeding	24
Albumin 5%	154	154			Carbonate, acetate	–	Safety in trauma	80–360
Albumin 25%	154	154				120–500		400–1100
Hetastarch	154	154				310	Coagulopathy	25–50

Note: Information on composition from package inserts.

^aWholesale price range for VA Palo Alto and Stanford University Hospitals.

Abbreviations: LR, lactated Ringers; NS, normal saline.

of LR and NS three to four times that of blood loss are required to maintain the same intravascular volume. Replacement of free water is often accomplished by using dilute forms of NS (i.e., 0.45% saline and 0.225% saline); the distributions of water and solutes follow the physiologic principles noted earlier. Thus, if 1 L of 0.45% saline is infused intravascularly, 500 mL will behave like free water and distribute throughout all aqueous compartments, and 500 mL will distribute as if it were NS—with 375 mL equilibrating with the interstitial space and 125 mL with the intravascular space. For 1000 mL 0.225% saline, only 165 mL will remain in the intravascular space (25% from the NS contribution and 8% from free water). The vast majority of crystalloid use involves either 0.9% NS or LR solutions. These and other preparations are described in Table 2.

Five Percent Dextrose Solution (D5W)

D5W provides a vehicle for replacing glucose and free water. Because D5W is iso-osmotic, intravenous administration of D5W does not produce hemolysis, as would occur with free water infusion. Typical uses of D5W are correction of hypernatremia and provision of glucose to patients who have received insulin. Frank hypoglycemia should be managed with administration of 50% dextrose solution. Combinations of dextrose with LR and with full-, half-, and quarter-strength saline are available and may be used as indicated by plasma tonicity and glucose concentration. In the past, many physicians used 5% dextrose and 0.45% saline as a “maintenance” fluid postoperatively. With recent data demonstrating decreased mortality and decreased multiple organ system failure with tight glucose control (15), the practice of routine glucose administration should be avoided.

Normal Saline

NS contains both sodium and chloride at 154 mM, with no other solutes or buffers. NS is used preferentially in the settings of hyponatremia and hypochloremic metabolic alkalosis, and in hyperkalemic patients who cannot tolerate additional potassium (as with LR). NS is generally preferred to LR in the setting of head injury, due to the relatively hypotonic sodium concentration of the latter. Despite being isotonic and iso-osmotic, the chloride anion exceeds plasma concentrations and will increase the latter in proportion to the volume infused. NS, as with all solutions having equal concentrations of sodium and chloride ions, can cause hyperchloremic nonanion gap metabolic acidosis (16). This problem is most prominent when large volumes of NS or hypertonic saline (HS) are used.

Lactated Ringers Solution

LR is a balanced salt solution with sodium, potassium, and chloride concentrations similar to plasma. Calcium and a lactate buffer are also present, with the latter readily metabolized. Some avoid infusing LR through the same intravenous line as banked blood, due to the theoretical risk of calcium-induced microaggregation of red blood cells (rouleaux formation). For the same reason, banked red blood cells usually are reconstituted in NS.

Hypertonic Saline

These preparations carry the advantage of a lower total volume requirement to achieve a given extent of intravascular expansion. In principle, as serum sodium increases, intracellular water moves from the intracellular to extracellular space to normalize plasma tonicity and ionic gradients. HS may be used during prehospital resuscitation, as well as for a maintenance fluid. Potential advantages when used for resuscitation include augmented intravascular volume expansion with limited volume administration and decreased cerebral edema and intracranial hypertension (17). Additional benefits may include decreased inflammation, increased myocardial contractility, and improved microcirculatory flow (18,19). Younes et al. demonstrated improved survival (73% vs. 64%) in patients with traumatic hemorrhagic shock (20). In a meta-analysis of six studies of HS administration in hypotensive trauma patients, Wade et al. (21) were unable to demonstrate any significant difference in mortality. Additional studies are required to define the role of HS, with or without colloid, in the treatment of hemorrhagic shock.

HS may also be administered in combination with dextran. Of the eight studies that examined HS–dextran administration, seven studies demonstrated a trend toward improved survival (odds ratio of 1:20 with an absolute 4% increase in survival). Wade et al. (21) concluded that HS alone was not different from standard care, but that HS–dextran may be superior. In an analysis based on individual patient cohort data from prospective randomized trials, HS–dextran improved survival to discharge (38% vs. 27%; odds ratio of 2:12) (22). Similarly, in a different meta-analysis, the use of combination hypertonic crystalloid–colloid versus isotonic crystalloid alone decreased mortality (relative risk 0.84) (23). Subsequent studies focusing on patients with traumatic brain injury have produced conflicting results on the utility of HS versus crystalloid for the management of patients with traumatic brain injury (24,25).

Hydroxyethyl Starch and Other Colloids

Colloids vary markedly in their size, number average molecular weight (the arithmetic mean of all particle molecular weights), and the weight average molecular weight (the sum of the number of molecules at each weight times the particle weight divided by the total weight of all molecules). Monodisperse solutions, such as albumin, have one size of particle so that weight average and the number average molecular weight are similar. Polydisperse solutions have a diverse range of molecular sizes and shapes, causing disparity between the weight average and the number average molecular weight. There are many colloid suspensions available with varying molecular sizes, half-lives, COPs, side effects, and costs (9). Studies have suggested that the effects of different colloids may be different.

Dextrans and Gelatins

Dextrans are composed of linear polysaccharide molecules whose molecular weight ranges from 10 to 90 kDa. Dextrans can improve microvascular circulation by lowering blood viscosity and by coating vascular endothelial cells to minimize platelet and red blood cell aggregation. However, dextrans may produce bleeding by the same mechanism and are associated with a 1% to 5% risk of anaphylaxis. Gelatins are polypeptides with a molecular weight of 35 kDa. They have limited utility as plasma expanders due to rapid migration from the intravascular space.

Hydroxyethyl Starch (Hetastarch)

Hetastarch compounds are synthetic polymers derived from amylopectin, a branched polysaccharide polymer. The attachment of hydroxyethyl ether groups to the glucose units in hetastarch slows degradation by serum amylase (26). The pharmacokinetic properties of hydroxyethyl starch (HES) are directly related to the size and the molar substitution ratio (the number of hydroxyethyl groups per molecule of glucose). A higher degree of substitution results in slower breakdown and elimination of the molecule. Particles less than 50 kDa are filtered by the kidneys within 48 hours, while larger particles are hydrolyzed by amylase and then excreted in urine and bile, or phagocytized by the reticuloendothelial system. The standard HES solution used in the United States (HES 450/0.7) has a high weight average molecular weight (450 kDa) and a high molar substitution ratio (0.7). Pentastarch is a modified HES, which is diafiltered to eliminate molecules outside a strict size range (10–1000 kDa). Pentafraction is even more homogeneous than pentastarch, with molecular weights ranging from 100 to 500 kDa. Studies suggest that adverse effects are minimized with the more

homogeneous solutions (14,27–31). A modified HES solution (HES 200/0.5) with a medium molecular weight and molar substitution ratio similar to pentastarch has been used in Europe. Previous studies have shown both medium- and high-molecular-weight starches to be as effective as 5% albumin when used for volume replacement (32). Current recommendations limit the maximum dose of HES to 20 mL/kg/day due to concerns of adverse effects on hematological, immunological, renal, and reticuloendothelial function (33,34). These limitations may not apply to the medium weight hetastarch preparations. Vogt et al. demonstrated that HES 200/0.5 at doses significantly greater (20–36 mL/kg) than those recommended for traditional HES therapy did not adversely affect hemodynamics, renal function, coagulation parameters, or total blood loss (28). Similar benefits may apply to a HES 130/0.4 solution (29–31) and to a new acetyl starch solution (34).

Hetastarch is as effective as albumin for volume expansion. However, studies have suggested that HES administration may adversely affect coagulation. Observed coagulation abnormalities include decreased Factor VIII and von Willebrand factor levels (35,36). The use of hetastarch has therefore been controversial in procedures such as cardiac surgery, which are likely to have coagulation abnormalities (37). Herwaldt et al. (38) identified the use of greater than 5 mL/kg of hetastarch as a risk factor (odds ratio 1:82) for hemorrhage after cardiac surgery; the costs of treating hemorrhage markedly exceeded any possible cost savings related to the substitution of HES for albumin. Similarly, Knutson et al. (39) identified the use of hetastarch as a factor resulting in increased hemorrhage and blood transfusion requirements after cardiac surgery. However, not all studies have demonstrated problems with HES. Recently, Canver and Nichols (40) demonstrated that the use of 500 mL of HES versus albumin did not influence the need for blood transfusion, ICU and hospital length of stay, and mortality.

In addition to causing fewer adverse effects, medium weight HES may improve physiology in inflammatory states by plugging leaky vasculature, decreasing release of vasoactive mediators, and improving microcirculatory flow by decreasing blood viscosity and maintaining plasma volume (41–43). Animal studies demonstrate decreased microvascular permeability, decreased inflammation, decreased neutrophil activation, and decreased ischemia–reperfusion injury (44,45). Studies have demonstrated preservation of microvascular architecture in septic animals treated with medium-molecular-weight starches compared to crystalloids (41) and higher-molecular-weight HES (42). Traber et al. (43) demonstrated that medium-molecular-weight starches decreased lung lymph flow after endotoxin administration in septic sheep. In an attempt to determine if these potential benefits applied to critically ill patients, Boldt et al. (46) randomized critically ill patients to treatment with modified 10% HES (COP 66 mmHg) versus 20% albumin (COP 78 mmHg) for volume replacement over five days. Cardiac index (CI), DO_2 , and VO_2 significantly increased only in the HES patients. Septic patients treated with HES had a significant increase in the PaO_2/FiO_2 ratio, suggesting improved pulmonary function. Patients treated with HES had decreasing APACHE II scores, indicating decreasing severity of illness and risk of death. The septic patients treated with albumin had a decrease in gastric intramucosal pH (pH_i), suggesting inadequate splanchnic perfusion; no such decrease occurred in the HES group. In a subsequent larger study, the same group demonstrated that HES was at least as effective as albumin, with no adverse effects on coagulation in both septic patients and trauma patients (47). Additional studies will define whether the medium weight hetastarch fluids are in fact a superior choice for resuscitation.

The Crystalloid Colloid Debate

Proponents of colloid solutions have emphasized the association between decreased COP and pulmonary dysfunction and mortality, and also have emphasized the greater increase in intravascular volume and the associated longer duration of intravascular volume expansion that occur with colloid solutions (48). The half-life of exogenously administered albumin is approximately 15 hours under normal conditions, but is markedly decreased during states of increased capillary permeability. Maintenance of stable hemodynamics requires two to six times the volume of crystalloid compared to colloid solutions (49,50).

The choice between crystalloid solutions for resuscitation can be considered separately for the cases of normal versus increased capillary permeability. When capillary permeability is normal, three potent antiedema safety factors minimize the risk of pulmonary edema, even with moderately increased capillary hydrostatic pressures. First, when capillary hydrostatic

pressure is increased, the increased fluid flux from the intravascular to the interstitial space involves primarily increased water and electrolyte movement; as a result, the protein concentration (π_{int}) in the interstitial space decreases and the COP gradient ($\pi_{\text{vas}} - \pi_{\text{int}}$) increases, tending to limit further fluid flux. Second, the increased fluid flux increases the interstitial hydrostatic pressure so that the hydrostatic pressure gradient ($P_{\text{vas}} - P_{\text{int}}$) decreases. Third, lymphatic drainage of low protein fluid can increase up to sevenfold so that accumulation of extravascular lung water is minimized. Thus, when capillary permeability is normal, there is likely to be little benefit from colloid resuscitation.

Analysis of influence of increased capillary permeability on accumulation of pulmonary edema involves understanding that the capillary filtration coefficient K_f is increased and the Starverman reflection coefficient σ is decreased. The increase in K_f indicates increased fluid filtration for a given net driving pressure. The decrease in σ has two effects. First, the effect of a given oncotic pressure gradient ($\pi_{\text{vas}} - \pi_{\text{int}}$) is decreased. More importantly, the actual interstitial oncotic pressure will increase. The equilibrium ratio of π_{int} to π_{vas} will vary inversely with σ . Thus, if σ decreases to 0.2 (a typical value for the pulmonary endothelium in acute lung injury, 1.0 representing complete impermeability), interstitial COP (π_{int}) will increase to 80% of intravascular COP (π_{vas}) and the oncotic pressure gradient ($\pi_{\text{vas}} - \pi_{\text{int}}$) will only be 20% of the plasma COP. Thus, attempts to increase the oncotic pressure gradient by colloid administration will have limited success in altering the Starling equilibrium. Some investigators have argued that colloid administration during the period of altered permeability will result in increased protein concentrations in the interstitial space, delaying resolution of edema once permeability has returned to normal.

These theoretical arguments have resulted in hundreds of animal and clinical studies. Despite this extensive investigation, no clear consensus has emerged. The University Health Care Consortium (UHC) guidelines published in 1995 supported the use of colloid solutions following initial crystalloid resuscitation (51). In contrast, the American College of Surgeons recommends the use of only crystalloid solutions for resuscitation of trauma patients (52). Despite these guidelines, the use of albumin remained high. Yim et al. reported that only 24% of albumin use at 15 academic medical centers met appropriate indications according to UHC guidelines (53).

Attempts to reconcile the multiple discrepant data on crystalloid versus colloid solutions have turned to the techniques of meta-analysis and evidence-based medicine. The findings from the largest and most comprehensive analyses are presented in Table 3. The meta-analysis by Schierhout and Roberts (23) has been criticized because it focused on colloids as a group rather than on specific colloids. However, randomized controlled trials have not usually demonstrated differences among colloids (59). In the meta-analysis, the colloids used included albumin in 381 patients, gelatin in 222, HES in 41, dextran in 652, plasma in 153, and combinations in 66. As a result, the Cochrane Injuries Group [Alderson et al. (56)] performed a subsequent meta-analysis of the specific fluids. This analysis suggested that the adverse effects identified in the initial report were not specific to the colloid used. In 18 albumin trials, mortality was increased from 11% to 17% (RR 1.52), in five HES trials, from 19% to 23% (RR 1.28), and in the eight dextran trials, from 18% to 27% (RR 1.24). Because albumin has been considered to be devoid of many of the adverse effects of other colloids, a subsequent meta-analysis of 30 randomized trials involving administration of albumin (rather than colloids in general) was also performed (58). The results were similar to those of the initial colloid meta-analysis. Albumin administration increased mortality for all three indications examined (hypovolemia, burns, and hypoalbuminemia) with odds ratios of 1:46, 2:40, and 1:69, with an overall increase in mortality from 10% without albumin to 16% with albumin. Thus, the current data available suggest that albumin administration should rarely, if ever, be used. Given the significant expense of albumin, this may be a hospital administrator's dream—a way to decrease costs while increasing survival.

The reasons for the increased mortality with albumin administration in these studies are not known, but may be related to albumin's relatively low molecular weight (69 kDa), which would allow it to leak into the extravascular space. The increased capillary permeability to albumin in sepsis may make this a particularly relevant complication. Additional possible adverse effects include the increased ability to produce fluid overload with albumin/colloid solutions, decreased myocardial contractility from calcium binding, increased blood loss from antihemostatic and antiplatelet effects, altered drug and endogenous protein binding,

Table 3 Meta-Analyses Comparing Mortality Associated with Crystalloid vs. Colloid Solutions

Author [year (Ref.)]	No. of studies	No. of patients	RR ^a	Comment
Velanovich [1989 (54)]	8	826	n.d.	5.7% increase in mortality with colloid (whole study)
<i>Trauma</i>	5	730	n.d.	12.3% increase in mortality with colloid
<i>Nontrauma</i>	2	50	n.d.	7.8% decrease in mortality with colloid
Schierhout [1998 (23)]	19	1315	1.29	Whole group analysis
<i>Trauma</i>	6	636	1.3	
<i>Surgical</i>	7	191	0.55	
<i>Burns</i>	4	416	1.21	
Choi [1999 (55)]	17	732	1.6	Whole group analysis
<i>Trauma</i>	5	302	2.56	
Alderson [2000 (52)] ^b				
<i>Albumin</i>	18	641	1.52	
<i>Hetastarch</i>	7	197	1.28	
<i>Dextran</i>	8	668	1.24	
Cochrane IG	24	1204	1.68	Whole group analysis
[1998 (57)] ^b				
<i>Burns</i>	3	163	2.40	
<i>Hypovolemia</i>	13	534	1.46	
<i>Hypoalbuminemia</i>	8	507	1.69	
Wilkes [2001 (58)] ^b	55	3504	1.11	Whole group analysis

^aRelative risk of mortality with colloid/crystalloid. Reciprocal of data reported by Choi et al. is presented here in order to conform to all other studies where a RR > 1 favored crystalloid.

^bDirect comparison between albumin and a crystalloid solution.

antioxidant effects, and altered immune responses. In addition, many of the early studies with albumin used production processes that may have permitted significant impurities such as endotoxins, aluminum ions, and prekallikrein activators (60).

Proponents of crystalloid solutions have emphasized their low cost and the demonstrated efficacy in expanding both intravascular volume and interstitial fluid. The latter point gained relevance from the work by Shires et al. (61) who demonstrated that the mortality rate in an animal model of hemorrhagic shock could be markedly reduced when infusion of blood was accompanied by infusion of a balanced salt solution. In this model, with no volume resuscitation, mortality was 100%. With reinfusion of shed blood alone, mortality was 80%. Mortality was reduced slightly by addition of blood plus plasma (70% mortality), and significantly with blood plus a balanced salt solution (30% mortality). Subsequently, crystalloid solutions became the mainstay for restoring the apparent interstitial fluid deficit that occurs in the initial stages of shock when fluid is mobilized from the interstitial space to the intravascular space.

Despite multiple studies that have suggested that albumin concentration predicts outcome in critically ill patients, albumin administration to correct hypoalbuminemia does not improve outcome (9,50,59,62). However, some studies on the use of albumin suggest benefits in certain patient populations. In a study presented in abstract form, Martin et al. (63) randomized 37 patients with acute lung injury or ARDS to standard therapy or to albumin and furosemide diuresis for five days; patients receiving albumin had higher COP, greater weight loss, better oxygenation, and a trend toward more ventilator-free days and a decreased ICU length of stay. In ascitic, cirrhotic patients, who have decreased plasma albumin concentrations and difficulty maintaining intravascular volume, Gines et al. (64) reported that those receiving albumin during large-volume paracentesis had a decreased incidence of renal dysfunction and hyponatremia. Fassio et al. (65) demonstrated that dextran 70 was as effective as albumin in patients undergoing large-volume paracentesis. Sort et al. (66) randomized 126 patients with cirrhosis and spontaneous bacterial peritonitis to receive antibiotics with or without albumin supplementation. Patients receiving albumin had a marked reduction in three important outcome measures: renal impairment, hospital mortality, and three-month mortality. The authors also noted a decrease in plasma renin activity, suggesting better maintenance of intravascular volume. Unfortunately, a control group receiving crystalloid volume expansion to a common end point [e.g., a central venous pressure (CVP) of 10–12] was not studied. Gentilini et al. (67) demonstrated that patients receiving albumin in addition

to diuretics for therapy of cirrhotic ascites had a greater rate of response, decreased hospital length of stay, decreased hospital costs, lower rate of recurrence of ascites, and a decreased rate of readmission in comparison to patients receiving diuretics without albumin. In a retrospective study, Dawidson et al. (68) reported that improved outcome after cadaveric renal transplantation was associated with decreased cold ischemia time, intraoperative administration of at least 1.2 g/kg albumin, increased duration of surgery, and increased recipient age. The benefits of albumin administration were dose related. However, whether the benefits of albumin were specifically related to the colloid or were due to more effective volume administration was not studied. Brown et al. (69) demonstrated decreased complications when albumin administration was used to increase serum albumin above 3 g/dL in patients receiving total parenteral nutrition. However, these benefits were not seen in a subsequent randomized controlled trial using a similar protocol (70). Finally, albumin used in the solution prime for cardiopulmonary bypass appears to coat the circuit and thereby attenuate the platelet decline (71,72). A retrospective analysis comparing patients who received albumin versus other colloids during hospitalization for coronary bypass surgery demonstrated a small survival benefit associated with the use of albumin (73).

PATIENT ASSESSMENT

Assessment of Intravascular Volume

Clinical assessment of intravascular volume is nonspecific and frequently misleading. Fluid deficits can be estimated by assessment of mucus membranes, venous filling, urine output, sensorium, blood pressure, and heart rate. While all of these findings are fairly nonspecific, the combination of several abnormal findings is consistent with fluid deficits in the range of 10% to 15% of total body weight (74). Fluid overload often is first suggested by dyspnea or oxygen desaturation. Distended neck veins suggest intravascular overload or right heart failure. Chest radiographs consistent with pulmonary edema must be carefully evaluated to determine whether the radiograph is more consistent with cardiac or noncardiac pulmonary edema. Increased central venous pressure and increased PAOP provide further support for the impression.

In surgical patients, objective information may be obtained from invasive monitors placed for a surgical procedure or postoperatively. Discussion with the anesthesiologist may identify a correlation between central venous or pulmonary pressures and CO, urinary output, and blood pressure. These values can serve as initial goals of fluid therapy. Several investigators have reported that increased variation in arterial systolic pressure during mechanical ventilation predicts fluid-responsive hypovolemia. Total systolic pressure amplitude changes of 12 to 15 mmHg correlate with clinically important hypovolemia (75,76), as does a late inspiratory decrease in systolic pressure of 6 mmHg or more (77).

Laboratory and radiological studies are helpful in establishing diagnoses and in creating milestones that evaluate the success of resuscitative efforts. Arterial blood gas values, serum electrolytes, and lactate levels are monitors of cellular metabolic activity. Solid organ perfusion deficits can be assessed by urinary output, serum creatinine, cerebral function, bilirubin, and liver enzyme levels. In any case, evaluation of the history and physical examination of a patient should be concurrent with the initiation of empiric therapy. The absence of a definitive diagnosis should not delay treatment of a severely dehydrated or hypotensive patient.

The Patient in Shock

Hypotension, tachycardia, tachypnea, mental status changes, and oliguria are common findings in shock. While a single set of vital signs is often the "call for action," consideration of the patient's baseline findings, including laboratory studies and recent trends, is often more informative.

The presence of hemorrhage requiring transfusion or reoperation should be addressed immediately. Increased abdominal girth, complaints of abdominal pain, decreased pulmonary compliance, decreased breath sounds, and increased output from surgical drains may indicate hemorrhage and therefore require evaluation. In the absence of obvious blood loss, the key physiologic parameters of preload, contractility, and systemic resistance require rapid assessment. The physical examination may provide some important clues. Patients with cardiac failure and hypovolemia typically have profound vasoconstriction, resulting in cold

extremities, decreased pulses, and slow capillary refill. Although blood pressures may be in the normal range, jugular venous distention will help identify the patient with myocardial dysfunction. In contrast, vasomotor dysfunction drives the hemodynamic picture of septic shock, as revealed by warm extremities, bounding pulses, and concomitant hypotension.

PRACTICAL ASPECTS OF FLUID MANAGEMENT IN THE INTENSIVE CARE UNIT

Maintenance of end-organ function requires both a blood pressure above the autoregulatory threshold and adequate DO_2 to meet metabolic demands. Because increases in CO can increase both blood pressure and DO_2 , the clinician should initially focus on evaluating and optimizing this parameter. The role of invasive monitoring in resuscitation will be discussed later (see section on Monitoring and End Points of Resuscitation).

Preoperative Care

Patients fasting for surgery have "maintenance" water deficits that can be estimated by the 4/2/1 rule: 4 mL/kg/hr for the first 10 kg of body weight, 2 mL/kg/hr for the second 10 kg of body weight, and 1 mL/kg/hr for each additional kilogram body weight. A 70 kg patient thus has a maintenance requirement of 110 mL/hr, equivalent to 1 L of "NPO fluid loss" for nine hours of fasting. Fasting outpatients rarely develop significant hypotension when 250 to 1000 mL of crystalloid is given 5 to 10 minutes prior to or during induction of anesthesia. When higher rates of fluid loss occur, such as with diarrhea, hemorrhage, infection, or prolonged nausea and vomiting, correction of fluid deficits should occur prior to anesthesia and surgery. Admission to the intensive care unit can be valuable prior to surgical operations in such cases.

Conditions commonly associated with fluid deficiency and excess are presented in Table 4. Invasive arterial and central venous pressure monitoring should be considered in selected patients while fluid resuscitation is in progress. Monitoring will enable the clinician to establish a correlation between preload, arterial pressure, and organ function (i.e., urinary output, acid-base status, and mental status). These correlations may guide the patient's intraoperative and postoperative management. For each patient, the intensivist and surgeon need to reach consensus on the relative priorities and time frame for preoperative stabilization and operation. A more comprehensive discussion on patient resuscitation and end points is presented later (see sections on Patient Resuscitation and Monitoring and End Points of Resuscitation).

The Hemodynamic "Tune Up" and Supranormal Cardiorespiratory Function

Considerable effort has been directed toward determining whether the targeting of fluid and vasoactive medication therapy to achieve specific hemodynamic values alters outcome in critically ill patients. Shoemaker reported a decrease in mortality with a strategy based on pulmonary artery catheterization (PAC) and the use of fluid and inotropic therapy to achieve a

Table 4 Common Abnormalities in Extracellular Fluid Volume

Decreased	Increased
Diabetes	Heart failure
Hypertension	Renal insufficiency
Spinal shock	SIADH
Sepsis	Iatrogenic overhydration
Recent hemodialysis	Recent transfusion
Diuretic use	Remobilization from interstitium
Prolonged fasting	
Vomiting	
Diarrhea	
Catabolic state	
Diabetes insipidus (recent CNS injury)	
Pre-eclampsia	
Burns	

Abbreviations: SIADH, syndrome of inappropriate antidiuretic hormone secretion; CNS, central nervous system.

DO₂ index (DO₂I) of 600 mL/min/m² in high-risk surgical patients (78). Decreased mortality was also reported in two studies of trauma patients, using a similar design, and in a study of high-risk surgical patients, which used dopexamine as a mixed inotrope/vasodilator (79–81). While many of the patients studied had preoperative pulmonary arterial catheters and preoperative recording of cardiorespiratory indices, none of these studies attempted to achieve supranormal values preoperatively, and there was no apparent survival benefit associated with preoperative (vs. postoperative) enrollment in a protocol group.

The high incidence of cardiac morbidity and renal injury associated with vascular surgery has created interest in whether preoperative hemodynamic optimization and resuscitation guided by PAC can improve perioperative outcomes. A historically controlled study of patients having abdominal aortic aneurysm (AAA) repair suggested a survival benefit associated with preoperative optimization of hemodynamics (82). Three subsequent randomized studies sought to replicate these findings; all aimed for a CI greater than 2.8 L/min/m², systemic vascular resistance less than 1100 dynes-sec/cm⁵, and PAOP between 8 and 15 mmHg through titration of fluids, inotropes, and vasodilators (83–85). Using these goals, Berlauk et al. found significantly less early graft thrombosis and fewer cardiac complications in the PAC group. There were no differences between patients who received PAC and fluid loading preoperatively in the ICU and those who received PAC placement just prior to surgery (83). A later study of patients having AAA repair and lower extremity revascularization compared routine use of the PAC with use dictated by clinical need. The study found that patients randomized to routine PAC placement received significantly greater amounts of fluid, but had no improvement in outcome (84). A trial by Valentine et al. found a higher complication rate in patients who received PAC and hemodynamic optimization preoperatively for AAA repair. The study did not differentiate whether the higher complication rate resulted from PAC use per se or its role in preoperative care (85).

Different preoperative goals have been studied in more general populations of patients undergoing high-risk surgical procedures. Wilson randomized patients undergoing major elective surgery to either control treatment or treatment designed to achieve a DO₂I of 600 mL/min/m² with either dopexamine or epinephrine for at least four hours prior to surgery (86). Significant decreases in mortality occurred in the group randomized to the supranormal DO₂, and dopexamine was linked to a shorter length of hospital stay. Wilson's findings contrast with a larger trial evaluating the use of pulmonary artery catheters in high-risk surgical patients. The Canadian Critical Care Trials Group conducted a study of patients older than 60 years, who were to have urgent or elective major operations with postoperative ICU stay. Goals of "directed" treatment were a DO₂I of 550 to 600 mL/min/m², a CI of 3.5 L/min/m², a mean arterial pressure of 70 mmHg, and a pulmonary capillary wedge pressure of 18 mmHg (87). No mortality benefit over usual care (fluids, CVP catheter) was achieved with the goal-oriented approach. While the latter study argues against the routine use of PAC in unselected patients, it does not completely address the issue of preoperative optimization. In contrast to the study by Wilson et al., only approximately 20% of the patients in the Canadian study achieved the targeted goal preoperatively and mortality in the control group was only 7.7% (in contrast to 17% in the Wilson et al. study).

Overall, there is still no consensus that the outcome of unselected ambulatory patients—even for major surgery—is improved by preoperative ICU admission for optimization of fluid status and hemodynamics. On the other hand, hospitalized patients with shock, sepsis, electrolyte abnormalities, large fluid redistributions, or organ failure are more likely to benefit from a physiologic-based approach to preoperative care.

Perioperative Management of Electrolytes

Decisions pertaining to analysis of electrolytes, blood proteins, and hematologic parameters are guided by the patient's history and physical findings. Comprehensive panels of lab studies are generally ordered for severely ill patients upon admission to the intensive care unit. Table 5 presents some common morbidities and the attendant electrolyte derangements.

Abnormally low concentrations of phosphate (<1.5 mg/dL), magnesium (<1.2 mg/dL), potassium (3.5 mEq/dL), and ionized calcium (<0.8 mmol/L) have been linked to increased perioperative morbidity and mortality and should be corrected prior to surgery (88–90). Treatment of hypomagnesemia is essential for effective treatment of hypocalcemia and

Table 5 Conditions Commonly Associated with Electrolyte Abnormalities

Condition	Associated abnormality
End-stage renal disease	Metabolic acidosis, \uparrow K^+ , \uparrow phosphorus, \downarrow Ca^{2+}
Hepatic failure	Metabolic acidosis, \downarrow glucose
Aggressive diuresis	Metabolic alkalosis, \downarrow Cl^-
Massive transfusion	\downarrow Ca^{2+}
Chronic alcoholism	\downarrow K^+ , \downarrow phosphorus
Gastric suctioning, emesis	\downarrow Cl^- , \downarrow K^+ , metabolic alkalosis
Diabetic ketoacidosis	\downarrow K^+ , \downarrow Cl^- , \downarrow phosphorus
Hyperparathyroidism	\uparrow Ca^{2+}
Diarrhea, malabsorption	\downarrow Phosphorus
SIADH	\downarrow Na^+ , \downarrow Cl^-

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone secretion.

hypokalemia (91). Treatment of acidosis can exacerbate hypokalemia if the latter is not first corrected. Free water excess or deficiency can often require days to correct and should not delay an operation as long as deficits in intravascular volume are corrected.

Routine Postoperative Care

Patients usually pass through three predictable stages of maintaining euvolemia after major surgery. In the first phase, patients require continuous fluid administration due to interstitial fluid accumulation. During the second phase, fluid balance remains constant as interstitial fluid accumulation reaches its maximum. In the third phase, fluid balance is negative due to mobilization of interstitial fluid. Although each phase typically lasts approximately one day, such expectations should not substitute for careful examination of the patient and evaluation of all concurrent physiologic processes.

A patient's initial postoperative requirement for fluids is based on replenishing intravascular fluid losses. Sources of fluid loss include those of sweat, metabolism, and respiration (insensible losses), "third space" interstitial losses, urine output, and bleeding. If the surgery was of low impact and uncomplicated, infusion of an isotonic crystalloid solution (LR or NS) at 1.5 to 3 mL/kg is usually sufficient to balance these losses.

Each disease process has a different rate and relative contribution from the various sources of fluid loss. Insensible losses vary according to temperature and metabolism and range between 200 and 1000 mL/day; insensible losses are markedly less in ventilated patients with humidification of inspired gas. The presence of systemic infection often causes a capillary leak, which leads to extensive extravasation of fluids to the interstitium. Likewise, loss of vascular tone with infection will increase venous capacitance and decrease effective circulating blood volume. Third-space losses in the postsurgical patient are the most difficult to predict, but typically vary according to the anatomy of the surgical resection and its duration. Emergency surgery, ischemic tissues, and contamination of the surgical site will all increase the likelihood of more extensive third-space loss. Examples of common operations and expectations of fluid requirements in the first 24 hours postoperatively are presented in Table 6 below.

Table 6 Examples of Typical Postoperative Fluid (Requirements for the First 24 Hours)

<i>Largest fluid requirements: 50–100 mL/kg/day</i>	
Transperitoneal abdominal aortic aneurysm repair	
Gastric or intestinal resection with multiple adhesions	
Tumor resection or debulking	
<i>Significant fluid requirements: 20–30 mL/kg/day</i>	
Radical prostatectomy	
Heart surgery	
Reoperations	
<i>Moderate fluid requirements: 10–20 mL/kg/day</i>	
Laparoscopic cholecystectomy	
Simple prostatectomy	
Appendectomy	

More extensive operations on sicker patients mandate a more precise definition of fluid status, because matching intake and measurable output may not address redistribution of fluid between the vasculature and interstitium. Many critically ill patients are markedly “fluid positive” but still intravascularly depleted. Redistribution of fluids to the interstitium varies according to the duration and severity of surgery and the presence of infection. Generally, hemodynamic stability can be achieved postoperatively with titrated administration of fluids adjusted to maintain warm extremities, normal acid–base status, and a urine output of at least 0.5 mL/kg/hr. When hypotension is not quickly corrected with fluid administration, the clinician should look for a concurrent process such as myocardial ischemia, infection, allergy, or concealed hemorrhage.

Patient Resuscitation

As a general rule, organ function is best preserved by approaching the critically ill patient in a systematic manner using the following set of priorities:

- Maintain intravascular volume
- Maintain erythrocyte mass
- Maintain hemostasis—surgical prior to medical
- Maintain electrolyte balance
- Acid–base status

Isotonic crystalloid infusions are the mainstay of management for patients with hemorrhage, septic shock, and other low-preload states. Aside from the crystalloid–colloid controversy that has been addressed, studies generally demonstrate similar effects on physiology and outcome when solutions are given based on physiologic indications (54). The consensus is that for a fixed volume of administration, colloid solutions provide a greater and more sustained increase in intravascular volume than do crystalloids. When intravenous access limits rapid administration of crystalloids, hetastarch (not in excess of the 20 mL/kg guideline) is a reasonable option for rapid plasma volume expansion. Cost and safety concerns limit the role of albumin. Currently, there is no justification for using platelets, fresh frozen plasma, or red blood cells solely for the purpose of volume expansion.

Significant Hypovolemia

In patients with significant hypovolemia—acute blood loss of greater than 500 mL, total body fluid deficit of greater than 10% of body weight, or sepsis with hypotension or end-organ failure—treatment begins with 1 to 2 L of isotonic crystalloid (LR or NS) infused over 5 to 15 minutes. Blood pressure, CO, and urine output often improve with this measure alone.

Bolus administration of fluid is essential in the early stage of fluid resuscitation, when optimal filling pressures are being evaluated. Many clinicians may then convert to an infusion of isotonic fluids to maintain these filling pressures. A common error is to give a modest amount—250 to 500 mL—of fluid more slowly and consider this an “adequate” challenge without documenting any change in cardiac preload by invasive hemodynamic monitoring. The follow-up mistake is to then maintain blood pressure with a vasopressor.

The disadvantage of relatively slow infusions of crystalloid fluids is their tendency to redistribute throughout the extracellular fluid space, so that there is no significant increase in intravascular volume. A further disadvantage is that maintenance infusions may continue beyond the period of capillary leak when fluid infusion is no longer necessary. For these reasons, many prefer to continuously monitor filling pressures and give fluids by bolus only as needed.

If the response to an initial adequate fluid bolus is transient, crystalloid boluses should be continued. Following multiple boluses, CVP monitoring may help define an optimum range of filling pressures that correlate with the patient’s condition. If the patient was healthy at baseline, the condition is fairly uncomplicated, and hemodynamic status normalizes with fluids, a CVP monitor is usually adequate to correlate changes in preload with other physiologic and clinical parameters. Pulmonary artery catheters are generally reserved for medical and surgical patients whose condition is more complex, who have significant cardiac or pulmonary pathology, or who have compromised end-organ function.

Issues Particular to Septic Shock

In patients with septic shock, the normal correlation between end-diastolic pressure (EDP) and end-diastolic volume (EDV) is altered such that values considered normal or desirable in other contexts may not be applicable. Right ventricular (RV) compliance is variable, so the RVEDP no longer correlates with RVEDV. Similarly, left ventricular (LV) compliance varies so that pulmonary arterial wedge pressure (PAWP) no longer correlates with LVEDV; RV and LV function may vary so that CVP does not correlate with PAWP and RVEDV does not correlate with LVEDV.

Studies in patients with septic shock have demonstrated *increased* ventricular compliance, resulting in markedly increased EDV despite low or normal EDP (92,93). This finding contrasts with the normal or decreased compliance observed in other shock states. Individual Starling curves in most patients with septic shock have demonstrated a plateau in CO at a PAWP below 12 mmHg (94).

Monitoring and End Points of Resuscitation

A general flow chart describing the integration of fluid administration with invasive monitoring and clinical end points is presented in Figure 2. Prior randomized clinical studies involving surgical and trauma patients have linked favorable outcomes with supranormal indices of DO_2 (600 mL/min/m²). Aiming for a lower target DO_2 (500 mL/min/m²) by a more recent study found a survival benefit equal to that of the former index, and less fluid administration was needed (95). Studies that have randomized more heterogeneous populations of critically ill patients, and specifically those with sepsis, to targeted indices of supranormal CO and DO_2 did not improve survival, and thus failed to define objective end points for administration of fluids and vasoactive therapy (96–99). Despite different patient populations and outcomes, the combined experience of these changed the way many view resuscitation goals. Many patients, regardless of intended treatment, readily demonstrate supranormal physiology with fluid loading and minimal pharmacologic support (e.g., DO_2I of 600 mL/min/m² and CI of 4.5 L/min/m²). The good prognosis of these patients is probably more reflective of their physiologic reserve than their attainment of “fixed goals.” In contrast, there are patients who are unable to achieve such goals despite therapy (including extensive fluid loading and high doses of inotropic support). Finally, the improved outcome that occurs with protocols designed for “goal-directed therapy” may be the result of a rapid and organized approach to resuscitation rather than to the specific goals achieved by such efforts (100).

An individualized approach to patient resuscitation is necessary. Physiologic measures of organ function that originally identified a problem with organ hypoperfusion are likely the best markers to guide the process of patient stabilization and resuscitation. An inventory of organ function can often be obtained from analysis of lactic acid concentration, arterial blood

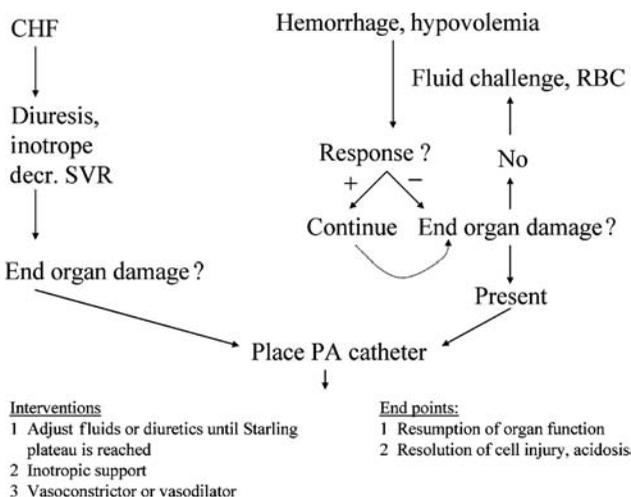


Figure 2 Patient outcomes are improved and organ failure risk is decreased with a rapid and organized approach to patient resuscitation; one such approach is described in the text and diagrammed here. Cardiac failure requires a separate set of tools and interventions and consideration of priorities that is not discussed here. With hypotension and in the absence of a primary cardiac event, aggressive fluid administration should begin. Often, empiric fluid therapy is required before a clear diagnosis. Physical examination and invasive monitoring should address the adequacy of cardiac output. The presence of questionable cardiac performance or tissue perfusion prompts many to titrate fluid and pharmacologic therapy according to data from pulmonary artery catheterization.

gases, anion gap, creatinine, urine output, blood pressure, mental function, liver enzymes, and gastrointestinal tract function. Abnormalities in these variables can be followed serially as one proceeds through sequential administration of fluids, inotropes, and vasopressors.

In both septic and hypovolemic shock, our approach is to maximize cardiac preload with boluses of intravenous crystalloids, as described above, until a plateau on the Starling curve is reached (Fig. 3). Clinical end points such as blood pressure, urine output, CVP, CO, DO_2 , and VO_2 often normalize with the aggressive fluid loading alone. In some patients, abnormalities in LV compliance may make higher filling pressures difficult to interpret. Numeric values that correlates with good ventricular filling in the general population may represent either under-filled or overfilled ventricles in many critically ill patients (e.g., point C in Fig. 3) (94,101). In such situations, echocardiography can help clarify the correlation between right and left atrial pressures and LV volume. Transesophageal echocardiography (TEE) has received increased attention as a tool in evaluating fluid status and cardiovascular dynamics in the ICU (101). Investigators are currently attempting to establish criteria for different levels of preload. In one study of critically ill patients, a LV end-diastolic area less than 20 cm^2 correlated with fluid responsiveness (102). While TEE provides the highest quality images, it is not practical in critically ill patients who are not intubated.

Role of Erythrocyte Transfusion in Fluid Management

Even in the absence of hemorrhage, anemia is an almost inevitable consequence of treatment in the ICU for more than five days (103,104). Depression of erythrocyte production due to stress and infection, occult gastrointestinal hemorrhage, and diagnostic phlebotomy all contribute to this condition (103). The presence of an arterial line is associated with a 30% increase in blood tests ordered as well as a 44% increase in daily loss from phlebotomy (105). Decisions regarding transfusion commonly arise in the course of the critically ill; indeed, 37% of patients in one recent survey received red cell transfusions as part of their ICU course (104).

Based on the physiologic principles of DO_2 , increasing hemoglobin concentrations in the circulation should create a more favorable balance between oxygen supply (DO_2) and demand

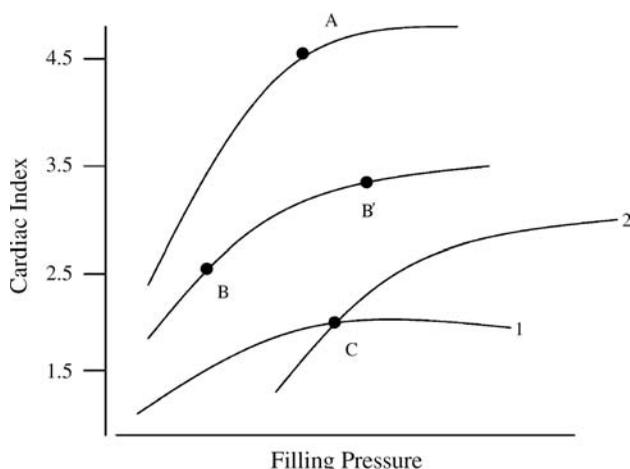


Figure 3 When organ failure is present, hemodynamic management depends upon fluid responsiveness and overall level of cardiac function as described by Starling curves. For the patient described with point A, interventions such as the administration of fluids and inotropes to achieve a higher CI or blood pressure are unnecessary. If a higher blood pressure is required for organ perfusion, it can be achieved with a direct vasopressor as long as existing filling pressures and cardiac output are maintained. For the patient described by point B, fluid resuscitation should continue until organ dysfunction resolves, or until a plateau in the curve is reached (B'). Inotropes may then need to be added, depending on the course and resolution of organ function. Point C describes a patient with marginal cardiac performance. Depending on clinical condition, this patient may benefit from either an inotrope or a vasodilator, or both (curve #1). Occasionally, point C describes a patient with poor ventricular compliance who may benefit from fluid administration (curve #2). Transesophageal or transthoracic echocardiography provides a valuable tool that can rapidly differentiate between the latter two scenarios. *Source:* From Refs. 101 and 102.

(VO_2), and potentially minimize cardiac work requirements. The observation that some patients cannot increase their CO to levels achieved by healthier individuals has led to the criterion of a 30% hematocrit as the minimum for maintaining adequate DO_2 . However, new data are actively contesting this conventional wisdom.

The viscosity of blood increases exponentially as the hematocrit increases over 30%. Decreased viscosity promotes blood flow through the microcirculation. DO_2 and tissue oxygen tensions are higher at a hematocrit of 30% than at 40%, and do not decrease below normal values until hematocrit is below 20% (106).

The effect of anemia is to increase CO by increasing stroke volume without affecting heart rate. Additional compensatory mechanisms for anemia include an increased oxygen extraction ratio so that the critical DO_2 required to prevent anaerobic metabolism is approximately 8 to 10 mL/kg/min, which corresponds to a hemoglobin of approximately 4 g/dL (hematocrit of 12%). In surgical patients who refuse transfusion, no deaths have occurred at hemoglobin levels above 5 g/dL (107).

The mathematical relationship between hemoglobin and DO_2 does not accurately predict the impact of transfused blood on oxygen metabolism *in vivo*. In septic shock, reasons may include the entire range of macrocirculatory to cellular defects: arteriovenous shunting, endothelial cell edema and thrombosis limiting access to the microcirculation, and cellular and enzymatic defects in oxygen utilization. Problems occur from the storage of red blood cells themselves, including potential capillary plugging related to loss of deformability of cell membranes, and impaired unloading of oxygen at appropriate oxygen tensions (108,109). The older the red blood cells, the lesser their ability to correct splanchnic acidosis and improve systemic oxygen uptake (110–112). Cellular metabolism and endothelial injury have been implicated in the inability of red cells to reverse anaerobic metabolism in sepsis.

A prospective randomized multicenter study comparing outcome between liberal and restrictive transfusion strategies (hemoglobin maintained between 10–12 g/dL vs. 7–9 g/dL) was performed by the Canadian Critical Care Trials Group (113). When the lower hemoglobin transfusion value was used, hospital mortality rate declined from 28% to 22% in 838 critically ill patients. The 30-day mortality decreased from 16% to 9% in less severely ill patients, and from 13% to 6% in patients younger than 55 years of age. Using the transfusion trigger of 7 g/dL hemoglobin, 33% of patients avoided transfusion altogether, and they required 56% less transfusions. The two transfusion criteria resulted in similar mortality rates (21% vs. 23%) in patients with cardiovascular disease. However, a subsequent analysis of the data in the subgroup of patients with severe ischemic heart disease suggested an increased mortality with the restrictive transfusion strategy (114). A study of elderly patients admitted with acute myocardial infarction demonstrated improved outcome with transfusion in patients whose admission hematocrit was below 33% (115), suggesting that higher transfusion triggers are appropriate for patients with acute myocardial ischemia.

Thus, recent literature suggests that the use of a transfusion trigger as low as 7 g/dL is as safe as, or safer than, the traditional value of 10 g/dL in most patients (113). Extrapolation to patients with active myocardial ischemia, however, is not justified, and most clinicians would still transfuse such patients to a hematocrit of 30% or higher. Erythropoietin therapy boosts erythrocyte production and can decrease transfusion requirements in critically ill patients (116). For reasons discussed, endogenous blood may have some qualitative advantages over transfused blood.

CONCLUDING REMARKS

The intensive care unit is a unique resource where the capability for obtaining continuous data streams is combined with close patient observation and the ability to produce changes in patients' physiology on a minute-to-minute basis. The ability to obtain data and institute corrective action can be one to two orders of magnitude faster than that obtainable in other hospital areas. The set of patient conditions one encounters in the ICU is highly dynamic, often challenging the resources and capabilities of even this technologically endowed setting. Some consensus is being reached on fluid use in the critically ill patient. We have tried to present some of the general principles of fluid physiology and the related controversies that the reader may find helpful in treating patients in the intensive care unit.

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Transfusion of Red Cells and Blood Components in Stressed, Trauma, and Critical Care Patients

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INTRODUCTION

This chapter will discuss (i) compensatory mechanisms in anemia and the transfusion decision in trauma and critical care patients; (ii) the controversy about optimal values for hemoglobin (Hb) and oxygen transport in critical situations; (iii) the current uses and indications for blood transfusion; (iv) the complications of blood transfusion; and (v) the current uses and indications for platelets, fresh frozen plasma (FFP), and cryoprecipitate in bleeding patients.

COMPENSATORY MECHANISMS FOR ANEMIA AND THE TRANSFUSION DECISION IN TRAUMA AND CRITICAL CARE PATIENTS

The function of red cells is to augment delivery of oxygen to the tissues. While the patient's Hb is one of the important determinants of the need for red blood cell transfusion, there are several other factors influencing the transfusion decision, including (i) oxygen loading, (ii) blood flow, (iii) Hb mass, (iv) Hb oxygen affinity, (v) tissue demands, (vi) expectations for continued blood loss, (vii) symptoms related to blood loss when crystalloid infusions have failed to correct intravascular volume depletion, (viii) rapid blood volume loss of 30% to 40% of the circulation, (ix) data from invasive monitoring and nature of bleeding (active, controlled, uncontrolled, etc.), (x) practice parameter guidelines for blood transfusion, (xi) the efficacy of the patient's compensatory mechanisms for decreased oxygen carrying capacity (1–5).

The category one evidence about physiologic adaptation to anemia has been summarized by Canadian investigators (Table 1) (2). Acute anemia per se has no direct effect on pulmonary function and oxygen loading. Arterial partial pressure of oxygen (PO_2) and saturation should remain within the normal range in uncomplicated anemia (1). Reduced Hb thus decreases arterial oxygen content and hence delivery of oxygen (O_2 content \times cardiac output). Increased blood flow, a physiological compensation for anemia, will cause a small reduction in the alveolar–capillary transit time, which, together with the reduced mass of Hb in the pulmonary capillaries, causes a modest decrease in diffusing capacity or transfer factor. However, this is unlikely to have a measurable effect on alveolar/end-capillary PO_2 gradient, which is only 10 to 6 mmHg (1). PO_2 in arterial blood will be reduced by venous admixture due to shunting and perfusion of relatively underventilated alveoli, because of ventilation–perfusion inequality. However, these factors are not enhanced by anemia, but may be significant causes of decreased O_2 delivery ($\dot{D}O_2$) in the critically ill patient, resulting in an intolerance of mild anemia.

The shift in the Hb dissociation curve increases P_{50} from 27 to 30 mmHg when Hb concentration is 6 g/dL (6). This has a negligible effect on arterial saturation, but does increase the PO_2 at which oxygen is unloaded in the tissues, compensating for the effects of reduced oxygen content with anemia. There is a hyperbolic increase in cardiac index (CI) as Hb decreases below 10 g/dL and 2,3-diphosphoglycerate (DPG) levels increase (Fig. 1). In the classic experiments of Woodson et al. (7) volunteers were hemodiluted with albumin to maintain iso-voolemia, while Hb was decreased from a mean 15.3 to 10 g/dL, where it was maintained for 14 days. There was an acute, 55% increase in cardiac output, but cardiac output was only 14% above control (preisovolemic hemodilution) levels after 14 days of sustained anemia (Fig. 2, open symbols upper curves). However, despite the acute reduction in Hb, cardiac output

Table 1 Category One Evidence Drawn from Literature Review About Anemia

Hb dissociation curve
 Anemia shifts the curve to the right because of increased 2,3-DPG levels
 Cardiac output
 Cardiac output increases with increasing degrees of normovolemic anemia provided that the blood volume is adequate
 Increased cardiac output in normovolemic anemia is a result of increased stroke volume
 The contribution of increased heart rate to the increase in cardiac output following normovolemic anemia is variable
 Other hemodynamic alterations
 Changes in blood viscosity result in many of the hemodynamic changes in normovolemic anemia
 Normovolemic anemia is accompanied by increased sympathetic activity
 Normovolemic anemia causes a decrease in systemic vascular resistance
 Normovolemic anemia results in a redistribution of cardiac output toward the heart and brain and airway from the splanchnic circulation
 Global oxygen delivery declines above and below Hb of 10–16 g/dL
 Coronary and CBF
 CBF is increased during anemia
 Coronary blood flow is increased during anemia
 Coronary artery disease in the presence of moderate degrees of anemia (Hb < 9 g/dL) results in impaired left ventricle contractility or ischemia
 Moderate anemia does not aggravate cerebral ischemia in patients with cerebrovascular disease

Abbreviations: DPG, diphosphoglycerate; Hb, hemoglobin; CBF, cerebral blood flow.

increased sufficiently to maintain near-normal $\dot{V}O_2$, whereas in sustained (chronic) anemia, cardiac output was insufficient and $\dot{V}O_2$ was decreased 25% below control levels. Duke and Abelmann (8) measured cardiac output in patients before and after treatment of uncomplicated anemia by increasing Hb from 5.9 to 10.9 g/dL (lower curves, Fig. 2). They also showed a negative correlation between age and CI in the anemic state, reflecting the inability of the older patient to compensate for anemia. In the heart that is under stress from coronary artery stenosis, the compensatory mechanisms for acute anemia are impaired. Levy et al. (9), in an elegant experiment in which coronary stenosis was induced followed by isovolemic hemodilution in animals, showed the detrimental effects of left anterior descending coronary artery lesions on cardiac performance (Fig. 3). Cardiac failure occurred at a hematocrit (Hct) of 17% in animals with coronary stenosis, whereas it occurred at a Hct of 8.6% in the control animals. Myocardial lactate production began when the Hct decreased below 20% and the O_2 extraction (ERO_2) was greater than 50% in both controls and animals with coronary stenosis. There was good correlation ($r = 0.88$) between whole-body ERO_2 and lactate metabolism in the region of the left anterior descending coronary artery blood supply (Fig. 4). ERO_2 was concluded to be a valid indicator of myocardial metabolism in acute anemia and was suggested as an indicator of transfusion need in coronary stenosis. Cardiac failure occurred at a higher Hct with critical coronary artery stenosis. In another animal study (10), the median lowest Hb tolerated without contractile dysfunction of the myocardium supplied by the left anterior descending coronary artery was 7.5 g/dL. At the mean Hb concentration of 6.0 g/dL, there was marked contractile dysfunction, which was restored when Hb was increased by 1.9 g/dL.

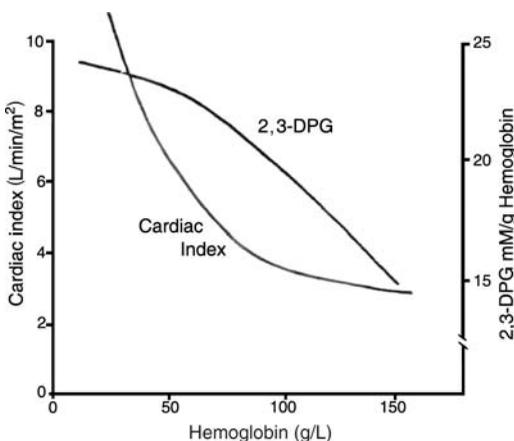


Figure 1 The relationship between cardiac index (CI), hemoglobin (Hb) levels, and 2,3-DPG is shown. At an Hb level of 8 to 9 g/dL, CI remains low, while 2,3-DPG levels are greater than 18 mM/g Hb. *Abbreviation:* DPG, diphosphoglycerate. *Source:* From Ref. 59.

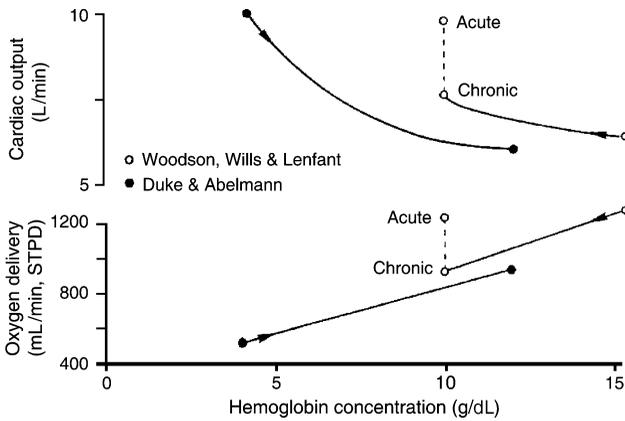


Figure 2 Changes in cardiac output and oxygen delivery as a function of hemoglobin concentration. The right-hand curves (*open symbols*) show the effect of induced anemia in volunteers (7). The left-hand curves (*closed symbols*) show the effect of treatment of anemia patients (8). *Abbreviation:* STPD, standard temperature and pressure, dry. *Source:* From Ref. 1.

How Do These Animal Studies Differ from Human Bedside Reality?

Acute normovolemic hemodilution is a controlled state, which lacks many of the physiological changes occurring in acute blood loss. The compensatory mechanisms activated by acute uncontrolled blood loss, as may occur in a hemorrhaging trauma patient, include adrenergic stimulation, release of vasoactive hormones, fluid shift from the intracellular fluid and interstitium into the vascular space, renal conservation of water and electrolytes, and hyperventilation. With continued blood loss, there is constriction of the perfusion to the skin, skeletal muscle, kidney, and splanchnic viscera due to adrenergic catecholamines and renin-angiotensin release (3,11). This causes increased cardiac afterload and redistribution of blood flow by autoregulation in the brain and heart. The bowel has no autoregulation of blood supply, so that ischemia can readily occur, especially if acute anemia is accompanied by hypotension. These compensatory mechanisms restore blood flow to critical organs such as the heart and brain within 60 to 120 seconds of the onset of acute blood loss (11). Shift of extracellular fluid may restore up to 50% of intravascular volume. Fluids also move from the intracellular compartment along an osmotic gradient induced by hepatic release of glucose, lactate, pyruvate, phosphates, amino acids, and urea due to release of vasoactive and metabolically active mediators in response to hemorrhage and hypotension. The increase in osmotic pressure is directly proportional to the extent of the blood loss. Release of vasopressin and adrenocortical steroids results in conservation of water and electrolytes by the kidney.

How Does the Clinician Acutely Determine the Need for Increased $\dot{D}O_2$ in the Hypotensive Patient?

It has been repeatedly shown that blood pressure and heart rate are unreliable indicators of shock in young trauma patients. Wo et al. (12), Shoemaker et al. (13), Bland et al. (14), and

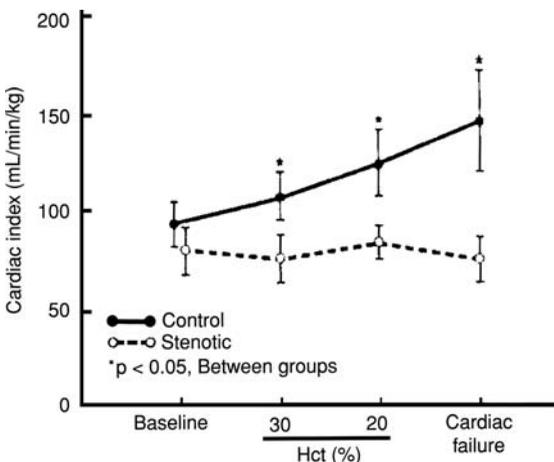


Figure 3 Cardiac index is plotted against Hct during progressive acute normovolemic hemodilution until cardiac failure was induced. *Abbreviation:* Hct, hematocrit. *Source:* From Ref. 9.

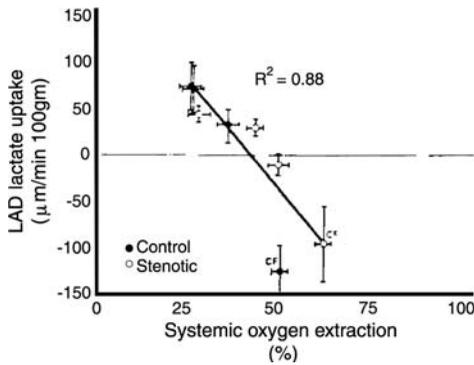


Figure 4 LAD coronary artery blood supply regional lactate uptake plotted against systemic oxygen extraction (ERO_2) during acute normovolemic hemodilution in control ($n=7$) dogs and dogs with stenotic LAD ($n=7$). Note that at an ERO_2 rate of 50%, myocardial lactate uptake equaled lactate production in both control and stenotic animals. The data of LAD lactate uptake is also shown in cardiac failure when the stenotic group had a value of about $100 \mu\text{m}/100\text{g}/\text{min}$. Abbreviation: LAD, left anterior descending. Source: From Ref. 9.

Abou-Khalil et al. (15) have shown how, despite demonstrating values of blood pressure, heart rate, and urine output that may be considered within the range of normality, many of these patients have myocardial depression, low mixed venous oxygen saturation, and high serum lactates. Urine flow may appear adequate, because in some instances of early incomplete resuscitation, the patients may already be developing high-output nonoliguric renal failure (16).

What Are the Appropriate Indicators of Hemorrhagic Shock?

Natanson's group at the National Institutes of Health (NIH) examined the ability of commonly used clinical parameters to quantify acute hemorrhage in awake nonanesthetized dogs, chronically instrumented with arterial and pulmonary artery catheters (17). As the animals were hemorrhaged, 10 hemodynamic and 20 blood laboratory data were obtained every 10 minutes to construct and validate models to quantify blood loss. The best indicator of quantity of hemorrhage was the arterial base deficit (Fig. 5). For values of base deficit, there were large amounts of variability before hemorrhage, but each animal followed the 45° slope of the ideal model, producing a consistent error and correlation coefficient (r) value of 0.84. Mean arterial pressure (MAP) had r of 0.71 and r for CI was 0.66. Heart rate in this model was not correlated with blood loss ($r=0.36$). Pulmonary artery pressure and CI were relatively poor predictors of blood loss. By constriction of the venous capacitance vessels, which contain 50% to 70% of the circulating volume, adequate filling pressures and cardiac output can be maintained. Therefore, this model confirms that heart rate and blood pressure are not particularly good predictors of hemorrhagic shock most probably because of the effect of compensatory mechanisms (17).

Dunham et al. have also shown the benefits of base deficit as a single guide to prediction of outcome (18). They studied 63 dogs and bled them to a specific level of oxygen debt. Figure 6 (top panel) shows linear regression of arterial lactate and probability of death, and Figure 6 (bottom panel) identifies the relationship between base deficit and probability of death. The correlation coefficients are 0.85 and 0.92, respectively, for lactate and base deficit. The lethal dose 50% (LD50) for lactate is 12.9 and LD50 for base deficit is -18.8 mMol/L . The base deficit is a piece of information that is readily available. Abnormal values should indicate the need for aggressive monitoring and resuscitation in patients suffering from hemorrhagic shock.

MIXED VENOUS OXYGEN SATURATION

Mixed venous oxygen saturation ($S\bar{v}O_2$) did not correlate very well with blood loss ($r=0.66$) in the serial hemorrhage dog model (17). One reason that $S\bar{v}O_2$ is not a good predictor of acute blood loss is that it is a crude indicator of what actually occurs in individual tissue beds (19). While $S\bar{v}O_2$ is helpful in indicating overall changes, it does not identify specific derangements in oxygen transport to vital organs such as the brain and heart. Figure 7 shows that venous oxygen saturations vary enormously depending on the oxygen demand relative to the blood flow of particular organs. In the heart, for example, blood flow through the coronaries is only about 5% of cardiac output, myocardial ERO_2 is very high, and venous saturations in the coronary sinus typically are low at 30% or less (20). The value of $S\bar{v}O_2$ of 75% in the pulmonary artery is more affected by organs such as kidney and skin having high blood flow relative to

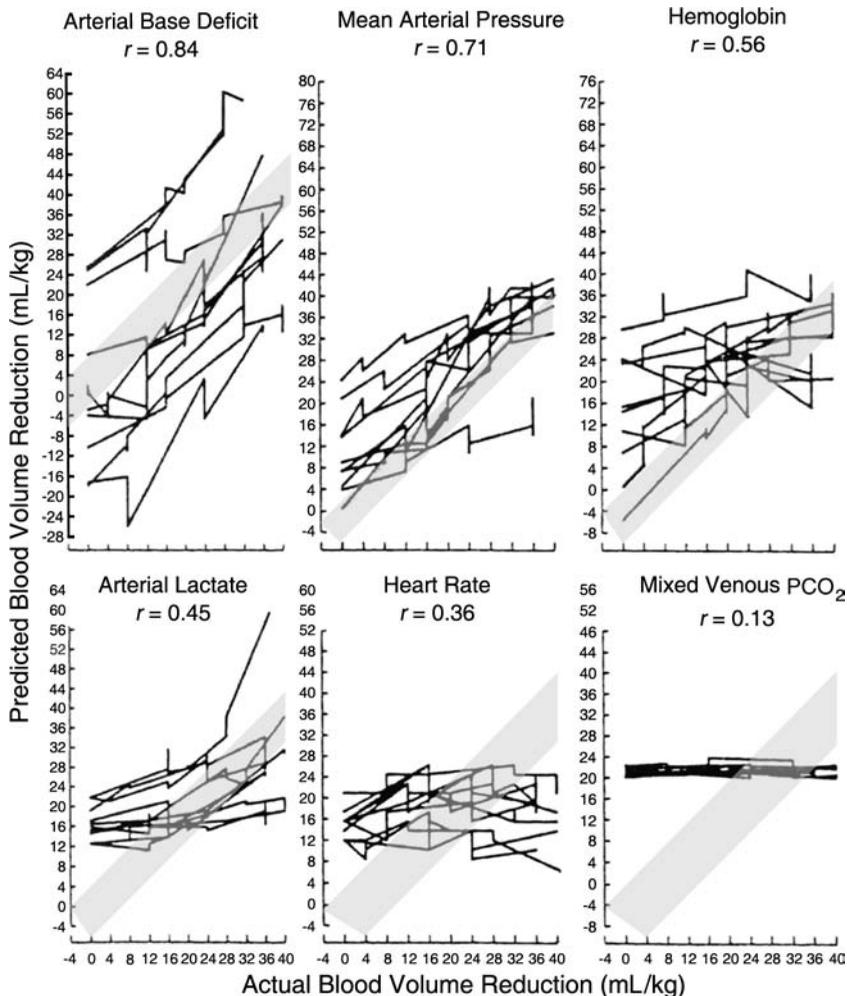


Figure 5 Comparison of model predictions versus actual blood volume reductions for six representative parameters. *Solid black lines* represent individual animals ($n = 10$). *Gray bar* represents an ideal model slope where model predictions equal actual blood volume reductions. For mean arterial pressure, predictions at large volume hemorrhage were more accurate than predictions with small volume bleeds. Models such as those for heart rate and lactate both showed significant variability before hemorrhage among animals and flat slopes (e.g., mixed venous PCO_2) indicated fixed-volume predictions regardless of actual degree of hemorrhage. *Source:* From Ref. 17.

their oxygen utilization than it is by heart and brain (20), yet maintenance of oxygenation to the heart and brain is much more important in terms of survival. Monitoring of the electrocardiogram (ECG) to detect ischemic changes, assess the patient's mental status after hemorrhagic shock, and measure arterial and jugular venous oxygen tension may provide more clinically relevant information about the need for blood transfusion and the adequacy of resuscitation of the brain and heart relative to ERO_2 , than the initial monitoring of $S\bar{v}O_2$.

CI and $S\bar{v}O_2$

Another reason why $S\bar{v}O_2$ is a poor predictor of CI and oxygen transport is the multifactorial nature of $S\bar{v}O_2$. The relationships between $S\bar{v}O_2$, CI, arterial oxygen saturation, oxygen consumption ($\dot{V}O_2$), and Hb levels can be appreciated by developing the Fick equation (Fig. 8) (21). Clinicians should bear this diagram in mind when interpreting changes in CI and $S\bar{v}O_2$. It illustrates the fact that $S\bar{v}O_2$ is not simply an indicator of CI. Also, it shows that the correlation between $S\bar{v}O_2$ and CI, for a constant $\dot{V}O_2$, will differ depending on whether a given intervention will be on a flat (A–B) or steep (C–A) portion of the $S\bar{v}O_2$ versus CI relationship. Previous investigators found that, on the steep portion of the relationship, the best-fit linear relationship

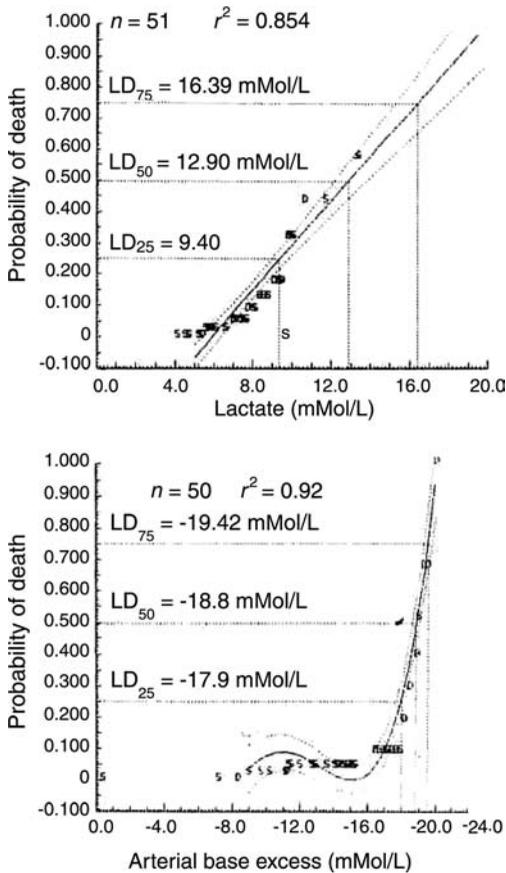


Figure 6 Regression-derived relation between the Kaplan-Meier probability of death (*vertical axis*) and arterial lactate (mMol/L) (*top panel*) and extracellular base deficit (mMol/L) (*bottom panel*). Shown are the mean regression lines with 95% confidence limits and LD 25%, 50%, and 75% (LD₂₅, LD₅₀, and LD₇₅, respectively) probabilities of death with their respective lactate and base deficit values. Note on the top panel that the zero intercept is at greater than 5 mMol/L of lactate and on the bottom panel that uncertainty exists regarding an increased probability of death at levels of base deficit between 1.0 and -16.0 mMol/L. This indicates that there was very little discrimination in probability of death at base deficits less than 16 mMol/L or for levels of lactate below 5 mMol/L, because of compensation by buffering and by intermittent anaerobic metabolism. *Abbreviation:* LD, lethal dose. *Source:* From Ref. 18.

between $S\bar{v}O_2$ and CI shows higher correlation coefficients on the slopes ($r^2 = 0.96$; slope = 31) than on the flat portion ($r^2 = 0.0036$; slope = -0.9). CI may even increase, and $S\bar{v}O_2$ decrease, if the relationship between $S\bar{v}O_2$ and CI moves to a higher value $\dot{V}O_2$ isopleth (A–D) exemplified in the clinical situation by the release of aortic cross clamp (21).

There are three main mechanisms by which global oxygen transport is maintained during acute progressive anemia: (i) increased ERO_2 ; (ii) reduction in oxygen affinity with a shift of the Hb disassociation curve to the right due to increased 2,3-DPG (Fig. 7); and (iii) increased cardiac output. A fourth mechanism is the use of 100% oxygen to increase the amount of oxygen carried in the plasma. In hemodiluted children undergoing orthopedic surgery (22), 37% of the oxygen delivered came from the plasma. In fact, at a Hb level of 3 g/dL and a normal cardiac output, 62% of the actual $\dot{V}O_2$ can be provided by the oxygen dissolved in the plasma. In addition, extraction of oxygen from plasma is much more efficient than from Hb, exceeding 85% removal so that acid-base status remains within normal range (Table 2). As with the acellular Hb-based oxygen-carrying solutions, the presence of larger quantities of oxygen in solution facilitates the diffusion of oxygen into the mitochondria by minimizing the oxygen gradient between the Hb in the red cells and the tissues (23). So high fraction of inspired oxygen (FiO_2) in excess of 0.8 should be used when Hb is low. Small quantities of added nitrogen, such as that found in air, minimize the microatelectasis that occurs with 100% inspired oxygen, caused by the resulting alveolar nitrogen washout (24). So 100% oxygen should not be used unless Hb gets below a level of about 5 g/dL.

Intentional Anemia in Humans and Risk of Mortality

Jehovah's Witness patients are a group of patients in whom low levels of Hb are reported. Various maneuvers have been used to sustain Hb levels and minimize $\dot{V}O_2$, including deep sedation, mechanical ventilation, and avoidance of blood sampling. Although erythropoietin

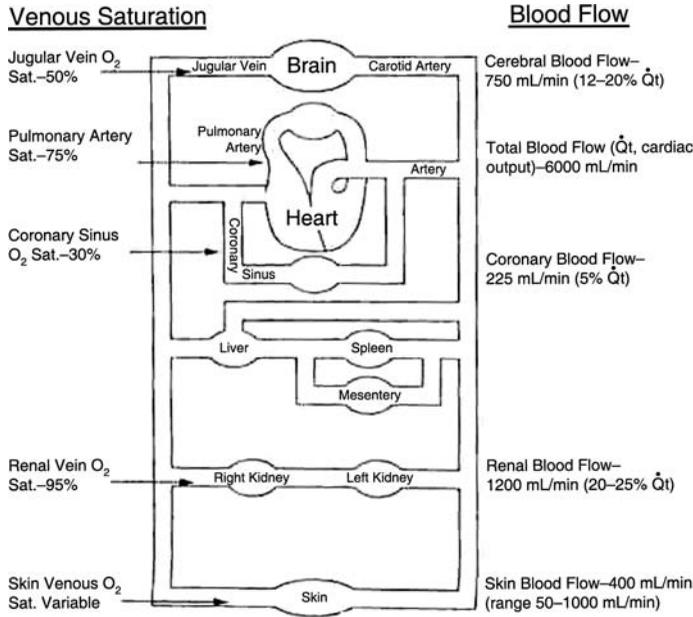


Figure 7 Venous oxygen saturations of blood leaving various organs are shown on the left side and blood flow expressed in mL/min and as a percent of \dot{Q}_t are shown on the right side of this figure. Note that the heart and brain with low blood flow relative to their oxygen requirements (e.g., coronary blood flow and carotid artery) have low venous oxygen saturations. In comparison, an organ such as the kidney has high blood flow, but little oxygen requirement and contributes relatively more to the final mixed venous oxygen saturation of 75% in the pulmonary artery than does the much smaller venous blood flow from the heart and brain. It is for this reason that a normal pulmonary artery oxygen saturation is not a good indicator of adequate resuscitation of the brain or heart. *Abbreviation:* \dot{Q}_t , total cardiac output.

is often used in such patients, reticulocyte counts begin to improve only after two to three weeks. There is a reported 20% mortality rate associated with a Hb concentration of 5 g/dL. However, there are a few reports of Jehovah’s Witnesses surviving with a Hb concentration near 3 g/dL, but most patients with a Hb concentration of less than 3 g/dL die (25).

Another group of patients in whom low Hb values are reported are those who did not receive a blood transfusion either because there was no blood available owing to a lack of resources or because of refusal to receive a blood transfusion. In one of these reports, pregnant women in West Africa with Hb values greater than 4.5 g/dL had no mortality or cardiac failure (26). In another study conducted in Romania, there was no postoperative mortality in 72

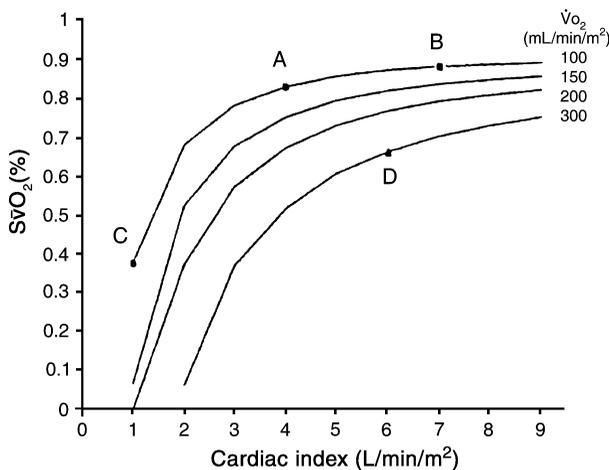


Figure 8 The relationship between cardiac index (CI), SvO_2 , $\dot{V}O_2$, hemoglobin (Hb), and arterial blood oxygen saturation (SaO_2) is expressed by the equation: $SvO_2 = SaO_2 - \dot{V}O_2 / CI \times Hb \times 13.4$. This diagram illustrates that the relationship between CI and SvO_2 depends on $\dot{V}O_2$. It assumes Hb equals 12 g/dL and SaO_2 equals 100%. *Abbreviations:* SvO_2 , mixed venous blood oxygen saturation; $\dot{V}O_2$, oxygen consumption. *Source:* From Ref. 21.

Table 2 Hb, Hct, and Acid–Base Status During Hemodilution and Reinfusion

Variable	T0	T1	T2
Hct (%) (range)	29.5 + 4.8 (20.3–36.1)	9.0 + 2.2 ^a (6.3–13.3)	16.7 + 3.1 ^a (12.2–21.6)
Hb (g/dL) (range)	10.0 + 1.6 (7.0–12.4)	3.0 + 0.8 ^a (2.1–4.5)	5.6 + 1.0 ^a (4.1–7.1)
Lactate (mmol/L) (range)	1.3 + 0.2 (1.0–1.5)	1.4 + 0.5 (0.9–1.95)	1.5 + 0.5 (1.0–2.2)
Arterial pH (range)	7.42 + 0.05 (7.33–7.50)	7.33 + 0.08 ^a (7.25–7.49)	7.37 + 0.06 (7.26–7.45)
Venous pH (range)	7.39 + 0.05 (7.34–7.46)	7.28 + 0.07 ^a (7.22–7.42)	7.33 + 0.06 (7.22–7.42)
PaCO ₂ (range)	34.1 + 6.5 (25.1–46.1)	37.9 + 3.4 (32.1–42.7)	39.2 + 4.1 (33.6–45.0)
PvCO ₂ (range)	38.3 + 4.0 (32.5–43.3)	43.4 + 2.5 ^a (39.3–45.9)	44.8 + 4.3 (39.2–50.8)
ABE (mmol/L) (range)	–1.1 + 2.3 (–6.1 to 0.6)	–50 + 3.6 ^a (–8.4 to 2.4)	–1.8 + 2.5 (–5.4 to 2.1)
VBE (mmol/L) (range)	–0.6 + 1.1 (–2.5 to 1.0)	–6.0 + 3.5 ^a (–8.9 to 1.4)	–2.3 + 2.5 ^a (–5.5 to 2.1)

^aSignificant difference ($P < 0.05$) from the mean value at the previous stage.

Abbreviations: T0, immediately prior to hemodilution; T1, the lowest hemoglobin level reached; T2, end of surgery; Hct, hematocrit; Hb, hemoglobin; PaCO₂, arterial partial pressure of carbon dioxide; PvCO₂, mixed venous partial pressure of carbon dioxide; ABE, arterial base excess; VBE, mixed venous base excess.

Source: Ref. 22.

patients with Hb values greater than 5 g/dL (27). In two studies in the United States, 44 pediatric patients undergoing cardiac surgery had no mortality despite blood being withheld, provided Hb was greater than 7 g/dL (28) (Table 3). In the other U.S. study, 59 patients successfully underwent surgery after refusing transfusion with no postoperative mortality when the blood loss was less than 500 mL and Hb greater than 8 g/dL (29). In a follow-up study of 1958 patients, 30-day mortality was 2.3% in 1411 patients with preoperative Hb of 12 g/dL or greater and mortality was 1.3% in 36 patients with preoperative Hb less than 6 g/dL. Low preoperative Hb increased the risk of death or serious morbidity in patients with cardiovascular disease more than in those without (30).

In a study of 2738 sequential isolated coronary artery bypass surgery patients, there was a significantly increased risk of mortality for Hct less than 14%. For high-risk patients, Hct less than 17% had increased mortality after adjusting for other risk factors (43). A meta-analysis of several studies of Jehovah's Witnesses found that of 50 reported deaths, 23 were primarily due to anemia. Except for three patients who died after cardiac surgery, all other patients died with Hb concentrations less than 5 g/dL (44).

Critical Oxygen in Hemodiluted Animals

In animals which were hemodiluted and monitored at intervals, while Hb decreased from 14, to 10, 8, 5, and then 2.4 g/dL, it was only at a Hb of 2.4 g/dL that a significant difference in brain pH and pressure of carbon dioxide (PCO₂) was detected, compared with baseline of

Table 3 Natural History of Untreated Anemia

Study	Year	Patients (n)	Site	Setting	Finding
Fullerton and Turner (59)	1969	Unknown	West Africa	Pregnant woman; no available transfusions	No mortality or cardiac failure in patients with Hb more than 45 g/L
Gollub and Bailey (61)	1966	5	New York City	Jehovah's Witness patients undergoing cardiac surgery	No postoperative mortality in patients with Hb more than 70 g/L
Alexiu et al. (62)	1975	72	Romania	Patients with bleeding ulcers undergoing surgery without transfusion	No postoperative mortality in patients with Hb more than 50 g/L
Kawaguchi et al. (64)	1984	44	Buffalo	Pediatric patients undergoing cardiac surgery	No mortality in patients for whom blood was withheld for Hb more than 70 g/L
Carson et al. (60)	1988	59	New Jersey	Patients undergoing surgery who refused transfusion	No postoperative mortality in patients with blood loss less than 500 mL and Hb more than 80 g/L

Abbreviation: Hb, hemoglobin.

Table 4 Physiological Variables at Baseline and During Anemia (mean±SEM)

	Baseline	D1	D2	D3	D4	I1
Hb (g/dL)	14.2±0.7	10.4±0.6 ^a	7.7±0.6 ^a	5.0±0.5 ^a	2.4±0.3 ^a	5.7±0.3 ^a
pH	7.34±0.02	7.31±0.01	7.28±0.01	7.27±0.01	7.25±0.02 ^a	7.26±0.02
PaCO ₂ (mmHg)	36.0±0.3	36.1±0.4	36.5±0.4	38.3±0.3	37.8±0.6 ^a	36.7±0.5
PaO ₂ (mmHg)	89±2	88±2	88±3	86±4	94±6	88±3
Temp (Brain) (°C)	37.6±0.4	37.6±0.4	37.6±0.5	37.7±0.4	37.6±0.05	37.8±0.5
MAP (mmHg)	81±3	77±3	74±3	70±2	63±1 ^a	68±2
CVP (mmHg)	6±0	6±1	6±0	7±1	9±1 ^a	9±1

Note: D1–D4: hemodilution; I1: red blood cell infusion. Physiological variables measured in anesthetized rabbits during progressive hemodilution from baseline of Hb 14.2 g/dL to the nadir of 2.4 g/dL at time point D4 before infusion of red cells at I1. Brain tissue PO₂ fell from 27 to 12 mmHg and brain pH decreased from 7.22 to 7.12 (see Fig. 12 for cerebral blood flow changes). Values are mean± standard error mean.

^aSignificant difference versus baseline ($P < 0.025$); $n = 12$.

Abbreviations: Hb, hemoglobin; MAP, mean arterial pressure; PaO₂, arterial partial pressure of oxygen; PaCO₂, arterial partial pressure of carbon dioxide; CVP, central venous pressure.

Source: Ref. 40.

14.2 g/dL. At the 2.4 g/dL Hb level, there was also a significant decrease in MAP and increase in central venous pressure (CVP) (Table 4). Brain tissue PO₂ fell from 27 to 12 mmHg, pH decreased from 7.22 to 7.12, cerebral blood flow (CBF) almost doubled to 66 mL 100/g/min, and cerebral metabolic rate was more than halved to under 2 mL 100/g/min. At this level of anemia—2.4 g/dL—the authors concluded that increases in CBF and cerebral oxygen extraction were only partially able to compensate for the decreased oxygen-carrying capacity induced by anemia (Fig. 9). Brain $\dot{V}O_2$ was also significantly lower and CBF significantly higher than baseline. Both were restored to normal baseline ranges by transfusion (40).

In mechanically ventilated (FiO₂ 0.21) anesthetized and paralyzed baboons, hemodiluted at constant left atrial pressure with 5% albumin, six of seven animals survived to Hct 4%. Adequate cardiac compensation occurred until hematocrit was less than 10%. Increased flow without increases in ERO₂ occurred in animals with healthy hearts and no coronary disease (31). Critical Hct values for intestinal $\dot{V}O_2$ were measured by Van Bommel et al. and compared with the critical value for intestinal microvascular O₂ (μPO_2). The critical values were almost

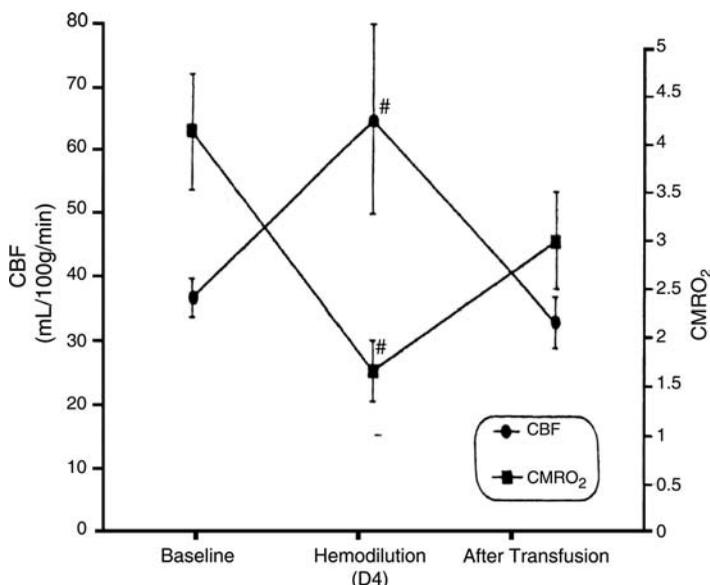


Figure 9 The time course of CBF, CMRO₂, and cerebral oxygen transport. Data are expressed as mean±SEM. Hemodilution=fourth blood draw; after transfusion=third red blood infusion. D4 corresponds to the physiological variables listed under D4 in Table 4. A significant difference ($P < 0.05$) versus baseline. Abbreviations: CBF, cerebral blood flow; CMRO₂, cerebral oxygen metabolism. Source: From Ref. 61.

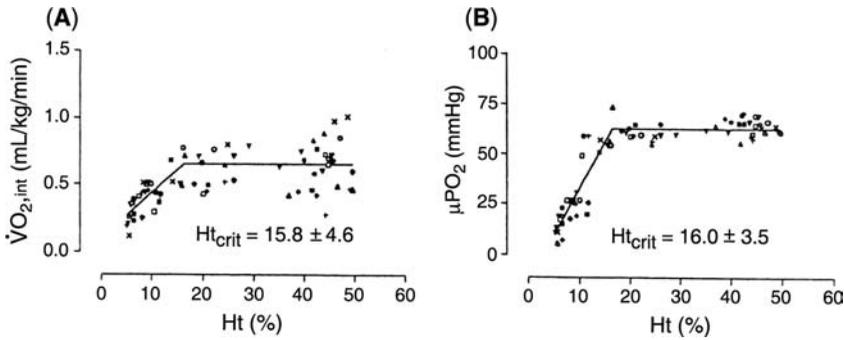


Figure 10 (A) Critical Ht_{crit} for the $\dot{V}O_{2, int}$. (B) Critical hematocrit value for the intestinal μPO_2 . Critical values were determined in each animal separately and are represented here as mean \pm SD. Data originating from the same animal are represented by a similar symbol. *Abbreviations:* Ht_{crit} , hematocrit value; $\dot{V}O_{2, int}$, intestinal oxygen consumption; μPO_2 , microvascular oxygen partial pressure. *Source:* From Ref. 45.

identical at 15.8 ± 4.6 and 16.0 ± 3.5 μPO_2 , respectively. These Hct represent a Hb value just above 5 g/dL (Fig. 10) (32).

Critical $\dot{D}O_2$ in Anesthetized Humans

At the Children’s National Medical Center, eight American Society of Anesthesiologists (ASA) I children undergoing scoliosis correction surgery were hemodiluted by exchanging whole blood for 5% albumin in 0.7% saline. On 100% oxygen ventilation, Hb fell from 10 to 3 g/dL, while $S\bar{v}O_2$ decreased from 90% to 72%, ERO_2 increased from 17% to 44%, and $\dot{D}O_2$ decreased from 532 mL M^2 /min (Fig. 11). When hemodiluted, one child had the Hb level fall to 2.1 g/dL and this was associated with ST segment depression, which resolved on reinfusion of autologous blood. The authors concluded that a Hb level of 3 g/dL was safe in anesthetized and monitored children, and that one should not hemodilute below a mixed venous saturation of 60% because levels above this have never been shown to produce lactic acidosis or compromise cardiac function (22). The “critical point” of global $\dot{D}O_2$ below which $\dot{V}O_2$ becomes linearly dependent on $\dot{D}O_2$ in anesthetized humans is estimated at 330 mL M^2 /min by Shibutani et al. (33) and as 300 mL M^2 /min by Komatsu et al. (34), while von Woerkens et al. (35) found that critical $\dot{D}O_2$ was lower in hemodilution when cardiac output was maintained. Rheology changes in blood were improved with hemodilution, resulting in increased capillary $\dot{D}O_2$ and a critical value of 184 mL M^2 /min in a patient with a Hb of 4 g/dL (Table 5). However, these studies were carried out either in anesthetized humans or when cardiac output was maintained. Such states are not representative of acute critical situations where there may be hypovolemia and significant catecholamine and other stress responses activated. Whether the existence of critical $\dot{D}O_2$ states can be identified in such trauma patients also remains controversial.

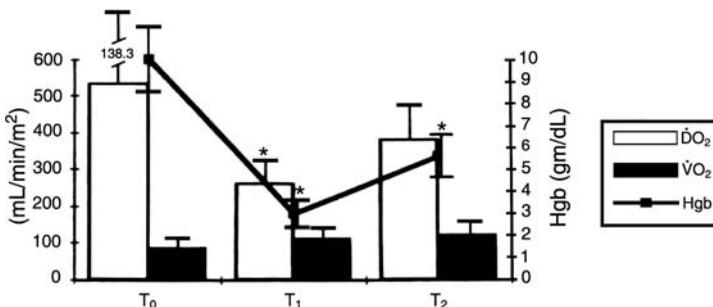


Figure 11 Relationship between $\dot{D}O_2$, $\dot{V}O_2$, and Hgb during the stages prior to hemodilution (T0), the lowest Hgb reached (T1), and at the end of surgery (T2). Values are mean \pm SD. *Significant difference ($P < 0.05$) from the mean value at the previous stage. *Abbreviations:* $\dot{D}O_2$, oxygen delivery; $\dot{V}O_2$, oxygen consumption; Hgb, hemoglobin concentration. *Source:* From Ref. 46.

Table 5 Critical Limit Global Oxygen Delivery

Shibutani et al. (33)	330 mL/M ² /min in anesthetized man
Komatsu et al. (34)	300 mL/M ² /min after cardiopulmonary bypass
Von Woerkens et al. (35)	184 mL/M ² /min in hemodiluted man

Relationship Between Oxygen Delivery and Oxygen Consumption

Some patients may benefit from the increase in $\dot{V}O_2$ that is expected to occur after blood transfusion. Whether there is an increase in $\dot{V}O_2$ has only been shown in a limited number of studies, in part possibly due to the frequency of such studies being carried out in septic patients rather than in impaired oxygen transport situations such as hemorrhagic shock. Surrogate markers to quantitate benefit from blood transfusion have been suggested, including lactate washout and decrease in oxygen debt (36,37), but confounding variables occur because, when blood is infused, reperfusion occurs and lactate rises. States with impaired ERO_2 (e.g., sepsis) limit the usefulness of such surrogate measures. The relationship of transfusion for anemia or ischemia with oxygen metabolism is shown in Figure 12. Factors alleviating ischemia include increased oxygen supply (and by inference, but not always true, reduced oxygen debt) and decreased oxygen demand, such as can occur with sedation, anesthesia, and decreased cardiac after load (38). Increased after load, increased blood viscosity, and decreased 2,3-DPG levels in stored blood will aggravate ischemia. Hb levels per se are nonlinearly related to CI, and 2,3-DPG with the lowest CI associated with the greatest 2, 3-DPG levels occurring at about 8 g/dL (Fig. 1) (5). Because data on ERO_2 is difficult to obtain in humans in emergency circumstances, much of this work has been done in animals. There are extraordinary compensatory abilities in the hemorrhagic shock model (Fig. 13). ERO_2 increased to more than 70% in anesthetized dogs exsanguinated of more than 60% of estimated blood volume during two hours when systolic blood pressure was maintained at 50 mmHg (39). Resuscitation with volumes of shed blood or Hb-based oxygen-carrying solutions produced supranormal CI with all these fluids, but only blood normalizes ERO_2 and CI six hours later. Total Hb concentration fell with the oxygen-carrying solutions due to endothelial and other interactions causing red cell sequestration.

Anemia in Critically Ill Patients

In bleeding, but otherwise healthy patients, cardiovascular compensation should be adequate to reach Hb levels of 5 g/dL. As blood loss continues and Hb falls further, compensatory responses begin to fail, and they become inadequate when Hb falls below 3 to 5 g/dL. Mortality rates are reported ranging from 50% to 95% when the Hb falls below 3.5 g/dL (25,41). Anemia is a common problem in critically ill patients. Some anemia can be accounted for

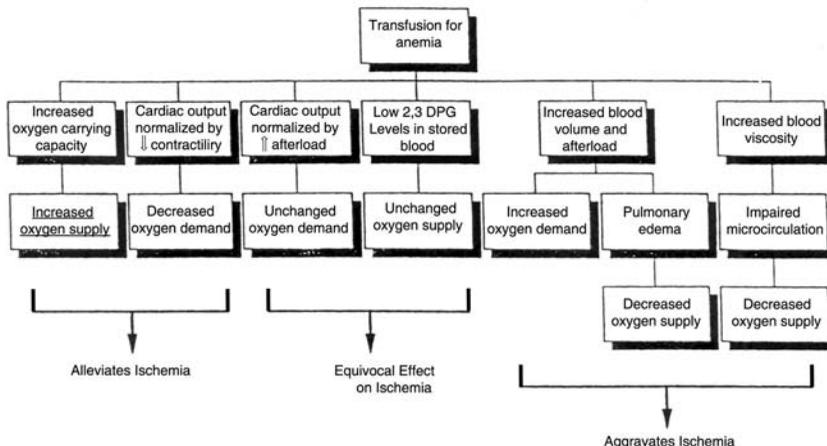


Figure 12 The effects of red cell transfusion for anemia, or the many variables that can impact myocardial oxygen metabolism and the ultimate impact on myocardial ischemia. *Abbreviation:* 2,3-DPG, 2,3-diphosphoglycerate. *Source:* From Ref. 38.

