Perioperative fluid management

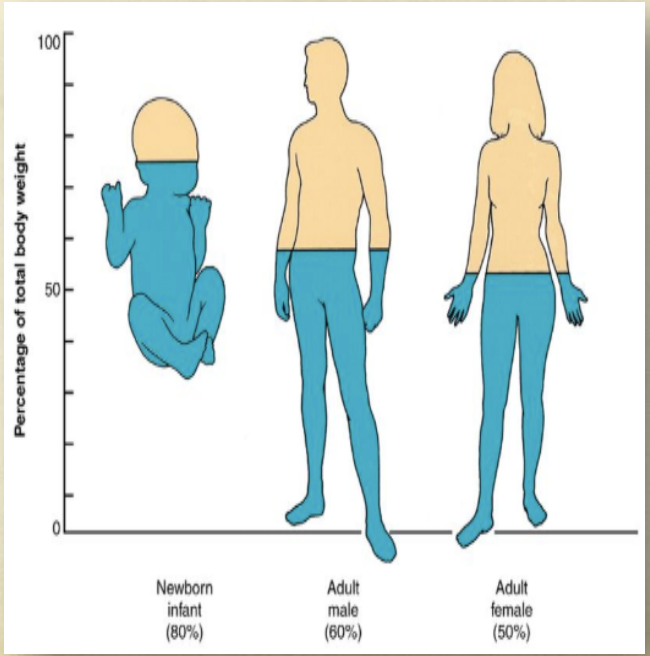
R_2Kiattisak /Lt.col.Ekkasak

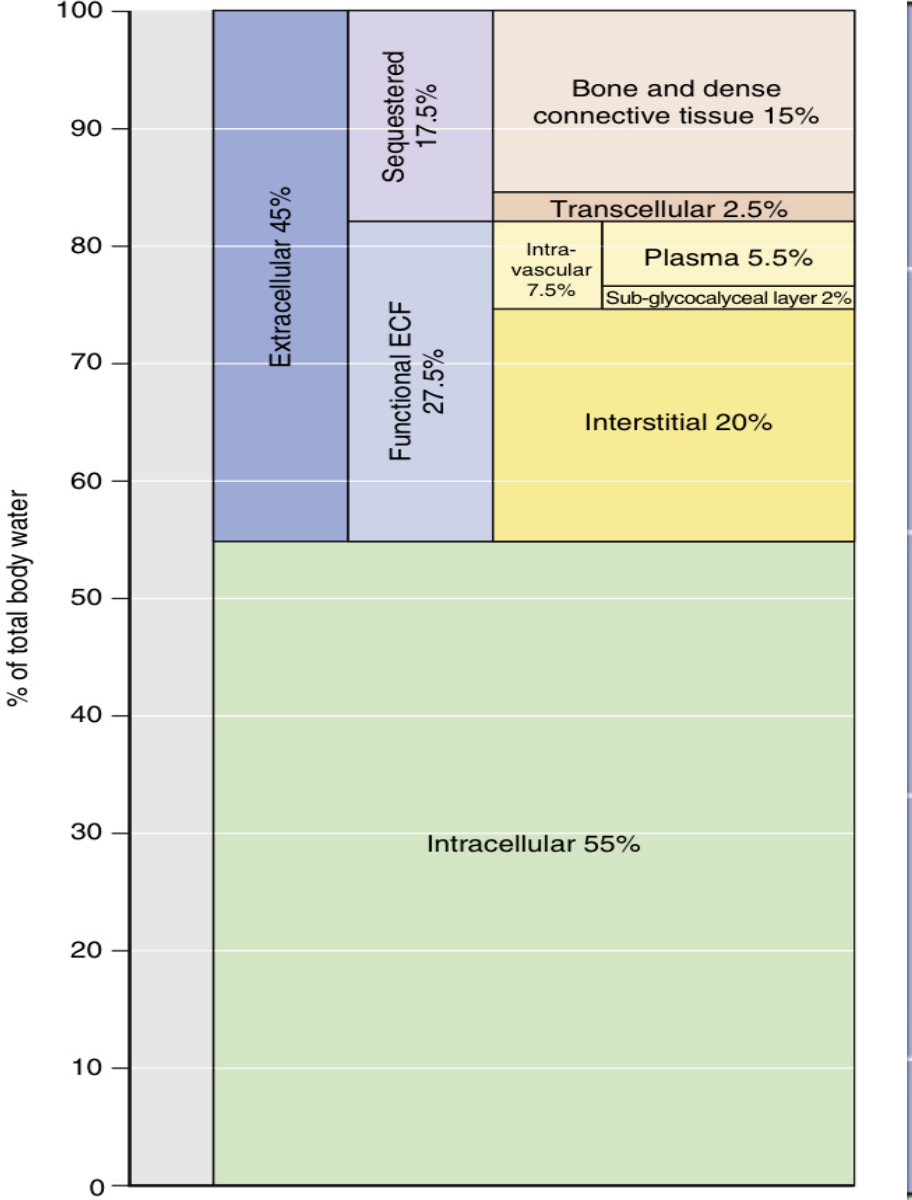
Outline

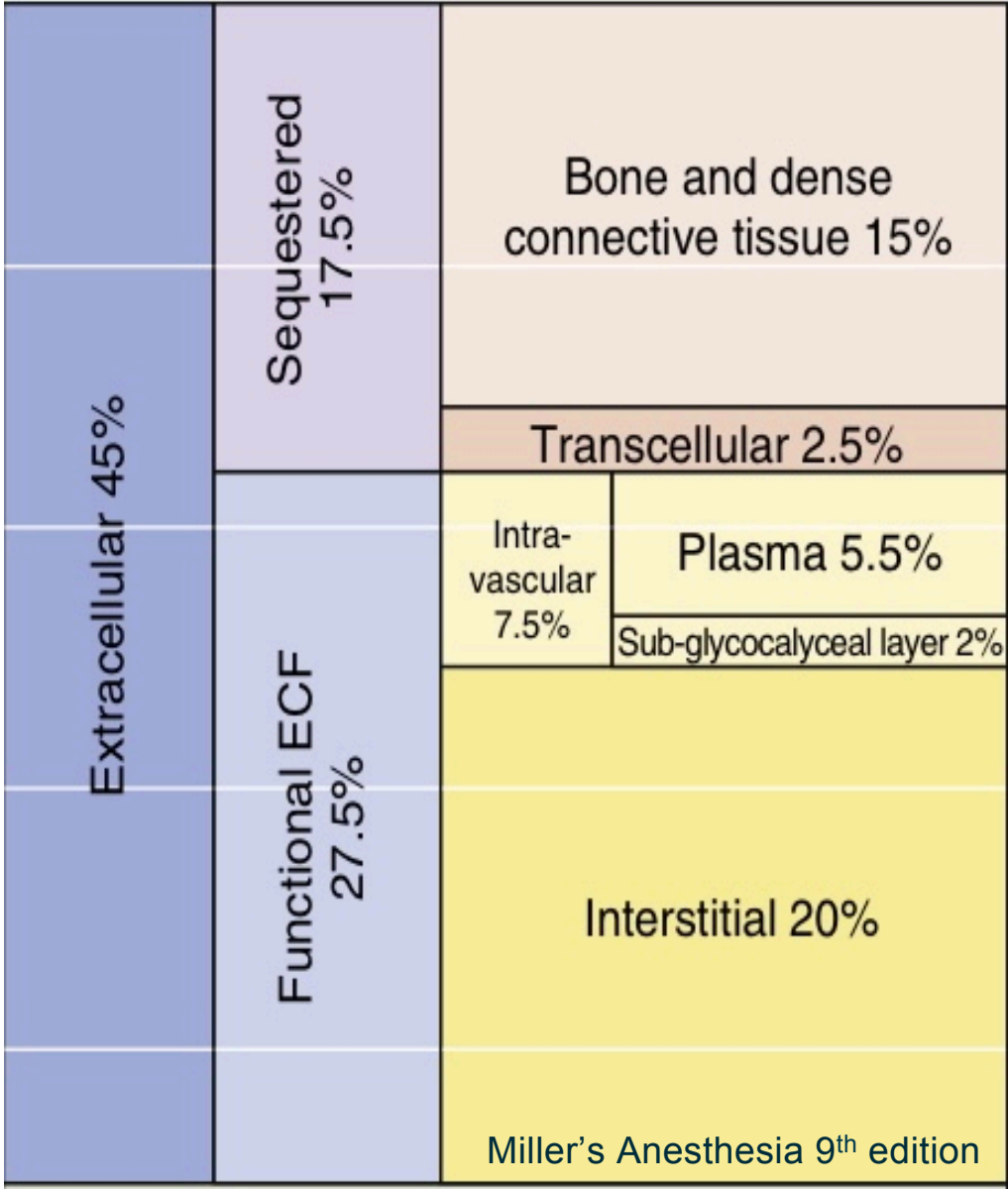
- Fluid compartment
- Physiochemical laws governing fluid and electrolyte movement
- Fluid compartment barriers and distribution
- Physiologic Control of Overall Fluid Balance
- Acid-Base Disturbances and Fluid Therapy
- Fluid pharmacology
- Clinical application

Fluid compartment

- TBW : 60 % of total body weight of adult
  - Varies with age, gender, body composition
- Adipose tissue contains little water compared with other tissue
  - Range can be 45% [obese] - 75% [lean] amount of adipose tissue




% of total body water
100
90
80
70
60
50
40
30
20
10
0
Extracellular 45%
Sequestered 17.5%
Bone and dense connective tissue 15%
Transcellular 2.5%
Functional ECF 27.5%
Intra-vascular 7.5%
Plasma 5.5%
Sub-glycocalyceal layer 2%
Interstitial 20%
Intracellular 55%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Sequestered 17.5%
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Functional ECF 27.5%
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Plasma 5.5%
Sub-glycocalyceal layer 2%
Interstitial 20%
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Total blood volume

- Extracellular
  - Plasma, subglycocalyx
- Intracellular
  - Blood cell element
- Nonfunctional ECF compartment excluded

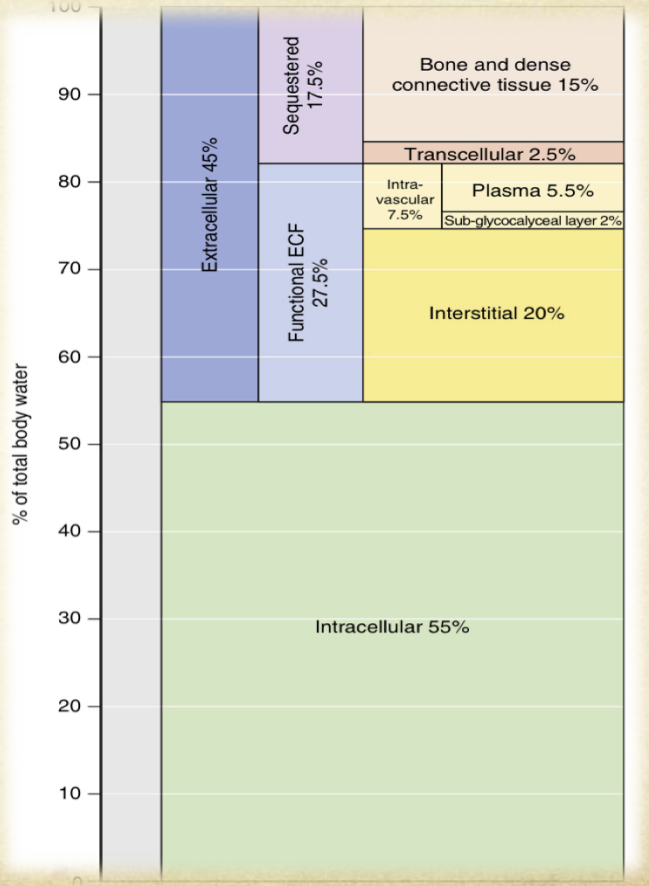

TABLE 47.1 Age-Related Variation in Total Body Water and Extracellular Fluid as Percent of Body Weight (MULTIPLY by 10 for mL/kg)