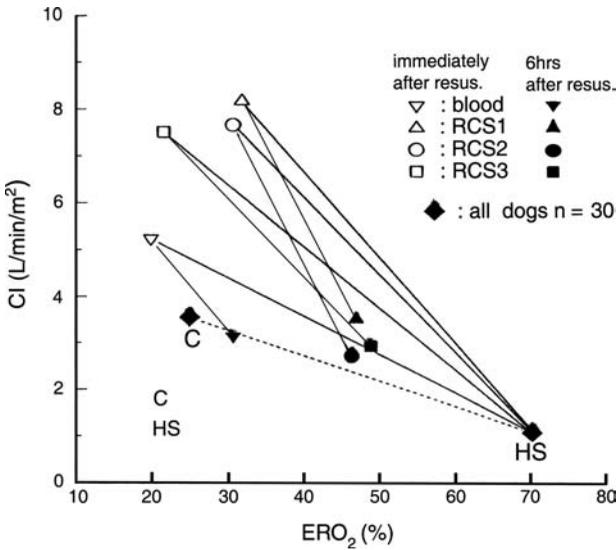


Figure 13 CI is plotted against ERO₂ for 30 anesthetized dogs exsanguinated over two hours from baseline C to an HS state by continuous withdrawal of more than 60% estimated blood volume. Resuscitation then occurred with either whole blood (*inverted triangle*), 8% pyridoxalated hemoglobin polyoxethylene (PHP) (*upright triangle*); 8% SFH (unmodified PHP) (*circle*) or 4% PHP (*square*). *Open symbols* represent data immediately after all resuscitation fluids were administered. *Closed (black) symbols* represent data six hours after resuscitation. Note the 70% ERO₂ in HS and that whole blood was the only solution that returned ERO₂ to the normal range of 25% six hours after resuscitation. *Abbreviations:* CI, cardiac index; ERO₂, O₂ extraction; C, control state; HS, hemorrhagic shock. *Source:* From Ref. 60.

by an average of 41 ± 39.7 mL of blood drawn for blood sampling per 24 hours. In a major European study involving 3534 patients, there was a positive correlation between organ dysfunction and the number of times blood was drawn and the volume of blood drawn. The mean Hb on critical care unit admission was 11.3 ± 2.3 g/dL with 29% (963/3295) having a Hb value less than 10 g/dL. The transfusion rate was 37% (1307/3534). Older patients and those with a longer critical care unit stay were more commonly transfused. Both critical care unit and overall mortality rates were significantly higher in patients who had received a transfusion (critical care unit rates 18.5% vs. 10.1%; overall mortality 29% vs. 14.9%). For similar degrees of organ dysfunction, patients who had received a transfusion had a higher mortality rate. For matched patients, the 28-day mortality was 22.7% among patients receiving blood transfusions and 17.1% among those who did not (*P* = 0.02) (42). The major points about anemia in stressed critically ill patients are summarized in Table 6.

WHAT IS THE OPTIMUM Hb AND CARDIAC OUTPUT IN THE TRAUMA PATIENT?

Two variables that contribute importantly to oxygen transport are Hb concentration and cardiac output. Surprisingly, there is controversy about what is the optimal value of both these variables during perioperative management of trauma and critically ill patients. Jehovah’s Witnesses may reach extreme hemodilution and still survive (25,44). Patients with Hb levels of 7 to 8 g/dL safely undergo anesthesia and surgery without increased perioperative morbidity and mortality (43). Physiologically isovolemic hemodilution is well tolerated until Hb levels approach 3 g/dL (46–49) due to increased cardiac output and ERO₂, especially when ventilation is controlled, inspired oxygen is increased, the patient is heavily sedated to reduce $\dot{V}O_2$, and mild hypothermia exists. An analysis of over 800 patients with total joint arthroplasty showed acute normovolemic hemodilution and reduced the need for allogenic blood transfusions (50). The losses in red cell volume are reduced during perioperative bleeding

Table 6 Summary Points About Anemia in Stressed Critically Ill Patients

In bleeding but otherwise healthy patients, cardiovascular compensation is adequate to Hb 5 g/dL
 Further compensation inadequate with mortality 50–95% at Hb < 3.5 g/dL
 Anemia is common in critical care units with 39% < 10 g/dL and 37% transfusion rate
 Association between blood draw frequency and volume transfusion and diminished organ function
 Critical care and 28-day mortality were higher in patients receiving blood

Abbreviation: Hb, hemoglobin.

because of the low Hct caused by hemodilution. Intraoperative recovery of surgical blood loss, possible in trauma patients, is reported to have no benefit in cardiothoracic surgical procedures or repair of abdominal aortic aneurysm in reducing blood transfusion or on improving clinical outcomes (51,52). Four deaths related to intraoperative recovery of blood were reported to the New York Department of Health from 1990 to 1995: a prevalence of 1 in 35,000 procedures (53).

Tissue oxygen deprivation does not occur in an anesthetized, nontrauma patient until $\dot{D}O_2$ is less than $330 \text{ mL M}^2/\text{min}$ or less, a limit that is easily avoided with compensatory mechanisms in a young, otherwise healthy trauma patient. There is, therefore, no physiologic basis for a minimum allowable Hb level of 10 g/dL or a Hct of 30% in young previously healthy patients. No experimental evidence supports this arbitrary limit, and clinical experience suggests that lower values are well tolerated (51,54). Depending on other coexisting medical problems and expected further blood loss, a Hb level of 7 g/dL may not require blood transfusions provided normal intravascular volume and tissue perfusion are maintained.

What Are the Benefits of Change in the Transfusion Trigger?

Reduction of the transfusion trigger in trauma patients has several important consequences, including medical, economic, and resource management (58). Trauma patients are the most frequent users of emergency blood transfusion. In civilian and military trauma, justification of a lower transfusion trigger would simplify the process of providing field management of casualties and conserve resources. At the Shock Trauma Center, using a transfusion trigger of Hb 10 g/dL from 1992 to 1993, about 8500 units of packed red blood cells were transfused to about 1300 patients/yr. It is estimated that if the transfusion trigger were reduced to Hb 7 g/dL , about 30% of these blood transfusions (2550 units/yr) could have been avoided. In specific patients with rare blood groups and incompatibilities, such a reduction in the transfusion trigger could result in an even greater conservation of resources.

The cost of blood banking includes the harvesting maintenance and distribution of blood and blood products. Conservation of the blood resource by reduction of the transfusion trigger would minimize all such costs. It is estimated that each unit of packed red cells (1991 \$) costs about \$155, and the patient is charged \$219 (58). It would be expected that a 30% reduction in packed red blood cell use accompanying a reduction of the transfusion trigger would have a parallel decrease in the complications of blood transfusion and an annual patient cost savings of \$558,450 in shock trauma alone. A reduction in the transfusion trigger in trauma patients may be generalized to other transfusion practices in nontrauma patients, and result in significant nationwide reduction in complications (see section "Indications for platelets, FFP, cryoprecipitate in bleeding patients") of blood transfusion and in increased patient safety. Some standardized approaches to transfusion may enable regional variations in practices to be prevented (56,57).

What Are the Risks?

There are potential risks of hemodilution in patients with cerebrovascular and cardiovascular disease. In patients undergoing coronary artery bypass grafting, one group in the study was maintained at Hb 12 g/dL postoperatively, while a second group had Hb levels of about 9 g/dL . Myocardial ischemia was demonstrated to occur more frequently in the second group with lower postoperative Hb levels (54). In addition, a 1992 study reported slight decreases in oxygen transport to the brain in normal hemodiluted volunteers, in spite of increases in the CBF (55). Lowering the transfusion trigger may possibly cause ischemia in patients with cardiac or cerebral disease, spinal cord injury, low cardiac-output states, sustained fever, poorly controlled tachycardia, unstable angina, incomplete coronary revascularization, severe aortic stenosis, and left ventricular hypertrophy. Patients unlikely to be able to increase cardiac output or regional blood flow, postoperative patients with severe problems with ventilation or increased oxygen demand, and elderly patients also may be at risk from a reduced transfusion trigger (59). Well-compensated patients with chronic anemia may tolerate the lower Hb concentration despite having some of these risks factors, although they may be at risk for a poor outcome after surgery for reasons other than a lower transfusion trigger, because of the etiological factors causing chronic anemia.

What Is an Optimal Level of Cardiac Output?

Is an adequate level of cardiac output for the trauma patient normal or supranormal? The arguments against supranormal cardiac output are that increasing cardiac output and $\dot{D}O_2$ above normal might be unwarranted and even dangerous if additional fluids or vasoactive agents are administered. The arguments for elevating cardiac output and $\dot{D}O_2$ above normal are that even young trauma patients have inadequate cardiovascular reserve and that inotropic support in conjunction with invasive monitoring is the way to improve outcome (60). The data supporting these opposing points of view are discussed below.

Data to Support Supranormal Cardiac Output

Despite improvements in resuscitation and supportive care, one or more vital organs fail in a large proportion of patients with acute trauma (61). It has been proposed that organ damage in critical illness is due to inadequate $\dot{D}O_2$, often exacerbated by a level of tissue ERO_2 that fails to satisfy metabolic demands (62). Consequently, some investigators have recommended that in patients at high risk who are undergoing surgery, the CI and the delivery and consumption of oxygen be increased to levels that have previously been identified as the median maximal values in survivors (CI, $> 4.5 \text{ L M}^2/\text{min}$ of body-surface area; $\dot{D}O_2$, $> 600 \text{ L M}^2/\text{min}$; and $\dot{V}O_2$, $> 170 \text{ L M}^2/\text{min}$) to replenish tissue oxygen and prevent organ dysfunction (63,65). One study demonstrated a marked reduction in mortality among postoperative patients at high risk who were treated in this way (32).

Under normal circumstances, in response to a decrease in oxygen transport, there should be an increase in ERO_2 . If $S\bar{v}O_2$ is unchanged despite a fall in oxygen transport, then there is a true oxygen supply dependency, and in this group of patients, Shoemaker's approach of providing a supranormal cardiac output is warranted. Abou-Khalil et al. (15) took the approach favored by Shoemaker's group that is to volume resuscitate, and then add inotropic agents. Many would say that values of 11 to 13 mmHg for CVP or pulmonary artery occlusion pressure that were achieved in their patients indicate that they did not adequately volume load their patients before starting inotropic agents. However, they found that in 39 patients who received more than six units of blood for penetrating trauma, when they increased oxygen transport to supranormal levels, they achieved normalization of serum lactate and non-flow-dependent $\dot{V}O_2$. All of the patients had normal vital signs postoperatively, but only 15% had optimum oxygen transport and normal lactate levels one hour postoperatively. Five patients never achieved optimum oxygen transport and normal lactate and they died early. Two patients achieved optimum oxygen transport and normal lactate but died late. Based on injury severity scores, the predicted mortality was 30%, but actual mortality was only 18%. So it appears that in some patients, producing supranormal levels of cardiac output will speed the normalization of arterial lactate and base-deficit levels and improve patient survival. The group of patients likely to benefit are those who show no change in ERO_2 ratio when oxygen transport falls.

Data Disputing the Need for Supranormal Cardiac Outputs

Some researchers, however, remain skeptical (63,66,67). Provided that the volume replacement is optimal, it remains unclear whether achievement of these target values simply indicates an adequate physiologic reserve and, therefore, a better outcome. Although the prognosis is very good for patients in whom $\dot{D}O_2$ and $\dot{V}O_2$ reach the target levels in response to intravenous fluids alone or only moderate inotropic support, in a substantial number of patients, it proves impossible to increase $\dot{V}O_2$ despite aggressive inotropic support (63,67). In such patients, the outcome is poor (66), and the use of high doses of inotropic agents may be associated with an increased incidence of complications such as tachyarrhythmias, myocardial ischemia, and maldistribution of tissue blood flow. Furthermore, inotropic support is frequently not started until the patient has been admitted to the intensive care unit (ICU), and then it is not clear whether boosting $\dot{D}O_2$ can improve the outcome.

Resuscitation with isotonic crystalloids to supranormal cardiac output may have adverse effects on neutrophil function (68). Neutrophil activation, as measured by CD18 expression and oxidative burst activity, was increased after dilution with all isotonic crystalloid and colloid solutions. There were no significant increases in neutrophil activation with albumin or hypertonic saline. These data may indicate a susceptibility to increased incidence of the

posttraumatic inflammatory state and organ failure, though this has not been proven (69). Rapid resuscitation does produce a prolonged depression of the immune response, whereas slower resuscitation results in a faster restoration of cell-mediated immunity (70). So, large volume resuscitation and hemodilution to increase cardiac output may be detrimental.

Many clinical studies calculate $\dot{V}O_2$ and $\dot{D}O_2$ using arterial and mixed venous oxygen content determined from arterial and mixed venous blood samples (71–73). To determine the true ERO_2 , $\dot{V}O_2$ must be measured independently of oxygen transport by measuring the difference in volumes between inspired and exhaled oxygen or by an oxygen replenishment method in a closed circuit with a metabolic cart, so that mathematical coupling of oxygen transport and $\dot{V}O_2$ is avoided (71–74). Coupling occurs when the common measurements of cardiac output, Hb concentration, and arterial oxygen saturation are used in calculations of both oxygen transport and $\dot{V}O_2$. As a result, in some papers, erroneous conclusions may have been drawn about benefits of supranormal $\dot{D}O_2$.

Inotropic agents have frequently been used to study the relationship between systemic $\dot{D}O_2$ and uptake, but in many circumstances, such as sepsis and respiratory distress syndrome, they do not increase ERO_2 . One school of thought is that it is not so much in hemorrhagic shock that ERO_2 becomes dependent on oxygen transport. Rather, in hemorrhagic shock, there is a failure of the usual compensatory mechanisms that ensure an increase in the ERO_2 ratio in response to increased oxygen transport (72).

One of the criticisms of the data produced by Shoemaker's and Scalea's group (15,75,76) is that the control groups in their studies were not given adequate treatment. This issue was addressed by Hayes et al. (67) in their study that examined elevation of systemic $\dot{D}O_2$ in 100 critically ill patients. The goals of treatment were those used by Shoemaker's group (64,65). If the goals were not achieved with a standardized fluid challenge, the patients were randomized to a control or treatment group. The treatment group received intravenous dobutamine until all three goals were achieved. Dobutamine was also administered to the control group, but only if CI was below $2.8 \text{ L M}^2/\text{min}$. In both the control and treatment groups, norepinephrine was also administered to maintain MAP at 80 mmHg. These investigators found that elevated cardiac output and oxygen transport at supranormal values were not beneficial and did not improve outcome. The increased $\dot{D}O_2$ was associated with decreased ERO_2 and no change in $\dot{V}O_2$. In patients receiving treatment, there was a greater incidence of complications from inotropic and vasoactive support and a greater mortality (54%) compared with the control group that had 34% mortality. An important difference between the patient population studied by Hayes et al. (63) and Shoemaker's group lies in the finding that two-thirds of Shoemaker's patients could achieve the three hemodynamic goals identified with fluid alone (75,76). This suggests that the ICU patients studied by Hayes et al. were probably more ill and treated later in the course of their disease than patients managed by Shoemaker's group. Hayes et al. (63) propose the concept that the ability to achieve the desired levels of $\dot{D}O_2$ and $\dot{V}O_2$ are by themselves favorable prognostic indicators. In 17 patients, they were unable to reach these values. Those patients achieving them probably had larger physiologic reserves, less severe illness, and as a result, had a better prognosis and outcome. The optimum cardiac output is time dependent. If oxygen transport can be restored early, lactate washout completed soon, and oxygen debt repaid expeditiously, it seems reasonable to advocate supranormal cardiac output early in the resuscitation phase, once all sources of bleeding have been controlled. Waiting more than 24 hours before normalizing lactate levels in patients following hemorrhagic shock and a failure to recognize oxygen debt is not optimal management. This practice is likely to increase mortality and morbidity as judged by indicators such as the multiorgan dysfunction score.

USE AND INDICATIONS FOR BLOOD TRANSFUSION IN TRAUMA AND CRITICALLY ILL PATIENTS

The traditional indication for administration of blood occurs when Hb values fall below 10 g/dL (77). This became known as the transfusion trigger and was used by clinicians to guide their decision about whether or not to administer blood. More recently, the benefits of blood transfusion have been questioned and the concept of a single laboratory value as a transfusion guide has been reviewed, because of the belief that the decision to transfuse is influenced by many factors including comorbidities (especially cardiac), age, the acuteness of onset of blood loss, expectations for continued future blood loss, and the physiological changes that the current blood

loss has produced (78). This section of the chapter will describe the physiological evidence to support a need for blood transfusion in critical situations.

Liberal vs. Restrictive Transfusion Practices

The Canadian Critical Care Trials group compared the outcome of a liberal strategy to a restrictive strategy of blood transfusion (79,80). In the first study in critically ill patients who were euvoletic, they compared mortality in just over 400 patients randomized to each of two groups, one to be transfused if Hb was less than 7 g/dL within 72 hours after their admission, the other group of patients to be transfused if their Hb fell below 10 g/dL. They found that overall 30-day mortality was similar (18.7% vs. 23.3%) in both the groups (79). However, mortality rates were significantly lower with the restrictive transfusion strategy, among patients who were less acutely ill, [with acute physiology and chronic health evaluation (APACHE) score ≤ 20], and among patients less than 55 years of age. The in-hospital mortality rate during hospitalization was also significantly lower in those randomized to the restrictive strategy. Although the restrictive strategy seemed at least as effective as liberal transfusion, one group of patients in whom there appeared to be an exception was those with acute myocardial infarction and unstable angina. In their follow-up study in critically ill patients with cardiovascular disease, they again compared the same groups of patients who received therapy according to the restrictive and liberal transfusion strategies. Mortality rates were similar in the two groups. However, changes from baseline in multiple-organ dysfunction scores were significantly less in the restrictive group with a transfusion trigger of 7 g/dL. The restrictive policy in these patients significantly reduced the average number of red cells transfused from 5.2 ± 5.0 units to 2.4 ± 4.1 , a 53% reduction. In 257 patients with severe ischemic heart disease, the restrictive group had a lower but nonsignificant absolute survival rate compared with patients in the liberal group, again repeating the finding that patients with acute myocardial ischemia and unstable angina are at risk from Hb levels below 10 g/dL.

Transfusion Guidelines Status

The Transfusion guideline produced from the NIH Consensus Panel published in 1988 (81) was that red cell transfusion should occur at a Hb value of 7 g/dL in patients free of cardiac and cerebral disease. The American College of Physicians (38), with many of the same participants, also identified 7 g/dL as an appropriate level for red cell transfusion. The ASA (83) proposed a range of 6 g/dL, when blood must be transfused, to 10 g/dL when it should not be transfused. The Canadian Medical Association identified 8 g/dL as the guideline for transfusion (84). So, the consensus panels do not have consistency with each other, and recently the concept of a single laboratory value as a guide to the need for transfusion has been discredited. The College of American Pathologists practice guidance recommended that in acute anemia, a fall in Hb values below 6 g/dL or a rapid blood volume loss of more than 30% to 40% requires red blood cell transfusion in most patients (4).

Trends in Transfusion Practice

Another way to look at guidelines for transfusion in critical situations is to look at actual clinical practice. In an article from the Trauma Program at the University of Toronto, Dr. Farion and his colleagues described trends in the use of blood among adult trauma patients admitted during 1991, 1993, and 1995 (Fig. 14) (85). There were between 500 to 560 patients in each year with similar admission Hb levels and injury severity scores. A significant reduction was found in the average 24-hour Hb levels, the lowest Hb levels, and the discharge Hb concentrations during the three years from 1993 to 1995. Discharge Hb levels fell significantly from 11.5 to 11.0 g/dL, lowest Hb levels from 9.6 to 9.2 g/dL (Fig. 15). These trends indicated significant reductions in both the number of trauma patients receiving blood products and the total number of units transfused. Three hundred fewer blood units were transfused, when 60 more patients were treated in 1995 with similar injury severity scores, compared with 1991 (Fig. 13). There was also more crossmatched blood and less type-specific and uncrossmatched blood used in 1995, indicating that the clinicians felt more comfortable in waiting the extra time necessary to obtain crossmatched blood and, therefore, were naturally more tolerant of acute anemia in the bleeding patient than previously in 1991.

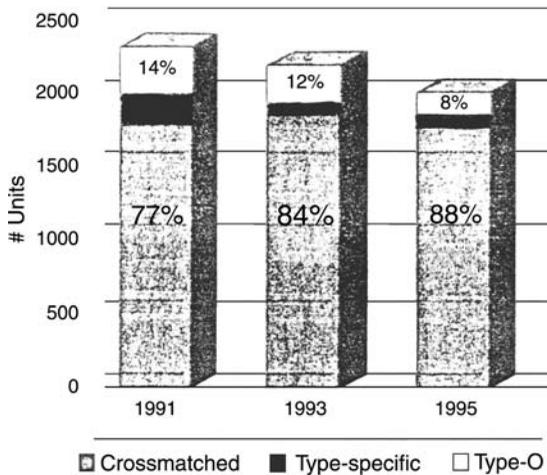


Figure 14 Trends in the type of blood transfused at the University of Toronto Trauma Program from 1991 to 1995 as a proportion of total blood. A reduction is seen in the use of type-specific and type O blood as well as a reduction in overall cross-matched blood administration between the three years. *Source:* From Ref. 9.

How Do the Bleeding Trauma Patient and the Stressed Critically Ill Patient Differ?

These low limits of Hb used in restrictive transfusion strategies, while apparently acceptable in elective surgical cases or in the critical care unit, might not be appropriate in management of the bleeding, critically ill patient for the following reasons. First, cardiac output may be inadequate in the bleeding trauma patient because of low circulating blood volume as in hemorrhagic shock. Second, in low cardiac output states, with low circulating volume, there is maldistribution of blood flow potentially placing vital organs at risk from ischemia (3,86). Third, when there is ongoing blood loss, it may be hidden when in association with fracture sites, or it may result from coagulopathies, especially likely with hypothermia. Fourth, if the patient is undergoing surgery, the extent and predictions for blood loss may be uncertain. Fifth, in certain patients such as those with multiple trauma, inadequate erythropoiesis occurs in response to low Hb, and a hypoferrin state secondary to a complex network of bleeding and inflammatory mediators appears within 12 hours of injury and lasts more than nine days (Fig. 16) (87). Last, there is always the element of uncertainty in estimating future blood loss when managing the recently admitted patient who is critically ill.

The two major organs at risk for impaired oxygenation are the brain and the heart. The brain is not often monitored in any quantitative way during critical illness or anesthesia; although transcranial cerebral oximetry and jugular venous oximetry may have some merit (12,88), these are not often monitored at the onset of an acute state. Although cardiac ischemia can be followed by ST segment analysis (27), and troponin analyses, very few clinicians actually do this in the midst of a busy resuscitation or anesthetic procedure for a patient with significant bleeding. Monitoring urine flow is not helpful as it is a poor indicator of

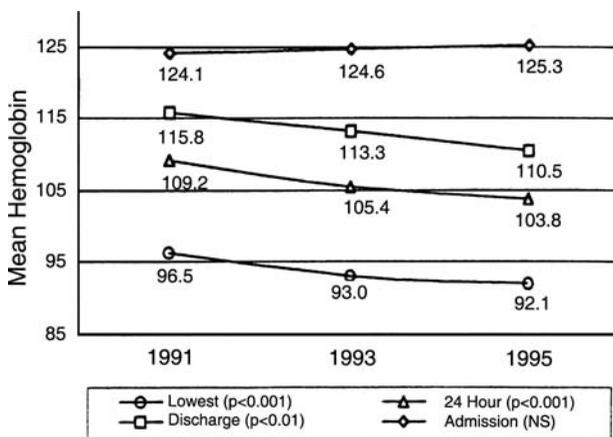


Figure 15 The mean hemoglobin (Hb) concentration of trauma patients on admission, after 24 hours, and on hospital discharge as well as their Hb nadirs shown among the University of Toronto Trauma Program from 1991 to 1995. Patient discharge Hb levels fell significantly over these years. *Abbreviation:* NS, not significant. *Source:* From Ref. 9.

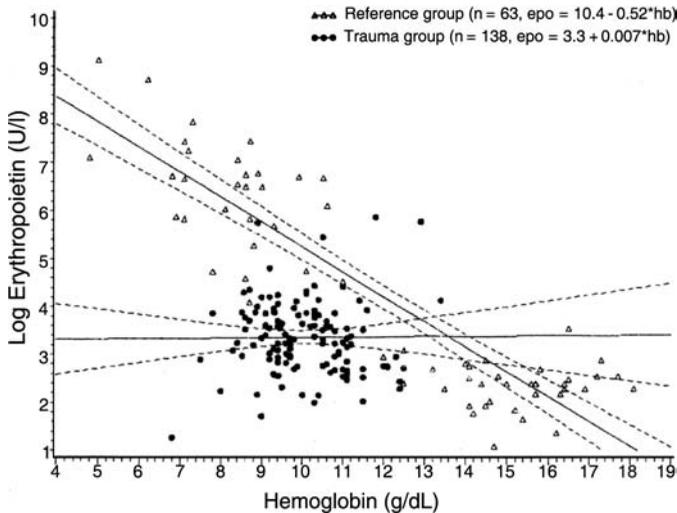


Figure 16 The Y axis shows a log plot of erythropoietin (μL) and the X axis is Hb in g/dL. Sixty-three patients with primary hemopoietic disorders (*triangles*) are compared with 138 multiple trauma patients (*black dots*). As Hb decreases in patients with primary hemopoietic disorders, erythropoietin levels rise (line of identify shown) exponentially. For trauma patients, there is no increase of erythropoietin as Hb levels decrease. *Abbreviation:* Hb, hemoglobin. *Source:* From Ref. 11.

resuscitation of the kidney. In fact, high-output renal failure (the frequent precursor to oliguric renal failure) is accompanied by increased urine flow combined with decreased creatinine clearance (13). The gut lacks autoregulation capability, so when blood pressure falls in the anemic hemorrhaging patient, the bowel becomes ischemic with the resulting changes being a probable cause of multiorgan dysfunction and peritonitis. The gut can be monitored by tonometers, but this requires special and repeated calibration and is not usually done during resuscitation in the hemorrhaging patient. So, for these reasons, the clinicians managing critical situations tend to err on the cautious side of 8 to 10 g/dL Hb levels during management of the acutely bleeding patient.

How Does the Need for Transfusion Differ in Critically Ill Patients?

The European multicenter study on blood draws in 46 ICUs reveals the common occurrence of anemia and the large use of blood transfusion in critically ill patients (89). While most clinicians prescribe blood in the belief that it enhances oxygen transport in critically ill patients, there is little data to identify increase in regional DO_2 (90). Efforts to identify the existence of pathological supply dependency and define optimal transport goals in critically ill and perioperative patients have generally been unsuccessful and continue to be controversial (90–98). There have been numerous studies evaluating the effects of blood transfusion on oxygen kinetics in a wide variety of critically ill patients. Although an increase in DO_2 was a consistent finding, an associated rise in VO_2 was observed only occasionally. A decrease in plasma lactate following transfusion was reported in only one of these studies (90). There is, therefore, very little evidence that blood transfusion relieves tissue hypoxia in these reports in critically ill patients. A factor that may influence the lack of correlation between blood transfusion and increased VO_2 is the age of the stored blood (96). Storage of blood decreases red cell 2,3-DPG concentration and thus the deformability of the red cell. Poorly deformable red cells flow through the microcirculation inefficiently. Increased splanchnic ischemia followed transfusion with old blood in patients with sepsis, whereas in a rat sepsis model, fresh blood increased VO_2 , and old blood failed to do so (99).

Blood transfusion also causes immunosuppression by decreasing cell-mediated immunity, reducing non-killer cell activity, suppressing macrophage antigen presentation, altering T-cell ratios, and decreasing the concentration of cytokines (tumor necrosis factor, interferon-8 alpha, and GM-CSF) that are vitally important to the immune response (90,100). There is evidence that the white cells present in transfused blood are the cause of this immunosuppression

because there is a lower incidence of postoperative infection in patients transfused with leukocyte-depleted blood (101,102) and these changes do not occur with autologous blood (103). While these studies suggest that there may be no advantages in blood transfusions in benefiting outcome, there may be specific advantages in not administering blood and maintaining a normovolemic hemodiluted state in some critically ill patients. Patients with skin flaps, reconstructive surgery, or impaired wound healing, may benefit from improved oxygenation (106).

At the capillary level, normovolemic hemodilution causes an acceleration of erythrocyte velocity because of reduced blood viscosity (106). The product of Hct and erythrocyte velocity determines the erythrocyte flux, which reaches its maximum at a Hct between 30% and 35% (104–106). In a study of ischemic flaps in adult minipigs, Schramm et al. (104) found a significant increase in blood flow to the ischemic flap with hemodilution, with a maximum benefit at an Hb of 8.5 to 9.1 g/dL (Hct slightly < 30%).

The Transfusion Requirements in Critical Care (TRICC) investigators, on behalf of the Canadian Critical Care Trials Group, have published several large multicentered randomized controlled clinical trials of TRICC, including some that have been described earlier in this chapter (107–109). In addition, and not so well publicized, is the Canadian Medical Association Supplement (2), which is highly recommended as a single source for reading about blood and component transfusion in adults and children (110). The supplement contains meta-analyses of the published evidence-based literature through to the year 1997. The essence of these Canadian studies is that less blood is transfused when a restrictive strategy (range of transfusion 7–9 g/dL) is compared with a liberal strategy (range of transfusion 10–12 g/dL). On average, a total of 2.6 units of blood were administered to patients randomized to the restrictive surgery group compared with 5.6 units for patients in the liberal strategy group. One-third of patients in the restrictive strategy did not require transfusion, whereas all the patients in the liberal strategy were transfused. There was a nonsignificant trend toward decreased overall 30-day mortality in the restrictive strategy patients. Young patients (< 55 years) and patients with APACHE II less than 20 had significantly reduced mortality when randomized to the restrictive strategy. A second study identified the need for a liberal strategy of transfusion in patients with coronary artery disease, angina, and myocardial ischemia (109). Similar findings were obtained in a retrospective study of 78,974 Medicare patients with acute myocardial infarction (111).

Erythropoietin is an alternative to the use of red cell blood transfusion as a means of increasing Hb levels (112). Recombinant human erythropoietin significantly increases the Hct and red cell mass in patients with chronic renal failure, both dialysis and nondialysis dependent (113). A similar rise in Hct was also noticed in arthritis and anemia of chronic disease (112). Erythropoietin takes 10 to 14 days to produce an increase in Hct. Studies of the use of erythropoietin in acutely burned patients do not show any reduction in postburn anemia or decreased transfusion requirements (114). It is unlikely that erythropoietin can benefit critically ill patients by elevating Hct in those who have a need for blood transfusion within their first 10 days of critical care management.

It seems that the previously healthy, critically ill patient under stress has reduced mortality, improved ischemic tissue perfusion, less complications, and a shorter critical care unit stay when Hb is maintained in the 7 to 9 g/dL range. It is, however, important to understand that normovolemia is essential for these favorable outcomes to be obtained. Fluid challenge is an important method to establish normovolemia, identify reserve cardiac function, and determine the need for fluid infusion (115), fluid restriction, or inotropic support. In patients with hip fractures, invasive perioperative hemodynamic monitoring with fluid challenge shortened hospital stay, and time to being medically fit for discharge (116).

What Sample Measures Can Be Used to Assess Bleeding?

As described earlier in this chapter, the correlation coefficient with hemorrhage volume was higher with base deficit than lactate, but both measures were reasonably correlated with blood loss. Arteriovenous pH and PCO₂ differences, as a measure of adequacy of resuscitation, were also beneficial in addition to base deficit and lactate as simple evaluations of the onset of tissue ischemia. In animal data, both arteriovenous pH and arteriovenous CO₂ differences have a high correlation with critical $\dot{D}O_2$ and lactate levels (Fig. 17). The practical measurement of these values is easy with venous samples for pH and P $\dot{V}CO_2$ being obtained from a central vein, not the pulmonary artery (82). The use of a colorimetric Hb meter in the operating room for serial

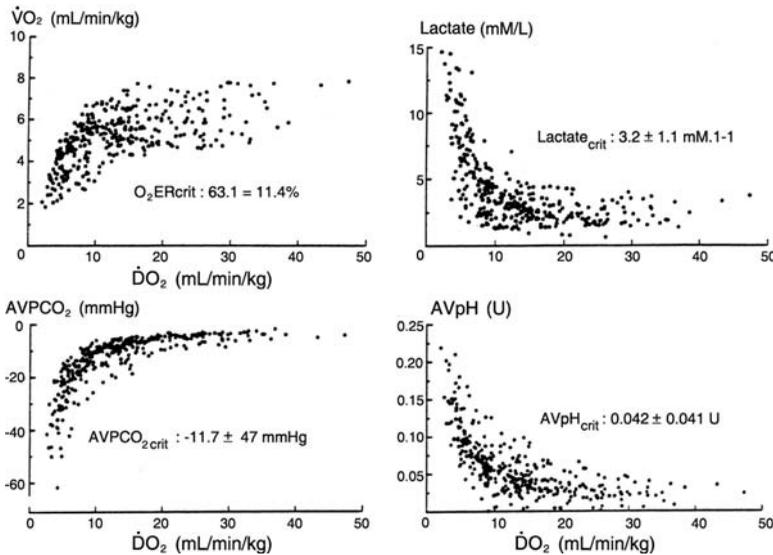


Figure 17 (Left upper and left lower panels) Pooled response of $\dot{V}O_2$ and arteriovenous gradient for PCO_2 to the progressive reduction in $\dot{D}O_2$. O_2ER_{crit} and arteriovenous gradient for PCO_2 at critical point were determined in each animal. (Right upper and right lower panels) Pooled response of blood lactate and arteriovenous gradient for pH to the progressive reduction in $\dot{D}O_2$. Blood lactate level at critical point and arteriovenous gradient for pH at critical point were determined in each animal. *Abbreviations:* $\dot{V}O_2$, oxygen consumption; $AVPCO_2$, arteriovenous gradient for PCO_2 ; $\dot{D}O_2$, oxygen delivery; O_2ER_{crit} , O_2 extraction ratio at critical point; $AVpH$, arteriovenous gradient for pH; $AVPCO_{2crit}$, arteriovenous gradient for PCO_2 at critical point; Lactate crit, blood lactate level at critical point; $AVpH_{crit}$, arteriovenous gradient for pH at critical point. *Source:* From Ref. 159.

monitoring of Hb concentration is also a sensible monitor of the anemia status. In addition to the above measures, a fiberoptic intramucosal PCO_2 monitor, sublingual PCO_2 , transcranial cerebral oximetry, and ST segment analysis capability on the ECG monitor provide optimum current “state of the art” monitoring for management of the hemorrhaging patient.

COMPLICATIONS OF BLOOD TRANSFUSION

More than 12 million units of blood are transfused annually in the United States (117). There is a 1:676,000 chance of getting HIV, a 1:103,000 chance of Hepatitis C, and a 1:63,000 of hepatitis B (Fig. 6) (118). Figure 6 does not show that nationally, the incidence of inconsistencies or errors in blood transfusion is about one mistake in blood administration per 3000 to 19,000 units (119). The chance of being given the wrong blood because of human error is about 1:37,000 (119), resulting in one fatality per 1.8 million units transfused (120). As a result of these data, the risks of blood transfusion have changed, and there has been a decrease in the historic trends in blood transfusion. As more autologous blood is used, there is more cell saving and less pooled blood components (119).

Mistransfusion and Underreporting of Blood Transfusion Complications

To protect patient safety, it is recommended that greater attention be paid to reducing the incidence and severity of noninfectious complications of transfusion. Hemovigilance programs from the United Kingdom, France, and the United States demonstrate that patients suffer significant transfusion-related morbidity and mortality, principally from noninfectious hazards of transfusion (120). Reduction of transfusion-transmitted diseases has been dramatic, with hepatitis risk being reduced from 1:10 in 1960 to 1:100,000 in the year 2000. In the last 20 years, the risk of HIV has also undergone a similar 10,000-fold risk reduction (121). Current data underestimate the occurrence of noninfectious transfusion risks. Nonhemolytic reactions (febrile nonhemolytic events) are major occurrences, e.g., 10% to 30% of labeled transfusions result in febrile nonhemolytic reactions, much more frequently than reported in transfusion

reporting sources (122). Prospective study of transfusions identified substantial underreporting of bedside transfusion errors in Belgium (123) with a rate of unintended recipients of red blood cells being 1 in 400 units. This Belgian study concluded that current passive reporting systems underestimate the true frequency of hazard from blood transfusion by 30-fold. Even fatal transfusion mishaps are significantly underreported. Despite the occurrence of 355 transfusion-associated deaths between 1976 and 1985, no fatalities were reported to the Food and Drug Administration (FDA) (124). The FDA reported transfusion-related death rate due to hemolytic reaction alone to be two times that due to all infectious hazards combined (125). Circulatory overload is a significant problem associated with red cell transfusion. A seven-year retrospective study at a single institution found the incidence to be 1 in 3168 patients (126). In 20% of patients, a single unit was sufficient to precipitate acute respiratory distress. In another study, 1% of orthopedic surgery patients developed circulatory overload, sometimes necessitating transfer to an ICU (127). Extrapolating these data nationally, it has been estimated that 30,000 to 40,000 patients annually might have circulatory overload as an avoidable complication of transfusion (121). When two groups of critical care unit patients were randomized to a liberal or restrictive use of blood, the patients randomly assigned to a more liberal strategy had a significantly higher incidence of cardiac and pulmonary morbidity.

Transfusion-Related Acute Lung Injury and Graft vs. Host Disease

Transfusion-related acute lung injury is a form of adult respiratory distress syndrome characterized by acute respiratory distress, severe bilateral pulmonary edema, hypoxia, tachycardia, fever, hypertension, and cyanosis. It occurs one to six hours after transfusion of blood plasma. It should be considered as a cause of respiratory distress along with other causes such as toxins, inhalation, trauma, sepsis, or aspiration. Mild-to-moderate transfusion-related acute lung injury requires mechanical ventilation, and may, in some cases, be fatal. It was the third most common reported cause of transfusion-related deaths. In the FDA reports, 31 reports (9%) were attributed to acute pulmonary problems (128). In another study, 46 of 2430 platelet transfusions (2%) were associated with severe respiratory reaction over a two-year period (129). FFP donated by women with a history of three or more pregnancies resulted in a significantly lower ERO₂ ratio and in 4 of 100 patients, a pulmonary transfusion reaction was noted (130).

Over 200 cases of transfusion-associated graft versus host disease have been reported and its occurrence is about 90% fatal (131). Irradiating cellular blood components will prevent this problem, but irradiation has detrimental effects on erythrocytes and there is no current standard for irradiation dosing. Noninfectious complications of blood transfusion are summarized in Table 7.

Massive Transfusion, Undertransfusion, and Myocardial Ischemia with Hct Less Than 28%

In neonates, exchange transfusion increases existing metabolic derangements and causes hypoglycemia (132). Among pediatric recipients of massive transfusion, hyperkalemia and hypocalcemia are well recognized and may cause cardiac arrest. Among 140 exchange transfusion recipients that included 106 neonates, more than 34% of the infants had documented hypoglycemia, 1/20 had ECG changes related to hypocalcemia and one had a cardiac

Table 7 Summary of Noninfectious Hazards of Red Cell Transfusion

The frequency of hazards from blood transfusion are underreported 30%
Noninfectious transfusion risk exceeds infectious hazard by 100–1000-fold
Infectious complications of blood transfusion have been reduced 10,000 fold in 20 yr
Transfusion-associated fatalities are particularly underreported
Circulatory overload (20% single unit) may occur in 30,000–40,000 patients/yr
Significantly higher incidence of cardiac and pulmonary morbidity occur in transfused critical care unit patients
Respiratory distress may occur 1–6 hr after transfusion of plasma-containing blood.
Indistinguishable from ARDS due to toxin, aspiration, sepsis, inhalation, and trauma
9% of transfusion-related deaths are pulmonary
Platelets and FFP may cause a pulmonary transfusion reaction as well as blood
Graft vs. host transfusion complication 90% fatal, prevented by irradiating blood components

Abbreviations: ARDS, acute respiratory distress syndrome; FFP, fresh frozen plasma.

arrest. In 25 ill neonates, 12% had severe complications (including two deaths) attributed to transfusion (133).

Undertransfusion, identified as a lack of transfusion when Hb concentration is less than 6 g/dL, can occur in certain populations of patients who are candidates for transfusion. The guidelines for transfusion are not standardized. Blood transfusion did not improve mortality when adjusting for cardiovascular disease in patients with Hb values between 8 and 10 g/dL. Mortality was lower in one study in patients managed so that blood was only transfused if Hb was less than 7.0 g/dL against transfusion with Hb less than 10 g/dL (134). However, those findings are not generally applicable to all transfusions.

In one study, among 190 patients undergoing radical prostatectomy, myocardial ischemic episodes occurred in 61 (34%) of 181 patients evaluated (135). After adjustments for other risk factors, the authors concluded that a Hct less than 28% is independently associated with a risk for myocardial ischemia during and after noncardiac surgery. In cardiac bypass patients randomly assigned to receive either blood and colloid or crystalloid fluids, the patients given crystalloids had delayed myocardial lactate extraction compared with patients receiving blood, indicating that anemia had a potentially deleterious effect on the heart (136). In peripheral vascular surgery, among 13 of 27 patients with a Hct less than 28%, 10 patients had myocardial ischemia and six sustained a morbid cardiac event, an overall incidence of 37% cardiac ischemia (137). A Hct of less than 28% was significantly associated with myocardial ischemia and morbid cardiac events.

Inappropriate Transfusion and Current Levels of Blood Collection and Transfusion in the United States

The use of blood components has come under increased scrutiny because of concerns over the safety of blood transfusion, rising costs of specialized blood components, problems with blood shortages, and questions about the efficacy of blood transfusion. The usefulness of behavioral interventions in reducing inappropriate transfusion rates was reviewed by Wilson et al. (138). They found nine articles between 1988 and 2000 in eight countries, with a three month to one year follow-up. The most frequently used interventions were prospective audit (two studies), education (four studies), transfusion algorithm, retrospective audit, and (one study each). Hct levels above 36 were considered as overtransfusion. All studies showed an impact of the intervention on reducing inappropriate transfusions.

In comparison to 1994, gross domestic blood supply in the United States in 1997 (12,602,000 units) was 5.5% less. The 1997 collection included 11,741,000 units of allogenic community blood, 643,000 units of autologous blood (5.5% of total), and 205,000 units of allogenic-directed blood. The rate of whole blood collections in 1997 per 1000 members of the population aged 18 to 65 years was 12.6% lower than in 1994. However, the red-cell transfusion rate per 1000 members of the population in 1997 remained nearly the same and this is a cause for concern.

There is a significant association between the number of blood transfusions and the risk of subsequent infection in patients following trauma, burns, and a variety of elective and significant emergency procedures (139,140). This increased morbidity is associated with longer hospital stay and higher costs. In addition, patients with malignancy may have earlier recurrences and lower survival rates when they receive blood transfusions (141). There are additional risks for trauma patients with impaired erythropoiesis and postoperative blood loss (Fig. 16).

INDICATIONS FOR PLATELETS, FFP, AND CRYOPRECIPITATE IN BLEEDING PATIENTS

Single-donor platelet transfusions have increased, whereas platelet concentrate (multiple donor) transfusions decreased between 1994 and 1997. Nine million platelet transfusion concentrate equivalent units occurred in 1997, of which 62.4% were apheresis packs (117). One platelet concentrate unit will generally increase the platelet count by approximately 5- to 10×10^9 /L in the average adult, when the usual therapeutic dose is one platelet concentrate per 10 kg body weight. The content of each random-donor unit may vary from 5.5- to 8.5×10^{10} /L platelets (141). Apheresis (single donor) platelets also have wide variation.

The American Association of Blood Banks' standards require a minimum of 3.0×10^{11} /L platelets in each platelet apheresis collection (142). If yields are greater than 6×10^{10} /L, then the collections are often split into two "doses" (143). The *in vivo* activity of stored platelets in a recipient is estimated to be reduced by 75% to 80% of their activity on collection and the half-life of transfused platelets is two days. Platelets should be given through an unused blood-giving infusion set with a 170 μ m filter (144). In 1997, 9,037,000 platelet concentrate equivalent units (62.4% apheresis packs) were transfused.

Single vs. Pooled Platelet Donors

Advantages of single-donor platelets over pooled random-donor platelets include reduction in the rate of alloimmunization, transfusion-transmitted infection, fewer transfusion reactions, and easier logistics (145). The risk of bacterial contamination is lower for single-donor platelets than pooled random-donor platelets, but was 0.42% in one study (146). White blood cell reduction appears to be causally related to a reduction in alloimmunization, regardless of whether single or pooled concentrates of platelets are used (147). From 1994 to 1997, single-donor platelet unit transfusions increased by 31.7%. Platelet concentrate transfusions decreased by 3.3% despite overall 14.9% increased use of platelets from 1994 to 1997. The NIH consensus document on platelet transfusion therapy (148) is in need of revision; this is believed to be in progress.

What Are the Safe Limits of the Platelet Count?

The consensus (140,143) is that a $10,000 \times 10^9$ /L platelet count provides a safe lower limit for the prescription of a prophylactic platelet transfusion in a routine setting with stable patients. A threshold of $20,000 \times 10^9$ /L should be used for those with fever, infection, and related conditions. The therapeutic threshold level is $50,000 \times 10^9$ /L for surgical settings (143), while the ASA believes that this level should be taken into consideration, but counts between 50 and $100,000 \times 10^9$ /L should merit platelet transfusions on the basis of individual patient risk for bleeding. If thrombocytopenia occurs due to massive transfusion or persists in the ICU, platelet infusion will be required. Thrombocytopenia due to consumption or dilution of dysfunctional platelets may increase morbidity and mortality from surgical and traumatic hemorrhage. In nonsurgical patients, spontaneous microvascular bleeding from gums, submucosa, and percutaneous catheter sites does not occur above platelet counts of $20,000 \times 10^9$ /L (149). In massively transfused patients receiving more than 20 units of blood, 75% had platelet counts less than $50,000 \times 10^9$ /L (150), whereas no patients receiving less than 20 units had counts less than $50,000 \times 10^9$ /L. Because six units of platelets contain the equivalent of 1.5 to 2 units of FFP, any benefit of platelet transfusion may not be solely due to platelets, but the FFP (151). In a study forty-one patients were randomized to receive platelets ($n = 22$) or FFP ($n = 19$), 32 of whom were trauma patients. They were prospectively studied after an average of more than 20 units of modified whole blood units (range 12–39 for platelet group and 14–41 units for FFP group). One patient randomized to FFP had microvascular bleeding after 20 units of modified whole blood (from which platelets and/or cryoprecipitate are salvaged before storage) (152) that was thought to be due to dilutional thrombocytopenia. Two patients receiving platelets and one other patient receiving FFP required multiple doses of platelet concentrates and the authors concluded that prophylactic platelet administration was not warranted in massive transfusion.

The ASA task force concluded that the need for platelet transfusion is dependent on multiple risk factors, not a single laboratory value such as platelet count. The risk for surgical patients is defined by the type and extent of surgery, the ability to control bleeding, the consequences of uncontrolled bleeding, the actual and anticipated rate of bleeding, and the presence of other factors adversely affecting platelet function (7). While the ASA task force did not single out critically ill patients, these conclusions seem applicable to nonsurgical patients who may be bleeding. Their final conclusion is that platelet transfusion is justified in bleeding patients, despite an apparently adequate platelet count, if there is known platelet dysfunction and microvascular bleeding, or there are (in the surgical patient) increased risks of complications. The limits and indications for platelet transfusion are summarized in Table 8.

In certain groups of trauma patients, including those with intracranial bleeding, it is recommended by the British Committee for Standards in Haematology that every effort

Table 8 Acceptable Limits and Indications for Platelet Transfusion

10,000 × 10 ⁹ /L safe in route setting with stable nonsurgical patient
20,000 × 10 ⁹ /L with fever, infection
50,000 × 10 ⁹ /L for surgery
50,000–100,000 × 10 ⁹ /L for emergency or if critical surgery
More than 20 units of blood will reduce platelets <50,000 in 75% of patients
Six units of platelets contain 1.5–2 units FFP
Dilutional thrombocytopenia rare, platelet transfusion not warranted prophylactically
Platelet transfusion warranted if microvascular bleeding despite normal count

Abbreviation: FFP, fresh frozen plasma.

should be made in intracranial or eye surgery (153) to maintain platelet counts above 100,000 × 10⁹/L. Clinicians appear to support this, without a great deal of regard being given to circulating platelet count, if intracranial bleeding is a possibility (144,145). These clinicians also identify the difficulty of obtaining platelets in emergency situations in Britain (144). In the United States, audit of underutilization of platelets at one hospital (a failure to administer platelets when platelet count as < 10,000 × 10⁹/L) was found in one patient among 89 during the 14-month period when 3967 units of apheresis platelets were transfused.

Drug-Induced Thrombocytopenia

Thrombocytopenia can be induced by heparin and other drugs. Two prospective studies of 113 patients with heparin-induced thrombocytopenia (HIT) and thromboembolic complications were treated with lepirudin. From the start of lepirudin therapy, thrombin–antithrombin levels decreased and partial thromboplastin time (PTT) ratios of 1.5 to 2.5 produced optimal clinical efficacy. Lepirudin was an effective and acceptable safe treatment for patients with HIT. Anesthetic drugs such as ketamine inhibit agonist-induced aggregation by suppression of platelet inositol 1,4,5-triphosphate formation, guanosine 5-triphosphatase activity, and calcium currents (155). The *in vitro* concentrations to produce the inhibition were in excess of the *in vivo* clinical concentrations (156). The intravenous induction agents, volatile anesthetics, and local anesthetics inhibit platelet function. Sevoflurane and propofol platelet inhibition seem to be greater than that with other agents. Aspirin, although it clearly has antiplatelet action, does not appear to be clinically relevant to bleeding complications (157).

Massive Transfusion and Thrombocytopenia

Prostaglandin E1 (PGE1) is a potent vasodilator that exerts antiplatelet and anti-inflammatory properties. PEG1 infusion resulted in decrease platelet aggregation and prevented decline in platelet count. This was tested to see if such an infusion would prevent thrombocytopenia in association with massive transfusion for major orthopedic surgery (158). The 22 patients who received PGE1 in doses up to 30 ng/kg/min for 72 hours after surgery, had no reduction in platelet counts after more than 10 units red cell infusion, whereas, the control groups of 23 patients had a significant drop in platelet counts three and five days after surgery, necessitating platelet transfusion. The PGE1-treated group was more stable and required fewer postoperative blood transfusions, suggesting that PGE1 might inhibit transfusion-induced coagulation disturbances (159).

Fresh Frozen Plasma

In 1997, 3,320,000 units of FFP/single-donor plasma were transfused in the United States. A recent audit (160), using the Canadian Medical Association published recommendations (160), found that FFP transfusions were appropriate for 167 patients (47%), probably appropriate for 31 (9%), and inappropriate for 160 patients (45%). The Canadian Medical Association guidelines recommended transfusion of FFP in three specific situations: for patients with significant coagulopathy because of acquired deficiencies of multiple coagulation factors in whom serious bleeding has occurred or for whom emergency surgery or other procedures are planned; for treatment of thrombotic thrombocytopenic purpura; for treatment of acquired

Table 9 FFP Indications and Use

For PT or PTT > 1.5 times normal
Dose of 10–15 mL/kg FFP will usually increase plasma factor concentration 30%
For coagulation deficiency in patients transfused >1 blood volume
For thrombocytopenia purpura or for single factor deficiency, where single factor unavailable or ineffective
Contraindicated for volume expansion, wound healing, nutrition
Transfusion of FFP increased 26.6% from 1994 to 1997

Abbreviations: FFP, fresh frozen plasma; PT, prothrombin time; PTT, partial thromboplastin time.

single-factor deficiencies where a product containing the single factor is unavailable or ineffective (160).

An NIH consensus conference concluded that FFP was indicated for documented coagulation protein deficiencies, selected patients with massive transfusions as well as patients with multiple coagulation defects (as in liver disease) in conjunction with therapeutic plasma exchange for thrombotic thrombocytopenia purpura, for infants with protein-losing enteropathy, and for selected patients with other immunodeficiencies. FFP use in other situations was discouraged (161,162). They noted that there was little scientific evidence to support the increasing clinical uses of FFP, although it does contain all the major plasma proteins, including the labile coagulation factors (V and VIII).

The Canadian committee noted that use of FFP as a volume expander or for wound healing was contraindicated (160). The British Committee for Standards in Haematology noted that four units of FFP will usually promote coagulation in adults (154). The ASA task force recommends FFP for correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume or for correction of bleeding in the presence of elevated (>1.5 times normal) prothrombin time (PT) or PTT. The dose should be that to achieve a minimum of 30% of plasma factor concentration (usually achieved with the administration of 10–15 mL/kg FFP). The ASA Task Force notes that four to five platelet concentrates, one unit of single-donor apheresis platelets, or one unit of whole blood provide a quantity of coagulation factors similar to that found in one unit FFP (7). FFP indications and use are summarized in Table 9.

Cryoprecipitate

In 1997, 816,000 units of cryoprecipitate were transfused (17). Cryoprecipitate contains Factor VIII, fibrinogen, fibronectin, Von Willebrand's factor, and Factor XIII, and is used for correction of inherited and acquired coagulopathies. One unit of cryoprecipitate per 10 kg body weight raises the fibrinogen concentration by approximately 50 mg/dL. The Canadian committee recommended cryoprecipitate transfusion in bleeding patients with hypofibrinogenemia, Von Willebrand's disease, and patients with hemophilia A (when Factors VII concentrate not available) (160). The British Committee also recommends that cryoprecipitate be given to massively transfused patients when fibrinogen is less than 80 mg/dL.

The ASA Task Force (7) had three recommendations about cryoprecipitate: (i) prophylaxis in nonbleeding perioperative or peripartum patients with congenital fibrinogen deficiencies, or Von Willenbrand's disease unresponsive to desmopressin acetate (DDAVP)—in consultation with hematology; (ii) bleeding patients with Von Willebrand's disease; and (iii) correction of microvascular bleeding in massively transfused patients with fibrinogen concentrations less than 80 to 100 mg/dL, or when fibrinogen concentrations cannot be measured in a timely fashion. Cryoprecipitate indications and use are summarized in Table 10.

CONCLUSION

Progress is needed not only in avoidance of the complications of blood transfusion, but also in strategies to reduce the need for blood and component therapy. The future methods of achieving this include improved methods of hemostasis at the site of specific injury; pharmacological and physical means for restricting blood flow to hemorrhage sites; increasing the tolerance of organs and tissues for hypoxia; and improved fluid and blood flow distribution to conserve

Table 10 Cryoprecipitate: Use and Indications

One unit cryoprecipitate/10 kg body weight increases fibrinogen 50 mg/dL
Administer cryoprecipitate in bleeding patients with hypofibrinogenemia, von Willebrand's disease, and hemophilia A
Massively transfused patients with fibrinogen 80–100 mg/dL
Prophylaxis for peripartum, perioperative, and congenital fibrinogen deficiency

function of vital organs such as the brain and heart. The future of blood and component transfusion includes prolongation of storage of red cells, improved uptake and release of oxygen, and avoidance of allogenic transfusion reactions. On the horizon, ongoing work will reduce ABO incompatibility issues by changing all blood to universal donor group O. Major advances are being made in blood safety and these will continue in the future with special emphasis on problems related to human error and the improved culture of patient safety for blood transfusion. Screening tests for West Nile Virus will be developed and earlier detection of HIV will occur. Hepatitis and other blood-borne infections will continue to decline in frequency because of better detection and eradication tools.

Oxygen carrying solutions will progressively get approved and may be used as substitutes for the oxygen-carrying capacity of blood. Because they are acellular, these solutions may be used like a drug to facilitate oxygen diffusion into the mitochondria for many purposes, including in ischemia, in trauma resuscitation, and in enhancing radiation therapy. Control of oxygen affinity for these oxygen-carrying solutions may enable better tissue oxygenation in Hbopathies such as sickle cell anemia. Endothelial interactions and binding of nitric oxide by free Hb oxygen-carrying solutions will be mitigated.

The indications for red blood cells, platelets, FFP, and cryoprecipitate transfusions will become more individualized than the current numerical transfusion triggers. Evidence-based practices will minimize overtransfusion and identify a constellation of indications for red cell and component therapy. Monitoring of ischemia and quantitation of the results of increased oxygen carriage will better indicate the circumstances where red cell transfusion may be beneficial. The brain and heart, as organs at risk from acute lack of oxygen, will be targets for improved monitoring during critical situations.

The concept of a single transfusion "trigger" is flawed; rather comorbidities should be taken into consideration in erring on the side of Hct greater than 28. These comorbidities include cardiac (unstable angina, myocardial infarction, etc.) risk, over 55 year of age, and the acuteness of ongoing hemorrhage and expectations for future blood loss. Blood loss in excess of one blood volume in six hours indicates a need to monitor Hb levels frequently. Clinicians should be aware that in 75% of patients receiving 20 units of blood, thrombocytopenia will occur, and FFP is needed should microvascular bleeding or PT and PTT be prolonged 1.5 times or more. Cryoprecipitate is indicated in trauma patients whose fibrinogen is decreased below 80 to 100 mg/dL with massive transfusion. Transfusion trends in many trauma centers have changed with much less type-O universal donor uncrossmatched blood being administered, and less type-specific blood indicating that clinicians have increased tolerance for anemia even in the acutely bleeding, recently admitted, trauma patient.

Noninfectious hazards of blood transfusion, including ABO/Rh incompatibility due to human error, cardiopulmonary toxicity, and transfusion-related acute lung injury are becoming more important complications of blood transfusion as infectious complications diminish in frequency. Errors occur one transfusion in 37,000 and cause one fatality for every 1.8 million transfusions. Generally, these noninfectious complications of transfusion are thought to be underreported by 30%. It is estimated that circulatory overload may occur in 30,000 to 40,000 patients every year. Base deficit, serum lactate, arteriovenous pH, and PCO₂ differences appear to be the simplest and most practical measures for quantitating the shock state and blood loss in hemorrhage. Sublingual PCO₂ monitoring may be a useful real-time monitor to assess the progress of resuscitation from shock. Real-time identification of lack of DO₂ to the brain and heart needs more sophisticated monitors than are currently routinely in use. Blood collection of about 12.5 million units in 1997 was 12.6% lower (1000 population) than in 1994, yet blood transfusion rates remain the same, indicating a cause for concern about future shortages. Tolerance for acute anemia is considerable in otherwise healthy individuals. Data from Jehovah's Witness patients indicate that mortality rates are 20% when Hb is around 5 g/dL, increasing to 90% to 95% when the Hb falls below 3.5 g/dL. Brain oxygenation

becomes critical in normovolemic animals at 2.4 g/dL. Hemodiluted anesthetized human children at Hb of 2.1 g/dL showed evidence of myocardial ischemia. Critical $\dot{V}O_2$ in anesthetized humans and animals varies between 330 and 184 mL M^2 /min.

Compensatory mechanisms in anemia include increased ERO_2 (up to 70%), reduced oxygen affinity, increased cardiac output, and more oxygen dissolved in plasma with supplementary oxygen. Blood transfusion, although increases oxygen carriage, does not necessarily increase tissue VO_2 . Particularly in sepsis, and maybe even in other shock states, ERO_2 does not increase with increased Hb. Red cell transfusion in critically ill patients with no cardiac or cerebrovascular disease, when Hb is 7 g/dL or above, increases mortality and prolongs hospital stay.

The therapeutic threshold for platelets is $50,000 \times 10^9/L$ for most elective surgical settings. For emergency surgery or for acutely hemorrhaging patients with many potential bleeding sites, platelet counts of $100,000 \times 10^9/L$ or even higher may indicate the need for platelets when associated with clinically apparent microvascular bleeding. Dilutional thrombocytopenia is less common than may be suspected. In 75% of patients receiving more than 20 units of blood, platelet transfusion will be required. The usual platelet dose is one platelet concentrate per 10 kg of body weight. Thrombocytopenia may be prevented in massive transfusion by PGE1 infusion. FFP is administered in a dose of 10 to 15 mL/kg for PT and PTT values more than 1.5 times normal. One single-donor apheresis platelet unit, four to five platelet concentrates, or one unit of whole blood provides one unit of FFP. Cryoprecipitate is indicated in massively transfused patients with fibrinogen concentrations 80 to 100 mg/dL to correct microvascular bleeding.

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23 | Fluid Management of Uncontrolled Hemorrhage

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INTRODUCTION

Resuscitation is the process of restoring homeostasis in a patient in shock. When considering shock as the result of hemorrhage, resuscitation implies the administration of fluids to restore or maintain vascular volume, oxygen-carrying capacity, and coagulation. “Resuscitation” also implies eliminating the source of shock, because until bleeding is controlled, resuscitation cannot be complete. Resuscitation from hemorrhagic shock thus consists of two steps—control of hemorrhage and restoration of blood volume.

Although it would be simpler to undertake these steps one after the other, in clinical practice, both activities must occur simultaneously. Time is required for transport to the hospital, for diagnostic studies to determine the site of hemorrhage, and for operative or angiographic procedures. Fluid administration is needed to support perfusion to vulnerable organ systems. At the same time, though, administration of fluid volume increases the rate and quantity of hemorrhage, contributes to hypothermia, and dilutes the normal constituents of blood, all of which further confound the process of resuscitation. This chapter reviews the recent literature on fluid resuscitation during uncontrolled bleeding, and presents the author’s recommendations for management of acute hemorrhagic shock.

UNCONTROLLED HEMORRHAGE

The phenomenon of uncontrolled bleeding is relatively rare. In most situations of tissue injury (whether by surgery or trauma), bleeding will stop spontaneously. This occurs as the result of confinement by surrounding tissues (tamponade), local vasoconstriction, and coagulation. Normal blood coagulates rapidly when exposed to the tissue factor released by injured vascular cells, forming a soft clot within minutes of injury. Hemostasis is dependent on maintaining a low-pressure environment for the minutes to hours required for fibrin deposition, to convert the soft clot to a hard clot. Uncontrolled hemorrhage occurs when one or the other of these mechanisms is inadequate. Clinically, there are three relevant causes of uncontrolled hemorrhage—surgery, trauma, and coagulopathy.

Bleeding from a surgical site passes directly to the external environment, meaning that natural tamponade cannot occur. Manual compression, cautery, and surgical ligation of large vessels are substituted, making most surgeries relatively bloodless. Uncontrolled hemorrhage in surgery usually results from misadventure (inadvertent perforation of an artery or vein), prolonged or extensive dissection, or surgery on highly vascular organs such as the brain or liver. Uncontrolled hemorrhage from a surgical wound usually occurs in an anesthetized, vasodilated patient.

Trauma can produce uncontrolled hemorrhage in any of five locations—the chest, the peritoneum, the retroperitoneum, the thighs, or outside of the body (1). Unlike surgical hemorrhage, where the site of bleeding is usually obvious, traumatic hemorrhage can be difficult to diagnose and even more difficult to control. Also, unlike hemorrhage from surgical wounds, traumatic hemorrhage occurs initially in unanesthetized patients, meaning that the trauma patient with uncontrolled hemorrhage will be vasoconstricted rather than vasodilated. Patients with a medical disease (such as a perforated ulcer) or complications of an invasive

procedure (such as bleeding into the groin following cardiac catheterization) may also present with uncontrolled hemorrhage. Like trauma patients, these patients will have vasoconstriction and be in shock.

A final cause of uncontrolled hemorrhage is coagulopathy. A patient with abnormal clotting function may bleed uncontrollably from even minor wounds, whether surgical or traumatic. Ongoing blood loss can occur from tissue injuries too small and numerous to repair physically, meaning that resuscitation must include diagnosis and treatment of the clotting defect.

Whatever the initiating cause, uncontrolled hemorrhage will soon become multifactorial. A new surgical wound is commonly necessary for control of hemorrhage from trauma, whereas patients with either surgical or traumatic hemorrhage may develop a dilutional coagulopathy. Fluid administration totaling 1 to 1.5 times the blood volume, without platelet or factor replacement, will predictably lead to clotting dysfunction (2). Shock, with its attendant acidosis and hypothermia, will further exacerbate this condition. Early administration of platelets and clotting factors may be as important for the control of ongoing hemorrhage as identifying the site of bleeding.

CONTROL OF HEMORRHAGE

Identification of the source or sources of bleeding is the first step in controlling hemorrhage. For medical or surgical misadventures, the source is usually obvious, and all efforts can be directed toward resolution. Traumatic hemorrhage may be obvious from the presentation of the patient, but its source may be difficult to identify. Plain film radiography will usually serve to diagnose hemorrhage in the chest, followed by tube thoracostomy, which is both diagnostic and therapeutic. Abdominal hemorrhage is diagnosed by focused abdominal sonogram for trauma in centers with experience in this technique, or by diagnostic peritoneal lavage. Retroperitoneal hematoma, usually from sacroiliac injury, can be guessed at by clinical examination, but only confirmed through computed tomography (CT) scanning or angiography. Long bone fracture is usually evident on physical examination, but is not usually actively bleeding at the time the patient presents to the hospital, although the associated loss of 1000 to 1500 mL of blood may contribute to ongoing shock from other causes. External hemorrhage from open wounds will be readily apparent to the clinician, and, with the exception of trauma from facial fractures, can be easily controlled by direct pressure or ligation of obvious bleeding vessels (1).

Table 1 lists clinical approaches to hemorrhage control. Mechanisms include surgical repair or ligation of lacerated blood vessels, partial or total excision of injured organs (spleen, kidney, liver, intestine, and lung), and aggressive packing with hemostatic materials. The concept of "damage control surgery" has evolved in the past decade to focus attention on the importance of early hemorrhage control in trauma patients (3). Initial surgery in the patient with uncontrolled traumatic hemorrhage is limited to vessel ligation, solid organ excision, and packing, with time-intensive procedures such as bowel anastomosis left for a future operation. This concept is also applied to orthopedic surgery in the unstable patient, with rapid external fixation of pelvic or long bone fractures substituted for longer (and more physiologically stressful) internal fixations (4). Angiographic embolization is an appropriate nonsurgical

Table 1 Mechanisms for Site-Specific Control of Hemorrhage, Organized from Simplest to Most Complex

Mechanism	Target source
Direct pressure	Any external hemorrhage, surgical hemorrhage from soft tissue
Fracture reduction and splinting	Long bone fractures
Tourniquet	Avulsed or severely macerated distal extremities
Pelvic stabilization (binder or external fixator)	Pelvic fractures
Surgical packing	Any surgical wound
Local thrombostatic materials (fibrin glue, thrombin dressings)	Any surgical wound
Ligation or repair of vessels	Large vessel injuries
Excision of organs	Liver, spleen, kidney, intestine, lung
Angiographic embolization	Liver, pelvis, soft tissue, face
Systemic administration of Factor VIIa	Potentially any nonsurgical hemorrhage

option for many sources of hemorrhage, including liver, spleen, or pelvic trauma and bleeding arising spontaneously from aneurysmal vessels. Hemorrhage from the low-pressure pulmonary or portal circulations will frequently resolve spontaneously in the presence of hypotension, although rebleeding is possible if subsequent fluid resuscitation is overly vigorous.

Laboratory isolation and mass production of the chemical components of the clotting cascade have led to new options for the treatment of uncontrolled hemorrhage, many of which are under active clinical investigation at this time. Fibrin “glue” is now available to seal any surgical wounds that can be localized and kept dry long enough for an external clot to form, whereas bulky bandages impregnated with thrombin will soon be available for the initial management of difficult liver, mesenteric, or pelvic hemorrhage. Thrombin cannot be administered systemically, because it will produce disseminated clot in all vessels, but an immediate precursor—activated Factor VII (FVIIa)—has shown promise as an intravenous agent that promotes coagulation only in the presence of an exposed tissue factor (5). FVIIa, originally developed to treat hemophiliacs with inhibitors to FVIII, has been documented in anecdotal reports, over the past three years, to have been used in more than a 100 applications for treating life-threatening surgical or traumatic hemorrhage, with the survival of 50% of patients treated with it (Martinowitz U, personal communication). Ongoing animal and human research with FVIIa is seeking to define appropriate indications and dosing regimens.

END POINTS OF RESUSCITATION

Before focusing on a specific strategy for fluid administration during active hemorrhage, it is worth repeating the recommendations of earlier chapters for the overall goals of resuscitation. Although specific parameters will differ from early resuscitation (during active bleeding) to late resuscitation (after control of hemorrhage), an understanding of the later goals will help to guide and inform initial efforts.

Shock is a disease of hypoperfusion, and the ultimate goal of resuscitation must be successful restoration of tissue oxygen delivery throughout the body. In general, resuscitation cannot be considered complete until the patient’s physiology has returned to normal. Vital signs (heart rate and blood pressure) do not reliably indicate adequate restoration of blood flow at the microcellular level (6). It is important to recognize the phenomenon of persistent shock despite normalization of blood pressure—the occult hypoperfusion syndrome—because timely resolution of shock will reduce the subsequent incidence of multiple organ system failure (MOSF) (7). Restoration of perfusion is more reliably confirmed by normalization of serum lactate and arterial base deficit. In more complex cases, where hemorrhagic shock is complicated by cardiac or neurologic dysfunction, active measurement and optimization of cardiac output may be required (8).

Failure to normalize oxygen delivery once hemorrhage is controlled is indicative of ongoing vasoconstriction, and should be treated with warming, aggressive fluid administration, and provision of adequate analgesia and sedation. Further failure to correct serum lactate may indicate ongoing or recurrent hemorrhage, leading to surgical or angiographic reexploration. Because the initial control of hemorrhage is usually accomplished in the presence of significant vasoconstriction (especially in trauma patients), it is relatively common for injured and vasospastic arteries to bleed following warming and volume administration.

RESUSCITATION DURING ACTIVE HEMORRHAGE

Early Research

Cannon, a surgeon who practiced on the battlefields of World War I, first described both the benefits and the drawbacks of fluid administration: “If the pressure is raised before the Surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost” (9). Similar observations followed World War II. The Office of the Surgeon General noted:

“When internal hemorrhage persisted, for instance, there could be no resuscitation without surgery and it was wasteful of both time and blood to attempt to raise the patient’s blood pressure to normal before the operation. The blood or plasma which was administered merely leaked into the traumatized regions and was wasted” (10).

Following World War II, CJ Wiggers developed the first reproducible laboratory model of hemorrhagic shock, using controlled bleeding. Titration to a given pressure for a given period of time produced predictable levels of mortality in study animals, laying the groundwork for comparison of resuscitation protocols. Experience with this model demonstrated the value of whole blood infusion in recovery from hemorrhagic shock (11).

Shires used a modified Wiggers protocol to demonstrate the value of crystalloid administration in restoring extracellular fluid volumes lost to cellular fluid uptake as a reaction to the hemorrhagic insult (12). His work led to the widely accepted Advanced Trauma Life Support (ATLS) standard for the initial resuscitation of hypotensive patients—two large bore IV catheters and up to 2 L of isotonic crystalloid (13).

In 1964, Shaftan et al. published the results of a study of native coagulation, demonstrating that formation of a soft extraluminal clot limits bleeding following arterial trauma (14). His study compared the quantity of blood lost from a standardized arterial injury in dogs under a variety of conditions, including maintenance of blood pressure with vasoconstrictors, hypovolemia induced by prebleeding, vasodilatation with a chemical agent, and replacement of lost blood with immediate transfusion. He found that the least blood loss occurred in the hypotensive animals (whether hypotensive from hemorrhage or from vasodilator administration), followed by the control group, and then by the vasoconstricted animals. The largest amount of blood was lost in animals that received vigorous reinfusion during the period of hemorrhage. Although this study correctly discredited the use of vasoconstrictive drugs in the management of hemorrhagic shock, the need to limit fluid administration pending control of hemorrhage was not widely recognized.

Animal Models of Uncontrolled Hemorrhage

The late 1980s saw the development of animal models of “uncontrolled” hemorrhage. Unlike the Wiggers’ model, standardized on the basis of a certain mean blood pressure, these preparations used a defined physical insult and then incorporated the animal’s natural hemostatic mechanisms into their results. These models share the advantage of being more applicable to the clinical presentation of hemorrhagic shock in trauma patients, than the Wiggers’ model. Normal mean arterial pressure (MAP) in the mammalian species summarized in Table 2 is similar to that in humans—80 to 90 mmHg (25).

Bickell tested the concept of 3:1 crystalloid replacement for lost blood. Hemorrhage was substantially greater in treated animals, and survival was dramatically lower (100% vs. 0%). Oxygen delivery was significantly lower 30 minutes after the initiation of hemorrhage, as a

Table 2 Animal Studies of Controlled Hypotensive Resuscitation from Hemorrhagic Shock

Author	Model	Results
Bickell et al., 1991 (15)	Swine aortotomy	100% survival if not resuscitated vs. 0% if resuscitated with 3:1 crystalloid
Kowalenko et al., 1992 (16)	Swine aortotomy	Survival better if MAP kept at 40 mmHg vs. no resuscitation or MAP = 80 mmHg
Stern et al., 1993 (17)	Swine aortotomy	Survival and oxygen delivery best at MAP = 60 mmHg vs. 40 mmHg or 80 mmHg
Owens et al., 1995 (18)	Swine aortotomy	Fluid titrated to cardiac index. Best results in group titrated to 60% of normal
Capone et al., 1995 (19)	Rat tail cut	Survival best in rats resuscitated to MAP = 40 mmHg vs. no resuscitation or MAP = 80 mmHg
Sakles et al., 1997 (20)	Sheep pulmonary artery	Longer time for spontaneous hemostasis, greater blood loss in immediate vs. delayed resuscitation
Riddez et al., 1998 (21)	Swine aortotomy	Resuscitation with 1:1, 2:1, 3:1 crystalloid; best survival and least rebleeding in 1:1 group
Smail et al., 1998 (22)	Rat venous injury	Liver perfusion best with moderate hyporesuscitation
Burris et al., 1999 (23)	Rat aortic puncture	Survival best and rebleeding least in moderate resuscitation. Different results with different fluids
Abu-Hatoum et al., 2002 (24)	Rat splenic injury	Hemorrhage volume decreased and survival improved with lower volume resuscitation

Abbreviation: MAP, mean arterial pressure.

result of hemodilution of red cells by the administered crystalloid (15). Stern used a similar aortic injury model, beginning with swine that had already been bled through a catheter to a mean pressure of 30 mmHg, to compare the effects of fluid regimens titrated to MAPs of 40, 60, or 80 mmHg. Survival in the two low-pressure groups was similar, with the swine in the middle group (MAP = 60) displaying the best overall metabolic profile (lactate level and calculated oxygen delivery) (17). Kowalenko's results were even more dramatic—only one of the eight unresuscitated animals and only three of the eight animals resuscitated to a normal pressure survived. The best survival, seven of eight animals, was seen in the group resuscitated to a MAP of 40 mmHg (16).

Owens titrated fluid therapy in accordance with cardiac index rather than blood pressure. Swine were randomized to either no therapy or to fluid administration to produce either 60% or 100% of the baseline cardiac index during a 20-minute "prehospital" phase, prior to the operative repair of the aortic injury and complete resuscitation. Results were similar—the largest volume of intraperitoneal hemorrhage was seen in the swine resuscitated to their baseline cardiac index, and these swine required a significantly greater volume of blood and fluid to achieve the same MAP at the end of the study (18). Riddez found similar survival rates and intraperitoneal hemorrhage volumes. Blood flow probes placed above and below the site of injury documented rebleeding in the 2:1 and 3:1 fluid replacement groups (21).

Sakles et al., in 1997, reported on the effect of fluid resuscitation on bleeding from a controlled pulmonary artery injury in sheep, and found that immediate resuscitation significantly increased the volume of blood lost and the time required for hemostasis to occur (20).

Capone et al. reported an uncontrolled hemorrhage model in rats, which superimposed a standardized tail cut injury on a controlled arterial bleed. He achieved a predictable mortality rate in a model incorporating the controlled bleed, the injury, a waiting period ("prehospital"), and a period of surgical repair ("hospital"). The timing of this protocol was designed to simulate, as closely as possible, the clinical care of a hemorrhaging trauma patient (19). Rats were randomized to no treatment at all, "prehospital" treatment to a MAP of 40 or 80 mmHg, or treatment only during the "hospital" phase. All of the untreated rats died early, demonstrating the lethality of the model. Rats treated only after a delay all died, as did rats maintained at a normal MAP while hemorrhaging. Long-term survival was seen only in those rats treated in the prehospital phase at a lower than normal MAP (26).

Smail et al. used radiolabeled microspheres to assess cardiac output and regional perfusion; no difference was found between moderate- and large-volume resuscitation in cardiac output, blood pressure, or diminished regional perfusion in the heart, kidneys, and intestines. Moderate resuscitation improved perfusion of the liver at all time points over both "no" resuscitation and large-volume resuscitation (22). Burris et al. studied both conventional resuscitation fluids and various combinations of hypertonic saline and dextran, finding that rebleeding is correlated with higher MAPs, and survival is best in groups resuscitated to a lower-than-normal MAP. The optimum target blood pressure for resuscitation varied with the composition of the fluid used (23). These results were echoed by Abu-Hatoum et al., on studying massive splenic injury in rats. The least rebleeding and best survival were found with moderate crystalloid resuscitation (24).

A 1994 consensus panel on resuscitation from hemorrhagic shock noted that the mammalian species is capable of sustaining MAPs as low as 40 mmHg for periods as long as two hours without deleterious effects. The panel concluded that spontaneous hemostasis and long-term survival were maximized by the least administration of resuscitation fluids during the period of active bleeding (25).

Human Studies of Delayed Fluid Resuscitation

Models of uncontrolled hemorrhage in animals, although highly suggestive, cannot fully predict the efficacy of this therapy in humans. Although baseline MAPs are similar among species, most animals have more robust coagulation mechanisms than humans. This is why a controlled "prebleed" is frequently required to produce a predictable mortality in animal trials. Furthermore, research animals are bred to have a consistent genetic makeup, in sharp contrast to the heterogeneity of the human trauma population. Laboratory studies of hemorrhage have generally examined only short-term outcomes, with no effort to assess the risk for subsequent organ system failure in the survivors. Finally, animal studies must be performed in

the presence of at least some level of anesthesia, in sharp contrast to many clinical situations. Hypotensive human trauma patients commonly receive a minimum of sedating or analgesic agents, because of the obvious effect of these drugs on the blood pressure.

The effect of anesthetic agents on the body's response to hemorrhage is an important difference between deliberate hypotension occurring in the elective operative setting and hemorrhagic shock presenting in the emergency department. Table 3 summarizes physiological contrasts between these two states. It should be noted that blood loss "without" shock does not generally produce systemic complications such as the adult respiratory distress syndrome (ARDS) (27).

To date there have been two published prospective studies of deliberate hypotensive resuscitation in human trauma patients. The first was that of Bickell and colleagues in 1994 (28,29). Working with paramedics in the City of Houston, the investigators randomized victims of penetrating torso trauma discovered with a systolic blood pressure (SBP) less than 90 mmHg to one of two treatment groups—standard of care (up to 2 L of crystalloid infused in the prehospital setting) or delayed resuscitation [no fluid until reaching the operating room (OR)]. This well-controlled, 37-month study eventually included 598 patients.

Average times of transport and care were 30 minutes from injury to the emergency department, and then 50 minutes before reaching the OR; the fluid-restricted group received an average of about 800 mL of fluid in this time. The immediate-resuscitation group received an average of 2500 mL of crystalloid and 130 mL of blood over this same period. Although substantially different during the period of study, the blood pressure on arrival to the OR was similar in both groups; the authors took this as evidence that the unresuscitated group had achieved spontaneous hemostasis. The unresuscitated group went on to receive less fluid intraoperatively than the immediate-resuscitation group, but this difference was not statistically significant. Survival to hospital discharge in the delayed-resuscitation group was significantly improved over the immediate-resuscitation group [70% vs. 62% ($p = 0.04$)].

Findings in the Houston trial were even more significant for patients with higher injury-severity scores (61% vs. 48%, $p = 0.02$) (30). Analysis of the data based on specific patterns of injury showed that the difference in outcome between the groups was driven by the difference in patients with cardiac injuries (31). The study has been criticized for its randomization mechanism (odd vs. even days), for its lack of applicability to blunt trauma, and for the termination of the study protocol prior to definitive control of hemorrhage. No data are available on the conduct of anesthesia prior to the control of bleeding, or on the incidence of rebleeding after volume loading and induction of anesthesia in patients who had achieved hemostasis preoperatively.

A retrospective review of trauma admissions to the Los Angeles Medical Center corroborated some of these findings. Patients brought to the hospital by private conveyance, without prehospital resuscitation, fared substantially better than those delivered by paramedics, even at high levels of injury severity (32). The authors attributed this finding to less prehospital fluid and more rapid surgical repair in the privately transported group.

Prompted by the publication of Bickell's work, we retrospectively examined outcomes in a population of hemorrhaging trauma patients presenting to our trauma center, beginning with all patients who had received fluids via a commercial rapid infusion system (RISTM, Haemonetics, Inc.) (33). The actual survival rate of this group was compared to the survival predicted by the trauma registry, with results as presented in Table 4. RIS patients, when

Table 3 Differences in Presentation Between Surgical Patients Undergoing Elective Deliberate Hypotension and Emergency Trauma Cases

Aspect	Elective	Trauma
Intravascular volume	Euvolemic	Hypovolemic
Temperature	Normal	Likely hypothermic
Capillary beds	Dilated	Constricted
Level of general anesthesia	Deep	Usually light
Preexisting mental status	Normal	May be impaired
Coexisting injuries	None	May be significant
Comorbid conditions	Known and managed	Unknown

Note: Each of these factors presents a real or perceived contraindication to the use of deliberate hypotensive technique in the trauma patient.

Table 4 Survival to Hospital Discharge in Hemorrhaging Trauma Patients Treated with the Rapid Infusion System (RIS™ Haemonetics, Inc.); Predicted Survival Based on Our Trauma Registry (Historical Controls)

Group	Number	Actual survival (%)	Predicted survival (%)
All RIS patients	451	52.9	61.8 ($p < 0.001$)
Penetrating trauma	225	56.9	60.1 ($p = 0.056$)
Blunt trauma	207	48.8	63.0 ($p < 0.001$)
Ps < 90% and > 10%	105	44.3	57.0 ($p = 0.008$)
Total volume infused > 6 L	180	37.2	57.2 ($p < 0.0001$)

Abbreviation: Ps, probability of survival.

subsequently compared to case-matched controls, had a survival of only 56.8%, compared to 71.2% for patients of similar age, with similar injuries ($p < 0.001$).

This retrospective review was followed by a study to prospectively compare the current standard of care to a protocol based on fluid restriction and delayed resuscitation (34). Patients presenting with SBP less than 90 mmHg and clinical evidence of blood loss were randomized to fluid resuscitation titrated to a SBP of 100 mmHg (normal group) or 70 mmHg (study group) until the end of surgical interventions to control hemorrhage. Patients older than 55 years, patients with no spontaneous pulse on arrival, patients with head or spinal cord injuries, and patients with known end-organ ischemic disease were excluded from study. The results are summarized in Tables 5–7.

Like Bickell, we observed that efforts to maintain deliberate hypotension were often thwarted by the patients themselves—once hypotension allowed for spontaneous resolution of hemorrhage, blood pressure would often rise without exogenous fluid administration. The typical patient began with a low initial pressure, followed by recovery to the vicinity of the target (over- or undershot), as bleeding and fluid administration continued, and demonstrated an eventual rise above the target when hemorrhage resolved, even in the absence of further fluid administration.

The 93% overall survival was higher than predicted from historical data, and substantially higher than that seen in Bickell's group. This reflects the point of enrollment—the group already excluded patients who died in the prehospital phase. It may also reflect improvements in care, an observation effect (i.e., patients in both groups received less fluid than patients not included in the study), or a bias in subject recruitment. Although the authors observed no effect on mortality, it is important to note some of the differences between the groups. The injury severity score (ISS) was higher in the low-pressure group, the presenting lactate and base deficit were greater, and their aggregate predicted survival [based on the TRISS methodology (35)] was lower. None of these differences were statistically significant, but taken together they suggest that the patients in the low-pressure group were more injured and had a greater depth of shock at the time of presentation. This difference, occurring through random chance, introduced a significant bias in our results.

Hemorrhage was controlled more quickly in the low-pressure group, although not significantly so. Lactate levels were equivalent, but base deficit was elevated in the low-pressure

Table 5 Data from the Fluid Resuscitation in Trauma Study: Demographics

	Conventional	Hypotensive	Total
Patients enrolled	55	55	110
Average age	30	32	31
Male	46	41	87
Female	9	14	23
Blunt trauma	22	31	53
Penetrating trauma	33	24	57
Injury severity score	19.65	23.62 ($p = 0.11$)	
Predicted survival	0.94	0.90 ($p = 0.19$)	
SBP during study period	114	100 ($p < 0.001$)	

Note: Probability of survival was calculated using the TRISS methodology.

Abbreviations: SBP, systolic blood pressure; TRISS, Trauma and Injury Severity Score.

Source: From Ref. 35.

Table 6 Data from the Fluid Resuscitation in Trauma Study: Outcomes

	Conventional	Hypotensive	<i>p</i>
Survival to discharge	51	51	–
Occurrence of death	4	4	–
Length of active bleeding (hr)	2.97	2.57	0.2
Total volume in 24 hr (mL)	9477	8882	0.56
Blood products in 24 hr (u)	16.12	19.83	0.45
Intensive care unit day	6.27	11.46	0.07
Hospital days	14.78	23.62	0.01

Source: From Ref. 35.

group. Over the first 24 hours, lactate and base deficit cleared to normal in both groups, requiring similar amounts of fluid and blood products, suggesting that both groups were reaching an equivalent resuscitation end point. The low-pressure group required a significantly longer stay in intensive care and in the hospital. This result was driven by a small number of patients in the low-pressure group who had significant multiple organ system failure (MOSF). It is unclear in what way this result reflects the initial resuscitation. One possibility is that a larger “dose of shock” resulting from deliberate hypotension predisposed patients to MOSF that would have been prevented by more aggressive fluid administration. A second possibility is that these were patients who would have bled to death acutely under conventional care, and developed MOSF as the result of their initial injuries. This is also the same cohort of patients who accounted for the increased ISS and decreased probability of survival in the low-pressure group.

Recommendations

Fluid Administration

Figure 1 is a simple algorithm for fluid resuscitation in the patient with uncontrolled hemorrhage. The emphasis is on the rapid diagnosis and control of ongoing hemorrhage, with fluid administration titrated to the least amount possible to avoid worsening ischemia. Deliberate hypotensive resuscitation—titrated to maintain a SBP of 70 to 80 mmHg—is at least as safe as conventional therapy, and potentially beneficial. Fluid is administered as would be any other medication, i.e., given in small doses and titrated to the patient’s response. The goal is to facilitate surgical control of hemorrhage.

Blood Composition

Many of the risks of aggressive fluid administration are related to dilution of the circulating blood volume. Would aggressive resuscitation be more effective if it better preserved blood composition? Although whole blood is not generally available for resuscitation, it is probably the best possible resuscitative fluid for the patient with massive hemorrhage (36). In fact, many of the concerns about aggressive resuscitation are really concerns about the “too rapid” administration of crystalloids. Recognition of this fact and continued improvement in the safety of donated blood have led clinicians to increase their use of blood products early in the management of hemorrhagic shock. The risk of systemic ischemia is clearly decreased by the maintenance of an adequate hematocrit, whereas the potential for dilutional coagulopathy can be avoided with the early administration of plasma and platelets.

Table 7 Data from the Fluid Resuscitation in Trauma Study: Blood Chemistry

	Conventional	Hypotensive
Lactate on admission	6.43	7.19
Lactate at end of bleeding	4.26	4.77
Lactate at 24 hr	1.99	3.04
Base deficit on admission	5.85	8.84
Base deficit at end of bleeding	2.96	5.04
Base deficit at 24 hr	–2.23	–1.17

Note: The difference in base deficit at the end of bleeding is statistically significant ($p < 0.05$).

Source: From Ref. 35.

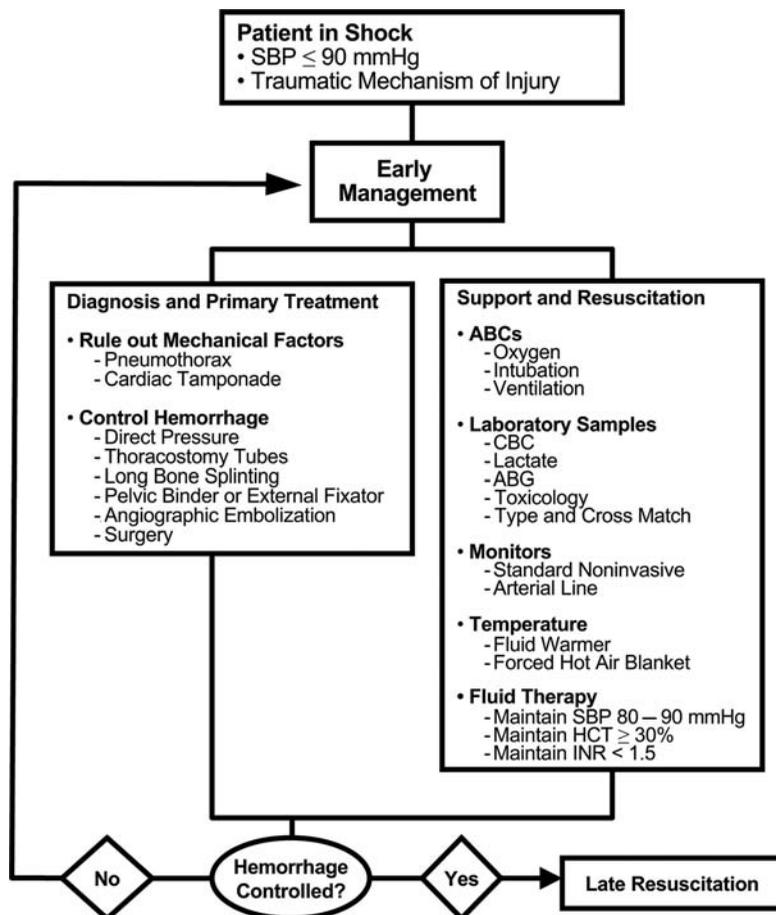


Figure 1 Algorithm for fluid resuscitation during uncontrolled hemorrhage.

The clinician must also monitor and maintain normal plasma electrolyte concentrations. Ischemia, administration of older red cell units, and minor transfusion reactions can all contribute to a rise in serum potassium, although seldom to levels that require active intervention. Excessive administration of hypertonic solutions, including normal saline, can lead to a hyperchloremic metabolic acidosis, although this complication is more commonly observed in the intensive care unit during late resuscitation (37). Finally, and most importantly, serum calcium concentration can fall significantly during rapid transfusion, as a result of chelation by the calcium-binding agents used to keep banked blood from clotting (38). Decreased serum calcium will depress the inotropic state of the heart, leading to decreased tissue perfusion even in the presence of adequate fluid volume resuscitation. It is imperative to monitor serum ionized calcium levels whenever blood products are administered more rapidly than two units per hour, and administer intravenous calcium as needed to support cardiac function.

Temperature

Hypothermia is a risk of both hemorrhage and rapid volume administration, particularly in trauma patients initially resuscitated in the prehospital environment. The effects of hypothermia on resuscitation are controversial. Reduction in body temperature reduces the rate constant for many physiologic processes, including coagulation, and imposes a thermal load on the patient that requires a future expenditure of energy to reverse (39). On the other hand, there is evidence in laboratory studies that mild hypothermia prolongs survival during shock, probably due to a reduction in oxygen demand in vulnerable tissues (40). A prospective multicenter human trial of deliberate mild hypothermia in trauma patients is underway at this time. Pending the results of this investigation, the conventional standard is to maintain

normothermia during uncontrolled hemorrhage, using blood and fluid warmers, forced hot-air blankets, and a warm clinical environment.

Open Questions

The Role of Anesthetic Agents

Deliberate hypotensive resuscitation limits hemorrhage from the actively bleeding patient, but how should hypotension be achieved? The common approach in clinical practice, employed in both of the prospective human trials referenced above, is to limit fluid administration, thus limiting cardiac filling and, by the Starling relationship, cardiac output. A second possibility exists, however, which is to give fluids generously but at the same time relax the constricted vasculature. Filling and cardiac output would remain low, but perfusion might be substantially better. Shaftan, in 1964, observed that dogs that received vasodilators during hemorrhage stopped bleeding soonest and lost the least amount of blood (14).

All anesthetic agents are vasodilators in hemorrhaging trauma patients. Many (barbiturates, benzodiazepines, and volatile gases) act directly on vascular smooth muscle, whereas others with no direct cardiovascular effect (narcotics, ketamine, and etomidate) have a profound indirect effect, through relief of pain and anxiety, and thus reduction of endogenous catecholamines. Deleterious effects of anesthetic agents on the blood pressure have limited their use in hemorrhaging patients. Even the patient developing uncontrolled hemorrhage during elective surgery will be managed with an immediate reduction in the anesthetic level, in order to allow improved blood pressure through native vasoconstrictive mechanisms. Pressor agents such as ephedrine or neosynephrine are frequently administered to increase blood pressure while fluid replacement is initiated. It is worth noting that Shaftan found his worst results (longest period of bleeding and most blood lost) in animals that received vasoconstricting agents (14).

It is likely that laboratory research has predicted a better effect of deliberate hypotension than has been observed in human clinical trials for exactly this reason. The majority of animal studies of deliberate hypotension are performed in the presence of some variety of anesthetic agents (15–20,22,24–26). This is necessary both to manage and manipulate the animal and to meet the requirements of the institutional research board.

The ideal resuscitation, therefore, might be one in which fluids and anesthetics are administered in equal measure, shifting the patient from low volume/vasoconstricted to high volume/vasodilated, without ever letting the blood pressure rise. This would move the patient closer to the population of elective surgical candidates referred to in Table 3, in whom the value of deliberate hypotension has been well established (41). This theory has not been prospectively tested in humans.

Vulnerable Patient Populations

Clinical trials of deliberate hypotensive resuscitation, including the authors' own, have avoided the application of this technique to populations perceived to be at greater-than-normal risk for ischemic complications (29,34). This includes patients with known ischemic coronary disease, elderly patients, and those with injuries to the brain or spinal cord. The prohibition against hypotension in patients with traumatic brain injury (TBI) is especially well established, because of the observed disparity in outcome between TBI patients who experience hypotension and those who do not (42,43). It is also well established that older trauma patients suffer significantly worse outcomes than younger ones from similar injuries, presumably because of their reduced physiologic reserve (44). Clinical care of these patients is focused on the avoidance of ischemic stress and the rapid correction of hypovolemia.

However, there is another side to this issue. If ischemia is worse than normal for the elderly or brain-injured patient, then perhaps hemorrhage is worse as well. It may be that benefits of rapid hemostasis in vulnerable patients are also significantly increased. Rather than tipping the risk/reward benefit of deliberate hypotension asymmetrically, perhaps the situation in a vulnerable patient is one of both increased risks and increased rewards. There have been no clinical trials to date on this subject, but one recently published laboratory study did find a benefit to deliberate hypotension in animals with TBI compounded by hemorrhagic shock (45). In the absence of convincing human evidence, however, the role for deliberate hypotension in older or brain-injured patients is likely to remain limited.