Age	TBW (%)	ECF (%)	Blood Volume (%)
Neonate	80	45	9
6 months	70	35	
1 year	60	28	
5 years	65	25	8
Young adult (male)	60	22	7
Young adult (female)	50	20	7
Elderly	50	20	

= 70 ml/kg

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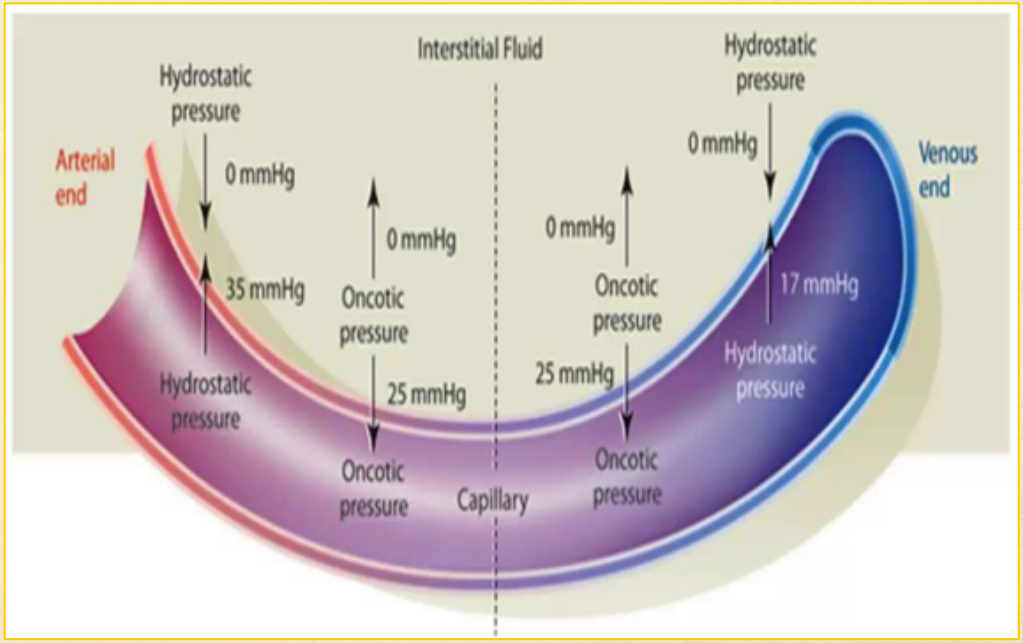
Physiochemical laws governing fluid and electrolyte movement

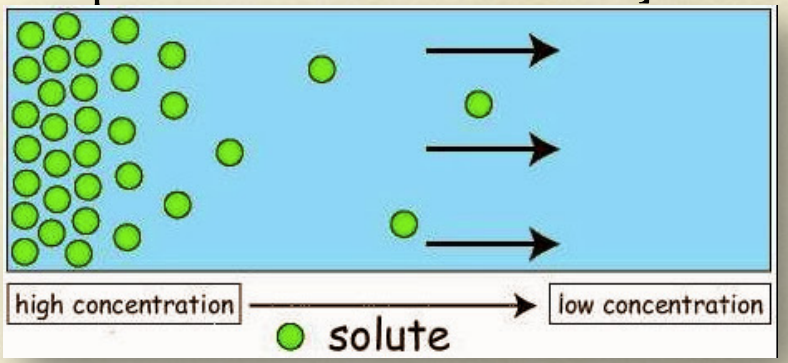
- Diffusion
- Osmosis
- Osmolality
- Tonicity
- Oncotic pressure



Diffusion

$$J = -DA\left(\frac{\Delta c}{\Delta x}\right)$$

- Solute particles fill the solvent volume by motion from areas of *high to low* concentration [across permeable membrane]

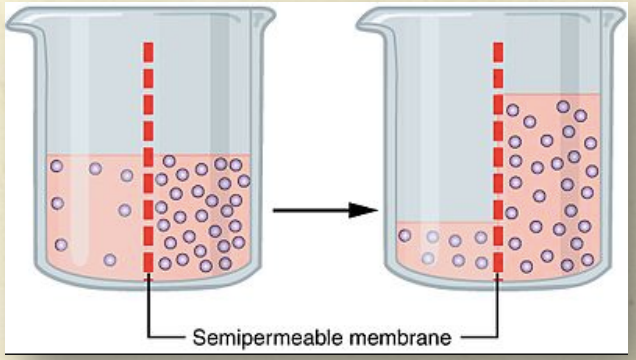


- **Fick's law of diffusion**
  - J = net rate of diffusion
  - D = diffusion coefficient
  - A =cross-sectional area
  - $\Delta c / \Delta x$ =concentration (chemical) gradient

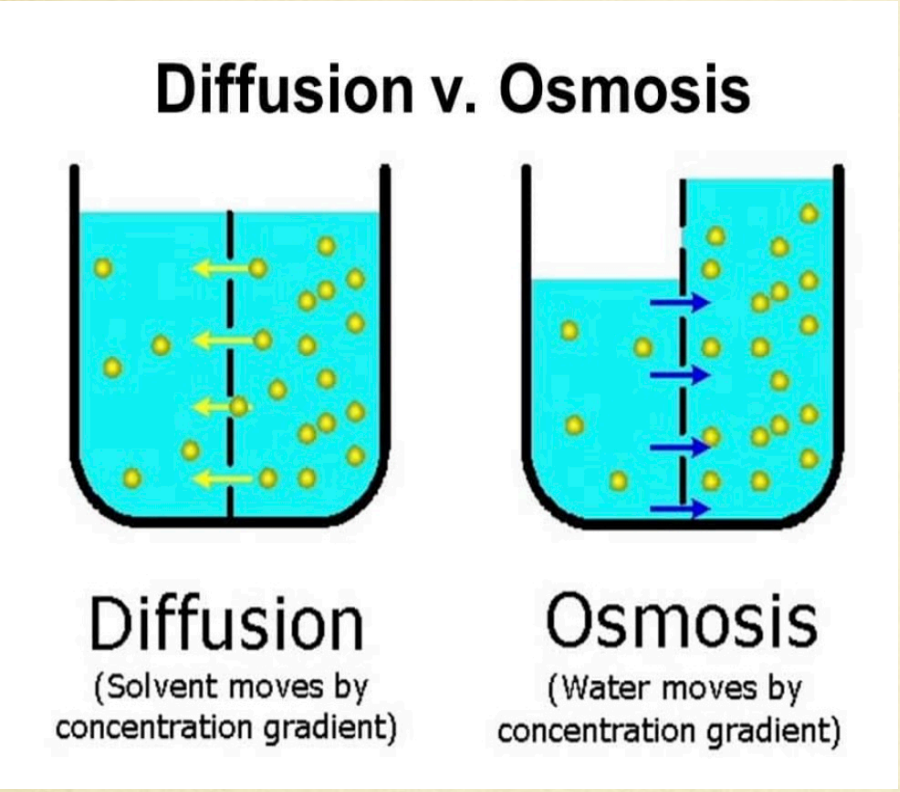
Osmosis

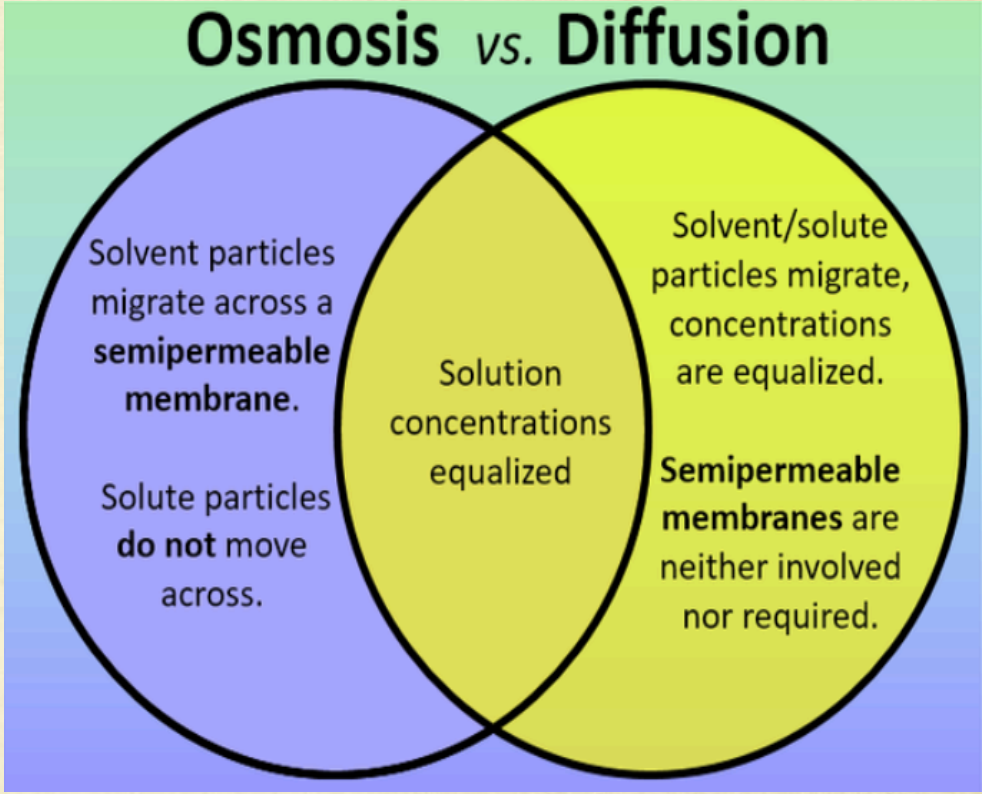
$$P = \frac{nRT}{V}$$

- Semipermeable membrane
  - *Water* molecules will diffuse across the membrane into the region of higher solute concentration [fluid distribution ICF, ECF]



- *P = osmotic pressure*
- *R = gas constant*
- *T = absolute temperature*
- *V = volume.*
- *n = number of particles* (mass of solute/molecular weight of solute) x number of particles into which the solute dissociates


Diffusion v. Osmosis
Diffusion
(Solvent moves by concentration gradient)
Osmosis
(Water moves by concentration gradient)


Osmosis vs. Diffusion
Solvent particles migrate across a **semipermeable membrane**.
Solute particles **do not** move across.
Solution concentrations equalized
Solvent/solute particles migrate, concentrations are equalized.
Semipermeable membranes are neither involved nor required.

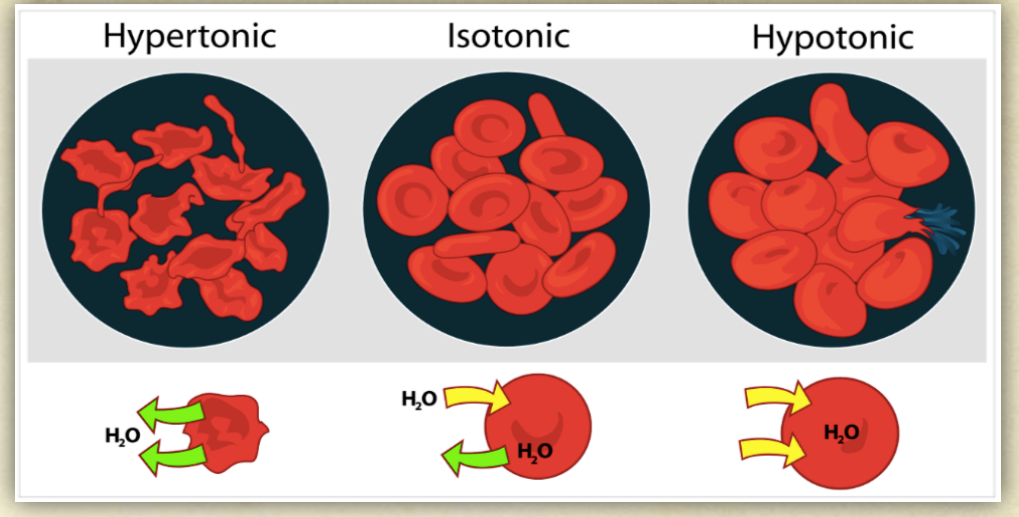
Osmo*lal*ity and Osmo*lar*ity

- Osmo*lar*ity : Number of osmoles per solution 1 L
  - affected by temperature change
- Osmo*lal*ity : Number of osmoles per solvent 1 kg

$$\text{Serum osmolality} = (2 \times \text{Na}) + (\text{glucose}/18) + (\text{urea}/2.8)$$

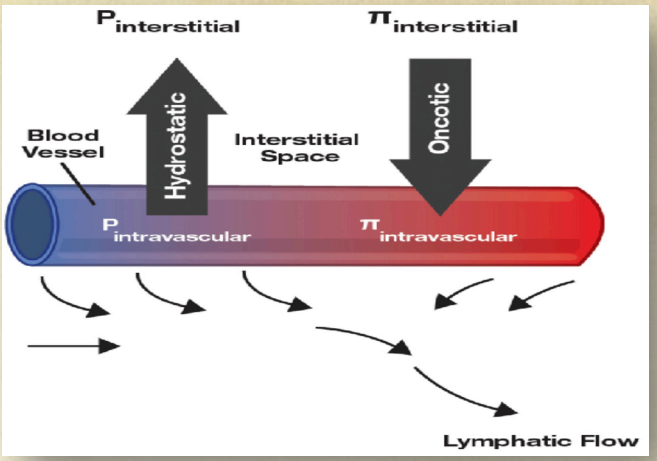
- Normal body osmolality 285-290 mOsm/kg

Tonicity



- Effective osmolality
- Determine fluid movement across cell membrane
- Sensed by the hypothalamic osmoreceptors

Oncotic pressure



- Component of total osmotic pressure that is due to the colloids
  - Large molecular-weight particles
  - Predominantly proteins (*Albumin*, globulins, fibrinogen)
  - Plasma oncotic pressure of 25-28 mm Hg

TABLE 47.3 Composition of Transcellular Fluids (mEq/L Unless Stated)

	Daily Volume (L)	Cations				Anions		pH
Fluid		Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	HCO_3^-	
Gastrointestinal tract								
Saliva	1-1.5	30-90	20-40	2.5	0.6	15-35	10-40	6-7
Gastric	1.5-2.5	20-60	10-20			20-160	0	1-3.5
Bile	0.7-1.2	130-150	5-12	10-50		25-100	10-45	7-8
Pancreatic	1-1.5	125-150	5-10			30-110	40-115	8-8.3
Small bowel (concentrations from proximal to distal)	1.8	140-125	5-9			110-60	100-75	7-8
Large bowel	0.2 (lost in feces)	20-40	30-90			0-15	40	7-8
Sweat	0.1-0.5	45-60	5-10			45-60	0	5.2
Cerebrospinal fluid		140	2.8	2.1	1.7	120		7.33

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TABLE 47.2 Composition of Intracellular and Extracellular Fluid Compartments (in mOsm/L Water)

		EXTRACELLULAR	
	Intracellular	**Intravascular**	**Interstitial**
CATIONS			
Na^+	10	142	145
K^+	157	4	4
Ca^{2+}	0.5*	2.5	2.5
Mg^{2+}	20	0.8	0.7
ANIONS			
Cl^-	10	103	117
HCO_3^-	7	25	27
$HPO_4^{2-}/H_2PO_4^-$	11	2	2
SO_4^{2-}	1	0.5	0.5
Organic acids		6	6
Protein	4	1.2	0.2

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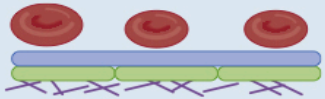
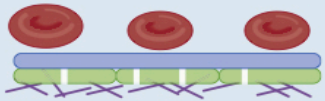
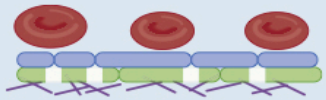
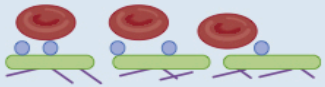
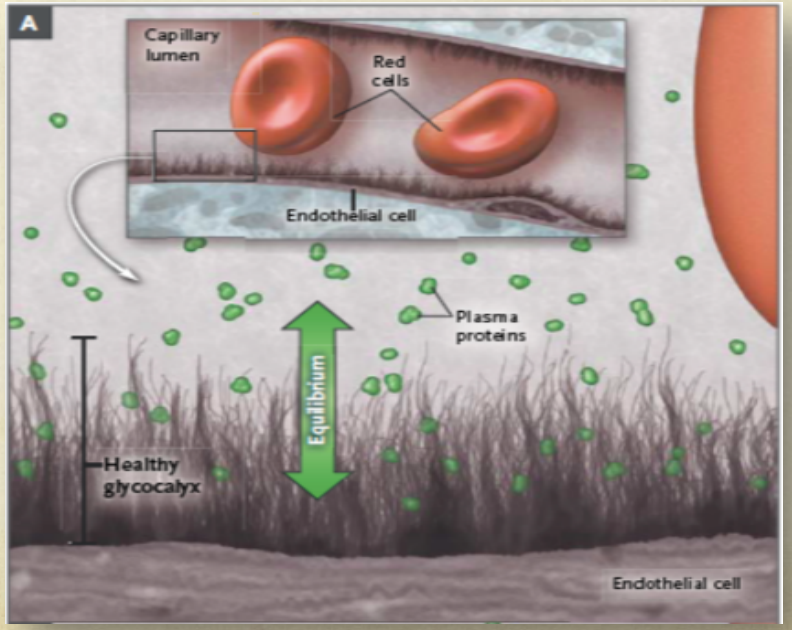
TABLE 47.4 Capillary Characteristics

Capillary Type	Site	Large Pores	Basement Membrane	Glycocalyx Layer	Notes on Function
Nonfenestrated (continuous)  Most common type	Muscle, connective tissue, lung, nervous tissue	None	Continuous	Continuous	Intercellular clefts are the main route for fluid filtration. These are partly occluded by junctional strands with multiple breaks. In the blood-brain barrier, these breaks are small (1 nm) and infrequent (zona occludens tight junctions), permitting passage of only the smallest non-lipid soluble molecules. In other tissues, the breaks are larger (5-8 nm) and more frequent (macula occludens loose junctions).
Fenestrated 	Endocrine, gut mucosa, choroid plexus, lymph nodes	Pores within endothelial cells with covering diaphragm 6-12 nm size	Continuous	Continuous	Fenestrations allow capillary reabsorption of fluid from ISF, in contrast to other capillary types.
	Glomeruli	Endothelial pore size up to 65 nm	Continuous	Discontinuous over pores, reducing *effective* pore size	Numerous pores allow large-volume filtration at the glomerulus. The effective pore size is reduced further to 6 nm by podocytes; thus, proteins not usually filtered.
Sinusoidal 	Liver, spleen, bone marrowd	Large intercellular gaps up to 120 nm	Discontinuous	No effective layer because of endothelial uptake of hyaluronic acid	Large fenestrations allow macromolecules (lipoproteins, chylomicrons) to pass between plasma and ISF; the result is no COP to oppose filtration, and the ISF in these tissues is effectively part of the plasma volume. Large volume filtration to the ISF here cannot be accommodated by tissue expansion because of fibrous capsules and is returned via lymphatics (e.g., liver lymph production accounts for 50% of total body lymph production)

Endothelial glycocalyx

- Glycosaminoglycan {syndecan-1, hyaluronic acid and glipican} glycoprotein and proteoglycan >> endothelial glycocalyx layers
- Physiological function
  - Prevent from platelet and leukocyte adhesion
  - Macromolecular sieve
  - Mechanotransducer : NO release
- Volume of SGL 700 - 1000 ml
  - Part of intravascular volume



Revised starling principle

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SPOTLIGHT REVIEW

Microvascular fluid exchange and the revised Starling principle

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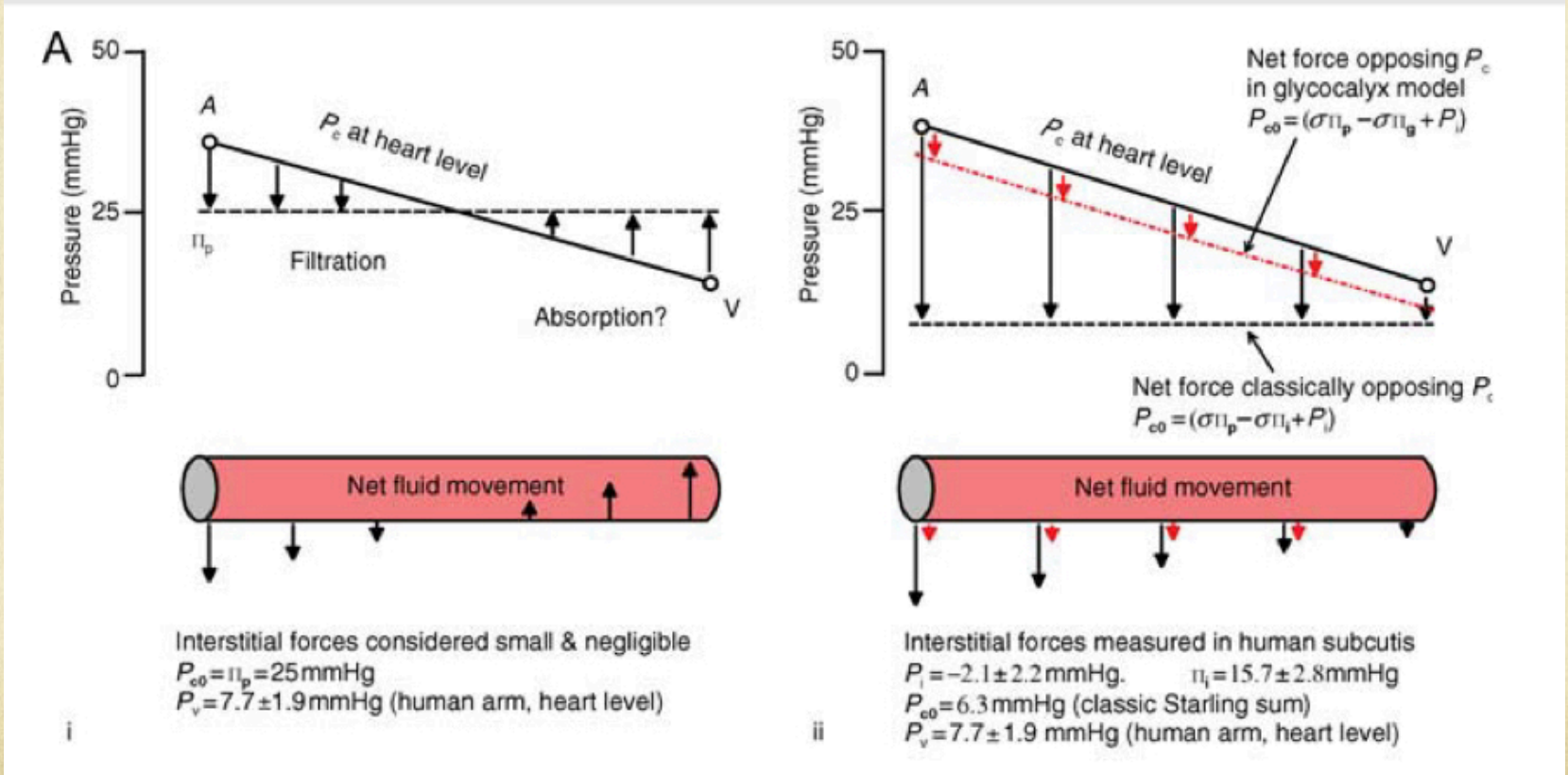
Revised starling equation