CONCLUSIONS

Fluid resuscitation during uncontrolled bleeding must be a delicate balancing act between too little, worsening perfusion, and too much, worsening hemorrhage. While recent advances such as damage control surgery, angiographic embolization, topical hemostatic agents, and recombinant FVIIa may dramatically shorten the period of active hemorrhage, informed management of the patient with uncontrolled hemorrhage will remain of critical importance.

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24 Spinal Anesthesia and Fluid Therapy

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INTRODUCTION

What is the role of fluid therapy in spinal anesthesia? Recommendations range from the use of significant amounts of fluid to abandoning preload completely. The natural variability of the physiological response both to the anesthesia and to the fluid load renders the validity of a single procedure such as preload questionable. Fluid deficit during anesthesia is a well-known risk factor. However, in an increasing number of reports, excessive fluid has also turned out to be associated with increased incidence of infections, organ failure, morbidity, and mortality (1–3).

August Bier and his assistant August Hildebrand described the first intrathecal injection in 1898, and they used an opioid. The intention to enable surgical access was not instantly realized. A breakthrough for this method came with the introduction of specific nervous inhibitors. Hypotension occurred frequently, but was utilized to reduce surgical hemorrhage, which was considered to be a major obstacle during surgical procedures. The treatment of hypotension involved raising the legs and tilting the head down. Fluids were given orally or rectally, with slow intravascular absorption and therefore almost absent volume support. Fluid administration was not sufficient for circulatory control: ergotamine and ephedrine were more efficient in treating hypotension.

Spinal anesthesia is an efficient and widely used method (4). In this chapter, perspectives on how fluid loading and regional anesthesia interact, a discussion about the physiological adaptation, and finally a theoretical layout of how fluids may oppose the circulatory effects of nerve blocking are given.

CRYSTALLOIDS

Management of fluid therapy during spinal block for a cesarean section is one of the most studied procedures and may hence serve as a model for this purpose. In most investigations, the breaking point of hypotension is defined as a systolic blood pressure below 90 mmHg or a reduction of more than 30%. In a survey in 2001 initiated to determine the fluid management routines in practice, 87% of the responders stated that they routinely administered preload, and the fluid of choice was Hartmann's solution, the volume used being 1 L (83%), and a left lateral tilt was used by 40%. When a vasopressor became necessary, ephedrine was used by 95% (5).

The beneficial effect of such a crystalloid preload on circulatory stability, as measured by stability of the systemic blood pressure, has been challenged in a variety of settings. In studies from the 1960s, preload was considered to be beneficial because a reduction in hypotension could be identified (6–8). Later, however, its efficiency in preventing hypotension was suggested to be inadequate and unpredictable, and the use of crystalloid preloading was called into question (9). Some abandoned the preload routine based on the finding that a preload of 200 mL or 1 L of Hartmann's solution in cesarean section, administered 10 minutes prior to a spinal block in 60 healthy women, resulted in similar hemodynamic responses. All blocks reached above the level of T6. However, the 1 L group had five hypotensive episodes of more than three minutes duration compared to nine in the controls. Fetal outcomes were similar. Preload was not considered essential (10). Immediate side effects of fluid loading, such as an increased susceptibility to accumulation of fluid in the lungs, which calls for caution, have also been reported (11). On the one hand, the benefit of preanesthetic fluid optimization is widely adopted; on the other hand,

exaggerated fluid therapy has recently appeared to aggravate morbidity and mortality, which highlights the importance of optimal fluid management.

It is of interest to consider not only the arterial pressure stability, but also the evolution of the preload effect on the central venous pressure (CVP) and cardiac output (CO). Elderly American Society of Anesthesiologists (ASA) III urology patients received crystalloid preload (16 mL/kg) before spinal block. When needed, treatment using up to three subsequent fluid doses of 2.5 mL/kg was given. Despite this dosing regimen, a failure to maintain pressure within 75% of baseline value was demonstrated in 50% of cases. However, cardiac index and CVP were maintained. Hypotension could not be prevented due to a loss of systemic vascular resistance (SVR) induced by the spinal block. Another common response to anesthesia was a reduction in heart rate (HR). Two groups in this study received metaraminol or ephedrine infusions as alternatives, and when these therapies failed to restore blood pressure, bradycardia was the mechanism that was considered responsible for the hypotension (12). The conclusion was that the loss of arterial resistance caused hypotension, while the intravascular volume was considered adequate, considering that CVP and cardiac index were maintained.

It was demonstrated in 1967, on 157 predominantly elderly patients, that spinal anesthesia produced early hypotension in 50%. Block above the level of T6 was observed in 65% of cases, and was correlated with a higher incidence of hypotension. The incidence of hypotension was 25% in patients under the age of 50 who had a low block, while block above the T6 level had a 40% incidence. Of those in the over-50 age group who had a low block, 61% experienced hypotension, and when the block was high, the incidence reached as high as 85%. Age and the level of block were clear determinants of hypotension. In this study, preload consisted of a 10 mL/kg, crystalloid solution. Hypotension was treated by an additional infusion of 10 mL/kg. This fluid treatment was significantly better than no treatment, but the effect was not striking. It is of interest that the elderly gained more from fluid treatment than the younger patients. Prevention was not considered a simple matter and the use of a standardized method for all patients was ruled out. Atropine and vasopressors were also evaluated. Atropine was not very successful, but vasopressors proved to be fairly efficient but did not alleviate all cases of hypotension. Occasionally, vasopressors caused adverse effects, and for that reason they were not suggested to be the preferred single routine (8).

To evaluate the significance of the amount of crystalloid preload, 60 elderly but physically fit ASA I-II patients, were given crystalloid preload of either 16 or 8 mL/kg. Controls were given no preload. No correlation was found between fluid dosing and hemodynamic stability, and the overall incidence of hypotension was 27%. However, the height of the block did influence the occurrence of hypotension, which increased to 60% when the block was above T6. All patients with a block higher than T4 required ephedrine therapy (13). The incidence of hypotension in 54 ASA I elective patients receiving spinal block was 55% after a crystalloid preload of 15 mL/kg. Infusion of ephedrine at a rate of 5 mg/min for the first two minutes and then 1 mg/min for the next 18 minutes only reduced the incidence to 22%. Although, ephedrine did not suffice for all patients, it was considered safe and superior to preload (14).

In 144 women scheduled for a cesarean section, it was shown that 20 mL/kg crystalloid preload reduced the incidence of hypotension slightly, from 55% when no preload was given, to 30%. It is somewhat confusing that the vasopressor requirements were similar in both groups. These investigators still recommend preload, but because of the persistent need for vasopressors, the mandatory administration of a fixed preload in cesarean section was abandoned (15). Increasing the dose to 30 mL/kg in this patient group produced no improvement in the hemodynamic stability, and again ephedrine requirements remained unchanged (16). In a review of subarachnoid block in the elderly, lower doses of IV fluid, 8 mL/kg were recommended to reduce hypotension. Administration of larger doses was found to produce little gain, but increased the risk of overload and urinary retention. One important reason for a preload procedure was that it was believed to reduce the incidence of sudden cardiac arrest. Additional treatment with vasopressors was recommended when systolic blood pressure decreases more than 25% or falls below 90 mmHg. It was concluded that the CO was not changed by anesthesia. The circulatory instability was proposed to be primarily related to a decrease in SVR (17).

When hypotension in parturients was subdivided into moderate, 20% to 30% pressure reduction, and severe, more than 30%, it was found that prophylactic infusion of ephedrine 0.25 mg/kg reduced the incidence of severe hypotension compared to preload with Hartmann's solution, 20 mL/kg, from 65% to 36%. Use of ephedrine correlated with a higher

umbilical pH, indicating less stress in these fetuses. Fluids and vasopressors prevented moderate hypotension similarly (18).

The influence of the time span of preload administration was investigated by administering 20 mL/kg crystalloid preload before cesarean section for durations of 10 and 20 minutes. The 10-minute infusion was effective in raising the heart preload and resulted in a CVP of 12 mmHg, whereas the 20-minute group recorded a raise to only 7 mmHg. It is worth noting that the 10-minute infusion caused unacceptably high CVPs in 3 out of 10 patients, without affecting the incidence of hypotension. Crystalloid preload was questioned (19).

In a large study ($n = 1066$), the time course of hypotension was investigated. Ringer's solution preload of 15 mL/kg, given within 15 minutes, was compared with dihydroergotamine 10 μ g/kg IM 15 minutes before induction of anesthesia. A third group received placebo. Hypotension or bradycardia occurred at any point in time during the observation period. The incidence of hypotension or bradycardia was 12% in the fluid group, 17% in the ergotamine group, and 23% in the placebo group. For the most part, fluid load prevented early events, whereas ergotamine prevented later events. This illustrates that it might be of importance how the desired preload effect is matched in time with the development of circulatory events. Another interesting finding was that opioids and sedatives reduced the incidence of hypotension slightly, indicating a role of the central nervous system in the development of side effects (20).

Hypertonic saline is another effective crystalloid fluid mainly for small-volume resuscitation after hemorrhage. In a randomized, double-blind study of 40 ASA I-II patients, two groups were preloaded with either 13 mL/kg isotonic saline or 1.6 mL/kg hypertonic saline 7.5% before induction of spinal anesthesia. These dosages were chosen to provide the same sodium load. Blood pressures evolved similarly, and plasma sodium was within the normal range in all patients. Both regimens were comparable in effect, but utilizing hypertonicity reduced the water load (21). The dose of hypertonic saline was very moderate, however, which may explain the insignificant difference in the hemodynamics. A larger dose in the elderly ASA I-III patients ($n = 33$) undergoing transurethral resection of the prostate showed beneficial results. It was found that preloading with 7 mL/kg of normal saline was associated with significantly more occasions of hypotension and required more vasopressor therapy than preloading with the same volume of hypertonic saline 7.5% (22).

In another study, prehydration with 7 mL/kg 3% saline was compared with the same amount of lactated Ringer's solution. The ASA I patients were scheduled for spinal anesthesia for herniorrhaphy. The use of hypertonic fluid reduced the incidence of hypotension by about one half. Hypotension occurred in 57% in the Ringer's group, and in 27% in the hypertonic fluid group. This dose was double the one in the study in which no benefit was recorded, which can explain the improvement in prevention (23). The amount of sodium might be more important than the volume and because this study compared similar volumes, the increased sodium load showed benefits. However, the effect of such solutions is transient, which is a limitation in longer observation times. In commercial solutions, hypertonic saline is often combined with dextran or hydroxyethyl starch (HAES) to prolong the volume effect.

COLLOIDS

To a question directed to anesthesiologists at the meeting of the ASA in 2002, the vast majority replied that they favored the traditional crystalloid fluid load routine. The effort to restrain such administration of fluid is inspired by the suspected correlation between excessive fluid use and complications (24,25). Excessive fluid may increase the incidence of infection and cause delayed wound healing, organ failure, and increased mortality. Colloids are more effective in terms of the produced intravascular expansion to the volume required, compared to crystalloids. Crystalloids become partly lodged outside the vascular system, while colloids are better preserved in the circulation. Apart from being more costly, colloids may cause itching and, occasionally, allergic reactions.

It was found in the elderly that spinal anesthesia reduced the SVR and arterial pressure by more than 25% in nearly 70% of the cases. Subsequent administration of colloid 8 mL/kg restored arterial pressure in full in half of the cases. The HR declined in response to anesthesia. Interestingly, colloid infusion acted to restore the HR. However, it did not restore the SVR, in fact, this was further reduced by infusion, which is partly attributed to the acute hemodilution.

Not surprisingly, vasopressor therapy was necessary to restore the SVR: fluids are not expected to increase the resistance (26).

In parturients ($n=40$) undergoing epidural anesthesia, it was demonstrated that 0.5 L polygelatin (Haemacel) together with 0.5 L Hartmann's solution was superior to preloading with 1 L Hartmann's solution alone. Hypotension occurred in 45% of the Hartmann-treated patients, and in only 5% of the colloid-treated patients (27). However, the authors concluded from this study that 2 L of crystalloid (no such group was initially studied) would be effective if administered over 30 minutes. Such a study group was subsequently incorporated into the project (which is an unusual action) and it was found that no hypotension was seen in these 25 patients. Another study on spinal anesthesia and cesarean section reported an incidence of 45% when anesthesia was preceded by 0.5 L 6% hetastarch plus 1 L lactated Ringer's solution. In contrast to the previous conclusion, the incidence was almost doubled if 2 L lactated Ringer's solution was used for preload compared to a colloid solution (28).

In comparing crystalloids and colloids, similar doses were used in the beginning. However, it seems more reasonable to compare similar levels of plasma expansion instead. Similar doses (7 mL/kg) of preload with 3% gelatin or isotonic saline in 32 elderly patients undergoing transurethral surgery resulted in the prevention of hypotension by the use of the colloid in most cases (not all) where isotonic saline failed (29). The investigators of a study on cesarean section ($n=160$) concluded that 15 mL/kg 10% pentastarch was superior to the same volume of Hartmann's solution for maintaining hemodynamic stability. Not surprisingly, hypotension occurred four times more often in the crystalloid group—48% versus 12%—than in the colloid group. Fetal outcome was similar, and it was suggested that colloid is an alternative to the use of vasopressors (30). When the colloid dose was reduced to make the plasma volume expansion more equal, 1 L Ringer's solution was still not comparable to 0.5 L HAES. This comparison demonstrated only a transient increase in CVP and an incidence of hypotension of 62% in the crystalloid group versus 38% in the colloid recipients. No differences were found in neonatal outcome or uteroplacental blood flow (31). A group of parturients scheduled for a cesarean section, were given either 0.5 L 10% dextran 40 or 1 L lactated Ringer's solution. Colloid preload was associated with about half the incidence (27%) of hypotension found in the crystalloid group (57%). Neonatal scores were, however, similar (32). A similar result was seen in 40 nonpregnant ASA I women (33). However, these investigations did not use equipotent dosing. To obtain equipotent dosing the crystalloid dose needs to be more than three times the colloid dose.

The larger amount of crystalloid load that does not contribute to a volume effect becomes distributed elsewhere, particularly in the lung. Crystalloid fluid loading during spinal anesthesia and cesarean section in 40 patients increased the thoracic fluid index more than that by preloading with 3% dextran. However, dextran use was paralleled by increased hemodynamic stability, regarding both pressure and CO (34). In the elderly ($n=85$), preloading with 1.5 L crystalloid, 0.5 L colloid, and no prehydration showed that the incidence of hypotension was 39% in the colloid group and 62% in the crystalloid group. The use of colloid fluid sustained systemic blood pressure at levels closer to baseline. However, the benefit of each therapy was considered to be equal, because the requirement of ephedrine was similar in all groups (35).

From the comparison between preload with (i) Ringer's solution 1.2 L, (ii) Ringer's solution 1 L plus 0.2 L albumin, and (iii) Ringer's solution 0.7 L plus 0.5 L albumin in cesarean section, it was demonstrated that all had equal effect on the circulation and pulmonary morbidity. Interestingly, hypotension was considered completely preventable (36). In a meta-analysis of fluid treatment for spinal block during cesarean section covering the period 1966–2000, 23 articles met all inclusion criteria. The review indicated that crystalloid preloading was inconsistent in preventing hypotension. However, its ability to do so increased with the dose in some of the studies. On the other hand, colloid proved effective in all but one study, although complete hemodynamic stability was never achieved. Both colloid fluid and leg wrapping augmented central blood volume better than did crystalloid loading. Central blood volume expansion and not vasopressors was suggested to be the primary therapy for preventing hypotension (37).

Colloids are expensive, but smaller volumes are needed. In Europe, the difference in price relative to the intravascular effect is of the order of 10. Colloid may produce anaphylactoid reactions: hetastarch with an incidence of less than 0.1%, while dextran and gelatins have higher percentages. Moreover, colloids interact with the coagulation system, but the medium-weight HAESs, such as pentastarch, do so to a lesser extent. Another potential dissimilarity

between crystalloids and colloids is that the association between the volume effect and preload could be due to their actions on the vasculature, recalling that colloids often produce a more pronounced reduction in the SVR. Colloids have a higher viscosity, which is sensed by the endothelium, which releases NO that slacks the vasculature (38). If one fluid type distends the venous system, the vasculature might hold a larger blood volume without concomitant increase in preload (39).

Vasopressors are frequently used to treat hypotension, and ephedrine is the common choice, although it is considered to be a mild constrictor. Its advantage is that it can affect both resistance and capacitance vessels, as well as the HR. Vasopressors may cause coronary vasoconstriction, which could evoke ischemic episodes in the predisposed heart (40) or other organs (41), but apparently does not produce fetal ischemia (42). It is often concluded that vasopressor therapy is safe and superior to fluid loading, and phenylephrine is now considered the drug of choice in parturients because of better laboratory results of the fetus. However, if fluid load is omitted, the question whether rare and serious events do not increase remains, because substantially larger studies are required. A recent study on 110 parturients scheduled for cesarean section showed that severe hypotension was avoidable by colloid preload. Crystalloid preload (1000 mL Ringer's solution) resulted in overall hypotension (systolic pressure < 100 mmHg) in 85%, whereas the colloid treated (1000 mL 3% dextran 60) reached 66%. Severe hypotension (systolic pressure < 80 mmHg) occurred significantly more often in the crystalloid group 23 vs. 4% (43).

Other benefits of preload include a reduced nausea (45,46), quicker mobilization (47–49), and improved postoperative well being (50). The IV line also ensures the venous access.

BLOOD PRESSURE AND AUGMENTATION OF BLOOD VOLUME

A degree of intravascular volume support seems to be essential to enable fluids to prevent hypotension (50). Therefore, it can be assumed that the relation in time between the volume effect of an infusion and the sympathicolysis of anesthesia should be matched. The impact of this time relationship was studied in 75 ASA I patients scheduled for orthopedic surgery. Patients were given crystalloids, 12 mL/kg, either for a duration of 20 minutes before the induction of spinal anesthesia or for a duration of 30 minutes starting from the induction. A third group did not receive fluid at all. It was shown that fluid administration increased CO but failed to maintain blood pressure. In the group that received fluid before anesthesia, CO increased by 20% during the infusion, but regressed to values below baseline after induction of anesthesia.

Receiving fluid at the same time as induction caused an increase in CO of about 14%, which also occurred during the critical onset time of the block, however, did not affect the pressure stability (51). The fluid volume was rather low, a rough estimation suggests that the intravascular gain over 20 minutes was only about 300 mL, which very well can explain the lack of effect when the resuscitation matched the development of anesthesia. Only a transient rise in CVP is produced, and the volume augmentation does not persist throughout the anesthesia. Therefore, it is rather difficult to draw any specific conclusions. If the increased CO is meant to counteract the decrease in resistance, the magnitude of its increase must be the same as the relative drop in resistance at all times. While the vascular distention appears after quite a while following an induction, there is a significant risk that the exponential volume decay of crystalloids is substantial just as it is needed.

To illustrate of how quickly volume escapes, volunteers received 1.9 L Ringer's solution over 30 min, which produced almost a 20% dilution. Dilution is a surrogate end point for blood volume expansion, and the 20% dilution corresponds to an expansion of about 650 mL. After ending the infusion, the effect disappeared exponentially: 30 minutes after the infusion, it was reduced by 50%, and after an additional 1.5 hours, the remaining effect was negligible (52).

The correlation between fluid infusion, hypotension, and blood dilution was challenged by giving (i) 1 L lactated Ringer's solution and up to 1 L modified gelatin or (ii) 1 L lactated Ringer's solution combined with up to 1 L 6% HAES or (iii) only 1 L 6% HAES in 90 patients before the cesarean section. The incidence of hypotension and need for vasopressors was significantly lower in the patients receiving crystalloid plus HAES. Blood dilution exceeded 20% in the groups treated with both colloid and crystalloid, but only a 14% dilution was observed

in the colloid-only group. Despite less hemodilution in this group, the frequency of hypotension was similar to that seen in the crystalloid-gelatin group. Crystalloid-gelatin was less effective in maintaining pressure in relation to the achieved volume effect (40). This indicates a difference elicited by some property of the gelatin versus HAES that needs to be investigated. The intravascular retention time of the colloid could be of importance because hypotension may occur during the exponential volume decline, and hence differences in elimination could well explain the hypotension. However, these results suggest that to produce a significant reduction in the incidence of hypotension, a strong hemodilution, and thus a significant plasma volume expansion, must be induced and it must persist for some time.

Preloading in parturients ($n = 36$) with 0.5 and 1 L colloid, in particular, was superior to 1.5 L crystalloid in preventing hypotension, due to its effectiveness in remaining intravascular (50). The causality can be understood from the correlation between the percentage increase in blood volume, which was measured by indocyanine staining, and CO ($r = 0.838$, $P < 0.001$). Hypotension occurred in 75% in the crystalloid group, 58% when 0.5 L of colloid was given, and in only 17% with 1 L colloid (53). Similar results were obtained in 24 ASA III patients undergoing emergency hip surgery. On infusing 1.5 L Ringer's solution or 0.5 L hetastarch the hemodynamic effect correlated with the blood volume increase resulting from the fluid load, and was therefore attributed to the augmentation in blood volume (54).

While hypotension might occur after the preload has been distributed to peripheral tissues, coload seems to be a better choice. A group of parturients who received a crystalloid coload of 20 mL/kg required less ephedrine than the preloaded women did, however, the difference was only present in the predelivery period (55). This conclusion was confirmed in surgical patients as well (56).

A strong augmentation of the plasma volume seems to be required to achieve any tangible pressure stability. Hypovolemia should be avoided and IV fluids can be very valuable in preventing circulatory impediment and even cardiac arrest under these circumstances. An unfortunate relationship between hypovolemia and anesthesia has been demonstrated. The combination of hemorrhage and subarachnoid block produced a 30% hypotension. Hemorrhage or block alone produced only a 10% hypotension: the combined effect was synergistic and not an additive one, and this combination should be carefully avoided; this is an important reason to await a sufficient preload (57).

PLASMA VOLUME EXPANSION

Tonicity is the physical ability to attract water across a semipermeable membrane. Tonicity acts by the attraction of fluid from large molecules, colloids that do not penetrate semipermeable membranes, or from small molecules, such as sodium, that easily penetrate such membranes. Large molecules such as albumin cross blood vessel walls to a very small extent and do not penetrate cellular membranes. Sodium, on the other hand, equilibrates rapidly across vessel walls but remains mainly outside the cells. This difference causes the large molecules to disperse in a smaller body compartment than do small molecules. Consequently, large molecules are better expanders in relation to their number because they are enriched in a smaller space. Related to weight, however, the lighter solutes are more efficient. The strength of tonicity is a major contributor to the extent of the intravascular volume effect of IV fluids. Colloid is added to solutions to increase the augmentation of plasma volume over time. Excess sodium is also used to enhance tonicity. For the treatment of shock, 7.5% sodium chloride and 6% dextran 70 or starch (RescueFlow[®] and hyper-HAES[™]) are available. RescueFlow exerts an average plasma dilution effect 4.4 times greater than that of normal saline, which is less than would be expected from the 8.3 difference in osmolality between the fluid and the body fluids: half the tonicity acts to support plasma volume and half is consumed by the increase in the total body tonicity that follows (52).

As stated before, time is often overlooked as an essential parameter. Textbooks assert that the portion that will remain intravascular ranges from one-third to one-fifth of the given crystalloid. Consequently, three to five times the required intravascular volume has to be given. But such a guideline does not take time or other influencing factors into consideration. Rigid guidelines are somewhat misleading because the plasma expansion is very time dependent (52). The expansion reaches its maximum when infusion is ended, and as much as four-fifths of the infused crystalloid volume may be located intravascularly. However, after

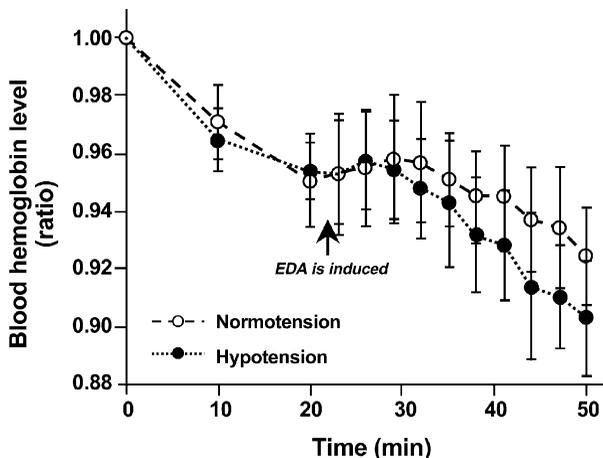


Figure 1 Blood pressure during regional anesthesia in the elderly during crystalloid infusion. Induction of anesthesia was given at 20 minutes. Infusion of 25 mL/kg was given over 50 minutes. The subjects that developed hypotension (*filled circles*) diluted rapidly from the infusion compared to the normotensive (*open circles*) subjects. Hemodilution occurred almost 15 minutes later than the hypotension. *Source:* From Ref. 59.

30 minutes, only about one-third will remain. After another 60 minutes, nearly all the infused fluid will be eliminated, although varying amounts may be distributed in peripheral tissues.

Hypovolemia is a state that increases the efficiency of infused fluid in expanding the plasma volume. This was shown in a study on healthy volunteers who received three 30-minute 25 mL/kg crystalloid infusions on different occasions: during normovolemia, and after 450 and 900 mL hemorrhage. The plasma volume expansion from Ringer’s solution correlated with the degree of hemorrhage (58). Hemorrhage resulted in a decreased rate of fluid elimination and slightly lesser volume of distribution of the fluid, which increased the efficiency of the fluid. A similar effect occurs with relative hypovolemia or hypotension. An ongoing crystalloid infusion during the onset of regional anesthesia in patients scheduled for transurethral resection of the prostate revealed that the patients who developed hypotension (greater than 25% of baseline pressure) became significantly more hemodiluted from the infusion than the others. Importantly, this excessive dilution appeared 15 minutes after the development of hypotension, which suggests that hypotension per se promoted the increased volume effect (Figs. 1 and 2) (59).

Similarly, spinal anesthesia in cesarean delivery caused a decrease in the volume at which crystalloid fluid distributes, which acts to increase the volume response. Colloid resuscitation showed at least a similar pronunciation (60).

REGIONAL ANESTHESIA AND PHYSIOLOGY

To understand how fluid can counteract hypotension induced by spinal block, it is essential to review how a spinal block acts. Events on several levels can be involved: (i) vasomotor center

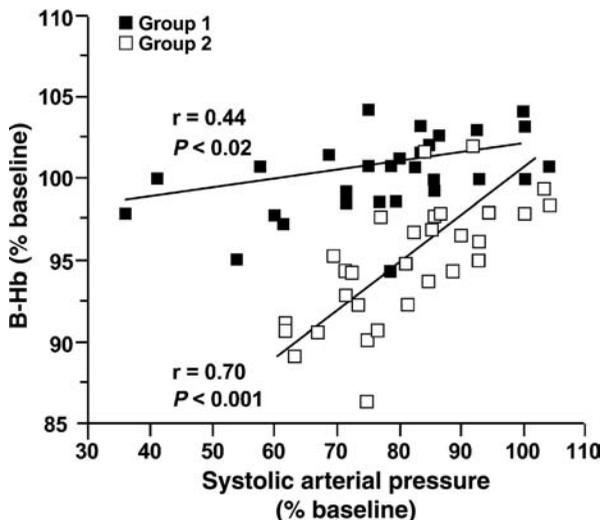


Figure 2 Regional anesthesia in the elderly. Crystalloid infusion (25 mL kg⁻¹) was given during onset of regional anesthesia. Correlation between dilution and reduction in blood pressure. Normotensive subjects (*filled squares*) diluted less at a given blood pressure compared to hypotensive subjects (*open squares*). *Source:* From Ref. 59.

paralysis, (ii) reduced secretion of catecholamines, (iii) paralysis of intercostal and abdominal muscles, (iv) pooling of blood in the venous system from venous distension, and (v) arteriolar dilation (61). Among these, principally two effects can be discerned: a reduction of precapillary tonus and an increase in venous pooling of blood. The loss of arterial resistance is evidently involved in the hypotension. Loss of resistance primarily reduces the arterial pressure. Pooling of blood in the venous system primarily reduces the venous return (VR), and CO, which causes a secondary pressure drop. The amount that becomes sequestered in the legs from a subarachnoid anesthesia has been estimated to be 0.5 to 0.6 L (62). This may be an underestimation, whereas a spinal block exerts a stronger sympathetic influence compared to a subarachnoid block. It is also likely that more blood would be pooled in the lower body if intravenous fluids are infused: the pooling of blood in the legs depletes the thoracic blood volume, which counteracts peripheral pooling of blood.

To evaluate how various parameters influence the incidence of hypotension, one investigation utilized a population pharmacodynamic kinetic model. Interestingly, the speed at which the block spreads turned out to be crucial for the development of hypotension, but was also highly variable and unpredictable (63). The response to the anesthesia was also determined by the degree of sympathetic block, patient age, body position, preanesthetic volume status, and the preexisting vascular resistance.

While the autonomic system strives to increase the vascular resistance in unblocked regions, to maintain the overall resistance, the relation between blocked and unblocked regions may play a role. A smaller degree of block produces less circulatory impediment, because it involves not only fewer blocked areas, but has more unblocked areas that can contract and offset the overall loss of resistance. Unilateral block in 60 ASA I-II patients scheduled for lower limb surgery was followed by a 5% incidence of hypotension compared to 22% when bilateral anesthesia was induced, thus a fourfold increase in hypotension due to the 50% block (64).

A suppression of the autonomic system has been associated with low spinal anesthesia for hip fracture surgery (65), by power spectral analysis. This method compares high- and low-frequency patterns hidden in the heart rhythm to evaluate the extent of suppressed sympathetic regulatory system. Both inhibition of the cardioaccelerator fibers and a decrease in the autonomic response develops. It is more pronounced in high block and general anesthesia. The significance of this is unclear, but severe paradoxical bradyarrhythmias are believed to be involved in some rare events of cardiac arrest during anesthesia. The degree of influence on the HR also depends on the level of the block. A block above the level of T4 blocks the cardioaccelerator fibers. This impairs the autonomic upregulation of HR. If the HR is not responding appropriately, it is likely that a drop in CO and blood pressure will develop (bradycardia often parallels a low CO). The level of autonomic block reaches a few segments above the sensory level.

Parasympathetic activation, the Bezold-Jarisch reflex, induces a somewhat paradoxical HR reduction in response to reduced VR or to hypovolemia (66). This reflex is probably mediated in part by afferents from the heart and noncardiac baroreceptors. Trigger factors include regional blocking, surgery in the lower abdomen, hypovolemia, and vena caval compression, during, for example, pregnancy. This reflex has been suggested to protect the heart when the VR declines. Hypothetically, the heart awaits filling to avoid "empty" contractions. This reflex might have been involved in some of the reported cardiac arrests during regional blocking (67) and it is likely that adequate preloading is beneficial in this respect. Such rare, but important occasions may potentially undermine the studies that argue for a "no preload routine," because these serious side effects are far beyond the power range of virtually all studies on fluid management. In a survey of 40,640 spinal anesthetics, cardiac arrests occurred in 6 out of 10,000 patients (68). When bradycardia develops, treatment includes restoration of VR by fluid loading. Using a colloid fluid load in the elderly during regional anesthesia the HR increased (28). Volume loading may induce an increase in HR through the Bainbridge reflex (69). Bradycardia occurs predominantly during sympathicolysis, hypovolemia, lower abdominal surgery, and from pain or fear, and from some of the medications used in the hospital.

A feasible way to explore how the vasculature adapts to regional anesthesia is to oppose the effects with drugs that have specific sites of action. In such an attempt, epinephrine, which contracts precapillary arteries and compliance vessels, and induces HR increase, was compared with phenylephrine, which mainly contracts precapillary arteries. Phenylephrine restored systolic and diastolic pressures, but not CO, and caused a reduction in HR. Epinephrine, however, restored HR, CO, and systolic but not the diastolic pressure (70). Thus, phenylephrine might

exaggerate the bradycardia that can be elicited by the block and an explanation can be that even though the resistance was restored, a relative hypovolemia persisted, which elicited the reflex bradycardia and loss of CO. The results also illustrate that neither drug reversed all circuit parameters. There is a risk, when focusing on the blood pressure only, that this end point will be treated while others are neglected.

VENOUS RETURN AND MEAN CIRCULATORY FILLING PRESSURE

Systemic blood pressure is surprisingly similar in all mammals. The heart loads the circulatory system with a pressure. Blood flows from the arterial system to the venous system through arteries, arterioles (resistance vessels), capillaries (exchange vessels), and small and large veins (capacitance vessels) down the pressure gradient. The mean arterial hydrostatic pressure (MAP) is approximately 100 mmHg, in the capillaries the mean pressure is 20 mmHg, and in the veins it ranges from 10 mmHg in the distal venous part to around 0 mmHg close to the heart.

The arterial part contains about 30% of the total blood volume, the capillaries 5%, and the venous part the remaining 65%. It is intriguing to consider why the distribution of blood requires only half the volume of that required to return it. The large venous volume is there for a reason. The extra amount parallels what can be tolerated during acute hemorrhage, but another important task for this extra amount of blood is to regulate CO. The well-known equation [Eq. (1)] suggests that HR and stroke volume (SV) regulate CO, because the CO appears to be the dependent variable.

$$\text{CO} = \text{HR} \times \text{SV} \quad (1)$$

Under normal conditions, the heart pressurizes the system, and the vessels regulate the circuit flow. Regional anesthesia acts on the circulation mainly through dilation of the arterial and venous vessels. Fluids, on the other hand, act mainly by the capabilities of the venous system.

The heart and the blood vessels operate as an integral unit, and the function of either component affects the other: the circulation constitutes a closed-loop system (71). This complicates the interpretation of how the circulation is altered by anesthesia and how such an effect can be counterbalanced by fluid. The heart is admittedly the limiting factor during heart failure. But during physical activity, or when circuit performance is compromised from anesthesia, the peripheral vascular system emerges as the key parameter. To support this statement, a few observations merit consideration. (i) Electrical pacing to increase the HR rarely produces any particular change in output (72). (ii) Heart transplant recipients may reach, without heart innervation, quite near the performance of sedentary controls (73,74). (iii) During heart-lung bypass surgery it is not possible to increase the circuit's flow significantly by increasing the pump outlet, because the venous reservoir will be quickly depleted due to the compliance in the system. (iv) The venous system holds about 95% of the total vascular compliance volume, which indicates its active role in circulatory performance by control of the VR. (v) It has been demonstrated in dogs that venous function is crucial in circulatory performance and that the control proceeds through regulation of VR. (vi) When CO is slowed down experimentally, *arterial pressure decreases* and *CVP increases* until they become identical, which coincides with zero flow: a pressure gradient is necessary to promote flow (Fig. 3). The pressure in the system at zero flow is the "ceasing" pressure, and it is normally around

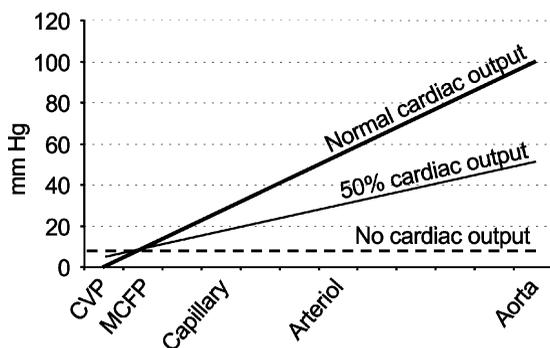


Figure 3 The blood pressure in the circulatory system. During normal cardiac output (*thick line*) it declines from about 100 mmHg in the arterial side, to zero before the right heart. The mean circulatory filling pressure (MCFP) can be measured right behind the capillaries and the difference between the MCFP and the central venous pressure constitutes the driving pressure for venous return. When the cardiac output is reduced to 50%, the pressure is lower (*thin line*) in the arterial part, but higher in the venous part. If the flow stops (*dashed line*) the pressure will be equal throughout the system and will stabilize at the MCFP. This depicts that the MCFP is constant if cardiac output is altered and equals the circuit pressure at zero flow.

10 mmHg. The ceasing pressure is thus lower than the MAP but higher than the CVP, and it is situated at the beginning of the venous system (Fig. 3). It constitutes the driving pressure for VR. Guyton named it the mean circulatory filling pressure (MCFP). (vii) The venous system is switched on instantly when physical activity is initiated: venous and muscular contraction returns, for a moment, more blood to the heart than is being pumped, which increases CO, which rapidly finds a new steady state at a higher level.

The MCFP constitutes the driving force for VR [Eq. (3)]. The region where this pressure can be measured in the circulation is the dividing point of the arterial and the venous systems [Eqs. (3) and (4)]. It is important that *it denotes the relative degree of filling of the circulation*, and if this pressure is reduced by blood loss or an increase in the venous capacity, IV fluid can restore it. If a venous dilation occurs, IV fluid can *fully* compensate for the effect on the circulation, and the MCFP can be restored: the volume fills the vascular tree. However, if precapillary tonus is reduced, the blood pressure cannot be restored even though the MCFP is restored.

The MCFP in mammals is approximately 10 mmHg (75). Hemorrhage reduces this pressure, and when regional blocking enlarges the vascular tree by distending the capacitance vessels, MCFP reduces. Increasing the autonomic tonus by physical activity causes MCFP to rise to its maximum at about 25 mmHg. This puts a better pressure gradient to the VR, which boosts CO. This increase in MCFP can also be obtained by volume loading.

The mean arterial pressure (MAP), SVR, CO, and VR can be described using the following equation:

$$CO = (MAP - CVP)/SVR \quad (2)$$

The pressure difference between the exit of the left heart ventricle and the CVP is the driving pressure for the circulatory system, the pulmonary circulation being excluded. This equation can be subdivided into the arterial and venous components. A distinction is necessary because the influence of preganglionic blocking affects both components, while volume substitution mainly counteracts the effect of venodilation. The arterial component is driven by the pressure difference between the entry, MAP, and exit of the arterial system, MCFP, as follows:

$$CO = (MAP - MCFP)/R_a \quad (3)$$

R_a and R_v are arterial and venous resistance. VR is described by the difference between the entry of the venous component, MCFP, and its exit, CVP:

$$VR = (MCFP - CVP)/R_v \quad (4)$$

These equations explain why a fluid load can increase the CO: fluid load increases MCFP through an increase in the filling level of the overall circulation, and therefore in the driving pressure for the VR. Another benefit is that the heart can work better if the filling is good according to the Starling mechanism.

Altogether, this also sheds some light on the question how fluid load could oppose the effect of reduced arterial resistance. We know that regional blocking reduces the resistance, and we try to compensate with fluid. But fluid does not act on resistances, and therefore a fluid load can only produce changes in the arterial pressure by increases in CO, which can be accomplished via the route of MCFP and VR. The use of fluid to correct arterial hypotension induced specifically by a reduction in arterial resistance is therefore more like an *indirect* method, and only an overshoot of CO can meet the demands from a reduced resistance if arterial pressure is the end point [Eq. (2)].

Fluid can compensate fully for volume deficits by venous distension, or blood loss, but only indirectly and with debilitated capacity for loss of arterial resistance. The model also explains why an unchanged CVP during spinal block does not necessarily mean that volume is not needed. Viewing from the MCFP model, the result from hypotension when the CVP is *not* decreased may be that CO is decreased, or that CO is unchanged during a drop in resistance (Fig. 4).

RAPID BLOOD VOLUME CHANGES

The speed at which blood volume changes occur could influence CO. To achieve an increase in CO during exercise, the VR must increase to a higher level than the CO for a brief period of

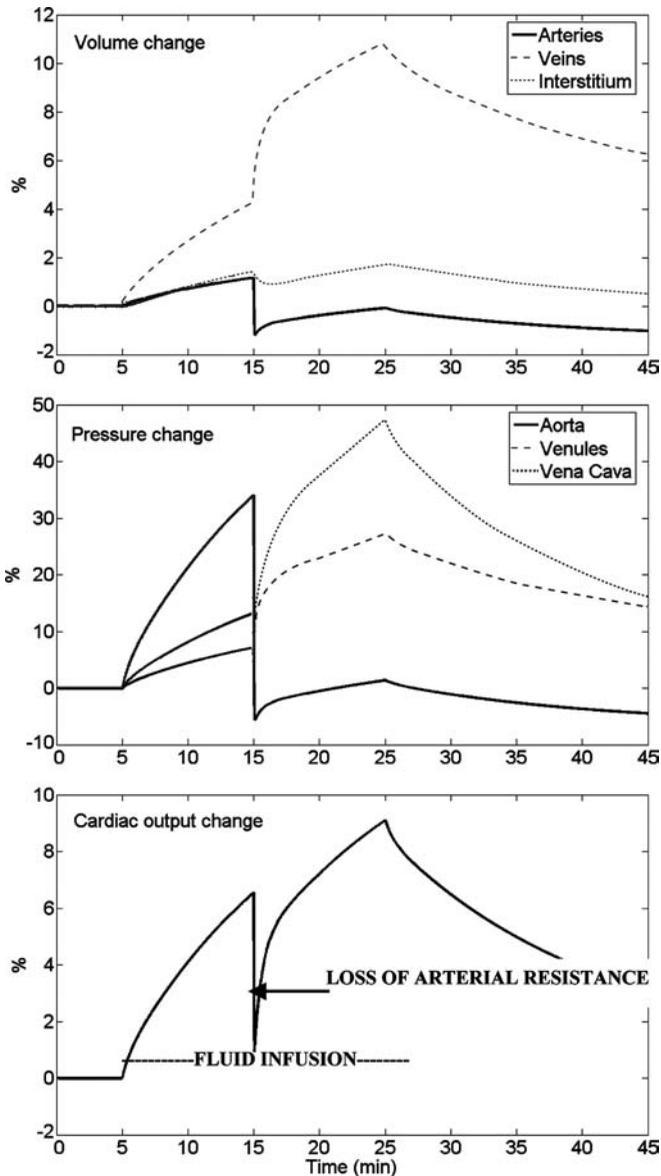


Figure 4 Physiological adaptation during a fluid load and a sudden loss of arterial resistance. Data are obtained using a computerized simulation model. The model describes the circulation using standard textbook circulatory pressures, vascular capacitances and blood volume distribution. The model also assumes that the heart is a permissive pump. An instant onset of reduced arterial resistance is introduced at 15 minutes to simulate the effect of a regional block. The venous system expands as a result of the fluid load. The venous expansion increases when the arterial resistance drops (*top*). The relative pressure change in the venous system is greater than the pressure change in the arterial system. The venular pressure (or mean circulatory filling pressure) increases more than the central vena cava pressure from the fluid load (*middle*), however, the venular pressure rises significantly more than the vena caval pressure, and the pressure gradient to venous return increases. This results in a pronounced increase in cardiac output (*bottom*).

time. The venous system contracts and adds blood flow to the right heart apart from what is delivered from the left ventricle. While the heart suddenly receives more than it pumps, the CO must increase to achieve a new steady state at a higher level. Evidently, the rate at which the venous system contracts impacts the increase in CO.

Assuming that the circulation flow is of 5 L min^{-1} and that the veins suddenly and for a brief instant return an additional flow rate of 2 L min^{-1} , the new flow will be $5 + 2 = 7 \text{ L min}^{-1}$. The period of time needed is just the short time it takes for the heart to stabilize at the new steady state. If the venous contraction continues after this, a new equilibrium will be reached

at 9 L min^{-1} and so on. The reverse can be seen during hemorrhage or when the venous system is dilated from nervous blocking. A theoretical consequence is that a volume depletion from hemorrhage or venodilation that equals the CO, even if for a few seconds, could lead to cardiac arrest, because it would drain the whole circuit flow away from the heart, leaving nothing for return to the heart despite the blood volume being reasonable. Normally, this is prevented by quick connection of regulatory systems. It might also explain why a rapid onset of regional block correlates to hypotension.

Fluids have an effect that counteracts the restoration of blood pressure. Fluids induce mild vasodilation in the resistance vessels due to the acute hemodilution (76) and possibly by the buffer lactate or acetate, both of which are mild vasodilators. The temperature of the infused fluid is also of some importance. Cold (18°C) and warm (36°C) fluids were infused in human volunteers. The HR, blood pressure, colloid osmotic pressure, and hemodilution were measured. When warm Ringer's was infused no changes in blood pressure or HR were observed. However, the HR declined and the blood pressure increased about 10% from cold infusion. The volume effect was similar in both groups (77).

The formulation of IV fluid could interact with coagulation and the renal function. Lactated Ringer's solution produced a hypercoagulative profile as measured by thrombelastogram, whereas patients receiving hetastarch in normal saline exhibited a hypocoagulative state (78). Oliguria and increased creatinine levels were observed when hetastarch in saline was given, but not after hetastarch in balanced saline or lactated Ringer's solution (79).

Predicting Development of Hypotension

If hypotension was predictable, a prophylactic regimen could be used. Some attempts to predict hypotension have been made, but no method is reliable. In one investigation, hypotension correlated with a high SVR and to an elevated baseline blood pressure (80). Recent studies show that genetic polymorphism could be involved in how patients respond to vasoactive drugs and how they adapt to the anesthetic drugs and techniques (81,82). In future, it might well be possible to detect individuals who are likely to develop hypotension and provide a targeted prophylactic program.

SUMMARY

The reported incidence of hypotension due to regional blocking is extremely variable. Figures ranging from 20% to 85% have been reported. The elderly population is more prone to develop hypotension, but benefits more from fluid loading. Hypertension might also be a risk factor for the development of hypotension. Hypovolemia should be carefully avoided when anesthesia is induced. High block correlates with the development of hypotension, as does the magnitude of the block and the speed at which the block spreads. Preload can reduce the incidence of hypotension to some degree. Fluid is more efficient when infused as the anesthetic block evolves. The dose needs to be quite large to be of particular use. Colloids are better than crystalloids and there seems to be an upper limit of the fluid volume. Fluid can reduce the incidence of severe hypotension. Fluid is rapidly eliminated, and therefore hypotension might develop after the induction of anesthesia. However, hypovolemia, hypotension, as well as anesthesia significantly reduce the elimination rate of fluid, which acts to increase its intravascular retention.

Spinal blocking induces vascular dilation that causes both reductions in arterial resistance and venous pooling of blood. Loss of resistance causes hypotension primarily, and venous pooling of blood results in a relative hypovolemia that induces a reduction of CO. Fluid can restore the relative hypovolemia but can only normalize blood pressure against a reduced resistance by increasing the CO over the normal as much as the resistance is lowered.

Owing to the finding that IV fluids cannot with certainty oppose hypotension as a single therapy, the need for vasoconstrictors remains. However, this does not necessarily call for omitting fluids from routine therapy in cases where other causes might be of importance, such as avoiding pre-anesthetic hypovolemia, to mitigate nausea, to reduce the postoperative mobilization time, and finally to ensure the IV connection. It also remains to be elucidated if volume loading can reduce the rare but severe cardiac arrests associated with regional block.

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25 | Fluid Balance in Day Surgery

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DAY SURGERY—A GROWING PART OF MODERN ANESTHESIA

Anesthesia provides service to both patient and surgeon, with the ultimate goal of achieving good intraoperative conditions. One of major challenges for the anesthesiologist is to meet all dynamics in the surgical requirements. In recent years, the surgical scenario has changed dramatically. In the past, patients remained in the hospital several days following surgery. Today, an increasing number of procedures are carried out on an outpatient basis. Ambulatory anesthesia has grown tremendously in terms of numbers and in quality during the last decade and has been predicted to continue to expand even after year 2000 (1,2). There are certainly many reasons for this trend toward a shift from in-hospital service to an ambulatory one. Cost has become increasingly important and is without doubt one of most powerful factors influencing this change in practice. The introduction of less invasive/traumatic surgical techniques and new fast-acting analgesics and anesthetics are also of importance. Of greater importance is, however, the improved understanding of the physiological processes associated with surgical trauma and the general management of these pathophysiological reactions (3,4). Regardless of the reasons, it is clear that many medical centers make great efforts to increase the balance in favor of ambulatory versus in-hospital procedures (5).

The goal in ambulatory surgery is not only to “produce” safe and efficacious surgery but also to achieve an acceptable postoperative course for each individual patient. For the anesthetist, it is not only a matter of creating optimal perioperative conditions for the surgeon and patient, but also a matter of assuring fast and complete recovery with a minimum of side effects. The goal for the day surgical unit is to return the patient to “street-fitness,” his full daily functional capacity, as soon as possible after surgery. Day surgery should therefore take into account not only the surgical procedure and anesthesia, but also all physiological reactions associated with perioperative stress/anxiety, fasting, and the surgical trauma. All efforts should be made to optimize physiology during the entire perioperative period.

Day surgery has a long history initially including less extensive procedures and usually involving healthy American Society of Anesthesiologists (ASA) I-II patients. Arthroscopy, groin hernia repair, uterine curettage and minor ear, nose, and throat procedures are and have been for many years “typical” cases. Dental surgery has also long been performed on an outpatient basis (2,4). Some of these minor procedures may today be performed in the outpatient clinic under local anesthesia eventually combined with sedation. At the same time, one can see that more extensive surgery is moving into the day surgical arena. There is an increasing interest to promote more complex procedures such as laparoscopic cholecystectomy being carried out on an outpatient basis and that elderly and sicker patients can become day surgical patients. In the relatively near future, one can foresee that ambulatory anesthesia will become a major part of the anesthesiologist’s workload. In a future perspective, one would imagine that even more complex procedures would be performed in day surgery. Day surgery will include not only more extensive procedures but also most certainly more fragile patients with a complex medical history (2,6). This will lead to a dramatic change in the concept of day surgery. More proactive preoperative planning and evaluation, thorough perioperative preparation, and different logistics for the postoperative period will be required.

Patients will probably be given various alternatives when they want to be seen in the outpatient clinics for preoperative assessment and also be given different options for the first and possibly second postoperative night. Medical wards offering “light medical service,” medical hotels, and other options to stay close to the hospital and to have some form of support/supervision during the early postoperative period will become available. By extending

the scope of day surgery to include at least a one-night stay, creating “short-stay surgery,” even more extensive surgery will be feasible. Radical prostatectomies have already been successfully performed as short-stay surgery (7). The goal of ambulatory surgery is to provide a safe and “comfortable” perioperative course and fast recovery of mental function with minimal undesirable side effects, such as pain, emesis, dizziness, headache, and drowsiness so that patients can be discharged without undue delay after surgery into their home environment under appropriate and controlled conditions. Major morbidity and mortality have been infrequent in ambulatory surgery. Studies from the early 1990s have shown a remarkably low incidence of major medical sequelae (8,9). Some have even proposed that day surgery is associated with fewer complications than in-hospital surgery. Early ambulation possibly decreases the risk for thromboembolic complications and shortening the stay in the hospital environment may decrease the risk for infections (10,11).

The low incidence of major complications in combination with “high” cost effectiveness is without doubt one of the major driving forces for the rapid growth of day surgery. One should, however, have in mind that these good results could be due to a combination of two factors: only “minor-to-medium” surgery is carried out on a patient population belonging almost exclusively to the ASA I–II class (6,8,9). Although major complications associated with ambulatory anesthesia are rare (8,9), minor complications and complaints are frequently recorded after day surgery. Pain from the incision area, emesis, dizziness, drowsiness, headache, and sore throat are symptoms that are frequently recalled (12–14). Pain and emesis are, in fact, major indications for nonanticipated readmission of the operated patient (15,16). Furthermore, other “minor” symptoms, such as varying degrees of mental/cognitive impairment and changes in sleep pattern lasting for several days do occur (17,18). Taken together, these symptoms may have implications for the postsurgical course. There is an absolute need for someone to escort the patient home after day surgery and to be available during the first postoperative night. Patients may not only feel distressed, but they may even forget instructions given at discharge and are often far from capable of performing normal daily activities. There are already those who are critical, stating that patient care is transferred from the hospital environment to the home environment, creating new socioeconomic consequences (19).

Without doubt surgery outside the ordinary in-hospital environment will become more common during the coming years. Procedures that can be carried out under local anesthesia, or local anesthesia in combination with light sedation, will certainly become more frequent in outpatient clinics. There will be a move for more extensive surgery to be carried out in day centers. Many day centers will create options for at least one overnight stay, going from being merely “day centers” including outpatient clinics and day surgery “short stay units,” to creating options for more extensive surgery to be done. This move will call for more vigilant anesthetic attention. All aspects of anesthesia should be analyzed and evaluated appropriately and repeatedly to meet the changing and challenging needs of ambulatory surgery.

FLUIDS: FLUID BALANCE IN DAY SURGERY

There are a number of question marks concerning fluid balance in day surgery (Table 1).

Day Surgery—Postoperative Nausea and Vomiting

Although complications in day surgery are infrequent, they should not be neglected. Bleeding is one of most common causes for hospital readmission (15). But, the “tip of the iceberg” clinical problem for day surgery is pain and postoperative nausea and vomiting (PONV) in

Table 1 Questions Concerning Fluid Balance in Day Surgery

Fasting hours prior to anesthesia
Drinking hours prior to anesthesia
Oral premedication
Fluid loading during surgery/anesthesia
Drinking before discharge
Passing urine before discharge
PONV

Abbreviation: PONV, postoperative nausea and vomiting.

combination with dizziness, fatigue and a more imprecise, vague sensation of not feeling completely "fit" (2–14). PONV has with all rights been named "the little big problem."

The etiology and pathophysiology associated with PONV are complex (20). A number of meta-analyses have examined the causes and the efficacies of various interventions (21). There are a number of "risk scores" available. From completing fairly simple and straightforward questionnaires, the risk for PONV can be assigned with a high probability for the individual patient (22). Guidelines for prophylaxis and the treatment of established symptoms have also been developed (23). Fluid administration has a clear place in patients with severe PONV. Replacement with an equal volume of sodium chloride and glucose to cover the losses are of value. Ringer's lactate is most certainly also an option, although the loss of H⁺ ions with gastric fluids potentially, in severe cases, may render a tendency to alkalosis.

Preoperative Preparation

Fasting and Drinking Prior to Surgery

There is today a fairly well-established consensus on guidelines concerning preoperative fasting, that is, when eating and drinking should be stopped before any surgery, including day surgery (24). The recommendations for a healthy adult without risk factors are to withhold solid food for six to eight hours prior to anesthesia and stop all intake of clear fluids also two to three hours before the start of anesthesia. Allowing patients to drink clear fluids until two to three hours prior to anesthesia is a major improvement. Changing recommendations to stop intake of food to six to eight hours before anesthetic or major anesthetic blocks, allowing afternoon patients to take a light breakfast is also of value, decreasing the time of "starvation." The same preoperative fasting routines are followed in most institutions for patients planned for minimal alveolar concentration (MAC)-sedation or other services where there could be a risk of regurgitation and aspiration, or loss of swallowing reflexes. These "new" and more liberal guidelines are adopted in most Western countries with only marginal variations (25). The introduction of these new guidelines, when used appropriately, have not had any major negative effects on surgical logistics nor increased the number of late cancellations (26). The lack of negative consequences of these more liberal guidelines may be partly due to the fact that they are not always followed; many patients have been fasting for longer time periods (27,28). There seems to be some discrepancy in the adoption of these new policies between Europe and the United States (27,28).

The effects of "overnight fasting" prior to surgery have been challenged recently. Several studies show changes in insulin resistance and changes in glucose turnover even after short periods of fasting. These effects of fasting and withholding nutrition should be seen in the perspective of the stress response from surgery (29). Even during typical day surgical procedures such as hernia repair, the insulin sensitivity is reduced by about 40% (30). There are studies supporting the intake of energy-rich carbohydrate drinks up to two hours prior to surgery in order to maintain glucose supply.

Premedication

Premedication in day surgery is not an essential or mandatory part of the anesthetic process. Adequate and reassuring information, in combination with efforts to minimize waiting times and delays, can successfully replace pharmacological premedication. In many institutions today, the ordinary anxiolytic premedication to be given one to two hours prior to surgery is no more routine. Also, the routine use of anticholinergics is discontinued. In day surgery, patients should come to the institution in appropriate time prior to the procedure but all unnecessary waiting times should be avoided. Minimizing waiting time and allowing the patient to drink clear fluids up to two hours before coming into the operating room has in most institutions replaced pharmacological premedication. In the United States, small doses of intravenous midazolam are frequently used, whereas in many institutions in Europe, small doses of Propofol, combined with a minimal dose of opioid (so-called coinduction), have become popular shortly before induction of anesthesia. Preoperatively administered analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and/or paracetamol have become popular in many hospitals. Paracetamol in initial doses of 30 mg/kg most often combined with an appropriate dose of a NSAID is frequently given orally with a minimal amount of clear fluid/water (31,32).

Intraoperative Fluids

Intravenous access and intravenous induction are regarded as the gold standard in day surgery as well as for in-hospital anesthesia. While establishing an intravenous line is more or less mandatory for the administration of drugs, there is no absolute consensus about starting the administration of intravenous fluids. To date, there are no well-established guidelines for perioperative fluid maintenance in ambulatory surgery. Both isotonic sodium-containing solutions such as lactated Ringer's solution and electrolyte/glucose combinations are frequently used. Glucose 4% to 5% solutions without electrolytes have also been used.

Although a balanced glucose/electrolyte fluid is administered in most institutions, it is not routine for all day patients. It is more likely that patients undergoing surgery in the afternoon are given fluids. Furthermore, both the volume and the composition of fluids given during day surgery vary considerably (33). The optimal electrolyte and glucose composition is, however, not known.

The fluid requirements during day surgery are no different from in-hospital surgery. One should, however, remember that ambulatory surgery is often of short duration and usually includes "only" minor to moderately extensive surgery. The surgical area is usually small, making evaporative losses almost negligible. Blood loss and other fluid shifts are also in most cases minor. Blood loss and other fluid losses having impact on the physiology are infrequently seen. When occurring, they should of course be handled appropriately, in accordance with the routine for in-hospital patients.

It seems reasonable to state that the day surgical procedures commonly seen today cause a lower trauma impact and do not initiate a stress response similar to that seen in more extensive in-hospital surgery. The need for intraoperative replacement therapy is therefore low, at least far less than when more extensive surgery is performed.

It is not known if the pattern of stress/hormonal response to ambulatory surgery is similar to that seen during more extensive surgery, for instance, if activation of antidiuretic hormone creates a potential risk for hyponatremia (34,35). The risk for a relative postoperative hyponatremia has been proposed following more extensive surgery, but the risk should be far less after minor ambulatory surgery (34,35).

It seems unlikely that ambulatory surgery causes profound shifts in fluid balance or electrolyte composition. Taking into account that day surgery has been performed in hundreds of thousands of patients and the extremely low morbidity associated with its use, major changes in body composition or water content seem hardly relevant. Whether a more aggressive intravenous fluid administration could have positive effects is not entirely clear. There are, however, studies supporting beneficial effects with regard to, for instance, increased speed and quality of recovery from volume loading. Receiving 1000 mL of sodium lactate decreased the incidence of PONV in a study involving minor gynecological surgery (36–38). The addition of dextrose to lactate appears to be somewhat better than the use of only lactated solutions (39). Fluid loading seems to have the greatest effect on patients who had some difficulties in recovery from anesthesia on previous occasions (40). Even the temperature of the intravenous fluid may have some impact. Warming fluids for intravenous administration may reduce the fall in core temperature, especially in patients undergoing laparoscopic surgery (41).

There are, however, also studies questioning the need for intravenous fluids in minor to moderate procedures, at least when given during recovery—the postoperative period (42). Other studies show no difference between oral and intravenous fluids given postoperatively following cholecystectomy (43,44).

The effects of fluid loading during ambulatory surgery have also been studied from the perspective of urinary production. The volume of fluids administered during surgery does not seem to have a major impact on postoperative voiding in patients without risk for urinary retention. Patients at risk, such as those having a history of urine retention or those undergoing pelvic surgery, should of course be observed until they have passed urine. In this patient population, the amount of fluids given does not seem, however, to have any major influence on the risk for retention (45).

To summarize, fluid administration is not a major concern during typical day surgery. During ambulatory surgical procedures, intravenous fluid administration seems to be a practical issue since it maintains vascular access which may be needed for the administration of drugs. In the postoperative period, however, fluid therapy is related to subjective or qualitative outcome which are probably not closely associated with strict physiological needs. The use

of dextrose 4% to 5% in 0.18% electrolytes given perioperatively seems to have a number of potential “minor” positive impacts without major risks and is associated with a low cost. The value may be to maintain the intravenous access, and the administration of drugs as well as eventually improving the quality of recovery.

Drink and Void Before Discharge

Common discharge criteria include ambulation, drinking, and voiding. In recent years, the necessity of drinking and voiding before discharge has been challenged (12,46). Early oral intake may be a factor predisposing to PONV. It may be that patients should not be encouraged to drink but rather be allowed to choose whether they drink before discharge (47). Requiring drinking before discharge has been shown to not decrease but actually increase the time to discharge.

Going to the restroom has long since been one of basic discharge criteria necessitating the ability to stand and walk and a reasonable amount of coordination. Whether voiding is mandatory in all day surgical patients may be questionable. Voiding should most certainly be seen as mandatory in every case with increased risk for urinary retention, such as all patients in whom spinal anesthesia has been used. Even after small doses of hyperbaric 0.5% bupivacaine, the ability to void has shown to be delayed to an unacceptable extent with the risk for urinary retention. Also, the more short-acting local anesthetics, such as lidocaine especially when combined with an opioid, may cause prolonged interruption of the micturition reflex, with a risk for urine accumulation (48,49).

In patients not at risk for urinary retention, the incidence of retention has been found to be low, less than 1% (45). Given appropriate information, these patients may well be discharged without voiding before leaving the hospital. Patients at risk should, however, be observed until voiding and liberal use of bladder scanning is of value (50). Bladder scanning has a clear place in the day surgical recovery area. Four hours seems an appropriate time limit before considering scanning of the bladder if spontaneous voiding has not taken place.

Special Procedures

- Transurethral surgery
- Hysteroscopic surgery
- Laparoscopic surgery
- Pediatric surgery
- Geriatric surgery

Some centers have started to carry out transurethral prostatectomies and internal urethral incisions on a day or short-stay surgery basis. The fluid balance problems associated with the use of hypotonic solutions are similar to those for in-hospital patients. Hysteroscopies are also frequently performed, with the associated risk for fluid absorption. The special problems associated with the use of hypotonic solutions are discussed elsewhere (see Chapter 35).

The physiological changes and effects of laparoscopic surgery including increased intraabdominal pressure, head up or down tilt in combination with anesthesia in most patients may require muscle relaxation and positive pressure ventilation which should be dealt with in accordance with the general guidelines for these procedures. Fluid administration should be the same as for the in-hospital patient.

The special factors to consider for children and patients are presented in separate chapters (see Chapter 31).

Drug Treatment with Possible Implication on Fluid Balance

Sevoflurane is one of the third-generation inhaled anesthetics with low blood gas solubility. Its use has become popular in ambulatory anesthesia. Sevoflurane has been shown in experimental settings to be associated with potential renal effects (51). In the United States, there is still a recommendation about avoiding lower flows when it is used (52). The most extensive use of sevoflurane without alarming reports of renal impairment promotes its continued use in day surgery.

There is an increasing use of corticosteroids, and, in particular, dexamethasone has been shown to have an impact both on postoperative pain and PONV (53). Whether these doses of

corticosteroids (betamethasone or dexamethasone 4–12 mg) have any impact on fluid balance has not been extensively studied. It has however been shown that they both decrease the incidence of PONV, shorten the time to first oral intake, and improve satisfaction scores (54).

NSAIDs are frequently used and have become more or less the gold standard for pain therapy in ambulatory surgery (55). There are case reports of renal impairment from the use of these agents (56). For ketorolac, it is recommended to use the lowest effective dose to minimize the risk for side effects (57). The use of NSAIDs, however, should not be withheld from patients with normal renal function (58). The new generation of selective cyclooxygenase (COX)-II inhibitors causes significantly fewer gastric ulcerations and bleeding as compared to nonselective NSAIDs (59). Theoretically, the new selective COX-II antagonists may cause water retention, peripheral edema, and hypertension. There is some physiological production of COX-II, although the inducible formation is highest in inflammatory cells. It seems likely that COX-II inhibitors share the adverse effects of other NSAIDs outside the gastrointestinal tract, which are dependent on COX-II inhibition (59,60). Further clinical studies are needed to clarify their effects on fluid balance.

CONCLUSION

In summary, the role of day surgery, for which the patient arrives at the hospital, undergoes surgery, and leaves the hospital the same day, is growing worldwide. As the extent of surgery is generally small to moderate with only minor physiological changes, fluid balance is not normally a major problem. Minimizing preoperative fasting and shortening the time without drinking prior to surgery in addition to allowing the patient to drink as soon as possible after surgery make the need for fluid replacement small.

Intravenous fluid administration during ambulatory surgery with, for example, dextrose 4% to 5% in 0.18% electrolytes (10–20 mL/kg) given prior to and/or during surgery seems, however, to have potential positive effects regarding safety and quality. It also assures an adequate intravenous line for drug administration and has qualitative impact on recovery. Its role in recovery may be most pronounced in patients at risk for PONV and in cases where early oral intake should not be aggressively promoted.

With increasingly complex surgery and more diseased patients coming into the day surgical arena, more attention to the fluid balance may be required even in the ambulatory setting. Prospective randomized studies dealing with the optimization of preoperative fluid treatment in intermediate day surgical patients are needed. The frequent use of NSAIDs with their potential side effects, water retention and renal impairment, should be kept in mind. The risk of renal effects associated with the release of fluoride ions and compound A from the use of sevoflurane seems to be of almost negligible clinical importance.

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26 Intravenous Fluid Therapy in Daily Practice: Intraabdominal Operations

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INTRODUCTION

The purpose of this chapter is to discuss the following:

1. Intravenous fluid replacement for intraabdominal (including vascular) surgery
2. Types of intravenous fluid
3. Methods of fluid administration

Deciding what quantity of which intravenous fluid solution to use during major abdominal surgery depends on many factors including the patient's preoperative condition, the type of surgery, and the duration of surgery. The type of fluid administered will depend on the fluid compartment that requires replenishing, and the amount of fluid given should be directed toward maintaining adequate blood pressure and blood flow. There is increasing evidence that goal-directed fluid therapy improves outcome and reduces the length of hospital stay following major abdominal surgery.

ASSESSMENT OF FLUID REQUIREMENT

Most patients presenting for major intraabdominal surgery will be fluid depleted due to a combination of preoperative fasting, bowel preparation, and the additional effects of vomiting, diarrhea, pyrexia, and dehydration in the more acute setting. These result in depletion of the extracellular fluid (ECF) which is made worse by further loss of fluid to the interstitial space in the presence of bowel obstruction, ascites, or sepsis.

Clinical examination and measurement of heart rate, blood pressure, central venous pressure (CVP), and urine output will at best provide an estimate of the fluid deficit but are poor indicators of end-organ perfusion. Measurement of CVP following a fluid challenge will provide a more accurate estimate of fluid status. A bolus of 3 to 5 mL/kg colloid solution should result in a rise in CVP. Further boluses of colloid will be required until this rise is sustained.

Additional monitoring may be required for the surgical procedures that are of higher risk, such as liver resection and abdominal aortic aneurysm repair to guide fluid therapy. Flow-based assessment of fluid status (e.g., stroke volume and cardiac output) may be a more sensitive indicator than the traditional pressure-based measurements of blood pressure or CVP. Blood flow may be assessed using a pulmonary artery flotation catheter (PAFC). This is, however, invasive and not suitable for use in all patients undergoing intraabdominal procedures. Less invasive techniques for monitoring blood flow include the esophageal Doppler monitor (EDM), the partial CO₂-rebreathing technique [noninvasive cardiac output (NICO)], lithium dilution [lithium dilution cardiac output (LiDCO)], plethysmography, and gastric tonometry. Refer to the chapter Hemodynamic Monitoring for further discussion of these techniques.

FLUID SHIFTS DURING SURGERY

During surgery, fluid loss can occur in many ways. In addition to blood loss, fluid is lost into the so-called functionless third space. This results in a temporary sequestration of ECF into a

space that does not contribute to the dynamic fluid exchanges at the microcirculatory level. The volume of this internal loss is proportional to the degree of injury, and its composition is similar to that of plasma or interstitial fluid (ISF). For moderate intraabdominal surgery, e.g., open cholecystectomy, third space loss is estimated to be about 3 mL/kg/hr. For more major procedures such as a bowel resection or abdominal aortic aneurysm repair, third space loss may be up to 6–8 and 10–20 mL/kg/hr, respectively (1). Third space losses are increased further in sepsis and trauma, when the inflammatory cascade leads to increased vascular permeability and further loss of fluid into the “transcellular” fluid space.

There are large insensible losses during surgery due to evaporation of fluid from a widely exposed abdomen. These evaporative losses increase with increasing duration of surgery and are of the order of 1 mL/kg/hr (1).

The amount of blood loss depends on the type of surgery and the surgical operator. It need not necessarily be replaced with blood. The “allowable blood loss” can be calculated, which can be replaced with fluid not containing red blood cells to maintain euvolemia and keep the hematocrit above a previously determined minimum value. The allowable blood loss is of the order of 10% to 20% of the estimated blood volume, depending on the chronic health status of the patient and the starting hematocrit. In some patients with a low starting hematocrit, blood may be replaced as soon as blood loss begins. In others, up to 20% of the estimated blood volume can be lost before replacement with packed cells is required.

The goal during the major vascular surgery, e.g., abdominal aortic aneurysm repair, is to maintain adequate hydration intraoperatively, to maximize perfusion and urine output, and to maintain an adequate intravascular volume prior to aortic clamp removal. Rapid severe hemorrhage is common, and blood loss must be replaced quickly in these circumstances.

TYPES OF FLUID

Crystalloids

The crystalloid solutions commonly used during intraabdominal surgery are as follows:

1. Lactated Ringer’s solution—a “balanced” crystalloid solution, containing K, Ca, and lactate (which acts as a buffer)
2. Sodium chloride 0.9%—an isotonic crystalloid solution with 154 mmol/L of Na and Cl
3. Dextrose 5%—an isotonic solution containing a small amount of glucose (50 mg/L)

Crystalloid solutions typically distribute within the entire interstitial space (except for dextrose 5%, which distributes within the total body water). They are not very effective at expanding plasma volume. Shoemaker (2) showed that, 30 to 40 minutes after fluid administration, only 20% of the infused volume of crystalloid remained within the intravascular space. Crystalloid solutions are, therefore, suitable for replacing small fluid deficits in the interstitial space. The use of large volumes of crystalloid to replace a decreased intravascular fluid compartment leads to an expanded interstitial space. This in turn can cause pulmonary and tissue edema due to the decreased colloid oncotic pressure of crystalloid solution and leakage of fluid across capillaries. It is, therefore, not recommended that crystalloid solutions alone be used to replace the loss of fluid from the intravascular space typical during major intra-abdominal surgery.

Furthermore, the use of large volumes of isotonic 0.9% sodium chloride is associated with the development of hyperchloremic metabolic acidosis due to a large chloride load, which may be clinically significant (3). Hyperchloremia produces a progressive renal vasoconstriction and fall in the glomerular filtration rate that is independent of the renal nerves (4). “Balanced” crystalloid solutions, e.g., lactated Ringer’s solution, have a composition closer to that of plasma. In one study, healthy human volunteers were given 50 mL/kg lactated Ringer’s solution over an hour on one occasion and 0.9% sodium chloride on another. The sodium chloride group experienced a drop in blood pH, subjective mental changes, and abdominal discomfort, and took a greater time for first urination (5). Two further recent randomized controlled trials (6,7) have shown that the use of “balanced” solutions resulted in less impairment of hemostasis, improved gastric perfusion, and better preservation of renal function.

Dextrose 5% has an osmolarity of 252 mosm/L and a pH of 4.5. It contains 50 mg/dL of glucose, which is rapidly metabolized in the body to water. It can be used to treat simple

dehydration and provide water replacement in the postoperative period, but is not a suitable fluid for resuscitation.

Hypertonic Saline

Hypertonic saline has been used successfully to raise blood pressure and cardiac output in refractory hypovolemic shock (8) and during cardiac surgery with cardiopulmonary bypass (9). Hypertonic saline appears to be safe and does not exhibit any effects on the coagulation cascade or on renal function (8). The use of hypertonic saline solution is also associated with less cerebral edema than that occurring with the use of isotonic crystalloid solutions in neurosurgery (10).

Hypertonic saline acts as a rapid and transient volume expander by increasing the plasma osmolality and drawing interstitial and intracellular water into the intravascular space. Hence, small volumes of hypertonic fluid can be infused to exert the same effect on plasma volume as that occurring when infused by larger volumes of crystalloid. This effect is further enhanced when hypertonic saline is combined with a colloid solution such as dextran. Although extensively studied in animals (11), the use of hypertonic saline for volume replacement in humans during intraabdominal surgery has not yet been evaluated.

Colloid Solutions

To avoid the problems associated with an overexpanded ISF compartment, larger fluid deficits should be replaced with an appropriate colloid solution. Colloid solutions contain naturally occurring or semisynthetic colloid molecules, which remain in the intravascular space for a longer period of time. The advantage of colloid solutions is that they increase the plasma colloid oncotic pressure and decrease fluid movement into the interstitial space. Many different colloid solutions exist, some of which have clinically important adverse effects, which have limited their use.

The colloid solutions commonly used during intraabdominal surgery are

1. human albumin 5% and 20%—naturally occurring human plasma derivatives,
2. Dextran 40 and 70—commercially biosynthesized from sucrose,
3. Gelofusine[®] and Haemaccel[®]—gelatins prepared by hydrolysis of bovine collagen, and
4. Hespan[®] and Hextend[®]—hydroxyethyl starches.

In addition to the ongoing crystalloid colloid debate, a similar debate exists regarding which colloid solution to use. The use of human albumin, 5% and 20% solutions, has fallen out of favor for the resuscitation of patients with severe hypovolemia or burns, following the 1998 Cochrane Review, which suggested an excess mortality after human albumin administration in critically ill patients (12). Other colloids such as the dextrans may interfere with blood coagulation by causing a reduction in fibrinogen levels and factors V, VIII, and IX (13). Dextrans should, therefore, be used with caution in patients with active hemorrhage, coagulation disorders, or thrombocytopenia and in patients who are receiving heparin. The dextrans are primarily excreted renally and should therefore also be used with caution in patients at risk of renal failure (13).

Gelofusine and Haemaccel are derived from bovine gelatin, and a theoretical risk of transmission of bovine spongiform encephalitis exists with their use. In addition, Haemaccel is presented in an isotonic solution of sodium chloride and contains a significant amount of calcium, which in theory prevents its infusion through a giving set previously used for blood. There are, however, no incidences of harm reported in the literature due to this effect, and it is probable that blood may safely be administered along with Haemaccel.

There are several commercially available solutions of hetastarch containing colloid molecules of varying molecular weights (MWs) and dissolved in different crystalloid solutions. Hetastarch displays the same volume expansion characteristics as albumin, but with a longer duration of action (13). Hextend is a plasma volume expander containing 6% hetastarch in a balanced solution of electrolytes, lactate, and glucose (7). Pentastarch is made up of medium MW starch molecules (MW 250,000). Its use is popular in Europe, but it is not approved for perioperative use in the United States. Please refer to the chapter on Colloids for a more detailed description.

All colloid solutions including human albumin solution can cause anaphylactoid and severe anaphylactic reactions.

Crystalloid vs. Colloid

The use of colloid solutions as opposed to crystalloids during fluid resuscitation to maintain a normal plasma colloid oncotic pressure has been shown to reduce intestinal edema and increase tissue pO₂ during gastrointestinal surgery (14). Prien et al. demonstrated a significant increase in the water content of a jejunal specimen in patients resuscitated with lactated Ringer's solution compared with those resuscitated with either hetastarch or albumin (14). Gastrointestinal dysfunction is the most common postoperative complication in patients undergoing laparotomy and is the most frequent reason for prolonged length of hospital stay (15). Reduced intestinal edema may lead, in turn, to earlier resumption of bowel sounds, earlier tolerance of oral diet, a decreased incidence of nausea and vomiting, and, subsequently, earlier discharge from hospital (7). Furthermore, a recent randomized controlled comparison of colloid and crystalloid showed that intraoperative fluid resuscitation with predominantly colloids was associated with a lower incidence and severity of nausea, emesis, and use of rescue antiemetics. Colloid-resuscitated patients also experienced less severe pain, periorbital edema, and double vision (16).

As with balanced crystalloid infusions, the use of a balanced colloid solution such as Hextend has recently been shown to avoid hyperchloremic acidosis and is associated with better indices of gastric mucosal perfusion than saline-based fluids (3,6).

TRANSFUSION OF BLOOD AND BLOOD PRODUCTS

Blood loss can initially be replaced with three times the volume of crystalloid. This is continued until blood loss equals 10% of the estimated blood volume, when colloid can be given in a volume equal to blood loss until the allowable blood loss is reached.

It is no longer considered the best practice to arbitrarily transfuse patients with a hemoglobin (Hb) level below 10 g/dL or a hematocrit below 31 (17). Lower thresholds for transfusion are now recommended except for patients with significant cardiovascular disease. No large randomized controlled trials have been conducted to determine the ideal trigger Hb for transfusion. Some evidence suggests that perioperative transfusion in patients with a Hb of 8 g/dL or higher did not influence the risk of 30- or 90-day mortality in an elderly orthopedic population (18). On the other hand, blood transfusion may be associated with potential harm. In a recent study, patients undergoing colorectal surgery for carcinoma who received blood transfusion had a significantly higher incidence of infections, which could adversely affect their prognosis (19). Transfusion of allogeneic blood compromises immunological factors and could contribute to an increase in infectious complications (20,21).

Hebert et al. (22) compared two groups of euvolemic patients randomly assigned to a restrictive transfusion group with red cells transfused if Hb < 7 g/dL (to maintain Hb between 7 and 9 g/dL) or a liberal transfusion group with red cells transfused if Hb < 10 g/dL (to maintain Hb between 10 and 12 g/dL) (22). The in-hospital and 30-day mortality was significantly less in patients in the restrictive transfusion group who were less than the age of 55 and had lower acute physiology and chronic health evaluation II (APACHE II) scores. Similar observations were not seen in patients with clinically significant cardiovascular disease. The authors concluded that "a restrictive strategy of red cell transfusion is at least as effective and possibly superior to a liberal transfusion strategy in critically ill patients with the possible exception of patients with acute myocardial infarction and unstable angina."

Perioperative blood transfusion in patients undergoing colorectal surgery is more likely in patients aged more than 65 years, having a body mass index less than 27, preoperative anemia, and ASA II or more, and those undergoing additional surgical procedures (23). In this study, 72% of patients received perioperative blood transfusion, a clear indication of the need for better guidelines on the more prudent use of this expensive and scarce resource.

In patients with cardiovascular disease, however, there exists a disproportionately higher risk of mortality with increasing blood loss and decreasing Hb levels (18). Other studies indicate that a clinically relevant compromise in the oxygen-carrying capacity of the blood occurs when the hematocrit decreases acutely to around 27%. This cutoff can sometimes be

considered the transfusion trigger, especially in patients with cardiovascular disease (24). The decision to transfuse red cells in a patient with a hematocrit between 27% and 31% or a Hb between 8 and 10 g/dL is one that should be made on an individual patient basis after a careful consideration of all the pros and cons of red cell transfusion.

Even less evidence exists as to when it is appropriate to transfuse blood products such as platelets and clotting factors. The decision is a clinical one, made on the basis of a preexisting clotting deficiency, low platelets, or abnormal platelet function due to an antiplatelet therapy such as aspirin or clopidogrel and continuing surgical blood loss. The decision may be helped by intraoperative measurements of prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count. However, these laboratory investigations can take time, and it must be noted that a platelet count is not an indication of the platelet function. In general, a patient who has received a transfusion of four or more units of red cells or has a PT or APTT less than 1.5-fold above control will require additional clotting factors such as fresh frozen plasma and cryoprecipitate. In addition, a patient with platelet count less than 50,000 undergoing abdominal surgery is likely to require platelet transfusion.

GOAL-DIRECTED THERAPY

“Goal-directed therapy” is the principle of plasma volume replacement targeted toward measurements of intravascular pressure, blood flow, and tissue perfusion. It is aimed at reducing the morbidity and mortality of high-risk surgical patients by increasing cardiac output and oxygen delivery. The relationship between a higher cardiac index and reduced mortality following surgery is a long established one, first demonstrated in a randomized controlled trial by Shoemaker et al. in 1998 (25) and supported by several further studies (26,27). These studies used flow goals measured using a PAFC. The use of specific hemodynamic goals for oxygen delivery, SvO₂, stroke volume, or cardiac index, the so-called “optimization,” resulted in a decreased mortality in the protocol groups. The use of PAFCs is declining, however, due to their associated complications (some life-threatening) and the lack of evidence that their use benefits patients (28).

Several less invasive cardiac output monitors have been investigated in the past decade. These include the EDM (EDM Deltex Medical, Inc., Irving, Texas, U.S.A. or Hemisonic Doppler Monitor, Arrow, Inc., U.S.A.), which measures blood flow velocity in the descending thoracic aorta (29). The EDM is as accurate at measuring cardiac output as the PAFC but is associated with fewer complications (30). In a study examining gut mucosal perfusion during cardiac surgery, the EDM was used to guide an intraoperative fluid therapy based on a fluid administration algorithm (31). During the intraoperative period, colloid boluses were given to the treatment group who were compared to another group receiving fluid according to standard practice. The treatment group showed an improvement in gastrointestinal perfusion measured by gastric tonometry and a reduced length of intensive care unit and overall hospital stay.

Three further studies using the EDM have demonstrated similarly encouraging results. The first showed a significant reduction in hospital stay but no decrease in mortality in patients undergoing repair of proximal femoral fracture, who were randomized to receive EDML (32). Another study on patients undergoing repair of fractured femur compared standard care to protocol groups receiving a colloid fluid challenge according to CVP or corrected flow time (FTc), measured by the EDM (33). The FTc has been shown to be a good index of systemic vascular resistance and is sensitive to changes in left ventricular preload (29). Both protocol groups showed a reduction in time to being medically fit for discharge but no reduction in overall mortality. A recent study employing goal-directed therapy in moderate-risk general surgical patients undergoing abdominal procedures compared a protocol group who received intraoperative plasma volume expansion guided by EDM to maintain maximal stroke volume to a control group who received standard care (34). The protocol group demonstrated an earlier return to tolerating solid food, a lower incidence of postoperative nausea and vomiting requiring rescue antiemetic therapy, and a reduction in hospital stay. This group had a significantly higher stroke volume and cardiac output at the end of surgery than the control group. The authors concluded that optimal fluid administration resulted in better gut perfusion in the protocol group and hence a lower incidence of gastrointestinal dysfunction. The reduction in hospital stay observed was primarily the result of patients tolerating a solid regimen earlier. There were no significant differences in the incidence of other complications.

Table 1 Fluid Management Strategy

Type of surgery	Insensible losses	Maintenance crystalloid	Colloid bolus
Moderate, e.g., open cholecystectomy	4 mL/kg/hr	5 mL/kg/hr	Rarely required
Major, e.g., bowel resection	7–9 mL/kg/hr	7.5 mL/kg/hr	250 mL ^a
Major vascular, e.g., AAA repair	10–20 mL/kg/hr	10 mL/kg/hr	250 mL ^a

^aRepeat as necessary according to the desired goal.

Abbreviation: AAA, abdominal aortic aneurysm.

Other methods of measuring cardiac output noninvasively are the NICO using partial CO₂ rebreathing, LiDCO, plethysmography, and transesophageal echocardiography. Tissue perfusion can be measured using gastric tonometry, which measures intramucosal pH (pHi), or laboratory measurements of blood lactate or arterial base deficit. A low pHi, increased blood lactate, or increased base deficit suggests poor tissue perfusion and may indicate a need for additional intravenous fluid therapy.

Despite significant evidence that goal-directed therapy works, its principles are rarely followed in practice. A survey in the United Kingdom recently reported that although 91% of respondents believed in preoperative “optimization” of the high-risk surgical patient, only 6% admitted more than a quarter of their patients to a critical care environment before surgery to institute flow-directed therapy (35). There are many reasons for this including lack of resources, but the evidence suggests that the initial increased costs of initiating goal-directed therapy are at least offset by savings made in the postoperative period from decreased morbidity and length of hospital stay (36).

CONCLUSION

Intravenous fluid therapy for high-risk intraabdominal surgery is aimed at maintaining hemodynamics and regional perfusion and reducing perioperative complications associated with hypovolemia, from postoperative nausea and vomiting to severe end-organ dysfunction. It should begin with an assessment of the patient’s preoperative fluid status. A decision to institute additional cardiovascular monitoring such as intra-arterial blood pressure, CVP, or pulmonary artery wedge pressure or less invasive hemodynamic monitoring should then be made according to the patient’s chronic health status and the type of surgery planned.

A preoperative bolus of crystalloid or colloid may be prudent prior to induction of anesthesia. Intraoperatively, maintenance fluid may be given in the form of a balanced crystalloid solution such as lactated Ringer’s solution at 5 to 10 mL/kg/hr. High-risk surgical procedures should be managed with goal-directed boluses of colloid solution as required to maintain adequate intravascular pressure, blood flow, and tissue perfusion (Table 1).

Blood loss should be replaced first with crystalloid, and then with colloid. When the pre-determined allowable blood loss has been reached and the hematocrit has dropped below 25% to 27%, packed red cells should be transfused, with the exception of those patients with significant cardiovascular disease in whom the transfusion threshold will be higher. Blood products such as fresh frozen plasma, cryoprecipitate, and platelets should be replaced according to clinical need and, if possible, guided by laboratory clotting values.

Volume and flow status must be frequently reassessed using hemodynamic monitoring, urine output, Hb, hematocrit, and acid–base status. This must be continued into the postoperative period, especially when continued fluid losses are expected.

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27 | Fluid Therapy in Cardiac Surgery

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INTRODUCTION

In cardiac surgery large amounts of allogeneic blood transfusions are still utilized every year. The inherent risk of transmission of viral and immunological diseases has forced us to reduce the use of allogeneic blood and blood products as far as possible. Reductions in hematocrit and arterial oxygen content are not deleterious, because compensating mechanisms are able to guarantee organ blood flow, tissue oxygenation, and systemic oxygen transport. Thus, blood/blood component therapy should be restricted to those patients presenting severe anemia or coagulation disorders, and nonblood alternatives for volume replacement have to be seriously considered.

Controversy still surrounds the type and regimen of fluids to be administered in this setting, and the question of the optimal strategy for volume replacement has been discussed very heatedly (1,2).

The long-standing debate concerning the “ideal” kind of fluid for volume replacement does not only include a crystalloid/colloid debate, but must also be enlarged to a colloid/colloid debate (3).

Pharmacokinetics and pharmacodynamics of the different solutions used for volume replacement differ widely (Table 1). When discussing different regimens of volume therapy in cardiac surgery patients, not only effects on systemic hemodynamics, but influence on microcirculation, on pulmonary function, on rheology, and possible alterations of coagulation must be taken into account. Finally, in today’s climate of cost consciousness, cost containment is an important issue (4).

WHAT IS SO SPECIAL ABOUT VOLUME THERAPY IN CARDIAC SURGERY?

Cardiac surgery is not completely comparable with other kinds of surgery. Due to extracorporeal oxygenation using cardiopulmonary bypass (CPB), “blood becomes a stew of powerful enzymes and chemicals” (5). Knowledge of the cellular and molecular pathophysiology of development of postperfusion organ dysfunction has been expanded in recent years. CPB has often been compared to the pathophysiologic alterations associated with sepsis or systemic inflammatory response syndrome (6). This systemic inflammatory response may lead to severe postoperative complications (7–10). The damaging effects of CPB are most likely related to exposure of blood to nonendothelial surfaces, shear stress, nonpulsatile blood flow (unphysiologic), and incorporation of abnormal substances during bypass. Production of complement and kinin, activation of the coagulation and fibrinolytic cascade, synthesis of various cytokines, activation of neutrophils with subsequent protease enzyme release, and production of oxygen radicals are involved in the development of organ dysfunction in cardiac surgery patients (11,12).

Within the first 24 hours after cardiac surgery, a reduction in blood and plasma volume is a common phenomenon (13). In patients undergoing coronary artery bypass grafting, preoperative measurement of blood volume revealed diminished blood volume in 42% of all cases (14). Preoperative medication, systemic hypothermia, anesthesia, vasoactive substances, and finally the underlying disease may significantly alter the patient’s circulating blood and plasma volume. Bleeding may cause an absolute volume-deficit, vasodilation mediated by vasodilating substances (e.g., anesthetics, nitroglycerine, and protamin) and rewarming is involved in producing a relative volume deficit. Hypovolemia may be associated with flow alterations that are inadequate to fulfill the nutritive role of the circulation. In spite of achieving “normal” systemic

Table 1 Characteristics of Commonly Used Synthetic Colloids

Colloid	MS	Mw (kDa)	COP (mmHg)	Initial volume support	Duration of intravascular persistence
3% dextran		60	22	Moderate	Prolonged
6% dextran		70	58	Good	Prolonged
10% dextran		40	Leakage	Pronounced	Moderate
Gelatin		35	Leakage	Poor	Limited
3% HES	0.5	200	12	Moderate	Prolonged
6% HES	0.5	200	34	Good	Prolonged
6% HES	0.62	200 (Elohes) [®]	34	Good	Prolonged
6% HES	0.7	450 (Hetastarch) [®]	29–32	Good	Prolonged
6% HES	0.5	260 (Pentastarch) [®]	40	Good	Prolonged
6% HES	0.4	130 (Voluven) [®]	36	Good	Moderate
10% HES	0.5	200	80	Good	Prolonged

Abbreviations: HES, hydroxyethyl starch; Mw, mean molecular weight; MS, molar substitution; COP, colloid osmotic pressure.

hemodynamics, it is not guaranteed that organ or tissue perfusion remains adequate. During hypovolemia, the organism tries to compensate for perfusion deficits by redistribution of flow to vital organs (e.g., heart and brain), resulting in an underperfusion of other organs (e.g., splanchnic bed, kidney, muscles, and skin). Various inflammatory mediators (e.g., cytokines) and vasopressors (e.g., norepinephrine) are released in this situation and are of particular importance for the development of impaired microperfusion. Recent evidence suggests that the endothelium is not only a passive barrier between the circulating blood and the tissue, but also markedly involved in the regulation of microcirculatory blood flow by producing important regulators of the vascular tone (e.g., prostaglandins, nitric oxide, endothelins, and angiotensin II) (15,16). The regional regulation of blood flow is likely to be a balance between systemic mechanisms (e.g., the autonomous nervous system) and other more locally active regulators of blood flow. Activation of the sympathetic nervous system (SNS) and the renin-angiotensin system are further compensatory mechanisms to maintain peripheral perfusion. This compensatory neurohumoral activation is beneficial at first, but may become harmful and may be involved in the development of multiple organ failure (MOF) after cardiac surgery (17).

One important aspect of fluid therapy in the cardiac surgery patient is the risk of interstitial edema formation. Tissue edema is the result of an imbalance in the sum of the Starling forces across capillary membranes or an increase in protein permeability, by which an increase in fluid flux to the interstitial space (ISS) is promoted. A decrease in membrane integrity, an increase in hydrostatic pressure, and a decrease in intravascular colloid oncotic pressure (COP) will induce a fluid shift across endothelium resulting in interstitial fluid accumulation (e.g., pulmonary edema). This fluid accumulation takes place also in the endothelium. By endothelial swelling, organ perfusion is further disturbed. Alterations in water and electrolyte homeostasis are known to occur with CPB. Peripheral edema resulting from CPB is located in the interstitial compartment including endothelium. This is associated with the risk of an impaired microcirculatory perfusion in the capillary network. However, the maintenance of microcirculatory flow appears to be essential to avoid tissue ischemia. One important approach to improve perfusion in this situation appears to be the use of an adequate volume.

PRINCIPLES OF VOLUME REPLACEMENT THERAPY IN CARDIAC SURGERY

The composition and the volume of each body compartment are controlled through complex mechanisms including antidiuretic hormone (ADH) system, renin-aldosterone-angiotensin (RAA) system, and the SNS. The principal actions of these systems are to retain water in order to restore intravascular volume deficit, to retain sodium in order to restore the intravascular volume, and to increase the hydrostatic perfusion pressure through vasoconstriction. The control of ADH secretion depends on plasmatic osmolality, whereas the most important stimulus for the activation of the RAA system is the depletion of the intravascular volume. Increased activity of the ADH-system, the RAA system, and the SNS is known to occur in stress situations, e.g., during trauma or surgery. Although the normal response to surgery and starvation results in improved metabolic activity, a preexisting deficit of water or intravascular volume further increases this activity. If the stimulus of water or intravascular volume deficit and

the stress-related stimulus of ADH-system, RAA system, and SNS are additive, fluid management inhibits them through a counter-regulatory mechanism. Several attempts to inhibit or attenuate the activity of ADH- and RAA-systems by administering isotonic crystalloid solutions have been made. ADH production is modulated by the extracellular and the intravascular compartments. Administration of a restricted volume of crystalloid solutions may replace a previous deficit of water, but the replacement of intravascular volume deficit would require large volumes to inhibit the secretory stimulus of ADH and other hormones. Thus, it can be assumed that the replacement of crystalloids alone will not inhibit the normal response of ADH and RAA, whereas administration of a combination of crystalloid and colloid solutions (replacement of water deficit and improvement of the effective intravascular volume) may achieve this goal.

The hypothesis of Starling describes and analyzes the exchange of fluid across biological membranes. Based on Starling's equation, the COP should theoretically be important to maintain fluid balance. The COP gradient between the intravascular and extravascular compartments opposes the hydrostatic pressure and promotes influx of fluid into the intravascular space. Thus, manipulation of COP appears to be promising for guaranteeing adequate circulating intravascular volume. The magnitude and duration of this volume replacement regimen depend on the specific water-binding capacity of the plasma substitute and the amount of the infused substance that stays in the intravascular space. Because of their varying physicochemical properties, commonly used colloids differ widely with regard to COP, initial effects, and duration of intravascular persistence (18).

HOW TO PERFORM VOLUME THERAPY IN CARDIAC SURGERY

When assessing the "ideal" volume replacement strategy in cardiac surgery, three different periods should be distinguished: the prebypass period, the period of CPB (priming of the CPB equipment), and the postbypass period [including the period on the intensive care unit (ICU)]. In only a limited number of studies, the different periods were separately analyzed. Several innovative strategies have been developed in the last 15 years, including the use of new membrane instead of bubble oxygenators, arterial filters, improved biomaterials of the tubing, and others. Thus, studies before 1985 are difficult to compare with today's situation.

Prebypass Volume Therapy

Few studies focus on volume replacement in the period prior to CPB (Table 2) (19–25). Criteria for volume administration differed widely. Some studies focused on maintaining circulating blood volume and stable systemic hemodynamics during acute normovolemic hemodilution or acute plasmapheresis prior to start of surgery. Others used fixed doses of different kinds of volume in patients with low filling pressures. Results from these studies suggest that the use of human albumin (HA) in comparison to modern synthetic colloids [e.g., medium-molecular-weight (MMw) hydroxyethyl starch (HES) preparations and gelatins] does not result in beneficial effects on systemic hemodynamics, microcirculation, or other important clinical data. There was even less increase in interstitial fluid accumulation and extravascular lung water (EVLW) after CPB with the administration of MMw-HES in comparison to albumin. Administration of crystalloids was associated with negative sequelae, e.g., an increased fluid accumulation or negative hormonal response. Outcome was not significantly affected by the choice of fluid for volume replacement. The study population of all studies, however, was always much too small to definitely decide whether the choice of fluid does have an impact on patient's outcome.

Priming of the Extracorporeal Circuit

An important interplay may exist between the metabolic and pathophysiologic responses associated with the exposure to CPB and the composition of the priming fluid (Tables 3a and 3b) (26). Nonsanguinous priming of the CPB circuit has been established because it has been found that homologous blood prime was an important reason for the development of postbypass pulmonary dysfunction ("pump lung"). Hypooncotic primes (e.g., using only crystalloids) may be associated with interstitial fluid expansion, with subsequent development of organ tissue edema. The sole use of crystalloid prime was associated with an increased

Table 2 Volume Given Before Start of Cardiopulmonary Bypass

References	Used substances	Aim	Result
20	6% HES 200/0.5 HA 20% Gelatin 3.5%	Fixed doses	HES: lowest lung water HES: improved PaO ₂ Outcome: no differences
21	6% HES 450/0.7 10% HES 200/ 0.5 6% HES 200/ 0.5 6% HES 40/ 0.5	Maintain stable hemodynamics during ANH	10% HES 200/0.5: best hemodynamics, lowest fluid balance Outcome: no difference
22	HES 200/0.5 RL	Maintain stable hemodynamics during AP	HES: less balance, better pulmonary function Outcome: no difference
23	6% HES 130/0.5 6% HES 200/0.5	Doubling low PCWP	HES: similar effects Outcome: no difference
19	6% HES 450/0.7 6% HES 200/0.5 HA 5% Gelatin 3.5%	Doubling low PCWP	HES 450/0.7: impaired platelet aggregation HES vs. albumin: no difference Outcome: no difference
24	RL + HES 200/ 0.5 RL	Fixed doses	RL + HES: improved hemodynamics beneficial hormonal response Outcome: no difference
25	6% HES 450/0.7 6% HES 200/0.5 6% HES 200/ 0.62 6% HES 40/0.5	Maintain stable hemodynamics during ANH	6% HES 200/0.5: best microperfusion Outcome: no difference

Abbreviations: RL, lactated Ringer's solution; HA, human albumin; HES, hydroxyethyl starch; PCWP, pulmonary capillary wedge pressure; ANH, acute normovolemic hemodilution; AP, acute plasmapheresis.

postoperative weight gain, whereas addition of colloids to the priming reduced the amount of postoperative fluid accumulation (27). Crystalloid priming gained popularity because of their ability to distribute beyond the intravascular space and because they can be removed by diuresis. This may be of importance because circulating volume is often expanded after termination of CPB. It has been generally accepted that dextrose-containing priming should be avoided, because elevated blood sugar levels have been associated with deteriorated neurologic outcome (28). It is not definitely clear whether adding colloids to the prime offers any significant advantage in comparison to a purely crystalloid priming (29,30). In several centers, colloids are routinely used for priming of the CPB circuit. In a postal survey including all National Health Service centers in the United Kingdom ($n=35$), the priming solutions of the CPB circuits were sought (31). Fifty-four percent answered they used only crystalloid priming (Hartmann's solution, Ringer's solution, Plasmalyte) and 44% used crystalloids plus synthetic colloids without specifying the added synthetic colloid.

A variety of priming compositions have been reported, the results are far from conclusive (27,32–50). There are only a moderate number of well-controlled, recent (i.e., <15 years old) studies on the effects of different priming solutions. It is not only the "crystalloid-versus-colloid priming" controversy, a variety of colloids (albumin, dextrans, gelatins, and different HES preparations) have been added to the priming as well. It is generally accepted that high-priced albumin appears to have no place in the priming of CPB.

End-point criteria for evaluating the used priming solutions differ widely including the influence on bleeding tendency, on COP, on complement system, or even on intraocular pressure. It still remains unclear whether manipulation of the composition of the priming solution has an impact on patients' outcome, because most studies did not show any differences in outcome or outcome was not mentioned. In a literature analysis covering the period from 1966 to 1999, 227 references dealing with priming were studied (51). Twenty-four prospective and randomized studies could be selected for outcome evaluation. Considerable benefits of adding a colloid to the priming were documented. Thus, it is difficult to understand that some guidelines still strictly recommend that "crystalloids should be the fluid of choice as the priming solution for CPB" (52).

Table 3a Priming Volume I

References	Used substances	Conclusion
32	Donor plasma	Dextran: improve COP
	Dextran 70	Outcome: not shown
33	6% HES 450/0.7	RL vs. colloids: colloids better
	HA 5%	HES vs. HA: equivalent
	RL	Outcome: no difference
34	4 different cryst	Best: glucose-free and lactate-free
		Outcome: not shown
35	Donor plasma	Evaluation: no differences
	Dextran 70	Outcome: no differences
36	6% HES 450/0.7	HES vs. HA: no differences
	HA	Outcome: not shown
37	Donor plasma	Plasma: higher complement activation
	Dextran 70	Outcome: not shown
38	Dextran 70	Dextran: lower antiplasmin activity
	RL	Outcome: no differences
39	Cryst	Gelatin: less complement activation
	HA	Outcome: not shown
	Polygeline	
40	HA	HA vs. cryst: no advantage
	Cryst	Outcome: no difference
41	HA	Coagulation: no differences
	Polygeline	Outcome: no differences
	Gelatin	
27	RL	RL: increase in lung water
	HA	Outcome: not shown
42	RL	Cryst and gelatin: less impaired platelet function
	HA 20%	Bleeding/use of blood: no differences
	6% HES 200/0.5	Outcome: no difference
	Gelatin	
43	RL	HES vs. HA: no differences
	HA	Colloid prime: lower fluid balance
	10% HES 260/0.45	Outcome: no difference

Abbreviations: RL, lactated Ringer's solution; HA, human albumin; Cryst, crystalloids; HES, hydroxyethyl starch; COP, colloid osmotic pressure.

Table 3b Priming Volume II

References	Used substances	Conclusion
44	6% HES 120	HES: depressed von Willebrand factor
	6% HES 400	Blood loss: no differences
	RL	Outcome: not shown
45	Cryst	Cryst: increased intraocular pressure
	Colloid	Outcome: not known
46	HA	Cryst: higher fluid balance
	Polygeline	Colloid vs. cryst: no differences
	Cryst	Outcome: no differences
47	HA	Gelatin: negative effects on hemostasis
	Gelatin	Outcome: not shown
48	Cryst	Gelatin: less fluid, shorter in hospital
	Gelatin	Outcome: better in colloid prime
49	HES	No difference in homeostasis/bleeding
	HA	Outcome: no difference
	Gelatin	
50	HA	HA vs. RL: no differences
	RL	Outcome: not shown

Abbreviations: RL, lactated Ringer's solution; HA, human albumin; Cryst, crystalloids; HES, hydroxyethyl starch; COP, colloid osmotic pressure.

Table 4 Volume Replacement After Cardiopulmonary Bypass

References	Used substances	Criteria	Conclusion
53	HA 20% 6% HES 200/0.5	Fixed dose	HA: lung water increased Hemodynamics: no differences Outcome: no differences
54	HA 5% 65 HES 450/0.7 RL	PCWP	EVLW: no differences PaO ₂ : no differences Outcome: not shown
13	RL Dextran 70	BP, PCWP	Dextran: better hemodynamics Outcome: no differences
55	Dextran 70 Gelatin Plasma protein	Fixed dose	Dextran: highest increase in PCWP and SI Outcome: not shown
56	6% HES 450/0.7 Plasma protein	MAP, RAP	Coagulation: no differences Outcome: no differences
57	Saline solution 6% HES 450/0.7	CI, MAP, PAD	HES: less time on ICU Outcome: no differences
58	6% HES 200/0.5 HA 5%	When CVP < 10 mmHg	Comparable hemodynamics Outcome: not shown
59	6% HES 260/0.45 HA	CI < 2 L/min/m ²	Coagulation/bleeding/hemodynamics: no differences Outcome: not shown
60	RL Gelatin	MAP, HR, PCWP "as necessary"	Hemodynamics: no differences Outcome: no differences
61	HA 5% 6% HES 450/0.7		HES: impaired hemostasis Outcome: not shown

Abbreviations: SI, stroke index; RAP, right atrial pressure; HA, human albumin; HES, hydroxyethyl starch; ICU, intensive care unit; RL, lactated Ringer's solution; PAD, pulmonary artery diastolic pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; EVLW, extravascular lung water; MAP, mean arterial pressure; BP, blood pressure; HR, heart rate.

Postbypass Volume Therapy

Immediately after CPB and postoperatively on the ICU, volume replacement is often necessary due to rewarming, the use of vasodilating substances (e.g., protamin and nitroglycerin), or bleeding (Table 4). A variety of fluids have been used in this situation to treat or prevent cardiocirculatory instability [e.g., saline solution, lactated Ringer's solution (RL), plasma protein fraction, albumin, and synthetic colloids (HES, dextrans, and gelatins)] (13,53–61). Criteria for volume administration were not uniformly defined: either fixed doses were used or infusion was adjusted to systemic hemodynamics [e.g., pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and cardiac index (CI)] or only "as necessary."

Only a few studies have compared crystalloids and colloids for volume replacement in this situation. The majority concluded that colloids resulted in improved hemodynamics. In one study even a shorter stay in the ICU was reported (57). Use of albumin was not associated with advantages with regard to hemodynamics, EVLW, pulmonary gas exchange, hemostasis, or postoperative bleeding tendency when compared with synthetic colloids [e.g., HES with low Mw and low degree of substitution (DS)]. In most studies outcome was not specified. In those studies in which outcome was mentioned, no differences between the different volume replacement strategies were seen. Although there have been some negative results with the use of crystalloids, some guidelines recommended crystalloids as first-line solution followed by nonprotein colloids, and, finally, albumin (52). However, it has been emphasized that "when systemic edema should be avoided," nonprotein colloids are recommended in these guidelines (52). Because cardiac surgery patients are especially prone to develop organ edema formation because of a generalized capillary leakage, it must be questioned whether exclusive use of crystalloids are beneficial in this situation (62).

Volume Therapy in Children Undergoing Cardiac Surgery

In infants and children undergoing cardiac surgery volume expansion is obligatory in the prebypass period or after weaning from CPB (Table 5). Whole blood, packed red blood cells (PRBC), blood products [fresh frozen plasma (FFP), platelets], and even warm fresh blood have been used in this situation. Nonblood volume replacement regimens have only very

Table 5 Volume Therapy in Children Undergoing Cardiac Surgery

References	Used substances	Conclusion
<i>Prior to CPB</i>		
63	HA 5% 6% HES 200/0.5	HA vs. HES: no differences Outcome: no differences
<i>Priming</i>		
64	WB/RL WB/FFP	Mortality rate: no different General: higher COP easier postoperative care Outcome: no differences
65	3 different cryst priming	Sodium concentration increased by Hartmann's and plasmalyte Outcome: not shown
66	HA Cryst	HA beneficial: less postoperative weight gain Outcome/deaths: Cryst: 3; HA: no
<i>Postbypass</i>		
67	HA 6% HES 450/0.7	HES safe, no differences to HA Outcome: not shown

Abbreviations: CPB, cardiopulmonary bypass; HA, human albumin; COP, colloid osmotic pressure; WB, whole blood; FFP, fresh frozen plasma; RL, lactated Ringer's solution; Cryst, crystalloids; HES, hydroxyethyl starch.

rarely been studied systematically in infants and children (63–67). HA and HES have been used pre- and postoperatively to treat hypovolemia. Systemic hemodynamics were sufficiently restored with both the fluids; coagulation parameters and laboratory data were also without differences between the two volume replacement strategies. Addition of colloids to the priming (albumin or FFP) elevated COP and was shown to reduce weight gain after CPB and to “improve” postoperative care (64).

HOW TO MONITOR VOLUME THERAPY IN CARDIAC SURGERY

At the bedside, hypovolemia is difficult to detect (68), and correct assessment of the required volume still remains a challenge. Monitoring should be additionally aimed at preventing fluid overload and improving organ perfusion. The optimal guide for volume therapy in cardiac surgery patients with obvious volume deficits has not been decided yet. In spite of some negative data, pulmonary artery catheters are still widely used, and information obtained by this monitoring instrument may be helpful in guiding volume therapy. However, cardiac filling pressures (CVP and PCWP) are often misleading surrogates for assessing optimal loading conditions. Filling pressures may be influenced by several factors other than blood volume, including those influencing cardiac performance, vascular compliance, and intrathoracic pressure. In patients with altered ventricular compliance, CVP, PCWP, right atrial pressure, or right ventricular pressure are not always proved valid enough to judge loading conditions. Measurement of right ventricular end-systolic and end-diastolic volumes by thermodilution technique is another, easy-to-perform bedside monitoring technique to monitor ventricular loading. There is no risk of accumulation of toxic indicators, it is unaffected by arbitrary and poorly reproducible zero points for pressure transducers, and it can be carried out at the bedside. Transesophageal echocardiography is a much more reliable monitoring instrument to assess filling volumes; due to its costs, however, it is not available to every cardiac surgery patient in the intra- and postoperative period. The importance of occult hypovolemia for the development of organ dysfunction has been supported by several studies (69). There does not exist a reliable, optimal routine clinical monitoring method to detect perfusion failure. The cardiovascular unstable patients appear to be at risk of experiencing significant splanchnic hypoperfusion with subsequent development of translocation and MOF (70). Intestinal ischemia continues to occur for at least eight hours after cardiac surgery. Tonometric measurement of gastric intramucosal pH has emerged as an attractive option for diagnosis and monitoring of splanchnic hypoperfusion. In patients undergoing major noncardiac surgery, maintaining hemodynamic stability was no guarantee of an adequate splanchnic perfusion and could not definitely protect against postoperative complications (71). Although this monitoring instrument has produced some promising results, it is far from being the new “gold standard” for guiding volume replacement.

SIDE EFFECTS OF DIFFERENT VOLUME REPLACEMENT STRATEGIES

Effects on Blood Coagulation in Cardiac Surgery

Cardiac surgery using CPB has a profound impact on the coagulation process including combined effects of activation of the intrinsic coagulation cascade, activation of tissue factor, and cellular and endothelial activation. Multiple activation of inflammatory pathways with subsequent activation of procoagulatory mechanisms and downregulation of anticoagulant pathways may also modify hemostasis. Because intra- and postoperative bleeding continue to be a problem in cardiac surgery, the choice of volume replacement must consider this specific situation.

All agents for volume replacement lower the concentration of clotting proteins by means of hemodilution. Crystalloids appear to have no specific deleterious effects on coagulation other than that attributable to hemodilution, although some studies showed a hypercoagulable state after hemodilution with crystalloids (72). More specific alterations of coagulation are known with some of the colloids used for volume replacement. Albumin is considered to have little or no significant effect on blood clotting. However, in an *in vitro* study using serial hemodilution and thrombelastography (TEG), albumin produced early and profound hypocoagulable effects (73). Concerns exist about adverse effects that synthetic colloids might exert on blood coagulation. Dextran are well known to negatively influence hemostasis either by reducing von Willebrand's factor (vWF) or by impairing platelet function (74). The mechanisms by which synthetic colloids exert platelet-inhibiting effects have not been fully elucidated. Both factor VIII related antigen (VIII:Ag) and factor VIII ristocetin cofactor activity (VIII:RCo) levels decrease significantly when using dextrans. With reduced VIII:RCo, there is reduced binding to platelet membrane receptor proteins glycoprotein (GPIb) and GPIIb/IIIa, which results in a decreased platelet adhesion. Gelatins have been judged to be without significant influence on blood coagulation. However, in an *in vitro* study, significant inhibition of platelet aggregation was demonstrated by two gelatin preparations (polygeline and succinylated gelatin) (75). In a study in six healthy men, administration of 1 L of gelatin resulted in a 1.7-fold increase in bleeding time, a substantial decrease in von Willebrand factor antigen (vWF:Ag) (−32%) and ristocetin cofactor (−29%), and significant impairment of ristocetin-induced platelet aggregation (76). Thus, the use of gelatin may alter hemostasis to some extent independently from its hemodilution effects. Bleeding complications after the use of HES have been extensively discussed, and the use of starch preparations in the cardiac surgery patient is restricted because of the fear of bleeding complications. Altered hemostasis has been demonstrated especially with the use of the first generation HES preparation, a high-molecular-weight (HMw) HES with an unfavorable high MS (7) (hetastarch (Hespan)). This HES preparation has been reported to induce a type I von Willebrand-like syndrome with decreased factor VIII coagulant activity, and vWF antigen and factor VIII-related ristocetin cofactor (77), which are very like those induced by dextrans (43). HMw-HES diminished also the concentrations of VIII:Ag and VIII:RCo. HES preparations with lower molecular weight and a lower MS [HES 70/0.5; HES 260/0.5 (pentastarch); HES 200/0.5; HES 130/0.4] were reported to have almost no negative effects on the coagulation system (78). HMw-HES resulted in the overall most pronounced impairment of platelet aggregation and should be avoided in patients with an increased risk of bleeding. Other HES preparations did not show the same negative effects on platelet aggregation as were seen after HMw-HES administration. It is long known that infusion of (high doses) the first generation HMw (Mw 450 kDa), highly substituted (MS 0.7) HES preparation (hetastarch) does increase the risk of bleeding complications in cardiac surgery considerably (79,80). Modern low- and medium-weight [70, 130, 200, 260 kDa (pentastarch)] HES preparations with a lower MS (0.4; 0.5) appear to have no direct negative effects on coagulation outside of hemodilution and can be used safely in the cardiac surgery patient (78,79).

Tissue Edema

Volume replacement may lead to fluid overload and extracellular fluid accumulation associated with an impaired pulmonary function. Venous congestion, reduced COP, arteriolar vasodilation/venous vasoconstriction, disorganization of interstitial matrix, increased endothelial permeability, and lymphatic dysfunction may contribute to tissue edema. Colloids may have some advantages, because they do not lower COP, whereas crystalloids cause

reduction in COP. The concept of “leaky capillaries” after CPB has been used as an argument against the use of colloids and pro-crystalloids. The rationale is that colloids also leak out of the capillaries into the interstitial space (ISS), increase COP in the interstitium, and thereby drag water into the ISS, resulting in exacerbation of interstitial edema. All colloids are not created equal (82), and it is not definitely clear whether all colloids are contraindicated in patients with capillary leakage. Some colloids may even prevent further leakage (83). There is experimental and clinical evidence that starch preparations with a narrow range MMw (Mw 200–250 kDa) are more effective in preventing or reducing capillary permeability edema (84,85). Use of crystalloids and albumin appear to be at a disadvantage in this situation: In an animal experiment in which myocardial ischemia was induced, it could be demonstrated that adding a starch preparation during the reperfusion period resulted in less interstitial edema than adding crystalloids and albumin (90).

Renal Function

Impaired renal function may be another problem especially when using synthetic colloids. Gelatin solutions appear to be without significant damaging effects. The elimination of HES molecules varies with molecular weight and, most importantly, with the MS. Large HES molecules are split by hydrolytic cleavage by alpha-amylase. The smaller HES molecules (and also gelatin molecules) are eliminated by glomerular filtration. Some histological studies have shown reversible swelling of tubular cells of the kidneys after the administration of HES or dextrans, which appears to be most likely due to reabsorption of macromolecules. Swelling of tubular cells may result in tubular obstruction and medullar ischemia and acute renal failure. Glomerular filtration of hyperoncotic molecules from colloids causes a hyperviscous urine, and stasis of tubular flow resulting in obstruction of tubular lumen (86). Increased creatinine levels in patients treated with first-generation, HMw HES (Mw 450 kDa) have been reported (87). In a retrospective analysis of patients undergoing kidney transplantation and in whom HES with a high MS (0.62) was infused, “osmotic-nephrosis-like lesions” were documented (88). These lesions had no negative effects on graft function or serum creatinine three and six months after transplantation. The same group of authors demonstrated that the use of HES 200/0.62 in brain-dead donors resulted in impaired renal function in kidney-transplant recipients (89). By contrast, HES preparations with different physicochemical characteristics (especially lower MS) appear to be not associated with the risk of impairing renal function (90). No negative reports on renal function in cardiac surgery patients after volume replacement with these starch specifications are available.

Storing, Accumulation, and Pruritus

Storing and accumulation may be an important problem with synthetic colloids. Gelatins and dextrans are naturally occurring substances and consequently they are fully metabolized. The modified starch molecule is the basis of the different HES solutions. All HES preparations are stored and may accumulate in the body depending on the preparation used. HES undergoes a slow intravascular catabolism by alpha-amylase. The smaller molecules are rapidly eliminated by glomerular filtration. A varying amount of the administered HES leaves the vascular system and is taken up by the reticuloendothelial system [mononuclear phagocytic system (MPS)]. With regard to the MPS, storage appears to have no detrimental consequences (91).

Itching after administration of HES is a topic of debate. In some recently published papers, occurrence of severe pruritus has been reported (92). Special features of HES-induced pruritus include long latency of onset and persistence. A dose dependent uptake of HES was first detected in macrophages and, thereafter, in endothelial and epithelial cells. Patients suffering from pruritus consistently showed additional deposition of HES in small peripheral nerves. Most of these reports originated from patients treated for sudden deafness. These patients have received over a long period (10–20 days) up to 2000 g (~20 L) of an HMw-HES with a high MS. The incidence of pruritus after cardiac surgery is not definitely known, because it may occur weeks or even months after administration, when the anesthetist is no longer in contact with the patient. Occasional reports on pruritus after HES use have been published in this situation: in 58 patients undergoing cardiac surgery, in whom a long-persistent starch with a high MS (HES 200/0.62) was used, mild (12%) and severe (10%) pruritus were documented by a questionnaire (93). In a study covering more than 700 general

surgical patients, no increased incidence of pruritus after infusion of two different HES preparations [LMw- and MMw-HES with a low MS (0.5)] in comparison with RL was shown (94).

ECONOMIC CONSIDERATIONS

The current pharmacoeconomics of the different volume replacement regimens are far from being complete. Limiting costly drugs where no outcome differences were expected compared to the use of a less costly alternative may be an attractive way to lower departmental costs. The total cost of a specific volume replacement strategy has never been addressed. In a retrospective study, the cost of substitution of HMw HES with a high MS [6% HES 450/0.7 (hetastarch)] for albumin as the CPB-priming fluid was associated with an increase in the incidence of hemorrhage (95). The resulting extra cost for treating hemorrhage was far greater than the difference in cost between HES- and albumin-based priming. The authors concluded that efforts to save money by substituting less-expensive products inadvertently may increase costs by increasing the probability of perioperative adverse events. However, increased bleeding tendency is widely known when using the first generation HES (hetastarch). Gelatins or modern HES preparations with a low Mw and low MS (e.g., HES 200/0.5; HES 130/0.4) are associated with almost no disturbances in coagulation and can be safely used in the cardiac surgery patient without increasing bleeding tendency. Thus costs can be markedly reduced when albumin is replaced by these colloids.

CONCLUSION

The search for the optimal approach to fluid management in cardiac surgery continues. The ideal solution for resuscitation for volume depletion should be free of risk of transmitting disease, promote minimal interstitial water accumulation, be free of side effects, and should be inexpensive (96). The American College of Surgeons Committee on Trauma recommended only two solutions for volume replacement: blood and crystalloids (97). Others prefer the use of colloids, because colloid solutions will largely remain within intravascular space, whereas crystalloids rapidly transude between intravascular and interstitial fluid compartments. Albumin is generally considered to have no place in volume replacement or priming in the adult cardiac surgery patient and should be completely banned. Several recently published meta-analyses have created uncertainties with regard to the appropriate volume replacement strategy (98). Outcome or mortality was the focus of most of the meta-analyses. However, in most studies on volume therapy, mortality was not the end point. Because the choice of fluid may have little or no effect on mortality (99), new concepts such as the influence on inflammation, microcirculation, or organ function may shed new light on this problem. Merits and demerits of each solution for volume replacement in cardiac surgery have to be considered carefully, including the effects on hemostasis, renal function, and other organ systems. The different physicochemical characteristics of the different substances have to be taken into account ("all colloids are not created equal"). Pressure to control costs has led to the belief that drugs with the lowest acquisition cost should be preferred. Those who show crystalloid to be superior often mention the lower cost of crystalloids. Although acquisition costs of crystalloids are without doubt lower than those of all synthetic colloids, total cost of a crystalloid-based volume replacement was only negligibly lower than that of a colloid-based volume replacement regimen (100). The choice of a substance to treat hypovolemia in cardiac surgery should not be justified by the acquisition cost alone; other aspects (e.g., hemodynamic stability and organ function) should also be considered. Perhaps we should remember Oscar Wilde: "Nowadays people know the price of everything and the value of nothing."

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28 | Urology

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INTRODUCTION

The surgical techniques used in urology have developed rapidly during the past decades. One example is the surgical removal of kidney stones, which was a common operation in the early 1990s. These operations were cumbersome for the anesthetic team, because the patients needed to rest on their lateral side while the body was kept hyperextended. Today, these patients are treated by extracorporeal shock-wave lithotripsy on an outpatient basis. The anesthesiologist does not even need to be involved. Another example is the rapid development of alternative treatments for benign prostatic hypertrophy, which include laser, thermotherapy, vaporization, and medication.

Patients undergoing surgical treatment for urology problems are mostly of old age and have a restricted cardiac reserve. The anesthesiologist can reckon that their tolerance for erroneous fluid administration is limited.

THE LITHOTOMY POSITION

Endoscopy is a cornerstone of urologic diagnosis and surgical treatment. Endoscopy is usually performed with the patient's legs placed in stirrups (lithotomy position). To prevent nerve injury, one must not forget to move the patient's legs around in the stirrups after approximately one hour of surgery. The anesthesiologist should also consider that the lithotomy position shifts blood from the raised legs to the central circulation. This shift masks hypovolemia and makes the cardiovascular status more stable during the actual operation. When the legs are lowered from the stirrups after surgery, however, any hypovolemia will become apparent as a sudden sharp drop in arterial pressure that is often accompanied by bradycardia. This drop develops within a few minutes, and often occurs when transporting the patient to the postoperative ward. A useful practice is to lower one leg at a time while measuring the arterial pressure every 30 seconds for two to three minutes after an operation in the lithotomy position, in which more than minimal bleeding has occurred. Any fall in blood pressure is treated by replacing the leg in the stirrup again while additional volume loading is performed.

The magnitude of the blood transfer by the lithotomy position can be estimated to be as much as 500 mL, provided that the operation is performed under spinal or epidural anesthesia. In a series of 60 transurethral prostatic resections (TURPs), arterial hypotension occurred in the lithotomy position when the blood volume was reduced by 300 mL or more (mean 500 mL) below baseline. When the legs were lowered from the stirrups, however, a sudden drop in arterial pressure occurred at an average blood volume of 100 mL below baseline. An increased blood volume by 400 mL "above" baseline was required to ensure a stable arterial pressure (Fig. 1). Regardless of body position, however, hypotension occurred when the central venous pressure was reduced by 2 mmHg below baseline (1).

These considerations suggest the practice of limiting the fluid administration somewhat during surgery in the lithotomy position, while the "saved" fluid be given as a volume load shortly before the legs are lowered from the stirrups.

BODY TEMPERATURE

Lowering of the body temperature is very common during surgery. Normal thermoregulation is impaired by general anesthesia and the almost naked patient is exposed to cold air and cold instruments. Heat is also removed by air currents and evaporation of moisture from the body.

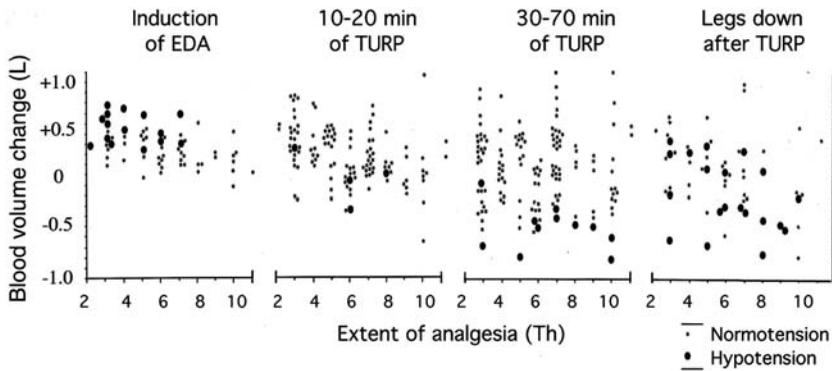


Figure 1 The blood volume change from baseline for normotensive and hypotensive patients, the latter being defined as a fall in systolic arterial pressure to below 85 mmHg or by more than 60 mmHg during 15 minutes, during various phases of transurethral resection of the prostate performed under epidural anesthesia. Each point represents one operation. The increased demand for a large circulating blood volume is apparent when the legs are lowered from the stirrups after the resection is completed. *Source:* From Ref. 1.

An intraoperative reduction in body temperature is so expected that most operating departments have adopted routines to prevent hypothermia (<35°C) from developing. These concerns apply to urology, although many urologic operations are fairly short, and evaporation is a minor problem when endoscopy is employed.

A major source of heat loss appears to be the practice of bathing the operating site in an irrigating solution. The purpose is to gently dilate a potential body space and also to wash away blood and pieces of removed tissue from the surgical field. Irrigation with large volumes of such fluid cools the body, which depresses myocardial performance (2) and may result in shivering (3,4). The time required to regain normal temperature after such cooling increases with the age of the patient (3). The use of irrigating fluids at room temperature results in a body temperature drop of between 1°C and 2°C during TURP (4–6). This decrease is smaller with an irrigant heated to 37°C than with a fluid used at ambient temperature, but it still averages 1°C during TURP (4,5). A continuously warmed irrigating medium is needed to limit the drop in body temperature to less than 1°C (6,7). An alternative is to maintain the body temperature by warming blankets (4).

The hypothermic tendency is aggravated by absorption of the irrigating medium by the patient (8), and postoperative freezing is a common complaint among patients who absorb large amounts of irrigating fluid (9).

BLOOD LOST IN IRRIGATING FLUID

The task of maintaining normovolemia by accurately estimating the amount of blood lost during surgery, and replacing it with clear fluids, is a major challenge for the anesthesiologist. However, the estimation of the blood loss by visual inspection is more difficult when the blood is dispersed in large amounts of irrigating fluid (10–15). The strong coloring effect of hemoglobin (Hb) can be illustrated by dispersing a single drop of blood in 1 L of fluid, which becomes intensively red after shaking. Therefore, guessing the amount of blood in a bucket of irrigating fluid is often associated with large errors.

A good alternative is to measure the amount of blood by a photometer, which is available for bedside use (15,16). To prevent clotting, a few drops of an anticoagulant such as heparin should be put in each bucket in which irrigating fluid is collected. After dispersal, a sample for measuring the Hb concentration is taken, and the blood loss is calculated using the following equation:

$$\text{blood loss} = \frac{\text{Hb conc.} \times \text{volume of irrigating fluid}}{\text{Hb in whole blood}}$$

For accurate results, the units must be the same, i.e., if Hb is measured in g/dL, the irrigating fluid volume should also be given in the dL unit. For Hb in whole blood, the preoperative



Figure 2 Example of a portable hemophotometer, which can be brought into the operating room for measuring the blood loss during urologic operations in which the blood is being dispersed in irrigating fluid.

concentration is normally used, although the plasma loss will then be underestimated by some 20% due to hemodilution during surgery (17).

The anesthesiologist can obtain help from the chemistry department for the installation of photometer equipment adjacent to or inside the operating room. The photometer should operate in the range of between 1 and 15 g/L (0.1–1.5 g/dL), i.e., in a range of about 10% of the normal Hb concentration in whole blood (Fig. 2).

There are alternative methods for measuring the blood content of irrigating fluid. The blood can be hemolyzed and the potassium concentration be measured (17). However, the subjective judgment involved in colorimetric measurements should render these approaches too old-fashioned for modern anesthesia.

REPLACING BLOOD LOST DURING TURP

Measuring the blood loss dispersed in irrigating fluid is particularly recommended for TURP. In this operation, which usually lasts for 30 to 45 minutes, the median blood loss is approximately 300 mL, but 15% of the patients bleed more than 1 L (Fig. 3) (15), with an ensuing risk for the development of arterial hypotension on the operating table if volume loading is insufficient (1). The amount of blood lost is heavily dependent on the extent of surgery, which varies considerably (Fig. 4). Other endoscopic operations in urology have a more predictable blood loss, and assessment using a technical method is less crucial.

When replacing blood loss with crystalloid fluid during TURP, the volume infused should be twice the bled amount. Hahn (18) studied the correlation between various operative factors during TURP, such as blood loss and the amount of administered Ringer's solution,

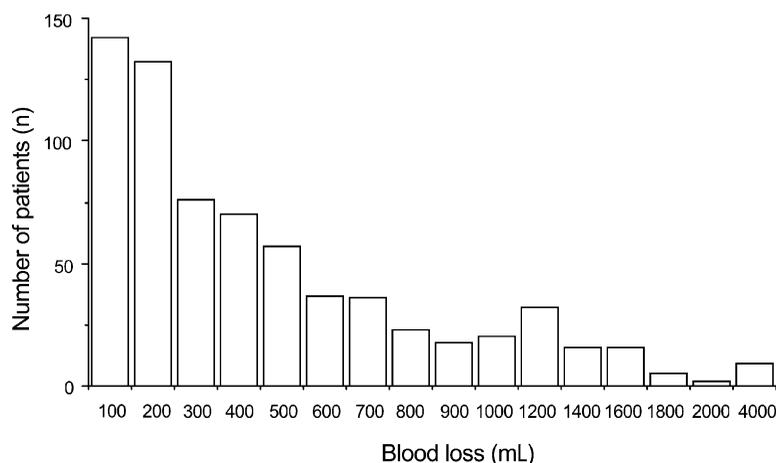


Figure 3 The blood loss during 700 transurethral prostatic resections. The median blood loss was only 300 mL, while 15% of the patients bled more than 1 L. *Source:* From Ref. 15.

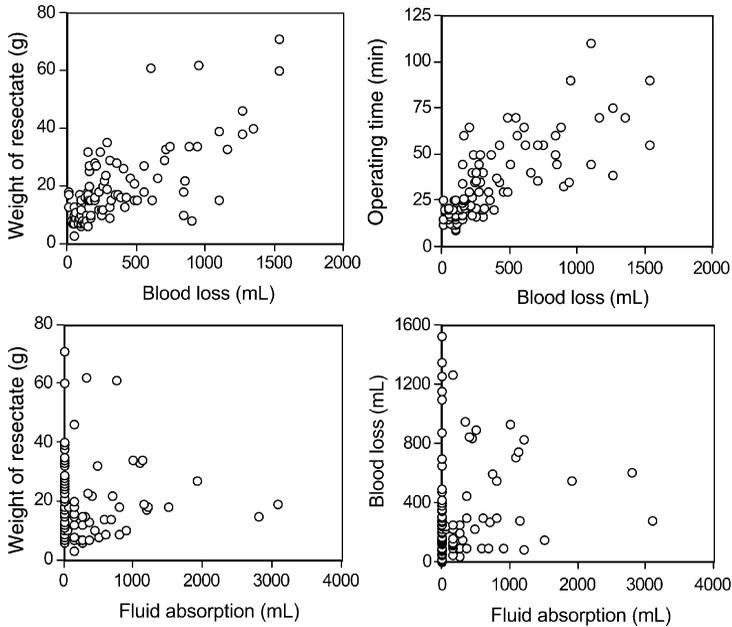


Figure 4 Typical relationships between surgical parameters during 100 transurethral prostatic resections. The blood loss increases with the extent of the operation, expressed as more resected tissue and a longer operating time, while fluid absorption cannot be predicted well by the extent of surgery. Fluid absorption was measured by the ethanol method.

and the blood volume as indicated by the relationship between blood loss and Hb changes in whole blood. The results showed that Ringer's solution increased the blood volume by 60% of the infused amount for each 10-minute period of TURP, while fluid absorption increased the blood volume by 35% to 40%. The calculations were validated by the blood loss, which correctly decreased the blood volume by 100% in the multiple regression model used.

The reason for the quite substantial volume increase for the amount of given Ringer's solution has been demonstrated using volume kinetic analysis. Ringer's solution is distributed between a central (V_1) and a peripheral (V_2) body fluid space between which equilibration requires as much as 30 minutes to be completed. As long as the infusion goes on, there is no final equilibration between V_1 and V_2 , and the volume effect in V_1 will be greater than anticipated, amounting to 45% of the amount of infused fluid for a 30-minute infusion in volunteers (19). Not until 30 minutes after the infusion is completed is the "normally" expected increase in blood volume obtained, which is 20% of the amount of infused Ringer's solution. However, the volume effect of infused fluid is higher in the operating room due to the low renal clearance of excess fluid, probably elicited by preoperative psychological stress, fasting, and trauma response (20).

These results indicate why one should replace bleeding during TURP with twice the bled amount of crystalloid fluid during TURP, plus administer an additional fluid load to prevent hypotension when the legs are lowered from the stirrups at the end of the procedure (Fig. 1). As mentioned previously, TURP may be performed at normovolemia, but at least if spinal or epidural anesthesia is employed, there should be hypervolemia when the legs are returned to the horizontal position.

Urologists have reported that treatment with oral finasteride for a few weeks prior to surgery reduces the total blood loss during TURP, but this has not been confirmed in company-sponsored randomized clinical trials.

FLUID ABSORPTION IN UROLOGY

Several different nonelectrolyte irrigating fluids may be used when electric cutting is performed during endoscopy (Fig. 5). Some basic facts about the characteristics of these fluids are explained in a separate chapter of this book, together with a discussion of the consequences



Figure 5 Examples of nonelectrolyte irrigating fluids, which are used during endoscopic surgery. These 3 L bags contain ethanol 1% as a marker for fluid absorption, which can be detected in the patient's exhaled breath.

of fluid absorption during TURP and endometrial resection, which are the two operations in which fluid absorption poses the greatest hazard. More detailed reviews are also available (21).

Fluid absorption may occur in any operation in which irrigating fluid is used. Adverse effects of irrigating fluids have been reported during percutaneous (22,23) and vesical (24) ultrasonic lithotripsy, clot retention removal (25), and transurethral resection of bladder tumours (26,27). The incidence of fluid absorption during these procedures is lower than for TURP. In contrast to TURP, however, fluid absorption usually results from instrument perforations, and the fluid is then deposited in an intra- and retroperitoneal pool from which it is slowly absorbed by the blood. Typical symptoms are abdominal pain and distention, arterial hypotension, and nausea. Contrary to common belief, patients with extravasation are hypovolemic, and no restriction of the intravenous fluid administration is therefore warranted (26). Fluid absorption, which occurs by the direct intravenous route as detected by ethanol or some other direct method, should be treated by a reduction of the intravenous infusion rate during the period of the absorption only. Thereafter, there is rather a risk of arterial hypotension due to hypovolemia.

Newer operations, which may replace TURP, are usually associated with a smaller blood loss and a lower risk of fluid absorption, although these complications still occur (28,29). The new bipolar technique even allows the use of normal saline for irrigation, which will alter the symptomatology of fluid overload in an as yet unknown way.

BLOOD LOSS IN MORE EXTENSIVE OPERATIONS

In contrast to most endoscopic operations in urology, which are performed with spinal anesthesia extending to the Th 10 dermatome or higher, nephrectomy is performed under general anesthesia. No electrolyte-free irrigating fluid is used, and the anesthesiologist therefore does not need to watch for accidental absorption. The attention required from the anesthesiologist is much dependent on the diagnosis. Extended growth of pathological vessels into a renal cancer indicates a risk of rapid massive bleeding during dissection. To prepare for such an event, the anesthesiologist is recommended to place an additional thick cannula in a cubital vein, and bring a colloid solution into the operating room, or alternatively, two crystalloid fluid bags after placing two venous cannulae. There is also a risk for postoperative bleeding, and the patient should be kept in the postoperative care unit overnight, preferably with invasive blood pressure monitoring, which allows immediate detection of hypovolemic hypotension.

Blood loss requiring deliberate hemodilution and possible transfusion with erythrocytes must also be expected during radical prostatectomy. As for TURP, the bleeding increases with

the amount of resected tissue (30). However, the amount of resected prostatic tissue is usually larger than during TURP. The blood loss is therefore larger and often amounts to 1 L.

INDICATION FOR TRANSFUSION OF ERYTHROCYTES

The decision to transfuse erythrocytes is a very important one. Erythrocytes carry a risk of viral infection, and bank blood might impair the microcirculation. Immunomodulation (TRIM or transfusion-associated immunomodulation) is a known consequence, even to the extent that organ dysfunction (TRALI or transfusion-related acute lung injury) develops. Septic reactions may occur, although such problems are more pronounced when platelets are transfused. Therefore, the anesthesiologist must have clear indications for when erythrocytes are to be given.

The indications for transfusion of erythrocytes in urology do not differ from those of other operations, but the patients are usually aged and quite sensitive to erroneous decisions. The topic is of interest here, because the decision to transfuse is often linked to the practice of normovolemic hemodilution. This means that blood loss is treated with infusion of salt solutions to maintain the blood volume. Such infusions dilute the blood Hb concentration. The body has sophisticated compensatory mechanisms to deal with an acute lowering of Hb levels, and these are more efficient than those that compensate for a lowered blood volume, the most important one being an increase of stroke volume to maintain oxygen delivery. Another mechanism constitutes an increase in the peripheral extraction of oxygen. At one point, however, the compensatory mechanisms simply are not sufficient for the body's need for oxygen, which is a limit called the "anaerobic threshold." If Hb level is further reduced, the delivery of oxygen to the tissues becomes too small. Lactate production increases and the patient becomes acidotic.

Efforts have been made to find a critical Hb level that signifies the anaerobic threshold. This Hb level is called the "transfusion trigger." However, each individual has a different capacity to deal with a low Hb. The cardiac capacity is reduced in elderly people, which limits their ability to increase stroke volume. The heart itself might also be susceptible to ischemia. Young healthy people withstand a low Hb much better, even down to 50 to 55 g/L (31).

There is consensus that the transfusion trigger should be between 60 and 100 g/L (6–10 g/dL) and that clinical judgment must determine what the trigger should be in the individual patient (32). If a lower Hb level is reached, the patient should be transfused with erythrocytes.

The "allowable blood loss" represents the volume of blood that can be lost until the transfusion trigger is reached. If the Hb concentration is the same in all blood that is lost, the allowable blood loss and the fall in Hb from before surgery to the transfusion trigger would be directly proportional. However, this is not the case, because the blood volume is constantly kept normal by infusions of salt solution. The last portion of the bled volume during a hemodilution process will therefore reduce Hb at a slower rate than the first portion. The following logarithmic equation by Bourke and Smith (33) estimates how large a bleed can be allowed. The relationship is based on the estimated blood volume at baseline (BV_0), the Hb level before the operation (Hb_0), and the transfusion trigger [$Hb(t)$], which is reached at time (t):

$$\text{allowable blood loss} = BV_0 [\ln Hb_0 - \ln Hb(t)]$$

This widely used equation shows that the amount of blood that can be lost until the transfusion trigger is reached varies greatly depending on the Hb concentration in the patient's whole blood before surgery starts. However, the equation is not a perfect one for use during surgery. Induction of anesthesia implies vasodilatation, which allows more fluid to accumulate in the blood, whereby Hb falls by 5% to 10%, which is not accounted for. The preoperative Hb may also be obtained with the patient in the sitting position, which becomes approximately 5% lower within 15 to 30 minutes when the patient lies down. Moreover, the equation assumes that the Hb level is always lowered in direct proportion to the blood loss, which means that the anesthesiologist has to make a perfect match between fluid therapy and bleeding at all times. Erroneous estimations will ensue if the hemodilution does not catch up with the bleeding, which is a common mistake. The hemodilution equation can be corrected for blood volume changes, but we then have a situation in which Hb losses are accounted for instead of volume losses, with an assumed Hb content, which may or may not be correct (34). The calculations involving Hb losses are further discussed under the Section "Hemoglobin Dilution During Surgery" in Chapter 5.

An alternative to the use of a hemodilution equation is simply to measure Hb in the operating room. This rests on the fact that the transfusion trigger is a Hb concentration, which is what a photometer measures. The same type of equipment as the one shown in Figure 2 can be used, but it must now be an apparatus calibrated to measure the range of Hb levels found in whole blood.

Transfusion of plasma is indicated to restore the plasma concentrations of coagulation proteins, which becomes an issue when more than half the blood volume has been lost. Human plasma should not be used as a volume expander, although it is as effective as albumin 5% as long as no immunological reaction occurs, which increases capillary leak (35).

LONG-TERM MORTALITY AFTER PROSTATECTOMY

Whether TURP is associated with "cardiac stress" and reduced long-term survival as compared to open prostatectomy was the subject of lively debate among urologists in the early 1990s (36). The increased mortality, which was primarily due to myocardial infarction, might be due to fluid absorption, because this factor differs between the two operations (37). Subsequent studies also found a higher long-term mortality after TURP (38,39), and in men with prostatism who did not undergo surgery (40,41). Others described a link between benign prostatic hypertrophy and the metabolic syndrome (42,43), which makes TURP patients vulnerable to hemodynamic stress. Evans et al. demonstrated cardiodepression during TURP (44,45), due to a cooling effect of the irrigating fluid (2). Warming the fluid also cools the body, however, particularly when fluid absorption occurs (8).

The incidence of acute myocardial infarction during TURP is between 1% and 3% (46,47). Evidence of cardiac ischemia was found in 25% of the TURPs using the Holter electrocardiogram, and mostly in patients with known cardiovascular disease (48). A marginal increase of cardiac enzymes occurred in 7% of TURP patients (47), but the incidence was higher in a case-control study of patients with fluid absorption (49).

Two studies address the possible role of fluid absorption in cardiac health. After correcting for confounders, Hahn et al. found in 846 patients that glycine absorption of more than 500 mL doubled the long-term risk of having an acute myocardial infarction, most of which occurred within two years after surgery (50). In the other study, Koshiba et al. did not find impaired long-term survival due to fluid absorption, which depressed serum sodium to 125 mmol/L (51). The explanation for the negative result might be that the morbidity begins to increase at a much lower cutoff point between absorbers and nonabsorbers than the one used in the second study.

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29 Fluid Therapy in Noncardiac Thoracic Surgery

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INTRODUCTION

The early development of thoracic surgery was limited by the availability of safe anesthetic techniques. Thoracotomy was fraught with problems associated with open pneumothorax. Early operations were carried out by using spontaneous ventilation in nonintubated patients. Cyanosis and hemodynamic instability associated with lung collapse and mediastinal shift often resulted in hurried operations with high mortality rates (1).

In the early to mid-1900s, significant advances in anesthetic care made it possible to perform thoracotomies under relatively stable conditions. Balanced anesthetic techniques, including inhalational anesthetics delivered through an endotracheal tube and muscle relaxants to render a patient apneic, facilitated open thoracic procedures. Positive-pressure ventilation provided an effective means of oxygenation and ventilation without the hazards of spontaneous ventilation. Lastly, advances in endotracheal intubation were of prime importance. Endobronchial intubation, first described by Joseph Gale and Ralph Waters, and later, the development of the double-lumen endotracheal tube by Eric Carlens increased the safety and ease of performing open thoracotomy by allowing lung isolation (2).

Although today noncardiac thoracic surgery is a relatively safe endeavor, the management of patients undergoing these procedures still invites debate. A leading area of interest is how to manage patients undergoing pneumonectomy, because these patients may develop postpneumonectomy pulmonary edema (PPE), a complication associated with a high mortality rate. Conventionally, patients undergoing noncardiac thoracic surgery receive standard fluid management. Yet there is a common belief that aggressive fluid infusion during pneumonectomy predisposes a patient to PPE. Fluid overload is, however, too simplistic an explanation for this complication. This chapter will focus on the pathophysiology of PPE and recommendations for minimizing its occurrence. As discussed below, a combination of factors most likely contributes to the genesis of PPE. In any case, fluid management strategies must balance the risk of increasing the likelihood of PPE against the necessity of sustaining perfusion to vital organ systems.

PULMONARY BLOOD FLOW, DRAINAGE, AND PHYSIOLOGY

Pulmonary Circulation

Under normal conditions, the pulmonary capillary has a basement membrane of the endothelial layer, which is fused with the basement membrane of the alveolar epithelium over a significant portion of the vessel's perimeter. The portion where the membranes are fused is the actual blood-air barrier, also called the "thin portion." The remainder of the capillary wall where the basement membranes are not fused is referred to as the "thick portion." Fluid and solute exchange is thought to occur there. Presumably, within this space there is an inherent ability to accommodate increases in fluid without impairing gas exchange.

Adjacent cells in the endothelium and the epithelium either overlap or abut bluntly, separated only by very narrow clefts. Furthermore, there is an inherent difference in the permeability of each layer. The intercellular junctions of the endothelial layer differ in structure from the junctions of the epithelial layer. The epithelial layer is tighter in its intercellular spaces and more restrictive to fluid and molecules, preventing them from entering the alveolar spaces.

The pulmonary alveolus is surrounded by blood and separated from the capillaries by the perivascular interstitial space, across which blood-gas exchange takes place (1). It is this

very gas exchange that is the “primary” function of blood delivery via the pulmonary circulation. The capillary bed encompasses 85% to 95% of the total alveolar surface.

The volume of blood that is circulated through the lung is comparable to the cardiac output of the left ventricle, averaging 5 to 8 L/min at rest. There is, however, a slight difference between the output of the two ventricles because of the drainage of bronchial veins and thebesian veins directly into the left heart. Being a high-flow system downstream from the right heart, the pulmonary circulation normally maintains a low intravascular pressure within. The volume of blood flow to the lungs is higher than that to any other organ. However, the pressure within the pulmonary vasculature is low, being about one-seventh (3) to one-fifth of that within the systemic circulation (4). Furthermore, when cardiac output increases, the inflow pressure in the pulmonary circulation demonstrates only a minimal rise. In other words, pulmonary vascular resistance, which is low at rest, is capable of decreasing even further when blood flow in the pulmonary circulation increases.

There are numerous factors that affect pulmonary blood flow. Green (3) classifies these factors as mechanical, neurogenic, and chemical. Green further proves that mechanical factors are the most important and influential, and the most critical mechanical feature is the collapsible nature of the pulmonary capillaries. Murray (4) classifies the factors into those causing passive and those causing active changes in the vascular resistance. His passive factors are analogous to Green’s mechanical factors, and the active factors comprise neurogenic, humoral, and chemical stimuli.

Passive/Mechanical Factors (Pressure and Resistance)

Pressure

The mechanical factors affecting blood flow through the lungs are related to pressure and resistance. The pulmonary vasculature is likened to an ideal Starling resistor, which is defined by three succinct statements:

1. When the pressure surrounding a tube (P_{palv}) is greater than the inflow pressure (P_{pa}), which is greater than the outflow pressure (P_{pv}), there is no flow ($P_{\text{palv}} > P_{\text{pa}} > P_{\text{pv}} = \text{no flow}$).
2. When the surrounding pressure (P_{palv}) is greater than the outflow pressure (P_{pv}), changes in the outflow pressure have no impact on flow; flow is proportional to the difference between the inflow pressure (P_{pa}) and the surrounding pressure (P_{palv}); i.e., $P_{\text{palv}} > P_{\text{pv}} = \text{flow proportional to } [P_{\text{pa}} - P_{\text{palv}}]$.
3. When the outflow pressure (P_{pv}) is greater than the surrounding pressure (P_{palv}), changes in the surrounding pressure (P_{palv}) have no impact on flow; flow is proportional to the difference between the inflow (P_{pa}) and the outflow pressures (P_{pv}); i.e., $P_{\text{pv}} > P_{\text{palv}} = \text{flow proportional to } [P_{\text{pa}} - P_{\text{pv}}]$.

Physiologically, the inflow pressure is reflective of the pulmonary arterial pressure, and the outflow pressure is reflective of the pulmonary venous pressure. The surrounding pressure represents the alveolar pressure. West and Jones (5) provided evidence that these three concepts can be applied to pulmonary blood flow, and in fact, the three situations exist in three distinct areas or zones of the lungs.

In an upright subject, the hydrostatic effect due to gravity causes the pulmonary arterial and venous pressures to increase from the apical region of the lung down to the diaphragmatic region. Thus, the vascular pressures are greatest in the most dependent portions of the lungs. According to measurements provided by Green (3), the typical human lung is 30 cm in height. At the diaphragmatic surface, the pulmonary venous and arterial pressures are 10 cmH₂O and 20 cmH₂O, respectively. Hence, moving up from this surface, at 10 cm above the diaphragmatic surface, the venous pressure would approach atmospheric pressure. Similarly, at 20 cm above this surface, the arterial pressure would approach atmospheric pressure.

Thus, the lungs can be divided vertically into three distinct zones, each 10 cm high and having distinct vascular pressures of the inflow and outflow tracts [zone 1 = no flow; zone 2 = flow proportional to ($P_{\text{pa}} - P_{\text{palv}}$); and zone 3 = flow proportional to ($P_{\text{pa}} - P_{\text{pv}}$)]. It is important to recognize that there is no true zone 1 in the lung because there is always flow unless the pulmonary artery pressure falls or alveolar pressure rises beyond a threshold level. In contrast to the dynamic nature of vascular pressures, the alveolar pressure remains essentially constant throughout the lung field.

Resistance

A second variable, identified as resistance, has an impact on the mechanical influence of blood flow. In general terms, the resistance of the pulmonary vasculature is calculated as the difference between pulmonary artery pressure and left atrial pressure, divided by cardiac output.

From the apex of the lung down to the diaphragmatic surface, there is a drop in resistance. The etiology of this is not clear, but there are two hypotheses.

1. Maseri et al. (6) proposed the "Recruitment Hypothesis," which is based on a concept of critical opening pressures for pulmonary vessels. For a vessel to become perfused, the arterial pressure must rise above the vessel's opening pressure. Because pulmonary artery pressure increases toward the base of the lung, more vessels are opened and perfused. Evidence has been found by Glazier et al. (7) that this recruitment occurs when venous pressure is less than arterial pressure, as is the case in zone 2.
2. West and Jones (5) proposed the "Distention Hypothesis," which is based on the concept that an increase in the transmural pressure moving down the lung is associated with an increase in the radius of the capillaries. This increase in vessel size results in a decrease in resistance to flow. Again, Glazier et al. (7) integrated this resistance hypothesis with vascular pressures and showed that distention predominantly occurs when venous pressure is greater than arterial pressure, as is the case in zone 3.

There are additional factors that affect the resistance within the pulmonary vasculature. Left atrial pressure acts as the back pressure to blood flow through the lungs. Lung inflation can affect pulmonary blood flow in two ways: it has a direct impact on vessel walls by compressing them during inflation and an indirect effect by influencing venous return. Finally, a change in blood volume or viscosity can affect the resistance in the pulmonary vasculature.

Influences on Mechanical Factors

The mechanical factors affecting the flow are altered when a patient is in the lateral decubitus position, which is the traditional positioning for thoracic operations. Gravitational forces result in an increase in perfusion of the dependent lung. Also, surgical retraction and compression, and ultimately, ligation of the pulmonary artery, compromise blood flow to the nondependent lung.

Because of the conditions of an open chest and paralysis, ventilation of the upper lung is greater than that of the dependent lung. Furthermore, the dependent lung experiences compression from the mediastinum, abdominal contents, and positioning. The increase in perfusion of the dependent lung and the increase in ventilation of the superior lung result in a ventilation-perfusion ratio (V/Q) mismatch.

Single-lung ventilation is often utilized in thoracic surgical cases. This further exaggerates the V/Q mismatch. When only one lung is ventilated, the alveolar-to-arterial oxygen tension difference is much greater than when two lungs are ventilated, with the same FIO_2 , hemodynamics, and metabolic status, although hypoxic pulmonary vasoconstriction tends to minimize this difference (1). Notably, because of the high solubility of carbon dioxide, the ventilated lung can eliminate enough of the gas so that the $PACO_2$ - $PaCO_2$ gradient is not as significantly affected.

Active Factors (Neurogenic, Humoral, and Chemical)

Neurogenic

There are two types of neurogenic influence on pulmonary blood flow. One is a direct influence on the blood flow within the pulmonary circulation, and one is an indirect influence caused by the pulmonary blood flow as a controlling impulse. Sympathetic fibers from the stellate ganglion and parasympathetic fibers from the vagus nerve innervate the pulmonary vasculature. However, studies show minimal responses to autonomic control, even with maximum stimulation.

The output impulses originating within the pulmonary vasculature are thought to be more important from a neurogenic point of view. The vagus nerve innervates mechanoreceptors located within the walls of the pulmonary trunk and in the left and right pulmonary arteries. In response to increases in pulmonary arterial pressure, these mechanoreceptors cause a reflexive decrease in heart rate and circulatory pressure analogous to the baroreceptor reflex (3).

Humoral

Many naturally occurring peptides have an influence on pulmonary vasculature. The pulmonary response to humoral agents is opposite to that of the systemic vasculature. Pulmonary vasoconstrictors are composed of catecholamines, angiotensin, histamine, prostaglandin F_{2α}, and fibrinopeptides. Pulmonary vasodilators include isoproterenol, prostacyclin, and (in an already constricted vascular bed) acetylcholine. Because these vasodilators have only been studied in animals, it is difficult to qualify their effects in humans.

Chemical

An incredibly important mechanism of the lungs is the capability of adjusting regional blood flow in response to local oxygen and carbon dioxide tensions. If an area of the lung is under-ventilated, oxygen tension falls and carbon dioxide tension rises, causing localized pulmonary vasoconstriction in an effort to shunt blood to an area that is more adequately ventilated. Likewise, in the face of hypocapnia from underperfusion, bronchial smooth muscle tone will increase in an effort to readjust the ventilation/perfusion relationship.

Lymphatic Drainage, the Starling Equation, and the Lung's Protective Mechanisms

Factors Affecting Lymphatic Drainage

As blood circulates through the lung at a normal rate and pressure, there is a net fluid movement across the capillary wall into the interstitium. This filtered fluid is picked up by the lymphatic channels and returned to the circulation (8).

Variables affecting lymphatic drainage include the intrinsic motion of the lung during respiration and the involuntary peristaltic motion of the lymphatic vessels. Normally, there is a slow, steady movement of fluid into the interstitium at a rate of 10 to 20 mL/hr, which is easily accommodated by the lymphatics. This movement of fluid is accomplished via one of three mechanisms: (i) by active transport, (ii) by vesicular transport, or (iii) through inter-endothelial clefts, whose junctions are 40 Å in diameter (albumin molecules are 80 to 100 Å).

Operative trauma of the chest can affect fluid transfer across the capillary membrane. Surgery results in a violation of the capillary–lung interface, as well as causing other physiologic effects such as an increase in cardiac output of up to twofold from the resting level. Increased perfusion through a decreased capillary bed leads to greater hydrostatic pressure. This is compounded by a reduction in the capacity of the lymphatic pump proportional to the amount of lung resected.

The Starling Equation

Starling forces help to determine whether fluid flows across a capillary wall. As seen in the Starling equation (Fig. 1), net fluid flux across the capillary membrane is calculated by the difference between net hydrostatic and oncotic pressures in the capillary and tissue.

The forces in the capillary and tissue can each influence the movement of the fluid in or out. For example, oncotic pressure in the capillary or tissue promotes the retention of fluid in each compartment, respectively. Conversely, hydrostatic pressure within the capillary or tissue promotes fluid flux out of the respective compartments.

The Lung's Protective Mechanisms

To keep Starling forces in balance, the lung has three protective mechanisms. The first is the lymphatics, which can accommodate an increase in the flow of five to seven times normal.

Once the lymphatic mechanism is exhausted, the interstitium acts to absorb additional fluid; this is described as the "two-compartment model." Increases in perivascular space fluid lead to an overflow in the peribronchial areas; this absorptive capacity of the lung can increase by a factor of eight. Once absorption is maximized, pressure begins to impinge on terminal airways and gas exchange is compromised. Clinically, dyspnea and cyanosis appear.

Finally, the alveoli themselves begin to absorb the fluid. The wall of the alveoli becomes edematous and traumatized, but the epithelial lining is thought to remain intact. At this stage, pulmonary water can increase by 1500 mL. Clinical manifestations are pathognomonic pink

$$J_v = K_f[(P_c - P_i) - (\Pi_c - \Pi_i)]$$

Figure 1 The Starling Equation, which describes the forces that govern fluid flux out of the pulmonary capillary.

frothy sputum and rales, reflecting fulminant pulmonary edema. Damage due to surgery increases the leakage of proteins into the interstitial space, platelet accumulation, and the associated release of serotonin. Protein flux across the capillary membrane leads to the development, in proportion to the flux, of interstitial fibrosis and hyaline membranes within about six days. The actual pathology resulting from this accumulation of fluid is due to collagen deposition, which is irreversible. A severe picture of this pathology is represented by PPE. The pathophysiology of this edema and recommendations for fluid management in patients undergoing pneumonectomy will be discussed in the following sections.

POSTPNEUMONECTOMY PULMONARY EDEMA

Definition, Onset, Incidence, and Mortality

Gibbon and Gibbon first induced PPE in animal models in 1942 (9), but it was not until 1984 that Zeldin et al. characterized PPE as a complication associated with pneumonectomy in humans (10). The clinical features of PPE include the aggressive onset of dyspnea, oxygen desaturation, and edema in the remaining lung of a pneumonectomy patient. To reach a diagnosis of PPE, other causes of pulmonary edema (such as cardiac failure secondary to myocardial infarction or arrhythmia, chest infection, aspiration pneumonia, pulmonary thromboembolism, acute respiratory distress syndrome (ARDS) secondary to septicemia, and bronchopleural fistula) must first be excluded (11,12). Classical PPE is characterized by high cardiac output accompanied by high pulmonary pressures in the setting of normal left ventricular filling pressures (13). The progression of cellular pathology in PPE mirrors that of ARDS, suggesting that PPE may be a variation of ARDS that occurs following lung resection (14).

In most instances, PPE occurs rapidly after surgery and carries a poor prognosis. PPE usually occurs one to three days postoperatively, although the range of occurrence is 12 hours to 7 days postoperatively (11,12,14,15). Figure 2 shows the typical radiographic presentation of PPE. PPE develops in 4% to 7% of postpneumonectomy patients and in 1% to 7% of postlobectomy patients (11,14,15). Unfortunately, PPE is resistant to conventional therapy for high-pressure pulmonary edema (i.e., diuretics, oxygen, fluid restriction, and positive-pressure ventilation); in fact, these therapies can even worsen the oxygen desaturation (16). Consequently, the mortality rate of PPE is as high as 50% to 100% (11,12,14,15,17). In comparison, the mortality rate associated with pneumonectomy is 5% to 23% (18).

Obviously, understanding the causes of PPE is integral to preventing and treating this serious complication. Although many factors most likely contribute to the development of PPE, much attention continues to be focused on the fluid management. A widely held belief is that aggressive fluid therapy increases the risk of PPE. In this chapter, we will examine the evidence for that correlation. We will also assess whether the essential role played by the fluids in maintaining adequate systemic perfusion justifies the risk of PPE if such a correlation exists.

Pathophysiology of Postpneumonectomy Pulmonary Edema

PPE may be induced by a multitude of factors, including variables of the Starling equation, stresses of surgery (including loss of a lung, mechanical ventilation, hyperinflation, etc.), disrupted lymphatics, and increased central venous pressure as a consequence of right ventricular dysfunction (Fig. 3). Each of these factors will be discussed below, followed by recommendations for management.

Starling Forces

Many factors are likely to contribute to the pathogenesis of PPE. Several of these factors, including pulmonary capillary hydrostatic pressure, the area of capillary bed perfusion, and serum colloidal oncotic pressure, are related to variables of the Starling equation.

As discussed in the section "Anatomy and Physiology" above, the Starling equation describes the forces that influence fluid flux through the pulmonary capillary. Oncotic pressure in the capillary draws fluid into the capillary, while hydrostatic pressure within the capillary drives fluid out; the balance of these two pressures determines net flux.

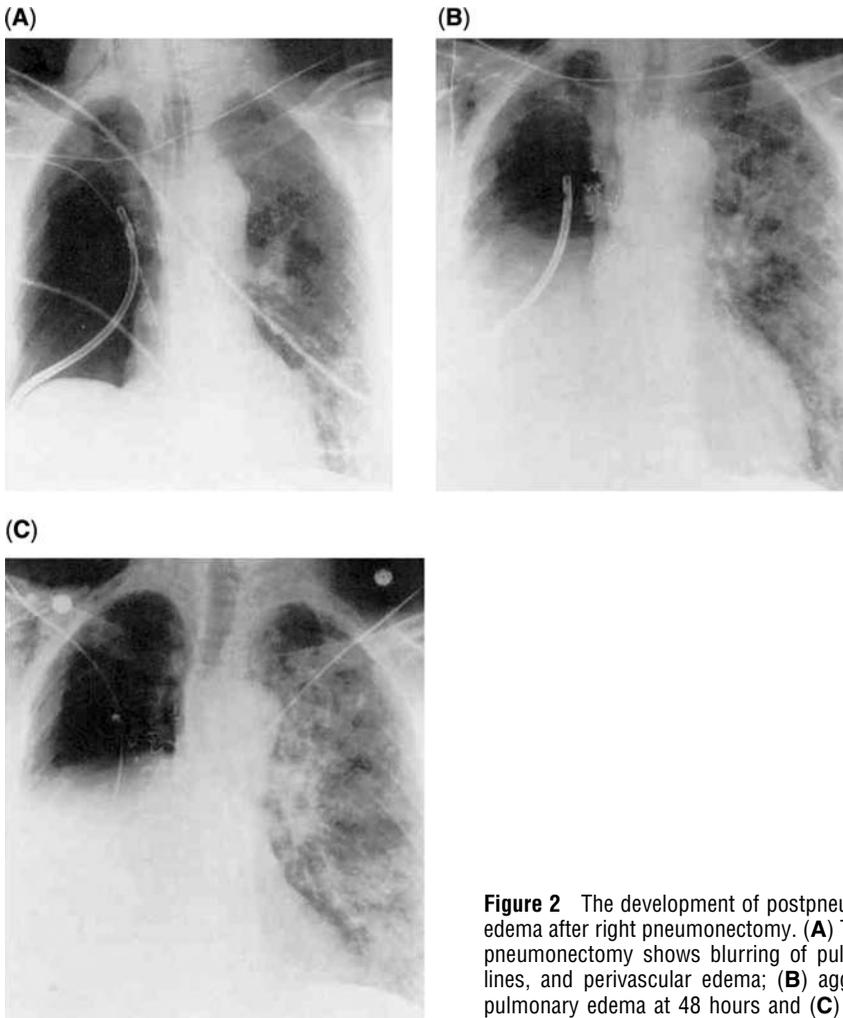


Figure 2 The development of postpneumectomy pulmonary edema after right pneumectomy. **(A)** Twenty-four hours post-pneumectomy shows blurring of pulmonary vessels, Kerley lines, and perivascular edema; **(B)** aggressive onset of florid pulmonary edema at 48 hours and **(C)** 72 hours postpneumectomy. *Source:* From Ref. 12.

Elevated Capillary Hydrostatic Pressures and Area of Capillary Bed Perfusion

We will first consider how fluids affect hydrostatic pressure. A prevailing hypothesis for the origin of PPE focuses on the notion of fluid overload. Overzealous fluid administration is likely to increase cardiac output and mean pulmonary artery pressures, resulting in a greater pressure gradient between the arterial and venous ends of the pulmonary capillary. This change in the pressure gradient shifts the mean capillary pressure point toward the venous end, thus increasing pulmonary capillary hydrostatic pressure (P_c) and favoring filtration (10). Additionally, the increased pressure gradient distends perfused capillaries and recruits previously unperfused capillaries, thus increasing the area (A) of the capillary bed that is perfused and, consequently, the quantity of fluid filtered (J_f) (19). It is worth noting that in animal studies, an increase in mean pulmonary arterial pressure may be accompanied by improved precapillary tone and resistance, which minimizes the effects on pulmonary capillary hydrostatic pressure (10).

Serum Colloidal Oncotic Pressure

Oncotic pressure (π_c), like hydrostatic pressure, is a key component of the Starling equation. It is widely believed that large amounts of crystalloid infusion decrease serum colloidal oncotic pressure by diluting plasma proteins (20). Various studies have suggested that low serum colloidal oncotic pressure is a risk factor for PPE (14,15,19,21). However, low plasma colloidal oncotic pressure has not been correlated with increased extravascular lung water (22). A possible explanation for this observation is that, when compared with the periphery, pulmonary

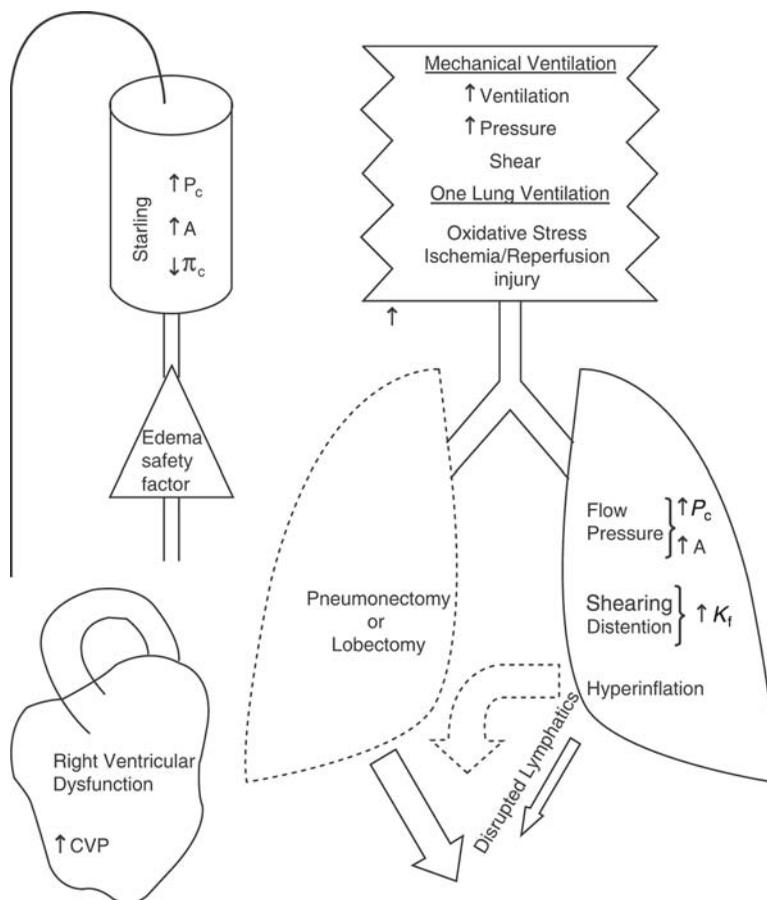


Figure 3 Overview of factors that may contribute to the development of postpneumonectomy pulmonary edema (PPE). Administration of fluids (*upper left*), mechanical ventilation, and other aspects of surgery/anesthesia (*right, upper*), changes in blood flow and lymphatic drainage (*right, lower*), and right ventricular dysfunction (*lower left*) may be involved in the pathogenesis of PPE.

capillaries are more permeable to small proteins even in the normal state. For example, in normal lungs, the protein concentration in the pulmonary extravascular space is approximately 70% that of the plasma (23), whereas the protein concentration in the skeletal muscle extravascular space is 55% that of the plasma (24). Changes in protein concentration across the pulmonary capillary membrane are quickly equilibrated, minimizing the effect of colloid dilution in the vessel (22). When capillary permeability (described by K_f , the filtration constant in the Starling equation) is increased further as a result of pathologic changes induced by PPE, the contribution of oncotic pressure to fluid flux is reduced even more.

Edema Safety Factor

The balance of Starling forces helps to maintain an edema safety factor: a window of P_c (7–25 mmHg) in which the accumulation of lung interstitial fluid is minimal (a sudden rise in fluid accumulation occurs above 25 mmHg) (25). Within this window, the following characteristics are found: (i) a net favorable balance of the Starling forces; (ii) a reduction in the tissue oncotic pressure as fluid filters out of the capillaries; (iii) an increase in tissue hydrostatic pressure; and (iv) a rise in lymphatic drainage that parallels increases in filtration (20). The safety factor exists only when lymphatic pump function is optimal and K_f is normal (20).

Surgical and Anesthetic Considerations in Pneumonectomy

In a study by Deslauriers et al., the duration of surgery and extent of resection correlated with the occurrence of PPE (16). This finding is not surprising, because surgery on the delicate

tissues of the lung may result in parenchymal damage similar to contusions, eliciting an inflammatory reaction (13).

The removal of lung tissue in itself predisposes the remaining lung to edema. Following resection, the remaining lung tissue assumes the burden of carrying blood and draining lymphatic fluid that once belonged to the excised portion. Following pneumonectomy, half of the total lung vasculature is lost, resulting in hyperperfusion of the remaining lung (13). Two major consequences ensue: P_c is increased and mechanical stresses and shear forces damage endothelial tissue.

Increased Flow and Pressure

To maintain adequate cardiac output in the absence of lung tissue, the flow rate and pressure must increase in the remaining lung. Increases in flow rate and pressure translate into increases in P_c and capillary surface area (A), as more capillaries are perfused (20). Consequently, net flux (J_f ; the product of A with hydrostatic and oncotic pressures) is increased, which predisposes the patient to PPE.

Blood Flow and Endothelial Damage

In addition to their influences on P_c and A , changes in flow rate and pressure in the remaining lung have a direct effect on the filtration constant (K_f) in the Starling equation. Greater permeability (that is, greater K_f) results from direct cell damage secondary to tangential and shearing forces acting on the capillary endothelium (26–28). Increased pressure also distends the capillaries, which may widen the endothelial intercellular junctions and result in net fluid flux out of the vasculature (29,30). In addition, mechanical damage may allow fluid rich in proteins to leak out of the pulmonary capillaries; in one study of PPE patients, edema fluid to serum protein ratios were found to be 0.6 or greater (an indication of pulmonary edema caused by high capillary permeability) (15).

Lymphatic Disruption

Pneumonectomy also impairs fluid drainage from the pulmonary interstitium secondary to removal of lymphatic tissue. Even during less extensive lung resections such as lobectomy, ipsilateral lymph vessels sustain damage secondary to the standard practice (for resection of lung cancer) of sampling ipsilateral and pericarinal lymph nodes (13,31). Nevertheless, studies have shown that lung lymph flow can increase up to sevenfold following pneumonectomy, without the risk of pulmonary edema (25,32). The percentage of lymphatic tissue lost during pneumonectomy depends on the side resected: right pneumonectomy removes 55% of the total lymph vasculature, and left pneumonectomy removes 45% (10). Mediastinal lymph node dissection further damages the lymphatic drainage system and may also impair the flow through complementary drainage routes along the perivascular peribronchial space to the mediastinum and through the pleura (20).

Right pneumonectomy results in the loss of just over half of the total lymph drainage, but many studies have found that the incidence of PPE is substantially greater when right (as opposed to left) pneumonectomy is performed (10,11,14,31,33,34). A proposed explanation for this observation is based on the studies of lymphatic spread in right versus left lung tumors, because tumor spread follows routes of lymphatic drainage. Ninety-four percent of right lung tumor metastases follow right side lymphatic drainage routes via the right hilum to the right superior mediastinal nodes (35). In addition, 56% of left lung tumors and 78% of left lower lobe tumors metastasize via right side lymphatic drainage (35). These statistics suggest that right lung pneumonectomy more severely cripples the total lymphatic drainage system. Accompanying the loss of lymphatic drainage routes in a right pneumonectomy is the large increase (more than double) in lymph production by the left lung resulting from increased perfusion. However, the side of the lung resected does not always correlate with the incidence of PPE (11,17,36). Parquin et al. have suggested that lung perfusion studies in a pneumonectomy candidate are more likely to predict the risk of developing PPE, as remaining lung perfusion below 55% is a significant risk factor (36).

Right Ventricular Dysfunction

Lymphatic drainage also is impaired by the effects of pneumonectomy and lobectomy on the heart. Right ventricular dysfunction (usually occurring on postoperative day 2) is not

uncommon following these procedures and is thought to occur because of increases in right ventricular afterload (31,37). Reed et al. (37) observed a 20% decrease in the right ventricle ejection fraction in 15 patients following pneumonectomy. Central venous pressure rises under conditions of right ventricular dysfunction, thus transmitting higher pressures to the lymph system and hampering drainage (31).

Mechanical Ventilation

A further risk factor for PPE results from the need for mechanical ventilation in patients undergoing pneumonectomy. Interestingly, it appears that the greater threat comes from volutrauma, rather than from barotrauma. In animal studies, higher tidal volumes delivered at low airway pressures were more detrimental to pulmonary tissues than were normal tidal volumes delivered at high airway pressures (38). High tidal volumes resulting in the overdistention of alveoli may (i) widen intercellular junctions and promote fluid and protein flux across the capillary–alveolar membrane (39), (ii) decrease lymphatic drainage (40), (iii) play a role in increasing pulmonary arterial pressures independently of cardiac output (31), and (iv) decrease lung compliance [compliance is ideal at normal functional residual capacity (FRC)] (31). Therefore, it appears that tidal volume (rather than pressure) is an important factor in the genesis of PPE. However, van der Werff et al. (12) found that mechanical ventilation pressures exceeding 40 cmH₂O correlated with PPE. In fact, the need for increased intraoperative ventilatory pressures (indicating decreased lung compliance) suggests that PPE may already be developing in a patient (12).

During mechanical ventilation, high tidal volumes and inadequate positive end-expiratory pressure (PEEP) cause the alveoli to open and close cyclically (41). This repeated opening and closing of alveoli subjects the lung tissue to shear forces and stretching (40) and results in clinical, radiological, and pathological changes consistent with ARDS (42). A systemic proinflammatory cytokine syndrome is likely to be involved in these changes, because patients with higher tidal volumes release higher levels of proinflammatory cytokines (43).

Hyperexpansion and Chest Drainage Systems

Hyperexpansion is also a danger in the recovery phase of a pneumonectomy. When conventional chest tubes are used to drain the operative side, excessive negative pressure may result in a mediastinal shift, with contralateral lung hyperinflation and increased FRC (31,44). In fact, the omission of chest tubes or the use of pressure balanced chest tubes has decreased the incidence of PPE (16). The relatively higher frequency of PPE following right pneumonectomies may also be attributable to the fact that the heart and great vessels displace more readily to the right than to the left, thus resulting in hyperinflation of the contralateral lung (this occurs in the left lung more frequently than in the right) (16).

One-Lung Ventilation

One-lung ventilation during pneumonectomy or lobectomy presents a hazard to both the nonoperative and operative lungs. In particular, exposing the nonoperative lung to high concentrations of oxygen may cause damage secondary to increased oxidative stress, although the level of oxygen required for inducing toxicity and lung damage is unknown (13). In both lobectomy and pneumonectomy, expanding and collapsing the lung several times is usually required to aid in resection (13). As a result of lung isolation, ischemia/reperfusion injury may result in the operative lung (13).

Recommendations

Fluids

As stated above, aggressive fluid therapy remains the most controversial of the possible causes of PPE. Some studies have found correlations between the amount of fluid administered and the risk of PPE (10,33,34), while others have found no such correlation (11,14–16,45–47). In fact, in one study, patients with PPE even had a lower mean positive fluid balance than were patients who did not experience PPE (11). Furthermore, even with severe fluid restriction, patients still experienced PPE (14).

The conflicting results of these studies may be explained by the investigators' attempts to oversimplify the role of fluids in the causation of PPE. It is most likely that fluids are not an initiating factor; however, combined with other forces that damage the capillary endothelium during

pneumonectomy, fluids may exacerbate and prolong the PPE. Evidence to support this hypothesis includes the high concentration of protein in edema fluid and the delay in onset of PPE (13).

Fluid Management Guidelines

Based on the likelihood that aggressive fluid therapy does play a role in PPE, conservative fluid management is essential. Current recommendations are outlined as follows:

1. A total *positive fluid balance* greater than 20 mL/kg in the first 24 perioperative hours should be avoided. For example, Margolis (48) and Slinger (31) recommend less than 2 L of fluid intraoperatively and less than 50 mL/kg postoperatively. Parquin et al. (36) found that intraoperative fluid infusion of more than 2 L increased the incidence of PPE. Furthermore, an increased mortality rate was observed in PPE patients who had received more than 3 L of fluid in the first 24 perioperative hours (34). Interestingly, although fluid administered in these 24 hours was critical, Swartz et al. found no correlation between fluid infusion and mortality when fluid was administered 24 to 72 hours postoperatively (18).

2. Peters (20) recommends that *blood transfusion* be avoided if blood loss is less than 750 mL. In this case, the lost volume should be replaced with crystalloid blood components, and the replacement volume should not exceed four times the volume of blood lost. The total replacement volume should be given in fractions: one-half immediately, one-fourth within 12 hours, and the final fourth in the next 12 hours (20). For blood loss greater than 750 mL, the patient should be given a blood volume equal to the amount lost plus an equal amount of crystalloid. Again, one half should be given immediately, followed by one-fourth in the first 12 hours, and one-fourth in the last 12 hours (20). When considering this strategy, organ system disease and the requirement for increased oxygen delivery must be taken into account, and the threshold for transfusion should be adjusted accordingly.

Vaporciyan et al. (47) examined the association of several pre- and perioperative factors with major pulmonary events (MPEs, defined as pneumonia or ARDS) following pneumonectomy. Transfusion of five or more units of packed red blood cells was associated with an increased risk of MPEs (47). Interestingly, intraoperative fluid balance and postoperative 24-hour fluid balance were not associated with an increased incidence of MPEs (47).

In addition to the possibility of contributing to PPE, blood transfusion during lung resection may have another unwanted side effect. Immunologic studies suggest that perioperative blood transfusion is an immunosuppressant that may lead to the growth of malignant tumors (49–57). Because the majority of lung surgeries performed today are tumor resections, this is an especially alarming possibility. Several studies have correlated intraoperative blood transfusion during resection of non–oat cell lung carcinoma with the recurrence of the cancer and decreased survival (52,53,56,57).

Transfusions of fresh frozen plasma (FFP) may also contribute to the development of PPE (58). FFP is rich in antibodies against leukocytic and, less frequently, granulocytic antigens (12). When FFP is administered, activated leukocytes and granulocytes localize to the interstitial space between the alveolus and capillary, resulting in immunologic damage and increased permeability (12). This syndrome, transfusion-related acute lung injury, is a variant of ARDS (59,60).

3. *Urine output* in the perioperative period should be no greater than 0.5 mL/kg/hr unless the patient shows signs of renal insufficiency (31). High urine output in the first 24 postoperative hours is correlated with PPE (10). It is interesting, however, that Alvarez et al. (61) found that oliguria, not polyuria, was associated with PPE, perhaps because fluid was being sequestered in the lungs, leading to intravascular volume depletion and resultant oliguria. Therefore, urine output may not always be an indicator of PPE.
4. *Inotropic therapy* guided by invasive hemodynamic monitoring is preferable to aggressive fluid resuscitation in cases of inadequate systemic perfusion (31). This therapy is especially relevant in cases of right ventricular dysfunction, in which inotropes, pulmonary vasodilators, and inodilators may improve ventricular function and lymphatic drainage (31).
5. For thoracic cases, recommendations in anesthesia textbooks (1) for *third-space fluid replacement* should be considered extreme. Instead, third-space losses in the thorax should be considered to be nonexistent (31).

Crystalloid or Colloid?

Much debate remains over the respective risks and benefits of crystalloid and colloid fluid administration in thoracic surgery. Both types of fluid have been hypothesized to play a role in PPE. Crystalloid, the standard choice for fluid maintenance, is believed to reduce serum colloidal oncotic pressure by diluting serum proteins. Reduced oncotic pressure has been shown in some studies to correlate with PPE (20). However, as discussed above, the significance of reducing pulmonary capillary oncotic pressure with crystalloid is unclear; the pulmonary capillary is highly permeable to small proteins, and oncotic pressure is likely to equilibrate across the capillary membrane rapidly (22).

The question of the effect of crystalloids on oncotic pressure has shifted attention to the possible use of colloid as an alternative fluid. However, some studies suggest that colloid may not have such a clear advantage. In animal studies, administered albumin has been shown to leak from the pulmonary capillaries into the extravascular space, where it may attract water and worsen pulmonary edema (62,63). In fact, other animal studies have shown that even the largest molecular weight colloids such as hetastarch readily cross the capillary membrane and drain into the pulmonary lymph system (64). Furthermore, pulmonary capillary permeability is increased even further in the setting of PPE; thus, colloids should be administered with greater caution (22).

Lung Volumes

After lung isolation, it may be prudent to maintain lower tidal volumes (e.g., 5–7 mL/kg). As mentioned above, volutrauma may predispose patients to PPE. During lung resection, anesthesiologists typically maintain the standard 10 mL/kg tidal volume, even after lung isolation. Slinger (31) has suggested that this value is too high. In animal studies, high tidal volumes (40 mL/kg, or 6–8 times the normal spontaneous tidal volumes), even when delivered at low airway pressures, were detrimental to the lungs (38). As shown in Table 1, FRC increases in the remaining lung following pneumonectomy, causing the total end-inspiratory lung volume to approach the value that caused volutrauma in animal studies. The administration of lower tidal volumes will result in lower peak pressures, which is desirable because ventilation pressures of 40 cmH₂O and higher are correlated with PPE. Slinger (65) has advised that peak airway pressures be kept below 35 cmH₂O and plateau pressures below 25 cmH₂O during one-lung ventilation. These lower tidal volumes and peak pressures will reduce the risk of PPE. However, in patients whose ventilation and oxygenation status cannot tolerate these values, appropriate adjustments must be made to balance the risk of PPE against the risk of inadequate oxygenation and ventilation.

Chest Drainage System

Pressure-balanced chest drainage systems must be used to ensure mediastinal midline stability and minimize increases in FRC in the remaining lung (16,31). Conventional chest tubes exert excessive negative pressure, resulting in mediastinal shift and contralateral lung

Table 1 Theoretical Postpneumonectomy Left Lung Volumes

Mechanical ventilation $V_T = 10$ mL/kg
Therefore, 70 kg patient left lung $V_T = 700$ mL
FRC 70 kg patient = 2200 mL
FRC left lung = $2,200 \times 0.45 = 1000$ mL
Increase FRC postpneumonectomy = 40% (estimated)
Therefore, postpneumonectomy left lung FRC = 1400 mL
Routine end-inspiratory lung vol = FRC + $V_T = 2100$ mL
Theoretical V_T to produce volutrauma = 40 mL/kg
Therefore, 70 kg patient V_T volutrauma = 2800 mL
Therefore, V_T volutrauma left lung = $2800 \times 0.45 = 1260$ mL
Normal FRC left lung = 1000 mL
End-inspiratory vol in left lung to produce volutrauma = 2260 mL

Abbreviations: V_T , tidal volume; FRC, functional residual capacity.

Source: From Ref. 31.

hyperinflation (20,31,44), with concomitant capillary leakage (20). Serial chest X rays are recommended to confirm mediastinal midline stability.

Position

During pneumonectomy, the patient should lie supine, with the head of the bed elevated by at least 35° (10,20,31). This head elevation will lessen the effects of gravity on P_c (20,31). If the patient lies on the side that is resected, the mediastinum is likely to shift (31), whereas if the patient lies on the nonoperative side, gravitational effects may increase the P_c (31). Early ambulation after surgery should be encouraged.

Pain, Hypoxia, and Hypercarbia

At The University of Texas M.D. Anderson Cancer Center, the standard method of pain control after thoracotomy is the thoracic epidural. Effective pain control is essential because inadequate pain relief is a risk factor for PPE (14,19,66). Pain and immobility may impair the lung's lymphatic drainage system (67) and increase circulating catecholamines, thus increasing cardiac output and P_c (10,20). Pain also increases P_c as a result of active pulmonary vasoconstriction (31).

Thoracic epidural pain relief has several advantages for thoracotomy: (i) effective and reliable pain relief, (ii) decreased circulating catecholamines, and (iii) less sedation when compared with systemic narcotics. However, in circumstances where thoracic epidurals may be contraindicated or not possible to perform, patient-controlled analgesia will usually suffice (68).

The technique of pain relief is not as important as the level of analgesia. Patients experiencing significant pain tend to splint when they breathe, which results in poor oxygenation and ventilation. Hypoxia and hypercarbia result in increased pulmonary vascular pressure, which predisposes a patient to PPE (11,31). Patients should be monitored closely for the side effects of analgesia, which may depress respiration, and supplemental oxygen should be administered if these effects are observed.

Intensive Care Unit Monitoring

Because PPE is most likely to manifest in the first 12 to 48 hours, patients should be monitored in an intensive care unit (ICU) setting during this period (10,20). In the event of rapid decompensation due to the onset of PPE, methods of intervention (i.e., intubation, invasive hemodynamic monitoring, etc.) are readily available in the ICU. Furthermore, early detection of PPE is likely to be improved in an acute care setting.

Management of Fulminant Postpneumonectomy Pulmonary Edema/Acute Respiratory Distress Syndrome

The management of PPE parallels that of ARDS (i.e., diuresis, nutritional support, lower cardiac filling pressures, and optimal PEEP) and is beyond the scope of this chapter [the reader is referred to papers by Deslauriers et al. (16), Alvarez et al. (61), and van der Werf (41) for additional guidance]. However, two points regarding fluid management must be addressed.

The pulmonary artery catheter (PAC) and other methods of invasive hemodynamic monitoring are useful in guiding fluid therapy during PPE. One study cautions, however, that the accuracy of pulmonary capillary wedge pressure (PCWP) may not be reliable in postpneumonectomy patients. Wittnich et al. (69) found that inflation of the PAC balloon (in the central vasculature of the remaining lung) may occlude flow in the pulmonary artery, resulting in a falsely low wedge pressure reading. Peripheral wedging resulted in higher PCWP readings than did central wedging (69). Thus, the accuracy of PCWP values may depend on where the PAC balloon is positioned.

Fluid restriction is recommended in cases of established PPE. In the past, the objective of treating ARDS was to optimize DO_2 by increasing cardiac output through volume loading. However, this treatment is damaging to the microvascular circulation and leads to an increase in extravascular lung water. In contrast, fluid restriction with a negative water balance is associated with increased survival rates (70), earlier extubation (71), and earlier discharge from the ICU (71). Furthermore, a reduction in extravascular lung water improves pulmonary compliance, allowing for less traumatic mechanical ventilation parameters (41).

FLUID MANAGEMENT IN ESOPHAGECTOMY AND LUNG TRANSPLANT

Esophagectomy and lung transplantation share characteristics of pneumonectomy that predispose patients undergoing these procedures to pulmonary edema. Fluid management strategies discussed above may also apply to these two surgeries. Below, we will briefly consider factors that contribute to pulmonary edema following esophagectomy and lung transplantation.

Esophagectomy

ARDS develops in 10% to 20% of esophagectomy patients (72,73). As in PPE, the cause of this pulmonary edema is not clearly defined but is most likely multifactorial. Two likely causative factors are aggressive fluid therapy and increased capillary permeability as a result of endothelial injury.

Aggressive Fluid Therapy

Kita et al. (74) observed an association between aggressive fluid management and postoperative respiratory distress. When fluid administration was decreased, the authors noted fewer postoperative complications (defined as the need for tracheostomy or bronchoscopic suctioning, or extubation failure on postoperative day 1) and a shorter recovery period (74).

Increased Capillary Permeability

One-lung ventilation may be harmful to both the ventilated and nonventilated lung. As discussed above, lung isolation subjects the nonventilated lung to re-expansion/collapse episodes that may cause ischemia/reperfusion injury (75). Lung isolation also exposes the ventilated lung to high concentrations of oxygen (and thus, to free radicals associated with lung damage) and the possibility of injury due to volutrauma or barotrauma (69).

Rocker et al. (76) observed subclinical lung injury and increased lung permeability following esophagectomy in nine patients. Furthermore, the increase in permeability was associated with the release of neutrophil elastase (76), a cytokine that has been shown to degrade type IV collagen, a critical structural component of the capillary wall (77). Esophagectomy has also been associated with elevated levels of endotoxins (78), substances that may contribute to lung damage and increased permeability (79).

Because injury to the vagus nerve normally occurs during esophagectomy, it is noteworthy that Kanamaru observed an increase in extravascular lung water following vagotomy in animals (80). Furthermore, vagotomized animals frequently developed extravascular lung water following a volume load of saline, whereas control animals did not. Measurements of hemodynamics and oncotic pressure were similar in both groups of animals, suggesting that an increase in permeability of the pulmonary capillary was responsible for the edema. Therefore, damage to the vagus nerve during esophagectomy may increase the risk of high-permeability pulmonary edema.

Lung Transplant

Several features of lung transplantation contribute to the increased risk of pulmonary edema. As in pneumonectomy, the remaining lung is forced to accommodate the entire cardiac output. Thus, the lung is subject to increased pulmonary artery pressures and other forces favoring fluid flux into the extravascular lung space (81,82). These conditions are not alleviated immediately upon transplantation of the new lung; transplanted lungs (and, in particular, the pulmonary capillaries) are damaged by warm and cold ischemic times (up to six hours) during extraction and transportation from donor to recipient (81). Furthermore, the transplanted lung suffers disruption of its lymphatic drainage and may sustain reperfusion injury once revascularized (83).

To aggravate the situation, lung transplant patients are usually in positive fluid balance for the first 24 hours following surgery. It is no wonder that pulmonary edema is commonly observed in both the native and transplanted lungs. To combat this occurrence, negative fluid balance should be attained as soon as possible. Invasive hemodynamic monitoring (especially pulmonary artery catheterization) is necessary to balance the use of inotropic and/or vasoactive medications and to guide fluid administration/diuresis. To achieve negative fluid balance,

diuretics are commonly instituted in the immediate postoperative period (hemodynamics permitting) and continued over a week with the goal of helping the patient attain the preoperative weight (81). Because transplant patients are exposed to nephrotoxic agents such as cyclosporine, renal function must be monitored carefully using blood urea nitrogen and serum creatinine levels (81,83,84). Impaired renal function may require intervention by slow continuous ultrafiltration, a procedure that allows the regulation of fluid balance with minimal effects on systemic perfusion pressure (85).