$$J_v = K_f([P_c - P_i] - \sigma[\pi_c - \pi_{sg}])$$

- J_v = *transcapillary flow*
- K_f = *filtration coefficient*
- P_c = *capillary hydrostatic pressure*
- P_i = *Interstitial* hydrostatic pressure
- σ = *reflection coefficient* (the degree to which the tendency of a macromolecule to cross the endothelial barrier is resisted),
- π_c = *capillary* oncotic pressure
- π_{sg} = *subglycocalyx oncotic* pressure

Cardiovascular Research 2010;87(2):198-210

Revised starling principle



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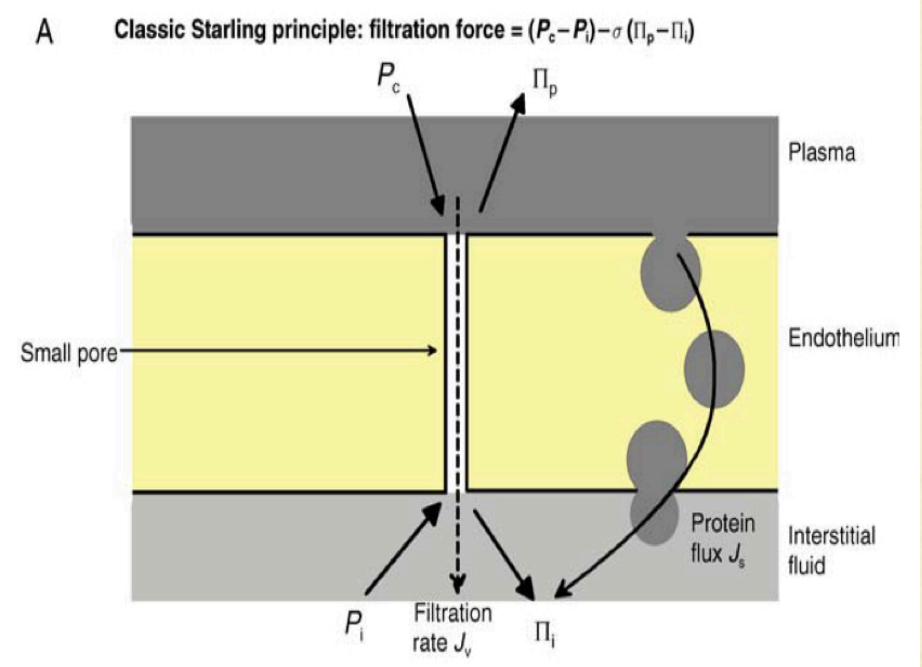
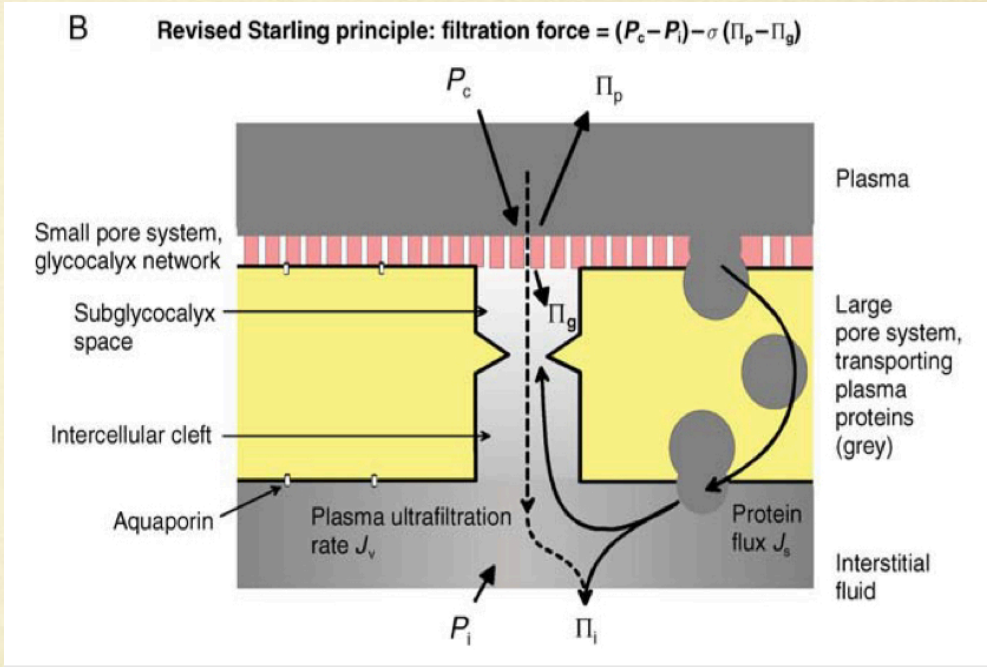
Glycocalyx cleft model





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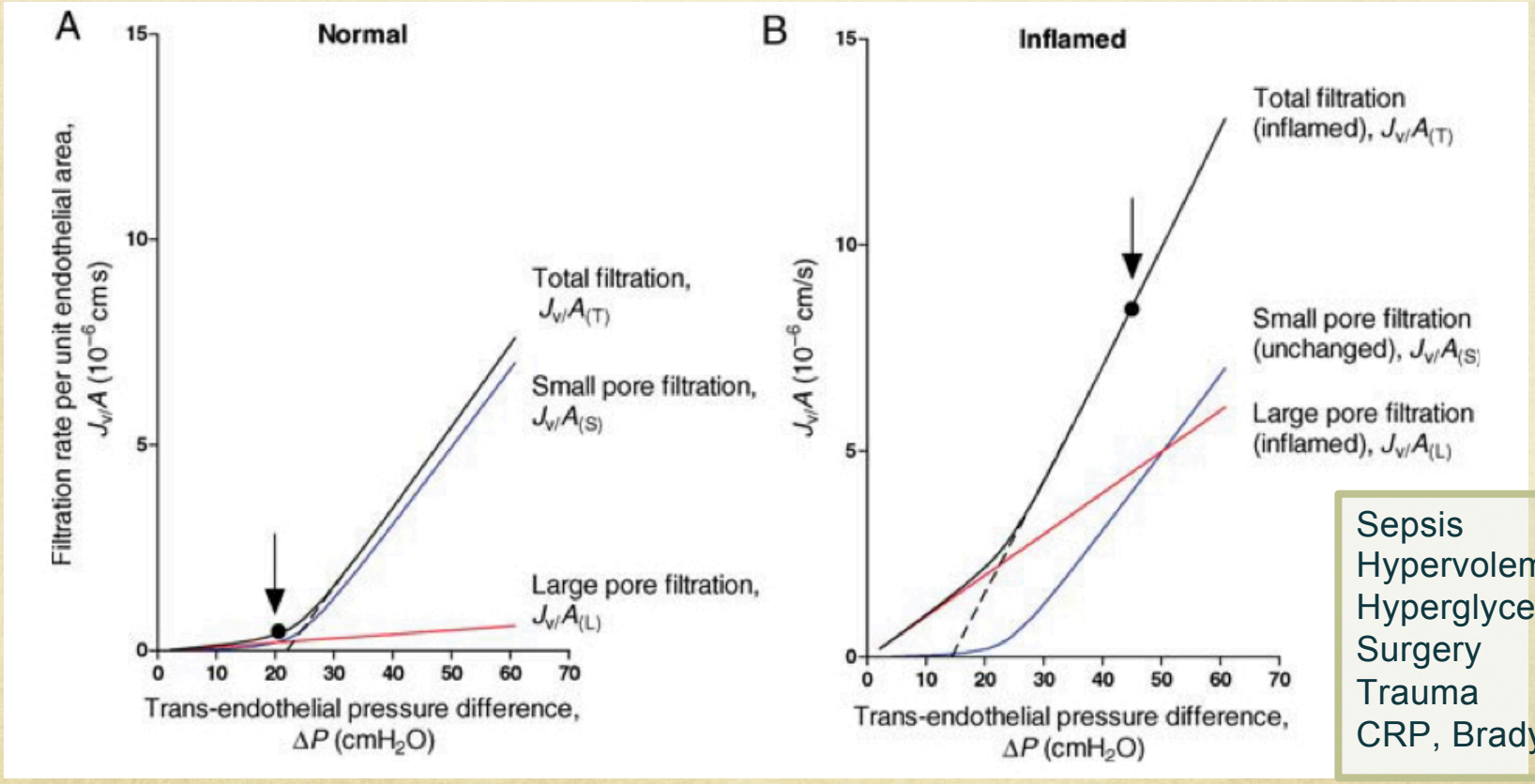
Endothelial permeability



Sepsis
Hypervolemia
Hyperglycemia
Surgery
Trauma
CRP, Bradykinin

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Revised starling principle

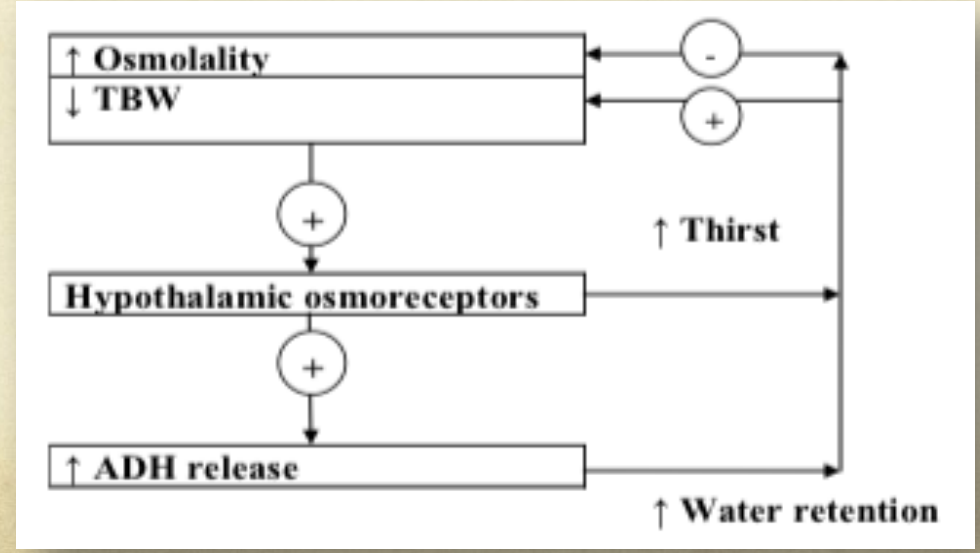
- Key different
  - fluid not reabsorbtion at end of venous capillary
  - Plasma COP – subglycocalyx COP
  - Interstitial COP is not involved
- Raising plasma COP [eg. Albumin infusion]
  - reduces J_v but not cause absorption
- Continuous capillaries exhibit “No absorption rule”