CONCLUSIONS

As in pneumonectomy, the injury sustained by the lung during esophagectomy and lung transplantation warrants the cautious administration of fluids. The use of vasoactive substances may prove more beneficial than volume loading in achieving adequate systemic perfusion, and invasive hemodynamic monitoring may be useful in guiding therapy.

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30 | Fluid Management in Obstetrics

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INTRODUCTION

Pregnancy represents a unique state in body fluid dynamics where dramatic alterations begin shortly after conception and almost totally resolve following delivery. Of interest, these anatomic, hormonal, and functional adaptations, which often represent signs of dysfunction in the nonpregnant individual, are considered normal during pregnancy. While these changes are well tolerated by most pregnant patients, health-care providers should be aware of their impact, because even subtle aberrations can have lasting impact on both maternal and fetal health. This chapter will review these changes in fluid dynamics occurring during pregnancy, assess the impact of various pregnancy-induced comorbidities on fluid dynamics, examine the impact of anesthetic interventions, and allow a fuller understanding of how and why fluid dynamics should be managed during pregnancy.

MATERNAL PHYSIOLOGIC CHANGES OF PREGNANCY

Pregnancy results in a number of physiologic changes that have a significant effect on the fluid management. As early as six to eight weeks of gestation, a progressive increase in plasma volume is observed, reaching a maximal volume of 4700 to 5200 at 32 weeks (1). This increase, which represents a 45% greater volume than nonpregnant states, is increased with multiple gestations and appears to be correlated with fetal weight (2). The mechanism by which this expansion of plasma volume occurs has been attributed to the renin-angiotensin-aldosterone system; however, this explanation remains incomplete as well as perplexing. Increased activity of this system is present despite increases in blood and extracellular fluid volume (3). Other variables, including estrogen, progesterone, aldosterone, atrial natriuretic peptide (ANP), vasopressin, and nitric oxide levels as well as a resetting of osmo- and chemoreceptors, play roles in the alterations in plasma volume as well (3). Pregnancy resets the normal osmoreceptor threshold for thirst to lower levels, accommodating for the increased insensible losses that occur and maintaining the increase in plasma volume (4). It is noteworthy that the presence of a fetus per se does not appear to be necessary for these changes to occur, because similar increases in plasma volume have been observed in the case of hydatidiform moles (5).

Placental chorionic somatomammotropin, progesterone, erythropoietin, and prolactin increase red blood cell mass by 250 to 450 mL at term, an increase of 20% to 30% over prepregnancy values (6). The disproportionate increase in plasma volume to red blood cell mass allows for relative hemodilution to occur, with maximal hematocrit decreases observed in the middle of the third trimester. These changes, which decrease blood viscosity, are believed to improve intervillous perfusion (7), reduce the risk of thromboembolic events, and decrease the red cell mass lost during delivery.

The changes in hematocrit and blood volume are partially reflected in maternal cardiac output, a product of heart rate and stroke volume. Maternal heart rate increases from the fifth week of gestation to a maximal increment of 15 to 20 beats/min by 32 weeks (8). This increase in heart rate is in response to the relative anemia, decreased vagal control, and increased sympathetic outflow to the heart noted during pregnancy (9). Stroke volume, which is primarily responsible for the early increase in cardiac output (10), is reflected by increases in ventricular muscle mass in the first trimester and end-diastolic volume in the second and early third trimesters (11). Despite an increase in maternal blood volume, elevated filling pressures are not observed, as compensatory hypertrophy and dilation of the myocardium is witnessed. Echocardiographic and histologic studies demonstrate increases in cardiac compliance during

Table 1 Cardiac Values at Baseline and Changes During Pregnancy

	Baseline	First trimester	Second trimester	Third trimester
Blood volume (mL/kg)	65	71	85	90
Plasma volume (mL/kg)	40	45	57	60
Red blood cell volume (mL/kg)	25	26	28	30
Cardiac output (L/min)	4.3	5.7	6.0	6.2
Stroke volume (mL)	63.4	74	85	83.3
Heart rate (beats/min)	70	75	80	80
CVP (mmHg)	6	6	6	6
SVR (dyne/cm/sec ⁻⁵)	1530	1200	990	1210
COP (mmHg)	20.8	19.2	18.1	17.7

Abbreviations: CVP, central venous pressure; SVR, systemic vascular resistance; COP, colloid oncotic pressure.

Source: From Refs. 1–4, 6, 8–11, 13, 14, 17, and 19.

pregnancy, with the left atrial diameter increasing in parallel to the increase in blood volume (12). Overall, cardiac output increases by 30% to 50% during pregnancy (13), with half of this increase occurring in the first eight weeks of gestation (14) and the greatest increases being observed in the immediate postpartum period (Table 1). Maternal position, which influences caval compression by the gravid uterus, can greatly affect cardiac output by diminishing lower extremity venous return. Beginning as early as the first trimester and notable at term, movement from the left lateral recumbent to the supine position can decrease cardiac output by as much as 25% to 30% (15). In extremis, this phenomenon, termed “supine hypotensive syndrome,” occurs in approximately 10% of particularly late gestation parturients, and is manifested by a sudden decrease in blood pressure, bradycardia, and syncope (16). Confirmed in animal studies, this response has been speculated to be a result of hormonal and mechanical changes, as well as alterations in the paravertebral collateral blood supply.

Systemic vascular resistance (SVR), a value calculated from mean arterial pressure, central venous pressure (CVP), and cardiac output, is noted to undergo progressive decreases from as early as five weeks of pregnancy. The vasodilatory effects of progesterone, prostaglandins, nitric oxide, and ANP are among the important contributors to this decrease. The addition of the low-resistance uteroplacental vascular bed may further contribute to this decrease. Reaching a nadir at 14 to 24 weeks gestation, SVR then progressively increases until term (17). Arterial blood pressure, the product of cardiac output and SVR, decreases from the seventh week (14) to a nadir at 24 to 32 weeks. In the standing or sitting position, systolic pressures remain relatively constant throughout pregnancy; however, diastolic pressures decrease to as low as 10 mmHg by the 28th week (18). By contrast, in the left lateral recumbent position, both the systolic and diastolic pressures decrease by 5 to 10 mmHg and 10 to 15 mmHg, respectively. This difference indicates the importance of consistency in position in recording successive blood pressure measurements.

Finally, although a gradual decrease in the colloid oncotic pressure (COP) occurs until 36 weeks gestation (19), a further reduction may occur following delivery (20). The resulting decrease in the COP to pulmonary capillary wedge (capillary hydrostatic pressure) gradient may place the parturient at a higher risk of pulmonary edema. Should pulmonary edema occur, visualization of cardiac function with echocardiography has been suggested to improve outcome (21).

The late changes in maternal hemodynamics have been summarized through the placement of Swan–Ganz catheters and arterial lines in 10 healthy primiparous women at 35 to 38 weeks gestation and again at 11 to 13 weeks postpartum (22). In late pregnancy, significant increases in heart rate, stroke volume, and cardiac output were noted; by contrast, significant decreases in systemic and pulmonary vascular resistance and serum colloid osmotic pressure were witnessed. No significant alterations were noted in pulmonary capillary wedge pressure, CVP, or mean arterial pressure. The curious maintenance, rather than increase, in capillary wedge pressure despite increases in blood volume and stroke volume has been attributed to ventricular dilatation and decreased pulmonary vascular resistance.

MATERNAL PHYSIOLOGIC CHANGES DURING THE PERIPARTUM PERIOD

Significant alterations in cardiac variables occur during labor. Uterine contractions result in a 12% to 31% rise in cardiac output, owing primarily to the increase in stroke volume with the

300 to 500 mL autotransfusion of uterine blood (23,24). With active expulsive efforts, an even greater increase in cardiac output (49%) is observed. Vaginal delivery is associated with a blood loss of approximately 500 mL, whereas a cesarean delivery is accompanied by a loss of 1 L in singleton gestations (25). The normal blood loss observed during a vaginal or cesarean delivery is partially offset by a reduction in the intervillous space volume of approximately 500 mL (24).

The greatest increase in cardiac output (80%) usually occurs in the immediate postpartum period due to the release of venocaval obstruction by the gravid uterus, the elimination of the low resistance placental vascular bed, and the rapid mobilization of extravascular fluid. M-mode echocardiographic studies reflect these changes through an increase in left atrial dimensions in the first one to three days postpartum, which in turn stimulates diuresis and natriuresis (26). Stroke volume, cardiac output, and SVR, as measured by echo, resolve over 12 to 24 weeks postpartum (27); however, left ventricular dimensions continue to decrease even beyond six months (28). Over the postpartum period, circulating blood volume declines from 94 mL/kg at term gestation to 76 mL/kg, allowing hemoconcentration to occur (1).

FLUID MANAGEMENT DURING LABOR AND VAGINAL DELIVERY

During labor and delivery, insensible (which includes fluid losses from the respiratory tract, sweat, feces, and urine) and blood volume losses occur with corresponding changes in interstitial and intra- and extravascular spaces. While normal losses are partially compensated by the increases in total body water observed, women during pregnancy and, especially labor (29), have been described as being in a state of accelerated starvation. This state, produced by the depletion of glycogen stores and the meeting of glucose demand with fat metabolism, leads to ketonemia, hypoglycemia, and acidosis (30). These alterations have been regarded, although not well investigated, as a cause of maternal distress, an etiology of inefficient uterine contractions, and an indication for the use of intravenous (IV) fluids during labor (31).

The value of IV hydration prior to and during labor has recently been challenged. As a means of preventing the contractions of preterm labor, two recent literature reviews have found IV fluid administration to be no more effective than bedrest in preventing uterine irritability and delivery (32,33). During labor, when uterine contractions are favorable and frequently augmented, the use of IV fluids to prevent dehydration and metabolic changes has also been questioned. One leading obstetric text has concluded "Although it has become customary in many hospitals to establish an IV infusion system routinely early in labor, there is seldom any real need for such in the normally pregnant woman at least until analgesia is administered. With longer labors, the administration of glucose, sodium, and water to the otherwise fasting woman at the rate of 60 to 120 mL/hr is efficacious to prevent dehydration and acidosis (34)." Although IV fluid administration is accepted as a supportive measure for hyperemesis gravidarum (35), it is doubtful that the normal labor and delivery process even when coupled with nil per oral (NPO) status produces such a degree of acidosis and dehydration. The impact of unreplaced fluid losses and NPO status during the normal labor and delivery process has been poorly investigated.

This being said, oral and IV fluids during labor may be beneficial. When compared with oral water consumption in laboring women who could receive epidural but not parenteral opioids, "sport" (isotonic, mixed carbohydrate) drinks have been observed to prevent ketosis, as measured by low plasma nonesterified fatty acids and beta-hydroxybutyrate levels and maintained glucose levels (36). In addition, these particular oral fluids were demonstrated by ultrasound to be rapidly emptied from the stomach. In terms of IV fluid administration, a difference between bolus and maintenance fluid appears to exist. While uterine activity has been noted to diminish for a limited period after an IV bolus of 1 L (but not 0.5 L or less) of normal saline (37) or lactated Ringer's (LR) (38), a study of 195 nulliparous women randomized to receive 125 mL/hr versus 250 mL/hr of IV fluids, found that the frequency of labor lasting more than 12 hours was statistically higher in the 125 mL group (26% vs. 13%; $P = 0.047$) (39). In addition, a trend toward a lower use of oxytocin for inadequate labor progress in the higher fluid rate group (65% in the 125 mL group vs. 49% in the 250 mL group; $P = 0.06$) was observed. Cesarean deliveries were more frequent in the 125 mL group ($n = 16$ vs. $n = 10$) but did not reach statistical significance. The authors concluded that inadequate hydration in labor may be a factor contributing to dysfunctional labor and possibly cesarean delivery.

Accepting that hydration during labor may be of some benefit, attention to the type of fluid administered may have relevance as well. Infusions of 5% and 10% volumes of dextrose in water have been associated with maternal hyponatremia (40), lactic acidosis (41), neonatal rebound hypoglycemia (42), and hyponatremia (43). These alterations are attributed to the rise in maternal blood glucose levels and its metabolic byproduct lactate. These findings have encouraged many practitioners to adopt IV infusions containing only electrolytes (44), or to limit the amount of glucose infusions to less than 30 g/hr (45).

Many institutions and academies including the American Society of Anesthesiologists (ASA) have adopted a more permissive attitude in terms of oral fluid intake and the need for IV fluid administration during labor. The ASA Task Force on Obstetric Anesthesia, citing the limited data available regarding the relationship between fasting times for clear liquids and the risk of emesis, reflux, or pulmonary aspiration during labor, has recommended that a modest amount of clear liquids be allowed for uncomplicated laboring patients (46). Noting that the volume is less important than the type of liquid, clear liquids have been delineated to include water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee. The task force continues by stating: "patients with additional risk factors of aspiration (e.g., morbid obesity, diabetes, difficult airway), or patients at increased risk for operative delivery (e.g., nonreassuring fetal heart rate pattern) may have further restrictions of oral intake, determined on a case-by-case basis." Oral intake does not extend to solid foods, which should still be avoided in laboring patients, and appropriate fasting periods for parturients undergoing elective obstetric surgery should be observed.

Parturients with certain maternal or fetal comorbidities, including certain endocrine disorders, gastrointestinal disturbances, bleeding per cervical os, preeclampsia, and diabetes (the last two considered later in this chapter), should have IV access and fluid administration. IV fluids or even blood products are sometimes necessary in the immediate postpartum period if large blood losses occurred during delivery, or when uterine atony or bleeding persists (47).

FLUID MANAGEMENT FOR OBSTETRIC ANALGESIA AND ANESTHESIA

When severe and sustained, maternal hypotension can lead to an impairment of uterine and intervillous blood flow, and result in fetal hypoxia, acidosis, and neonatal depression (48–50). As such, optimizing maternal, uteroplacental, and fetal perfusion during pregnancy and delivery remains the primary goal of fluid management before and following the administration of central neuraxial blockade. Because the maintenance of maternal blood pressure and circulation is usually accompanied by preservation of fetal perfusion, limiting the influence of central neuraxial blockade on maternal hemodynamics is important.

Because reductions in blood pressure can be related to the level and speed of blockade onset, alterations to the anesthetic techniques and the types and doses of medications used have been evaluated. The consistent use of uterine displacement (51) and vasopressor administration as a prophylactic or early treatment measure has met with some success in minimizing the degree of hypotension produced (52). Alterations in fluid management offer another potential route of limiting the effects of central neuraxial blockade and will be described for both labor analgesia and anesthesia.

The literature on prophylaxis and treatment of maternal hypotension should be interpreted with caution. In addition to validity and statistical concerns regarding the study design (53), differences in analgesic and anesthetic interventions, methods of and thresholds for treatment (including the definition of hypotension), and measured outcomes prevent direct comparison. More importantly, alterations in systemic blood pressure may not be the most ideal index to evaluate the value of fluid administration; other indices such as cardiac output, peripheral (including myocardial) oxygenation, and fetal blood parameters may ultimately be more relevant. Systematic reviews and meta-analyses must also be carefully interpreted and translated into clinical practice, because the applicability of overall benefit may not convey the same benefit to an individual patient or group (54). For instance, most if not all of the investigations occurred with healthy parturients and fetuses; thus, the results may not be applicable in the setting of maternal or fetal compromise. The fluid management for parturients during labor analgesia, cesarean section, and the postpartum period, and in special pregnancy states, can now be evaluated.

FLUID MANAGEMENT FOR LABOR ANALGESIA

The epidural and combined spinal epidural (CSE) techniques used for labor and delivery analgesia usually employ an opioid with a low-dose local anesthetic to initiate and maintain a dermatomal sensory level of approximately T10. As such, the incidence of hypotension with either technique is low, with the CSE technique being no more likely to lead to hypotension (55). The incidence of a greater than 20% decrease in systolic blood pressure in parturients (32%) was comparable in those receiving 10 µg sufentanil intrathecally or 12 mL 0.25% bupivacaine via the epidural route (55). Of interest, the use of intrathecal opioids has suggested that decreases in blood pressure are more frequently the result of analgesia rather than the sympathetic nervous system attenuation (56,57). Greater degrees of sympathetic blockade, however, would be expected to contribute to more hypotension, and thus the addition of local anesthetics or clonidine would be expected to produce lower blood pressures (58,59). The incidence of hypotension following the use of similar anesthetics has been noted to be less in parturients in labor than those presenting for elective cesarean section (60). In part, this difference has been attributed to laboring parturients receiving continuous IV hydration during labor versus elective cesarean delivery patients being NPO.

Despite a low incidence, the risk of adverse sequelae from maternal hypotension prompted the use of IV fluids for prevention and treatment. Unfortunately, few investigations have evaluated the impact of the use of labor analgesic doses on the incidence of hypotension, and even fewer have used fluid manipulation as a method of prevention. To date, only a single study has supported the use of fluid prior to epidural labor analgesia as a method to reduce hypotension (61). The incidence of hypotension decreased from 28% to 2% with and without a crystalloid (1 L of Hartmann's solution) preload, respectively; however, the amount of local anesthetic used to establish analgesia (10 mL of 0.375% bupivacaine) is greater than that in common use (approximately 12 mL of 0.125% bupivacaine or less). With identical amounts and types of preload solutions, but lower amounts of local anesthetic (15 mL of 0.1% or 0.2% bupivacaine), no differences in the incidence of hypotension or fetal heart rate abnormalities were observed (62). These studies appear to indicate that lowering the total labor analgesia dose of local anesthetic can reduce the incidence of hypotension and limit the contribution and need for fluid preloading.

Another possible conclusion is that fluid administration prior to epidural analgesia has no effect. In comparing 0.5 L and 1 L LR with no fluid bolus prior to epidural analgesia, no difference in the incidence of hypotension was observed (the actual incidence of hypotension was not noted) (37). In a similar study comparing 0.5 L or 1 L LR prior to epidural analgesia (10 mL of 2% lidocaine with epinephrine 1:200,000) in healthy laboring parturients (38), no difference in the incidence (4%) or severity of hypotension between the two groups was identified. In addition, the 1 L fluid preload produced a delay in the initiation of the epidural technique and a slowing of uterine contractions.

The limited hemodynamic sequelae of epidural and CSE labor analgesia techniques suggest that IV fluid preloading prior to these techniques is not necessary in healthy laboring parturients.

FLUID MANAGEMENT FOR CESAREAN SECTION

Historically, hypotension resulting from central neuraxial anesthesia in parturients was believed to be minimized or prevented by adequate prehydration and left uterine displacement. This concept was originally explored in gravid ewes, where hypotension and impaired uterine blood flow following spinal anesthesia was corrected by rapid IV infusions of 5% dextrose or 6% dextran (63). By contrast, vasopressors, including phenylephrine, levarterenol, and angiotensin, restored only maternal blood pressure without correction of uterine perfusion. Shortly thereafter, significant maternal blood pressure decreases were noted to occur by aortocaval compression alone, even in the absence of anesthesia (64). These two observations led to the successful demonstration and clinical use of prehydration with 1 L of crystalloid (5% dextrose in LR) together with left uterine displacement to prevent hypotension in parturients receiving spinal anesthesia for a cesarean section (65,66). Subsequent work has questioned the success and role of fluid preloading in preventing adverse hemodynamic sequelae of neuraxial blockade in parturients (67–71).

Investigations into the use of fluid prehydration in parturients have focused most recently on spinal anesthesia for cesarean delivery, when both the potential for uterine aorto-caval compression and the rapid onset of hemodynamic effects are observed. Such trials are difficult to compare due to differences in study design and quality; heterogeneity exists in the types and volumes of fluids in both the experimental and control groups, the coexisting use of vasopressors, the occasional noted absence of uterine displacement, and the presence of labor. These difficulties noted, a few general observations can be made through individual trials or by evaluating a number of these studies as a group. The incidence of hypotension, as defined as a 10% to 30% decrease from the baseline systolic blood pressure or a systolic blood pressure ≤ 100 mmHg following spinal anesthesia in parturients undergoing cesarean delivery without fluid administration, is high, ranging between 30% and 100% (Table 2) (65,70,72). A lower incidence of hypotension (5–63%) has been observed following the use of epidural anesthesia for cesarean delivery, most likely owing to the slower onset of blockade, study objectives less focused on hypotension per se, and the earlier provision of treatment (Table 3) (67,73–76).

Crystalloid preloading has been noted to reduce the incidence of hypotension in this population; however, a high incidence of hypotension (50–70%) is still observed (69), with most patients requiring treatment with vasopressors to maintain blood pressure (72). For example, when 20 mL/kg of crystalloid (Plasma-Lyte L) administered over 15 to 20 minutes was compared to no preload, the incidence of hypotension in parturients scheduled for cesarean delivery was reduced (55% vs. 71%, respectively). The severity of the hypotension, requirement for ephedrine, and neonatal umbilical blood gases, however, were no different (69). Even with limited bolus or infusion doses of ephedrine given with crystalloid preloading, the incidence of hypotension remains between 30% and 70% (77–79). Overall, as noted in a recent analysis (80), six of nine studies indicated a trend or a reduction in the incidence of hypotension with crystalloid preloading prior to spinal anesthesia for cesarean delivery. The crystalloid type, volume, rate of administration, and timing of administration are relevant determinants that should be discussed.

Few studies directly compare crystalloid fluids on the incidence of hypotension; however, one issue of controversy is the use of glucose-containing fluids. Although a small case series of three parturients suggested that regional anesthesia-induced hypotension could be severe, refractory to common treatment measures, and responsive only to an IV bolus of dextrose (81), subsequent investigations have failed to demonstrate a benefit in giving preoperative dextrose prior to cesarean section. Parturients randomized to receive normal saline with and without dextrose 5% at 125 mL/hr for two hours prior to delivery had the same incidence of hypotension (82). The overall incidence of hypotension was 67% despite an IV preload with 15 mL/kg of fluid in both groups. Although maternal hypoglycemia was observed in 17% of the parturients, most likely reflecting a dilutional effect, dextrose infusions

Table 2 Spinal Anesthesia and Crystalloid Preload

Study	Definition hypotension	Intervention	Incidence hypotension	Technique
Marx et al. (65)	Any change in blood pressure	D5LR 1000 mL vs. no preload	0% vs. 100% ($p < 0.05$)	Spinal
Rout et al. (68)	SBP < 100 mmHg and $< 80\%$ baseline	Plasmalyte-L 20 mL/kg over 20 min vs. 10 min	60% vs. 70% (NS)	Spinal-1.5 mL 0.5% plain bupivacaine
Rout et al. (69)	SBP < 100 mmHg and $< 80\%$ baseline	Plasmalyte-L 20 mL/kg vs. no preload	55% vs. 71% ($p < 0.08$)	Spinal-1.5 mL 0.5% plain bupivacaine
Jackson et al. (70)	SBP < 90 mmHg or $< 30\%$ baseline	Hartmann's solution 1000 vs. 200 mL	33% vs. 30% (NS)	Spinal-2–2.5 mL 0.5% heavy bupivacaine
Park et al. (71)	MAP $< 80\%$ baseline and SBP < 100 mmHg	Lactated Ringer's 10, 20 or 30 mL/kg	66.7% vs. 55.6% vs. 47.4% (NS)	Spinal-1.5 mL 0.75% bupivacaine with 10 mcg fentanyl
Ngan Kee et al. (108,109)	1. SBP $< 80\%$ baseline 2. Prophylactic use of metaraminol once SBP $< 90\%$	Lactated Ringer's 20 mL/kg vs. no preload	1. 43% vs. 65% ($p = 0.08$) 2. No difference in cumulative metaraminol use	Spinal-2 mL 0.5% bupivacaine with 15 mcg fentanyl

Abbreviations: LR, lactated Ringer's; SBP, systolic blood pressure; MAP, mean arterial pressure; NS, non-significant.

Table 3 Epidural Anesthesia and Colloid Preload

Study	Definition hypotension	Intervention	Incidence hypotension	Technique
Hallworth et al. (86)	SBP <80% baseline	Polygelatin 0.5 L + Hartmann's solution 0.5 L vs. Hartmann's solution 1 L	5% vs. 45% ($p=0.008$)	Epidural-22 mL 0.5% bupivacaine with 1:400,000 epinephrine
Ramanathan et al. (87)	SBP <100 mmHg	25% albumin 200 mL + LR 1 L vs. 5% albumin 500 mL +700 mL LR vs. RL 1200 mL	25% vs. 25% vs. 30% (NS)	Epidural-1.5% lidocaine with 1:200,000 epinephrine
Murray et al. (67)	SBP <80% baseline	HES 1 L vs. LR 1 L	63.3% vs. 40% (NS)	Epidural-23 mL 0.5% bupivacaine with 1:200,000 epinephrine
Wennberg et al. (76)	SBP <100 mmHg	3% Dextran 70 7.5 mL/kg vs. LR 15 mL/kg	5% vs. 25% ($p<0.05$)	Epidural-18–30 mL 0.5% bupivacaine

Abbreviations: SBP, systolic blood pressure; LR, lactated Ringer's; HES, hydroxyethyl starch.

immediately prior to delivery should remain less than 6 g/hr to prevent fetal hyperglycemia and hyperinsulinemia, followed by neonatal hypoglycemia and jaundice (42). Of interest, the use of 2 L LR (Hartmann's solution) did not result in any cases of maternal hypoglycemia (83). The reason suggested for this observation is that sodium lactate is oxidized to bicarbonate or becomes a gluconeogenic precursor, and counteracts the dilutional effects of the fluid preload.

The volume and rate of crystalloid administration do not appear to make a significant difference on the incidence or severity of hypotension. When parturients were randomized to receive 10, 20, and 30 mL/kg LR 15 to 20 minutes prior to spinal anesthesia for elective cesarean delivery, no difference in the incidence or severity of hypotension or total ephedrine use was observed (71). A dose of 20 mL/kg of crystalloid (Plasma-Lyte L, Baxter, Deerfield, Illinois, U.S.A.) given over 10 versus 20 minutes prior to a spinal anesthetic for elective cesarean section resulted in no alterations in the incidence of hypotension, the use of ephedrine, and the results of umbilical venous and arterial blood gas measurements (68). Despite significant increases in CVP during preloading, no significant changes in arterial pressures were observed during this period; CVP values decreased below the preload baseline for the first 10 minutes after the spinal injection.

The timing of fluid administration, however, does appear to be important when longer time periods are considered. In an elegant clinical study using indocyanine green and pulse spectrophotometry to noninvasively measure blood volume and cardiac output, the effect of crystalloid and colloid preload was examined in parturients prior to spinal anesthesia for cesarean delivery (84). When 1.5 L of LR, 0.5 L of hydroxyethyl starch (HES) 6%, and 1 L of HES 6% were used as preload volumes, an 8%, 10%, and 20% expansion, respectively, of the blood volumes were observed. However, at 30 minutes following the preload infusion, only 28% of LR remained intravascular in comparison to 100% for the colloid solutions; significant increases in cardiac output were produced in the colloid groups only. Following the spinal anesthetic, the resulting incidence of hypotension was 75% in the crystalloid group, 58% in the colloid group receiving 0.5 L, and 17% in the colloid group receiving 1 L. These results suggest that a volume preload effect is achieved when the amount and type of fluid utilized is enough to exert a change in cardiac output at the time of the administration of the spinal anesthetic. This appears most readily achievable with colloid solutions in amounts greater than 1 L.

The perception that crystalloid fluids have short intravascular half-lives encouraged investigation into the use of colloid solutions to prevent spinal anesthesia-induced hypotension (Table 4). Initial studies using combinations of crystalloid and colloid solutions achieved mixed results (Table 4). Prior to cesarean delivery, the addition of 5% albumin to 5% dextrose in LR (15 mL/kg over 15–20 minutes) resulted in the incidence of spinal anesthesia-induced hypotension being reduced from 33% to 0% (85). In addition, the use of 1 L of crystalloid (Hartmann's solution) versus 0.5 L of Hartmann's with 0.5 L of colloid (polygelatin, Haemacel) prior to epidural anesthesia for cesarean section was associated with a reduction in hypotension from 45% to 5% (86). By contrast, no alterations in the incidence of hypotension were

Table 4 Spinal Anesthesia and Colloid Preload

Study	Definition hypotension	Intervention	Incidence hypotension	Technique
Mathru et al. (85)	SBP <100 mmHg or MAP < 85 mmHg	5% albumin in D5LR vs. D5LR 15 mL/kg	0% vs. 33% ($p < 0.05$)	Spinal
Karinen et al. (89)	SBP <90 mmHg and <80% baseline	HES 6% 500 mL vs. LR 1000 mL	38% vs. 62% (NS)	Spinal-2.6 mL 0.5% hyperbaric bupivacaine
Riley et al. (90)	SBP <100 mmHg and <80% baseline	HES 6% 500 mL + LR 1 L vs. LR 2 L	45% vs. 85% ($p < 0.05$)	Spinal-1.6 mL 0.75% bupivacaine in 8.5% dextrose with fentanyl 10 mcg and morphine 0.2 mg
Vercauteren et al. (91)	SBP <100 mmHg or <75% baseline	Modified gelatin 1 L + LR 1 L vs. HES 6% 1 L + LR 1 L vs. HES 6% 1 L	60% vs. 27% ^a vs. 53% ^a ($p < 0.05$) compared to the other two groups	Spinal-1.33 mL 0.5% bupivacaine with sufentanil 3.33 mcg
French et al. (94)	SBP \leq 90 mmHg or <70% baseline	Pentastarch 10% 15 mL/kg vs. Hartmann's solution 15 mL/kg	12.5% vs. 47.5% ($p < 0.0001$)	Spinal-2.5–3 mL heavy 0.5% bupivacaine
Ueyama et al. (84)	SBP <100 mmHg and <80% baseline	HES 6% 0.5 L vs. 1 L vs. LR 1.5 L	58% vs. 17% ^a vs. 75% ^a ($p < 0.05$) compared to the other two groups	Spinal-8 mg tetracaine with 0.1 mg morphine in 10% dextrose
Siddik et al. (93)	SBP <100 mmHg and <80% baseline	HES 10% 0.5 L vs. LR 1 L	40% vs. 80% ($p < 0.05$)	Spinal-1.73 mL bupivacaine 0.75% in dextrose 8.5%
Ngan Kee et al. (108,109)	1. SBP <80% baseline 2. Prophylactic use of metaraminol once SBP <90%	Gelatin solution 4% 15 mL/kg vs. no preload	31% vs. 64% ($p = 0.01$) 2. Greater metaraminol use at 5 and 10 min in the no preload group ($p = 0.01$ and $p = 0.02$ respectively)	Spinal-2 mL 0.5% bupivacaine with fentanyl 15 mcg

^aBoth of the later groups, rather than a single group, was statistically significant when compared to the first group.

Abbreviations: SBP, systolic blood pressure; MAP, mean arterial pressure; LR, lactated Ringer's; HES, hydroxyethyl starch.

observed when 1.2 L LR, 0.7 L LR plus 0.5 L 5% albumin, and 1 L LR plus 0.2 L of 25% albumin were compared (87). Although plasma oncotic pressure decreased in the first two groups and increased in the group receiving 25% albumin, no differences in alveolar-arterial oxygen partial pressure gradients (AaDO₂) or pulmonary morbidity were observed. In a more direct comparison between colloid and crystalloid solutions, 3% dextran 70 (7.5 mL/kg) versus LR (15 mL/kg) given prior to epidural anesthesia for cesarean section was observed to have greater hemodynamic stability, CVP values, and cardiac output (76). In addition, greater decreases in the maternal COP and transthoracic fluid index, indicating an increase in lung water, were observed in the crystalloid group. Overall, no differences in neonatal outcomes or in umbilical cord COP were observed between the two groups. Due to the limited number of healthy parturients who ultimately suffer from fluid-induced pulmonary morbidity, these studies cannot provide an adequate assessment of the impact of fluid management on this outcome.

Other variables to distinguish colloid and crystalloid solutions have been better defined. In a pharmacodynamic and pharmacokinetic study performed in instrumented gravid ewes, 0.5 L HES 10% given over 30 minutes increased uterine blood flow, cardiac output, total oxygen delivery capacity, and uterine artery oxygen delivery without significant HES transplacental transfer (88). This contrasted with 0.75 L LR, which was associated with no significant changes in any of the above-mentioned variables. In the clinical setting, these variables appear to have a relationship with the volume of fluids, including colloids, as evidenced in the pulse spectrophotometry study mentioned previously (84). No statistical differences in the incidence of hypotension, changes in uteroplacental vascular resistance, Apgar scores, and umbilical blood gases were observed when 0.5 L 6% HES or 1 L LR were given over 10 minutes prior to spinal anesthesia for cesarean section (89). When the preload of 0.5 L of 6% HES was added to 1 L LR solution and compared to 2 L of LR, a 45% (vs. 85%) incidence of hypotension was observed (90). However, despite a greater duration of hypotension, more ephedrine boluses, and a higher maximum heart rate in the crystalloid group, similar neonatal outcomes were observed.

The incidence of hypotension following spinal anesthesia for cesarean section may be different among colloids (Table 4). A comparison of 1 L LR plus 1 L of modified gelatin (Geloplasma, Merieux, France), 1 L LR plus 1 L 6% HES, and 1 L of HES as preload fluids identified the 1 L LR plus 1 L 6% HES combination as being the most effective in preventing hypotension and requiring less ephedrine (91). With the volume given, the packed cell volume decreased by 20% in both crystalloid–colloid groups, versus 14% in the colloid-only group. This change in cell volume could potentially alter maternal and fetal oxygen-carrying capacity, and as such, coupled with the inability to reliably prevent hypotension, fluid preloading of this amount and type is not uniformly recommended.

Among colloid solutions, variations in size, molecular weight, half-life, COP, and side effects exist (92). A naturally occurring protein that accounts for 60% to 80% of normal plasma oncotic pressure, albumin is derived from pooled human plasma, is expensive, and carries the potential of transmitting bloodborne infections. Dextrans are linear polysaccharide molecules that can decrease blood viscosity and produce bleeding. Gelatins are polypeptides with the smallest molecular weight and intravascular half-life of the commonly used colloids. HESs are synthetic polymers that vary in size and number; with greater numbers of hydroxethyl groups, the molecular weight and half-life increase. A 10% solution of HES has greater oncotic effect (COP 66 mmHg) than a 6% solution, and a similar incidence of anaphylaxis (93). Maximal volume expansion occurs within 10 to 15 minutes and lasts approximately 60 minutes. Adverse hematological effects limit the maximum recommended dose to 20 mL/kg/day. Pentastarch, a colloid associated with lower antigenic potential, has a higher COP than HES 6% (40 mmHg compared to 30 mmHg); however, the effect is shorter lasting (12 and 36 hours, respectively) (94). Unlike HES at higher doses, pentastarch does not affect clotting activity.

The growing association with anaphylactic reactions has limited the use of colloid solutions (95) and has encouraged further investigation. Reports from the 1980s described the incidence of allergic reactions to dextran and HES as 0.03% (96,97). By 1994, an overall frequency of allergic reactions was reported in France to be 0.22%, with gelatins (0.34%) and dextrans (0.27%) being more likely to cause a reaction than albumin (0.1%) or HES (0.06%) (98). Prior drug allergies corresponded with a three times greater likelihood of developing anaphylaxis, and overall, the male gender was associated with a higher frequency of reactions (98). Intraoperatively, a 2.9% incidence of anaphylaxis due to colloids has been reported (99), and one report discussed the case of a fetal cardiopulmonary arrest resulting from a maternal anaphylactic reaction to dextrans (100).

Although colloids have a proven ability to prevent hypotension resulting from central neuraxial anesthesia in the obstetric population, ultimately the neonatal outcome may not be improved. A comparison between 15 mL/kg of 10% pentastarch in 0.9% saline versus Hartmann's solution prior to spinal anesthesia for elective cesarean section observed a lower incidence of hypotension with the pentastarch (12.5% vs. 47.5%) (94). Neonatal outcomes, however, were similar in both groups. A comparison with 0.5 L HES 10% solution versus 1 L LR for preloading prior to spinal anesthesia for cesarean section led to the observation that the incidence and severity of hypotension, the requirement for ephedrine, and the incidence of nausea and/or vomiting were lower in the HES 10% group (93). Neonatal outcome again, however, was comparable between the two groups.

Attempts have been made to identify parturients at risk of developing hypotension following regional anesthesia for the purpose of using prophylactic or early treatment measures. Although a high baseline SVR index ($SVRI > 500 \text{ dyne}\cdot\text{cm}\cdot\text{sec}^{-5}\cdot\text{m}^{-2}$) has been associated with postspinal hypotension in parturients (101), similar correlations have not been found in other investigations using the same thoracic electrical bioimpedance methodology in a similar setting (102,77). A significant correlation between a high baseline heart rate, hypotension, and ephedrine use following a spinal anesthetic for elective cesarean section has been observed (103). A high initial heart rate and/or a high SVRI may reflect a higher sympathetic tone or a lower intravascular fluid status, two states that may benefit from prophylactic or early treatment measures.

FLUID MANAGEMENT IN POSTPARTUM PATIENTS

The physiological changes that accompany pregnancy resolve over days to months. The aortocaval compression by the uterus, however, undergoes an almost immediate resolution,

thereby making the postpartum patient less prone to hypotension in the supine position and following regional techniques. The hormonal changes of pregnancy may also quickly return to their baseline following delivery, and this may decrease the sensitivity to the blockade produced by local anesthetics during pregnancy, further decreasing the incidence of epidural and spinal technique-induced hypotension (104). Postpartum, parturients experience a 500 and 1000 mL blood loss during vaginal and cesarean deliveries, respectively, and attention to and prompt correction of fluid and blood deficits should be a priority.

The incidence of spinal anesthesia-induced hypotension in parturients undergoing postpartum (15–24 hours postpartum) tubal ligation was compared following a preload with 0.5 L HES or 1 L of LR (105). The incidence of hypotension in the colloid and crystalloid groups was 16% and 52%, respectively, with a lower need for ephedrine boluses in the colloid group. Because the severity of hypotension was mild, transient, and readily reversed by ephedrine, the use of colloids may not outweigh the increased cost and potential for anaphylaxis. Overall, the use of fluids and pressors in the treatment of regional anesthesia-induced hypotension in the postpartum period may have different goals than the prepartum situation, when preservation of uterine blood flow and oxygen delivery are paramount.

VASOPRESSORS IN THE MANAGEMENT OF REGIONAL ANESTHESIA-INDUCED HYPOTENSION

The failure of IV fluid administration to reliably prevent hypotension following regional anesthesia has prompted the prophylactic and treatment use of vasopressors. Ephedrine, considered the vasopressor of choice for the treatment of hypotension in the obstetric population, has been utilized as an adjuvant, and replacement for fluid preloading with some success. The hemodynamic changes following epidural anesthesia for cesarean section were compared in parturients receiving a colloid only (15 mL/kg of 3% Dextran 70) versus half the dose (7.5 mL/kg) plus ephedrine 17.5 mg IV (76). Although 25% experienced systolic arterial blood pressure less than 100 mmHg in demographically similar groups, the colloid plus ephedrine group had a greater cardiac output, less hemodilution, and less nausea. These findings may be of special relevance to parturients at high risk of pulmonary edema, such as those on tocolytic agents for preterm labor or therapy for preeclampsia.

A prophylactic IV ephedrine bolus (0.25 mg/kg) appears superior to a crystalloid (Hartmann's solution 20 mL/kg) preload in preventing a greater than 30% reduction in systolic blood pressure following spinal anesthesia for cesarean section (106). Although this degree of hypotension still occurred in the ephedrine group to a lesser extent (35% vs. 65%), and the total amount of additional ephedrine was similar, the mean umbilical venous pH was higher in the ephedrine group. This being said, the umbilical venous pH was in the normal range for both groups. Higher doses of ephedrine have been used as prophylaxis prior to regional anesthesia in an attempt to decrease the incidence of hypotension. Following 20 mL/kg LR prior to a spinal anesthetic, one recent study compared a 10 mL saline control with 10, 20, or 30 mg of ephedrine given IV one minute after the spinal anesthesia injection (107). Although the lowest incidence of hypotension (35%) occurred in the group receiving 30 mg of ephedrine, as doses of ephedrine increased, more parturients experienced hypertension. No differences in the total ephedrine requirement, the incidence of nausea and emesis, or neonatal outcomes were observed.

One measure of preload effectiveness is the amount of vasopressor required to maintain the baseline blood pressure following a regional anesthetic. By this measure, a 20 mL/kg crystalloid preload appears no better than no preload as measured by total metaraminol requirements (108). Metaraminol requirements were higher in the first five minutes after the administration of the spinal anesthetic in the no-preload group and although 43% versus 65% in the preload and control groups, respectively, experienced a greater than 20% decrease in systolic arterial blood pressure, the difference was not statistically significant. No differences in maternal or neonatal outcomes were observed between the two groups, as well. In another study using a colloid preload of 15 mL/kg 4% gelatin solution (Gelofusine), a reduction in the incidence of spinal anesthesia-induced hypotension was observed when compared to a no-preload control group (31% vs. 64%) (109). Although the metaraminol requirements were greater at 5 and 10 minutes after the spinal anesthetic in the no-preload group, the total vasopressor requirements were the same between the groups. The incidence of nausea and vomiting, which

usually correlates with hypotension, was lower in the colloid group. No differences in neonatal outcomes were observed. The results of these two trials were similar to previous trials evaluating the incidence of spinal induced hypotension in parturients receiving a fluid preload.

In summary, hypotension following central neuraxial anesthesia occurs in a significant number of parturients despite fluid preloading, although colloids are more effective in preventing this outcome. Vasopressors, when used as adjuvants or in lieu of fluid preloading, have been noted to be successful in reducing the incidence and severity of hypotension and improving maternal and neonatal outcomes.

FETAL RESPONSE TO FLUID PRELOAD

Maternal fluid management can have secondary effects on the fetus, although these effects may be limited. Investigations with pregnant ewes have demonstrated that acute increases in maternal vascular volume, as reflected by increased venous pressures of 5 to 10 mmHg, do not promote fluid transfer into the fetus per se, nor result in changes in fetal arterial or venous pressures, blood volume, or urine flow (110). However, with acute decreases in maternal osmolality by 3% to 10%, which is more likely with the administration of hypotonic solutions, fluid shifts into the fetus can occur, as reflected by decreases in fetal plasma osmolality and increases in fetal urine flow. This appears to demonstrate that maternal plasma oncotic pressure is a more important determinant than vascular hydrostatic pressure changes in determining fetal fluid shifts (111). As such, it is conceivable that large infusions of maternal crystalloids are more likely to pass to the fetal circulation than similar infusions of colloids, which are iso-osmotic solutions. However, such an effect has failed to be demonstrated when preloading with crystalloid (LR 15 mL/kg) or colloid (HES 7.5 mL/kg) solutions in 20 parturients undergoing elective cesarean section under epidural anesthesia (112). No changes in fetal myocardial function or ventricular size occurred after either crystalloid or colloid administration, and neonatal outcomes were comparable between the groups. Moreover, in comparing the fetal effects of crystalloid (1 L LR) or colloid (0.5 L HES) preloading in parturients undergoing elective cesarean section under spinal anesthesia, no difference in the uteroplacental vascular resistance as measured by the mean pulsatility index in the uterine arteries was observed (89).

Although not uniformly observed to be different than infants of parturients undergoing vaginal deliveries (113), infants born to mothers via cesarean section have been noted to have low colloid osmotic pressures (114). Among the factors believed to affect fetal COP are the amount of maternal fluid administration, mode of delivery, differences in the water distribution between the tissues and the lung, and the presence of labor-induced activation of the sympathoadrenal system. Overall, it appears as if preloading with either crystalloids or colloids have minimal to no effects on the fetus, unless there is marked decrease in maternal plasma oncotic pressure by the infusion of large amounts of hypotonic solutions. Early evidence supports the concept that the placenta and the fetus are capable of altering their own colloid osmotic pressure to a limited degree (95).

FLUID MANAGEMENT IN SPECIAL PREGNANCY STATES

Fluid Management in Preeclampsia

Preeclampsia is a pregnancy-specific disorder developing after the 20th week of gestation and defined by a blood pressure $\geq 140/90$ mmHg, and a 24-hour urinary protein ≥ 300 mg (115). Severe preeclampsia is characterized by the presence of any of the following additional signs or symptoms: urinary protein ≥ 2 g/24 hrs, epigastric or right upper quadrant pain, diastolic blood pressure ≥ 110 mmHg, headache or visual disturbances, oliguria, creatinine > 1.2 mg/dL, elevated liver function tests, pulmonary edema, thrombocytopenia, or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) (115). Characterized by a reduction in intravascular volume with low central venous and pulmonary wedge pressures, preeclampsia is also associated with an increase in capillary permeability. Oliguria, which may signify a further reduction in intravascular volume or renal insufficiency, is not uncommon with this disorder, but must be evaluated with caution. Although a diagnostic IV fluid challenge with a generous amount of crystalloid (1 liter) can be considered, an exaggerated increase in CVP (116) may result in pulmonary and cerebral edema due to the existing capillary

permeability, the concurrent beta antagonist use for blood pressure control, and the pregnancy induced reductions in plasma oncotic pressure (117).

Moderate amounts of fluid administration, (250-500 mL of crystalloid), however, may be beneficial. Although ANP, a protein released in response to intra-atrial pressure or distension with natriuretic, diuretic, and smooth muscle relaxant properties, already exists at higher levels in preeclamptic parturients, a greater amount is released with fluid administration than commonly observed in normal parturients (116). As such, it is possible that a reduction in peripheral vascular resistance and systemic blood pressure, an elimination of excessive extracellular fluid, and an improvement in vasospasm may occur with mild volume expansion. Further evaluation will be necessary to determine other factors responsible for the complex volume homeostasis and vasodilation issues observed in preeclamptic patients.

The optimal fluid to administer to patients with preeclampsia remains controversial. Currently no data exist to definitively address this issue; however, the 3 to 5 mmHg difference in COP with the use of colloids versus crystalloids during elective cesarean delivery may have significance (111). All sources of fluids, including those used for magnesium and oxytocin, the treatments of choice to prevent progression to eclampsia and to induce labor, respectively, should be taken into consideration. Urine output, with a goal of 0.5 mL/kg/hr, should also be monitored to assist with IV fluid management.

Gestational Diabetes

Pregnancy induces complex energy metabolism changes that are manifested by increased insulin resistance and secretion, low fasting blood glucose levels, and a predisposition to ketosis. Insulin plays a critical role in maternal and fetal health through the control of maternal glucose, fat, and protein metabolism. Diabetes mellitus is a common disorder during pregnancy, affecting 3% to 5% of parturients in the United States (118). Representing approximately 90% of the cases observed during pregnancy, gestational diabetes mellitus (GDM) occurs due to an enhanced resistance to insulin. Fetal developmental disorders, macrosomia, birth injuries or death, and significant neonatal hypoglycemia may result. Moreover, approximately half of all women who have GDM develop type 2 diabetes within the subsequent 20 years (118,119).

GDM is divided into two classes: Class A represents an abnormal carbohydrate tolerance during pregnancy. The fasting and two-hour postprandial glucose levels are less than 105 mg/dL and less than 120 mg/dL, respectively. This class is diet controlled and does not require insulin. Class B also represents an abnormal carbohydrate tolerance during pregnancy, but has fasting and two-hour postprandial glucose levels of above 105 mg/dL and above 120 mg/dL, respectively. Class B requires insulin for its treatment (120,121), with management of GDM directed toward achieving tight euglycemic control. Because glucose crosses the placenta to a significantly higher degree than insulin, fetal hyperglycemia and hyperinsulinemia occur, with the potential for neonatal hypoglycemia following delivery. Women with GDM Class A do not require insulin during labor and delivery, and their fluid management is very similar to that of other healthy parturients. By contrast, parturients with GDM Class B are treated similar to other forms of diabetes, with one suggested labor management schedule as follows: The morning dose of intermediate-acting insulin is given at one-third the daily dose required during the third trimester of pregnancy. An IV infusion of normal saline is initiated, and should glucose levels fall below 70 mg/dL, the infusion is changed to 5% dextrose and delivered at a rate of 2.5 mg/kg/min. Glucose levels are checked hourly using a portable meter, and adjustments can be made based on the readings. Should fasting blood glucose levels be greater than 120 mg/dL, an insulin infusion is started at 0.5 to 2.0 U/h and titrated based on glucose levels (122). One interesting observation is that the sodium lactate in LR can either be oxidized to bicarbonate or become a gluconeogenic precursor that may elevate blood glucose levels; as such, this solution is frequently avoided in such patients (123).

When a GDM Class B presents for an elective cesarean delivery, another algorithm has been suggested: The morning dose of insulin is usually withheld or given at one-third the pregnancy requirement. Because dextrose-containing solutions may lead to acute maternal hyperglycemia and fetal acidosis (124), these fluids are avoided as preload and infusion fluids unless the blood glucose level is less than 70 mg/dL. Should a low glucose level be recorded, solutions containing dextrose can be administered by a constant infusion pump at a rate of 7.5 g/hr.

Insulin requirements usually decrease significantly following delivery, and for the first 24 to 48 hours glucose levels are not controlled as tightly as during labor and delivery. Parturients who delivered vaginally, who resume their usual oral intake, are given a third or half of their end-of-pregnancy dose of Neutral Protamine Hagedorn (NPH) and short-acting insulin the morning of the first postpartum day. Frequent glucose determinations are then used to guide further insulin dosing. Most parturients with GDM do not receive insulin postpartum, because increases in glucose are no longer associated with fetal risk. Parturients with GDM usually return to normal glucose levels by two weeks postpartum, and a workup for adult onset diabetes is initiated should increased blood glucose levels persist beyond six weeks.

Obstetric Hemorrhage

Peripartum hemorrhage is the most common cause of maternal mortality in the world. Adequate surgical hemostasis and careful fluid and blood replacement are essential to achieve good hemodynamic control. As discussed earlier, increases in maternal blood volume and coagulation proteins compensate for the average blood loss from vaginal and cesarean deliveries and patients are often able to tolerate 1000 to 1500 mL of blood loss without major hemodynamic changes (125). With approximately 600 to 700 mL of blood flowing through the placental intervillous spaces each minute, obstetric hemorrhage can occur rapidly especially if difficulties in placental separation or resuming good uterine tone are experienced. In addition, with the mixing of fetal and maternal blood and other cellular products, disseminated intravascular coagulation may occur with little or no warning and intensify blood loss. The normal alterations of pregnancy may allow signs of significant hemorrhage to be masked until sudden hypotension and tachycardia occur. With the onset of these signs in the absence of symptoms or suggestions of embolic phenomena, aggressive volume replacement should be considered to maintain tissue perfusion and oxygenation (126). Rapid volume replacement is more important than the type of fluid given, although colloids and blood products should be given early consideration, along with a request for assistance, a second IV line (18 gauge or greater), and pressurized transfusion equipment. Although many institutions require that a type and screen be held for parturients at high risk for hemorrhage undergoing a vaginal delivery and all parturients undergoing cesarean delivery, a crossmatch for two to four units of packed red blood cells should be considered when the potential for significant blood loss appears imminent. Such cases include a known placenta previa or partial abruption, as well as placenta accreta, increta, or percreta. In situations where the need for emergent blood transfusion precedes the availability of typed blood, uncrossmatched, type O, Rh-negative blood should be utilized. Continued blood loss and hemodynamic instability despite transfusion of packed red blood cells is often an indication for an arterial line and consideration of more invasive monitoring; however, restoration of circulating volume takes precedence. Urine output, heart rate, and blood pressure assessments can assist in rapidly assessing volume resuscitation.

In situations of rapid blood loss and volume replacement, the need for blood component therapy other than red cell mass may be more limited than previously thought. Following the delivery of the fetus when uterine perfusion and oxygenation become less relevant, parturients are usually able to tolerate low hemoglobin, coagulation proteins, and platelets. The task force on blood component therapy by the ASA have recommended that transfusion of packed red blood cells, platelets, and fibrinogen component therapy be rarely indicated unless the hemoglobin is less than 6 g/dL, the platelet count is less than $50 \times 10^9/L$ (unless platelet dysfunction and microvascular bleeding is present), and the fibrinogen concentration is less than 80 to 100 mg/dL in the presence of microvascular bleeding (127).

Attention has recently been given to the use of autologous donation, intraoperative salvage, and acute normovolemic hemodilution in the parturient population at high risk of maternal hemorrhage (128). Additional investigation will be required to validate the safety and utility of these approaches.

CONCLUSION

The physiological, mechanical, and hormonal changes of pregnancy represent adaptations that have significant impact on fluid management. Although a better understanding of these alterations has resulted in improved investigations during pregnancy, the value of fluid preloading prior to central neuraxial blockade for analgesia and anesthesia remain controversial. A number

of studies support the use of crystalloid and colloid solutions as a preload fluid; however, differences in the definitions of hypotension, regional anesthetic techniques, and the amount, type, and timing of fluid administration make direct comparisons complicated.

The use of the left uterine displacement, vigilant monitoring, and aggressive, early treatment of the hemodynamic effects of epidural and spinal techniques with fluid and vasopressors remain the most effective means of ensuring favorable maternal and fetal outcomes. Special states observed with pregnancy, such as preeclampsia, gestational diabetes, and maternal hemorrhage, require special attention to the type and amount of fluid and blood product administration.

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31 | Perioperative Fluid Therapy in Pediatrics

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INTRODUCTION

Old concepts such as age-related changes in body fluid composition as well as relatively new concerns such as the danger of hyperglycemia support modern management of perioperative fluid therapy in pediatrics. Neonates (0–28 days) and premature infants represent a subgroup with special requirements that differ considerably from common guidelines described for infants and children.

PHYSIOLOGY

Body Composition

Throughout fetal life and during the first two years of life, the distribution of body fluid undergoes a gradual but significant change (1). Total body water (TBW) represents as much as 80% of body weight in premature infants, 78% in full-term newborns, and 65% in infants of 12 months of age compared to 60% in adults (Table 1).

These age-related changes of TBW mainly reflect changes in extracellular fluid (ECF) with growth. As the body cells proliferate and organ development progresses, ECF volume decreases proportionally. It represents 50% of body weight in premature infants, 45% in full-term newborns, and 25% in infants of 12 months of age compared to 20% in adults. Intracellular fluid compartment increases only moderately during the first year of life, representing 33% of body weight at birth and 40% of body weight by the end of the first year, and does not change any more after that.

Renal Maturation

Maturation of renal function is basically achieved by the end of the first month of life. Glomerular filtration increases rapidly from the gestational age of 34 weeks, when kidneys have completed their nephronic structure (2–4). After birth, renal vascular resistances decrease abruptly, whereas systemic vascular resistances and arterial pressure increase. As a consequence, renal blood flow increases dramatically. This explains why the glomerular filtration rate, still low during the first 24 hours of life, rises very rapidly thereafter. During the first six weeks after birth, the area of cortical and juxtaglomerular nephrons, as well as the volume of glomerular capillaries and the size of glomerular membrane pores, increases. Tubular function is less mature than glomerular function at birth. Renal threshold for glucose is low, explaining the high incidence of glycosuria even after moderate hyperglycemia. The tubular capacity to reabsorb sodium is low in premature infants (5). At term, the neonatal nephron begins to reabsorb sodium more actively in response to growth requirements. Sodium excretion in response to parenteral sodium load is also reduced. Careful control of sodium balance is essential in premature surgical neonates, because both hypernatremia and hyponatremia may have detrimental effects on the brain.

At birth, the newborn is unable to effectively concentrate urine. Clearance of free water is lower than that of adults, which explains the impaired ability of newborn infants to cope with excessive water loading or water deprivation.

Finally, the renin–angiotensin–aldosterone system is functional in neonates (6), but feedback mechanisms are immature, especially in premature infants (7).

Developmental Cardiovascular Changes

Newborns and premature infants have limited cardiovascular reserves in response to an increased preload or afterload (8–10). Any reduction in preload is also poorly tolerated owing

Table 1 Body Composition and Morphometric Data in Children

	Premature	Full-term	1 yr	3 yr	9 yr	Adult
BW (kg)	1.5	3	10	15	30	70
BSA (m ²)	0.15	0.2	0.5	0.6	1	1.7
BSA/BW	0.1	0.07	0.05	0.04	0.03	0.02
Total body water (% BW)	80	78	65	60		
ECF (% BW)	50	45	25	20		
ICF (% BW)	30	33	40	40		

Abbreviations: BSA, body surface area; BW, body weight; ICF, intracellular fluid; ECF, extracellular fluid.

to the reduced compliance of the right ventricle and is rapidly followed by a reduction of systolic ejection volume. Cardiac output is high to compensate for the high oxygen affinity of fetal hemoglobin and to match the high oxygen consumption (11). Cardiac output is highly dependent on the heart rate in the neonatal period (9). However, by the end of the first month of life, adaptation capacities of the cardiovascular system are close to those of adults. In premature infants, an excess of fluid will promote the persistence of patent ductus arteriosus (12).

MAINTENANCE REQUIREMENTS

Calorie Requirement

The metabolic rate of a full-term newborn in a neutral environment is 32 kcal/kg/d during the first hours of life. Requirements increase rapidly during the first week of life, and then linearly with growth but at a slower rate (13).

In 1957, Holliday and Segar (14) estimated the metabolic requirements of patients at bed rest, and this estimation is still used in daily practice. The calorie expenditure is 100 kcal/kg for infants weighing 3 to 10 kg, 1000 kcal + 50 kcal/kg for each kg over 10 kg but less than 20 kg for children ranging from 10 to 20 kg, and 1500 kcal + 20 kcal/kg for each kg over 20 kg for children 20 kg and up. Half of those calories are required for basic metabolic needs and the remainders are required for growth.

Fever increases calorie needs by 10% to 12% per degree centigrade elevation.

General anesthesia essentially reduces calorie requirements to close to that required at basal metabolic rate (15).

Water Requirement

Under normal conditions, 1 mL of water is required to metabolize 1 kcal. This takes into account insensible water losses across the skin and respiratory tract, and urinary water loss. Therefore, when the child is awake, the calorie and water consumption are considered equal (Table 2).

In anesthetized children, Lindahl (15) calculated that 166 mL of water was required to metabolize 100 cal. Using indirect calorimetry, he calculated the hourly maintenance fluid to be equal to the following equation:

$$\text{Maintenance fluid per hour (mL} \cdot \text{h}^{-1}) = 2.5 \times \text{kg} + 10$$

Insensible water loss increases with decreasing body weight in premature infants, especially when they are kept under a radiant warmer (16). Several factors contribute to this large insensible water loss in premature infants: small size, an increased body surface area to body weight ratio, increased thermal conductance, thinner, more permeable and vascularized skin, and a higher respiratory rate.

Table 2 Hourly and Daily Maintenance Fluids According to the Child's Weight

Weight	Hourly fluid requirements	Daily fluid requirements
< 10 kg	4 mL/kg	100 mL/kg
10–20 kg	40 mL + 2 mL/kg above 10 kg	1000 mL + 50 mL/kg above 10 kg
> 20 kg	60 mL + 1 mL/kg above 20 kg	1500 mL + 25 mL/kg above 20 kg

Electrolytes Requirements

Daily sodium and potassium requirements are 2 to 3 and 1 to 2 mmol/kg, respectively, in children. The combination of maintenance fluid requirements and electrolyte requirements results in a hypotonic electrolyte solution. Therefore, the usual intravenous maintenance fluid given to children by pediatricians in the hospital is one-fourth- to one-third-strength saline. In premature infants, sodium and potassium requirements are higher than later in life, 3 to 5 mmol/kg for sodium and 2 to 4 mmol/kg for potassium. Calcium requirements range between 0.8 and 1 mmol/kg/d.

PREOPERATIVE ASSESSMENT

The preoperative assessment of fluid volume and state of hydration varies from elective surgery patients with no or slowly developing fluid deficit to the severely traumatized patient who is undergoing a dynamic deficit in blood and interstitial volume and in whom it is more difficult to evaluate fluid balance. Only some specific pediatric situations will be reviewed.

Dehydration

Dehydration is observed in many common clinical situations such as vomiting, diarrhea, and fever. Estimation of the degree of dehydration is based on classical clinical signs (Table 3). In an acute clinical situation, the weight loss of the child is usually a very good indication of total water loss. It should be kept in mind that the most important sign of normal hydration status is kidney function. Thus, monitoring urinary output is essential for evaluating and treating any fluid deficit. Correction of 1% of dehydration requires about 10 mL/kg of fluids. The rate of fluid administration depends on the seriousness and rapidity of dehydration.

When water loss is relatively larger than sodium loss, hypernatremic dehydration is observed. Signs of cerebral impairment may be observed for plasma sodium values in excess of 165 mmol/L. Correction should be progressive, using hypotonic dextrose solution containing 1–2 g NaCl per liter, the rate being adapted to water depletion.

Hyponatremia is most commonly observed in the postoperative period and in emergency departments when hypotonic solutions have been administered or when salt loss is greater than water loss (18,19). Hyponatremia is an emergency and should be treated rapidly by administering normal saline or hypertonic sodium chloride when neurological disorders are present. The most common neurological disorders are seizures, usually occurring when natremia is below 120 mmol/L. Hyponatremia may also be due to inappropriate secretion of the antidiuretic hormone (ADH), usually after a major intracranial surgery or even after more minor surgical procedures (20–22). Treatment consists of water restriction and the administration of isotonic saline. Hyponatremia after the administration of desmopressin (e.g., in patients with Von Willebrand disease for prevention of perioperative bleeding) requires similar treatment.

In all the clinical situations described above, the administration of potassium depends on urinary output.

The ultimate goal of perioperative fluid therapy is to maintain a correct fluid and electrolyte balance and, as a consequence, normal cardiovascular stability. Indeed, dehydration and some medical conditions associated with third-space sequestration of fluids (e.g., intestinal

Table 3 Estimation of the Degree of Dehydration Expressed in Percents of Body Weight, According to the Physical Signs

Sign	< 5%	5–10%	10–15%
Skin turgor	Good	Tenting	Poor
Feel of skin	Moist	Dry	Clammy
Mucous membranes	Moist	Dry	Parched
Eyeballs	Normal	Deep set	Sunken
Fontanelles	Flat	Soft	Sunken
Central nervous system	Consolable	Irritable	Lethargy, coma
Cardiovascular system	Normal	Normal	Decreased blood pressure and capillary filling

Source: Adapted from Ref. 17.

occlusion) will in turn affect vascular fluid volume. Restoration of an adequate vascular fluid volume is essential to maintaining cardiovascular stability, organ perfusion, and adequate tissue oxygenation. Isotonic transfer of fluid from the extracellular compartment to a nonfunctional interstitial space forms the third-space volume. Replacement of intravascular volume loss should be performed by the administration of normotonic and normo-osmolar solution. Crystalloid solutions such as Ringer lactate or normal saline, or even a colloid solution such as albumin, can be used. The prognosis of some medical conditions such as septic shock depends on the quantity and the rapidity of vascular loading—the younger the child, the greater the quantity of fluid loading related to body weight (23).

Fasting Guidelines

Preoperative fasting has been a prerequisite for elective surgery since the demonstration by Mendelson of a link between feeding and pulmonary aspiration of gastric contents in parturients (24). However, recent work has shown that prolonged fasting does not reduce the risk of aspiration pneumonitis during anesthesia and highlighted the need to avoid regurgitation of gastric contents. This has led to a reduction in fasting times and a greater appreciation of the several risk factors for regurgitation and aspiration (25–27). Reduced fasting increases patient comfort and hydration and reduces the potential for hypoglycemia during anesthesia in neonates aged less than 48 hours (28).

There is now a large body of evidence that free intake of clear fluids (defined as those through which it is possible to read newsprint) up to two hours preoperatively does not affect the pH or volume of gastric contents at the induction of anesthesia in children (29–33) or adults (34). Although many of these studies can be criticized for lacking adequate controls and/or sample sizes, a meta-analysis of 12 adult studies did not change the main conclusion that intake of clear fluids up to two hours preoperatively was safe (35). While there have been relatively few studies in infants, these suggest that infants may be allowed clear fluids up to two hours and breast milk four hours preoperatively (36,37). There is also evidence that infants aged less than three months may safely be given infant formula (cow's milk) up to four hours preoperatively (36). However, a six-hour fasting time was recommended by the American Society of Anesthesiologists (ASA) task force on preoperative fasting, although pediatric anesthesiologists agreed to a four-hour fasting period for infant formula in infants aged less than three months (Table 4) (26). By contrast, there is little evidence to support a reduction in the present six-hour fasting time for cow's milk or solid food in older infants and children.

Compliance with fasting guidelines is a potential problem whether preoperative fluids are allowed or not. Although one study suggested that liberalization of fluid could lead to noncompliance for solid food, this has not been confirmed (31). On the contrary, parents of children who were allowed clear fluid up to two hours preoperatively reported less difficulty in adhering to preoperative feeding instructions, rated their children as less irritable, and rated the overall preoperative experience as better than did the parents of controls (32). Furthermore, when children inadvertently ingested clear fluid within two hours of operation, this resulted in only moderate delays to surgery (30–60 minutes) and no cancellations.

INTRAOPERATIVE FLUID MANAGEMENT

Quantity of Intraoperative Fluids

The intraoperative fluid therapy is aimed at providing basal metabolic requirements (maintenance fluids), at compensating for preoperative fasting deficit, and at replacing losses from the surgical field.

Table 4 Fasting Guidelines for Elective Surgery

Ingested material	Minimum fasting period (hr)
Clear liquids	2
Breast milk	4
Infant formula	6 (not suggested by consultants)
Nonhuman milk	6
Light meal	6

Source: From Ref. 26.

Table 5 Guidelines for Fluid Administration of Balanced Salt Solution in Children According to the Age and to the Severity of Tissue Trauma

First hour	25 mL/kg in children aged 3 yr and under 15 mL/kg in children aged 4 yr and over
All other hours	Maintenance + trauma = basic hourly fluid Maintenance volume = 4 mL/kg/h Maintenance + mild trauma = 6 mL/kg/h Maintenance + moderate trauma = 8 mL/kg/h Maintenance + severe trauma = 10 mL/kg/h
Blood replacement	1:1 with blood or colloid or 3:1 with crystalloid

Source: From Ref. 39.

When new Nil Per Os (NPO) guidelines are followed, fasting fluid deficit is expected to be minimal. However, this is not always applicable or followed, and some children are fasted for several hours prior to surgery. Fasting deficit is calculated by multiplying the hourly maintenance fluid requirement (Table 2) by the number of hours of restriction. In 1975, Furman et al. (38) proposed to replace 50% of the fasting deficit in the first hour and 25% in the second and third hours. In 1986, Berry (39) proposed simplified guidelines for fluid administration, indicated in Table 5, according to the child's age and to the severity of surgical trauma. The amount of hydrating solutions required during the first hour of anesthesia was greater in infants and young children than in older children, to take into account the larger deficit due to larger losses of ECF volume. These guidelines are adapted to children who fasted for eight hours following the classical recommendation "NPO after midnight." The amount of fluid given during the first hour should be reduced if children were fasting for a shorter period of time or if the child was already receiving intravenous fluid prior to surgery. These guidelines are only guidelines and should be adapted to the clinical situation. Third-space losses may vary from 1 mL/kg/h for a minor surgical procedure to as much as 15 to 20 mL/kg/h for major abdominal procedures, or even up to 50 mL/kg/h for surgery of necrotizing enterocolitis in premature infants. Blood losses are replaced with either a 1:1 ratio of blood or colloid, or a 3:1 ratio for crystalloid. Third-space losses should be replaced with crystalloid (normal saline or Ringer lactate), but maintenance fluids are basically hypotonic as discussed above. Thus, intraoperative fluid administration requires two different types of fluids to be administered at different rates—one with maintenance fluids, at a set rate (Table 2), and the other for replacement fluids. This is often unnecessary, and most anesthesiologists will choose to administer only a balanced salt solution, assuming that the kidney can excrete any extra sodium and water. This will in turn decrease the risk of postoperative dilutional hyponatremia (see below) (40,41).

Glucose: Necessary or Harmful?

The next question is whether or not the administration of dextrose is necessary during surgery. In the last several years, there has been a complete reevaluation of the place of glucose in routine intraoperative solutions. As already discussed above, energy requirements during anesthesia are close to the basal metabolic rate. The administration of dextrose was deemed mandatory in the early days to avoid perioperative hypoglycemia, which may be difficult to diagnose in an anesthetized child, but the risk of hyperglycemia was at that time underestimated.

Some children are prone to hypoglycemic episodes, such as those undergoing open-heart surgery or those taking beta-blocking agents (42–45). Neonates are also at risk of hypoglycemia during surgery, particularly if glucose solutions have been given preoperatively and are interrupted intraoperatively (28). Conversely, the risk of preoperative hypoglycemia has been demonstrated to be very low in normal healthy infants and children (1–2%), despite prolonged fasting periods (40,41,46–51). There is, however, no agreement in the literature regarding the definition of hypoglycemia (52). The value of 2.4 mmol/L is often proposed as the acceptable level in infants and children. Therefore, the risk of hypoglycemia may not be as common in occurrence as was thought, even in infants below one year of age. Thus, it would appear that in the vast majority of patients, there is no need to administer glucose in the perioperative period or to monitor blood glucose.

Conversely, the danger of hyperglycemia in the perioperative period is a real clinical issue that has been extensively reviewed (53,54). It is well known that hyperglycemia can induce diuresis and, consequently, dehydration and electrolyte disturbances, especially in small premature infants with immature tubular function. More recently, several studies have demonstrated that hyperglycemia will increase the risk of hypoxic–ischemic brain or spinal cord damage (55–60). In infants subjected to profound hypothermic circulatory arrest for cardiac surgery, high prearrest blood glucose levels are associated with postoperative neurological deficits (61). In 1995, Bush and Steward described permanent brain damage associated with marked hyperglycemia (blood glucose 24 mmol/L) in an eight-year-old girl operated on for suspicion of appendicitis who received a large amount of a glucose-containing solution during surgery; but perioperative hypoxic–ischemic episodes cannot be entirely excluded in this report (62,63).

On the basis of all these studies, unnecessary glucose administration leading to intraoperative hyperglycemia should be avoided, especially in children at risk of hypoxic–ischemic episodes, such as during cardiopulmonary bypass or resuscitation, because hyperglycemia can worsen the neurological outcome, or hyperglycemia per se may cause cerebral damage.

Therefore, intraoperative administration of glucose-free isotonic hydrating solutions is the routine practice for most procedures in children over four to five years of age. In infants and young children, 5% dextrose solutions should be avoided, but 1% or 2.5% dextrose in lactated Ringer's is appropriate (40,41,50). Glucose infusion at a rate of 120 mg/kg/h is sufficient to maintain an acceptable blood glucose level and to prevent lipid mobilization in infants and children (64–66). These glucose-containing solutions may be indicated in children receiving regional anesthesia as a part of their anesthesia, because caudal, epidural, and spinal anesthesia have been shown to attenuate the stress response to surgery (67–69). Blood glucose levels in children receiving combined general and regional anesthesia are significantly lower than those in children receiving general anesthesia alone (70,71). The lack of a hyperglycemic response indicates that glucose administration may be needed during surgery to prevent hypoglycemia in children receiving combined general and regional anesthesia, or that blood glucose levels should be monitored if glucose-free solutions are administered (70,72).

Special Concerns in the Neonatal Period

Most of the concerns of the neonatal period have already been outlined in the previous paragraphs. These include the larger ECF volume, and the consequences of the immaturity of renal system and of cardiovascular function. In addition, newborn infants have low glycogen stores and impaired gluconeogenesis. Premature infants and neonates less than two days old are known to be susceptible to hypoglycemia, especially if they are already on parenteral nutrition. For these reasons, usually two distinct intravenous lines are useful—one for providing glucose and metabolic requirements and the second for fluid replacement. As for older children, hyperglycemia should be avoided, because of the increased likelihood of brain damage in the presence of transient cerebral ischemia or osmotic cellular dehydration leading to intraventricular hemorrhage in the premature infant. However, the risk of hypoglycemia should not be minimized. It has been suggested that moderate hyperglycemia is less deleterious than normo- or hypoglycemia in asphyxiated newborn animals (73,74). It is therefore desirable to monitor blood glucose during long surgical procedures in the neonatal period.

VOLUME REPLACEMENT DURING INFANCY

Indications and Choice of Crystalloid and Colloid

Crystalloids (normal saline or Ringer lactate) are first administered to treat absolute or relative blood volume deficits frequently observed during surgery in children. Their advantages include their low cost, their lack of effect on coagulation, and the absence of the risk of anaphylactic reaction and of the risk of transmission of any known or unknown infectious agent. This practice should also apply to premature and newborn infants. Indeed, recent studies performed in hypotensive premature infants or polycythemic newborns have demonstrated that normal saline is as effective as albumin in restoring and maintaining arterial pressure or to treat neonatal polycythemia (75,76). In addition, in premature infants, the crystalloid administration caused less fluid retention in the first 48 hours than 5% albumin. The administration

of a large volume of normal saline can cause dilutional acidosis or hyperchloremic acidosis (77), whereas a large volume of balanced salt solution (78), such as lactated Ringer's solution, can decrease serum osmolality, which is not beneficial in patients with decreased intracranial compliance (77–80). The rate of fluid administration will be indicated by the cardiovascular condition. Normally, 15 to 20 mL/kg of Ringer lactate solution over 15 to 20 minutes will reestablish cardiovascular stability. After the administration of a total of 50 mL/kg of crystalloid solution, administration of a colloid solution (albumin or synthetic colloid) to maintain the intravascular osmotic pressure is indicated (81).

Hydroxyethyl starch (HES) preparations are becoming very popular for vascular loading in adults and children (82). However, the number of pediatric studies aimed at evaluating HES efficacy and tolerance is limited. HES preparations have been used as replacement solution for hemodilution in children (83,84). Volumes of HES as high as 55 mL/kg have been well tolerated without deleterious consequences on the renal and liver function and blood coagulation. HES preparations were as effective as 6% dextran 60 for maintaining global tissue oxygenation (84). HES administration was associated with less postoperative edemas compared with Ringer lactate in infants and children (83). Three studies have compared HES preparations with 5% or 20% albumin during general surgery or cardiac surgery in infants and children (85–87). In these three studies, HES was as effective as albumin, and no undesirable side effects were reported. However, short-term and long-term side effects have been recently reevaluated after HES administration (88–90). In most countries, both the daily allowed quantity and daily allowed duration of HES administration have been limited by health authorities. In children, only one case report described severe coagulopathy following volume replacement with HES in a 13-year-old child who was a Jehovah's Witness (91). Better knowledge of undesirable effects of HES has led most pediatric anesthesiologists and pediatricians to avoid the use of HES in premature and newborn infants. In the latter, the choice of colloid will therefore be restricted to gelatins or albumin.

Gelatins have been used for many years in children but also in early infancy to treat intravascular fluid deficits. HaemaccelTM is no longer used in many countries owing to its high risk of anaphylactic reaction. HaemaccelTM was demonstrated to be as effective as 4.5% albumin in maintaining blood pressure during major surgery in neonates, but less effective in maintaining plasma colloid osmotic pressure and plasma albumin concentration (92).

Although the use of albumin has been challenged owing to its high cost and to its uncertain risk of transmission of nonconventional agents, it remains the main colloid used in the neonatal period and early infancy for volume expansion (93,94). In hypotensive premature infants, 4.5% albumin was demonstrated to be as effective as fresh frozen plasma to restore blood pressure, but more effective than 20% albumin (95). This suggests that the volume of albumin administered is more important than its concentration in maintaining or restoring cardiovascular stability. Thus, 5% albumin is the preferred colloid in newborn infants, because it is iso-oncotic to plasma and very effective in maintaining blood pressure and plasma colloid perfusion pressure (92).

The use of fresh frozen plasma should be restricted to neonates and children with proven coagulation disorders.

POSTOPERATIVE FLUID PROBLEMS

Oral fluid intake is usually allowed within the first three postoperative hours in most pediatric patients. Early oral fluid intake was required in most institutions, before discharging the patient from hospital. This view is now challenged because it has been reported that withholding oral fluids postoperatively from children undergoing day surgery reduces the incidence of vomiting (96–98).

If oral intake should be delayed (e.g., after abdominal surgery), fluid therapy should be administered usually on a peripheral venous access, if duration of intravenous infusion is not expected to exceed five days or on a central venous access when long-term parenteral nutrition is necessary. Fluid therapy should provide basic metabolic requirements, and compensate for gastrointestinal losses (e.g., gastric suctioning) and additional losses (e.g., fever). Basal metabolic requirements are usually covered with hypotonic fluids, as discussed above, but all other losses should be replaced with a balanced salt solution. The appreciation of the quantity of gastrointestinal losses is frequently underestimated, explaining the high incidence of

dilutional hyponatremia in the postoperative period resulting from a relative deficit in sodium intake and/or from postoperative secretion of ADH.

Postoperative hyponatremia is the most frequent electrolyte disorder in the postoperative period. Severe hyponatremia ($< 120\text{--}125\text{ mmol/L}$) may result in transient or permanent brain damage (18,21,22,99–102). Most postoperative hyponatremia observed in ASA 1 children are due to the administration of hypotonic fluids when capacities of free water secretion are impaired (18). Other causes of hyponatremia include pituitary or adrenal insufficiency, brain injuries or brain tumors associated with salt losses, and inappropriate secretion of ADH. Plasma ADH is often increased in the postoperative period as a result of hypovolemia, stress, pain, or traction of the dura mater. The combination of ADH secretion and infusion of hypotonic fluids will produce dilutional hyponatremia. Profound hyponatremia promotes cerebral edema, which includes clinical signs such as a decreasing level of consciousness, disorientation, vomiting, and, in severe cases, seizure activity. Acute symptomatic hyponatremia is a medical emergency that requires immediate therapy. Hypertonic NaCl should be administered to increase plasma sodium up to 125 mmol/L , because above this value, the risk of seizure decreases. Water restriction may be sufficient only in normovolemic patients without clinical signs. Diuretic may be used in patients with a normal or high vascular volume. Postoperative hyponatremia should be prevented by avoiding hypotonic solutions during surgery and in the early postoperative period.

CONCLUSION

Old concepts such as age-related changes in body composition explain the necessity to provide larger volumes of fluid during infancy because maintenance requirements are higher than later in life, but also to administer a larger quantity of fluids to compensate for third-space losses or to restore an effective vascular volume in septic shock. Recent studies have reevaluated the risk of hyperglycemia, especially in children at risk of hypoxic–ischemic episodes and hyponatremia, the most frequent postoperative electrolyte disorder, both of them likely to promote or aggravate permanent or transient brain damage. Finally, the choice of colloid during infancy is an unsolved question owing to the on-going adult literature that questions the potential short-term (on blood coagulation) and long-term (resulting from accumulation and storage) effects of HES and of albumin (unknown risk of transmission of variant of Creutzfeldt–Jacob disease).

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32 | Restricted Intravenous Fluid Therapy in Elective Surgery

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INTRODUCTION

Intravenous fluid resuscitation is a key component in the management of surgical patients, and the fluid is usually administered to serve two objectives that supplement rather than exclude each other:

- Replacement of fluid lost;
- Maintenance of physiological functions.

However, for determination of the optimal fluid volume to be administered, both approaches have limitations because they rely on two preconditions: First, that fluid loss be accurately measured and that replacement be beneficial for outcome; and second, that changes in physiological parameters with adequate sensitivity are proportional to changes in blood volume and that obtaining the parameters within a certain range with fluid is beneficial for outcome.

In daily clinical practice, fluid therapy is guided by a combination of measured lost volume and physiological changes. Protocols for postoperative fluid management usually recommend frequent monitoring of fluid volume status, utilizing readily available clinical parameters including blood pressure (BP), heart rate, urinary output, blood pH, fluid balance, and bodyweight measurements. Even so, data from Great Britain reveals that only in 17% of surgical patients a record of the patient's bodyweight is available (1). Moreover, during and after surgery, anesthetic and analgesic drugs decrease arterial BP, release of stress-induced hormones decrease urinary output, and acidosis may be inflicted on the patient by the very administration of saline-containing fluids intravenously (2–5).

Hypovolemia may lead to poor tissue perfusion, suboptimal organ function, and organ failure. Fluid overload may, however, be just as harmful to tissue oxygenation as hypovolemia (6). Currently, the volumes of fluid administered during surgery far exceed the volumes lost. The observed postoperative bodyweight increase of 3 to 7 kg following major surgery reflects this (7–10). The effects/adverse effects of intravenous fluid overload have, however, not favored the same scientific interest, as has the effects of hypovolemia. Cases of pulmonary edema have been described as possible sequelae of iatrogenic fluid overload (11,12), and it may occur in patients without pre-existing cardiac disease (13–16). Associations have been shown between intraoperative fluid overload and complications (17–20) and mortality following major surgical procedures (21).

Only few clinical randomized trials have examined possible effects (or adverse effects) of administered fluid volume on outcome of surgery, and the theoretical and thus the therapeutic approach of the trials are opposite:

- Trials examining standard fluid therapy versus more fluid (goal directed fluid therapy);
- Trials examining standard fluid therapy versus less fluid (fluid restriction).

The trials of goal-directed fluid therapy are testing the effects of extra fluid given to obtain central hemodynamic parameters on certain targets that is thought to be beneficial for outcome [typically maximal stroke volume (SV)].

The trials examining restricted fluid therapy claim that all fluid in excess of measured losses (and thus increasing bodyweight) will result in tissue edema that may be harmful for organ function and tissue healing.

The aim of this chapter is to present the existing (or missing) evidence behind the current "standard fluid therapy" as well as to review the literature concerning the influence of administered intravenous fluid volumes on outcome of surgery.

Based on this evidence a clinical guideline for perioperative fluid therapy will be presented.

THE (MISSING) EVIDENCE FOR CURRENT FLUID THERAPY IN MAJOR SURGERY

"Standard fluid therapy" includes:

- The replacement of fluid lost:
 - Basal fluid requirements (deficit from fasting, insensible perspiration, and urinary output).
 - Perspiration through the surgical wound.
 - Exudation through the surgical wound.
 - "The loss to third space."
 - Blood loss.
- The maintenance of physiological functions:
 - "Preloading" of neuroaxial blockade.

THE REPLACEMENT OF FLUID LOST

Basal Fluid Requirements (Deficit from Fasting, Insensible Perspiration, and Urinary Output)

Patients planned for elective surgery are allowed to drink clear fluids until two hours before anesthesia (22), and should therefore be well hydrated. For several reason this is, however, not always the case. An obvious approach to determine the volume needed for replacement of the fluid deficit because of fast would be to ask the patient when and how much he has last been drinking, and replace the deficit with approximately 80 mL/fasting hour.

The insensible perspiration is in normal conditions approximately 10 mL/kg/day, and does not change much during surgery. About 2/3 of this perspiration is lost from the skin, and 1/3 is lost through the airways, dependant on the humidity of the inhaled air. In the patients ventilated with air of 100% humidity, the loss is close to zero. During ventilation with dry air the loss is 0.5 mL/kg/hr (23).

As insensible perspiration is, and deficit from fasting primarily is, a water loss, the logical approach would be to replace it with a water preparation (i.e., glucose 5%). Previously, preoperative or intraoperative glucose infusions were discouraged because the surgical stress (and the disease induced stress) causes a rise in blood glucose, and intravenous glucose administration enhances this hyperglycemia. It has, however, been shown that glucose administered preoperatively either intravenously or orally reduces the postoperative cellular insulin resistance (24,25). The importance of this on outcome of surgery is not clarified, but well-being may increase (26); and a clinical randomized trial has shown a preoperative glucose load to improve postoperative muscle strength (27). Preoperative rehydration with glucose-containing fluids may therefore be a good choice for the fasting patient.

The role of glucose infusions during surgery is still controversial. Intraoperative glucose administration has been examined in two clinical randomized trials of patients undergoing gynecological laparoscopy with contradictory results. One trial has shown intraoperative glucose infusions to improve recovery (28), but the other could not confirm this (29).

A large urinary output cannot be expected during surgery because the release of stress-induced hormones will tend to reduce the excretion of salt and water. As hypovolemia causes both renal failure and small diuresis, it may be reassuring for the doctor to observe a large urinary output during surgery. It is, however, not evident that a large urinary output is necessary to prevent postoperative renal failure, or that a small urinary output is associated with renal failure in the absence of hypovolemia (30,31). A small diuresis may therefore be accepted during surgery as long as hypovolemia is not the cause.

As body fluids are regulated through diuresis, the diuresis should not always be replaced. It may be that a fluid overload is excreted.

The Perspiration from the Surgical Wound

The perspiration through the surgical wound is often confused with the loss to third space, but it is an external loss that especially in abdominal surgery has been highly overestimated.

Measurements of the evaporative loss from abdominal incisions show that the loss is dependant on the size of the incision and the exposure of the intestines (32).

- The loss from minor incisions with slightly exposed but nonexteriorized viscera is 2.1 g/hr.
- The loss from moderate incisions with partly exposed but nonexteriorized viscera is 8.0 g/hr.
- The loss from major incisions with completely exposed and exteriorized viscera is 32.2 g/hr.

The loss from exteriorized viscera decreases by 50% after 20 minutes of incision (32), and wrapping the exteriorized viscera in plastic reduces the evaporative loss by 87.5% (33). Note that the loss is independent of the size of the patient. There is no reason to believe that the loss from incisions in other anatomical regions is much different.

Exudation Through the Surgical Wound

In addition to an evaporative loss, an exudative loss may occur from the wound, and during abdominal surgery from the intestines as well. This fluid is often lost in the surgical dressings, and its volume therefore based on an estimate. In abdominal surgery with the exteriorized viscera in a plastic bag, however, the loss can be measured rather accurately. The exudation contains protein, and manipulation of the intestines increases the protein content (34).

“The Loss to Third Space”

The loss to third space can be divided into an anatomical and a nonanatomical loss (35,36).

The Anatomical Third Space Loss (or Pathological Fluid Accumulations)

Before, during, or after surgery fluid may be sequestered in an anatomical third space because of disease or the trauma and cause an expansion of the extracellular volume (ECV). Examples are ascites in the peritoneal cavity, fluid in the plural cavity, or intra- or extracellular accumulations of blood or edema.

Ascites or pleural fluid emptied through drains or during surgery can be measured, and will cause a postoperative weight loss. Any regeneration of such fluid can be identified by a postoperative weight gain or by clinical and paraclinical examination with, for example, ultrasound imaging.

The volume of fluid sequestered in traumatized tissue may be more difficult to assess. In an experimental study, the formation of a small bowel anastomosis caused a water increase of 5% to 10% in the surrounding tissue if no intravenous fluid was administered. When 15 mL/kg/hr of intravenous fluid was administered, the edema increased to 10% to 20% (36). Thus third space sequestration of fluid and edema formation is increased by administration of intravenous fluids. If equivalent changes occur in humans, and the tissue surrounding a large-bowel anastomosis weighs approximately the same as the specimen removed by the reversal of Hartman's procedure (50 g) (37), a fluid accumulation of 2.5 to 5 g may occur if no fluid is administered, and of 5 to 10 g if 15 mL/kg/hr was given. Such a small volume is of no importance for the development of hypovolemia, but may be of importance for the healing of the bowel anastomosis.

The Nonanatomical Third Space Loss (or Deficit in Functional Extra Cellular Volume)

During surgery it is believed that the trauma per se is causing a contraction of the ECV (38). This phenomenon was first described in 1960 (39). ECV was measured before and after anesthetized dogs were bled into severe shock (no trauma was imposed). The ECV measured during shock was found diminished far beyond the volume of lost blood. The tracer used for measurement was the radioactive-labeled sulphate tracer ($^{35}\text{SO}_4$), the sampling method was single sampling, and the ECV was determined from a single blood sample withdrawn after

only 20 minutes of equilibration. The following year a similar investigation of patients undergoing abdominal surgery was performed. Despite correction for external losses, the measured ECV during surgery was found largely diminished (up to 28% or 3.7 L) compared to similar measurements before surgery (40). Increased severity of trauma seemed to correlate with the ECV lost (41). The fate of the fluid volume missing from the ECV could not be explained. Theories of sequestration of the fluid in the intracellular compartment could not be confirmed by investigations including measurements of total body water (42–45). It was therefore speculated that the trauma caused a redistribution of fluid in the body to a compartment that at present could not be accounted for and was named the third space. In the beginning this extensive volume was thought sequestered in the intestinal lumen, but this hypothesis was later rejected (46). A last hypothesis, that the fluid was sequestered in traumatized tissue, could not be confirmed when measuring ECV in American soldiers with extensive trauma and severe shock during the armed conflict of Vietnam (47,48).

The literature concerning measurements of ECV changes during surgery or hemorrhagic shock reveals that only trials utilizing the labeled sulphate tracer and including the samples collected following 20 to 30 minutes of equilibration in the calculation of ECV have demonstrated a nonanatomical third space loss (39–41,49–55). All other studies identified utilizing various different tracers, multiple sampling techniques, and longer equilibration times have not been able to measure a third space loss neither in surgery nor in hemorrhagic shock (42–48,56–92). Furthermore, when utilizing the labeled bromide tracer, investigators have found the opposite of a third space loss (43,45,60–62,79–82), i.e., corrected for the blood lost an expansion of the ECV instead of a contraction was found following surgery. Thus the volume of the ECV seems to be very dependant on the utilized tracer and the sampling method. A systematic review of this literature has recently been published, and the conclusion is that the nonanatomical third space loss most probably is based on flawed methodology (93).

Nevertheless the loss to third space is still replaced according to algorithms (38,94,95). Volumes up to 15 mL/kg/hr are recommended during the first hour of abdominal surgery, with decreasing volumes the following hours (95). In thoracic or orthopedic surgery up to 4 to 7 mL/kg/hr is recommended (95).

In conclusion:

- The evidence supporting the existence of a nonanatomical third space loss (a contraction of the ECV) is weak and most probably based on flawed methodology.
- The volume of fluid sequestered in an anatomical third space (and causing an expansion of the ECV) can (at least to some extent) be quantified (ascites, pleural fluid, blood accumulations, etc.).
- The edema of traumatized tissue is small but increases with intravenous fluid administration.

The Maintenance of Physiological Functions

Preloading of the Neuroaxial Blockade

Neuroaxial blockade affects both sympathetic nerve fibers and sensory fibers (96) and causes a relaxation of the vascular bed innervated by the affected segments of the spinal cord. This in turn causes a decrease in peripheral vascular resistance with a decrease in arterial BP. To comply with this BP decrease, it is common to preload a spinal or epidural blockade with either 500 mL of colloid or 1000 mL of crystalloid. No effectiveness of this treatment has, however, been shown. The earliest nonrandomized trials and retrospective investigations (97–99) suggested fluid preloading to reduce the incidence of hypotension in 20% to 35% of patients, but this has not been confirmed in clinical randomized trials of preloading versus no preloading (100–104). Neither the decrease in BP nor the need for pressor substances was significantly altered by fluid preloading of the neuroaxial blockade.

TRIALS OF GOAL-DIRECTED FLUID REGIMENS (STANDARD FLUID VS. EXTRA FLUID)

When attempting to assess the requirements for intravenous fluid therapy in apparently hypovolemic patients, it is routine to observe the effect of a volume load of saline or colloid

on central hemodynamic variables. Two assumptions are, however, inherent in this strategy: First, that the hemodynamic variable has a clinically adequate sensitivity to reveal varying plasma volumes; second, that the volume load given is followed by a proportional increase in plasma volume. Unfortunately, studies of critically ill patients have shown poor correlation between BP, central vein pressure (CVP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), haematocrit, and diuresis on the one hand and measured blood volume and the volume expanding effect of intravenous fluids on the other hand (105). Furthermore, a large individual variation in the plasma expanding effect of a single dose of hydroxyethyl starch (HES) has been found (106). Despite these shortcomings, measurement of physiological parameters may currently be the only way to quickly assess plasma volume in patients with acute surgical conditions, trauma patients with uncontrolled bleeding, or the critically ill.

Several trials on goal-directed fluid therapy in surgical patients have been performed. The majority of these trials examine the effect of fluid therapy in addition to other therapies using pressor substances, vasodilating drugs, or diuretic drugs.

Six trials were, however, found designed to examine the effect of fluid therapy alone (107–112). The trials of good methodological quality (see beneath) are shown in Table 1.

The goal of the trials was to obtain a maximal stroke volume determined by esophageal Doppler or CVP. The study populations of these trials are rather small, reflecting that power was calculated not to show a difference in postoperative complications, but in intestinal pH (109) or length of hospital stay; thus complications was not defined by protocol as the primary outcome measure. The difference in fluid volume given to the groups compared is also very small, and none of the trials controlled pre- or postoperative fluid therapy. Another serious weakness of all the trials is that the fluid was given in addition to “standard fluid therapy,” without questioning the basis for conventional therapy as discussed above, and ignoring the fact that “standard fluid therapy” varies very much between institutions and doctors and may represent a genuine fluid overload. In addition, only one trial (108) attempted blinded registration of outcome measures; none of the trials followed the patients after discharge.

In the trial of Mythen and Webb (109), the difference in pre- and intraoperative fluid volume between the groups was 200 to 300 mL (exact numbers not given). With no pre- or postoperative registration of fluid therapy, neither in the recovery room nor at the surgical ward, it is doubtful that such a small volume difference can be responsible for the differences observed.

In the trial of Conway et al. (107), the total intraoperative fluid volume was not significantly different between the groups, and pre- or postoperative fluid therapy was not registered. No significant difference between the groups in complication frequency or in length of hospital stay was found. One patient with severe cardiac co-morbidity belonging to the control group died.

Gan et al. performed the trial with the greatest number of patients (108). No difference in postoperative complication frequency was found, but shorter time in hospital, shorter duration of postoperative nausea, and earlier return to solid food were found in the intervention group. Mortality was not reported. The difference in intraoperative fluid volume between the groups compared was 595 mL (5252 mL vs. 4657 mL). Pre and postoperative fluid therapy was not registered, but this trial was the only one performing a blinded assessment of the outcome measures.

The remaining three trials, concerning patients with fractures of the hip, have recently been analyzed in a Cochrane review (113). One trial was excluded because of methodological problems (110), but two trials were included in the meta-analysis (111,112). In the trial of Sinclair et al. (111), the difference in intraoperative fluid volume between the groups was 475 mL (1000 mL vs. 1475 mL), and neither preoperative nor postoperative fluid therapy was registered. Based on the treatment, “standard therapy,” optimization of SV guided by CVP, or esophageal Doppler technique, Venn et al. (112) have randomized 90 patients into three groups. Administered intraoperative fluid volumes were 1392 mL (standard), 1850 mL (CVP), and 2051 mL (Doppler). Although the preoperative waiting time for surgery was similar between the groups (two days), the preoperative intravenous fluid administration was not similar. The total volumes administered were 3392, 3350, and 3076 mL, respectively, if the pre- and intraoperative intravenous volumes are summarized. Both trials found that the fluid optimization regimens shortened hospital stay. No difference in morbidity was reported.