Physiologic Control of Overall Fluid Balance

- 60 % daily water loss >> urinary excretion
- Perioperative maintain >> reduced fluid intake, blood loss, IV fluid
- <u>Total body water control sensor</u>
  1. Hypothalamic osmoreceptors : Change ECF tonicity
  2. Low-pressure baroreceptors in the large veins and right atrium that : Sense Central venous pressure [CVP]
  3. High-pressure baroreceptors in the carotid sinus and aortic arch : Sense mean arterial pressure [MAP]

Physiologic Control of Overall Fluid Balance

- Sensory input >> Hypothalamus
- Effect : Thirst and ADH release → water reabsorption → low volumes of concentrated urine



Acute disturbances in circulating volume

- Response to rapid blood loss
  - Minimizing change in effective blood volume
    - Venoconstriction, reduce urine production
  - Maintain cardiac output and arterial pressure
    - Tachycardia, increased inotropy, vasoconstriction
- Low and high pressure baroreceptor >> increase sympathetic out flow
  - Renal vasoconstriction, activate RAA, ADH release

Acute disturbances in circulating volume

- Overall result:
  - ↑ Renal salt and water retention
  - ↑ Peripheral vascular resistance
  - ↑ Cardiac output
- In the absence ongoing loss
  - Restore plasma volume in 12-72 hour
  - Restore RBC level by erythropoiesis in 4-8 wk

Acid-Base Disturbances and Fluid Therapy

- Interpretation of acid-base balance : 3 main ways

1. Henderson-Hasselbach equation
2. Anion gap model
3. Stewart's strong ion model

Henderson-Hasselbach equation

- Represent HCO_3^- buffer systems
- Plasma HCO_3^- concentration independent plasma pH

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

$$pH = pK_a + \log\ [HCO_3^-]\ /\ [H_2CO_3]$$

$$\text{Total } CO_2 = [HCO_3^-] + [\text{Dissolved } CO_2] + [\text{Carbamino } CO_2] + [H_2CO_3]$$

$$\approx P_{CO_2} \times 0.03 \text{ mmol } CO_2/\text{L/mm Hg}$$

$$pH = 6.1 + \log\ [HCO_3^-]\ /P_{CO_2} \times 0.03$$

Anion gap model

- Measured cation and anion concentrations in plasma
  - $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$
  - Normal anion gap is 4 to 11 mEq/L
- Excess organic acid [eg. Lactic acid, ketoacid]
  - Accumulate unmeasure anion >> ⬇ HCO_3^- to buffer excess H^+ >> increase anion gap
  - In case Cl^- infusion even ⬇ HCO_3^- >> anion gap remain normal

Stewart's strong ion model

- Plasma pH is dependent on :
  1. pCO_2 (the plasma CO_2 tension)
  2. A_{tot} , nonvolatile buffers (albumin, globulins, and PO_4^{3-})
  3. Strong ion difference (SID) : explaining acid-base disturbances caused by fluid administration
     - **SID = ($[Na^+]$ + $[K^+]$) – ($[Cl^-]$ +[lactate])**
     - Normal plasma SID : 42 mEq/L
     - ↓ SID→ ↓ plasma pH

Fluid Pharmacology

- Type of fluid
  - Crystalloids
  - Colloids

Crystalloid

- Solution : Contain e'lyte found in plasma and buffer [lactate, acetate]
- Use for : Replace free water, electrolyte or volume expansion
- Tonicity : Hypotonic, isotonic, hypertonic
- Concept : E'lyte distribute freely ECF, water follow osmotic gradient
  - Only 20% remain intravascular [in the past]
  - *Recent model : 70% of crystalloid remain intravascular at 20 mins*
    - *50% after 30 mins*

Crystalloid

- Resuscitate with crystalloid
  - Positive fluid balance more than volume expansion effect
  - Tissue edema may increase in normovolemic patient
  - Large-volume crystalloid infusion >> hypercoagulable state by dilution of circulating anticoagulant factors

Saline solution

TABLE 47.6 Composition of Fluids Available for Intravenous Administration*

Fluid	Sodium	Potassium	Chloride	Calcium	Magnesium	Bicarbonate	Lactate	Acetate	Gluconate	Glucose $(g/L)^{-1}$	Other	Osmolarity	Notes	pH (In Vitro)
Plasma	140	5	100	4.4	2	24	1	—	—	—	—	285	SID 42	7.4
0.9% NaCl	154	—	154	—	—	—	—	—	—	—	—	308	SID 0	6.0

- 0.9 % sodium chloride
  - $[Na^+]$ and $[Cl^-]$ > plasma level
  - Osmolality > plasma level
  - SID >> $([Na^+] + [K^+]) - ([Cl^-] + [\text{lactate}]) = 154 - 154 = 0$

Saline solution

- Hyperchloremic metabolic acidosis [30 mL/kg/hr of 0.9% saline]
  - Henderson-Hasselbach : Dilution of bicarbonate, base deficit
  - Stewart model : ⬆ Cl^- , ⬇ SID >> ⬇ plasma pH
  - Renal vasoconstriction, ⬇ GFR, ⬇ renal cortical perfusion
  - Coagulopathy and GI dysfunction

- Meta-analysis >> compare saline vs balance fluid regimen
  - Hyperchloremia and acidosis in saline group [1-2 day]
  - No different kidney injury, coagulopathy, GI symptoms

Saline solution

- One trial patient undergo renal transplant
  - saline administration induce hyperkalemia cause by cellular extrusion K+ due to extracellular acidosis
- Large trial in emergency department and ICU
  - Increase outcome >> death, adverse renal effect [more than balance crystalloid]
  - Greatest in sepsis patient

Hypertonic saline

- Solutions of 1.8%, 3% and 7.5% NaCl
  - Hypertonic : draw water into extracellular
  - Plasma volume expansion >> minimize fluid administration
- Correction of hypoosmolar hyponatremia
- Treatment of increase intracranial pressure [traumatic brain]
  - ⬆ Plasma osmolality >> ⬇ cerebral edema , ⬇ ICP
- NaCl conc > 7.5% : endothelial damage

Balance crystalloid solutions

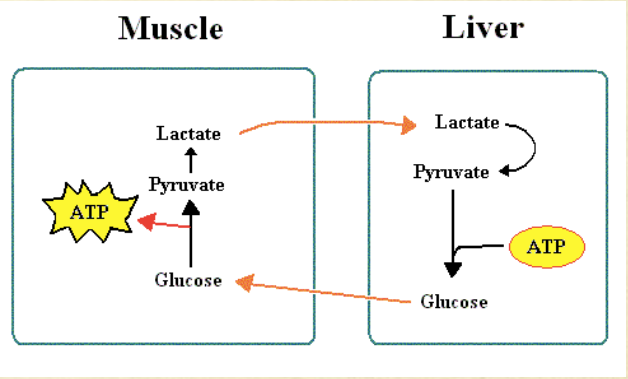
- Lower [Na^+] and lower [Cl^-] : plasma level
- Reduction anionic content : add stable organic anionic buffer
  - Lactate, gluconate or acetate
  - Osmolality ~ 265 mOsm/kg >> mild hypotonic
  - Buffer metabolite to produce HCO_3^-
    - Lactate >> hepatic oxidation or gluconeogenesis >> HCO_3^-
    - Acetate >> oxidize by liver, muscle and heart >> HCO_3^-

Balance crystalloid solutions

- Excretion of excess water and electrolyte more rapid than isotonic saline
  - ⬇ Plasma tonicity
  - ⬇ ADH secretion >> diuresis
- Reduce plasma SID less than NaCl solution ➡ no acidosis
  - In vitro : SID = 0 After administration the lactate undergoes metabolism
    In vivo SID ~29 mEq/L (counteract any alkalosis caused by dilution of A_{tot})
  - HCO_3^- concentration maintain or slightly elevate

Lactate ringer's solution

- Lactated Ringer solutions contain racemic (D- and L-) lactate, although D-lactate is only found in trace quantities in vivo
- Large doses of D-lactate may be associated with encephalopathy and cardiac toxicity in patients with renal failure
- Lactated solutions should be avoided severe liver failure
- Caution in DM patients



Acetate ringer's solutions

- Change lactate >> acetate : no effect glucose homeostasis, insulin level
- Acetate turnover is limited in patients with end-stage kidney disease
- Possible that critically ill patients or those with advanced kidney disease may exhibit biochemical acetate intolerance
  - Effects of high acetate levels manifest as nausea, vomiting, headaches, and cardiovascular instability
- Acetate intolerance experienced by patients undergoing hemodialysis with acetate-based dialysate [not in acetate intravenous solution]

TABLE 47.6 Composition of Fluids Available for Intravenous Administration*

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0.9% NaCl	154	—	154	—	—	—	—	—	—	—	—	308	SID 0	6.0
1.8% NaCl	308	—	308	—	—	—	—	—	—	—	—	616		
0.45% NaCl	77	—	77	—	—	—	—	—	—	—		154		
5% dextrose	—	—	—	—	—	—	—	—	—	50		252		4.5
5% dextrose/0.45% NaCl	77	—	77	—	—	—	—	—	—	50		406		4.0
4% dextrose/0.18% NaCl	33	—	33	—	—	—	—	—	—	40		283		
Lactated Ringer solution (U.S. composition)	130	4	109	3	—	—	28	—	—	—		273		6.5
5% dextrose in lactated Ringer solution	130	4	109	3	—	—	28	—	—	50		525		5.0
Hartmann solution/compound Na^+ lactate	131	5	111	4	—	—	29	—	—	—		275	In vivo SID 27	6.5
Plasma-Lyte 148/ Normosol-R	140	5	98	—	3	—	—	27	23	—	—	294		4-6.5
Plasma-Lyte 56 and 5% dextrose/ Normosol M with 5% dextrose	40	13	40	—	3	—	—	16	—	50		389 / 363		3.5-6
Plasma-Lyte A pH 7.4	140	5	98	—	3	—	—	27	23	—	NaOH for pH	294		7.4
Sterofundin	140	4	127	5	2	—	—	24	—	—	Maleate 5	309		5.1-5.9
Plasma-Lyte R	140	10	103	5	3	—	8	47	—	—		312		
Hemosol	140	—	109.5	3.5	1	32	3	—	—	—			In vivo SID 33	
4%-5% albumin	†	—	†	—	—	—	—	—	—	—	Stabilizer: octanoate (caprylate)	†		7.4
20% albumin	†	—	†	—	—	—	—	—	—	—	Stabilizer: octanoate (caprylate)	†		
Plasmanate: Plasma protein fraction (human) 5%	145	0.25	100	—	—	—	—	—	—	—	88% human albumin, 12% α-/β-globulins		COP 20 mm Hg	7.4