Table 1 Trials of "Goal-Directed Fluid Therapy" with Extra HES to Maximal Stroke Volume

Author	Surgery	No. of patients	Primary intervention	Volume difference between groups compared	Results
Sinclair S. (1997)	Orthopedic surgery	40 in 2 groups	Optimizing SV with extra HES evaluated by esophageal Doppler vs. "standard treatment"	475 mL Total 1475 mL vs. 1000 mL Unknown postoperative fluid therapy	Time in hospital significantly shorter in the intervention group No significant difference for complications Mortality: 1 in each group
Mythen M.G. (1999)	Thoracic surgery	60 in 2 groups	Optimizing SV with extra HES evaluated by esophageal Doppler vs. "standard treatment"	200–300 mL Total ~2100 mL vs. 1800 mL Unknown postoperative fluid therapy	More patients with complications in the control group (6 vs. 0) Mortality: 1 in the control group
Venn R. (2002)	Orthopedic surgery	90 in 3 groups	Optimizing SV with extra HES evaluated by esophageal Doppler vs. CVP vs. "standard treatment"	600 mL Total 2300 mL vs. 2300 mL vs. 1700 mL, including fluid given in the recovery room Unknown fluid therapy on the surgical ward	Time in hospital significantly shorter in the intervention group No significant difference in complications Mortality: 9 in the intervention groups vs. 2 in the control group
Conway D.H. (2002)	Abdominal surgery	57 in 2 groups	Optimizing SV with extra HES evaluated by esophageal Doppler vs. "standard treatment"	658 mL Total 4522 mL vs. 3864 mL Unknown postoperative fluid therapy	No significant differences for complications or time in hospital
Gan T.J. (2002)	Mixed surgery	100 in 2 groups	Optimizing SV with extra HES evaluated by esophageal Doppler vs. "standard treatment"	595 mL Total 5252 mL vs. 4657 mL Unknown postoperative fluid therapy	Mortality: 1 in the control group Time in hospital significantly shorter in the intervention group No significant difference for complications Mortality not reported

Abbreviations: HES, hydroxy ethyl starch; SV, stroke volume.

One patient in each group died in the trial of Sinclair et al. (111), whereas two patients in the control group, six in the CVP group, and three in the esophageal Doppler group died in the trial of Venn et al. (112).

The conclusion of the Cochrane review was that the number of trials and included patients were few and that fluid optimization regimens tended to increase the administered fluid volume and may have a benefit in shortening hospital stay, but also a possible adverse effect of increased mortality—control versus intervention: 3/50 versus 10/80 (Peto's odds ratio 1.44, 95% CI: 0.45–4.65).

The total intravenous fluid volumes in the trial of Venn et al. (112) illustrate the need for registration of fluid volumes beyond the intraoperative period. Moreover, the difference in fluid volume between the groups compared was very small, adding to the difficulties in interpretation of the results of these trials.

Eleven trials were found testing "standard fluid therapy" versus "extra fluid, inotropic, and other-drug therapy" (114–124), thus not investigating the isolated effect of intravenous fluid therapy. Even though fluid therapy was the first treatment of choice, the administered fluid volume is described in only four trials (114,116,117,123).

Wilson et al. (123) randomized 138 high-risk patients undergoing major surgery into three groups, two "optimization groups" and one group receiving "standard therapy." The intervention groups received preoperative fluid in addition to either Dopexamine or adrenaline. Information on preoperative fluid therapy was given for the two intervention groups, but not for the control group. The control group received the largest intraoperative fluid volume. Only the Dopexamine group had a reduction in postoperative morbidity, whereas the mortality was significantly reduced in both the intervention groups. The importance of the fluid therapy for the results of this trial is difficult to interpret, mainly because information on the preoperative fluid treatment is missing for the control group and all patients in the intervention groups received pressor substances.

Boyd et al. (117) randomized 107 patients undergoing major surgery, but the difference in intravenous volume between the groups was only 183 mL, and the trial will not be discussed further.

Bender et al. (114) investigated the effect of a pre-, intra-, and 16-hour postoperative optimization program with the administration of fluid, dopamine, nitroprusside, and/or diuretics to obtain physiological goals that are measured with a catheter in the PAC. The control group received a PAC only if needed by clinical judgment. One-hundred-and-four patients undergoing vascular surgery were randomized. The volume difference between the two groups was 1348 mL (intervention vs. control: 5137 mL vs. 3789 mL). An intra- or postoperative complication was developed in 13 patients in the intervention group versus seven patients in the control group, but the result was nonsignificant. One patient in each group died.

Bonazzi et al. (116) randomized 100 male patients undergoing major vascular surgery, all < 75 years and free of cardiac diseases, into two groups. On the day before operation, the patients in the treatment group were transferred to the ICU, and fluid (crystalloid), Dobutamin, and Nitroglycerin were administered to obtain physiological goals measured with a PAC. Patients in the treatment group but not in the control group stayed in the ICU for the first two postoperative days. The fluid difference between the groups, on the day of operation, was a median of 1250 mL (intervention group 4500 mL vs. control group 3250 mL). The differences between the groups on the first and second postoperative days were 580 and 170 mL. No significant differences in clinical outcome or hospital stay were found.

In general, the importance of the administered fluid for the results of these trials is difficult to interpret, because it is impossible to determine the influence of the fluid therapy from the influence of the additional therapy. Moreover, only one trial registered the postoperative fluid administration (117), blinding of outcome measures was not attempted, and the patients were not followed after discharge in any of the trials.

The most exhaustive trial of the effect of goal-directed therapy using a PAC has recently been published (120). One thousand nine hundred ninety-nine patients undergoing various types of urgent or elective surgery were randomized to either a goal-directed optimization program using a PAC or "standard therapy." Even though "fluid optimization" was the first treatment of choice for optimizing oxygen delivery and cardiac index in the PAC group, no information on administered fluid volume were given. No beneficial effects of the use of a

PAC, however, were found on postoperative mortality, morbidity, or time in hospital; on the contrary, the use of a PAC had significant adverse effects.

TRIALS ON RESTRICTED INTRAVENOUS FLUID THERAPY

As seen from the above discussion, current standard fluid therapy is not at all evidence based.

The evidence supporting the existence of the nonanatomical third space loss is not convincing; no effect of the preloading of the epidurals has been shown; giving fluid to maximal SV has regrettably, not convincingly, improved the clinical outcome.

The postoperative weight gain of 3 to 7 kg in patients undergoing major elective surgery therefore seems to represent a genuine fluid overload.

As already mentioned, fluid overload has been associated with increased postoperative morbidity and mortality (6,11–13,15–21,125). For a thorough review on the physiological (adverse) effects of fluid overload refer the work of Holte et al. (126).

We therefore performed a clinical randomized assessor blinded multicenter trial, designed to answer the following two questions (127):

1. Is current fluid therapy beneficial for tissue healing?
2. Is current fluid therapy causing cardiopulmonary complications?

A total of 172 ASA group I to III patients planned for colorectal resection were randomized to either a restricted (R) or a standard (S) intra- and postoperative intravenous fluid regimen.

The idea of the R-regimen was that measured fluid loss should be replaced with a fluid of (nearly) equal quality and quantity, but a postoperative weight gain should be avoided. In fact this trial may be interpreted as a “goal directed” trial, where the goal, however, is not to achieve maximal SV, but to unchanged body weight.

During surgery this was achieved by omission of fluid preloading of the epidurals, omission of fluids for the nonanatomical third space loss, replacement of fasting deficit with 5% glucose, and replacement of lost blood with HES 6% but with allowance for maximum 500 mL extra. Postoperatively the same principles were followed, and a bodyweight increase of more than 1 kg was (in the absence of pathological fluid accumulations) treated with furosemide.

On the day of operation, the resulting fluid administered to the groups was (median) 2740 mL (range: 1100–8050) in the R-group versus 5388 mL (range: 2700–11083) in the S-group, $p < 0.0005$, and on the first postoperative day was R versus S—500 mL (range 0–5000) versus 1500 mL (range 0–6000), $p = 0.003$. No significant differences in administered volume were observed on postoperative day 2 to 6. The patients were followed-up for 30 days.

The restricted intravenous fluid regimen significantly reduced the incidence of postoperative complications (R vs. S—intention-to-treat analysis: 28 (33%) vs. 44 (51%), $p = 0.013$; per-protocol analysis: 21 (30%) vs. 40 (56%), $p = 0.003$). The incidence of both tissue healing complications and cardiopulmonary complications was significantly reduced (R vs. S—tissue healing complications: 11 (16%) vs. 22 (31%); $p < 0.040$; cardiopulmonary complications: 5 (7%) vs. 17 (24%), $p = 0.007$).

A dose–response relation between postoperative complication frequency and administered fluid volume as well as bodyweight increase, on the day of operation, was found ($p < 0.001$).

Four included patients died, all of cardiopulmonary complications and belonging to the standard group [absolute risk reduction 5.6% (95% CI: 0.3–10.9%)].

No adverse effects of the restricted fluid regimen were found, but patients in the S-group showed potential deleterious physiological changes in the form of lower arterial pH, lower concentration of bicarbonate, and negative base excess in the immediate postoperative period compared to the patients in the R-group ($p < 0.005$) (37). Furthermore, the S-regimen caused haemodilution with lower concentrations of serum albumin and total protein.

Intra- and postoperative arterial BPs were similar between the groups, as were the administration of pressor substances (37).

Higher concentrations of serum creatinine but not urea were found in the R-group on the day of operation, but no significant differences between the groups were found on the

following days. One case of renal failure was observed in the trial. The patient allocated to the S-group developed pneumonia, sepsis, and multiorgan failure, and died.

In conclusion, the restricted fluid regimen reduced postoperative complications and improved physiology in patients undergoing elective colorectal resection.

These results are in agreement with the results of Lobo et al. (7) who randomized 20 patients undergoing colonic resection to either a restricted postoperative fluid regimen or a standard regimen to investigate the effects on gastric emptying time and complications. The restricted group received no more than 2 L of intravenous fluid and 77 mmol of sodium, daily. The control group received at least 3 L of water and 154 mmol of sodium, daily. Even though the intervention did not include the intraoperative fluid therapy, the administered fluid volume between the groups on the day of operation was approximately 3000 mL versus 5700 mL, very much resembling the volume differences of our trial. The patients in the restricted group had significantly shorter solid- and liquid-phase gastric emptying times on the fourth postoperative day and a significant reduction in postoperative complications compared to the patients in the standard group (R vs. S: 1 vs. 7, $p < 0.05$). Included as complications were peripheral edema, hyponatremia, and hypokalemia. However, two patients in the standard group had respiratory infection and one had wound infection with no such complications registered in the restricted group, thus supporting the findings of our trial.

The results of both the above trials have recently been confirmed by Nisanevich et al. (128). One hundred and fifty six ASA group I to III patients undergoing various major gastrointestinal procedures were randomized to either a restricted intravenous fluid protocol (R) of 4 mL lactated Ringers (LR) solution/kg/hr or a liberal intravenous fluid protocol (L) of 12 mL LR/kg/hr. In both groups, blood loss was replaced by LR solution by 1:3, and in case of low diuresis, low BP, or increased heart rate, a fluid bolus was given. The intraoperative volume difference for L versus R was 3871 mL (SD 1170) versus 1408 mL (SD 946), and the administered fluid volume on the rest of the day of operation was L versus R: 2012 mL (SD 475) versus 2170 mL (SD 476). Thus the total volume difference between the groups on the day of surgery was very similar to the volume differences of the two above trials. No difference in fluid volume between the groups was observed on postoperative day 1 and 2.

Significantly, fewer patients in the restricted group had a postoperative complication R versus L: 13 versus 23, $p < 0.05$. Patients in the restricted group had significantly shorter time to first flatus and stool ($p < 0.001$), and hospital stay was significantly reduced. The trial has the weakness that the patients were not followed after discharge, with the consequence that late complications may be overlooked.

In conclusion, in major gastrointestinal surgery restricted intravenous fluid therapy has convincingly improved clinical outcome.

TRIALS OF OUTPATIENT SURGERY

Nine randomized trials testing effects of different intravenous fluid volumes on outcome of outpatient surgery were found (Table 2) (28,29,129–135). The patients included underwent dental extraction, diagnostic gynecologic laparoscopy, or minor orthopedic-, gynecologic-, or abdominal procedures. The outcome assessed was not complications or death but thirst, dizziness, drowsiness, and well-being and for some of the trials nausea, vomiting, and overnight stay in hospital.

Seven of the trials found intravenous fluid administration to cause some degree of improvement in self-reported drowsiness and dizziness (28,129–134), and three of the trials reported improvement of postoperative nausea (130,132,133), whereas one did not find any significant differences between the groups (29). The intravenous volume administered, however, equals very well the deficit from fasting, and may even be small if the fasting lasted more than 12 to 24 hours. Thus the results confirm that fluid losses should be replaced, but does not assess the problem of fluid administration in excess of external losses in major surgery.

The last trial examined the effect of 15 mL/kg (a mean volume of 1 L) versus 40 mL/kg (mean of 2.9 L) LR solution in 48 patients undergoing laparoscopic cholecystectomy (135). The trial found that 2.9 L of fluid improved thirst, dizziness, drowsiness, nausea, fatigue, well-being, pulmonary function, and exercise capacity when assessed two and four hours postoperatively, and thereby reduced overnight stay in hospital. This trial is, however, biased by the fact that significantly more patients in the low volume group received Sufentanil,

Table 2 Clinical Randomized Trials of Outpatient Surgery

Author	Surgery	No. of patients	Blinding	Duration of surgery (min)	Intervention	Duration of fast	Post-op. oral fluid intake	Outcome measures	Results
Keane P.W. (1986)	Mixed outpatient surgery	212 2 groups	No	18	1 L Hartman's solution and 1 L DW vs. no fluid	?	?	Dizziness, thirst, drowsiness, nausea, well-being	Fluid reduces thirst, drowsiness, and increases well-being. No effect on nausea
Spencer E.M. (1988)	Minor gynecologic surgery	100 2 groups	No	8	1 L CSL vs. no fluid	?	?	As above	Fluid reduces dizziness and nausea
Cook R. (1990)	Gynecologic laparoscopy	75 3 groups	Yes	20	CSL 20 mL/kg vs. CSL + DW 20 mL/kg vs. no fluid	11–16 hr	?	As above + overnight stay	Fluid reduces dizziness and drowsiness. Hospital stay reduced in Dextrose group
Yogendran S. (1995)	Mixed outpatient surgery	200 2 groups	Yes	28	Plasmolyte 20 mL/kg (total mean 1215 mL) vs. plasmolyte 2 mL/kg (total mean 164 mL)	8–13 hr	?	As above	Fluid reduces thirst, dizziness, and drowsiness. No effect on nausea
Elkahim M. (1998)	Day case termination of pregnancy	100 2 groups	Yes	12	1 L CSL vs. no fluid	9.66 hr	1.5–2 hr	As above	Fluid reduces nausea and vomiting
Bennet J. (1999)	Dent-alveolar surgery	90 2 groups	Yes	?	NS 16 mL/kg vs. NS 1 mL/kg	8–13 hr	?	As above	Fluid reduces dizziness and drowsiness. No effect on nausea
McCaul C. (2003)	Gynecologic laparoscopy	108 3 groups	Yes	22	CSL 1.5 mL/kg/ fasting hr (total mean 1115 mL) vs. CSL + Dextrose 1.5 mL/kg/ fasting hr (total mean 1148 mL) vs. no intravenous fluid	11.5 hr	?	As above	No significant differences between the groups
Magner (2004)	Gynecologic laparoscopy	141 2 groups	Yes	20	CSL 30 mL/kg vs. CSL 10 mL/kg	13 hr	?	As above	Fluid reduces nausea and vomiting. No effect on dizziness or thirst
Holte K. (2004)	Laparoscopic cholecystectomy	48 2 groups	Yes	68	LR 15 mL/kg (total mean 998 mL) vs. 40 mL/kg (total mean 2928 mL)	2 hr	Mean 600 mL	As above + overnight stay	Fluid reduces thirst, nausea, dizziness, and drowsiness; improves well-being, pulmonary function, and shortens hospital stay

Abbreviations: DW, dextrose in water 5%; CSL, compound sodium lactose (Na: 131, K: 5, Ca: 2, Cl: 111, lactate: 29 mmol/L); NS, normal saline 0.9%; LR, lactated Ringer's solution.

Morphine, or Pethidine in significantly larger doses at the recovery room than did the patients in the high volume group. As all the above outcome measures are well-known Morphine side effects, it is a major weakness not to control the postoperative Morphine administration, making the result most difficult to interpret.

RECOMMENDATION: RESTRICTED INTRAVENOUS FLUID THERAPY IN MAJOR ELECTIVE SURGERY

It may be argued that the number of clinical randomized trials and included patients for examining restricted intravenous fluid therapy are too few to alter current practice. One must, however, remember that current practice varies very much between institutions and individual doctors. More over "standard fluid therapy" has never been proven beneficial in randomized trials, but is based on physiological considerations that most probably are false (i.e., the nonanatomical third space and preloading of the neuroaxial blockade).

The overall principle of restricted intravenous fluid therapy is that fluid loss should be replaced quantitatively and qualitatively, but fluid overload should be avoided.

The volumes given in the following are calculated to fit a 70 kg patient that is normovolemic and without electrolyte disturbances. The volumes need adjustment if the bodyweight deviates from this.

Deficit from fasting: Is ideally replaced on the surgical ward. Ask the patient when and how much he has been drinking and replace the deficit with 80 mL fluid pr. fasting hour.

Preloading of neuroaxial blockade: Is not performed. If an ongoing infusion is wanted during induction of anesthesia, 500 mL of a colloid (e.g., HES) may be given. The volume should, however, be regarded as an early replacement of expected blood loss (see blood loss) and calculated as such.

Insensible perspiration and the evaporation from the surgical wound: Has a maximum of 35 mL/hr (insensible perspiration) + 32 mL/hr (evaporation with exteriorized viscera), and is usually fully replaced by the saline and water used for the dissolving of antibiotics and other medication given during surgery. This loss needs consideration only in prolonged surgery (more than five hours).

Pathological fluid accumulations (or anatomical third space losses): The fluid accumulation in traumatized tissue is very small and needs usually no consideration in elective surgery. Loss of ascites, pleural exudation, or other fluid accumulations is replaced during surgery only if haemodynamics is altered. Otherwise, the volume is noted on the fluid chart and replaced if the pathological fluid is regenerated postoperatively.

Blood loss and exudation from the surgical wound: Is replaced volume for volume with a colloid [for example, HES (Voluven[®])], with allowance for a maximum of 500 mL extra (Table 3). Transfusions with erythrocytes must be individually adjusted to a target blood hemoglobin of > 4.5 mmol/L in young healthy adults and up to 6.0 mmol/L in elderly patients with ischemic heart disease.

Table 3 Replacement of Lost Blood

Blood loss (% blood volume)	Replacement with HES (Voluven [®]) (mL)	Erythrocyte portions	FFP
Up to 1000 mL (20%)	1000–1500	-	-
Up to 1500 mL (30%)	1500–1750	-	-
Up to 2000 mL (40%)	1750–2000	1 (~300 mL)	-
Up to 2500 mL (50%)	2000–2250	2 (~600 mL)	-
Up to 3000 mL (60%)	2250–2500	3 (~900 mL)	-
Up to 3500 mL (70%)	2500	4 (~1200 mL)	1 (~250 mL)
Up to 4000 mL (80%)	2500	5 (~1500 mL)	2 (~500 mL)
Up to 4500 mL (90%)	2500	6 (~1800 mL)	2 (~500 mL)
Up to 5000 mL (100%)	2500	7 (~2100 mL)	3 (~750 mL)

Note: Loss >100% of blood volume (~5000 mL) is replaced with equivalent portions of erythrocytes alternating with FFP.

Number of thrombocytes <10⁹ U/L: concentrated thrombocytes is given.

Postoperative body weight ideally equals preoperative body weight, and should not increase more than 1 kg.

If administration of HES (Voluven) reaches the maximum dose (50 mL/kg/day), albumin 5% is given following the same principles or LR-solution or NaCl 0, 9% in the ratio 2 mL LR/NaCl per 1 mL blood loss.

Abbreviations: FFP, fresh frozen plasma; HES, hydroxy ethyl starch; LR, lactated Ringer's.

Urinary output: Is not replaced. Small diuresis is acceptable as long as the patient is not hypovolemic.

The postoperative bodyweight ideally equals the preoperative bodyweight, and should at no time increase more than 1 kg. If a large tissue preparation has been surgically removed, a corresponding postoperative weight loss should be expected.

Fluid Therapy the Rest of the Day of Surgery

It is ensured that the total administration of fluid and blood is in accordance with the measured losses and desired hemoglobin. The overall rule is continued: loss should be replaced but fluid overload avoided.

Basal requirements: Administration of 1000 mL glucose-containing fluid is started, e.g., Na-K-glucose. The patient is encouraged to drink as soon as swallowing is safe. Low plasma potassium is corrected.

Diuresis should be 0.5 to 0.1 ml/kg/hr.

Fluid loss through drain tubes is replaced as a blood loss by continuation of the Table 3.

Gastric and intestinal loss is replaced with saline (or LR), and large gastric loss with potassium containing fluids as well.

Nutrition is commenced approximately four hours postoperatively. The patient is encouraged to drink protein rich beverages or if a naso-duodenal feeding tube was placed during surgery, then enteral feeding is started (136).

If all losses are replaced during surgery and the surgical hemostasis is sufficient, the total nutrition and fluid volume (orally and intravenously) should approximate 100 mL pr. postoperative hour or 2000 to 3000 mL/day.

Fluid Therapy on the Surgical Ward

Oral intake is preferred but if inadequate (fluid intake < 1500 mL, individually adjusted), oral intake is supplemented with intravenous fluids.

Nutrition is continued—the patients should be fed. The total nutrition and fluid volume (orally and intravenously) should approximate 2000 to 3000 mL/day.

Bodyweight measurements are at present the most reliable tool for the estimation of fluid balance in surgical patients and should consequently guide the *quantity* of perioperative fluid administration. Registration of fluid losses should guide the *quality* of fluid replacements.

Furosemide should in uncomplicated cases treat a postoperative weight increase of more than 1 kg. However, clinical judgment is indispensable: bodyweight changes do not recognize internal loss of vascular volume. Careful examination of patients with hypotension or low postoperative diuresis should be performed and the cause should be treated. If the cause is loss of volume, intravenous fluids should be supplemented; if vasodilatation (f. ex. due to large doses of epidural analgesia or habitual anti-hypertensive medication), the treatment is not fluid but is the dose adjustment of the provoking factor or vasoconstricting agents as e.g., Ephedrine. If the cause is development of a complication, action should be taken to treat the complication, etc.

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33 Outcome Studies

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INTRODUCTION

The results of fluid therapy can be evaluated in many ways. The most common one is to study how much blood volume has become expanded or, otherwise, how the fluid improves a compromised cardiovascular status. It is less common to report an effect on the result of the entire surgical treatment (outcome). One reason for the relatively few such studies made is that the success of surgical treatment is multifactorial. To overcome the other factors, a large number of patients need to be included. Nevertheless, such studies have been conducted. They have often been in the form of a meta-analysis, which means that a reviewer has scanned the literature and put together results from different studies that meet certain predetermined criteria. The purpose of doing so is to find results that have not been apparent in the separate studies due to their small size.

A few studies that compare fluid therapy in a single study have appeared in the first years of the new millennium. They suggest that the effect of fluid therapy on clinical outcome is quite substantial. To link a predetermined fluid regimen with outcome in a prospective study makes strong evidence. There is every reason to believe that such studies will be much more common in the years to come.

ALBUMIN

For decades, intravenous infusion of albumin in an iso-oncotic 5% concentration or a hyperoncotic 20% solution has been a popular colloid therapy. In Europe, however, the use started to decline in the 1980s, because the cost of the albumin therapy is much higher than for synthetic colloids. Furthermore, no benefit of albumin over the synthetic colloids could be demonstrated (1,2). In 1998, the Cochrane Collaboration in the United Kingdom published a meta-analysis of 1419 patients from 30 studies in which albumin was used. The results were surprising, because the albumin treatment seemed to increase mortality. The relative risk of death was 1.46 when albumin was given to treat hypovolemia, 1.69 if the indication was hypoalbuminemia, and 2.40 when albumin was given for burns (3,4).

A lively debate began in the British Medical Journal during the fall of 1998. Criticism was focused on the fact that no alternative to albumin was given. In the study, albumin could be compared to crystalloid, some other colloid, or no therapy at all. The quality of the studies included in the meta-analysis was also quite variable. Most of them used a predetermined amount of albumin to be infused, and these volumes were occasionally quite large, whereas today's anesthesiologist normally titrates the dose of albumin against the hemodynamic response, at least if the albumin is given to treat hypovolemia. Thus, the included studies did not necessarily reflect the modern practice of providing colloid fluid in the late 1990s. However, at the same time the debate went on, the physician's practice rapidly changed. In the United Kingdom, the use of albumin went down by 40% during the months following publication of the review (5).

Another review of the same topic was published three years later (6). This systematic review of the literature, which was sponsored by the albumin industry, comprised 3504 patients from 55 studies, which was many more than in the Cochrane Study. There were few requirements for inclusion, the principal one being that treatment should be randomized

between albumin and crystalloid fluid. The results showed a general tendency toward increased mortality after albumin infusion, but the difference from crystalloid treatment was not statistically significant (relative risk of death 1.11 with a 95% confidence interval of 0.95–1.28). The risk of death was not statistically increased in any of the subgroups either; the relative risk was 1.12 when albumin was used in surgery and trauma, 1.76 for burns, 1.59 for hypoalbuminemia, 0.93 for ascites, and 1.19 in neonates. However, important differences were disclosed depending on how well the studies had been conducted.

The authors evaluated the four quality aspects of blinding, mortality as end point, crossover, and the number of patients studied. The risk associated with the use of albumin appeared to be lower, the better the study was conducted. For example, the five studies that were blinded sooner demonstrated a reduced mortality from albumin (relative risk 0.73). The 17 studies that used death as the end point did not show any increased mortality (relative risk 1.0). The reason for this was suggested to be that the mortality was not well recorded in the other studies. "Crossover" means that the randomized treatment could be switched if the patient was felt to be in danger. In all cases, this would mean that a patient scheduled for a crystalloid received albumin instead, thereby assigning patients who were close to death to albumin. Such a change of therapy is scientifically unsound if the purpose of the study was to record mortality. However, most of the studies of fluid therapy have usually focused on other issues. Studies that were free from crossover effects did not show any increased mortality from albumin (relative risk 1.04) in contrast to the other studies (relative risk 1.43).

The risk of death associated with albumin appeared to be higher in larger studies, which may be explained by selective publication. This means that papers showing a surprising result, in this case being that albumin is dangerous, are more likely to be published than studies with a neutral result. Selective publication may indeed be a problem in meta-analyses, and illustrates that a study should be judged on the basis of the questions asked rather than on the result delivered.

An unfortunate characteristic of these meta-analyses is that no anesthesiologist seems to have been involved in the projects. This would have prevented mistakes. For example, the Cochrane Study used both the colloid fluid therapy and the crystalloid fluid therapy as control treatments. The later albumin review included both the isotonic fluid therapy and the hypertonic fluid therapy in the control group, although there is evidence that hypertonic fluid affects the immune system and that considerably less fluid is needed to obtain a specific volume effect. The slightly confusing results of the albumin studies illustrate the fact that a meta-analysis must be read with a clear and critical mind. Guidelines have been published, which specified what to look for (7,8).

The meta-analyses on albumin encouraged the conduct of a large, prospective and randomized study in Australia and New Zealand (the Saline vs. Albumin Fluid Evaluation Study) that compared clinical outcome of critical care after treatment with 4% albumin or normal saline (9). The number of randomized patients was 7000, and no difference in outcome was disclosed. In fact, the mortality after 28 days in the groups was almost identical (726 vs. 729). The authors concluded that albumin did not increase the risk of death. This study has been gently criticized because the optimal alternative to 4% albumin would rather be a lactated or an acetated Ringer's solution than normal saline.

CRYSTALLOID VS. COLLOID THERAPY

Two meta-analyses from the late 1990s indicate that volume substitution with colloid fluid is associated with a higher mortality than with crystalloid fluid. Schierhout and Roberts (10), who worked in the Cochrane group that wrote the albumin review, put together results from 37 randomized controlled trials comprising 1622 patients. Many of these studies were the same as the ones included in the albumin review (4). The patients studied were subjected to surgery or had trauma or burns. The overall risk of death in the colloid group was 24% and in the crystalloid group 20%, giving a relative risk of 1.29 for death by treatment with a colloid (95% confidence interval 0.94–1.77).

The other meta-analysis, which was authored by Choi et. al. (11), reviewed 105 studies and found 17 relevant ones comprising 814 patients. There was no overall difference in mortality between colloid and crystalloid, but a lower mortality for crystalloid resuscitation in the subgroup of trauma patients (relative risk 0.39, 95% confidence interval 0.17–0.89).

In an older meta-analysis, Velanovich (12) also concluded that crystalloid fluid is superior in trauma because this choice of fluid was associated with a 12.3% lower mortality than colloids. When nontrauma patients were studied, however, there was a 7.8% difference in favor of "colloid" therapy. The overall result was a 5.7% relative difference in mortality rate in favor of crystalloid therapy. This meta-analysis from 1989 was based on only eight studies, most of which were also included in the reviews from the late 1990s.

MORBIDITY AS THE END POINT

The outcome of fluid therapy beyond what becomes immediately evident during resuscitation can be described in other terms than mortality. Surgical complications include sepsis, renal failure, pulmonary edema, and prolonged hospitalization. One might believe that such complications would be too few in number in routine surgery to make them useful as end points in evaluations of fluid therapy. If morbidity is carefully recorded, however, complications appear to be quite common. Using a nine-point survey, Bennett-Guerrero et al. (13) recorded a 27% complication rate in 438 patients undergoing routine elective surgery. Among the patients with complications, gastrointestinal (51%) and pulmonary (25%) problems were most frequent (Table 1). Important predictors of postoperative morbidity were a large blood loss and acidosis, while hemodynamic variables were relatively less important.

Arieff (14) reported a development of pulmonary edema in 7.6% of 8195 patients who underwent major surgery at two university hospitals in 1993. The mortality in this group was 11.9%, which the author attributed to fluid retention in excess of 67 mL/kg/day. The patients undergoing major surgery received almost 10 L of intravenous fluid during the first 27 hours after surgery. Excessive volume loading with crystalloid fluid is known to cause a transient reduction of the total lung capacity, whereas an increased risk of and postoperative pulmonary edema in response to perioperative fluid administration has primarily been an issue after lung surgery (15).

There are also prospective studies relating the administered fluid volume and the type of fluid to morbidity. Lobo et al. (16) randomized postoperative patients who had undergone elective colonic resection to 3 L of water per day and 154 mmol of sodium per day (conventional group) and 2 L of water and 77 mmol of sodium (restricted group). The restricted group turned out favorably with respect to recovery of gastrointestinal function, complications, and hospital stay. Significant differences were reported despite the fact that each arm of the study comprised only 10 patients.

Brandstrup et al. (17) compared complications following colonic surgery in 172 patients randomized to a restrictive and a "standard" fluid program. The latter comprised replacement of perceived third-space losses and also included preloading before induction of epidural anesthesia, whereas the restricted group was only given replacement for external losses. Patients in the restricted group were also given furosemide as soon as their preoperative weight exceeded more than 1 kg. The results show that the patients in the liberal fluid group had a higher incidence of cardiopulmonary complications. Moreover, there were three

Table 1 A Survey for Evaluation of Postoperative Morbidity^a

Morbidity type	Criteria
Pulmonary	Requiring supplemental oxygen or respiratory support
Infectious	Temperature >38° C or treatment with antibiotics
Renal	Oliguria, rise in serum creatinine >30%, or urinary catheter in place
Gastrointestinal	Unable to tolerate enteral diet for any reason
Cardiovascular	Diagnostic tests or therapy for myocardial ischemia or infarction, arterial hypotension requiring volume loading or pharmacological treatment, cardiac arrhythmias, or cardiogenic pulmonary edema
Neurological	New focal deficit, confusion, or coma
Wound complication	Requirement for surgical exploration or drainage of pus from the operation wound
Hematological	Requirement for transfusion of a blood product
Wound pain	Requirement of parenteral opioids or regional anesthesia

^aBennett-Guerrero et al. used this checklist on days 5, 8, and 15 after an elective moderate-risk surgery.

Source: From Ref. 13.

cases of sepsis in the control group but none in the restricted fluid group. A similar result was later obtained in another study of intraabdominal operations by Nisanevich et al. (18). The patients receiving the restrictive fluid program, 4 ml/kg/hour of lactated Ringer's, had fewer complications, shorter hospital stay, and an earlier passage of flatus than those patients who were allocated to the more liberal program which comprised three times more fluid.

In a French multicenter study of 129 intensive care patients, it was found that a hydroxyethylstarch (HES) infusion was more likely to be followed by acute renal failure than a gelatin infusion (19). The fluid used was HES, with a molecular weight of 200 kDa and a degree of substitution of 0.6. However, this product is not recommended by the European HES manufacturer today. This study and also the report by Lobo (16) point out that statistically significant differences in the incidence of complications, depending on how the fluid therapy is managed, can be obtained by studying a relatively limited number of patients. More studies of this kind are underway.

The relatively high postoperative morbidity after major surgery, between 25% and 50%, captured by thorough evaluation protocols makes it the strongest approach for evaluating perioperative strategies. Hospital stay is a surrogate end point, which reflects morbidity but is much less informative (13,20). Major changes in fluid therapy should be evaluated using a follow-up of morbidity before being implemented in clinical practice. Mortality as measured 30 days after surgery should also be recorded, but figures are usually too low to make a difference.

GOAL-DIRECTED FLUID THERAPY

The outcome of surgery may be related to some monitoring method used to guide the fluid therapy in the individual patient according to certain predetermined goals. Here, we do not deal with the type and volume of infusion fluid used, but rather with their effects on the body.

Maintaining no more than a slightly reduced blood pressure during surgery is probably the most widely used goal-directed fluid therapy today. A sharp drop in arterial pressure indicates that the intravascular volume is low, but the reaction requires that the hypovolemia amounts to at least 1 L in an adult male when awake. The blood flow rates become reduced at a much earlier stage, and the arterial pressure can therefore be regarded only as a rough guide to the volume status (21). The arterial pressure is also affected by other factors, such as direct effects of the anesthesia.

Urinary excretion is another commonly used guide for monitoring fluid administration, which is hampered by the fact that anesthesia and surgery greatly inhibit diuresis (22). When an indwelling bladder catheter has been applied, however, a reduction of urinary flow from one point in time to another during surgery does indicate hypovolemia.

More sophisticated measures have also been used. Mythen and Webb (23,24) optimized cardiac patients by monitoring gut mucosal pH. A reduction of pH is strong evidence of insufficient tissue perfusion, which should act as an alert for an increased rate of administration of infusion fluids. Due to practical problems associated with placing the tonometer correctly, this monitoring method is better suited for intensive care than for the perioperative setting. However, the results corroborate later findings that hypovolemic events and acidosis promote complications and prolong hospitalization.

The central venous pressure and pulmonary artery pressure have been used to optimize the perioperative fluid therapy. Venn et al. (25) used the responses of these pressures to a fluid challenge (200 mL of HES over 10 minutes) to examine whether the cardiovascular system was sufficiently filled in patients about to undergo surgery for acute hip fracture. Only the patients who are slightly hypovolemic will show an increase in cardiac output in response to the volume load, and new loads are provided until cardiac output does not increase any more. Those patients who were optimized according to these principles could be discharged at an earlier stage from the hospital than others who were treated according to the regular routines.

Fluid therapy during surgery can also be directed by cardiac output. Sinclair et al. (26) were able to reduce the hospital stay of patients undergoing surgery for acute hip fracture by guiding the fluid therapy by esophageal Doppler method to maintain an acceptable stroke volume. Gan et al. (27) applied the esophageal Doppler to patients undergoing various types of major elective surgery. An earlier return to normal bowel function and a shorter stay in hospital (five vs. seven days) was recorded for the patients receiving goal-directed fluid therapy.

The major difference between the study group and the control group with respect to the amount of fluid actually infused was that the former received three times as much HES, whereas both groups received approximately 4.4 L of lactated Ringer's solution during the operation. Mythen and Webb (24) also showed that fluid optimization using esophageal Doppler improves perfusion of the gut, as measured by gut tonometry.

An older but similar approach is to optimize oxygen delivery, which has been advocated by Shoemaker's group. Calculating oxygen delivery requires a figure for cardiac output and, in addition, an arterial blood sample for the determination of the blood gases along with a measurement of the hemoglobin concentration. Several studies show that this more invasive and complex way of monitoring fluid therapy has a beneficial effect on patients undergoing high-risk surgery, including even a reduced mortality (28–30).

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34 Adverse Reactions to Infusion Fluids

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INTRODUCTION

Intravenous (IV) infusion of fluid for correction of fluid and plasma volume disturbances in connection with surgical procedures or in the treatment of critically ill patients includes a potential risk of adverse effects. This is true for crystalloid type solutions as well as for the different commonly used artificial/synthetic (hydroxyethyl starches, HES; gelatins, GEL; and dextrans, DEX) or natural (albumin, plasma proteins, and blood plasma) colloids. Adverse effects associated with IV fluid therapy can, according to Table 1, be classified as either mainly local responses or more generalized systemic reactions, which, in severe cases, may even be life threatening.

The present survey of adverse effects of IV fluids will focus on fluids that are rather commonly used for plasma volume support in the treatment of manifest or threatening hypovolemia, for trauma resuscitation, perioperatively in connection with anesthesia and surgery, or in the treatment of critically ill patients in the intensive care unit (ICU). Crystalloid type solutions and commonly used artificial/synthetic colloids (HES, GEL, and DEX) will be discussed, while specific concerns associated with the transfusion of blood, plasma, and plasma protein fractions (including human serum albumin, HSA) will not be considered.

LOCAL ADVERSE EFFECTS

Pain/Thrombophlebitis/Thrombosis

Isotonic crystalloid and colloid solutions are mainly nontoxic and do not adversely affect the vessel wall at the site of infusion unless the fluid is extremely cold or warm, or the osmolality of the fluid is grossly nonphysiological. Glucose solutions with a glucose concentration of more than 10%, i.e., osmolality of more than 600 mOsm/kg H₂O, when infused into a peripheral vein, are considered associated with a potential risk of local inflammatory reactions that may lead to the development of painful thrombophlebitis in the vessel. Solutions with a high osmolality (greater than 600 mOsm/kg H₂O) should therefore preferably be infused via a central venous line so that the local osmolar load will be moderated by the rather high blood flow in the central vein.

Hypertonic saline (HS) (7.5%), used for acute fluid resuscitation in trauma situations or perioperatively in the management of surgical patients, has a high osmolality of about 2400 mOsm/kg H₂O and may consequently induce local inflammatory responses. Therefore, it is not surprising that this type of hyperosmolar fluid has been reported to cause sensations of heat and compression around the arm at the infusion site (1). These sensations seem to last during the ongoing infusion of the fluid and will disappear immediately after the completion of the infusion. Because usually a small volume (about 4 mL/kg BW) of HS is infused, it appears that these local adverse effects of HS fluid therapy are rather mild and seem well tolerated (1).

SYSTEMIC ADVERSE EFFECTS

Temperature- and Osmolality-Associated Sensations

Infusion of cold fluid may sometimes cause shivering in response to the temperature change, whereas fluid at body temperature may cause an unpleasant feeling of “heaviness” in the chest (2). Rather rapid IV infusion of HS [7.5% NaCl + 6% DEX 70, hypertonic saline dextran (HSD)] at a dosage of 4 mL/kg BW within 10 minutes has, in addition to previously mentioned

Table 1 Local and Systemic Adverse Effects Caused by Intravenous Fluids and Colloidal Plasma Volume Expanders

Local	Systemic
Pain	Unspecific sensations
Thrombophlebitis	Hypervolemia/hypertension/hypotension
Thrombosis	Excessive tissue hydration/edema formation
	Hypothermia
	Acid–base balance derangements
	Hemostatic disturbances
	Hypersensitivity/anaphylactoid/anaphylactic reactions
	Tissue deposition/pruritus/interference with renal function
	Interference with typing and cross-matching of red blood cells

local sensations (1), been reported also to cause a sensation of heat starting in the upper part of thorax and spreading upward to the throat, face, and head (2). Slight headache for a few minutes or euphoric feelings may ensue. Such unpleasant transitory sensations of headache and/or heat in the thorax following infusion of HSD seem more pronounced in normovolemic than in hypovolemic individuals (3). Adverse central (cerebral) effects in a subgroup of patients suffering from mental disorders are also indicated in a study by Peskind et al. (4). It was shown that hypertonic sodium solution, containing either chloride or lactate anions, could induce panic in patients with panic disorders but not in normal healthy subjects.

Hypervolemia/Hypertension/Hypotension

Hypervolemia/Hypertension

Colloids

The plasma volume–expanding capacity of colloid-containing IV plasma replacement solutions is dependent on the molecular size and concentration of the osmotically active colloid molecules and the extent to which they remain in the intravascular compartment (5). Colloids with a colloid osmotic pressure (COP) equal to or lower than that of plasma will, even at a rather high infusion rate, result in a mainly isovolemic plasma volume expansion (Table 2). Colloids with a COP higher than that of plasma will in addition mobilize extravascular fluid from the interstitial compartment into the intravascular compartment. Therefore, the initial intravascular plasma volume–expanding capacity of such solutions will exceed the actually infused volume. As shown by Tønnessen et al. (6), the *in vitro* measured COP of commonly used plasma replacement fluids may vary from half that of normal human serum (4% HSA—about 14 mmHg) up to a level about eight times higher (20% HSA—about 195 mmHg). DEX 70 (6%) has a COP more than twice that of serum and thereby it has a potential to increase plasma volume about 1.4 times the infused volume (Table 2). The corresponding plasma volume–expanding capacity of DEX 40 (10%) is about 1.8 (5). COP variations between half and three times that of normal human serum, depending on molecular weight and concentration of colloid, have been observed for HES indicating that 10% HES solutions have the potential to expand plasma volume considerably, whereas the volume effect of 6% HES 200/0.5 is about 1.1. The medium-molecular-weight HES 130/0.4 with a colloid concentration of

Table 2 Approximate COP and Initial Plasma Volume Expanding Capacity of Different Commonly Used Colloids

Colloid	COP (mmHg)	Approximate volume effect
Dextran-70, 6%	58	1.4
Dextran-60, 3%	22	1.0
Dextran-40, 10%	High	1.8–1.9
Gelatins (molecular weight about 35 kd)	Moderate	<1
HES 200/0.5, 6%	34	1.1
HES 200/0.5, 10%	80	1.4
HES 130/0.4, 6%	?	1.0
HSA 4%	14	<1
HSA 20%	195	3–5

Abbreviations: HES, hydroxyethyl starch; HSA, human serum albumin; COP, colloid osmotic pressure.

Source: From Refs. 5 and 6.

6% has a volume effect of about 1.0, while that of GEL solutions (3.5%) is less pronounced and more difficult to assess due to a rapid leakage of the small molecules out of the circulation (5).

Considering the rather high plasma volume-supporting efficacy of several of the clinically routinely used colloids, it is obvious that for the euvolemic or only moderately hypovolemic patient, there is a potential risk of plasma volume overload and increased blood pressure. Therefore, rapid infusion of a colloid with a good plasma volume-supporting capacity may, in the patient with latent or manifest cardiac failure, cause intravascular volume overload resulting in circulatory deterioration. Proper measurement of the hemodynamic and cardiac functional consequences of IV volume load in patients with suspected cardiac dysfunction is consequently always clinically indicated.

Hyperosmolar Solutions

The mobilization of fluid from the intracellular into the extracellular compartment is dependent on the osmotic gradient across the cell membrane. IV administration of concentrated (high osmolality) solutions at a high infusion rate, therefore, includes a potential risk of transiently increased intravascular volume load.

Infusion of a small volume of HS (7.5% NaCl) is considered of value in the early resuscitation of shock and trauma patients, in connection with the perioperative management of surgical patients, and in some specific ICU situations. The high osmolality (about 2400 mOsm/kg H₂O) of HS will induce an efficient mobilization of fluid from extravascular sources into the intravascular compartment. Therefore, plasma volume expansion is achieved with less free-water administration than with isotonic plasma expanders, which explains a good plasma volume expansion despite the small volume principle (usually about 4 mL/kg BW of HS). In spite of the small volume infused, there can be a pronounced hemodynamic response, especially in normovolemic or only slightly hypovolemic patients, resulting in a markedly increased blood pressure and increased heart rate (3). Such a response pattern may be hazardous for a patient with critical cardiovascular disease and could include a risk of myocardial ischemia and cardiac failure. Therefore, it is of importance to have strict blood pressure criteria for prehospital or early intrahospital start of HS therapy for resuscitation of trauma patients. Infusion of HS for indications other than acute volume resuscitation should be carried out with longer infusion times than for emergency trauma resuscitation (1,7).

Similar osmotic fluid mobilization from extravascular sources may be expected at the infusion of other types of hyperosmolar solutions (urea, mannitol, and glucose). Infusion of hyperosmolar glucose solutions may in addition be associated with risks of hyperglycemia and glycosuria, which in cases of pronounced glycosuria may result in fluid losses leading to dehydration.

Hypotension

The patient with latent or manifest cardiac failure may, at too vigorous IV volume load, suffer circulatory deterioration and hypotension (see above). HS resuscitation in hypovolemic conditions, especially at rapid infusion rates, also includes a risk of early detrimental rather than beneficial effects on cardiac performance by induction of cardiac arrhythmias, transient myocardial depression, and a drop in blood pressure (8,9). Kien et al. (10) suggested that the acute hypotension caused by rapid infusion of HS may not have been mediated by cardiac depression but rather by a marked decrease in total peripheral vascular resistance. Studies of the effects of HS on the isolated denervated, ischemic as well as nonischemic heart, however, indicate transient direct myocardial depressant effects of HS infusion (9). Therefore, a risk of initial transient hypotension due to myocardial depression as well as reduced total peripheral resistance must be taken into account in association with HS-based fluid resuscitation, especially in the case of rapid IV infusion of HS.

Excessive Tissue Hydration/Edema Formation

IV infusion of crystalloid solutions for plasma volume support in the hypovolemic patient necessitates infusion of a relatively large volume of fluid, about three to four or even up to five times the estimated intravascular volume deficit, to achieve normovolemia and hemodynamic stability (11). This is explained by the rather rapid redistribution of crystalloid from the intravascular space throughout the whole extracellular fluid compartment. Most (75–80%) of the

infused fluid will consequently, within 20 to 40 minutes, lodge in the interstitial space (11). At the same time, plasma COP will be reduced and a new Starling equilibrium for transcapillary fluid exchange will be established between the intravascular and the interstitial compartments.

Pulmonary edema has been considered a risk factor associated with crystalloid fluid resuscitation. Experimental studies indicate that extravascular fluid will accumulate mainly in tissues with a high compliance such as skin and connective tissue, but at the same time, there is also an increased fluid content in vital organs, e.g., in the lungs and the gastrointestinal tract (12). Therefore, it may be assumed that excessive crystalloid resuscitation could not only include a rather harmless cosmetic problem but also affect vital organ function (11). However, clinical data supporting significant deleterious effects of crystalloid resuscitation on vital organ function are scarce. Several meta-analytic systematic reviews of randomized controlled studies indicate that the choice of crystalloid-based rather than colloid-based fluid resuscitation regimen for critically ill patients may be advantageous and even reduce overall mortality (13–16). Such a beneficial effect of crystalloid resuscitation seems more obvious for trauma patients than for other groups of critically ill patients. Wisner and Sturm (17) have even claimed that the shift to the use of vigorous crystalloid resuscitation in injured patients at their institution has resulted in decreases in both mortality rate and the rate of dialysis-dependent renal failure, i.e., data in support of the hypothesis that crystalloid resuscitation may be beneficial rather than deleterious in trauma care.

There is, however, a more general practical clinical experience indicating that a significant weight gain at the fluid resuscitation is associated with increased need of respirator treatment, impaired wound healing, and prolonged ICU stay (18,19). Especially in elderly patients with reduced functional capacity of vital organs, including the cardiovascular and respiratory systems, such a fluid overload may disturb the recovery process after surgery and trauma. Arieff (20) has retrospectively assessed the possible cause of fatal postoperative pulmonary edema. It was found that patients suffering fatal pulmonary edema had a net fluid retention of at least 67 mL/kg in the initial 24 postoperative hours, i.e., mean net fluid retention of 7.0 ± 4.5 L. Of the 13 patients facing mortality, 10 were generally healthy, whereas only three had serious associated diseases prior to surgery and fluid resuscitation. Autopsy revealed pulmonary edema with no other possible cause of death. It was commented that among 8195 major operations, 7.6% of the patients were found to develop pulmonary edema and the mortality rate of these patients was 11.9%. No predictive warning signs of a fluid overload were found, and the most frequent clinical presentation was cardiorespiratory arrest. Møller et al. (21) have also identified positive fluid balance exceeding 4 L in elective pneumonectomy as a strong risk factor for postoperative pulmonary complications and in-hospital mortality. Late adverse effects on cardiorespiratory function after an initial resuscitation with large quantities of crystalloid, seen as a “third-day” transient circulatory overload, may be explained by a redistribution of tissue edema (5,11).

The problem of extravascular fluid accumulation after crystalloid volume loading seems even more critical for trauma patients suffering head injury (11). Although most of the extravasating crystalloid will distribute within the interstitial space, some will probably also leak into hypoxic or traumatized cells in connection with surgery or trauma, i.e., into cells with a reduced functional capacity to regulate their membrane electrolyte balance and hence their volume (22). Therefore, as pointed out by Lowell et al. (23), fluid overload may not be a benign problem and the morbidity associated with fluid overload may be significant.

In the meta-analysis of Velanovich (13) as well as of Schierhout and Roberts (14) it was found that for surgical nontrauma patients, there was a difference in mortality in favor of colloid treatment. The effects of intraoperative fluid administration and COP on the formation of intestinal edema during gastrointestinal surgery have been studied by Prien et al. (24). They found that the formation of intestinal edema could be prevented during lengthy gastrointestinal surgery by avoiding COP decreases. In a recent study, Lang et al. (25) reported perioperative fluid resuscitation with lactated Ringer's solution in major abdominal surgery caused a reduction of tissue oxygen tension in the deltoid muscle of about 23%, whereas 6% HES (130 kDa/0.4) improved skeletal muscle oxygenation by up to 59% from the baseline level. As pointed out by the authors, fluid administration should not only stabilize macrohemodynamics but also have beneficial effects on microcirculation and tissue oxygenation. Similar advantages of colloid administration on tissue (gastrointestinal) perfusion, clinical outcome, and costs in connection with cardiac surgery have been reported by Mythen and Webb (26).

Hypothermia

The importance of warming IV administered fluids, not only of cold fluids such as blood and blood products but also of all types of fluids in case of massive volume therapy, has been recognized for many years. The deleterious effects caused by infusion of cold fluids and the development of hypothermia are risk of cardiac arrhythmias, impaired tissue perfusion, metabolic disturbances, and coagulopathy (27,28). Many of the coagulation reactions occur insufficiently at a temperature below 37°C, and platelet function is impaired. Hypothermia will furthermore reduce the hepatic synthesis of coagulation factors. Therefore, in cases of hypothermia induced by infusion of cold fluids in connection with trauma and surgery, there is an obvious risk of coagulopathy due to the temperature effect in addition to effects resultant from the direct dilution of coagulation factors.

The risk of bleeding complications and excessive blood loss may be attenuated by proper warming of the infusion fluids. The technical requirements of equipment for optimal warming during fluid replacement have been well characterized, but although the optimal infusate temperature should be close to 37°C, in massive transfusions it may still be difficult to reach this optimal temperature level even with modern fluid warmers. It should furthermore be kept in mind that in connection with trauma and major surgical procedures, e.g., open prolonged laparotomies, there is an additional risk of hypothermia due to heat losses from the surgical site. At the same time, the heat production of the anesthetized, muscle-relaxed patient is reduced. Therefore, in addition to warming of cold blood products and fluids at room temperature, it is of importance also to prevent heat losses and, whenever indicated, to supply external heating to prevent hypothermia and hypothermia-associated adverse events.

The temperature of the infused fluid has been reported to affect the overall distribution of the fluid between the intra- and extravascular spaces and, furthermore, to influence transcapillary filtration rate as well as atrial natriuretic factor production and diuresis (2). In healthy volunteers, infusion of cold (18°C) Ringer's acetate has been shown to increase blood pressure in response to the volume load (2). Furthermore, increased atrial natriuretic factor production was found to enhance urine output. Heart rate reduction was also observed, which could be caused by the decrease in temperature of the blood returning to the heart. Infusion of warm (36°C) Ringer's acetate, on the other hand, was shown not to influence blood pressure, but instead to induce peripheral vasodilation, increased skin temperature, and capillary leakage (2). The increased capillary filtration of fluid into the interstitial space was considered to reduce interstitial COP and promote edema formation. The clinical relevance of these changes observed in healthy volunteers for the response pattern of critically ill, hypovolemic patients is not known. The general clinical concept to be favored, however, is that IV administered fluids should be warmed, especially if massive volume therapy is needed, unless body temperature of the fluid recipient is increased in response to infectious complications or septic states.

Effects on Acid–Base Balance

Physiological Saline

Most crystalloid solutions are acidotic and have a high chloride content. Therefore, infusion of such fluids (e.g., physiological, 0.9% NaCl) may cause hyperchloremic acidosis and thereby worsen any prevailing acidosis due to tissue hypoperfusion prior to the fluid administration (29). In shock resuscitation, a hyperchloremic response associated with sodium chloride infusion has been reported in humans, but the acidotic response was found to be rather transient with minor impact on acid–base balance (30). Prolonged surgery (four hours or more) has been shown to result in increased chloride levels, and a highly significant correlation was reported by Waters et al. (31) between the volume of normal saline administered, the chloride change, and the change in base excess. Considering that dilutional acidosis, i.e., volume expansion leading to diluted plasma HCO_3^- and renal HCO_3^- wasting, usually is thought to explain some of the acid–base change, still no such plasma volume changes were seen in the study. Therefore, it was considered that the increase in the chloride concentration could cause a decrease in the strong ion difference (SID; $[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{lactate}^-]$), which would create an acidosis (31,32). It was recommended that chloride levels should be assessed whenever a metabolic acidosis is seen perioperatively.

Hyperchloremic metabolic acidosis may in addition, as pointed out by Stephens and Mythen (32), induce hemostatic defects and impair urine output. The risk of persistent base

deficit associated with 0.9% saline resuscitation has also been demonstrated in septic children (33). Therefore, it is obvious that saline-based fluid resuscitation can cause acidosis that may be clinically relevant. It should furthermore be remembered that in addition to saline administration, the infusion of several of the available colloids, also containing 0.9% NaCl, will additionally influence the total chloride load.

Balanced Crystalloid Solutions

The use of Ringer's type solutions, having a lower chloride concentration (usually about 110 mmol/L), will prevent the occurrence of metabolic acidosis resulting from hyperchloremia and the concomitant decrease in SID (34). Ringer's solutions have, in addition, a buffering capacity due to their content of either lactate or acetate. In the metabolic breakdown of these substances, bicarbonate will be formed. It was recently shown by Wilkes et al. (35) that by infusion of balanced (lactate containing) crystalloid solutions combined with colloid (HES) instead of saline combined with colloid (HES), it was possible to prevent the development of hyperchloremic metabolic acidosis in elderly surgical patients. Furthermore, the balanced crystalloid–colloid combination also improved gastric mucosal perfusion when compared with saline-based colloid solutions.

Acetate-containing Ringer's solutions seem even more advantageous than lactate-containing ones because the capacity of the body to metabolize lactate is mainly dependent on the functional capacity of the kidneys and the liver. In case of severe hypovolemia or shock, the metabolic capacity of these organs may be severely limited. Acetate, on the other hand, is metabolized by all tissue cells and therefore not dependent of kidney or liver cell function (36).

Hypertonic Saline

In experimental hemorrhagic shock, HS (7.5% NaCl) resuscitation, providing a rather high chloride load in spite of the small volume principle, has also been shown to induce transient mixed acidosis (37). Over time, however, the acid–base status appeared to improve more effectively with the HS/DEX resuscitation than with the isotonic saline resuscitation, indicating that the transient acidotic effect of the chloride load is probably of minor clinical importance.

Hemostatic Disturbances

Hemostatic disturbances that may be caused by all available infusion fluids are given in Table 3. The basic mechanisms involved are dilution of circulating coagulation factors, hypothermia (see above), and specific interactions of fluid components (usually colloid associated) with normal hemostatic mechanisms.

Crystalloids

Crystalloid fluid therapy exerts only minor effects on coagulation and hemostasis (Table 3). The plasma volume expansion achieved with crystalloids is rather small, and balanced physiological Ringer's type of solutions do not exert any specific effects on hemostatic mechanisms. Therefore, crystalloid resuscitation does not significantly affect hemostatic competence unless an extensive volume of fluid is infused. The hemodilution achieved at more extensive plasma volume expansion will lower the concentration of coagulation factors and, in cases of excessive chloride load (infusion of physiological saline), hemostatic defects may be caused by the ensuing hyperchloremic metabolic acidosis (32). Therefore, Ringer's type of fluid with a lower chloride content and buffering capacity (lactate or acetate content) should be preferred to minimize hemostatic effects. As previously considered, negative effects on hemostatic competence may be caused by crystalloids in case of infusion of a large volume of cold fluids (27,28).

Dilution of blood *in vitro* with saline has been shown by Ruttmann et al. (38) to increase whole blood coagulation, as measured by the thrombelastogram (TEG). It was considered that the hemodilution *per se* increased the coagulability of whole blood *in vitro* and that the saline component in addition exerted a marked effect on final clot strength. In additional studies (39,40), it was reported that hemodilution of normal blood seemed to exert a procoagulant effect, possibly by enhancement of thrombin formation. Circulating concentrations of anti-thrombin III were also found to be more depleted than could be explained by hemodilution alone. The hypercoagulable state could be moderated or prevented when the reduction in

Table 3 Influences of Infusion Fluids on Blood Coagulation and Hemostasis

Type of fluid		Effects on hemostatic mechanisms
Crystalloids	Impaired hemostasis	Excessive dilution of coagulation factors Hypothermia (27,28) Hyperchloremic metabolic acidosis following NaCl-infusion (32)
	Enhanced coagulation	In vitro TEG-signs at moderate (up to 20%) blood dilution (38–41)
Colloids	General effects	Dilution of plasma-clotting proteins (42) Hypothermia
	Colloid-specific impairment of hemostatic competence	Dose dependent—dextrans > hydroxyethyl starches > gelatins (42,58)
	Hydroxyethyl starches (high MW > medium or low MW) (42,43, 48–50)	Decrease of factor VIII/von Willebrand complex (more pronounced in patients of O-blood group) (47) Inhibition of platelet function (45) Accelerated fibrin clot formation (42,43)
	Dextrans (a general “antithrombotic” potency) (5,51)	Decrease of factor VIII/von Willebrand complex (42,51,52) Enhanced fibrinolytic activity (42,51,52) Moderation of molecular structure and tensile behavior of fibrin (51,52)
	Gelatins (minor intrinsic effects) (42,58,59)	A von Willebrand–like syndrome (59) Impaired ristocetin-induced platelet aggregation (59)
	Enhanced coagulation	In vitro TEG-signs at moderate blood dilution (57)

Abbreviations: TEG, thrombelastogram; MW, molecular weight.

antithrombin III caused by dilution was prevented by antithrombin III supplementation (40). A similar hypercoagulable in vitro effect of Ringer’s acetate at a concentration of up to 20% vol. has been demonstrated by Niemi and Kuitunen (41). Dilution of blood with Ringer’s in excess of the 20% concentration, however, was found to decrease coagulability. The clinical importance of these in vitro TEG-measured alterations in blood coagulation induced by saline or Ringer’s is not fully understood and therefore disputed.

Colloids

Risk of coagulopathy associated with infusion of larger volumes of the artificial colloids, especially DEX and HES, has been recognized for years, and this fact has often resulted in words of caution for the use of these colloids for patients with disturbed hemostasis. The influences of DEX and HES on coagulation are explained by their pronounced hemodilutional capacities, influencing the concentration of circulating coagulation factors, as well as direct pharmacological interactions of the substances with normal coagulation processes (Table 3).

Hydroxyethyl Starches

Bleeding complications after infusion of HES have repeatedly been reported, as recently reviewed by Treib et al. (42), and therefore, the safety of HES has remained a matter of controversy (43). It is obvious, however, that high-molecular-weight HES (more than 400,000 Da) with a high degree of substitution with hydroxyethyl radicals (more than 0.6) will affect coagulation more than medium- or low-molecular-weight HES (Table 3; 42,44). The effects of HES on coagulation are dose dependent. Infusion of moderate doses produces rather trivial and transient effects on blood clotting, whereas the higher the initial dose, the molecular weight, the C2/C6 hydroxyethyl ratio, and the degree of hydroxyethyl substitution, the more pronounced are the effects on factor VIII or on the von Willebrand complex (42,44).

HES preparations have also been shown to exert inhibiting effects on platelet function by reducing the availability of the functional receptor for fibrinogen on the platelet surface (45).

HES does not, however, seem to affect fibrinogen levels in excess of what can be attributed to hemodilution, whereas the effects on factor VIII exceed such an effect and result in prolonged partial thromboplastin time (42). Mean bleeding time seems prolonged by HES, but in a similar way as that following hemodilution with albumin or saline (46). The major effects of HES on hemostatic function are dilution of plasma-clotting proteins, decrease of factor VIII or von Willebrand complex, inhibition of platelet function, and accelerated fibrin clot formation in the final stage of clotting (42,44). The ABO blood group of the patient may be an additional factor of importance. Huraux et al. (47) have shown that patients of the O blood group are more likely to develop a von Willebrand-like syndrome after HES infusion (HES 200/0.6) than non-O blood group patients. Therefore, it was suggested that the use of HES 200/0.6 should be restricted in patients with O blood group undergoing surgical procedures (47).

The high-molecular-weight HES preparations available in the United States as plasma expanders are more commonly associated with bleeding complications than the more recent medium- or low-molecular-weight European HES preparations (42,44). In recent years, a new medium-molecular-weight HES preparation (HES 130/0.4) with a lower molecular weight and a lower degree of hydroxyethyl substitution (four hydroxyethyl groups/ten units of glucose) has been introduced. This type of HES preparation has been shown to inhibit platelet function and affect blood coagulation to a lesser extent than high-molecular-weight HES (48–50). The safe daily dosage of HES is consequently dependent on the characteristics of the HES preparation chosen.

Dextrans

DEX is not an anticoagulant per se, but it has been shown to exert potent antithrombotic effects by inducing hemodilution, enhancing microvascular blood flow, and modulating the hemostatic system (5,51). Therefore, before the introduction of low-molecular-weight heparin (LMWH), DEX was used rather extensively in some countries not only for plasma volume support but also to achieve safe prophylaxis of perioperative deep venous thrombosis and pulmonary embolism (51). DEX seems to reduce the hemostatic competence more than HES preparations and GEL (Table 3) (44). Combined effects of DEX on the concentration of coagulation factors, red blood cell aggregation, platelet activity, plasma levels of von Willebrand factor (vWF) and associated factor VIII (VIII:c), plasminogen activation, and plasma fibrinogen levels all seem to contribute to the reduced hemostatic competence induced by DEX (44,51,52). The enhanced fibrinolytic activity has been reported also to reduce heparin-mediated platelet aggregation, possibly by blocking of heparin binding to the platelet membrane. The molecular structure and tensile behavior of fibrin are modulated by DEX so that clots formed in the presence of DEX are more fragile, which, together with the enhanced fibrinolytic activity, results in increased lysis of already formed clots (51,52). Because DEX counteracts the hypercoagulable state induced by surgery and other types of trauma, it has been considered the only plasma substitute that may significantly reduce the risk of postoperative pulmonary embolism and adult respiratory distress syndrome (51).

It has sometimes been claimed that the use of DEX could be somewhat limited in clinical practice due to its effects on hemostasis. However, with IV dosages of DEX not exceeding 1.5 g/kg BW/24 hours, the risk of hemorrhagic complications is insignificant in patients with undisturbed hemostasis prior to the infusion. The combination of DEX with LMWH also seems safe because no increased risk of bleeding has been reported when thrombo-prophylactic doses are administered (53). Therefore, the combination of LMWH and DEX in clinical practice could rather be beneficial because the thrombo-prophylactic efficacy is increased without increasing the risk of bleeding complications. Safe use of DEX requires, however, that the maximal recommended dose of 1.5 g/kg BW/24 hours not be exceeded. Within the recommended dose ranges (10–20 mL/kg BW), which permit hemodilution down to the normal operating range (27–33% hematocrit), modern DEX preparations do not significantly interfere with normal hemostasis or normal platelet function. At doses exceeding 1.5 g/kg BW (20 mL/kg BW), however, DEX may increase bleeding by depressing factor VIII and platelet activity. Desmopressin has been suggested to be of potential value in reducing DEX-induced bleeding (54), although the clinical experience in connection with total hip replacement surgery has been reported rather discouraging (55). More recent experimental data also indicate insignificant effects of desmopressin on thrombus formation in synthetic vessel grafts at isovolemic hemodilution with DEX (56).

Gelatin

GEL solutions seem to affect hemostasis, in addition to direct dilutional effects, to a lesser extent than HES and DEX preparations (Table 3; 44). Karoutsos et al. (57) reported on the basis of TEG recordings the presence of hypercoagulability after administration of GEL solution. Other *in vitro* thromboelastograph assessments of hemostatic effects of blood hemodilution with GEL indicate, however, that GEL solutions have less intrinsic effects on blood coagulation than HES or DEX (58), but, as shown by de Jonge et al. (59), a von Willebrand-like syndrome with lengthening of bleeding time, impaired ristocetin-induced platelet aggregation, and decreased levels of plasma vWF may occur due to binding of vWF to GEL. The effects of GEL preparations with a high concentration of Ca^{2+} (Haemaccel) on platelet aggregation may, however, differ somewhat from those of preparations with a lower Ca^{2+} level (60). The clinical experience of volume replacement with GEL in connection with major abdominal surgery (61) and orthopedic surgery (62) is that platelet function usually remains mainly within the normal range and therefore GEL appears to be rather safe concerning hemostasis.

Hypersensitivity/Anaphylactoid/Anaphylactic Reactions

All IV colloids, including HSA, can induce anaphylactoid reactions, but the available incidence numbers vary to a considerable extent between different countries, depending on efficacy of official reporting systems, true local variations in predisposition or endemic antibody titers, and use of prophylactic measures (63–65). Laxenaire et al. (64), in a French prospective multicenter study, reported a rather high overall frequency of reactions of 0.219%, which is much higher than the frequency of 0.033% reported about 15 years earlier by Ring and Messmer (66). The difference in frequencies could be explained by the fact that the latter study (66) used the number of bottles distributed to the hospital pharmacies as a reference basis, whereas Laxenaire et al. (64) referred the number of reactions to the number of patients treated. It has been suggested that a history of drug allergy as well as being a male may influence the relative risk of anaphylactoid reactions to colloid plasma substitutes (64). The severity of anaphylactoid reactions is usually graded according to Table 4 (65,67).

Hydroxyethyl Starches

In the prospective study by Laxenaire et al. (64), a frequency of anaphylactoid reactions to HES of 0.058% was noted, i.e., a frequency lower than that noted for DEX (0.273%) and GEL (0.345%). In spite of reports on allergic reactions to HES (64,68), the mechanism of HES-induced reactivity is not fully understood (Table 5). In 1992, Kraft et al. (69) could not find any evidence for the existence of preformed antibodies against HES in man, but in 1995, one report on the presence of HES-specific antibodies at the time of reaction was published (70). However, a subsequent assessment of antibody titers to HES in more than 1000 patients who had received HES, has shown that the antigenicity is very low (71). Therefore, the etiology of HES reactions is still not fully established, and it should also be remembered that all

Table 4 Severity Grading of Anaphylactoid/Anaphylactic Reactions

Grade I	One or several of the following symptoms: Feeling of heat Skin manifestations (flush, erythema, urticaria, and itching) Nausea Conjunctivitis Lumbar pain
Grade II	Some of Grade-I symptoms and Mild-to-moderate hypotension (SAP 40–60 mmHg) Gastrointestinal disturbances Respiratory distress (mild bronchospasm)
Grade III	Some of Grade-I symptoms and Blood pressure fall (SAP <40–60 mmHg to non-measurable level) Severe bronchospasm
Grade IV	Some of Grade-I symptoms and: cardiac and/or respiratory arrest
Grade V	Lethal reaction

Source: From Refs. 67 and 73.

Table 5 Hypersensitivity, Anaphylactoid/Anaphylactic Reactions Induced by Artificial/Synthetic Colloids

Colloid	Basic pathomechanisms (Refs.)
Hydroxyethyl starches	Mainly unknown (64) Preformed hydroxyethyl starch-specific antibodies? (70) Not verified (69,71) No prophylactic measures
Dextran	Dextran-induced anaphylactoid/anaphylactic reactions Immune complex mediated (IgG-class) (64,67) Prophylaxis by preinjection of dextran-1 (65,67,74)
Gelatins	Histamine mediated (63,75,76) IgE-dependent? (64,77) Prophylaxis by preinjection of H ₁ + H ₂ -receptor blockers (63)

available HES preparations are not the same (72). Therefore, the effects, including the anaphylactoid reactivity, may differ depending on the origin of the polysaccharide, the degree of hydroxyethyl substitution, and other product-specific characteristics. The general concept is, however, that the safety profile of modern HES preparations is rather optimal considering the very low risk for occurrence of anaphylactoid reactions.

Dextrans

The pathomechanisms of DEX-induced anaphylactoid/anaphylactic reactions were described in the early 1980s by Hedin and Richter (67). It was found that the clinical picture could range from mild skin manifestations to circulatory and respiratory deterioration, sometimes with fatal outcome (cf. Table 4). Mild reactions were assumed to be either antibody dependent or unspecific. Patients reacting at the infusion of DEX were found to have rather high titers of preformed, circulating DEX-reactive antibodies of predominately immunoglobulin (Ig) G class (Table 5). In patients with a high DEX-reactive antibody titer, the infusion of DEX results in generation of large immune complexes leading to release of vasoactive mediators and to clinical symptoms. DEX reactions do not seem to involve direct histamine release in man.

It had already been suggested in 1982 (67) that the application of the hapten inhibition principle could be an effective way of preventing adverse DEX-induced reactions in patients with reactive antibodies (Table 5). Such an approach has been used in Sweden since 1982, consisting of preinjection of 20 mL of low-molecular-weight dextran-1 (1000 Da MW) prior to infusion of a DEX plasma volume expander. According to Ljungström et al. (73), this approach has led to a reduction in reports of severe reactions to dextran, from 22/100,000 units of DEX used to only 1.2/100,000 units. A 10-year experience with hapten inhibition was presented in 1993 by Ljungström (65), showing that severe reactions (Grades III–V) after the prophylactic use of hapten inhibition was seen in approximately 1/200,000 patients receiving DEX-1. Mild, not antibody-mediated side effects, were reported in approximately one case per 100,000 doses. The differences in reported frequencies of anaphylactoid reactions to DEX in the French study by Laxenaire et al. (64) as compared to the Swedish experiences reported by Ljungström (65) is probably partly due to the fact that hapten inhibition with DEX-1 (Promit) was not routinely used in France.

Safe clinical use of DEX should always include preinjection of DEX-1 for prevention of DEX-associated hypersensitivity reactions. By applying the hapten inhibition principle to clinical practice, any anti-DEX antibodies present in the recipient will be inactivated because complexes too small to be reactive will be formed between the antibodies and DEX-1. As suggested by Ljungström (65,74), DEX used together with hapten inhibition may constitute the safest plasma substitute in current clinical practice.

Gelatin

Anaphylactic or anaphylactoid reactions to GEL solutions are rather common and it has been known for decades that the dominating mechanism seems to be histamine release (Table 5; 75). Clinically relevant or life-threatening histamine-related cardiorespiratory disturbances have been found to occur in 26% of patients receiving GEL (Haemaccel) as compared to 8% of patients receiving Ringer's solution at anesthesia induction (63). The potential benefits of routine antihistamine prophylaxis with H₁ + H₂ receptor blockers have been discussed (63).

In connection with cardiac surgery, GEL has recently been reported the second most common cause of anaphylactoid reactions prior to bypass and it was suggested that, in case of a severe reaction, rapid institution of cardiopulmonary bypass may be a life-saving measure (76).

Skin tests and in vitro assessment of leukocyte histamine release have been suggested to be of potential value in the diagnosis of patients reactive to GEL, especially because positive skin tests indicate immunological origin, including specific IgE-dependent allergic mechanisms (64,77). Anti-GEL IgE and IgG have been demonstrated in children who experienced systemic immediate-type reactions to varicella vaccine with GEL (78). It may be questioned if such a sensitization to GEL in children with systemic nonimmediate-type reactions to varicella vaccines could predispose them to reactions in case of clinical GEL fluid infusion.

The allergic/anaphylactoid potential of GEL solutions will probably differ considerably between different GEL preparations. GEL is available commercially as succinylated GEL, dialdehyde cross-linked GEL, and di-isocyanate urea-linked GEL. The 3.5% urea cross-linked GEL with high calcium and potassium contents (Haemaccel) has been dominating the world market and seems to be the GEL preparation associated with most anaphylactoid reactions (63,64,75). The clinical experience, according to the Cochrane Database Systematic Review (79) of colloid solutions (for fluid resuscitation based on randomized and quasi-randomized trials comparing colloid solutions in critically ill and surgical patients thought to need volume replacement), however, is that there is no evidence that one colloid solution is clearly more safe than another.

Tissue Deposition/Pruritus/Interference with Organ Function

Tissue Deposition

Isotope studies indicate that both DEX and GEL are fully metabolized to CO₂ and H₂O, whereas HES is not completely degraded or metabolized (51). Therefore, concerns related to tissue deposition and interference with organ function are mainly associated with the use of HES preparations. As pointed out previously, however, all available HES preparations are not the same (72). Therefore, tissue metabolism may differ depending on the origin of the polysaccharide and the degree of hydroxyethyl substitution, as well as other product-specific characteristics (42). Most large HES molecules will eventually be cleaved by serum amylase to residues small enough to permit renal excretion, but each dose of HES inevitably contains a minority of molecules whose degree of substitution is so uniformly high that it sterically hinders amylase cleavage (51). Insufficient metabolic breakdown and tissue deposition is a problem associated mainly with older types of high-molecular-weight variants of HES (450/0.7), whereas medium-molecular-weight HES preparations with a lower degree of substitution (130–200/0.4–0.5) are more rapidly metabolized and eliminated (42).

Modern HES (200/0.5) preparations have been shown to persist in human lymph nodes and muscle biopsies for at least 10 months after a dose of only 1 g/kg BW, and HES residues were still found in human skin macrophages 19 months after HES was administered (80). Therefore, some concern has arisen that HES residues may irreversibly block the reticuloendothelial system (RES), but no concrete evidence of severe immunosuppression has emerged to date.

Effects of GEL on the RES and thereby on immunocompetence have also been suggested. Comparative clinical evidence indicates that one unit of GEL may reduce the opsonizing function of fibronectin, essential for phagocytosis, to half the normal level, whereas DEX does not seem to exert such effects (81).

HES-Associated Pruritus

Tissue deposition of starch molecules is considered to include a potential risk of pruritus, sometimes severe and lasting for weeks, months, or even years (82). In 1982, Parker et al. (83) reported severe pruritus in four healthy males who in connection with leukapheresis had received HES, and who about two weeks later had developed generalized itching, worse in the perineal region and exacerbated by warm water, exercise, scratching, or rubbing with towels. No external visible skin changes could be seen and the itching subsided slowly in three to six months. Since the report by Parker et al. (83), quite a number of case reports and clinical studies, also recent ones (80,84,85), on the prevalence of itching following HES infusion have been published.

It is obvious that a rather large dose of HES is needed to induce pruritus. When a relatively small volume of HES is infused, it seems that the incidence of itching eight weeks after surgery is similar to that seen after infusion of Ringer's solution (86). When, on the other hand, following a rather large total volume of about 5 L or more of 10% HES (200/0.5) given over about 10 days, an incidence of pruritus as high as 54% has been reported with a median duration of 15 weeks (84). Because there is an obvious dose-response relationship, the patient at risk is the one receiving repeated HES infusions for several days, often infused for otological and neurological reasons to achieve hemodilution, improved microvascular blood flow, and enhanced organ perfusion.

It was shown in 1993 by Jurecka et al. (87) that cultured human monocytes and keratinocytes ingest HES. This phenomenon was considered indicative of a possible connection between the storage of HES in dermal cell populations and itching. Light and electron microscopic, immunohistochemical, and immunoelectron microscopic studies of skin biopsies of patients who had received HES and suffered subsequently from itch have revealed deposition of HES in a variety of skin cell populations, including dermal macrophages, endothelial cells of blood and lymph vessels, some perineural cells and endoneural macrophages of larger nerve fascicles, some keratinocytes, and Langerhans cells (87). No morphological signs of histamine release from mast cells, were found, which could explain the fact that treatment with antihistaminic agents has proved ineffective in patients suffering from HES-induced pruritus. In subsequent studies, a dose-dependent uptake of HES in macrophages followed by deposition for prolonged periods of time, for several years, in vacuoles in endothelial and epithelial cells could be demonstrated (88). In patients with itching, there was also a deposition of HES in the Schwann cells of unmyelinated as well as myelinated nerve fibers and in endoneural and perineural cells. A minimal cumulative dosage of 210 g was observed to be associated with the occurrence of pruritus, and the onset of symptoms usually started within three weeks of the last HES administration (88).

Pruritus after high cumulative doses of HES seems closely correlated with the HES deposition in cutaneous nerves (89). The itch is usually generalized and of a burning character, affecting most commonly the trunk and genital areas. Pruritic crises triggered by friction, bathing in warm water, or physical stress and lasting for 5 to 60 minutes have been described (88). Most therapy modalities, including antihistamines, hydroxyzine, paracetamol, psoralen ultraviolet A (PUVA) and topical treatment tar, sulfite, and steroids have been found ineffective, but the symptoms usually seem to subside spontaneously within 6 to 18 months. Some therapeutic response has been reported to topical treatment with polidocanol and capsaicin ointment (88).

Chemical improvement of starch colloids has taken place in recent years, which has affected the metabolic degradation and tissue storage. The newer 130/0.4 HES preparation is, for instance, not accumulated in plasma, even in cases of repeated application, and tissue storage is reduced by approximately 75%. Therefore, it may be assumed that the more efficient metabolic degradation in the body and reduced tissue deposition will influence the safety profile and reduce the high incidence of HES-induced pruritus previously seen after large-dose administration of older types of HES preparations.

Colloids and Organ Function

Renal failure has been reported following infusion of DEX 40 (10%), HES, as well as GEL (51,90–92). Usually, increased risk of renal failure seems associated with dehydrated patients with latent renal failure, who receive repeated high doses of hyperoncotic solutions (51).

Following the infusion of HES, there is initially a rapid amylase-dependent breakdown and urinary excretion of about 40% to 50% of the administered dose within 24 to 48 hours. Renal functional impairment related to trauma may impair the excretion of HES. In such situations, it is possible that the renal load of low-molecular-weight HES fractions may induce renal functional disturbances or aggravate preexisting renal insufficiency. HES as a plasma volume expander in brain-dead kidney donors has been shown to impair the immediate renal function in kidney transplant recipients (93). Renal biopsy specimens have revealed osmotic nephrosis-like lesions in proximal and distal tubules (93). In a subsequent retrospective, multicenter analysis, however, no clear association between HES and impairment of immediate renal function in kidney transplant recipients could be verified (94).

In 2001, on the basis of data from a prospective randomized French study (95), an association between HES (200 kDa; 0.60–0.66 substitution) administration and increased incidence of acute renal failure in septic patients was reported. GEL was used as the alternative colloid in the reference group of septic patients, and in these patients, no corresponding adverse effects on kidney function were noted. The suggested pathophysiological mechanisms are increase in intravascular COP resulting in decreased glomerular filtration rate in combination with increased resorbance from proximal tubulus, decrease in sodium excretion, vasoconstriction of renal vessels, reduction of oxygen supply to renal tissue, and damage of tubular cells. Although HES was found to be an independent risk factor for acute renal failure in patients with severe sepsis in the study by Schortgen et al. (95), the relevance of the study may be questioned. Pretreatment differences in the degree of dehydration, seen as differences in serum creatinine concentration and urinary sodium retention prior to the infusion of HES or GEL, could have influenced the outcome data. Furthermore, in patients without preexisting renal dysfunction, Dehne et al. (96) have shown that HES administration appears to be risk-free with regard to renal function. Even in case of volume replacement in critically ill patients with acute renal failure, GEL and HES solutions with low in vivo molecular weight have been suggested to be the colloids of preference (97). It should be remembered, however, as pointed out by Ragaller et al. (97), that adequate amounts of crystalloid solutions must be administered to patients with acute renal dysfunction to avoid the risk of hyperoncotic renal failure.

The combination of HES and other potentially nephrotoxic substances (e.g., cyclosporin A), especially in cases of impaired liver function, may be an additional cause for renal insufficiency. Peron et al. (98) have reported on HES-induced renal insufficiency after plasma exchange in a patient with polymyositis and liver cirrhosis. Repeated HES infusions have been found by Christidis et al. (99) to worsen preexisting hepatic dysfunction. Liver biopsies taken after HES infusion were found to present diffuse microvacuolization of Kupffer cells, often in association with focal hepatocyte vacuolization. On the basis of these findings, it was concluded that repeated administration of HES could favor severe portal hypertension, liver failure, and sepsis, particularly in the setting of chronic liver disease (99). However, tissue deposition of HES is not only dose dependent and time related (80) but also dependent on the molecular characteristics of the HES infusion fluid administered (42,43,49,50,72). In the study by Christidis et al. (99), HES 200 (0.60–0.66 substitution) was used, which is tissue deposited to a much greater extent than the medium-molecular-weight type of HES with a lower degree of hydroxyethyl substitution, e.g., HES 130/0.4 (42,72). Therefore, it remains to be documented if the more recent HES preparation also will be deposited in tissues to such an extent that kidney and liver function may be adversely affected.

Interference with Typing and Crossmatching of Red Blood Cells

It was suggested in the 1950s that DEX may interfere with typing and crossmatching of red blood cells (100,101). Induction of aggregation and rouleaux formation resulting in pseudoagglutination was considered to cause the problems. The effects on blood typing were found to depend on the molecular weight and the chemical characteristics of DEX. Adverse effects associated with DEX seem to be specific for high-molecular-weight DEX, i.e., DEX with a molecular weight exceeding 150,000 Da (101). Enzymatic pretreatment of red cells was also commonly used at the crossmatching in the 1950s and 1960s, a process that seemed to influence the results. The DEX 70, DEX 60, and DEX 40 solutions with molecular weights of 70,000 to 40,000 Da, used commonly at present, do not induce any adverse effects on presently used blood serological tests (101,102).

The combined use of colloid together with HS (7.5%) is becoming an increasingly popular fluid regimen not only for resuscitation of shock and trauma patients but also during surgery and in the postoperative phase. Fluid resuscitation based on DEX 70 in combination with HS (7.5%) has been shown not to affect blood group determinations or red cell stability (103). Therefore, there is no longer any scientific evidence indicating that modern DEX preparations interfere with presently used methods for typing and crossmatching of blood.

CONCLUSIONS

All types of IV fluids, crystalloids as well as colloids, may induce adverse reactions in cases of improper use or presence of patient-associated specific risk factors. Local adverse effects at the

site of infusion caused by inappropriate temperature, molecular composition, or osmolality of IV fluids are rather uncommon and of minor clinical importance. Systemic adverse responses to fluid therapy caused by too rapid infusion or too excessive fluid administration resulting in hypervolemia, circulatory overload, or, in cases of fluid therapy with mainly crystalloids, formation of tissue edema or development of hyperchloremic acidosis can be avoided by proper choice of the type of fluid and by adequate monitoring of the fluid therapy. Clinical consequences of adverse effects of colloids on hemostasis can mainly be avoided if the choice of colloid for plasma volume support is based on a proper knowledge of the specific molecular characteristics of each available colloid and the way in which and at what dosage the colloid compromises the hemostatic competence. Colloid-associated problems due to tissue deposition resulting in adverse effects on organ function (renal failure and itching) seem to be decreasing because newer types of colloids that are more rapidly metabolized and eliminated have been introduced. One remaining clinical problem is the occurrence of hypersensitivity or anaphylactoid type of reactions due to histamine release or the presence of specific antibodies in some recipients. Antihistamine prophylaxis with H₁ + H₂ receptor blockers prior to infusion of GEL (Haemaccel) and the use of the hapten principle by administration of dextran-1 prior to dextran infusion are possible means for prevention of such adverse events. A most important factor that should be considered for safe use of IV fluids is that the fluid therapy is always based on a proper knowledge of the specific needs of the individual patient and that the potential hazards associated with the infusion of the different available fluids are known.

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35 Absorption of Irrigating Fluid

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INTRODUCTION

Evaporation, blood loss, and urinary excretion are the principal mechanisms for losses of fluid during surgery. The magnitude of these losses is often difficult to measure precisely. The accurate assessment or their combined effects, which needs to be based on observation and experience, is one of the major challenges to the anesthesiologist. In contrast, the administration of fluid to the patient is extremely well controlled because virtually all of it is provided as intravenous infusions by the anesthetic team. Besides uptake of fluid from the gut, the only major exception to this rule is systemic absorption of the fluid used to rinse surgical areas free of blood and debris. Here, fluid is administered to the patient without anyone being aware of it.

In certain endoscopic operations, primarily, transurethral resection of the prostate (TURP) and transcervical resection of the endometrium (TCRE), fluid absorption may be large enough to markedly alter the fluid balance and even pose a threat to the patient's life. These operations are usually performed using such electric cutting which prevents the use of physiological (0.9%) saline as the irrigating medium. The choice of fluid is then restricted to nonelectrolytic solutions such as sterile water or glycine 1.5%. The composition of these fluids is more or less unphysiological, which factor governs the adverse effects that develop when they are absorbed (Table 1).

The amount of irrigating fluid used varies with the procedure and with the length of the operation. During a 45-minute TURP, the average amount of fluid used is 15 L and, during a TCRE, the corresponding amount is about 9 L. However, as much as 40 to 50 L may occasionally be used during a single procedure. This fluid comes into contact with the tissue or mucosa at the operating site and nearly all of it is expected to be recovered immediately after use, the exception being absorbed fluid.

Nonelectrolyte irrigating fluids are also used in other operations such as transurethral vaporization of the prostate, lithotripsy, and arthroscopy. The risk of fluid absorption is lower during these operations than during TURP and TCRE. Important issues in this field are how various irrigating fluids compare when they are absorbed, how fluid absorption is monitored, and how massive fluid overload should be treated.

A new development is that resection can be performed with a bipolar resectoscope which does allow the use of 0.9% saline for irrigation. The bipolar technique is likely to shift the clinical appearance of fluid overload in a yet undefined way. Signs of acute cardiovascular overload and mental changes would probably still occur, but not cerebral edema.

STERILE WATER

Sterile water was the first irrigating solution to be used during TURP. In 1947, Creevy (3) reported that absorption of the water may occur, and that such absorption was the cause of the hemolysis and kidney damage frequently observed in those days. The effects of hemoglobinuria on the kidneys consist in vasoconstriction, which leads to hypoxia and the cellular damage sometimes called "lower nephron nephrosis" (4). The kidneys were in danger particularly when there was preexisting renal disease. These concerns resulted in the development of the nonhemolyzing nonelectrolyte irrigating solutions, i.e., glycine, mannitol, and sorbitol.

Laboratory investigations of sterile water as an irrigating fluid include work by Berg et al. (5), who compared water with a sorbitol-mannitol solution (Cytal) by infusing them intravenously in dogs. Water decreased the serum sodium concentration much less than sorbitol-mannitol did, but death occurred in 8 out of 20 animals given 100 mL/kg of sterile water

Table 1 Characteristics of the Solutes Used in Irrigating Fluids When Administered Intravenously in a Volume of 1–1.5 L

	Glycine	Mannitol	Sorbitol
Volume of distribution (L)	20	20	23
Half-life (min)	40	100	30
Main site of elimination	Liver	Kidney	Liver
Vascular load	+	++	+
Diuretic effect	++	+++	++
Toxicity	++	0	(+)

Note: The half-lives of glycine (1) and sorbitol (2) increase with the dose.

while all animals receiving Cytal survived. Interestingly, water caused a marked rise in blood pressure, similar to that observed after glycine absorption (6), whereas the blood pressure decreased after infusion of Cytal. Wakim (7) performed experiments with irrigating fluids in dogs and rats and strongly warned against the use of sterile water due to its cytotoxic properties. To maintain good vision in the operating field, however, some authors have prevented adverse effects by infusing hypertonic mannitol intravenously in all patients when using sterile water for irrigation (8).

Numerous case reports are available in which irrigation with sterile water alone has caused death (3,4,9,10). Nevertheless, several recent authors use distilled water during TURP and even compared the results in small series of between 50 and 60 patients, but without finding any untoward effects (11,12).

Today, sterile water as an irrigating fluid is indicated for routine cystoscopy and may also be used for transurethral resection of bladder tumors, while its place is controversial in TURP. For financial reasons, however, sterile water is the main irrigating solution used for TURP in most developing countries.

GLYCINE

Glycine solution (usually 1.5%) was proposed for use together with electric cutting in the late 1940s because it prevents hemolysis, is transparent, and is inexpensive to manufacture. Furthermore, the solution does not cause allergic reactions because it is an endogenous amino acid. In the 1950s, however, it became increasingly apparent that severe and life-threatening adverse effects due to absorption of irrigating fluid could occur although hemolysis was no longer a part of it. Such severe complications were summarized as the “transurethral resection syndrome,” which was described in detail in 1956 (13). The early literature described the early signs to consist in apprehension, hypertension, and possibly pulmonary edema on the operating table. After surgery, there is hypotension, anuria, and confusion. Death might occur from circulatory shock or brain edema.

Glycine 1.5% is currently the most widely used irrigating fluid in Europe and the United States. Many papers challenge its use, however. During the 1980s, reports of hyperammonemic encephalopathy from the metabolism of glycine were published (14,15). Later studies demonstrate that glycine 1.5% has slight cardiotoxic properties in vitro, which are not shared by mannitol and sorbitol solutions (16). Rabbits overhydrated with irrigating fluid showed the least damage to various tissues (such as the heart, liver, and kidneys) with mannitol solution, intermediate damage with sorbitol–mannitol, and the most damage with glycine (Fig. 1) (17). The mortality of live mice receiving irrigating fluid showed the same pattern (18). In the clinic, absorption of glycine 1.5% gives rise to more symptoms than the comparable amounts of mannitol 3% (19).

MANNITOL

The idea of irrigating the bladder with mannitol 3% during TURP also appeared in the late 1940s. This agent was well known from the clinic where it was used in a 15% solution to combat cerebral edema and/or renal insufficiency. The most common strength today is probably the isotonic 5% concentration, which, in contrast to glycine 1.5%, does not promote cerebral edema (20). Kirschenbaum (21) reported a patient in whom severe mannitol-induced hyponatremia did not give rise to any symptoms of the transurethral resection syndrome. The reason is probably that mannitol 5% is the only irrigating fluid today which maintains an

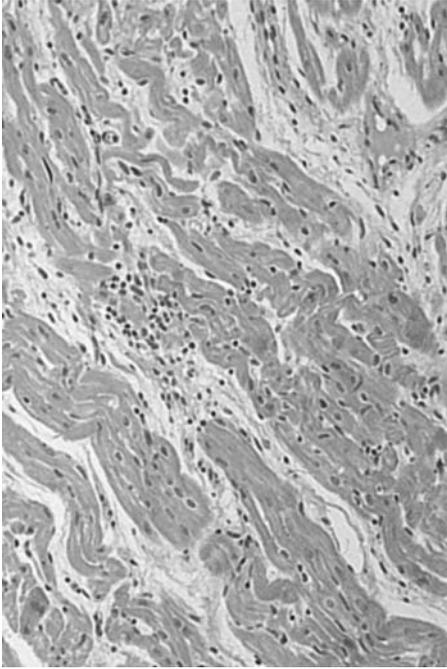


Figure 1 Light microscopy of the pig's heart showing focal necrosis of cardiac tissue two hours after intravenous infusion of 150 mL/kg of mannitol 3% over 90 minutes (hematoxylin-eosin stain). *Source:* Courtesy of Professor Jovan Rajs, Karolinska Institute, Stockholm, Sweden.

unchanged serum osmolality (22). If very large amounts of mannitol 5% are administered to laboratory animals, however, the volume overload damages the cytoarchitecture of the vital tissues, such as the heart (Fig. 2). After administration, the animals develop hypodynamic hyponatremic shock (20). Death is likely if hypertonic saline is not given for treatment (23).

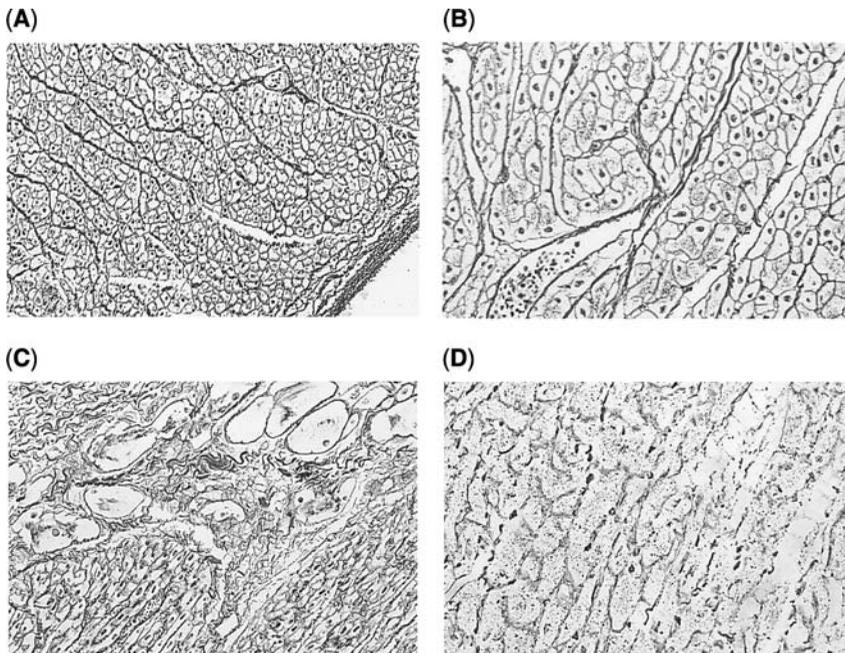


Figure 2 Cytoskeleton of the subendocardium in animals infused with irrigating fluid. Light microscopy with Gordon and Sweet's silver impregnation for reticulin fibers. **(A,B)** Normal appearance in pigs given mannitol 3% (different magnifications). **(C)** Swollen and defragmented reticular fibres in a pig that received mannitol 5%. **(D)** Severe damage to the cytoskeleton in a mouse that died after receiving normal saline. *Source:* Courtesy of Professor Jovan Rajs, Karolinska Institute, Stockholm, Sweden.

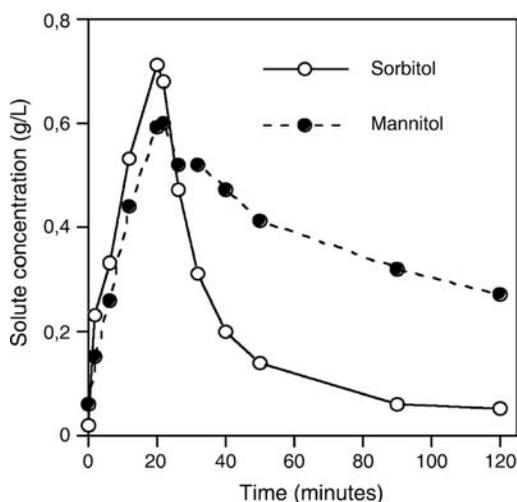


Figure 3 Sorbitol and mannitol concentrations in serum after intravenous infusion of 1.2 L of sorbitol 2% with mannitol 1% over 20 minutes in 10 volunteers (mean values). Although more sorbitol is infused, its shorter half-life soon makes mannitol the predominant solute.

MIXTURES OF SORBITOL AND MANNITOL

Since the early 1970s, sorbitol 2.7% with mannitol 0.54% has been a popular nonhemolytic irrigating fluid in the United States. Sorbitol with mannitol has also been widely used in various solute concentrations in Central Europe (mostly Germany), where it has a reputation of being "gentle" by virtue of lacking the toxic properties of glycine. Although the content of sorbitol is always higher than that of mannitol, the short half-life of sorbitol makes mannitol the predominant solute soon after an absorption event (Fig. 3).

Despite the long-term use of sorbitol-mannitol combinations, there have been surprisingly few clinical studies evaluating the associated adverse effects. However, Inman et al. (24) could not find any difference in adverse effects between sorbitol-mannitol and glycine 1.5% when absorbed during TURP. Other comparisons between these fluids have been made in laboratory animals. In dogs, Marx et al. (25) showed that sorbitol-mannitol increases the blood volume to the same degree as 5% glucose. Glenn et al. (26) reported that sorbitol-mannitol induced diuresis in dogs to a lesser degree than glycine 1.5% and 5% glucose. In a crossover study, Masloff et al. (27) infused 2 L of sorbitol-mannitol and glycine 1.5% in two patients. Sorbitol-mannitol was not associated with any symptoms, while one of the patients became agitated and restless at the end of the glycine infusion.

The studies at the author's laboratory from the 1990s suggest that sorbitol-mannitol takes an intermediate position between the irrigating fluids that contain mannitol alone (most suitable) and glycine (worst) (16-18). Moreover, an intravenous infusion study in volunteers (1.2 L over 20 minutes) shows that sorbitol-mannitol has a very limited effect on central hemodynamics, except for a late reduction in stroke volume which is shared by other irrigating fluids, and which is probably due to cooling (28). Hemodilution and urinary excretion were also intermediately pronounced after sorbitol-mannitol.

Sorbitol is metabolized to glucose and fructose, and the latter sugar might induce lactic acidosis when given in large amounts (29,30). There is also a potential risk that the patient absorbing sorbitol-mannitol may be allergic to fructose, which causes hemodynamic shock (31,32). The latter complication is very rare and has not been described in connection with absorption of sorbitol solution during endoscopic surgery.

SYMPTOMS OF FLUID ABSORPTION

The incidence and symptoms of fluid absorption during surgery have been well investigated regarding glycine 1.5%. "Absorption" usually means that the irrigating solution is transferred directly into the patient's bloodstream, a route that is called "intravascular" in older literature. The absorbed volume varies greatly and cannot be predicted in the individual patient, although it tends to be larger in extended and bloody operations (33). Small amounts of the fluid are being absorbed during every TURP and almost every TCRE (34) and are usually without consequence, although slight facial flush and prickling sensations around the lips may be reported.

Table 2 Risk of Developing Neurological Symptoms During and After Transurethral Resection of the Prostate^a

Type of symptom	Absorption volume (L)	Patients (N)	During surgery (odds ratio, 95% CI)	After surgery (odds ratio, 95% CI)
Neurological (blurred vision, nausea, vomiting, uneasiness, confusion)	0.0–0.3	118	Reference	Reference
	0.3–1.0	45	Not significant	2.9 (1.1–7.8)
	1.0–2.0	65	8.6 (1.7–42.4)	6.3 (2.6–15.2)
	2.0–3.0	17	38.5 (7.0–212)	8.3 (2.5–28.1)
	> 3.0	12	77.0 (12.5–474)	91.9 (10.3–819)

^aNotes: Depending on the extent of absorption of irrigating fluid containing glycine. Circulatory symptoms do not show the same steep increase. Data are the odds ratio (95% CI) and adjustment has been made for the intensity and the duration of the symptom on a 3-graded "severity score" scale.

Source: Adapted from Ref. 35.

Infusion experiments and clinical studies show that the risk of symptoms increases statistically when more than 1 L of glycine 1.5% has been absorbed (35), which seems to occur in between 5% and 10% of the TURPs performed (19,35–37). The occurrence of fluid absorption during TCRE does not differ much from that during TURP.

Symptoms arise from the circulatory and central nervous systems. The former group of symptoms comprises chest pain, hypertension, hypotension, and failure to void. The latter group includes nausea, vomiting, blurred vision, prickling sensations, tiredness, uneasiness, confusion, headache, and depressed consciousness (35). Other symptoms, such as epileptic seizures and pulmonary edema, have been reported but are very rare. Coma due to brain edema has been described after TURP (38) and also after TCRE (39).

Although more than 100 cases of severe "transurethral resection reactions" using glycine 1.5% have been reported, a more statistical approach to the risks of different symptoms developing was not published until 1995. In a retrospective review, Olsson et al. (35) recorded an average of 1.3 symptoms from the circulatory and nervous systems in each TURP during which very little or no glycine 1.5% was absorbed (0–300 mL). This figure increased to 2.3 when between 1 and 2 L of fluid was taken up, while 5.8 symptoms occurred when more than 3 L were absorbed (Table 2). The dose-dependent increase in the number of symptoms has been corroborated in subsequent prospective studies (19,37).

Thus, these investigations show that the risk of having symptoms following absorption of glycine 1.5% increases progressively as more glycine solution is absorbed. Most of them develop between 30 and 60 minutes after the completion of surgery, which is a fact rarely acknowledged. Patients who absorb moderately large amounts of irrigating fluid, such as between 1 and 2 L, typically exhibit an "incomplete" transurethral resection syndrome that may include only nausea and arterial hypotension after the operation. Such mild forms of the syndrome are easily misinterpreted as being due to old age, medication, or the anesthesia.

EXTRAVASATION

Instrumental perforation of anatomic structures sometimes occurs during endoscopy. Perforation of the bladder neck or the prostatic capsule is one possibility during TURP while uterine perforation may complicate TCRE. These events occur in 1% to 2% of both operations performed and result in extravasation of irrigating fluid into the retro- or intraperitoneal space (40).

Extravasation, which is sometimes called "extravascular fluid absorption" in the older literature, results in a flow of electrolytes from the extracellular space to the pool of absorbed fluid, which promotes hypovolemia. These pathophysiological events were first studied in animals by Mahoney et al. (41) while later studies were conducted in humans (42,43). Absorption of all electrolyte-free irrigating fluids results in hyponatremia, but, for direct intravenous absorption, the lowest serum sodium value is obtained at the end of the absorption. For extravasation, the lowest value is recorded between two and four hours after the perforation.

The number of symptoms for different volumes of extravasated fluid is the same as for absorption directly into the vascular system. The tendency to cause abdominal pain, bradycardia, and arterial hypotension is greater, while the incidence of hypertension and nausea is lower than for intravascular absorption (35).

ASSESSMENT OF FLUID ABSORPTION

The oldest way to assess fluid absorption is to rely on the symptoms arising on the operating table. When symptoms of the transurethral resection syndrome become apparent, the urologist tries to conclude the operation and hypertonic saline is given intravenously to combat the hyponatremia (13). One way to confirm that fluid absorption is the cause of the symptoms is to measure the serum sodium concentration, which then should be low (120–130 mmol/L or less). The amount of absorbed fluid can be measured directly by gravimetric weighing of the patient, volumetric measurement of all fluid that enters and leaves the patient, or by adding a tracer to the fluid (44). The direct measurements have the benefit of making it possible to indicate fluid absorption before it becomes large enough to cause symptoms. The surgeon can then do a shorter operation and the anesthesiologist can give the earliest possible treatment, which may prevent the development of a severe transurethral resection syndrome (33).

Direct measurements of fluid absorption are often hampered by practical problems. Gravimetric weighing uses a bedscale, which is expensive, and also requires that all fluids given to the patient are accounted for. The volumetric balance is confused by spillage on the floor, bag-to-bag variation in fluid content, and blood added to the irrigating fluid returns. In fact, very rigid measurements of the volumetric fluid balance must be adopted to make it useful during TURP (45). The volumetric method is more accurate during TCRE because this operation is associated with smaller blood losses. Automatic devices have been marketed which calculate the volumetric fluid balance during TCRE.

Radioisotopes were the first tracers to be added to the irrigating fluid, although radiation hazards limited their use to research projects. Today, it is hardly possible to use radioisotopes for this purpose at all. The only current alternative to them is ethanol.

The addition of a small amount of ethanol (usually 1%) to the irrigating fluid makes it possible to monitor the volume of fluid absorbed from the amount of ethanol measured in the patient's exhaled breath. This monitoring serves to enhance patient safety by allowing decisions made by the operating team to be based on accurate and updated information on intraoperative absorption events. The ethanol method provides essentially the same information as serum sodium, but noninvasive way and with a better resolution.

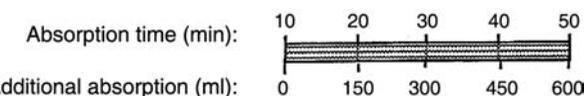
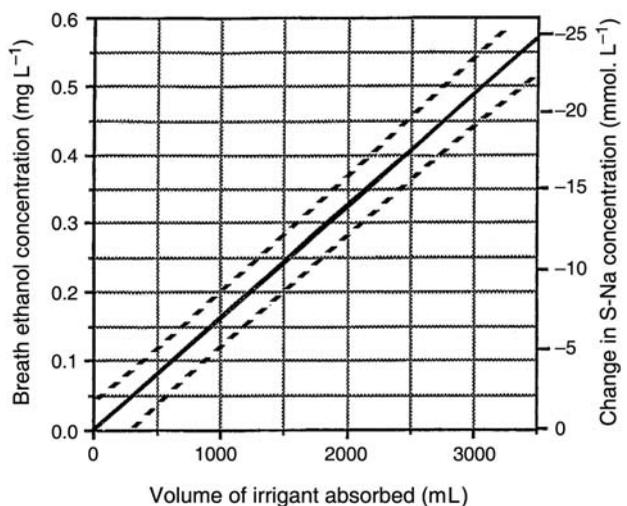
Ethanol monitoring requires an ethanol-containing irrigating fluid, a breathalyzer for measuring the ethanol concentration in the patient's exhaled breath, and a nomogram for estimation of the amount of fluid absorbed (Figs. 4 and 5). Several pocket-sized devices of good quality are available at a cost of 500 dollars or less. Calibration should be checked regularly according to the instructions of the manufacturer.

The awake patient is asked to breathe into the alcohol breathalyzer every 10 minutes throughout the surgical procedure. If ethanol is detected, new samples should be taken at five-minute intervals. When irrigation is performed intermittently, the breath test is best performed when the bladder has just been evacuated. One should have the patient do a comfortable and moderate exhalation into the device. Forceful exhalation may be tiring as well as disturb the operation and does not markedly improve the accuracy of the monitoring. The ethanol method can also be employed during general anesthesia (Fig. 6) and during TCRE. Reviews that describe the technique in detail are available (46,47).

A drawback with ethanol monitoring is the patient's active exhalation. The surgeon must then make a temporary stop of the resection because the patient sometimes moves when making this effort. The anesthesiologist must also remember to make the measurement and to document



Figure 4 A reliable device used in most of the early studies of the ethanol monitoring method was the Alcolmeter S-D2 (Lions Laboratories Ltd, South Glamorgan, Wales, U.K.).



R. Hahn 1995

Estimate intravascular fluid absorption

(90% prediction interval indicated)

1. Use upper nomogram
2. Add the effect of distribution and elimination of ethanol by using the scale

Estimate the change in serum sodium

Use upper nomogram directly

Figure 5 Nomogram for estimating the amount of irrigant absorbed and the degree of hyponatremia from the breath ethanol concentration during TURP. The dilution of the serum sodium concentration correlates directly with the breath ethanol level at all times during TURP. The volume of irrigant absorbed is estimated in two steps. A first approximation is made from the simple correlation relationship previously established between known absorbed volumes of irrigant solution and the corresponding exhaled concentrations measured within the first 10 minutes; this is then corrected for the time for which absorption has been demonstrated—to allow for the effects of distribution and elimination of the ethanol. The diagonal correlation relationship is used to read off an absorbed volume from a measured ethanol concentration, and an additional volume is added (using the subsidiary scale that runs to 50 minutes) that is dependent on the period of time during which ethanol has been recorded in the breath. **Example:** Consider that a patient has a breath ethanol concentration of 0.18 mg/L after 55 minutes of surgery. Ethanol has been detected during 30 minutes. The nomogram gives an estimate of the fluid absorption to 1200 mL plus 300 mL for the time. The decrease in the serum sodium concentration at 55 minutes is approximately 8 mmol/L. **Please note:** The nomogram presented here uses the measured concentration of ethanol in mg/L of exhaled air instead of the corresponding estimate of the blood ethanol concentration: 0.10 mg/L in exhaled air is equivalent to 0.23 g/L in blood. *Abbreviation:* TURP, transurethral resection of the prostate. *Source:* From Ref. 46.

the result. A novel approach, which overcomes these practical problems, is to add nitrous oxide (N_2O) to the irrigating fluid up to a concentration of 40 mL/L. The N_2O concentration corrected for the CO_2 level as measured during normal breathing is used as the index of fluid absorption. Toxicity is not an issue because the associated gas concentrations of N_2O are very low.

After electric cutting is completed and the patient is transferred to the postoperative ward, irrigation is no longer made with an electrolyte-free fluid but with 0.9% saline. Some further absorption may take place, but always at a much lower rate than during the operation. The “physiological” nature of 0.9% saline makes symptoms arising from such postoperative absorption less severe. An interest in controlling this postoperative absorption has never been expressed in the literature.



Figure 6 Ethanol monitoring during transurethral resection of the prostate performed during general anesthesia. The Alcolmeter is placed close to the tracheal tube with the edge in the breathing circuit, and a sample is taken at the end of the expiration. *Source:* Courtesy of Dr. Joel Olsson, Hudiksvall Hospital, Sweden.

PATHOPHYSIOLOGY

The pathophysiology of fluid absorption can be divided into fluid-specific and general aspects. Certain consequences are unique to the fluid used, such as the transient visual disturbances and the hyperammonemic encephalopathy associated with glycine solution. Large amounts of glycine (25–30 g) have the unique feature of stimulating the release of vasopressin from the hypophysis, which makes it more difficult for the kidneys to restore the reduced serum sodium level (48–50). Furthermore, glycine solution has a marked tendency to cause postoperative nausea and feelings of uneasiness, which do not seem to be shared to the same extent by other fluids (19,22). Another example is the lactic acidosis that may occur in response to absorption of large amounts of sorbitol (29,30). Moreover, arterial hypertension has not been observed with all irrigating fluids.

The general symptoms of fluid absorption consist in a transient volume overload with associated signs, such as pulmonary edema and chest pains, and progressive development of low-flow low-pressure shock (20). The shock is associated with osmotic diuresis as long as solutes, such as glycine or mannitol, are present in the fluid. The diuresis brings along electrolytes, which then represent a net loss from the body because the irrigating fluids do not contain electrolytes. The natriuresis soon reduces the overload of the extracellular fluid space, and this is further decreased by uptake of solutes into the cells (51). These events lead to cerebral edema, which may become manifest within a few hours after endoscopic procedures.

There are also less well-validated pathophysiological mechanisms. For example, fluid absorption spreads substances from damaged prostatic cells into the bloodstream, which elevates the plasma acid phosphatase level (52) with an implicated effect on patient symptoms (53,54) as well as the coagulation system (55,56). However, the acid phosphatase level is increased by both fluid absorption and blood loss (57), but a correlation with coagulation changes has been difficult to demonstrate clinically (56). Another view is that intermediate products in the glycine metabolism other than ammonia, such as glycolic acid and glyoxylic acid, would exert toxic effects (58).

Finally, there has been a fear that oxalate, which is an end product in the glycine metabolism, might form kidney stones (59). In the rat, however, only 1% of a glycine load is converted to oxalate (60) and studies of TURP patients (61) and volunteers (62) refute the assertion that glycine markedly increases oxalate excretion.

MILD AND SEVERE TUR SYNDROMES

Severe cases of the transurethral resection syndrome are rare, but it is most important to consider the diagnosis and to start appropriate treatment at an early stage. Unfortunate outcomes are associated with passive handling of patients with this iatrogenic complication (e.g., doctor's delay).

Mild and incomplete forms of the syndrome are much more common and often remain misunderstood. In these cases, the hospital stay merely becomes less pleasant for the patient. The fluid absorption of 1 to 2 L increases the workload for the postoperative staff because acute neurological and hemodynamic investigations are often initiated to find the reason for the unexplained symptoms. At this time, much of the initial reduction of the serum sodium level of 6 to 12 mmol/L has been restored, and the residual hyponatremia is due to natriuresis (51).

Surgeon's pride is a common reason why fluid absorption is rarely monitored, which leads to limited awareness of the common mild forms of the transurethral resection (TUR) syndrome. The anesthesiologist should collaborate with the surgeon around the problem and encourage the view that fluid absorption may occur even if the surgery is performed by the most experienced surgeon.

TREATMENT

The dilution of serum sodium and the natriuresis form the physiological basis for the treatment of fluid overload with hypertonic saline. There is a renal loss of sodium ions and the fluid also enters the cells, causing edema, as the solutes (except mannitol) become distributed intracellularly. These problems are solved by the additional sodium, which has also been found to reverse symptoms and promote survival (23,63,64). The two most common clinical pictures in patients dying of fluid absorption are those of hypovolemic hypotension and/or cerebral

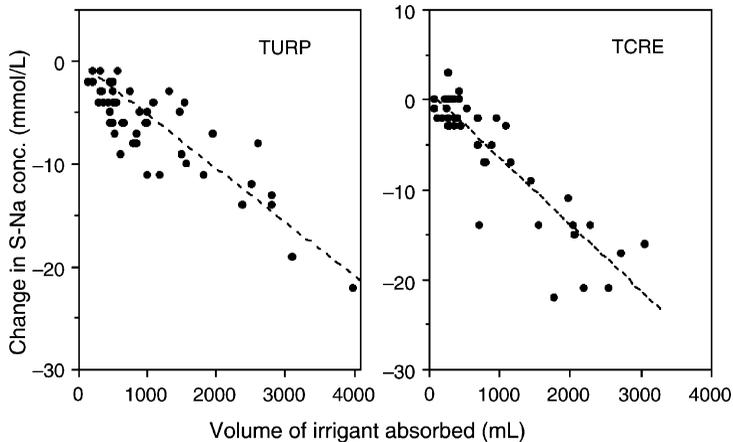


Figure 7 The hyponatremia resulting from absorption of increasing amounts of irrigating fluid (glycine 1.5%) during transurethral resection of the prostate (TURP) in males and transcervical resection of the endometrium (TCRE) in women. The hyponatremia is more pronounced in the latter group, mostly depending on the lower body weight in the females. A stronger linear correlation between fluid absorption and hyponatremia can be obtained by considering the absorption time, like in Figure 5, while the breath ethanol level and hyponatremia correlate directly without correction for absorption time. *Source:* From Refs. 35, 73.

edema (38,65–67), and both are counteracted by hypertonic saline. Hyponatremia per se might also result in epileptic seizures, although this is quite rare. The normal dose in an adult is 500 mL saline 3% over four hours, which can probably be accelerated if symptoms are severe.

Warnings about pontine myelinolysis resulting from rapid correction of hyponatremia originally pertained to chronic hyponatremia, but recent studies question rapid correction also in acute hyponatremia (68,69). However, Ayus and Arieff found no brain damage in 14 such patients when hypertonic saline raised the serum sodium level by 1 mmol/L/hr (64). In the past, there was a fear of hypertonic saline inducing pulmonary edema (11,65), but this has not been a clinical experience.

The practice of administering a diuretic-like furosemide is more questionable because this adds to the sodium deficit (51,70). Furosemide may be given if blunt symptoms of fluid overload develop on the operating table, but the phase of cardiac strain is quite short and will soon be turned into a hypovolemic state. At this time, furosemide should not be administered unless additional sodium is provided and the cardiovascular status is stable. Hypertonic mannitol (15%) may be considered an alternative if a diuretic is desired (63).

In addition to these specific treatments, more general measures must be applied to support bodily functions in case consciousness is lowered due to hyperammonemic encephalopathy, or the patient becomes hypothermic or shows electrocardiographic changes.

Extravasation should be treated with the same measures as when the irrigating fluid passes directly into the circulation. Morbidity and mortality can also be reduced by surgical drainage of the retroperitoneal fluid, but this treatment seems to be necessary only after massive absorption (71).

Females who absorb irrigating fluid are more prone than males to develop cerebral damage from the hyponatremia (72). This increased susceptibility, which seems to be related to the menstrual cycle, warrants an active approach with hypertonic saline if fluid absorption occurs during TCRE. Females also develop hyponatremia more easily than males due to their lower body weight (Fig. 7).

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36 Effects of Perioperative Fluids on Acid–Base and Electrolyte Status

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INTRODUCTION

As a consequence of underlying diseases and of therapeutic manipulations, patients may present for surgery with potentially harmful disorders of acid–base equilibrium and serum electrolytes. Perioperative fluids also exert predictable effects on acid–base status and serum electrolytes that can alter underlying acid–base and electrolyte disorders or generate new disorders. Precise perioperative management of acid–base status, fluids, and electrolytes may limit perioperative morbidity and mortality.

ACID–BASE INTERPRETATION AND TREATMENT

To facilitate the management of perioperative acid–base disturbances, this chapter will first review the pathogenesis, major complications, physiologic compensatory mechanisms, and treatment of the four simple acid–base disorders: metabolic alkalosis, metabolic acidosis, respiratory alkalosis, and respiratory acidosis. Subsequently, the chapter will review rapid interpretation of acid–base examples that are relevant to perioperative fluid management.

Overview of Acid–Base Equilibrium

The conventional approach to describing acid–base equilibrium is the Henderson–Hasselbalch equation:

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \times \text{PaCO}_2} \quad (1)$$

where 6.1 is the pK_a of carbonic acid, and 0.03 is the solubility coefficient of carbon dioxide (CO_2) in blood. In commercial blood gas analyzers, the pH and the partial pressure of arterial carbon dioxide (PaCO_2) are measured and the $[\text{HCO}_3^-]$ is calculated from those measurements, using the Henderson–Hasselbalch equation. Conventional acid–base terminology defines acid–base disturbances as metabolic [i.e., those in which the bicarbonate concentration ($[\text{HCO}_3^-]$) is primarily increased or decreased] and respiratory (i.e., those in which PaCO_2 is primarily increased or decreased). The term “pH,” used to define the acidity or alkalinity of solutions or blood, is the negative logarithm of the hydrogen ion concentration ($[\text{H}^+]$). The simpler Henderson equation clearly expresses the relationship between the three major variables measured or calculated in blood gas samples:

$$[\text{H}^+] = \frac{24 \times \text{PaCO}_2}{[\text{HCO}_3^-]} \quad (2)$$

where 24 is the normal serum $[\text{HCO}_3^-]$, and the calculated $[\text{HCO}_3^-]$ is inserted in the denominator. If total CO_2 (which exceeds $[\text{HCO}_3^-]$ by approximately 1 mmol L^{-1}) is used in the denominator, then 25 should be used in the numerator. To convert pH to $[\text{H}^+]$, the following rules-of-thumb approximate the logarithmic relationship between pH and $[\text{H}^+]$. First, $[\text{H}^+]$ is 40 mmol L^{-1} at a pH of 7.4. Second, assume that an increase in pH of 0.10 mpH units reduces $[\text{H}^+]$ to 0.8 times the starting $[\text{H}^+]$ concentration and that a decrease in pH of 0.10 mpH units increases the $[\text{H}^+]$ by a factor of 1.25. To calculate the effects of small changes (i.e., less than 0.05 mpH units), assume that a decrease of 0.01 mpH units produces approximately a 1.0 mmol L^{-1} increase in $[\text{H}^+]$ and that an increase of 0.01 mpH units produces a decrease in $[\text{H}^+]$ of 1 mmol L^{-1} .

The alternative "Stewart" approach to acid–base interpretation distinguishes between the independent variables and dependent variables that define pH (1,2). The independent variables are PaCO_2 , the strong (i.e., highly dissociated) ion difference (SID), and the concentration of proteins, which usually are not strong ions. The strong ions include sodium (Na^+), potassium (K^+), chloride (Cl^-), and lactate. The SID, calculated as $(\text{Na}^+ + \text{K}^+ - \text{Cl}^-)$, normally is approximately 42 mEq/L . In general, the Stewart approach provides more insight into the mechanisms underlying acid–base disturbances, in contrast to the Henderson–Hasselbalch approach, which is more descriptive. However, the clinical interpretation or treatment of common acid–base disturbances is rarely, if ever, handicapped by the simpler constructs of the conventional Henderson–Hasselbalch or Henderson equations.

With this background, the influence of intravenous fluid administration on acid–base status becomes evident. Rapid infusion of commonly used intravenous solutions can alter $[\text{HCO}_3^-]$, either by dilution with fluids such as 0.9% saline or by provision of $[\text{HCO}_3^-]$ substrate in fluids such as lactated Ringer's solution. Alteration of $[\text{HCO}_3^-]$ will necessarily alter the Henderson–Hasselbalch equation. From the perspective of the Stewart approach to acid–base physiology, infusion of fluids can alter the "independent" variables, the SID and protein concentrations.

Metabolic Alkalosis

Metabolic alkalosis, usually characterized by an alkalemic pH (greater than 7.45) and hyperbicarbonatemia (less than 27.0 mEq/L), is the most common acid–base abnormality in critically ill patients and is associated with increased cost, morbidity, and mortality (3). Factors that generate metabolic alkalosis include nasogastric suction and diuretic administration (Table 1) (4). The maintenance of metabolic alkalosis is dependent upon a continued stimulus for distal tubular reabsorption of $[\text{HCO}_3^-]$. Such stimuli include renal hypoperfusion, hypokalemia, hypochloremia, or hypovolemia.

Metabolic alkalosis exerts multiple physiologic effects. It is associated with hypokalemia, ionized hypocalcemia, secondary ventricular arrhythmias, increased digoxin toxicity, and

Table 1 Generation and Maintenance of Metabolic Alkalosis

Generation	Example	Maintenance
I. Loss of acid from extracellular space	Vomiting; nasogastric drainage	↓ EAV
A. Loss of gastric fluid	1. Primary aldosteronism	1. K^+ depletion + aldosterone excess
B. Loss of acid into urine; continued Na^+ delivery to the distal tubule in presence of hyperaldosteronism	2. Diuretic administration	2. ↓ EAV + K^+ depletion
II. Excessive HCO_3^- loads		
A. Absolute		
1. HCO_3^-	NaHCO_3 administration	↓ EAV
2. Metabolic conversion of salts of organic acid anions to HCO_3^-	Lactate, acetate, citrate administration	↓ EAV
B. Relative		
Alkaline loads in renal failure	Alkali administration to patients with renal failure	Renal failure
III. Posthypercapnic state	Abrupt correction of chronic hypercapnia	↓ EAV

Abbreviation: EAV, effective arterial volume.

Table 2 Rules of Thumb for Respiratory Compensation in Response to Metabolic Alkalosis and Metabolic Acidosis

Metabolic alkalosis	
PaCO ₂ increases approximately 0.5–0.6 mmHg for each 1.0 mEq/L increase in [HCO ₃ ⁻]	
The last two digits of the pH should equal the [HCO ₃ ⁻] + 15	
Metabolic acidosis	
PaCO ₂ = [HCO ₃ ⁻] × 1.5 + 8	
PaCO ₂ decreases 1.2 mmHg for every 1.0 mEq/L in [HCO ₃ ⁻] to a minimum of 10–15 mmHg	
The last two digits of the pH equal [HCO ₃ ⁻] + 15	

compensatory hypoventilation (hypercarbia), although PaCO₂ rarely exceeds 55 mmHg (compensatory responses are summarized in Table 2) (4). Alkalemia also increases bronchial tone and, through a combination of increased bronchial tone and decreased ventilatory effort, may promote atelectasis. Alkalemia may reduce tissue oxygen availability by shifting the oxyhemoglobin dissociation curve to the left and by decreasing cardiac output. During mechanical ventilatory management, inadvertent addition of iatrogenic respiratory alkalosis to preexisting metabolic alkalosis may produce cardiovascular depression, dysrhythmias, and other complications of severe alkalemia (Table 3).

In patients for whom arterial blood gases have not yet been obtained, serum electrolytes and a history of major risk factors, such as vomiting, nasogastric suction, or chronic diuretic use, can suggest metabolic alkalosis. Total CO₂ (usually abbreviated on electrolyte reports as CO₂) should be about 1.0 mEq/L greater than [HCO₃⁻], calculated on simultaneously obtained arterial blood gases. If either the calculated [HCO₃⁻] on the arterial blood gases or “CO₂” on the serum electrolytes exceeds normal (24 and 25 mEq/L, respectively) by more than 4.0 mEq/L, the patient either has a primary metabolic alkalosis or has conserved bicarbonate in response to chronic hypercarbia. Recognition of hyperbicarbonatemia on the preoperative serum electrolytes justifies arterial blood gas analysis and should alert the anesthesiologist to the likelihood of factors that generate or maintain metabolic alkalosis.

Treatment of metabolic alkalosis consists of etiologic and nonetiologic therapy. Etiologic therapy consists of measures such as expansion of intravascular volume or the administration of potassium. To restore intravascular volume, administration of 0.9% saline tends to increase serum [Cl⁻] and decrease serum [HCO₃⁻] (5). Table 4 illustrates the effects of administration of 2 L of 0.9% saline to a patient with a metabolic alkalosis. Given sufficient time and normal kidneys, expansion of intravascular volume with lactated Ringer’s solution also would reverse metabolic alkalosis maintained by hypovolemia, e.g., vomiting-induced hyperbicarbonatemia. Although hypoproteinemia can cause a mild metabolic alkalosis, such changes usually require no specific treatment. Nonetiologic therapy includes the administration of acetazolamide (a carbonic anhydrase inhibitor that causes renal bicarbonate wasting) or, occasionally, [H⁺] as ammonium chloride, arginine hydrochloride, or 0.1 N hydrochloric acid (100 mmol L⁻¹), or acid dialysis.

Metabolic Acidosis

Metabolic acidosis, usually characterized by an acidemic pH (less than 7.35) and hypobicarbonatemia (less than 21 mEq/L), can be innocuous or reflect a life-threatening emergency (6).

Table 3 Metabolic Alkalosis Plus Hyperventilation

	Normal	Chronic diuretic administration	Mechanical hyperventilation
Blood gases			
pH	7.40	7.47	7.62
PaCO ₂ (mmHg)	40	45	30
[HCO ₃ ⁻] (mEq/L)	24	32	29
Electrolytes			
“CO ₂ ” (mEq/L)	25	33	30

Note: Respiratory alkalosis, produced by inappropriately high minute ventilation, has been added to the previously compensated metabolic alkalosis induced by chronic diuretic administration.

Table 4 Metabolic Alkalosis Plus Saline Infusion

	Normal	Chronic diuretic administration	0.9% saline infusion
Blood gases			
pH	7.40	7.47	7.45
PaCO ₂ (mmHg)	40	45	42
[HCO ₃ ⁻] (mEq/L)	24	32	28
Electrolytes			
"CO ₂ " (mEq/L)	25	33	29
Cl ⁻ (mEq/L)	100	92	

Note: Two liters of 0.9% saline has been added to the previously compensated metabolic alkalosis induced by chronic diuretic administration. The above example assumes a weight of 70 kg and an extracellular volume (the primary distribution volume for both chloride and bicarbonate) of 14 L.

Metabolic acidosis occurs as a consequence of buffering by bicarbonate of endogenous or exogenous acid loads or as a consequence of abnormal external loss of bicarbonate. Approximately 70 mmol of acid metabolites are produced, buffered, and excreted daily; these include about 25 mmol of sulfuric acid from amino acid metabolism, 40 mmol of organic acids, and phosphoric and other acids (7). In a 70-kg adult, extracellular volume (ECV) contains 336 mmol of bicarbonate buffer (24 mEq/L 14 L of ECV). Glomerular filtration of plasma volume (PV) necessitates reabsorption of 4500 mmol of bicarbonate daily, of which 85% is reabsorbed in the proximal tubule, 10% in the thick ascending limb, and the remainder is titrated by proton secretion in the collecting duct (7).

Calculation of the anion gap ($\text{Na}^+ - [\text{Cl}^-] + [\text{HCO}_3^-]$) distinguishes between two types of metabolic acidosis (Table 5) (8). The anion gap is normal (< 13 mEq/L) in situations such as diarrhea, biliary drainage, and renal tubular acidosis, in which bicarbonate is lost externally. The anion gap also is normal or reduced in hyperchloremic acidosis associated with perioperative infusion of substantial quantities of 0.9% saline (5,9,10). Figure 1 illustrates changes in serum pH and [HCO₃⁻] in gynecologic surgical patients receiving 60 mL kg⁻¹ of 0.9% saline or lactated Ringer's solution over two hours. Metabolic acidosis associated with a high anion gap (more than 13 mEq/L) occurs due to excess production of lactic acid or ketoacids, increased retention of waste products (such as sulfate and phosphate) that are inadequately excreted in uremic states, and ingestion of toxic quantities of substances such as aspirin, ethylene glycol, and methanol. In those circumstances, bicarbonate ions are consumed in buffering hydrogen ions, whereas the associated anion replaces bicarbonate in serum. Because three-quarters of the normal anion gap consists of albumin, the calculated anion gap should

Table 5 Differential Diagnosis of Metabolic Acidosis*Elevated anion gap*

Endogenous

Uremia

Ketoacidosis

Lactic acidosis

Exogenous toxins

Methanol

Ethylene glycol

Salicylates

Paraldehyde

Normal anion gap

Renal tubular acidosis

Diarrhea

Carbonic anhydrase inhibition

Ureteral diversions

Early renal failure

Hydronephrosis

HCl administration

Saline administration

Note: Correction of the anion gap for hypoalbuminemia is essential for effective perioperative use.

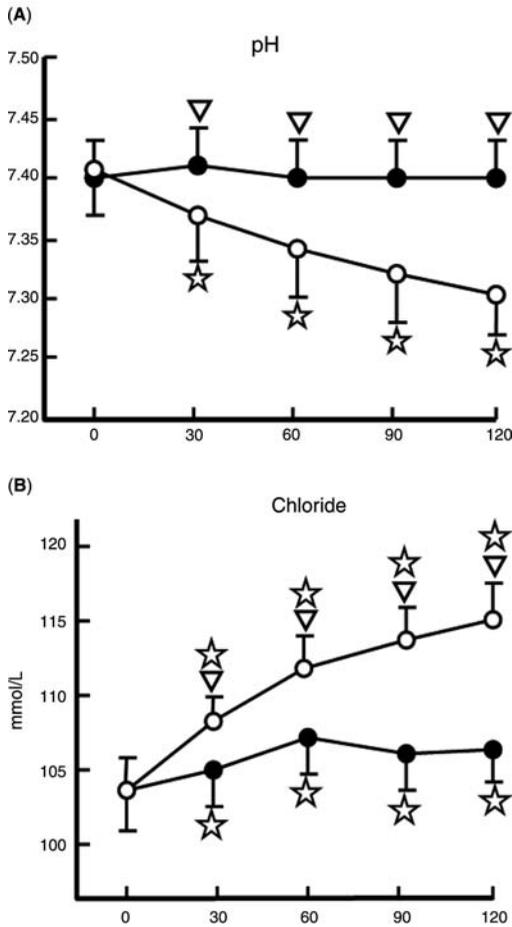


Figure 1 Changes in pH (A) and serum chloride (B) in gynecologic surgical patients receiving 60 mL/kg of 0.9% saline (open circles) or lactated Ringer's solution (closed circles) over two hours. Infusion of 0.9% saline is associated with a progressive decrease in pH and a progressive increase in serum chloride concentration. *Source:* From Ref. 5.

be corrected for hypoalbuminemia by adding to the calculated anion gap the difference between measured serum albumin and a normal albumin concentration of 4.0 g dL^{-1} multiplied by 2.0 to 2.5 (11,12).

Sufficient reductions in pH may reduce myocardial contractility, increase pulmonary vascular resistance, and decrease systemic vascular resistance. It is particularly important to note that failure of a patient to appropriately hyperventilate in response to metabolic acidosis is physiologically equivalent to respiratory acidosis and suggests impending deterioration. If a patient with metabolic acidosis requires mechanical ventilation, measurement of PaCO_2 or end-tidal CO_2 can facilitate the maintenance of an appropriate level of ventilatory compensation (Table 2) until the primary process can be corrected. Preoperative compensatory hyperventilation should be maintained during anesthesia and monitored using capnography and arterial blood gases. Hyperventilation, though an important compensatory response to metabolic acidosis, is not a definitive therapy for metabolic acidosis.

The risks of metabolic acidosis are proportional to the severity of the underlying process. Although a patient with hyperchloremic metabolic acidosis may be relatively healthy, those with lactic acidosis, ketoacidosis, uremia, or toxic ingestions will be chronically or acutely ill. Preoperative assessment should emphasize volume status and renal function. If shock is the etiology, direct arterial pressure monitoring and preload may require assessment via echocardiography or pulmonary arterial catheterization. Drugs and positive pressure ventilation may precipitate exaggerated hypotensive responses. In planning intravenous fluid therapy, consider that balanced salt solutions tend to increase $[\text{HCO}_3^-]$ and pH (Table 6), whereas 0.9% saline tends to decrease $[\text{HCO}_3^-]$ and pH (5,9).

The treatment of metabolic acidosis consists of the treatment of the primary pathophysiologic process, i.e., hypoperfusion, hypoxia, and if pH is severely decreased, administration

Table 6 Infusion of 3 L of Lactated Ringer's Solution in a Patient with Diabetic Ketoacidosis

Arterial blood gases	Spontaneous ventilation	Lactated Ringer's
PH	7.29	7.37
PaCO ₂ (mmHg)	29	39
[HCO ₃ ⁻] (mEq/L)	14	22

Note: Infusion of lactated Ringer's solution provided substrate for production of bicarbonate; in addition, concurrent infusion of insulin terminated ketoacidosis. This example assumes an extracellular volume of 14 L.

of NaHCO₃⁻. The initial dose of NaHCO₃ can be calculated as:

$$\text{NaHCO}_3^- \text{ (mEq/L)} = \frac{\text{Wt (kg)} \times 0.3 \times (24 \text{ mEq/L} - \text{actual HCO}_3^-)}{2} \tag{3}$$

where 0.3 is the assumed distribution space for bicarbonate and 24 mEq/L is the normal value of [HCO₃⁻] for arterial blood gas determination. However, this calculation markedly underestimates dosage in severe metabolic acidosis. In infants and children, an appropriate initial dose is 1.0 to 2.0 mEq kg⁻¹ of body weight.

One continuing controversy is the use of NaHCO₃ to treat acidemia induced by lactic acidosis. In critically ill patients with lactic acidosis, there were no important differences between the physiologic effects (other than changes in pH) of 0.9M NaHCO₃ and 0.9M sodium chloride (13). Importantly, NaHCO₃ did not improve the cardiovascular response to catecholamines and actually reduced plasma ionized calcium (13). Although many clinicians continue to administer NaHCO₃ to patients with persistent lactic acidosis and ongoing deterioration, neither NaHCO₃ nor dichloroacetate (14) improved the outcome in clinical trials. The buffer trishydroxymethyl aminomethane (THAM) is effective at reducing [H⁺] and does not generate CO₂ as a byproduct of buffering (15); there is, however, no generally accepted indication for THAM.

Respiratory Alkalosis

Respiratory alkalosis, usually characterized by an alkalemic pH (more than 7.45) and always characterized by hypocarbia (PaCO₂ ≤ 35 mmHg), describes an increase in minute ventilation that is greater than that required to excrete the metabolic CO₂ produced. Because respiratory alkalosis may be a sign of pain, anxiety, hypoxemia, central nervous system (CNS) disease, or systemic sepsis, the development of spontaneous respiratory alkalosis in a previously normo-carbic patient requires prompt evaluation.

Respiratory alkalosis, like metabolic alkalosis, may produce hypokalemia, hypocalcemia, cardiac dysrhythmias, bronchoconstriction, and hypotension; it may also potentiate the toxicity of digoxin. In addition, both brain pH and cerebral blood flow are tightly regulated and respond rapidly to changes in PaCO₂ (16). Doubling minute ventilation reduces PaCO₂ to 20 mmHg and halves the cerebral blood flow; conversely, halving minute ventilation doubles PaCO₂ and doubles the cerebral blood flow. If PaCO₂ is maintained at abnormally high or low levels for 8 to 24 hours, cerebral blood flow will return to near previous levels.

Treatment of respiratory alkalosis per se is often not required. In most patients, the most important steps are the recognition and treatment of the underlying etiology. For instance, correction of hypoxemia should decrease hypoxic ventilatory stimulation.

Respiratory Acidosis

Respiratory acidosis, usually characterized by a low pH (less than 7.35) and always characterized by hypercarbia (PaCO₂ ≥ 45 mmHg), occurs due to a decrease in minute alveolar ventilation (V_A), an increase in the production of carbon dioxide (V_{CO₂}) or both, from the equation,

$$\text{PaCO}_2 = K \frac{V_{\text{CO}_2}}{V_A} \tag{4}$$

where *K* is the constant. This equation assumes that inspired CO₂ is negligible; rebreathing of exhaled, CO₂-containing gas may also increase PaCO₂. Respiratory acidosis may be either

Table 7 Rules of Thumb for $[\text{HCO}_3^-]$ and pH Changes in Response to Acute and Chronic Changes in PaCO_2

Decreased PaCO_2
pH increases 0.10 for every 10 mmHg decrease in PaCO_2
$[\text{HCO}_3^-]$ decreases 2 mEq/L for every 10 mmHg decrease in PaCO_2
pH will nearly normalize if hypocarbia is sustained
$[\text{HCO}_3^-]$ will decrease 5–6 mEq/L for each chronic 10 mmHg ↓ in PaCO_2 ^a
Increased PaCO_2
pH will decrease 0.05 for every acute PaCO_2 increase of 10 mmHg
$[\text{HCO}_3^-]$ will increase 1.0 mEq/L for every PaCO_2 increase of 10 mmHg
pH will return toward normal if hypercarbia is sustained
$[\text{HCO}_3^-]$ will increase 4–5 mEq/L for each chronic 10 mmHg increase in PaCO_2

^aCritically ill patients rarely excrete $[\text{HCO}_3^-]$ in response to hypocarbia because of stimuli that enhance distal tubular reabsorption of sodium.

acute, without compensation by renal $[\text{HCO}_3^-]$ retention, or chronic, with $[\text{HCO}_3^-]$ retention offsetting the decrease in pH (Table 7). A reduction in V_A may be due to an overall decrease in minute ventilation (V_E) or to an increase in the amount of wasted ventilation (V_D), according to the following equation:

$$V_A = V_E - V_D \quad (5)$$

Decreases in V_E may occur because of central ventilatory depression by drugs or CNS injury, because of increased work of breathing, or because of airway obstruction or neuromuscular dysfunction. Increases in V_D occur with chronic obstructive pulmonary disease, pulmonary embolism, and the most acute forms of respiratory failure. V_{CO_2} may be increased by sepsis, high-glucose parenteral feeding, or fever.

Patients with chronic hypercarbia due to intrinsic pulmonary disease require careful ventilatory management if intubation or ventilation is required for surgery. In general, a patient with chronic hypercapnia should be ventilated to approximately their usual level of PaCO_2 in order to maintain a normal pH. An abrupt increase in minute ventilation may result in profound alkalemia because of the chronic compensatory retention of $[\text{HCO}_3^-]$.

Treatment of respiratory acidosis depends upon whether the condition is acute or chronic. Acute respiratory acidosis may require mechanical ventilation unless a simple etiologic factor (i.e., narcotic overdose or residual muscular blockade) can be treated quickly. Treatment with sodium bicarbonate is rarely indicated, unless severe metabolic acidosis is also present or unless mechanical ventilation is ineffective in reducing acute hypercarbia. In contrast, chronic respiratory acidosis is rarely managed with ventilation. Rather, efforts are made to improve pulmonary function to permit a more effective elimination of CO_2 .

PRACTICAL APPROACH TO ACID–BASE INTERPRETATION

A rapid interpretation of a patient's acid–base status involves the integration of three sets of data: arterial blood gases, electrolytes, and history. A systematic, sequential approach facilitates interpretation (Table 8). Acid–base assessment usually can be completed before initiating therapy; however, the first step in interpretation may disclose disturbances (e.g., respiratory acidosis or metabolic acidosis with $\text{pH} < 7.1$) that require immediate attention.

The second, optional step is particularly useful if the arterial blood gases to be interpreted have been manually transcribed, e.g., from a telephone report. Although typical blood gas analyzers calculate $[\text{HCO}_3^-]$ from the measured pH and PaCO_2 and therefore generate internally consistent values, inaccurate transcriptions of data can still cause diagnostic confusion. To begin this optional step, calculate $[\text{H}^+]$ from the pH using the rules-of-thumb provided earlier in the chapter.

The next step is to determine whether a patient is acidemic ($\text{pH} < 7.35$) or alkalemic ($\text{pH} > 7.45$). The direction of the change in pH will usually indicate the predominant primary process, i.e., acidosis produces acidemia, whereas alkalosis produces alkalemia. (Note: The suffix “-osis” indicates a primary process that, if unopposed, will produce the corresponding pH change. The suffix “-emia” refers to the pH. A compensatory process is not considered an “-osis”). Of course, a patient may have mixed “-oses,” that is, more than one primary process.

Table 8 Sequential Approach to Acid–Base Interpretation

-
1. Is the pH life-threatening, requiring immediate intervention?
 2. *Optional:* Are the arterial blood gases internally consistent, i.e., do the two sides of the Henderson equation balance?
 3. Is the pH acidemic or alkalemic?
 4. Could the entire arterial blood gas picture represent only an acute increase or decrease in PaCO₂?
 5. If the answer to question No. 3 is “No,” is there evidence of a chronic respiratory disturbance or of an acute metabolic disturbance?
 6. Are appropriate compensatory changes present?
 7. Is an anion gap present?
 8. Do the clinical data fit the acid–base picture?
-

The next step is to determine whether the entire arterial blood gas picture is consistent with a simple acute respiratory alkalosis or acute respiratory acidosis (Table 7). For example, a patient with acute hypocapnia (PaCO₂ 30 mmHg) would have a pH increase of 0.10 units to a pH of 7.50 and a calculated [HCO₃⁻] of 22.

If changes in PaCO₂, pH, and [HCO₃⁻] are not consistent with a simple acute respiratory disturbance, chronic (24 hours or more) respiratory acidosis or alkalosis, or metabolic acidosis or alkalosis should be considered. In chronic respiratory acidosis, pH becomes nearly normal as bicarbonate is retained by the kidneys (Table 7), usually at a ratio of 4 to 5 mEq/L per 10 mmHg chronic increase in PaCO₂ (17). For example, chronic hypoventilation at a PaCO₂ of 60 mmHg would be associated with an increase in [HCO₃⁻] of 8 to 10 mEq/L, to a [HCO₃⁻] of 32 to 34 mEq/L, and a pH of 7.35 to 7.38. If neither an acute nor a chronic respiratory change could have resulted in the arterial blood gas measurements, then a metabolic disturbance must also be present.

Respiratory compensation for metabolic disturbances occurs more rapidly than renal compensation for respiratory disturbances (Table 2). Several general rules describe compensation. First, overcompensation is rare. Second, inadequate or excessive compensation suggests an additional primary disturbance. Third, an increased anion gap almost invariably indicates that hypobicarbonatemia is not compensatory.

The next question, whether an anion gap is present, should be assessed even if the arterial blood gases appear straightforward. The simultaneous occurrence of metabolic alkalosis and metabolic acidosis may minimize the influence of either disturbance on pH and [HCO₃⁻]; the combined abnormality may only be appreciated by examining the anion gap, if the metabolic acidosis is generated by a process that increases the anion gap. As noted previously, correct assessment of the anion gap requires correction for hypoalbuminemia (11,12). Metabolic acidoses associated with increased anion gaps require specific treatments, thus necessitating correct diagnoses. This is particularly important in assessing hyperchloremic metabolic acidosis after perioperative administration of large volumes of 0.9% saline (18). In these circumstances, no anion gap would be expected and no specific treatment of metabolic acidosis would be required (5,19).

The final question is whether the clinical data are consistent with the arterial blood gas data. Failure to consider the clinical status also may lead to serious errors in acid–base interpretation.

Examples

The foregoing has summarized an approach that simplifies interpretation. The following two hypothetical cases will be approached using the rules-of-thumb and sequential approach discussed above.

Example No. 1

A 65-year-old female has undergone 12 hours of an expected 16-hour radical neck dissection and flap construction. Estimated blood loss is 1000 mL. She has received three units of packed red blood cells and 9 L of 0.9% saline. Her blood pressure and heart rate have remained stable while anesthetized with 0.5% to 1.0% isoflurane in 70:30 nitrous oxide and oxygen. Urinary output is adequate. Arterial blood gas levels and serum electrolytes are shown in Table 9.

The step-by-step interpretation is as follows:

1. The pH is not life threatening and does not require immediate treatment.

Table 9 Hypobicarbonatemia and Hyperchloremic Acidosis During Prolonged Surgery and 0.9% Saline Infusion

Arterial blood gases	
pH	7.38
PaCO ₂	30 mmHg
[HCO ₃ ⁻]	17 mEq/L
Electrolytes	
Na ⁺	140 mEq/L
Cl ⁻	116 mEq/L
CO ₂	18 mEq/L
Anion gap	6 mEq/L
Serum albumin	2.0 g/dL

- Optional: The [H⁺] calculated from the pH is 42 nmol L⁻¹ (normal 40 nmol L⁻¹ plus 2 nmol L⁻¹), because the pH was 0.02 pH units below 7.40. Therefore, the Henderson equation balances.
- pH < 7.40, but is not frankly acidemic.
- The arterial blood gases cannot be adequately explained by acute hypocarbia. The predicted pH would be 7.48 and the predicted [HCO₃⁻] would be 22 mEq/L (Table 7).
- The data suggest metabolic acidosis.
- The question of compensation is not pertinent during general anesthesia with controlled mechanical ventilation, given that the patient's ventilatory drive does not determine PaCO₂. However, in a spontaneously breathing patient, hypocapnia of this magnitude would represent slight overcompensation (Table 2) and should prompt a search for a reason for primary respiratory alkalosis.
- During prolonged anesthesia and surgery, one might assume the presence of lactic acidosis and provide additional fluid therapy or otherwise attempt to improve perfusion. However, serum electrolytes reveal (Table 9) an anion gap that is slightly less than normal, indicating that the metabolic acidosis is probably the result of dilution of the ECV with a high-chloride fluid (or, in Stewart terms, reduction of the SID) (5). Correction of the anion gap for the serum albumin of 2.0 g dL⁻¹ only increases the anion gap to 10 to 11 mEq/L, again consistent with a hyperchloremic metabolic acidosis (9) and excluding an intercurrent anion-gap metabolic acidosis. Hyperchloremic acidosis secondary to infusion of high-chloride fluid requires no treatment.
- The clinical picture is compatible with the interpretation of the arterial blood gases and serum electrolytes.

Example No. 2

A 35-year-old male develops nausea with recurrent emesis persisting for 48 hours. An arterial blood gas reveals the results shown in the middle column of Table 10.

- The pH of 7.50 requires no immediate intervention.
- Optional: The [H⁺] is 32 nmol L⁻¹ (40 nmol L⁻¹ × 0.8); the Henderson equation balances.

Table 10 Metabolic Alkalosis Secondary to Nausea and Vomiting with Subsequent Lactic Acidosis Secondary to Hypovolemia

	Normal	Metabolic alkalosis	Metabolic acidosis
Blood gases			
pH	7.40	7.50	7.40
PaCO ₂ (mmHg)	40	45	40
[HCO ₃ ⁻] (mEq/L)	24	35	24
Serum electrolytes			
Na ⁺ (mEq/L)	140	140	140
Cl ⁻ (mEq/L)	105	94	94
CO ₂ (mEq/L)	25	36	25
Anion gap (mEq/L)	10	10	21

Table 11 Infusion of Lactated Ringer's Solution to Improve Perfusion in a Patient with Both an Underlying, Vomiting-Induced Metabolic Alkalosis and a Superimposed Lactic Acidosis Secondary to Hypovolemia

	Vomiting-induced metabolic alkalosis	Superimposed metabolic acidosis	Infusion of lactated Ringer's solution
Blood gases			
pH	7.50	7.40	7.52
PaCO ₂ (mmHg)	47	40	49
[HCO ₃ ⁻] (mEq/L)	35	24	39
Serum electrolytes			
Na ⁺ (mEq/L)	140	140	139
Cl ⁻ (mEq/L)	94	94	89
CO ₂ (mEq/L)	36	25	40
Anion gap (mEq/L)	10	21	10

- The pH is alkalemic, suggesting a primary alkalosis.
- An acute PaCO₂ of 46 mmHg would yield a pH of approximately 7.37; therefore, this is not simply an acute ventilatory disturbance.
- The [HCO₃⁻] of 35 mEq/L suggests a primary metabolic alkalosis.
- The limits of respiratory compensation for metabolic alkalosis are wide and difficult to predict for individual patients. The rules-of-thumb, summarized in Table 2, suggest that [HCO₃⁻] + 15 should equal the last two digits of the pH and that the PaCO₂ should increase 5 to 6 mmHg for every 10 mEq/L change in serum [HCO₃⁻], i.e., pH = 7.50 and PaCO₂ = 45 mmHg.
- The anion gap is 12 mEq/L.
- The diagnosis of a primary metabolic alkalosis with compensatory hypoventilation is consistent with the history of recurrent vomiting. Consider how the arterial blood gases would change if vomiting were sufficiently severe to produce hypoperfusion and lactic acidosis (third column, Table 10).

Now consider the likely consequences of infusing lactated Ringer's solution to improve perfusion in a patient with this combination of metabolic alkalosis and metabolic acidosis (Table 11). Not only does fluid infusion reverse lactic acidosis, restoring the acid-base picture of the original vomiting-induced metabolic alkalosis, but there is a further increase in serum [HCO₃⁻], reflecting the generation of bicarbonate from lactate. Of course, given sufficient time and restoration of normovolemia, the consequent severe metabolic alkalosis should resolve.

This sequence illustrates the important concept that the final pH, PaCO₂, and [HCO₃⁻] represent the result of all of the vectors operating on acid-base status. Complex or "triple disturbances" can only be interpreted using a thorough, stepwise approach.

INFLUENCE OF FLUID INFUSION ON SERUM ELECTROLYTES

Sodium

Physiologic Role

Na⁺, the principal extracellular cation and solute, is essential for the generation of action potentials in neurologic and cardiac tissue. Disorders (pathological increases or decreases) of *total body sodium* are associated with corresponding increases or decreases of ECV and PV. Disorders of sodium *concentration* result from relative water excesses (hyponatremia) or deficits (hypernatremia). Regulation of total body sodium and [Na⁺] is accomplished primarily by the endocrine and renal systems. Secretion of aldosterone and atrial natriuretic peptide control *total body sodium*. Antidiuretic hormone (ADH), which is secreted in response to increased osmolality or decreased blood pressure, primarily regulates [Na⁺].

Hyponatremia

Hyponatremia, defined as [Na⁺] < 130 mEq/L, is the most common electrolyte disturbance in hospitalized patients. In the majority of hyponatremic, hospitalized patients, total body sodium is normal or increased. The most common clinical associations with hyponatremia

include recent surgery, acute intracranial disease, malignant disease, medications, and acute pulmonary disease. Hyponatremia is associated with substantially increased mortality, both as a direct effect of hyponatremia and because hyponatremia is associated with severe systemic disease. The signs and symptoms of hyponatremia depend on both the rate and severity of the decrease in plasma $[\text{Na}^+]$. Symptoms that can accompany severe hyponatremia ($[\text{Na}^+] < 120 \text{ mEq/L}$) include loss of appetite, nausea, vomiting, cramps, weakness, altered level of consciousness, coma, and seizures.

At least 4.0% of postoperative patients develop plasma $[\text{Na}^+] < 130 \text{ mEq/L}$ [20]. Although neurologic manifestations usually do not accompany postoperative hyponatremia, signs of hypervolemia are occasionally present (20). Much less frequently, postoperative hyponatremia is accompanied by mental status changes, seizures, and transtentorial herniation symptoms (21), attributable, in part, to the intravenous administration of hypotonic fluids, secretion of ADH, and other factors, including drugs and altered renal function, which influence perioperative water balance (22). Menstruant women may be particularly vulnerable to brain damage secondary to postoperative hyponatremia (23). In smaller patients, plasma $[\text{Na}^+]$ changes more than in larger patients, in response to similar volumes of hypotonic fluids. In an editorial accompanying a report (24) of an apparent postoperative syndrome of inappropriate antidiuretic hormone excess (SIADH) in a 30-kg, 10-year-old girl, Arieff (25) suggested that children receive no sodium-free water perioperatively. Postoperative hyponatremia can develop even with infusion of isotonic fluids, if ADH is persistently increased. Twenty-four hours after uncomplicated gynecologic surgery, the mean plasma $[\text{Na}^+]$ in 22 women (mean age 42 years) had decreased from 140 ± 1 to $136 \pm 0.5 \text{ mEq/L}$ (26). Although the patients retained sodium perioperatively, they retained proportionately more water (an average of 1.1 L of electrolyte-free water). Careful postoperative attention to fluid and electrolyte balance may minimize the occurrence of symptomatic hyponatremia.

Acute CNS manifestations relate to brain overhydration. Because the blood–brain barrier is poorly permeable to sodium but freely permeable to water, a rapid decrease in plasma $[\text{Na}^+]$ promptly increases both the extracellular and intracellular brain water. Because the brain rapidly compensates for changes in osmolality, acute hyponatremia produces more severe symptoms than chronic hyponatremia. The symptoms of chronic hyponatremia probably relate to depletion of brain electrolytes. Once the brain volume has compensated for hyponatremia, rapid increases in $[\text{Na}^+]$ may lead to abrupt brain dehydration.

Hyponatremia is classified as pseudohyponatremia or true hyponatremia. Pseudohyponatremia was an artifact associated with the use of flame photometry, now an obsolete technique, to measure plasma $[\text{Na}^+]$ in severely hyperproteinemic or hyperlipidemic patients. The current analytic method, direct potentiometry, directly measures $[\text{Na}^+]$ and is uninfluenced by nonaqueous components such as proteins and lipids.

In true hyponatremia, serum osmolality may be normal, high, or low. Hyponatremia with a normal or high serum osmolality results from the presence of a nonsodium solute, such as glucose or mannitol, which holds water within the extracellular space and results in dilutional hyponatremia. The presence of a nonsodium solute (or of factitious hyponatremia) may be inferred if measured osmolality exceeds calculated osmolality by more than 10 mOsm kg^{-1} . For example, plasma $[\text{Na}^+]$ decreases by approximately 2.4 mEq/L for each 100 mg dL^{-1} rise in glucose concentration, with perhaps even greater decreases for glucose concentrations more than 400 mg dL^{-1} (27). A common perioperative cause of hyponatremia associated with normal osmolality is the absorption of large volumes of sodium-free irrigating solutions (containing mannitol, glycine, or sorbitol as the solute) during transurethral prostatic resection (28). Neurologic symptoms are minimal if mannitol is employed, because the agent does not cross the blood–brain barrier and is excreted with water in the urine. In contrast, as glycine or sorbitol is metabolized, hyposmolality will gradually develop and cerebral edema may appear as a late complication, i.e., hyposmolality is more important in generating symptoms than hyponatremia per se (28). True hyponatremia with a normal or elevated serum osmolality also may accompany renal insufficiency. Blood urea nitrogen (BUN), included in the calculation of total osmolality, distributes throughout both ECV and intracellular volume (ICV). Calculation of *effective* osmolality ($2[\text{Na}^+] + \text{glucose}/18$) excludes the contribution of urea to tonicity and demonstrates true hypotonicity.

True hyponatremia with low serum osmolality may be associated with a high, low, or normal total body sodium and PV. Therefore, hyponatremia with hyposmolality is evaluated

by assessing the total body sodium content, BUN, serum creatinine (SCr), urinary osmolality, and urinary $[\text{Na}^+]$. Hyponatremia with increased total body sodium is characteristic of edematous states, i.e., congestive heart failure, cirrhosis, nephrosis, and renal failure. Aquaporin 2, the vasopressin-regulated water channel, is upregulated in experimental congestive heart failure (29) and cirrhosis (30) and decreased by chronic vasopressin stimulation (31). In patients with renal insufficiency, reduced urinary diluting capacity can lead to hyponatremia if excess free water is given.

The underlying mechanism of hypovolemic hyponatremia is secretion of ADH in response to a volume contraction in association with ongoing oral or intravenous intake of hypotonic fluid (32). Angiotensin II also decreases renal free water clearance. Thiazide diuretics, unlike loop diuretics, promote hypovolemic hyponatremia by interfering with urinary dilution in the distal tubule (32). Hypovolemic hyponatremia associated with a urinary $[\text{Na}^+] > 20 \text{ mmol L}^{-1}$ suggests mineralocorticoid deficiency, especially if serum $[\text{K}^+]$, BUN, and SCr are increased (32). In functionally hypovolemic postoperative patients, Arief (25) has argued that the diagnosis of SIADH may be inaccurately applied, because, by definition, ADH secretion in such patients would be "appropriate."

The cerebral salt-wasting syndrome is an often severe, symptomatic salt-losing diathesis that appears to be mediated by a brain natriuretic peptide (33) and is distinct from SIADH; patients at risk include those with cerebral lesions due to trauma, subarachnoid hemorrhage, tumors, and infection (34–36).

Euvolemic hyponatremia most commonly is associated with nonosmotically mediated vasopressin secretion, e.g., glucocorticoid deficiency, hypothyroidism, thiazide-induced hyponatremia, SIADH, and the reset osmostat syndrome. Total body sodium and ECV are relatively normal, and edema is rarely evident. SIADH may be idiopathic but also is associated with diseases of the CNS and with pulmonary diseases (Table 12). Euvolemic hyponatremia is usually associated with exogenous ADH administration, pharmacologic potentiation of ADH action, drugs that mimic the action of ADH in the renal tubules, or excessive ectopic ADH secretion. Tissues from some small-cell lung cancers, duodenal cancers, and pancreatic cancers increase ADH production in response to osmotic stimulation (38).

If both $[\text{Na}^+]$ and measured osmolality are below the normal range, hyponatremia is further evaluated by assessing volume status using physical findings and laboratory data. In hypovolemic patients or edematous patients, the ratio of BUN to SCr should be greater than 20:1. Urinary $[\text{Na}^+]$ is generally less than 15 mEq/L in edematous states and volume depletion, and more than 20 mEq/L in hyponatremia secondary to renal salt wasting or renal failure with water retention.

Table 12 Causes of the Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Neoplasms	Pulmonary diseases
Bronchogenic carcinoma	Tuberculosis
Pancreatic carcinoma	Pneumonia
Carcinoma of the duodenum	Bronchiectasis
Prostate carcinoma	Aspergillosis
Thymoma	Cystic fibrosis
Lymphoma	Positive pressure ventilation
Mesothelioma	Medications
Central nervous system diseases	Opiates
Head trauma	Chlorpropamide
Subdural hematoma	Carbamazepine
Subarachnoid hemorrhage	Phenothiazines
Cerebrovascular accident	Tricyclic antidepressants
Meningitis	Clofibrate
Encephalitis	Vincristine
Brain abscess	Cyclophosphamide
Hydrocephalus	Oxytocin
Brain tumors	Miscellaneous
Guillain-Barré	Acute intermittent porphyria
General surgery	Pain
Delirium tremens	Nausea
	Psychosis

The criteria for the diagnosis of SIADH include hypotonic hyponatremia, urinary osmolality more than 100 to 150 mmol kg⁻¹, absence of ECV depletion, normal thyroid and adrenal function, and normal cardiac, hepatic, and renal function. Urinary [Na⁺] should be more than 30 mEq/L, unless fluids have been restricted.

Strategies for treatment of hyponatremia are dependent on appropriate management of fluid administration. In hypovolemic, hyponatremic patients, the blood volume must be restored, usually by infusion of 0.9% saline, and excessive sodium losses must be curtailed. Correction of hypovolemia usually results in removal of the stimulus for ADH release, accompanied by water diuresis. Treatment of hyponatremia associated with a normal or high serum osmolality requires reduction of the elevated concentrations of the responsible solute. Uremic patients are treated by free water restriction or dialysis. Treatment of edematous (hypervolemic) patients necessitates restriction of both sodium and water (Fig. 2). Therapy is directed toward improving cardiac output and renal perfusion and using diuretics to inhibit sodium reabsorption.

The cornerstone of SIADH management is free water restriction and elimination of precipitating causes. Water restriction sufficient to decrease total body water (TBW) by 0.5 to 1.0 L day⁻¹ decreases ECV even if excessive ADH secretion continues. The resultant reduction in the glomerular filtration rate (GFR) enhances proximal tubular reabsorption of salt and water, thereby decreasing free water generation, and stimulates aldosterone secretion. As long as free water losses (i.e., renal, skin, and gastrointestinal) exceed free water intake, serum [Na⁺] will increase. During the treatment of hyponatremia, increases in plasma [Na⁺] are determined both by the composition of the infused fluid and by the rate of renal free water excretion (39). Free water excretion can be increased by administering furosemide.

Neurologic symptoms or profound hyponatremia ([Na⁺] < 115–120 mEq/L) require more aggressive therapy. Hypertonic (3%) saline is most clearly indicated in patients who have seizures or patients who acutely develop symptoms of water intoxication secondary to intravenous fluid administration. In such cases, 3% saline may be administered at a rate of 1 to 2 mL kg⁻¹ hr⁻¹, to increase plasma [Na⁺] by 1 to 2 mEq/L hr⁻¹; however, this treatment should not continue for more than a few hours. Three-percent saline may only transiently increase plasma [Na⁺], because ECV expansion results in increased urinary sodium excretion. Intravenous furosemide, combined with quantitative replacement of urinary sodium losses with 0.9% or 3.0% saline, can rapidly increase plasma [Na⁺], in part, by increasing free water clearance.

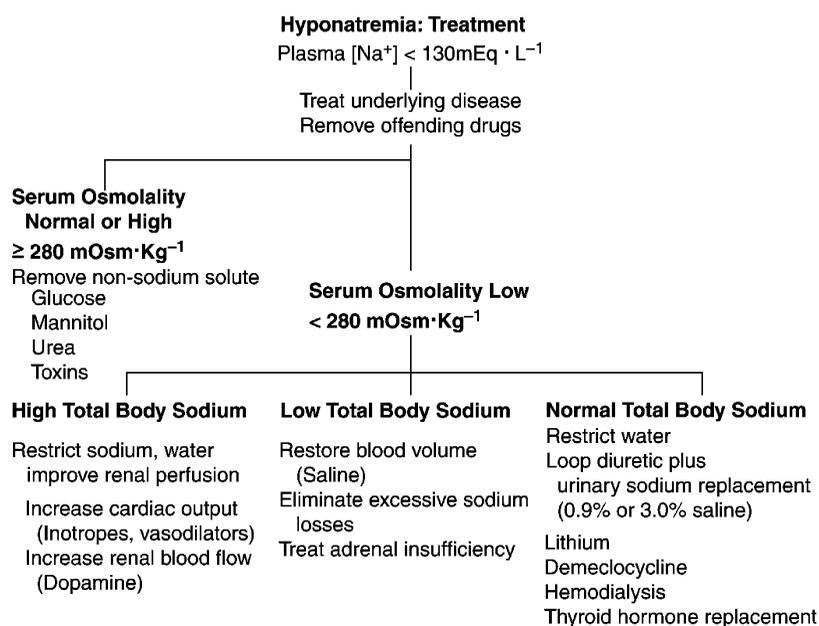


Figure 2 Hyponatremia is treated according to the etiology of the disturbance, the level of serum osmolality, and a clinical estimation of total body sodium.

The rate of treatment of hyponatremia continues to generate controversy, extending from “too fast, too soon” to “too slow, too late.” Although delayed correction may result in a neurologic injury, inappropriately rapid correction may result in abrupt brain dehydration (Fig. 3) or permanent neurologic sequelae (i.e., osmotic demyelination syndrome) (41), cerebral hemorrhage, or congestive heart failure. The symptoms of the osmotic demyelination syndrome vary from mild (transient behavioral disturbances or seizures) to severe (including pseudobulbar palsy and quadriparesis) (42).

The principal determinants of neurologic injury appear to be the magnitude and chronicity of hyponatremia and the rate of correction. The osmotic demyelination syndrome is more likely when hyponatremia has persisted for more than 48 hours (43). Most patients in whom the osmotic demyelination syndrome is fatal have undergone correction of plasma $[Na^+]$ of more than 20 mEq/L day⁻¹. Other risk factors for the development of the osmotic demyelination syndrome include alcoholism, poor nutritional status, liver disease, burns, and hypokalemia.

The clinician faces formidable difficulties in predicting the rate at which plasma $[Na^+]$ will increase, because increases in plasma $[Na^+]$ are determined both by the composition of the infused fluid and by the rate of renal free water excretion (39). The expected change in plasma $[Na^+]$ resulting from 1 L of selected infusate can be estimated using the following equation (44).

$$\Delta[Na^+]_s = \frac{[Na^+]_{inf} - [Na^+]_s}{TBW + 1} \tag{6}$$

where $\Delta[Na^+]_s$ is the change in the patient’s serum $[Na^+]$; $[Na^+]_{inf}$, $[Na^+]$ of the infusate; $[Na^+]_s$, the patient’s serum $[Na^+]$; TBW, the patient’s estimated TBW in liters; and 1, a factor added to take into account the volume of infusate.

Treatment should be interrupted or slowed when symptoms improve. Frequent determinations of $[Na^+]$ are important to prevent correction at a rate greater than 10 mEq/L in 24

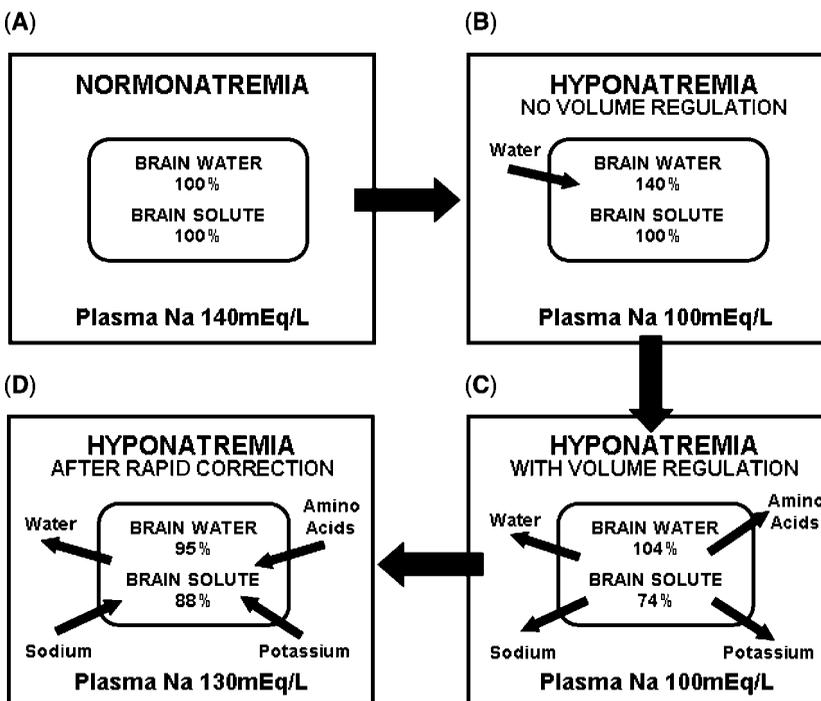


Figure 3 Brain water and solute in concentrations in hyponatremia. If normal plasma sodium (Na) (A) suddenly decreased, the increase in brain water theoretically would be proportional to the decrease in plasma Na (B). However, because of adaptive loss of cerebral intracellular solute, cerebral edema is minimized in chronic hyponatremia (C). Once adaptation has occurred, a rapid return of plasma Na concentration toward a normal level results in brain dehydration (D). *Source:* From Ref. 40.

hours (43). Initially, plasma $[\text{Na}^+]$ may be increased by 1 to 2 mEq/L hr^{-1} ; however, to limit the possibility of osmotic demyelination, plasma $[\text{Na}^+]$ should not be increased more than 10 mEq/L in 24 hours or 25 mEq/L in 48 hours (42). Another proposed sequence for treating symptomatic hyponatremia is to increase $[\text{Na}^+]$ promptly by about 10 mmol L^{-1} , then to proceed more slowly. The rationale is that cerebral water content is increased by approximately 10% in chronic hyponatremia (32). Hyponatremia should be avoided. Once plasma $[\text{Na}^+]$ exceeds 120 to 125 mEq/L, water restriction alone is usually sufficient to normalize $[\text{Na}^+]$. As acute hyponatremia is corrected, CNS signs and symptoms usually improve within 24 hours, although 96 hours may be necessary for maximal recovery.

For patients who require long-term pharmacologic therapy of hyponatremia, demeclocycline is now the drug of choice (32). Although better tolerated than lithium, demeclocycline may induce nephrotoxicity, a particular concern in patients with hepatic dysfunction. Hemodialysis is occasionally necessary in severely hyponatremic patients who cannot be adequately managed with drugs or hypertonic saline. Once hyponatremia has improved, careful fluid restriction is necessary to avoid recurrence of hyponatremia. In the future, vasopressin receptor antagonists may be used to treat hyponatremia (45). The vasopressin antagonist tolvaptan has been used in clinical trials to enhance water excretion (46).

Hypernatremia

Hypernatremia ($[\text{Na}^+] > 150 \text{ mEq/L}$) indicates an absolute or relative water deficit. Normally, slight increases in tonicity or $[\text{Na}^+]$ stimulate thirst and ADH secretion. Therefore, severe, persistent hypernatremia occurs only in patients who cannot respond to thirst by voluntary ingestion of fluid, i.e., obtunded patients, anesthetized patients, and infants.

Hypernatremia produces neurologic symptoms (including stupor, coma, and seizures), hypovolemia, renal insufficiency (occasionally progressing to renal failure), and decreased urinary concentrating ability (47,48). Because hypernatremia frequently results from diabetes insipidus (DI) or osmotically induced losses of sodium and water, many patients are hypovolemic or bear the stigmata of renal disease. Postoperative neurosurgical patients who have undergone pituitary surgery are at particular risk of developing transient or prolonged DI. Polyuria may be present for only a few days within the first week of surgery, may be permanent, or may demonstrate a triphasic sequence—early DI, return of urinary concentrating ability, then recurrent DI.

The clinical consequences of hypernatremia are most serious at the extremes of age and when hypernatremia develops abruptly. Geriatric patients are at an increased risk of hypernatremia because of decreased renal concentrating ability and thirst. Brain shrinkage secondary to rapidly developing hypernatremia may damage delicate cerebral vessels, leading to subdural hematoma, subcortical parenchymal hemorrhage, subarachnoid hemorrhage, and venous thrombosis. Polyuria may cause bladder distention, hydronephrosis, and permanent renal damage. At the cellular level, restoration of cell volume occurs remarkably quickly after tonicity is altered (Fig. 4) (49). Although the mortality of hypernatremia is 40% to 55%, it is unclear whether hypernatremia is the cause or a marker of severe associated disease.

Surprisingly, if plasma $[\text{Na}^+]$ is initially normal, moderate acute increases in plasma $[\text{Na}^+]$ do not appear to precipitate central pontine myelinolysis. However, larger accidental increases in plasma $[\text{Na}^+]$ have produced severe consequences in children. In experimental animals, acute severe hypernatremia (acute increase from 146 to 170 mEq/L) caused neuronal damage at 24 hours, suggestive of early central pontine myelinolysis (50).

By definition, hypernatremia indicates an absolute or relative water deficit and is always associated with hypertonicity. Hypernatremia can be generated by hypotonic fluid loss (as in burns), gastrointestinal losses, diuretic therapy, osmotic diuresis, renal disease, mineralocorticoid excess or deficiency, and iatrogenic causes; it can also be generated by isolated water loss, as in central or nephrogenic DI. The acquired form of nephrogenic DI is more common and usually less severe than the congenital form. As chronic renal failure advances, most patients have defective concentrating ability and produce hypotonic urine, resulting from resistance to ADH. Because hypovolemia accompanies most pathologic water loss, signs of hypoperfusion also may be present. In many patients, before the development of hypernatremia, an increased volume of hypotonic urine suggests an abnormality in water balance. Although uncommon as a cause of hypernatremia, isolated sodium gain occasionally occurs in patients who receive large quantities of sodium, such as treatment of metabolic acidosis with 8.4% sodium

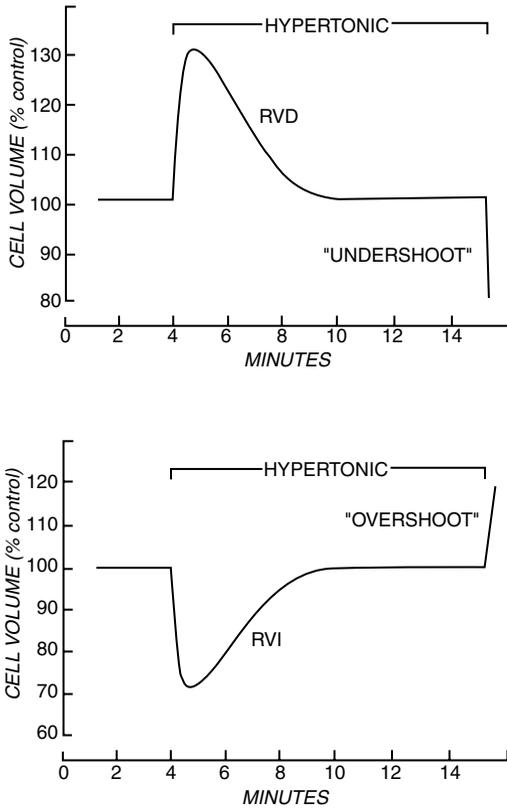


Figure 4 Activation of mechanisms regulating cell volume in response to acute osmotic stress. Regulatory volume decrease and regulatory volume increase refer to compensatory losses and gains of solutes. Although the course of these regulatory volume decreases and increases varies with the type of cell and experimental conditions, typically the responses occur over a period of minutes. Returning volume-regulated cells to normotonic conditions causes shrinkage or swelling. *Source:* From Ref. 49.

bicarbonate, in which $[\text{Na}^+]$ is approximately 1000 mEq/L, or perioperative or prehospital treatment with hypertonic saline resuscitation solutions.

Hypernatremic patients can be separated into three groups, based on clinical assessment of ECV. In evaluating hypernatremia, it is important to note that plasma $[\text{Na}^+]$ does not reflect total body sodium, which must be estimated separately based on signs of the adequacy of ECV. In polyuric, hypernatremic patients, the next differential diagnostic decision is between solute diuresis and DI. Measurement of urinary sodium and osmolality can help to differentiate the various causes. A urinary osmolality less than 150 mOsm kg^{-1} in the setting of hypertonicity and polyuria is diagnostic of DI.

Fluid management is central to the management of hypernatremia. In hypernatremia produced by water loss, treatment consists of repletion of water as well as associated deficits of total body sodium and other electrolytes (Table 13). Common errors in treating hypernatremia include excessively rapid correction as well as failure to quantify the magnitude of the water deficit, failing to account for ongoing maintenance requirements, and continued fluid losses in planning therapy.

The first step in treating hypernatremia is to estimate the TBW deficit, which can be accomplished by inserting the measured plasma $[\text{Na}^+]$ into the equation:

$$\text{TBW deficit} = 0.6 \times \text{body weight (kg)} \times \left(\frac{[\text{Na}^+] - 140}{140} \right) \quad (7)$$

where 140 is the middle of the normal range for $[\text{Na}^+]$.

Hypernatremia must be corrected slowly because of the risk of neurologic sequelae such as seizures or cerebral edema (51). At the cellular level, restoration of cell volume occurs remarkably quickly after tonicity is altered; as a consequence, acute treatment of hypertonicity may result in overshooting the original, normotonic cell volume (49,51). The water deficit should be replaced over 24 to 48 hours, and the plasma $[\text{Na}^+]$ should not be reduced by more than 1 to 2 mEq/L hr^{-1} . Reversible underlying causes should be treated. Hypovolemia should be corrected promptly with 0.9% saline. Although the $[\text{Na}^+]$ of 0.9% saline is 154 mEq/L, the

Table 13 Hyponatremia: Acute Treatment

Sodium depletion (hypovolemia)
Hypovolemia correction (0.9% saline)
Hyponatremia correction (hypotonic fluids)
Sodium overload (hypervolemia)
Enhance sodium removal (loop diuretics, dialysis)
Replace water deficit (hypotonic fluids)
Normal total body sodium (euvolemia)
Replace water deficit (hypotonic fluids)
Control diabetes insipidus:
Central diabetes insipidus:
Desmopressin, 10–20 µg intranasally; 2–4 µg subcutaneously
Aqueous vasopressin, 5 U q 2–4 hours intramuscularly or subcutaneously
Nephrogenic diabetes insipidus:
Restrict sodium, water intake
Thiazide diuretics

solution is effective in treating volume deficits and will reduce $[\text{Na}^+]$ that exceeds 154 mEq/L. Once hypovolemia is corrected, water can be replaced orally or with intravenous hypotonic fluids, depending on the ability of the patient to tolerate oral hydration. In the occasional sodium-overloaded patient, sodium excretion can be accelerated using loop diuretics or dialysis.

The management of hyponatremia secondary to DI varies according to whether the etiology is central or nephrogenic (Table 13). The two most suitable agents for correcting central DI (an ADH deficiency syndrome) are desmopressin (DDAVP) and aqueous vasopressin. DDAVP, given subcutaneously in a dose of 1 to 4 µg or intranasally in a dose of 5 to 20 µg every 12 to 24 hours, is effective in the vast majority of patients. DDAVP is less likely than vasopressin to produce vasoconstriction and abdominal cramping (52). Incomplete ADH deficits (partial DI) often are effectively managed with pharmacologic agents that stimulate ADH release or enhance the renal response to ADH. Chlorpropamide, which potentiates the renal effects of vasopressin, and carbamazepine, which enhances vasopressin secretion, have been used to treat partial central DI, but are associated with clinically important side effects. In nephrogenic DI, salt and water restriction or thiazide diuretics induce contraction of ECV, thereby enhancing fluid reabsorption in the proximal tubules. If less filtrate passes through into the collecting ducts, less water will be excreted.

Potassium

The serum $[\text{K}^+]$ measures about 0.5 mEq/L higher than plasma $[\text{K}^+]$ due to cell lysis during clotting. Total body potassium in a 70-kg adult is approximately 4256 mEq, of which 4200 mEq is intracellular; of the 56 mEq in the ECV, only 12 mEq is located in the PV. The ratio of intracellular to extracellular potassium contributes to the resting potential difference across cell membranes and, therefore, to the integrity of cardiac and neuromuscular transmission. The primary mechanism that maintains potassium inside cells is the negative voltage created by the transport of three sodium ions out of the cell for every two potassium ions transported, as given in Fig. 5 (53). Both insulin and β agonists promote potassium entry into cells (53,54). In contrast, α adrenergic agonists impair the cellular potassium uptake (55). Metabolic acidosis

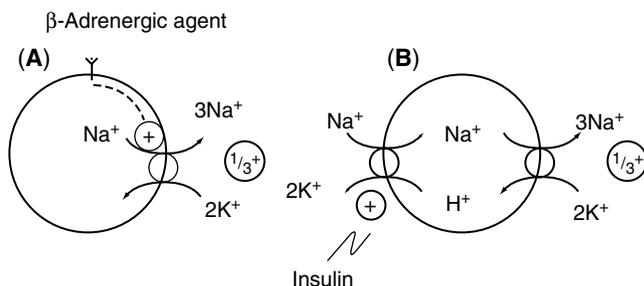


Figure 5 Hormones shifting potassium into cells. Major hormones involved are (A) insulin and (B) β_2 -adrenergic agents. Source: From Ref. 53.

tends to shift potassium out of cells, whereas metabolic alkalosis favors movement into cells. As long as the GFR is more than 8 mL/kg, dietary potassium intake, unless greater than normal, can be excreted.

Hypokalemia

Hypokalemia ($[K^+] < 3.0$ mEq/L), which is uncommon among healthy persons, is a frequent complication of treatment with diuretic drugs and occasionally complicates other diseases and treatment regimens (55). As a general rule, a chronic decrement of 1.0 mEq/L in plasma $[K^+]$ corresponds to a total body deficit of approximately 200 to 300 mEq. In uncomplicated hypokalemia, the potassium deficit exceeds 300 mEq if plasma $[K^+]$ is less than 3.0 mEq/L and 700 mEq if plasma $[K^+]$ is less than 2.0 mEq/L. Plasma $[K^+]$ poorly reflects total body potassium; hypokalemia may occur with normal, low, or high total body potassium.

Hypokalemia causes muscle weakness and, when severe, may even cause paralysis. With chronic potassium loss, the ratio of intracellular to extracellular $[K^+]$ remains relatively stable; in contrast, acute redistribution of potassium from the extracellular to the intracellular space substantially changes resting membrane potentials.

Cardiac rhythm disturbances are among the most dangerous complications of potassium deficiency. Acute hypokalemia causes hyperpolarization of cardiac cells and may lead to ventricular escape activity, reentrant phenomena, ectopic tachycardias, and delayed conduction. In patients taking digoxin, hypokalemia increases toxicity by increasing myocardial digoxin binding and pharmacologic effectiveness. Hypokalemia contributes to systemic hypertension, especially when combined with a high-sodium diet (56). In diabetic patients, hypokalemia impairs insulin secretion and end-organ sensitivity to insulin. Although no clear threshold has been defined for a level of hypokalemia below which anesthesia and surgery should be delayed, $[K^+] < 3.5$ mEq/L has been associated with an increased incidence of perioperative dysrhythmias, especially atrial fibrillation/flutter, in cardiac surgical patients (57).

Potassium depletion also induces defects in renal concentrating ability, resulting in polyuria and a reduction in the GFR. Potassium replacement improves GFR, although the concentrating deficit may not improve for several months after treatment. If hypokalemia is sufficiently prolonged, chronic renal interstitial damage may occur. In experimental animals, hypokalemia was associated with intrarenal vasoconstriction and a pattern of renal injury similar to that produced by ischemia (58).

Hypokalemia may result from chronic depletion of total body potassium or from acute redistribution of potassium from the ECV to the ICV. Redistribution of potassium into cells occurs when the activity of the sodium-potassium adenosine triphosphatase (ATPase) pump is acutely increased by extracellular hyperkalemia or increased intracellular concentrations of sodium, as well as by insulin, carbohydrate loading (which stimulates release of endogenous insulin), β_2 agonists, and aldosterone (53). Both metabolic and respiratory alkalosis lead to decreases in plasma $[K^+]$ (53,56).

Causes of chronic hypokalemia include those etiologies associated with renal potassium conservation (extrarenal potassium losses; a low urinary $[K^+]$) and those with renal potassium wasting (53,56). A low urinary $[K^+]$ suggests inadequate dietary intake or extrarenal depletion (in the absence of recent diuretic use). Diuretic-induced urinary potassium losses are frequently associated with hypokalemia, secondary to increased aldosterone secretion, alkalemia, and increased renal tubular flow. Aldosterone does not cause renal potassium wasting unless sodium ions are present; i.e., aldosterone primarily controls sodium reabsorption, not potassium excretion. Renal tubular damage due to nephrotoxins such as aminoglycosides or amphotericin B may also cause renal potassium wasting.

Initial evaluation of hypokalemia includes a medical history (e.g., diarrhea, vomiting, and diuretic or laxative use), physical examination (e.g., hypertension, cushingoid features, and edema), measurement of serum electrolytes (e.g., magnesium), arterial pH assessment, and evaluation of the electrocardiogram (ECG). A majority of trauma patients develop hypokalemia that returns to normal within 24 hours without specific therapy (55). Measurement of 24-hour urinary excretion of sodium and potassium may distinguish extrarenal from renal causes. Magnesium deficiency, associated with aminoglycoside and cisplatin therapy, can generate hypokalemia that is resistant to replacement therapy. Plasma renin and aldosterone levels may be helpful in the differential diagnosis. Characteristic electrocardiographic

Table 14 Hypokalemia: Treatment

Correct precipitating factors
Increased pH
Decreased $[Mg^{2+}]$
Drugs
Mild hypokalemia ($[K^+] > 2.0$ mEq/L)
Intravenous KCl infusion ≤ 10 mEq/hr
Severe hypokalemia ($[K^+] \leq 2.0$ mEq/L, paralysis or ECG changes)
Intravenous KCl infusion ≤ 40 mEq/hr
Continuous ECG monitoring
If life-threatening, 5–6 mEq bolus

Abbreviation: ECG, electrocardiogram.

changes associated with hypokalemia include flat or inverted T waves, prominent U waves, and ST segment depression.

The treatment of hypokalemia consists of potassium repletion, correction of alkalemia, and removal of offending drugs (Table 14). Hypokalemia secondary only to acute redistribution may not require treatment. There is no urgent need for potassium replacement therapy in asymptomatic patients with mild-to-moderate hypokalemia (3–3.5 mEq/L). If total body potassium is decreased, oral potassium supplementation is preferable to intravenous replacement. Potassium is usually replaced as a chloride salt because coexisting chloride deficiency may limit the ability of the kidney to conserve potassium.

Potassium repletion must be performed cautiously (i.e., usually at a rate of 10–20 mEq hr⁻¹ or less), because the magnitude of potassium deficits is unpredictable. Plasma $[K^+]$ and ECG must be monitored during rapid repletion (more than 10–20 mEq hr⁻¹) to avoid hyperkalemic complications (55,59). Plasma $[K^+]$ and the ECG should be monitored to detect inadvertent hyperkalemia. Particular care should be taken in patients who have concurrent acidemia, type IV renal tubular acidosis, or diabetes mellitus, and in patients receiving nonsteroidal anti-inflammatory agents, angiotensin converting enzyme inhibitors, or beta blockers, all of which delay movement of extracellular potassium into cells.

However, in patients with life-threatening dysrhythmias secondary to hypokalemia, serum $[K^+]$ must be rapidly increased. Assuming that PV in a 70-kg adult is 3.0 L, administration of 6.0 mEq of potassium in 1 minute will increase serum $[K^+]$ by no more than 2.0 mEq/L, because redistribution into interstitial fluid will rapidly decrease the quantity remaining in the PV (53).

Hypokalemia associated with hyperaldosteronemia (e.g., primary aldosteronism and Cushing's syndrome) usually responds favorably to reduced sodium intake and increased potassium intake. The adverse effects of hypokalemia are aggravated by hypomagnesemia, which also impairs potassium conservation and should be treated as a part of the management of hypokalemia. Potassium supplements or potassium-sparing diuretics should be given cautiously to patients who have diabetes mellitus or renal insufficiency, which limit compensation for acute hyperkalemia. In patients such as those having diabetic ketoacidosis (and thus are both hypokalemic and acidemic), potassium administration should accompany correction of acidemia to avoid a precipitous decrease in plasma $[K^+]$ as the pH increases.

In patients with normal serum potassium accompanied by symptoms of potassium depletion (e.g., muscle fatigue), history of potassium loss, or insufficient intake, or in patients in whom potassium depletion may be a special threat, e.g., patients on diuretics, digitalis, or β_2 agonists, muscle biopsy with measurement of the muscle potassium concentration may be a useful procedure to detect and quantify potassium depletion.

Hyperkalemia

The most lethal manifestations of hyperkalemia ($[K^+] > 5.0$ mEq/L) involve the cardiac conducting system and include dysrhythmias, conduction abnormalities, and cardiac arrest. If plasma $[K^+]$ increases but remains below 6.0 mEq/L, cardiac effects are negligible. As the concentration increases further, the ECG shows tall, peaked T waves, especially in the precordial leads. With further increases, the PR interval becomes prolonged, followed by a decrease in the amplitude of the P wave. Finally, the QRS complex widens into a pattern resembling a sine wave, as a prelude to cardiac standstill (Fig. 6) (60). In anesthesia practice, the classic example

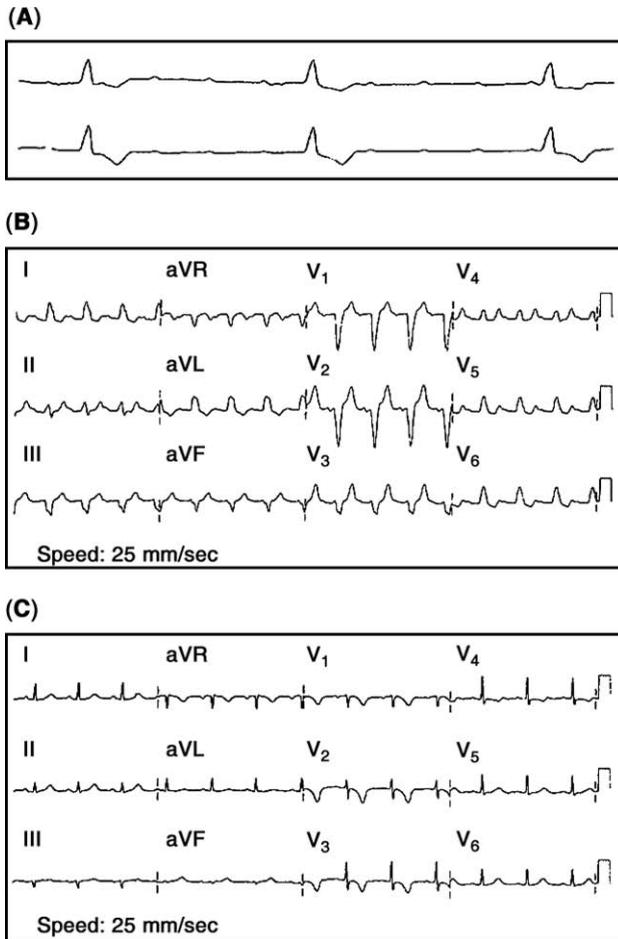


Figure 6 Electrocardiographic changes due to hyperkalemia occurring in a 42-year-old woman undergoing placement of an arteriovenous fistula for permanent hemodialysis access to treat end-stage renal disease. During dissection of the brachial artery under local anesthesia, her cardiac rhythm converted from normal sinus rhythm to complete heart block with ventricular escape (approximately 25 beats/min) (Panel A). Two ampules of calcium gluconate (9.2 mEq) were administered intravenously. An electrocardiogram revealed sinus tachycardia with profound prolongation of the QRS interval (left-bundle-branch morphology), first-degree atrioventricular block, and “peaked” T waves (Panel B). The serum potassium concentration was 8.6 mmol/L. After reduction of the serum potassium concentration, the electrocardiogram showed sinus rhythm with normalization of the PR and QRS intervals. Anteroseptal ST wave and T wave changes were noted on subsequent electrocardiograms (Panel C). A cardiac exercise imaging study did not show ischemia. *Source:* From Ref. 60.

of hyperkalemic cardiac toxicity is associated with the administration of succinylcholine to paraplegic or quadriplegic patients or patients with severe burns (61). Hyperkalemic cardiotoxicity is enhanced by hyponatremia, hypocalcemia, or acidosis. Because progression to fatal cardiotoxicity is unpredictable and often swift, the presence of hyperkalemic ECG changes mandates immediate therapy. The life-threatening cardiac effects usually require more urgent treatment than other manifestations of hyperkalemia. However, ascending muscle weakness appears when plasma $[K^+]$ approaches 7.0 mEq/L, and may progress to flaccid paralysis, inability to phonate, and respiratory arrest.