Electrolytes	Human plasma	NSS	Ringer's lactate	Ringer's acetate
Na^+	142	154	130	130
K^+	4.5	-	4	4
Ca^{2+}	5	-	3	3
Mg^{2+}	2.5	-	-	-
Cl^-	103	154	109	109
HCO_3^-	24	-	-	-
$Lactate^-$	1.5	-	28	-
$Acetate^-$	-	-	-	28
$Malate^-$	-	-	-	-
Real osmolality	288	286	254	256
In vivo SID	40 - 42	0	28	28

Isotonic balance crystalloid solution

- ⬆ Tonicity >> ⬆ Na^+ 140-145 mOsm/L
- Plasma-Lyte, Sterofundin

TABLE 47.6 Composition of Fluids Available for Intravenous Administration*

Fluid	Sodium	Potassium	Chloride	Calcium	Magnesium	Bicarbonate	Lactate	Acetate	Gluconate	Glucose $(g/L)^{-1}$	Other	Osmolarity	Notes	pH (In Vitro)
Plasma	140	5	100	4.4	2	24	1	—	—	—	—	285	SID 42	7.4
Plasma-Lyte 148/ Normosol-R	140	5	98	—	3	—	—	27	23	—	—	294		4-6.5
Plasma-Lyte 56 and 5% dextrose/ Normosol M with 5% dextrose	40	13	40	—	3	—	—	16	—	50		389 / 363		3.5-6
Plasma-Lyte A pH 7.4	140	5	98	—	3	—	—	27	23	—	NaOH for pH	294		7.4
Sterofundin	140	4	127	5	2	—	—	24	—	—	Maleate 5	309		5.1-5.9

Dextrose solution

- Two main indications in the perioperative setting

1. As a source of free water
   - In vitro osmolality is similar to that of plasma
   - after infusion the dextrose is taken up into cells , leaving free water
   - Hypotonic >> dilute plasma electrolytes and osmolality
   - less suitable for intravascular plasma volume expansion

Dextrose solution

2. Source of metabolic substrate:

- Although the caloric content of 5% dextrose is inadequate to maintain nutritional requirements
- Glucose solutions also may be coadministered with IV insulin to patients with diabetes to reduce the risk for hypoglycemia

Colloid

- Colloid is defined as large molecules or ultramicroscopic particles of a homogeneous noncrystalline substance
- Colloid molecules above 70 kDa are too large to pass through the endothelial glycocalyx
- Colloids have a higher COP and minimize transcapillary filtration
  - Maximizes their potential intravascular plasma volume expansion effect

Colloid

- Colloid molecules may be lost from circulation in several ways
  - By filtration across capillaries whose barrier function is impaired by glycocalyx shedding
  - Endothelial cell pore formation in inflammation or other stressors, or both
  - By renal filtration of smaller colloid molecules
  - By removal from the circulation by metabolism
- Colloid varible effective plasma half life

Colloid

- Semisynthetic colloids
  - Gelatins
  - HydroxyethylStarches
  - Dextrans

Gelatins

- Hydrolysis of Bovine collagen
- Excretion primary in renal route
- Least impact on clinically relevant hemostasis of all the semisynthetic colloids despite reductions in von Willebrand factor (vWF), factor VIIIc, and ex vivo clot strength
- Highest estimated incidence of severe anaphylactic and anaphylactoid reactions (<0.35%)
- Commonly used in Europe but not U.S. FDA approved

Hydroxyethyl starches

- Modified natural polymers of amylopectin from maize or potato
- Classified by in vitro MW
  - high MW (450 to 480 kDa)
  - medium MW (200 kDa)
  - low MW (70 kDa)
- Size of starch molecule is responsible for both the therapeutic volume effects and adverse side effects

Hydroxyethyl starches

- Excretion accounts for the elimination
  - Smaller HES molecules >> renal
  - Medium-sized molecules >> bile and feces
  - Larger molecules, resistant to hydrolysis >> mononuclear phagocyte [may persist for several weeks or more]

Hydroxyethyl starches

- Prolonged metabolism >> plasma volume effects typically last longer than those of gelatins or crystalloids
- Larger MW starches increasing intravascular volume by approximately 70% to 80% of the infused dose at 90 minutes

Hydroxyethyl starches

- Coagulation
  - Dilutional effects in the circulation
  - MW-dependent reductions in vWF, factor VIII, and clot strength
  - Occure with large MW , slowly degraded medium MW
  - In patients with sepsis, even lower MW HES is associated with an increased risk of bleeding and blood transfusion

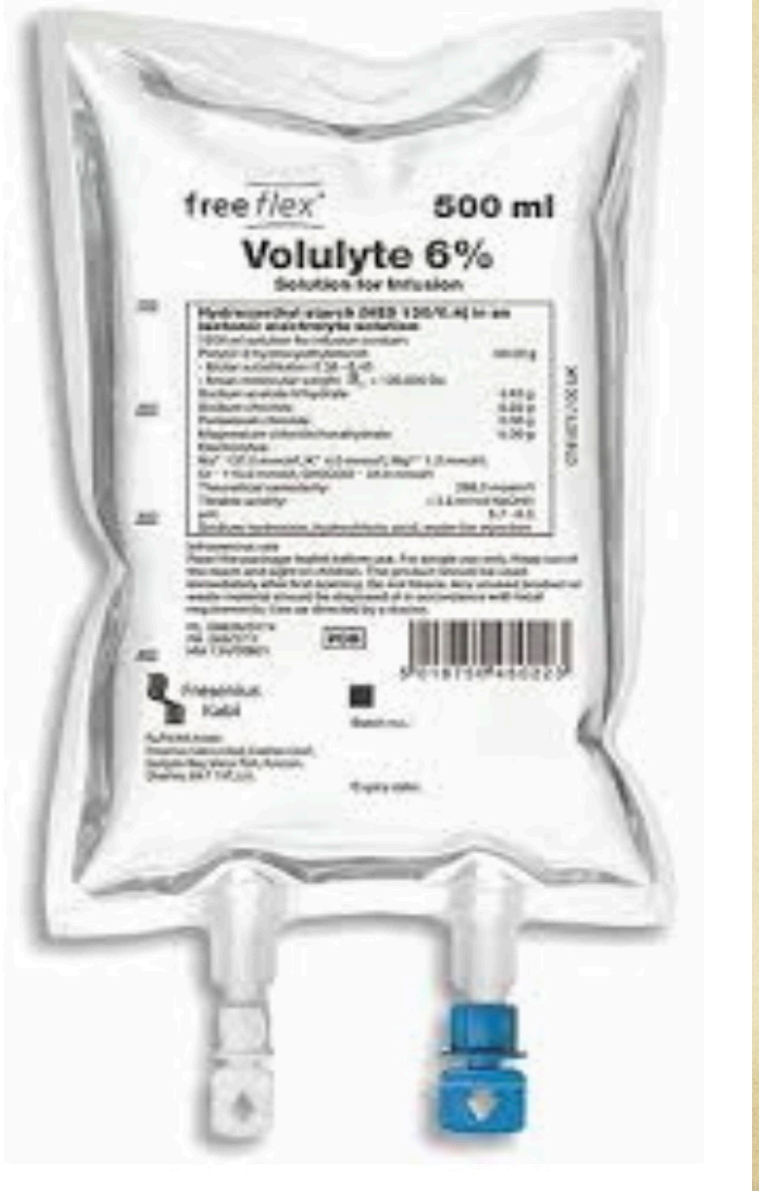
Hydroxyethyl starches

- Accumulation
  - Accumulation HES molecule in the mononuclear phagocyte system and skin, liver, muscle, and gut is a dose dependent effect
  - May persist for several years
  - Larger degree of tissue deposition is associated with pruritus
- Anaphylactoid reaction
  - The incidence of severe anaphylactoid or anaphylactic reactions with HES products less than other colloids (<0.06%)

Hydroxyethyl starches

- Renal dysfunction
  - Medium to high MW are associated with oliguria, increased creatinine, and acute kidney injury in critically ill patients with preexisting renal impairment
  - Comparing HES with isotonic saline also reported an increase in renal replacement therapy with the starch solution
- Should avoid in sepsis patient


freeflex
500 ml
Voluven®
6% solution for infusion
100
200
300
400
Hydroxyethyl starch (HES 130/0.4) in isotonic sodium chloride solution
1 litre contains:
Poly(O-2-hydroxyethyl)starch 60.00 g
- Molar substitution 0.38 - 0.45
- Mean molecular weight (Mw) = 130,000
Sodium chloride 9.00 g
Electrolytes: Na+ 154 mmol/l, Cl− 154 mmol/l
Other ingredients: Sodium hydroxide, hydrochloric acid (25%), water for injections.
Theoretical osmolarity: 308 mosm/l
Titratable acidity: < 1.0 mmol NaOH/l
pH: 4.0 - 5.5
0xxxxx1/00 V3
For continuous intravenous infusion
Maximum daily dose: 50 ml/kg b.w.
To be used immediately after the bag is opened.
Do not use Voluven® after expiry date.
Any unused solution should be discarded.
Use only clear solutions and undamaged containers.
Keep out of reach of children
Do not store above 25°C.
Do not freeze.
Registration no.:
FRESENIUS KABI
Fresenius Kabi Deutschland GmbH
D-61346 Bad Homburg v.d.H.
Germany
Batch no.:
Manufact. date:
Expiry date:


freeflex
500 ml
Volulyte 6%
Solution for infusion

EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

- HES solutions for infusion are used to replace fluids in the body after acute (sudden) blood loss.
- Because of the risk of kidney injury and death, HES solutions for infusion must not be used in patients with blood infection or kidneys problems or in critically ill patients.
- If you are given a HES infusion, your doctor will monitor your kidneys to check that they are working well enough.
- Patients who have questions or concerns should speak to their treating doctor.

- Because of the risk of kidney injury and mortality, HES solutions for infusion are contraindicated in patients with **sepsis or in critically ill patients**.
- HES solutions for infusion should be used for managing hypovolaemia due to acute blood loss only when crystalloids alone are not considered sufficient. HES solutions should not be used for fluid maintenance.
- Use of HES solutions for infusion should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 hours. Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as haemodynamic goals have been achieved.
- Additional studies are ongoing with HES solutions in patients with trauma and those undergoing elective surgery to further investigate the long-term safety of HES prescribed according to the recommendations for use (dose less than 30 ml/kg and duration less than 24 hours).
- The expected benefit of treatment should be carefully weighed against the uncertainties with regard to long-term safety.
- Alternative therapeutic options are available for routine clinical practice and should be considered according to relevant clinical guidelines.
- HES solutions for infusion are contraindicated in patients with **renal impairment or undergoing renal replacement therapy**. The use of HES must be discontinued at the first sign of renal injury. An increased need for renal replacement therapy has been reported up to 90 days after HES administration. Patients' kidney function should be monitored after HES administration.
- HES solutions for infusion are contraindicated in **severe coagulopathy**. HES solutions should be discontinued at the first sign of coagulopathy. Blood coagulation parameters should be monitored carefully in case of prolonged use.
- HES solutions for infusion are also contraindicated in **dehydrated patients, hyperhydrated patients, patients with intracranial or cerebral haemorrhage, burn injuries, severe hyperkalaemia, hypernatraemia, hyperchloraemia, congestive heart failure, organ transplant patients and patients with impaired hepatic function.**

Dextrans

- Polysaccharide molecules
- Dextrans have an average MW of 40 kDa or 70 kDa
- Dextrans have a plasma volume effect similar to that of starches, with a duration of 6 to 12 hours
- Dextran 40 may be used in microvascular surgery
  - Dilutional effects on blood viscosity and anticoagulant effects favor flow in the microcirculation >> increase flap survival rate