The most important diagnostic issues are medical history, emphasizing recent drug therapy, and assessment of renal function. Although the ECG may provide the first suggestion of hyperkalemia in some patients, and despite the well-described effects of hyperkalemia on cardiac conduction and rhythm, the ECG is an insensitive and nonspecific method of detecting hyperkalemia (62). If hyponatremia is also present, adrenal function should be evaluated.

Hyperkalemia may occur with normal, high, or low total body potassium stores. A deficiency of aldosterone, a major regulator of potassium excretion, leads to hyperkalemia in adrenal insufficiency and hyporeninemic hypoaldosteronism, a state associated with diabetes mellitus, renal insufficiency, and advanced age. Because the kidneys excrete potassium, severe renal insufficiency commonly causes hyperkalemia. Patients with chronic renal insufficiency can maintain a normal plasma $[K^+]$ despite a markedly decreased GFR, because urinary potassium excretion depends on tubular secretion rather than glomerular filtration if the GFR exceeds 8 mL min^{-1} .

In patients who have normal total body potassium, hyperkalemia may accompany a sudden shift of potassium from the ICV to the ECV because of acidemia, increased catabolism, or rhabdomyolysis. Metabolic acidosis and respiratory acidosis tend to cause an increase

in plasma $[K^+]$. However, organic acidoses (i.e., lactic acidosis and ketoacidosis) have little effect on $[K^+]$, whereas mineral acids cause significant cellular shifts. In response to increased hydrogen ion activity because of the addition of acids, potassium level will increase if the anion remains in the ECV (53). Neither lactate nor ketoacids remain in the extracellular fluid. Therefore, hyperkalemia in these circumstances reflects tissue injury or lack of insulin (53). Pseudohyperkalemia, which occurs when potassium is released from the cells in blood collection tubes, can be diagnosed by comparing serum and plasma K^+ levels from the same blood sample. Hyperkalemia usually accompanies malignant hyperthermia.

An interesting issue related to actual or potential perioperative hyperkalemia is the choice of fluids for infusion during renal transplantation. Theoretically, infusion of lactated Ringer's solution could be deleterious, because it contains potassium, albeit a trivial quantity per liter of fluid. However, during renal transplantation, 0.9% saline, which contains no potassium, actually is associated with a higher incidence of intraoperative hyperkalemia requiring treatment because of the reduction in pH due to hyperchloremic acidosis (Fig. 7) (63).

The treatment of hyperkalemia is aimed at eliminating the cause, reversing membrane hyperexcitability, and removing potassium from the body (Fig. 8) (53,64). Emergent management of severe hyperkalemia is listed in detail in Table 15 (64). Mineralocorticoid deficiency can be treated with 9- α -fludrocortisone (0.025 – 0.10 mg day $^{-1}$). Hyperkalemia secondary to

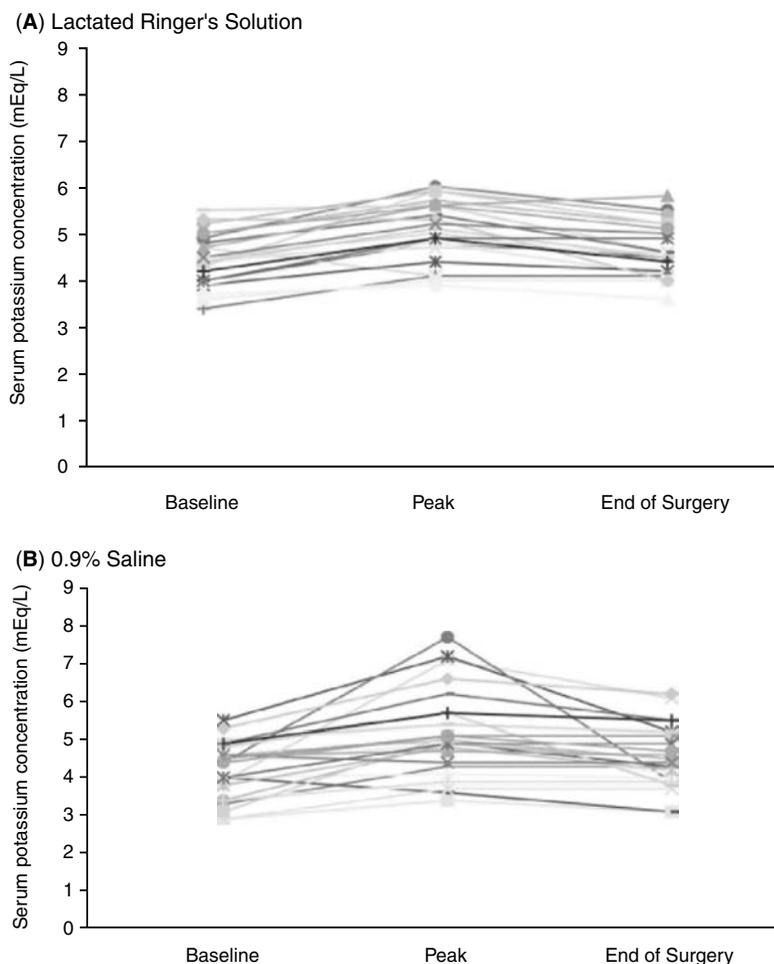


Figure 7 Changes in serum potassium during renal transplantation during 51 renal transplantations in which patients were randomized to intraoperative infusion of lactated Ringer's solution (**A**) or 0.9% saline (**B**). In the 0.9% saline group, five patients required treatment for plasma potassium exceeding 6.0 mEq/L in contrast to zero patients in the lactated Ringer's group. Eight patients in the 0.9% saline group required treatment for acidemia *Source*: From Ref. 63.

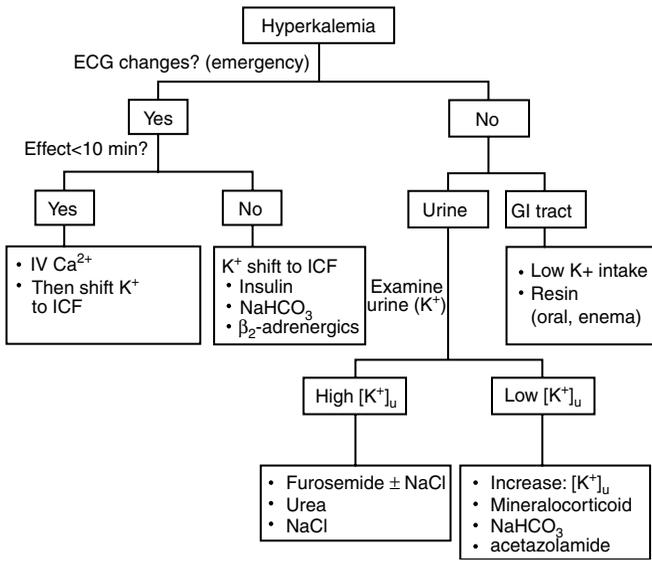


Figure 8 Treatment of patient with hyperkalemia. If an emergency is present (usually cardiac), intravenous Ca²⁺ must be given. This treatment should act promptly. Efforts are also taken to shift potassium into cells with insulin, with or without NaHCO₃. Longer-term strategies are to limit intake of potassium, prevent its absorption in the gastrointestinal tract, and promote its excretion; the latter includes measuring urine [K⁺] and flow rate to decide leverage for therapy. *Source:* From Ref. 53.

digitalis intoxication may be resistant to therapy, because attempts to shift potassium from the ECV to the ICF are often ineffective. In this situation, the use of digoxin-specific antibodies has been successful.

Membrane hyperexcitability can be antagonized by translocating potassium from the ECV to the ICF, removing excess potassium, or (transiently) by infusing calcium chloride or calcium gluconate to depress the membrane threshold potential. Pending definitive treatment, rapid infusion of calcium chloride (1 g of CaCl₂ over three minutes, or two to three ampules of 10% calcium gluconate over five minutes) may stabilize cardiac rhythm (Fig. 6). Calcium should be given cautiously if digitalis intoxication is likely. Acute alkalization using sodium bicarbonate (50–100 mEq over 5–10 minutes in a 70-kg adult) transiently promotes the movement of potassium from the ECV to the ICF. Bicarbonate can be administered even if pH exceeds 7.40; however, it should not be administered to patients with congestive cardiac failure or hypernatremia. However, when used alone, bicarbonate is relatively ineffective and is no longer favored (64).

Insulin, in a dose-dependent fashion, causes cellular uptake of potassium by increasing the activity of the sodium-potassium ATPase pump. Insulin increases cellular uptake of potassium best when high insulin levels are achieved by intravenous injection of 5 to 10 U of regular insulin, accompanied by 50 mL of 50% glucose (64). β₂-Adrenergic drugs such as salbutamol and albuterol also increase potassium uptake by skeletal muscle and reduce plasma [K⁺]. β₂ Agonists have been used to treat hyperkalemia (65). Salbutamol, a selective β₂ Agonist, decreases serum potassium acutely when given by inhalation or intravenously. In 15 pediatric patients with a baseline serum [K⁺] of 6.6 mEq/L, a single infusion of salbutamol (5 μg kg⁻¹ over 15 minutes) reduced serum [K⁺] to 5.7 mEq/L after 30 minutes

Table 15 Severe Hyperkalemia:^a Treatment

Reverse membrane effects
Calcium (10 mL of 10% calcium chloride intravenous over 10 min)
Transfer extracellular [K ⁺] into cells
Glucose and insulin (D10W + 5–10 U regular insulin per 25–50 g glucose)
Sodium bicarbonate (50–100 mEq over 5–10 min)
β ₂ agonists
Remove potassium from body
Diuretics, proximal or loop
Potassium-exchange resins (sodium polystyrene sulfonate)
Hemodialysis
Monitor electrocardiogram and serum [K ⁺] level

^aPotassium concentration ([K⁺]) > 7.0 mEq/L or electrocardiographic changes.

and to 4.9 mEq/L after 120 minutes (66). When using β_2 -adrenergic agents to reduce serum $[K^+]$, the potential for generating cardiac dysrhythmias should be recognized (67). Endogenous catecholamine secretion may explain hypokalemia accompanying severe, acute illness.

Potassium may be removed from the body by the renal or gastrointestinal routes. Furosemide promotes kaliuresis in a dose-dependent fashion. Sodium polystyrene sulfonate resin (Kayexalate), which exchanges sodium for potassium, can be given orally (30 g) or as a retention enema (50 g in 200 mL of 20% sorbitol). However, sodium overload and hypervolemia are potential risks. Rarely, when temporizing measures are insufficient, emergency hemodialysis may remove 25 to 50 mEq hr^{-1} . Peritoneal dialysis is less efficient.

Calcium

Physiologic Role

Calcium is a divalent cation found primarily in the extracellular fluid. The free calcium concentration ($[Ca^{2+}]$) in ECV is approximately 1 mM, whereas the free $[Ca^{2+}]$ in the ICV approximates 100 nM, a gradient of 10,000 to 1. Circulating calcium consists of a protein-bound fraction (40%), a chelated fraction (10%), and an ionized fraction (50%). The ionized fraction is the physiologically active and homeostatically regulated component (68). Acute acidemia increases and acute alkalemia decreases ionized calcium. Because mathematical formulae that “correct” total calcium measurements for albumin concentration are inaccurate in critically ill patients (69), ionized calcium should be directly measured.

In general, calcium is essential for all movements that occur in mammalian systems. Essential for normal excitation–contraction coupling, calcium is also necessary for the proper function of the muscle tissue, ciliary movement, mitosis, neurotransmitter release, enzyme secretion, and hormonal secretion. Cyclic adenosine monophosphate and phosphoinositides, which are major second messengers regulating cellular metabolism, function primarily through the regulation of calcium movement. Activation of numerous intracellular enzyme systems requires calcium. Calcium is important both for generation of the cardiac pacemaker activity and for generation of the cardiac action potential and, therefore, is the primary ion responsible for the plateau phase of the action potential. Calcium also plays vital roles in membrane and bone structure.

Serum $[Ca^{2+}]$ is regulated by multiple factors (70), including a calcium receptor (71,72) and several hormones. Parathyroid hormone (PTH) and calcitriol, the most important neurohumoral mediators of serum $[Ca^{2+}]$ (73), mobilize calcium from bone, increase renal tubular reabsorption of calcium, and enhance intestinal absorption of calcium. Vitamin D, after ingestion or cutaneous synthesis under the stimulus of ultraviolet light, is 25-hydroxylated to calcidiol in the liver and then is 1-hydroxylated to calcitriol, the active metabolite, in the kidney. Even in the absence of dietary calcium intake, PTH and vitamin D can maintain a normal circulating $[Ca^{2+}]$ by mobilizing calcium from bone.

Hypocalcemia

Hypocalcemia (ionized $[Ca^{2+}] < 4.0 \text{ mg dL}^{-1}$ or $< 1.0 \text{ mmol L}^{-1}$) occurs as a result of failure of PTH or calcitriol action or because of calcium chelation or precipitation, not because of calcium deficiency alone. PTH deficiency can result from surgical damage or removal of the parathyroid glands or from suppression of the parathyroid glands by severe hypo- or hypermagnesemia. Burns, sepsis, and pancreatitis may suppress parathyroid function and interfere with vitamin D action. Vitamin D deficiency may result from lack of dietary vitamin D or vitamin D malabsorption in patients who lack sunlight exposure. Hyperphosphatemia-induced hypocalcemia may occur as a consequence of overzealous phosphate therapy, from cell lysis secondary to chemotherapy, or as a result of cellular destruction from rhabdomyolysis. Precipitation of $CaHPO_4$ complexes occurs with hyperphosphatemia. However, ionized $[Ca^{2+}]$ only decreases approximately by 0.019 mM for each 1.0 mM increase in phosphate concentration. In massive transfusion, citrate may produce hypocalcemia by chelating calcium; decreases, however, are usually transient and produce minimal cardiovascular effects. A healthy, normothermic adult who has intact hepatic and renal function can metabolize the citrate present in 20 units of blood per hour without becoming hypocalcemic (74). However, when citrate clearance is decreased (e.g., by hepatic or renal disease or hypothermia) and when blood transfusion rates are rapid (e.g., more than $0.5\text{--}2 \text{ mL kg}^{-1} \text{ min}^{-1}$), hypocalcemia and cardiovascular compromise

may occur. Alkalemia resulting from hyperventilation or sodium bicarbonate injection can acutely decrease $[Ca^{2+}]$.

The hallmark of hypocalcemia is increased neuronal membrane irritability and tetany. Early symptoms include sensations of numbness and tingling involving fingers, toes, and the circumoral region. In frank tetany, tonic contraction of respiratory muscles may lead to laryngospasm, bronchospasm, or respiratory arrest. Smooth muscle spasm can result in abdominal cramping and urinary frequency. Mental status alterations include irritability, depression, psychosis, and dementia. Hypocalcemia may impair cardiovascular function and has been associated with heart failure, hypotension, dysrhythmias, insensitivity to digitalis, and impaired beta-adrenergic action.

Reduced ionized serum calcium occurs in as many as 88% of critically ill patients, 66% of less severely ill intensive care unit (ICU) patients, and 26% of hospitalized non-ICU patients (75). Patients at particular risk include patients after multiple trauma and cardiopulmonary bypass. In most such patients, ionized hypocalcemia is clinically mild ($[Ca^{2+}] = 0.8\text{--}1.0\text{ mmol L}^{-1}$).

Initial diagnostic evaluation should concentrate on history and physical examination, laboratory evaluation of renal function, and measurement of serum phosphate concentration. Latent hypocalcemia can be diagnosed by tapping on the facial nerve to elicit Chvostek's sign or by inflating a sphygmomanometer to 20 mmHg above systolic pressure, which produces radial and ulnar nerve ischemia and causes carpal spasm known as Trousseau's sign. The differential diagnosis of hypocalcemia can be done by addressing four issues: age of the patient, serum phosphate concentration, general clinical status, and duration of hypocalcemia (76). High phosphate concentrations suggest renal failure or hypoparathyroidism. In renal insufficiency, reduced phosphorus excretion results in hyperphosphatemia, which downregulates the 1α -hydroxylase responsible for the renal conversion of calcidiol to calcitriol. This, in combination with a decreased production of calcitriol secondary to reduced renal mass, causes reduced intestinal absorption of calcium and hypocalcemia (73). Low or normal phosphate concentrations imply vitamin D or magnesium deficiency. An otherwise healthy patient with chronic hypocalcemia probably is hypoparathyroid. Chronically ill adults with hypocalcemia often have disorders such as malabsorption, osteomalacia, or osteoblastic metastases.

The definitive treatment of hypocalcemia necessitates the identification and treatment of the underlying cause (Table 16). Symptomatic hypocalcemia usually occurs when serum ionized $[Ca^{2+}]$ is less than 0.7 mM. The clinician should carefully consider whether mild, asymptomatic ionized hypocalcemia requires therapy, particularly in ischemic and septic states in which experimental evidence suggests that calcium may increase cellular damage.

Unnecessary offending drugs should be discontinued. Hypocalcemia resulting from hypomagnesemia or hyperphosphatemia is treated by repletion of magnesium or removal of phosphate. Treatment of a patient who has tetany and hyperphosphatemia requires a coordinated reduction of phosphate and replacement of calcium to avoid the consequences of metastatic soft tissue calcification (77). Potassium and other electrolytes should be measured and abnormalities should be corrected. Hyperkalemia and hypomagnesemia potentiate hypocalcemia-induced cardiac and neuromuscular irritability. In contrast, hypokalemia protects against hypocalcemic tetany; therefore, correction of hypokalemia without correction of hypocalcemia may provoke tetany.

Mild, ionized hypocalcemia should not be overtreated. For instance, in most patients after cardiac surgery, administration of calcium only increases blood pressure and actually attenuates the β -adrenergic effects of epinephrine (78). In normocalcemic dogs, calcium

Table 16 Hypocalcemia: Acute Treatment

Administer calcium

Intravenous: 10 mL 10% calcium gluconate^a over 10 min, followed by elemental calcium 0.3–2.0 mg/kg/hr

Oral: 500–100 mg elemental calcium q 6 hr

Administer vitamin D

Ergocalciferol, 1200 μ g/day ($T_{1/2} = 30$ days)

Dihydrotachysterol, 200–400 μ g/day ($T_{1/2} = 7$ days)

1,25-dihydroxycholecalciferol, 0.25–1.0 μ g/day ($T_{1/2} = 1$ day)

Monitor electrocardiogram

^aCalcium gluconate contains 93 mg elemental calcium per 10-mL vial; $T_{1/2}$ = half-life.

Table 17 Serum Ionized $[Ca^{2+}]$ Concentration and Hemodynamic Variables One Minute After Calcium Administration (5 mg/kg Intravenous Bolus) in Normocalcemic and Hypocalcemic (Produced by CPD Administration) Dogs

	Normocalcemic		Hypocalcemic		
	Baseline	1 min	Baseline	CPD	1 min
Ca^{2+} (mmol/L)	1.24± 0.04	1.47± 0.06 ^a	1.24± 0.03	0.76± 0.03 ^a	1.42± 0.22 ^b
E_{1ves} (mmHg/mL)	4.06± 1.00	2.16± 0.90 ^a	5.03± 0.47	3.76± 0.61 ^a	4.87± 0.64 ^b
HR (beats/min)	159± 8	260± 9	154± 6	144± 7 ^a	148± 6 ^a
PAOP (mmHg)	9± 2	9± 1	7± 1	10± 2	9± 2
MAP (mmHg)	120± 6	137± 8 ^a	157± 6	131± 6 ^a	154± 6 ^b
SVR (dyne sec/cm ⁵)	3858± 458	4347± 596 ^a	4067± 550	3697± 479	4548± 904
CO (L/min)	2.7± 0.4	2.7± 0.4	3.4± 0.2	3.0± 0.3	3.1± 0.4

Note: Values are mean± SEM ($n=6$).

^a $p < 0.05$ vs. baseline.

^b $p < 0.05$ vs. CPD.

Abbreviations: E_{1ves} , slope of the left ventricular end-systolic pressure-volume relationship; CPD, citrate-phosphate-dextrose; HR, heart rate; PAOP, pulmonary arterial occlusion pressure; MAP, mean arterial pressure; SVR, systemic vascular resistance; CO, cardiac output.

Source: From Ref. 79.

chloride primarily acts as a peripheral vasoconstrictor, with transient reduction of myocardial contractility; in hypocalcemic dogs, calcium infusion significantly improves contractile performance and blood pressure (Table 17) (79). Therefore, calcium infusions should be of limited value in surgical patients unless there is demonstrable evidence of hypocalcemia (79). Calcium salts appear to confer no benefit to patients already receiving inotropic or vasoactive agents.

The cornerstone of therapy for confirmed, symptomatic, ionized hypocalcemia ($[Ca^{2+}] < 0.7$ mM) is calcium administration. In patients who have severe hypocalcemia or hypocalcemic symptoms, calcium should be administered intravenously. In emergency situations, in an averaged-sized adult, the “rule of tens” advises infusion of 10 mL of 10% calcium gluconate (93 mg elemental calcium) over 10 minutes, followed by a continuous infusion of elemental calcium, 0.3 to 2 mg kg⁻¹ hr⁻¹ (i.e., 3–16 mL hr⁻¹ of 10% calcium gluconate for a 70-kg adult). Calcium salts should be diluted in 50 to 100 mL D5W (to limit venous irritation and thrombosis), should not be mixed with bicarbonate (to prevent precipitation), and must be given cautiously to digitalized patients because calcium increases the toxicity of digoxin. Continuous ECG monitoring during initial therapy will detect cardiotoxicity (e.g., heart block and ventricular fibrillation). During calcium replacement, the clinician should monitor serum calcium, magnesium, phosphate, potassium, and SCr. Once the ionized $[Ca^{2+}]$ is stable in the range of 4 to 5 mg dL⁻¹ (1.0–1.25 mM), oral calcium supplements can substitute for parenteral therapy. Urinary calcium should be monitored in an attempt to avoid hypercalciuria (more than 5 mg kg⁻¹ per 24 hours) and urinary tract stone formation.

SUMMARY

Perioperative fluid administration has many clinically important interactions with acid–base and electrolyte status. In patients without preexisting acid–base or electrolyte disorders, perioperative fluids can induce disturbances sufficiently severe to require evaluation and sometimes therapy. In patients with preexisting acid–base or electrolyte disorders, the choice of perioperative fluids can aggravate or ameliorate those disturbances.

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37 | Fluids and Coagulation

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OVERVIEW OF COAGULATION

The integrity of the circulation is maintained through the provision of a rapid, potent, but tightly localized coagulation response to vascular damage. There is, however, one extraordinary problem in the regulation of hemostasis—blood flows. Normal hemostasis is the ability of the hemostatic system to control activation of clot formation and clot lysis to prevent hemorrhage without causing thrombosis. It classically involves vasoconstriction, platelet adhesion, and aggregation at the site of injury, leading to a plug formation. This is followed by fibrin formation consolidating the plug and rendering it stable. All of this occurs without clotting occurring elsewhere. Procoagulant products, whether clotting factors or platelets, must therefore be spatially localized to the site of damage for activation, and/or kinetically controlled so that they are inactive when distant from the damaged vessel.

The blood coagulation cascade is initiated when subendothelial tissue factor is exposed or expressed to the blood following either the damage or activation of the endothelium (1–3). As a result, the hemostatic mechanism is invoked through a complex series of regulated events, involving the interactions of the components of blood and tissue proteins, resulting in a spectrum from hemorrhage, through controlled hemostasis, to thrombosis (Fig. 1).

The Tissue Factor/Factor VIIa complex of the classic “Extrinsic Pathway” not only activates Factor X of the “Common Pathway,” but also directly activates Factor IX of the classic “Intrinsic Pathway,” making Factor XII redundant. This response has been characterized as a “cascade or waterfall” of enzymatic reactions, which result in α -thrombin converting soluble plasma fibrinogen to the insoluble fibrin polymer (4,5), making the coagulation process a series of reactions in which the sequentially derived products have the capacity to amplify small stimuli to result in the rapid generation of large amounts of α -thrombin (6). Tissue Factor, Factor Xa, and thrombin are pivotal, along with physiological controls (positive- and negative-feedback loops and natural anticoagulants) that first enhance thrombin generation but then preserve vessel patency by limiting hemostatic plug formation to areas of injury. Abnormalities in these mechanisms can increase thrombosis risk (7).

OVERVIEW OF INTRAVENOUS FLUIDS AND COAGULATION

For many years, the assumption has been made that most intravenous colloid solutions cause a decreased coagulation of blood, while with moderate crystalloid dilution (20–40%), coagulation remains inert. This was based on the fact that hemodilution decreases the concentration of clotting factors in the blood and thus should intuitively result in a decreased ability to form a clot. Indeed, this assumption was borne out in various studies comparing the effect of colloid hemodilution with a crystalloid-diluted “control group” (8–11), or not making allowance for any crystalloid the patient was given in addition to the colloid (12,13). The induction of some degree of impairment of coagulation is certainly the case once hemodilution in excess of 60% has occurred. One of the reasons for this may well be that the ionized calcium has been decreased below the critical level of 0.55 mmol/L (14).

In a clinical setting, mild trauma prolongs the intravascular persistence of isotonic and hypertonic crystalloid fluid as compared to a control group (15). It was noted that patients receiving crystalloids demonstrated an increase in coagulability as measured by the thrombelastograph (TEG), but this was not attributed directly to the crystalloid infusions (16,17), even though it might have implied that moderate hemodilution could cause blood to clot more readily.

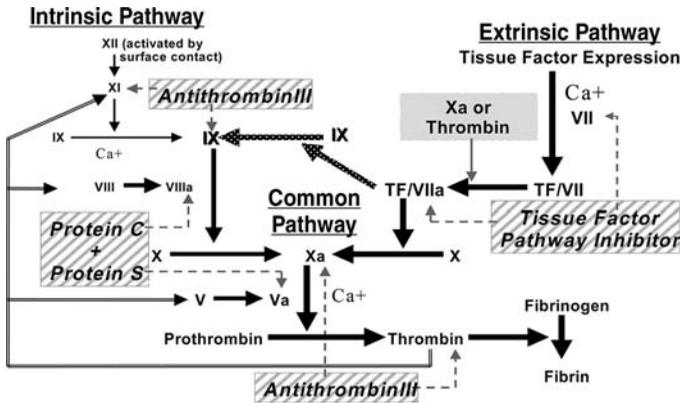


Figure 1 The coagulation cascade.

Colloids are known to provide highly effective volume expansion, but there is still a question about all of the synthetic colloid solutions regarding their effects on hemostasis. Common practice is to limit their use to 2 units (1000 mL) in the average 70 kg adult (9). Mardel et al. have suggested that gelatin-based products may become incorporated into developing clots and reduce the function of fibronectin in forming covalent cross-linkages and normal covalent associations with fibrin, thus interfering with polymerization of fibrin monomers (18). The dextrans are thought to pose a greater risk than either modified gelatins or hydroxyethyl starch (HES) (19). Similarly, TEG measurements indicate that high-molecular-weight (HMW) starches and dextrans may attenuate the hypercoagulability related to surgery (20).

In general, colloids such as plasma, albumin, and the synthetic colloids may all be used. Synthetic colloids are made up of three groups: dextrans, gelatins, and HESs (21). The effects of HES on blood coagulation have been shown to depend on its molecular weight and rate of elimination (22) and therefore the HES intravenous solutions should not be addressed as a group, but rather separately according to their molecular weight as well as their degree and site of substitution when commenting on their effect on coagulation (23). All colloids can induce a specific decrease of von Willebrand factor and factor VIII:c, but, in general, coagulation is most impaired by dextran and the HMW, highly substituted starches (> 200 Da; degree of substitution > 0.6).

Various clinical studies have been conducted on the effect of the HESs on coagulation, with conflicting results. There appears to be an increased risk of bleeding, including small, but significant prolongation in partial thromboplastin, prothrombin, and bleeding times; decreases in fibrinogen, antithrombin (AT), and factor VIII concentrations; and an increase in clot lysis (24,25), but these tests do not reflect any potential effect on the dynamic enhancement of the onset of coagulation. It must also be noted that many of the studies have used a crystalloid dilution as control, rather than taking the undiluted base sample as the control. For example, Kuitunen et al. demonstrated two types of HES solutions (hetastarch: HMW—450,000 Da; and pentastarch: medium molecular weight (MMW)—264,000 Da) to have adverse effects on laboratory indices of hemostasis compared with Ringer's acetate when used as priming solutions for cardiopulmonary bypass (8), while replacement of blood loss using HES was reported to have no adverse effects on coagulation when compared with the use of 5% albumin in gynecological and neurosurgery (26). Pentastarches have been found by Strauss et al. (27) to exert significantly lesser effects on standard tests of blood coagulation than hetastarch despite a greater effect on hemodilution. Penner et al. (28) considered specific dilutions (20%) of a 10% HES and its effect on hemostasis and found no apparent clinical effects. In a recent study, the influence of moderate and profound in vitro hemodilution with different HES low-molecular-weight solutions (70.000/0.5, 130.000/0.4, 200.000/0.5) on blood coagulation was investigated. HES 130.000/0.4 had some advantages over others of the lower molecular weight (LMW), but more highly substituted HES solutions the range of 70.000/0.5, 200.000/0.5–0.65 (23) Da is the lower range, but 0.5 + 0.6 is a higher substitution. So all three fall into the lower MW group, but 130/0.4 has a lower substitution than the other. It must be noted that many of these studies were limited because they were performed in conjunction

with surgery where multiple factors such as surgical trauma, heparinization, protamine reversal, stress response, endothelial exposure, etc. could all play a role in altered hemostasis.

HEMODILUTION AND COAGULATION

It has been demonstrated that a crystalloid, for example, "normal," 0.9% saline, is not inert as an intravenous fluid, but that it has an effect of "enhancing" the onset of coagulation—the onset of coagulation is more rapid after hemodilution with crystalloid and some colloid (gelatin) hemodilution (29). As far back as 1951, it was suggested that the enhancement was present with whole-blood dilutions of up to 40% (30). This was confirmed in 1959, with Monkhouse speculating on an imbalance between pro- and anticoagulants (31). It was further borne out by Janvrin et al. (32) in a clinical trial that investigated the incidence of postoperative deep vein thrombosis (DVT) related to intraoperative fluid administration and correlating this with the laboratory findings confirming dilution-induced enhanced coagulability using the Biobridge[®]. This effect is related to hemodilution per se, with any confounding variables having been avoided (16,17,33–41). It may be speculated that the evolution of this system may have survival advantages in decreasing the amount of blood loss after injury, ensuring that coagulation remains effective in the face of plasma dilution by mobilized extracellular fluid.

In a study by Butenas and Mann, the concentrations of blood coagulation proteins and their inhibitors were varied from 50% to 150% of their mean plasma values, i.e., in the range that is generally considered as being "normal." The difference in thrombin generation for these two extremes reached almost 30-fold. The dominant contributors to clotting are thrombin and AT, with a marked influence of the ratio between the two being demonstrated (42). Hemodilution reduces the concentration of the clotting precursors, but has almost no effect on the continuous generation of active factors, especially thrombin, until dilution reaches extreme levels. However, coagulation inhibitors including AT, α_2 -macroglobulin, protein C, and protein S are all present in their active form and their effectiveness is therefore susceptible to a reduction in their concentration by dilution (43). In the normal setting, a one-to-one, enzyme-to-inhibitor reaction of thrombin with the anticoagulants occurs forming thrombin/antithrombin (TAT) complexes (44). The ability of the entire system to cope with idling, nonzero levels of activated clotting enzymes without generating a response implies that there is a threshold above which positive feedback occurs, and that the balance of intravascular coagulation is protected against subthreshold stimuli. The role of inhibitors is critically important in control and cessation of this cascade, with dilution changing the thrombin-to-antithrombin ratio, which impacts on the threshold (43) and in so doing removes the "break" of the positive feedback (45,46). As a result, if the thrombin level is below threshold, no response will occur, whereas if the threshold is decreased by dilution to below the active thrombin level, the response should be at, or near, maximum, resulting in an exponential increase of further thrombin activation and so ensuring that a clot is formed.

With "hemodilution" creating an imbalance between active clotting and anticoagulant factors, the colloid solutions ought to exert a similar or even greater procoagulant effect to that seen with crystalloids; however, the influence of various colloids on the coagulation process itself, specifically platelet activation, offsets the effects of dilution of anticoagulant factors. This results in little difference from the undiluted blood with the lower-molecular-weight starches (34).

Conversely, a lowering of hematocrit has been described as decreasing coagulation on the basis of decreased blood viscosity, leading to a faster arterial blood flow (47). However, there is a difference between aggregating platelets at the site of an arterial plaque fissure ("white" clot) and the development of a meshwork of fibrin, thrombin, and entrapped blood cells ("red" clot) (48), the latter occurring predominantly on the venous side. The process of "red clot" formation in the microvascular circulation is not greatly dependent on rheology, because flow does not impact on the intrinsic ability of blood to clot at this level.

Clinical work has suggested that the procoagulant effect of crystalloid infusions may be of relevance during surgery (37), with Ng and Lo (40) demonstrating that during surgical blood loss with crystalloid volume replacement, a hypercoagulable state developed, which was related to the degree of hemodilution. Heather et al. reported the "saline predictor test," the probability of patients developing a postoperative DVT (49), which could be used as a predictor of the risk of DVT formation, confirming the suggestion by Janvrin et al. (32). A recent study in patients undergoing knee surgery demonstrated enhanced coagulation related to all

fluids administered to patients (50). Isovolemic hemodilution is reported to be associated with hypercoagulability when using albumin, but not Hextend, due to a loss of AT activity through dilution with simultaneous maintenance of Factor VIII complex activity (VIII:C) (51). Hypertonic saline dextran (RescueFlow[®]) also resulted in an initial mild procoagulant effect followed by an anticoagulant effect at higher levels (52).

MONITORING OF COAGULATION

As the understanding of the normal mechanisms of coagulation grows, so does the ability to monitor hemostasis. Evaluation of hemostasis will become more specific and accurate and instrumentation techniques will become simpler and more efficient as technology progresses, facilitating the monitoring of hemostasis in the clinical setting (53).

Any medical coagulopathy, as opposed to a surgical bleed, needs the actual underlying cause determined in order to direct the therapy appropriately. Traditionally, hematological tests such as prothrombin time (PT) and its derived value, the international normalized ratio (INR), activated partial thromboplastin time (aPTT), bleeding time, and activated clotting time (ACT) have been performed. However, while they are useful static endpoint markers to identify the lack of a given factor, they do not reflect the dynamic interaction between the different systems, because blood coagulation occurs efficiently on cell surfaces such as activated platelets, monocytes, and fibroblasts. Both PT and aPTT are highly artificial *in vitro* systems with major limitations (54). More specific coagulopathy tests are described below.

AT (55): In the test, the paranitroaniline released, monitored at 405 nm, is inversely proportional to the AT level in the test sample. The result is reported in percentage activity and is automatically calculated, with the method being linear from 10% to 150%. The normal range is 85% to 120%.

TAT complex (56): This is an enzyme immunoassay for the quantitative determination of human TAT complex in human plasma and is used for the diagnosis of disturbances in blood coagulation, which are associated with changes in the activity of the coagulation system. Persons predisposed to thrombosis and disseminated intravascular coagulopathy (DIC) are found to have elevated concentrations of TAT.

D-dimer cross-linked fibrin degradation products (XDP) (57): D-dimer-containing moieties are formed by plasmin degradation of factor XIIIa cross-linked fibrin, with elevated levels being found in clinical conditions such as DVT, pulmonary embolism, and DIC.

Quantitative test: The quantitative cross-linked fibrin degradation products (QXDP) test is used and results are reported in ng/mL, with the interpretation of results being that agglutination will occur within 180 seconds for samples containing more than 250 ng/mL D-dimer. The mean level of D-dimer (XDP) in the healthy population is between 8 and 135 ng/mL, and neat plasma from normal healthy individuals should not agglutinate.

Fibrinogen: This is a test based on a combined assessment of the PT and fibrinogen level by the addition of recombinant rabbit thromboplastin to the plasma. The fibrinogen is quantified by relating the absorbance or light scatter during clotting to a calibrator.

Whole-Blood Dynamic Tests of Coagulation

These are tests using whole blood to measure clot formation rather than measuring end points as is done in the standard tests. They assess the coagulation process in whole blood and may therefore be physiologically more relevant than assays of isolated hemostatic components. Hypercoagulability is detected in a high proportion with the clotting rates of the Sonoclot and TEG being significantly correlated (58,59). The hemostasis profile is a measure of the time it takes for the first fibrin strand to be formed, the kinetics of clot formation, the strength of the clot, and dissolution of the clot—clot quality.

In essence, the dynamic analyzers measure the ability of the clot to perform mechanical work throughout its structural development with kinetics, strength, and stability of a clot being determined by using a native whole-blood sample. This has provided a sensitive method for monitoring coagulation, with patterns being quantified as to the degree of abnormality.

Sonoclot: Sonoclot analysis provides a simple test of cellular and plasmatic coagulation properties (60). It correlates better with blood loss than aPTT and platelet count in the routine coagulation analyses (61).

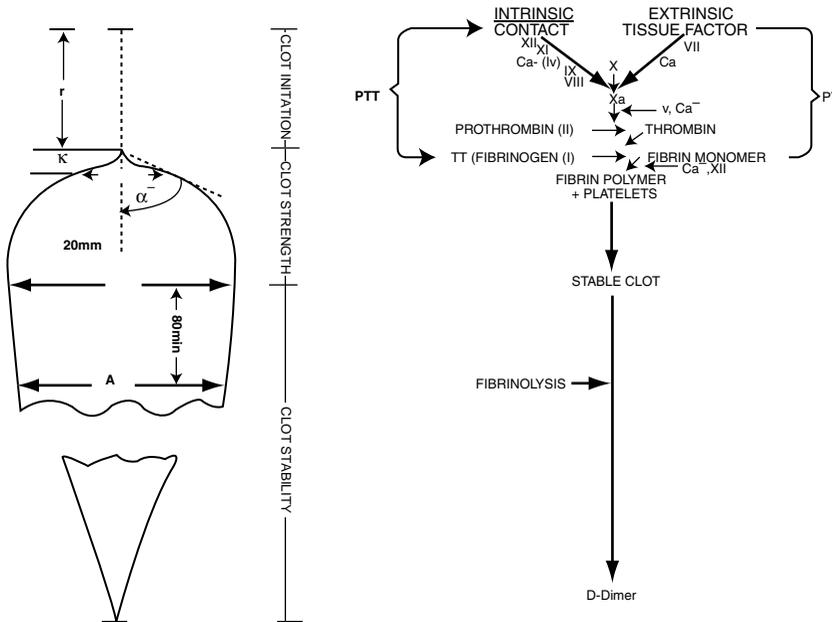


Figure 2 Thromboelastograph tracing parameters. *Abbreviations:* PT, prothrombin time; PTT, partial thromboplastin time. *Source:* Courtesy of Haemoscope Corp., Chicago, Illinois, U.S.A.

Thromboelastography: The TEG is a noninvasive diagnostic instrument designed to analyze the coagulation state of a blood sample to assess hemostasis from hemorrhage through thrombosis, measuring the clot’s physical properties (rate, strength, stability, and shear elasticity). It is, therefore, sensitive to all the interacting cellular and plasmatic components in the blood that affect the rate or structure of a clotting sample and its breakdown (Fig. 2.).

The TEG pattern is divided into component variables that are shown in Table 1.

PERIOPERATIVE COAGULATION AND DIC

Wound treatment has been receiving considerable attention since the Trojan War. By the American Civil War, shock was being described as a distinct entity and efforts were directed at more than just treatment of the wound. The need for fluid resuscitation in hemorrhagic shock was first recognized in the Spanish–American War and by World War I the need for blood in the treatment of “wound shock” was identified. Studies in the Korean War described the concept of DIC and multiple organ dysfunction syndrome (MODS), and the existence of DIC was confirmed by studies in Vietnam (62).

When internal hemodilution occurs after blood loss, enhanced coagulability may prevent further hemorrhage. However, a point may be reached where bleeding occurs, because the clotting factors are used up through enhanced clot formation at a capillary level. This in turn leads to a marked increase in bleeding, as an imbalance between procoagulant factor

Table 1 Thromboelastograph Variables

r	r-time is the period of time of latency from the time that the blood was placed in the TEG analyzer until the initial fibrin formation
k	k-time is a measure of the speed to reach a certain level of clot strength
α	Alpha angle measures the rapidity of fibrin buildup and cross-linking (clot strengthening)
MA	MA is a direct function of the maximum dynamic properties of fibrin and platelet bonding via GPIIb/IIIa and represents the ultimate strength of the fibrin clot
CI	CI—linear coagulation index using above-mentioned parameters
LY30	LY30 measures the rate of amplitude reduction 30 min after MA

Abbreviations: CI, coagulation index, MA, maximum amplitude; TEG, thromboelastography.



Figure 3 The two stages of disseminated intravascular coagulation as measured by thromboelastograph. *Abbreviation:* DIC, disseminated intravascular coagulopathy. *Source:* Courtesy of Haemoscope Corp., Chicago, Illinois, U.S.A.

activation and anticoagulants as well as enhanced fibrinolysis, occurs—the syndrome of DIC. DIC is a condition occurring in two stages, primarily of uncontrolled systemic fibrin deposition and simultaneous fibrinolysis with procoagulant factor activation followed by secondary hemorrhagic disorders due to consumption of platelet and procoagulant factors (Fig. 3) (63).

Its multiple action of thrombin formation and widespread depositions of fibrin in the microvasculature form a link to the development of MODS and this makes a poor prognostic sign—baseline coagulation values correlating with mortality (64). AT concentrations decrease in DIC, with lower levels in trauma patients being related to the severity of damage.

Clinically, DIC manifests as bleeding “and” organ failure. While bleeding tendency can be treated, the organ failure is often irreversible. In the natural state, a DIC leads to a speedy demise of the individual. Traumatic coagulopathy has been described as being potentially caused primarily by fluid administration and hypothermia (65).

When it comes to therapy, the pathophysiologic mechanisms and clinical and laboratory manifestations of a coagulopathy are complex, in part, due to interrelationships within the hemostasis system. There are often confusing clinical and laboratory findings in patients with DIC. Patients who have sustained sufficiently severe trauma to require major resuscitation represent a considerable problem in terms of the management of their coagulation status. There is no measurement-based protocol for the administration of blood products for the support of coagulation (66). Guidelines generally assume the presence of hypocoagulability when more than one individual circulating blood volume is lost; however, this is not necessarily true for every patient, and routine coagulation tests are insufficient in predicting this. Therefore, the occurrence of diffuse microvascular bleeding is often used as the clinical sign to start hemostatic therapy. However, such severe derangement of hemostasis might lead to the development of secondary tissue damage and frequently is unresponsive to conventional treatment. Evidence exists that the amount of blood loss, the presence of coagulopathy, and the number of transfusions needed are associated with poor outcome in bleeding patients (67).

At present, treating the triggering event is part of the treatment for DIC, as is heparin, antithrombin, etc. DIC is a phenomenon in itself and treatment thereof is as much treating the triggering event as it is giving blood products (68). A better rational approach will need to be developed as the understanding of the complex underlying mechanisms grows. To this end, dynamic tests such as the TEG may be a useful tool (Fig. 3).

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38 Multiple Organ Failure

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DEFINITIONS PERTINENT TO MULTIPLE ORGAN FAILURE

Systemic Inflammation Response Syndrome

This term describes the similar physiologic response that is provoked by both noninfectious and infectious insults. Systemic inflammation response syndrome (SIRS) is defined as two or more of the following conditions: (i) temperature above 38°C or below 36°C; (ii) heart rate greater than 90 beats/min; (iii) respiratory rate more than 20 breaths/min or a PaCO₂ of less than 32 mmHg; and (iv) white blood count (WBC) greater than 12,000 cells/mm³ or less than 4000 cells/mm³, or greater than 10% immature (bands) forms.

Sepsis

This term is to be reserved for situations in which SIRS exists in the presence of an identifiable source of infection.

Multiple Organ Failure

Several clinical scoring systems were developed during the last two decades to define and quantitate organ dysfunctions (1–3). Since 1987, the Denver multiple organ failure (MOF) Score (4,5) has undergone several revisions to improve it as a descriptive end point for clinical studies (Table 1). Each organ function is graded on a scale of zero to three (0: normal, 1: mild, 2: moderate, and 3: severe). Individual organ failure is defined as a dysfunction grade of 2 or more, whereas MOF is defined as the sum of simultaneous individual organ dysfunction grades of 4 or more, 48 hours after admission. MOF was defined as “early” if it was present on hospital day 3 and “late” if it occurred after day 3. We do not recommend the use of organ dysfunction scores obtained in the first 48 hours to define MOF, because they may reflect reversible derangements induced by the inciting event or incomplete resuscitation.

Abdominal Compartment Syndrome

Case reports in the 1980s described this apparently new syndrome (6,7). Abdominal compartment syndrome (ACS) became an accepted entity in the mid-1990s after a series of trauma centers reported a high incidence of ACS in severely injured patients undergoing “damage control” surgery (8,9). ACS is defined as a combination of (i) urinary bladder pressure >25 mmHg, (ii) progressive organ dysfunction [urinary output <0.5 mL/kg/h or PaO₂/FiO₂ <150 or peak airway pressure >45 cmH₂O or cardiac index (CI) <3 L/min/m² despite resuscitation], and (iii) improved organ function after decompression.

Primary ACS

Primary ACS is a complication of damage control laparotomy (8). The space-occupying nature of abdominal packs together with ongoing bleeding and the progressive bowel edema all contribute to increased abdominal content. If the fascia is closed, the volume of the abdominal cavity is returned to its original uninjured volume, and, therefore, intra-abdominal pressure

Table 1 Denver MOF Score

	Grade 0	Grade 1 dysfunction	Grade 2 dysfunction	Grade 3 dysfunction
Pulmonary ^a	PaO ₂ /FiO ₂ ≥ 250	PaO ₂ /FiO ₂ = 175–249	PaO ₂ /FiO ₂ = 100–174	PaO ₂ /FiO ₂ < 100
Renal	Normal	Creatinine > 1.8 mg/dL	Creatinine > 2.5 mg/dL	Creatinine > 5 mg/dL
Hepatic ^b	Normal	Bilirubin > 2 mg/dL	Bilirubin > 4 mg/dL	Bilirubin > 8 mg/dL
Cardiac ^c	Normal	Minimal inotropes	Moderate inotropes	High inotropes

^aPCWP ≤ 18 cmH₂O, or clinical setting where high PCWP is not anticipated. Adjusted for altitude: Grade 0: P/F ≥ 208; Grade 1: P/F = 165–207; Grade 2: P/F = 84–164; and Grade 3: P/R < 83.

^bBiliary obstruction and resolving hematoma excluded.

^cCardiac index < 3.0 L/min/m² requiring inotropic support. Minimal dose, dopamine or dobutamine < 5 μg/kg/min; moderate dose, dopamine or dobutamine 5–15 μg/kg/min; high dose, greater than moderate doses of above agents.

Abbreviations: MOF, multiple organ failure; PCWP, pulmonary capillary wedge pressure.

(IAP) increases. Primary ACS can also occur in patients who fail nonoperative management of abdominal organ injuries because of ongoing bleeding.

Secondary ACS

This typically occurs in the setting of severe shock requiring massive resuscitation (10,11). Because there are no abdominal injuries to draw the clinicians' attention to the abdomen, secondary ACS is more elusive, and recognition is often delayed. Here, the abdominal content is increased by bowel edema and ascites, and the volume of the abdominal cavity can be decreased by retroperitoneal hematoma originating from pelvic fractures.

Damage Control

Patients undergoing laparotomy for major abdominal bleeding that places them at risk for entering the "bloody vicious cycle" of acidosis, hypothermia, and coagulopathy benefit from an abbreviated laparotomy (damage control) (8). The goals are to control bleeding quickly and to prevent further contamination/spillage from hollow viscus perforations. The abdomen is temporarily closed without fascial approximation, and the patient is triaged to the intensive care unit (ICU) where resuscitation can be optimized and the "bloody vicious cycle" pathophysiology corrected. Damage control has saved the lives of severely injured patients who could have previously died, but has caused new challenges including ACS, open abdomens, and early MOF.

THE HISTORICAL PERSPECTIVE OF POSTINJURY ORGAN FAILURE AND DEATH

Failure of vital organ function has long been a major cause of postinjury deaths, and the medical history of fluid resuscitation is closely related to it (Table 2). In World War I, injured soldiers died of profound cardiac failure in the battlefield. No defined resuscitation was performed at that time, because the cause of shock was believed to be due to wound toxins. By the 1940s, due to the work of Blalock, Wiggers, and others, the loss of blood volume was recognized to be the primary cause of traumatic shock (12,13). In World War II, and to a greater extent, in the Korean War, battlefield casualties were resuscitated with blood and plasma until blood pressure returned to normal. Additionally, wounded soldiers were rapidly transported for definitive care provided in field units. As a result, more soldiers survived their initial insult. However, the severely injured often succumbed to oliguric renal failure. In the mid-1960s, Moyer et al. emphasized that extracellular fluid deficits (third-space losses) coexist with traumatic shock (14,15). In controlled hemorrhagic shock models, they demonstrated that the best survival was obtained with large-volume isotonic crystalloid infusions that replenished both intravascular and extracellular fluid deficits. Using a triple isotope methodology, they demonstrated that, with shock, interstitial fluid moved into both the intravascular and the intracellular spaces. They empirically observed the ratio of crystalloids and blood infusion for best survival to be 3:1. Thus, in the Vietnam War, crystalloid infusion was added to blood

Table 2 Historic Perspective of Postinjury Organ Failure

	Perceived problem	Intervention	Outcome
WWI	Wound toxins	None	Cardiac failure
WWII Korea	↓ Plasma volume		
Vietnam	↓ Plasma volume	Plasma/blood	Renal failure
	↓ ECF volume	Resuscitation	
Late 1970s, early 1980s	Sepsis	Nutrition	↓ Sepsis/MOF
		Antibiotics	↑ SIRS/MOF
		CT scans	
Late 1980s	Exsanguination	Level I trauma centers	↓ Exsanguination
	Bloody vicious cycle	Shock trauma ICUs	↑ MOF
	Unrecognized shock	Damage control	
		Goal-oriented resuscitation	
1990s	ACS	Decompressive laparotomy	↓ MOF deaths
		Bogata bag closure	Open abdomens
		Wound vac closure	

Abbreviations: WWI, World War I; WWII, World War II; CT, computed tomography; SIRS, systemic inflammation response syndrome; ICU, intensive care unit; MOF, multiple organ failure; ACS, abdominal compartment syndrome; ECF, extracellular fluid.

replacement, and the end point of resuscitation was an adequate urine output. This, together with the rapid helicopter transport, resulted in decreased mortality and less frequent renal failure. However, a new entity termed “shock lung” became the primary cause of late deaths. In the early 1970s, the term “adult respiratory distress syndrome (ARDS)” was coined to describe this new syndrome that was being seen with increasing frequency in civilian ICUs (16). In the mid-1970s, widespread application of advanced organ support (mechanical ventilators, inotropic support, total parenteral nutrition, and hemodialysis) increased the capacity to sustain critically injured patients, but the type of fluid resuscitation (crystalloid and blood) remained unchanged. No longer were patients dying of isolated pulmonary failure; rather, a new syndrome of MOF emerged as the leading cause of late postinjury. Reports from Eiseman et al. noted a strong association between uncontrolled infection (principally intra-abdominal infection) and subsequent MOF (17–19). Research in the early 1980s was directed at understanding two issues: (i) how does trauma cause infection and (ii) how does infection cause MOF. With a better understanding of the pathogenesis of sepsis-induced MOF, advances in care (optimal operations, perioperative antibiotics, enteral nutrition, computed tomography scanning, and interventional radiology) changed the epidemiology of trauma deaths. By the late 1980s, the incidence of sepsis-induced MOF decreased, and it became widely recognized that traumatic shock could cause early MOF in the absence of an identifiable infection (1,20,21).

In the late 1980s, several significant changes occurred in the management of civilian trauma, which again changed the epidemiology of trauma deaths. The first was the development of Regional Level I Trauma Centers that have significantly reduced early mortality from exsanguination. These centers created specialized shock trauma ICUs, and over the years, care has evolved such that mortality from MOF is decreasing. It was recognized that despite successful operative interventions, patients often died due to continued bleeding because they had entered the “bloody vicious cycle” of coagulopathy, hypothermia, and acidosis (8). Alternatives to definitive operative repair (e.g., liver packing) evolved into the concept of “damage control” surgery. In “damage control,” the principal goals of the initial operation are to control hemorrhage and spillage of gastrointestinal content from hollow viscus injuries. The patient is then triaged to the ICU for the correction of “bloody vicious cycle” physiology and optimized resuscitation before they are returned to the OR for definitive repair.

Another major change in care was the concept of goal-oriented resuscitation. This was championed by Shoemaker et al., who proposed the important hypothesis that flow-dependent oxygen consumption was an important cause of MOF and death in surgical ICUs. They demonstrated in two trials (one perioperative and the other trauma) that increasing oxygen delivery (DO_2I) to supranormal levels (600 mL/min/m^2) resulted in improved survival (22,23). With the widespread availability of pulmonary artery catheters that are capable of continuously monitoring cardiac output and mixed venous oxygen saturation, the concept of preload-directed, goal-oriented resuscitation became the standard of care in many U.S. Trauma Centers.

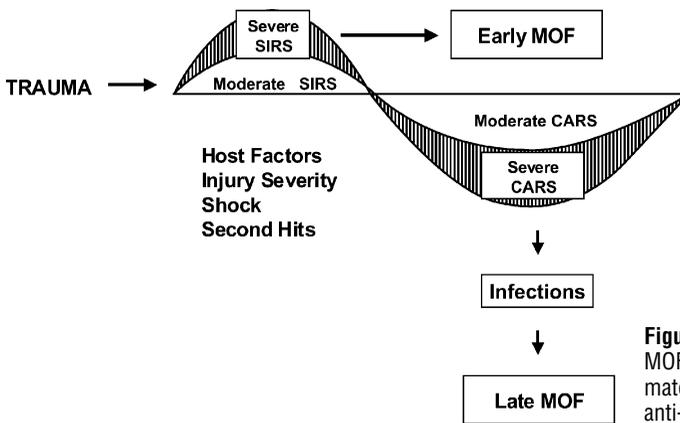


Figure 1 Dysfunctional inflammation causes MOF. *Abbreviations:* SIRS, systemic inflammatory response syndrome; CARS, counter anti-inflammatory response syndrome; MOF, multiple organ failure.

EPIDEMIOLOGY OF POSTINJURY MOF

With the recognition that MOF was the leading cause of late trauma deaths and prolonged ICU stays, a prospective MOF database was started in 1990. After five years of data collection, an analysis was performed, which revealed that MOF occurs in at least two distinct patterns (early and late) (5). The following conceptual framework of MOF pathogenesis was proposed (Fig. 1). Following major trauma, patients are resuscitated into an early state of systemic hyperinflammation (i.e., SIRS). The initial intensity of SIRS is dependent on the amount of tissue injury, the degree of shock, and the presence of host factors (such as age, comorbid disease, and genomics). Mild-to-moderate SIRS is presumed to be beneficial and resolves as the host recovers. However, if the initial insult is massive (“one-hit” model), the resulting severe SIRS can precipitate early MOF. Alternatively, early MOF can occur when vulnerable patients are exposed to early secondary inflammatory insults (“two-hit” model). At the same time, negative feedback systems (i.e., counter anti-inflammatory response syndrome) attempt to limit certain components of SIRS so it does not become an autodestructive process. This results in delayed immunosuppression. Again, mild-to-moderate delayed immunosuppression is presumed to be beneficial, but when severe, it is associated with major infectious complications, principally pneumonia and late MOF.

SHOCK IS A POTENTIAL MODIFIABLE RISK FACTOR

Shock has long been recognized as a prime inciting event for MOF. A strong statistical association between the severity of shock and subsequent MOF was demonstrated by multiple logistic regression (MLR) analysis of data from the MOF database. This analysis demonstrated that MOF could be accurately predicted within 12 hours of admission. The independent risk factors included increased age, high-injury severity scores, and severe shock as quantitated by elevated base deficit and lactate levels and by increasing the number of units of transfused blood (24). Of these risk factors, only the severity of shock is potentially modifiable by clinical intervention. Not surprisingly, the optimal resuscitation became the focus of interest.

RESUSCITATION MODULATES ISCHEMIA/REPERFUSION-INDUCED SIRS

Traditional resuscitation (volume loading with isotonic crystalloids and banked blood) is aimed at limiting the severity of the ischemic insult, but recent evidence indicates that it can also modulate (both improve and worsen) reperfusion-induced inflammation and injury. The type, timing, and magnitude of fluid resuscitation are important factors.

Type of Fluid

The crystalloid-versus-colloid debate has been ongoing for over 50 years. A series of prospective randomized trials performed from the mid-1970s through the early 1990s offered conflicting

results. Six meta-analyses have been performed on these data. The first two showed that resuscitation with colloids has a slightly higher mortality, but their methodology had limitations (25,26). When trauma trials were analyzed separately, the difference was more marked: 12.3% and 10.8% increased risk of mortality associated with colloids. The new generation of meta-analyses with manual searching, multiple author-independent data collection, and funnel plot asymmetry analysis are highlighted by two studies from England (27,28). Both studies identified a slight increase in mortality (4% and 6%), with the use of colloids. The major criticisms of these studies were (a) hypertonic saline (HS) was often administered in the colloid group in conjunction with dextrans, (b) the low mortality rate, and (c) the limitation of the primary studies. Choi et al. excluded the studies that used HS and showed no overall difference between crystalloids and colloids. But when the subgroup analysis was performed in trauma studies, there was a statistically significant increase in mortality with colloid use (29). The authors suggested that the results of this meta-analysis are best viewed as hypothesis-generating rather than a reason to ban colloids. The most recent and comprehensive meta-analysis focused on albumin versus crystalloids in critically ill patients (30). This study included 3504 randomly assigned patients and found no evidence that albumin significantly affects mortality overall or in the surgery-trauma subgroup. Contrary to the authors' conclusions, their point estimates indicate a relative risk of death of more than 10% for surgical and trauma patients resuscitated with albumin. This relative risk is similar to the results of the first two meta-analyses, but the authors derived different conclusions from them.

Lactated Ringer's Solution

Because there is no convincing laboratory or clinical evidence to support colloid-based resuscitation, the current practice of resuscitation recommended by the Advanced Trauma Life Support (ATLS) guidelines of the American College of Surgeons is aggressive crystalloid fluid resuscitation. It begins with a two-liter bolus of lactated Ringer's (LR) solution and continues with blood and subsequent boluses of LR simultaneously with the systematic search and repair of the surgically correctable sources of blood loss (31). LR is generally preferred over normal saline because the latter increases the risk of hyperchloremic metabolic acidosis (32). Crystalloids (electrolytes and water) do not remain in the vascular space and are rapidly distributed into the interstitial space. Generalized edema is an acknowledged outcome of the crystalloid-based resuscitation. In resuscitation of severe shock, high volumes of crystalloid infusion are needed to maintain adequate preload, which results in problematic edema in the lung, worsening acute lung injury (ALI), increased intracranial pressure, and in the gut abdominal compartment syndrome (ACS).

Apart from the straightforward physical effects of crystalloids, recent laboratory studies demonstrate that LR can adversely modulate reperfusion-induced inflammation. Animal and human studies have convincingly linked shock resuscitation to early polymorphonuclear neutrophil (PMN) activation and subsequent MOF (33). An important question is whether reperfusion injury is purely responsible for PMN activation or if the quality of resuscitation is also important. Rhee et al. published the astonishing results that LR infusion alone (without hemorrhage) caused PMN activation (oxidative burst), but the infusion of fresh blood or 7.5% HS solution did not cause activation (34). The authors did not find any difference in PMN activation by changing the electrolyte composition, pH, or osmolarity. However, the lactate isomer composition of the resuscitation fluid is an important determinant of the immunological responses. The commercially available LR used in these experiments contains equal amounts of L-lactate (14 mmol/L) and D-lactate (14 mmol/L) isomers. The D isomer, which is not normally present in the human body, causes PMN activation. The LR containing only the natural L-lactate (28 mmol/L) causes significantly less activation on human PMNs than LR containing the racemic mixture of L and D isomers. Similar PMN attenuation can be achieved with the replacement of the L-D-lactate in the LR solution for ketone bodies (35). Intravital microscopic observations in the dog mesentery after hemorrhagic shock revealed that resuscitation with LR caused more PMN-endothelial cell interactions (both rolling and firm adhesion) than the resuscitation with shed blood (36). LR infusion, alone or after shock, causes increased expression of intercellular adhesion molecules. The resuscitation with HS has a less-pronounced effect on adhesion molecule expression, and the effect of fresh blood is minimal (37). LR resuscitation compared with plasma, fresh blood or HS resuscitation increased apoptosis (a consequence of increased cellular damage) in the gut, liver, and lung (38).

Colloid Solutions

Despite the lack of convincing laboratory and clinical data, colloid resuscitation is a standard of care in Europe and Australia. It is not possible to discuss the generic immunological effects of colloid resuscitation, because many different colloids with very distinct molecular characteristics are being used. The interpretation of the results of colloid-based resuscitation is further complicated by the fact that dextrans are often used in combination with HS, which has recently been shown to have profound anti-inflammatory effects (39). Most studies have used albumin. Human albumin is the natural plasma colloid and has been shown not to activate PMNs after hemorrhagic shock. Additionally, albumin is a very efficient plasma expander. A question, however, remains whether albumin resuscitation in the setting of I/R-induced increased endothelial permeability might worsen tissue injury and edema. Albumin is expensive, and supply is at times limited. These considerations, combined with the clinically unproven beneficial effects on mortality reduction, hinder the widespread use of albumin as a first-line resuscitation fluid.

Gelatin Solutions

Gelatin solutions derived from bovine collagen are liberally used in Europe and Australia, without convincing scientific evidence of improved outcome. Contradictory results are published about gelatins regarding their effects on coagulation and anaphylactoid reaction (40). Their immunological effects are not as widely investigated as other colloids. Recently, it was shown that gelatin resuscitation (similarly to starch), compared with fresh blood, increases the susceptibility to sepsis after hemorrhagic shock in a mouse model by inhibiting the reticuloendothelial system (RES) (41). The effect is transitory because the RES recovers after 48 hours, but the animals were significantly more vulnerable to *Escherichia coli* sepsis early after shock resuscitation when most of the operative interventions occur in trauma care. The gelatin resuscitation does not influence the respiratory burst activity of the PMN in clinical scenarios of gelatin infusion during surgery (42).

Dextrans

Dextrans are bacterium-produced polysaccharides that are available in 6% and 10% solutions. Because of the concerns with anaphylaxis and anticoagulant effects, their use in acute trauma scenarios is less feasible. Dextran resuscitation decreases the PMN survival after shock resuscitation by inducing apoptosis, and inhibits leukocyte–endothelial cell interactions (43).

Hydroxyethyl Starch

Hydroxyethyl starch (HES) solutions are modified natural polymers of amylopectin. The lower-molecular-weight HES solutions have less effect on coagulation, which makes them more applicable for posttraumatic resuscitation (44). HES causes less expression of E-selectin (adhesion molecule) after tumor necrosis factor- α stimulation compared with dextran and gelatin solutions and may be beneficial in trauma patients who are at risk for developing capillary leak (45). In concentrations used in clinical practice, HES does not block RES function (46). Novel balanced HES products address the previous concerns of hyperchloremic acidosis after massive administration and minimize the organ damage caused by ischemia–reperfusion injury compared with other resuscitation fluids such as albumin and LR (47).

Hypertonic Saline

It has long been recognized that a small bolus (4 mL/kg) of 7.5% HS is quite effective in expanding intravascular volume in the initial phases of shock resuscitation (48). Unfortunately, numerous prospective randomized clinical trials (PRCTs) performed in the late 1980s and early 1990s failed to demonstrate any outcome advantage of HS (with or without dextran) compared with isotonic crystalloid resuscitation (principally LR) (49–51). As a result, interest in HS resuscitation faded until the recent recognition in models of hemorrhagic shock and sepsis that HS compared with LR resuscitation markedly reduces PMN cytotoxicity and ALI (39). More recent studies have linked this beneficial effect of HS shock resuscitation to the gut

(52). Hemorrhagic shock causes ALI that can be prevented by mesenteric lymph diversion (53). The collected lymph *in vitro* primes and activates PMNs, increases intercellular adhesion molecule (ICAM)-1 expression, and potentiates endothelial cell injury (54). In these models, compared with LR resuscitation, HS prevents these *in vitro* effects and prevents *in vivo* ALI (55). Additionally, in "two-hit" models of hemorrhage and subsequent infection, HS resuscitation dramatically reduces organ injury and reduces mortality. The mechanism of the beneficial effects of HS is mainly membrane associated through the activation of protein tyrosine kinases (intracellular second messengers), which lead to nuclear activation, protein synthesis, and proliferation (56). HS can reverse the effect of immunosuppressive trauma serum on cells. Another significant mechanism is the reduction of the synthesis of intercellular adhesion molecules, which lead to decreases of leukocyte-endothelial cell interactions and organ failure in animal models. There is some preliminary evidence that HS infusion can regulate human PMN function.

Banked Blood

Blood transfusion has been consistently identified to be a predictor of infections, ARDS, MOF, and death following major trauma (57). A systematic analysis of the MOF database was, therefore, studied to determine if a cause-and-effect relationship exists. A dose-response relationship between the number of units of blood transfused in the first 12 hours and the development of MOF was observed (58). For controlling the potential confounding effects of shock variables, a series of MLR analyses were performed in which other shock parameters were progressively added. Blood transfusion consistently emerged as an independent risk factor with very high odds ratios. While these MLR analyses do not exclude that early blood transfusion simply reflects shock, the relatively low coefficients of determination between blood transfusion and the other indexes of shock suggest that blood transfusion is reflecting something else.

One popular hypothesis is that blood transfusions are immunosuppressive and thus responsible for major septic morbidity that causes late MOF (59). The immunosuppressive effect of blood transfusion can be found in the transplantation literature of the late 1970s (60). It was clearly demonstrated that kidney transplants were less likely to be rejected if the patient received preoperative blood transfusions from different donors. Soon thereafter, in the surgical oncology literature, it was observed that perioperative blood transfusions were associated with tumor recurrence, and, more recently, in the trauma literature, blood transfusions have been shown to correlate with major infections. These clinical studies, however, have failed to differentiate whether these associations are due to the blood products *per se* or the conditions for which they were needed (e.g., extensive tumor resection, major pelvic fracture, and severe shock). Additionally, the epidemiologic features of late MOF-associated infections have changed. Patients with MOF continue to have a high rate of major infections, but less than 40% of the infectious insults are associated with the onset or worsening of MOF. Thus, blood transfusions may contribute to delayed immunosuppression and infections, but this may not contribute directly to the pathogenesis of MOF.

Our interest in this topic was prompted by the recent observation that stored blood primes neutrophils (i.e., PMNs) (61) for enhanced cytotoxicity, presumably via platelet activating factor (PAF) and possibly amplified by interleukin (IL)-6 and IL-8. This type of PMN priming occurs early in high-risk trauma patients in whom MOF later develops. These observations may be consistent with the two-hit hypothesis for early MOF (62). Specifically, this analysis indicates that blood transfusion is a powerful, independent risk factor for early MOF (adjusted odds ratio 7.4–13.2). In clinical studies of early MOF, it has been difficult to establish the second hits. Moreover, inflammatory agents can usually serve as primers and activators. It is conceivable that the initial insult (consisting of tissue injury and ischemia/reperfusion) primes the inflammatory cascade, and a subsequent blood transfusion serves as the activating agent (63). If this hypothesis proves true, there are conspicuous clinical implications and possible therapeutic interventions. Most injured patients at risk for MOF unfortunately require moderate hemoglobin loading to meet oxygen transport demands. This clinical dilemma may be answered with the availability of blood substitutes (64). Alternative strategies include using only short-storage blood products, more extensive washings of blood before infusion, and simultaneously administering antagonists to proinflammatory mediators (e.g., recombinant PAF acetyl hydrolase) with stored blood transfusion.

Blood Substitutes

The potential avenue to reduce the need for massive crystalloid administration is the earlier administration of blood. Specifically, the ATLS guidelines for initiating resuscitation of class IV hemorrhagic shock with LR may not be optimal. The current limited supply of stored blood and potential adverse effects, however, makes the option of earlier administration of blood logistically impractical. Hemoglobin-based oxygen carriers (HBOC) for trauma resuscitation may provide a workable compromise. The most successful HBOCs clinically are polymerized Hb solutions (64). Interest in HBOCs dates back to the 1933 report of Amberson et al., who demonstrated that hemolysates could transport oxygen in mammals (65). Unfortunately, when infused into humans, these Hb solutions caused excessive toxicity (vasoconstriction, ARF, and abdominal pain) that was attributed to stromal contamination (66). The next generation of HBOCs were "stroma free," but excess toxicity persisted and was attributed to instability of the Hb tetramer, which spontaneously dissociates into dimers and monomers. One formulation of stabilized tetramer was authorized for a phase-III study in trauma (67). This product, however, failed, and the trial was prematurely terminated due to unexpectedly high mortality in the treatment group [24/52 (46%) vs. 8/46 (17%)]. Although this was considered a major setback for clinical implementation of HBOCs, it is important to emphasize that the product used was diaspirin cross-linked hemoglobin (DCLHb). DCLHb had been shown to markedly increase pulmonary and systemic vascular resistance in several animal models. Tetrameric Hb extravasates from the vascular space, binds nitric oxide within the vessel wall, and thereby results in unopposed vasoconstriction. This issue was addressed by polymerizing the HB tetramer (68). The additional benefit of these larger Hb moieties is that they exert less colloid osmotic activity, and therefore a higher dose can be administered. A further limitation of earlier HBOCs is that due to loss of two to three DPG, oxygen affinity was greatly increased (normal P50 of 26 mmHg decreased to 12 mmHg). This was addressed by pyroxidation of the Hb tetramer, which increased the P50 to 29 mmHg. One polymerized Hb solution has been tested extensively in phase-I and phase-II trauma trials and has been shown to be safe and effective (69–71). A phase-III prehospital trial is currently under review by the Food and Drug Administration. The polymerized Hb solution is currently the closest to the optimal resuscitation fluid because it carries oxygen, remains in the vascular space, is nontoxic, has a long shelf life, does not need crossmatching, and does not transmit infections. Apart from these favorable characteristics, it abrogates the pathologic postinjury PMN cytotoxic function and attenuates the pathologic postinjury hyperinflammation compared with stored blood (72,73).

Timing

Aggressive isotonic crystalloid resuscitation (ATLS standard of care) during the uncontrolled hemorrhage could adversely affect outcome by increasing bleeding and diluting coagulation factors that set the stage for the "bloody vicious cycle" of acidosis, hypothermia, and coagulopathy. In animal studies of penetrating aortic injuries, the only variable associated with rebleeding during resuscitation was blood pressure. The systolic blood pressure of 90 mmHg and mean arterial blood pressure of 60 mmHg appear to be the critical values (74). "Hypotensive resuscitation" is becoming the standard of care for penetrating injuries (75). How this concept applies to blunt trauma is not clear. Blunt trauma typically presents more complex clinical scenarios in which some bleeding is not readily amenable to surgical intervention (e.g., pelvic fractures and extremity fractures). If one were to intentionally not resuscitate these patients, at some point, they will progress to an irreversible shock state. Another confounding issue is associated with closed-head injury (CHI), which is present in at least 25% of blunt trauma patients who suffered shock. Discerning these patients is difficult. Their Glasgow Coma Scale scores may be low, either as a result of brain injury or as a result of low cerebral blood flow. Maintaining cerebral perfusion pressure is believed to improve outcome in CHI patients. As a result, it is difficult not to normalize systolic blood pressure (SBP) initially until the issue of whether a CHI coexists has been resolved.

The Magnitude of Resuscitation

A recent review of four years of prospectively collected data from a computerized decision-support resuscitation protocol identified that ACS has become a frequent complication

(14%) of severe traumatic shock (11,76). Postinjury ACS is associated with poor outcome (55% incidence of MOF and 55% mortality rate). Multivariate analysis showed that ACS is a predictor of MOF and mortality. The multivariate prediction model for ACS revealed that the amount of infused crystalloid (LR) is an independent predictor of the syndrome. At the time of discharge from the emergency department, a crystalloid infusion of more than 3 L is an independent predictor with the odds ratio of 23, 89% sensitivity, and 75% specificity. The model developed at the time of the ICU admission showed that more than 7.5 L of crystalloids is an independent predictor of ACS, with the odds ratio of 166, sensitivity of 77%, and specificity of 70%. Given the strong relationship between ACS and the subsequent development of MOF, limiting indiscriminant crystalloid infusion is paramount. Traditionally, it has been recommended that the early signs of organ dysfunctions associated with intra-abdominal hypertension (IAH) should be treated with hypovolemic resuscitation (77,78). Our data show that hypovolemic resuscitation is efficient in increasing the pulmonary capillary wedge pressure (PCWP) in both ACS and non-ACS patients, but only the non-ACS patients respond to increased preload with increased CI. Cardiac function in patients with impending ACS does not improve. As a result of volume loading, patients with impending ACS develop pathologic increases in IAP and impaired gastric mucosal perfusion consistent with mucosal ischemia (79). These findings suggest that volume loading with crystalloids in scenarios with impending ACS is inefficient and potentially harmful.

Discussing the magnitude of the resuscitation brings up the question of end points. As previously discussed, preload-directed goal-oriented shock resuscitation has become a standard of ICU care in many U.S. Trauma Centers. During the 1990s, a series of PRCTs were performed to test whether supranormal resuscitation improves outcomes. Other investigators have had a difficult time duplicating Shoemaker's results. In September 2000, Shoemaker and associates published a third trial (80) that demonstrated no difference in outcome in critically injured patients resuscitated to normal or supranormal DO_2I . Given the results of this trial, combined with ongoing analysis of how patients responded to the computerized resuscitation protocol and the recognition that ACS was a frequent complication, the end point of resuscitation for this protocol was decreased from a DO_2I of 600 to 500 mL/min/m² in January 2001. This provided a unique opportunity to compare posttraumatic shock resuscitation outcomes with supranormal (600) and normal (500) DO_2I goals. With regard to resuscitation interventions and responses, the only significant difference was that the supranormal DO_2I patients received more crystalloids. There was a trend ($p = 0.07$), however, that they also received more blood transfusions, suggesting that more aggressive volume loading was promoting more bleeding. The difference of outcomes was astonishing: the supranormal group had significantly worse intestinal perfusion measured by tonometry, higher frequency of IAH/ACS, increased incidence of MOF, and higher mortality rate (81). With the available evidence, it can be concluded that aggressive goal-oriented resuscitation, especially with supranormal end points, could lead to early organ failure via the mechanism of IAH/ACS, if the pathological

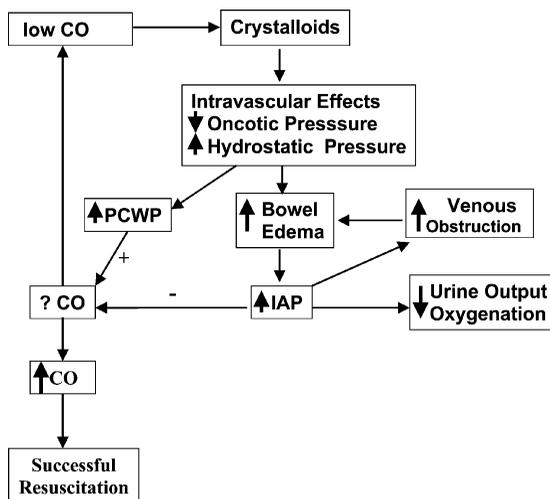


Figure 2 Futile crystalloid preloading. *Abbreviations:* CO, cardiac output; IAP, intra-abdominal pressure; PCWP, pulmonary capillary wedge pressure; ↑, increased; ↓, decreased; +, positive effect; −, negative effect.

elevation of the IAP is not recognized. The term “futile crystalloid preloading” was coined to describe the “salty water vicious cycle” of aggressive shock resuscitation (Fig. 2).

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39 Perioperative Fluid Therapy: Predictions for the Future

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During the last several decades, basic scientists and clinical investigators have rapidly advanced our understanding of perioperative fluid management. The results of those investigations, which are the substance of this book, have helped make great progress in quantifying the physiological effects of fluid replacement and demonstrating the adverse effects of insufficient or excessive fluid administration. However, existing data are insufficient to facilitate development of evidence-based standards that apply to individual patients undergoing diverse surgical procedures. To reach those evidence-based standards requires that investigators overcome many challenges.

Although current approaches are satisfactory for most patients, those approaches lack precision and require intensive further investigation. In daily practice, we lack essential information. At present, clinicians caring for surgical patients cannot accurately evaluate blood volume, fluid overload, hypovolemia, or tissue perfusion. In addition, clinicians require much more detailed information regarding the influence on fluid management of the type of surgery and of intercurrent treatments, and on patient factors such as age and preexisting disease. Recent important class I evidence from randomized clinical trials has provided tantalizing glimpses of the types of information that will be available in the future. However, clinicians must acquire sufficient information to determine whether to base perioperative fluid management, especially of patients undergoing more complex surgical procedures, on a simple dose-per-procedure concept or on the attainment of a yet-to-be-defined physiologic goal.

Certainly the overall conceptual basis for perioperative fluid management has undergone substantial evolution. Before approximately 1965, perioperative fluid management was governed by the concept that additional fluid would inevitably lead to a greater percentage of complications. Perioperative patients were permitted to receive little, if any, salt water (Fig. 1A). After the important work of Shires and others in the early-to-mid-1960s, the conceptual relationship between complications and fluid administration began to reverse (Fig. 1B). During the subsequent two decades, the clinical management began to reflect the assumption that perioperative administration of large volumes of fluid was completely defensible, particularly if a procedure was associated with tissue fluid accumulation. Of course, neither an uncritical "more is worse" nor "more is better" relationship is likely to be broadly applicable; the exact shape of the curve relating perioperative complications to perioperative fluid volume in a specific patient undergoing a specific procedure is unknown. However, in the most likely relationship, the incidence of perioperative complications would be least at an optimal rate and volume of fluid administrations and complications (presumably different sets of complications) would be increased at either extreme, i.e., excessive fluid restriction or excessive fluid administration (Fig. 1C). This concept is reflected by the recent concern by numerous investigators, including Holte et al. (3), that perioperative fluid excess has become a more common problem

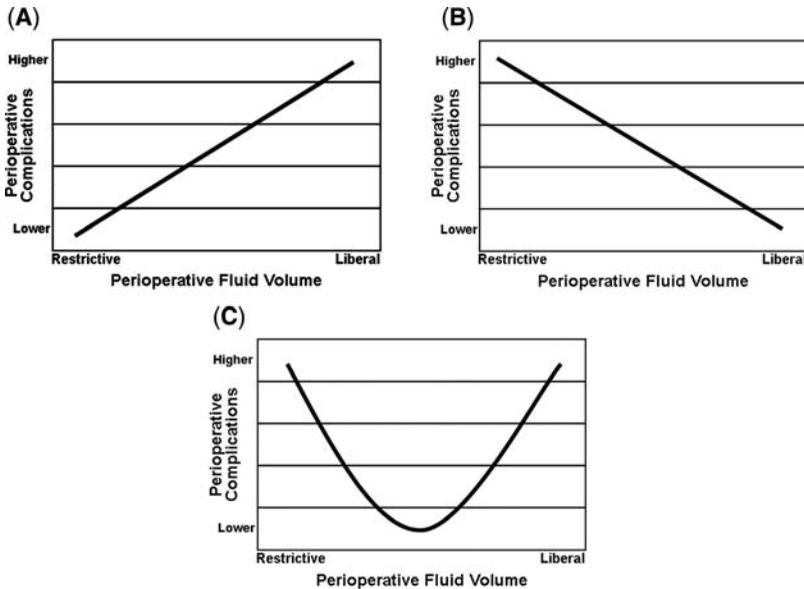


Figure 1 (A) The assumed relationship between perioperative complications and perioperative fluid volume through approximately the mid-1960s. Fluid administration was governed by the concept that additional fluid would inevitably lead to a greater percentage of complications and that patients should be managed perioperatively such that they would retain little, if any, salt water. (B) The work of Shires et al. (1,2) in the 1960s almost completely reversed the conceptual relationship between complications and fluid administration, with many clinicians arguing that administration of substantial volumes of fluid was completely defensible and appropriate. (C) More recently, clinicians have generally adopted the approach that neither extreme offers an ideal approach to perioperative fluid administration and that the best patient outcomes probably result from fluid administration in moderate, individualized volumes. One consequence of this has been the emergence of goal-directed fluid therapy.

than inadequate fluid administration and that randomized trials are necessary to determine whether “dry” or “wet” fluid regimens are associated with the fewest complications.

Complications related to either inadequate or excessive fluid administration can be broken down into lethal and nonlethal consequences. Potentially lethal consequences of inadequate fluid administration include lactic acidosis, acute renal failure, and multiple organ system failure; nonlethal complications include thirst, drowsiness, dizziness, postoperative nausea and vomiting, and increased pain. Lethal complications of excessive perioperative fluid administration include pulmonary edema and cardiac failure, whereas nonlethal complications include peripheral edema, periorbital edema, impaired gut function, and impaired wound healing.

Several clinical trials have addressed the question of appropriate quantities of fluid administration in relatively simple surgical procedures involving general anesthesia. Those trials have generally consisted of dose-per-procedure designs, usually comparing a low dose to a high dose. Yogendran et al. (4) randomized 200 ASA I-III ambulatory surgical patients to receive a preoperative bolus of Plasmalyte[™] of either 2 or 20 mL/kg over 30 minutes. The higher dose was associated with decreased thirst, decreased drowsiness, decreased dizziness, and decreased nausea. Maharaj et al. (5) randomized 80 ambulatory patients undergoing gynecologic laparoscopy to preoperative infusion of either 3 mL/kg (total dose) or 2 mL/kg for every hour of preoperative fasting. The smaller dose was equivalent to 180 mL in a 60 kg patient whereas the larger dose was equivalent to approximately 1440 mL in a 60 kg patient who had had nothing per mouth for 12 hours. Once again, the larger volume was associated with a decrease in postoperative nausea, vomiting, and pain. This type of study, which distinguishes between two widely varying dose regimens, is highly valuable for guiding clinical management, but does not clarify the impact of intermediate doses. From a pharmacologic perspective, comparison of not only low and high doses but also intermediate doses would greatly enhance the clinical utility of the investigators' observations, although of course a multiple-arm study would be considerably more difficult to perform and to analyze statistically.

To further explore possible dose-response relationship, Figure 2 displays the relationship between postoperative nausea and vomiting and intraoperative fluid management

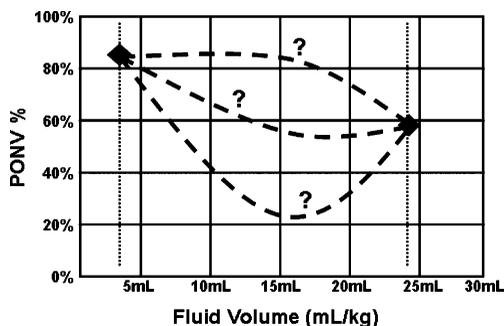


Figure 2 This chart, based on the work of Maharaj et al. (5), suggests the limitations of two-arm, low- and high-dose clinical protocols. While the overall incidence of postoperative nausea and vomiting (PONV) was lower in patients receiving higher volumes of fluid, the two extremes (3 or approximately 24 mL/kg, respectively) do not clarify the more subtle effects of moderate fluid administration. In other words, what is the shape of the curve relating intermediate fluid volumes to perioperative complications?

in the study by Maharaj et al. (5). From this study, one should conclude that 3 mL/kg was insufficient for patients undergoing this type of surgery and one could further infer that even lower doses would be even less desirable; similarly, in this specific population, 24 mL/kg (from the calculations above) was superior to the lower dose. An inference that somewhat larger volumes would also be preferable could be appropriate. However, this two-dose study did not address any intermediate doses. We cannot infer whether an intermediate dose would be better, worse, or equivalent.

The same concerns apply to a third important study, by Holte et al. (6), who randomized patients undergoing laparoscopic cholecystectomy that was expected to last 90 to 120 minutes to receive either 15 or 40 mL/kg of lactated Ringer's solution intraoperatively. Primary outcome variables included respiratory spirometry, cardiovascular hormonal responses, balance function, pain, nausea and vomiting, hospital stay, and exercise capacity assessed using a sub-maximal treadmill test. Patients randomized to the higher volume of fluid had improved pulmonary function, reduced stress response, and earlier discharge than those randomized to the lower volume. In addition, patients in the group receiving the higher dose of fluid had less nausea, decreased thirst, decreased dizziness, decreased drowsiness, decreased fatigue, improved balance function, and an improved sense of general well-being. Perhaps most strikingly, those randomized to the higher fluid group had improved exercise capacity, as evidenced by early return of treadmill capacity to nearly that present at the baseline preoperative evaluation. Of course, the question again arises as to the possible effects of intermediate doses of perioperative fluids.

The foregoing three studies, each of which evaluated a lower versus a higher dose of perioperative fluids for relatively limited surgical procedures, showed substantial advantages to more liberal, in comparison to more restrictive, fluid administration. However, it would be incorrect to conclude that greater fluid administration is generally associated with better outcomes, especially in more substantial surgery. In abdominal surgical procedures, especially those involving colonic surgery, restrictive fluid management appears to be associated with better outcomes. Nisanevich et al. (7) randomized 152 patients undergoing elective intra-abdominal surgery to either a liberal protocol group or a more restrictive protocol group. The liberal protocol group received 10 mL/kg followed by 12 mL/kg/hr; the restrictive protocol group received 4 mL/kg/hr, without a preceding bolus. The restrictive protocol group had fewer total complications, earlier flatus, earlier stools, and a shorter hospital stay. In addition, as the protocol would suggest, those patients in the restrictive protocol group gained less weight and had higher hematocrit and albumin concentrations immediately after surgery. Similar results were obtained by Brandstrup et al. (8), who conducted a randomized, observer-blinded, multicenter trial in 172 elective colon surgery patients, who received either restrictive perioperative fluid management or a regimen considered to reflect prevailing standards of care. The protocols in the two studies are complicated. However, the goal of the restrictive protocol was to maintain preoperative body weight into the postoperative period, suggesting quite marked fluid restriction (1 L of accumulated fluid will add 1 kg of weight). The primary outcome measures included death and adverse effects. As in the study by Nisanevich et al. (7), the restrictive protocol was associated with improved outcome. The weight-gain target was nearly attained in the restrictive protocol group, with the total weight gain less than 1 kg versus 3 kg in the liberal protocol group. Total postoperative complications were 33% in the restrictive and 51% in the standard group, cardiopulmonary

complications were 7% in the restrictive and 24% in the standard group, and tissue-healing complications were 16% in the restrictive and 31% in the standard group.

Taken together, the studies by Nisanevich et al. and Brandstrup et al. (7),(8) strongly suggest that strict fluid restriction is a superior strategy to conventional management in patients undergoing major intra-abdominal surgery, especially surgery of the colon. Again, however, the influence of an intermediate strategy was not investigated.

Based upon these several interesting clinical trials, we can conclude that in less extensive surgery, more liberal (but not massive) fluid administration is associated with improved outcomes, primarily a reduced incidence of nonlethal complications. In more extensive intra-abdominal surgery, strict fluid restriction appears to be associated with improved perioperative outcomes. However, the use of fixed-dose protocols that are not individualized for specific patients seems less likely to be suitable for most patients than protocols that emphasize goal-directed fluid therapy. Unfortunately, goal-directed fluid therapy has been investigated in relatively limited numbers and types of surgical patients and has been based on diverse goals.

Goal-directed fluid therapy is based on the hypothesis that subtle deficits of tissue perfusion may be inapparent but may lead to complications that could be avoided by increasing hemodynamic variables to attain predetermined goals. Several goals that have been proposed include the use of central venous oxygen saturation in septic patients undergoing resuscitation in the emergency department (9), systemic oxygen delivery greater than or equal to 600 mL/minute/ M^2 in high-risk surgical patients (e.g., Wilson et al.) (10), and the somewhat less-invasive use of the esophageal Doppler monitor, which quantifies both stroke volume and corrected flow time in the descending aorta.

In high-risk surgical patients, the use of systemic oxygen delivery (the product of cardiac index and arterial oxygen content) as a target necessitates the use of invasive pulmonary arterial catheterization, so that cardiac index can be measured and multiplied by arterial oxygen content. Despite the success of some groups with this strategy in high-risk surgical patients, the strategy has not achieved universal approval and has frankly failed in some populations, such as trauma patients and medical intensive care unit patients. The use of systemic oxygen delivery as a goal also presupposes application of an appropriate algorithm that will increase or maintain oxygen delivery while minimizing risk. This may be important, as is evident in the study by Wilson et al. (10), in which either dopexamine (a catecholamine not currently available in the United States) or epinephrine were combined with monitoring and fluid administration to increase oxygen delivery. In both groups, mortality appeared to be reduced in comparison to a group that received routine care without specific management of systemic oxygen delivery. However, the complications were substantially higher in the group receiving epinephrine than in the group receiving dopexamine, suggesting that there might be substantial differences between the overall effects of various possible algorithms for enhancing oxygen delivery.

In contrast to the invasive techniques necessary to monitor systemic oxygen delivery, the esophageal Doppler monitor uses a minimally invasive probe that can be easily placed in anesthetized patients. The esophageal Doppler measures several variables that can be used as goals for perioperative fluid management protocols. Perhaps the most promising is corrected flow time, which is a measure of the duration of the systole in the descending aorta. Use of corrected flow time as a goal requires some hemodynamic sophistication on the part of clinicians, who must first understand the relationship among various hemodynamic variables and who then must recognize that corrected flow time is an alternative indicator of preload, which compares favorably to pulmonary arterial occlusion pressure. Perhaps the most successful demonstration of the potential value of goal-directed therapy based on esophageal Doppler monitoring is the study by Gan et al. (11), who randomized 100 patients expected to undergo surgery with predicted estimated blood loss exceeding 500 mL to fluid administration based on clinical criteria or to a treatment group in which hydroxyethyl starch in 0.9% saline was infused in 200 mL increments to maximize stroke volume and keep the corrected flow time at a value exceeding 0.35 seconds. The protocol (Fig. 3) emphasizes corrected flow time and can be conceptualized as a preload augmentation protocol. The patients who were randomized to receive treatment guided by corrected flow time received more hydroxyethyl starch than the standard therapy group and also had a reduced length of stay and earlier return to solid diet in comparison to those in the standard therapy group.

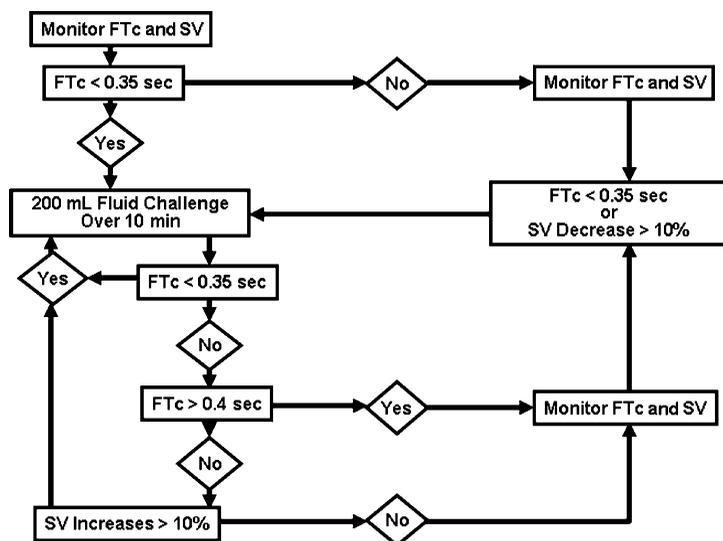


Figure 3 Protocol diagram used by Gan et al. [11]. The protocol emphasizes corrected flow time (FTc) more than it emphasizes the management of stroke volume (SV) and so can be interpreted as primarily a preload augmentation protocol in which colloid (6% hydroxyethyl starch in saline) was used as a fluid challenge.

In the future, it seems likely that additional class I evidence (randomized clinical trials) will further refine perioperative fluid management. The amount of class I evidence has dramatically increased in the last decade and will continue to increase in coming years. In particular, one would expect to see studies that refine some of the apparently large differences between strict fluid restriction and liberal fluid administration. In addition, one would expect that clinical trials will further resolve the question of whether goal-directed administration of fluids provides a more precise, individualized strategy.

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about the book . . .

Perioperative fluid therapy requires the correct selection, amount, and composition of fluids based on the patient's underlying pathology, state of hydration, and type and duration of surgical stress. Filling a gap in the literature, this source provides a solid foundation to practical perioperative fluid management, fluid solutions, and the utilization of fluids in clinical and surgical environments, and analyzes the composition of body compartments, the regulation of water and electrolytes, and bodily response to traumatic and surgical conditions.

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