Dextrans

- Antithrombotic effect:
  - Inhibition of aggregation, factor VIIIc and vWF reductions, and impaired activity of factor VIII
  - Platelet aggregation is also inhibited
  - Impaired hemostasis and increased perioperative blood loss
- Blood cross matching: Dextrans coat the erythrocyte cell membrane and may interfere with blood type cross matching
- Anaphylactoid reactions: (<0.28%), renal dysfunction
- Dose limit 20 ml/kg , sepsis 10 ml/kg

Human plasma derivatives

- The human plasma derivatives include
  - human albumin solutions, plasma protein fractions, fresh frozen plasma, and immunoglobulin solution
- Preparation techniques result in relatively purified solutions with the elimination of infective agents
- Solutions such as 5% albumin have a near physiologic COP of 20 mmHg and are used for volume expansion

Albumin

- Same indication like other colloids
- Perioperative resuscitation in hypoalbuminemia patient after substantial amounts of crystalloids
- Using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock
  - When patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence) >> sepsis guideline 2016

Clinical fluid management

- Preoperative
  - Fasting should be consider
    - Oral fluid 2 hour before elective surgery [ERAS]
    - Over night fasting blood volume no change
    - Bowel preparation >> weight loss 1.5-1.7 kg, ⬆ water , ⬆ k+
      - Compensate for fluid loss : crystalloids

Clinical fluid management

- Preoperative
  - Direct intravascular bleeding
  - Loss fluid from GI tract
    - Obstruction, vomiting, NG suction : loss Na^+, K^+, Cl^-, acid
    - Small bowel secretion : loss Na^+, Cl^-, $HCO3^- > K^+$
    - Large bowel loss, diarrhea : loss $K^+ > Na^+$, $HCO3^-$
  - Inflammation >> redistribution intravascular to extravascular
  - Fluid in third space [edema, pleural effusion, ascites]

Clinical fluid management

- Intraoperative : factor influence intraoperative fluid balance
  - Altered distribution of intravascular volume
    - Anesthetic agent : vasodilation , ⬇ inotropic effect
    - Central neuraxial block : sympathetic blockade
  - Direct loss intravascular volume from hemorrhage
  - Insensible loss : little effect [1ml/kg/hr in major laparotomy with extensive bowel exposure]

Clinical fluid management

- Intraoperative : factor influence intraoperative fluid balance
  - Inflammation >> redistribution fluid intravascular to extracellular
  - Renal output >> ADH secretion [positive pressure ventilation]
    - Suppression ANP release >> ⬇ GFR, ⬇ urine output
    - Urine output may be low regardless from IV fluid administered

Intraoperative : fluid balance

- Maintenance fluid :
  - Holliday-segar
  - 1-1.5 ml/kg/hr crystalloids
- Deficit fluid
  - NPO : NPO time * maintenance fluid
  - Recently NPO overnight : blood volume not change
  - Bleeding, vomiting, gut obstruction

TABLE 47.15 The 4-2-1 Estimation of Maintenance Water Requirements

Weight	Fluid Prescription
First 10 kg	4 mL/kg/h
Second 10 kg	2 mL/kg/h
All subsequent kilograms	1 mL/kg/h

Example: A 25-kg patient would require (4 × 10) + (2 × 10) + (1 × 5) = 65 mL/h "maintenance" water.

Intraoperative : fluid balance

- Concurrent loss
  - insensible loss : little effect < 1 ml/kg/hr
  - Sensible loss : blood loss
    - Crystalloid used to replace blood loss ratio 3:1
    - New Glycocalyx model : ratio 1.5:1
  - Third space loss
    - Clinical evaluation

Assessment of perioperaitve fluid imbalance

- Intravascular volume : Hypovolemia
  - Tachycardia, ⬇ pulse pressure, hypotension, ⬆ capillary refill time
  - In healthy patient : loss blood volume 25% H/D may be stable
  - Urine output : adequate end organ perfusion
  - CVP : influenced by venous compliance >> trends CVP value
    - Static CVP : poorly predictive response to fluid challenge
  - GDT : Stroke volume, Cardiac output, oxygen deliver [DO_2]

Assessment of perioperaitve fluid imbalance

- Intravascular volume : Hypervolemia
  - Iatrogenic problem >> excess volume administered
  - Tissue edema >> lung, muscle, bowel
  - Hypercoagulability, hypocoagulability, hyperchloremic acidosis, renal dysfunction

CLINICAL FOCUS REVIEW

Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

Perioperative Fluid Therapy for Major Surgery

Timothy E. Miller, M.B.,Ch.B., F.R.C.A., Paul S. Myles, M.B., B.S., M.P.H., D.Sc., F.A.N.Z.C.A.

Table 1. Recommendations for Perioperative Fluid Therapy in Major Surgery

1. Minimize preoperative fasting times. Encourage unrestricted intake of clear fluids until 2 h before elective surgery.[13,14]
2. Passive leg raising followed by measurement of blood pressure or (ideally) stroke volume is a useful test for predicting fluid responsiveness in hemodynamically unstable adults throughout the perioperative period.[20]
3. Aim for a moderately liberal IV fluid regimen with an overall positive fluid balance of 1–2 l at the end of surgery.[30] For major abdominal surgery, an average crystalloid fluid infusion rate of 10–12 ml · kg^{-1} · h^{-1} during surgery, and 1.5 ml · kg^{-1} · h^{-1} in the 24-h postoperative period should be used.
4. Ensure that intravascular volume status is optimized before adding vasopressor therapy.
5. Use an advanced hemodynamic monitor to measure fluid responsiveness in higher-risk patients having major surgery.
6. A goal-directed hemodynamic strategy may perform better if a patient's IV fluid status is first optimized, and if needed, introduce a vasopressor or inotrope.[37,38]
7. It is unclear whether crystalloid or colloid should be primarily used for perioperative fluid resuscitation.
8. Aim for early transition from IV to oral fluid therapy after surgery (usually within 24 h).[1,2]

IV, intravenous.

Anesthesiology 2019

Liberal VS restrictive

- Brandstrup et.al : liberal fluid >> more complication
- RELIEF trail
  - Liberal fluid VS restrictive fluid
    - Restrictive group : higher risk acute kidney injury
  - Suggest moderate liberal : positive fluid balance 1-2 L at end of surgery
  - ERAS : early transient IV to oral fluid

Goal-directed therapy

- OPTIMISE trial : fewer complication not statistical significant
- FEDORA trial : significant ⬇complication and length of stay
  - Optimize fluid to maximize stroke volume
  - Keep MAP > 65 mmHg, cardiac index > 2.5 L/min/m^2

Goal-directed therapy

- Key : cardiac output, global O_2 delivery, administering fluids and possible inotropes, vasopressors, vasodilators and RBC to improve tissue perfusion

- Continue dynamic process : "survival values"
  - Cardiac index > 4.5 L/min/m^2
  - O_2 delivery index > 600 ml/min/m^2
  - O_2 consumption index > 170 ml/min/m^2

Goal-directed therapy

- Monitor target of GDT
  - Pulmonary artery catheter [PAC] : goal standard >> to invasive
  - Esophageal Doppler monitor [EDM] : TEE >> flow time
  - Arterial pressure and waveform analysis : A-line
    - Pulse pressure is proportional to stroke volume >> PPV
    - SV, SVV [volume responsive] : FloTrac, Vegilio
  - CVP : poorly predictive fluid responsive [trend]
  - Lactate level : successful resuscitation

Table 3

Parameters in early goal-directed therapy[15]

Parameters	Range to target	Interventions
CVP	8-12 cmH_2O	Early use of mechanical ventilation
MAP	65-90 mmHg	Fluid resuscitation
SvO_2	>70%	Use of vasoactive agents
$ScvO_2$	>65%	Noradrenaline
Urine output	>0.5 ml/kg/h	Dobutamine
Hematocrit	>30%	Transfusion

Parameters, range to target, and interventions in goal-directed fluid therapy. CVP=Central venous pressure, MAP=Men arterial pressure, SvO_2=Mixed venous oxygen saturation, $ScvO_2$=Central venous oxygen saturation

FEDORA trial

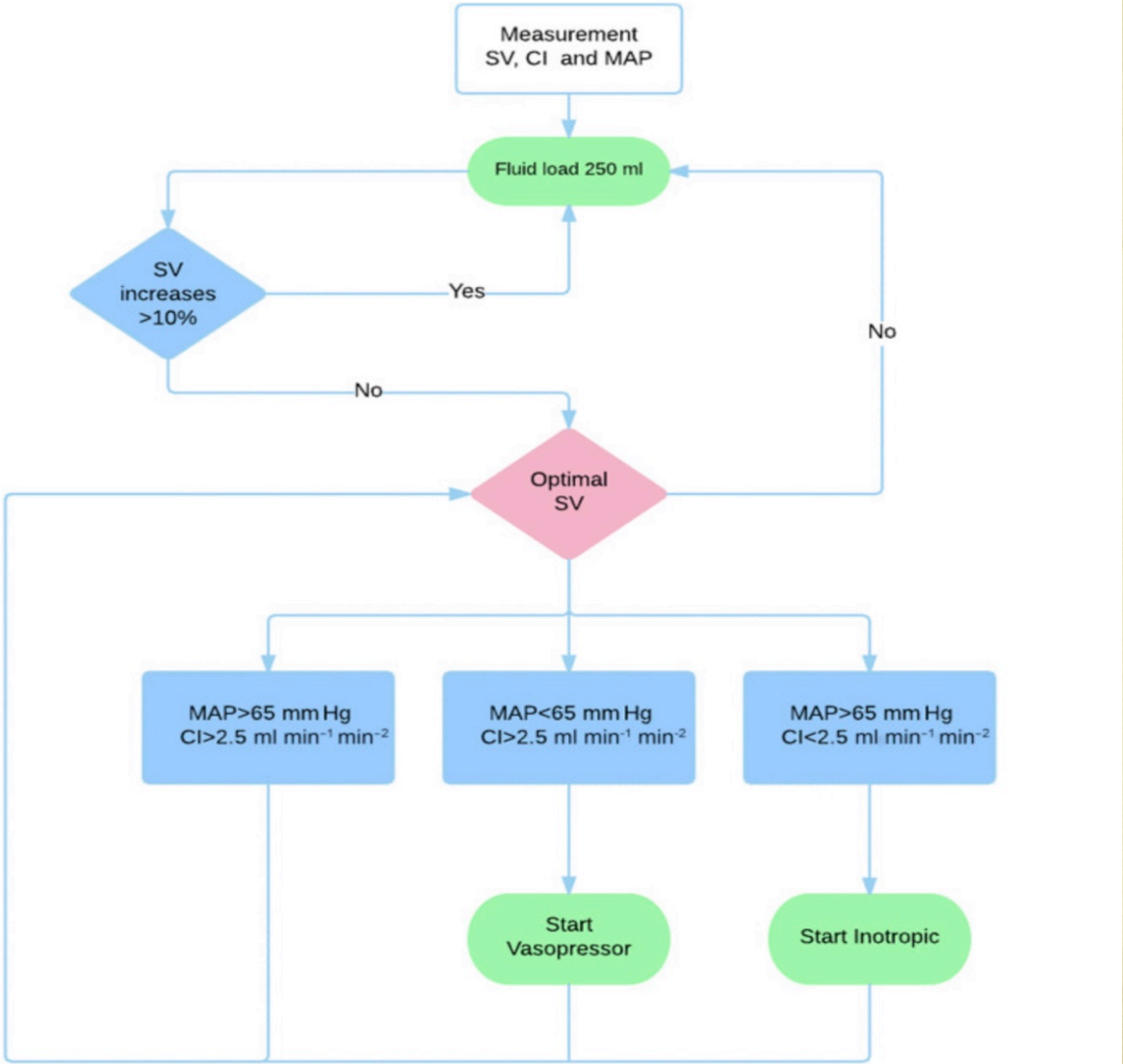


Fig 1 Algorithm for goal-directed haemodynamic therapy group. CO, cardiac output; SV, stroke volume; CI, cardiac index;

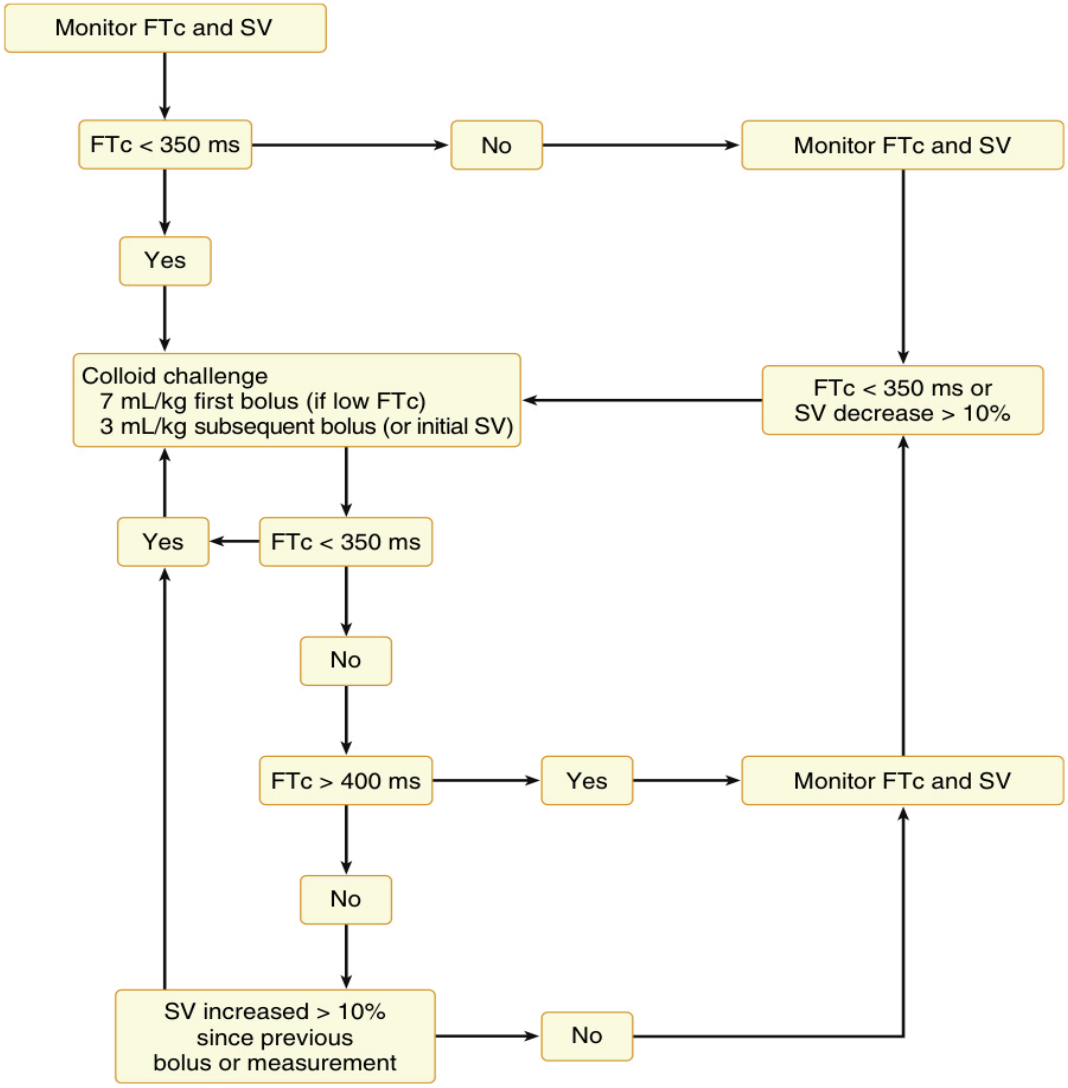


Fig. 47.6 Protocol for EDM-based intraoperative goal-directed fluid therapy. *FTc,* Heart rate-corrected descending aorta flow time; *SV,* stroke volume. (Redrawn from Noblett SE, Snowden CP, Shenton BK, et al. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg.* 2006;93:1069.)

RESEARCH ARTICLE Open Access

Pleth variability index versus pulse pressure variation for intraoperative goal-directed fluid therapy in patients undergoing low-to-moderate risk abdominal surgery: a randomized controlled trial

Sean Coeckelenbergh[1,2*†], Amélie Delaporte[1,2†], Djamal Ghoundiwal[1,2], Javad Bidgoli[1,2], Jean-François Fils[1,3], Denis Schmartz[1,2] and Philippe Van der Linden[1,2]

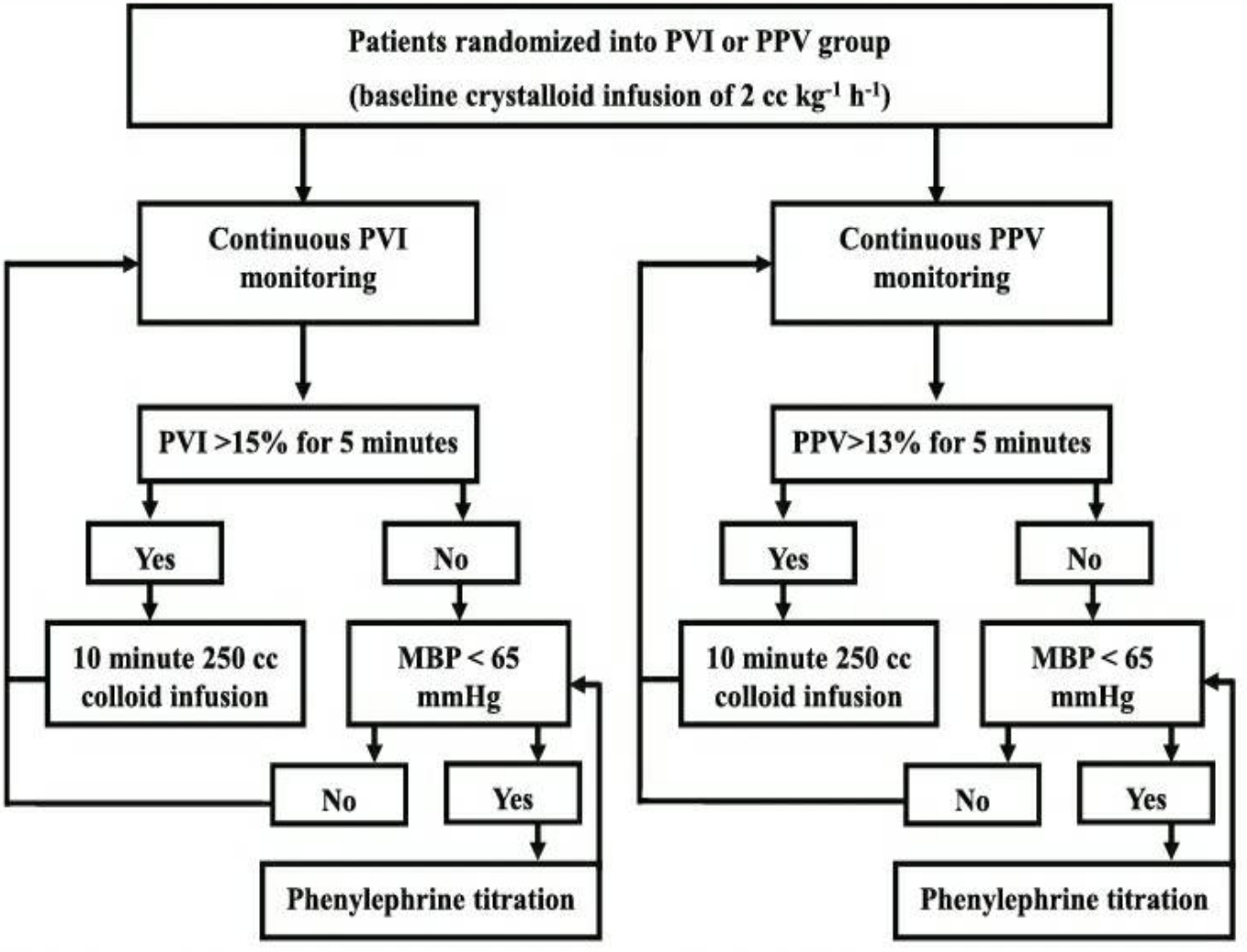


Fig. 1 Goal-directed fluid therapy protocols. Patients were randomized into either PVI or PPV guided groups. *PPV pulse pressure variation, PVI Pleth variability index*

Malbouisson et al. BMC Anesthesiology (2017) 17:70
DOI 10.1186/s12871-017-0356-9

RESEARCH ARTICLE Open Access

A pragmatic multi-center trial of goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery

Luiz Marcelo Sá Malbouisson[1*], João Manoel Silva Jr.[1], Maria José Carvalho Carmona[1], Marcel Rezende Lopes[1], Murilo Santucci Assunção[3], Jorge Luís dos Santos Valiatti[2], Claudia Marques Simões[1] and José Otavio Costa Auler Jr.[1]

Results: After matching, 84 patients remained in each group. Baseline characteristics, surgical procedure duration and physiological parameters evaluated at the start of surgery were similar between the groups. The volume of crystalloids (4500 mL [3200-6500 mL] versus 5000 mL [3750-8862 mL]; $P = 0.01$), the number of blood units infused during the surgery (1.7 U [0.9-2.0 U] versus 2.0 U [1.7-2.6 U]; $P = 0.01$), the fraction of patients transfused (13.1% versus 32.1%; $P = 0.003$) and the number of patients receiving mechanical ventilation at 24 h (3.2% versus 9.7%; $P = 0.027$) were smaller postoperatively in PPV group. Intraoperative PPV-based improved the composite outcome of postoperative complications OR 0.59 [95% CI 0.35-0.99] and reduced the postoperative hospital length of stay (8 days [6-14 days] versus 11 days [7-18 days]; $P = 0.01$).

Conclusions: In high-risk surgeries, PPV-directed volume loading improved postoperative outcomes and decreased the postoperative hospital length of stay.

Clinical fluid management

- Postoperative : 1.5 ml/kg/hr
  - Inflammation & immune response
    - Tissue injury >> local vasodilate, ⬆ endothelial permeability
    - Severe case >> endothelial leak syndrome
  - Catabolic metabolism
    - Tissue injury >> require more energy
  - Regulation of salt and water Balance
    - ADH release, activate RAA >> temporary oliguria

Take home massage

- Basic principle and adverse reaction of each fluid type
- Key : which fluid to use and how much to give
- No clear consensus which IV administered with the best outcome >> crystalloid or colloid [patient , surgical factor]
- Goal directed fluid therapy >> reduce post operative morbidity

THANK YOU

Special consideration

- Heart failure : perioperative fluid therapy : two goals
  1. Preserve cardiac output >> preload, after load ,contractility
     - Forward failure : excess volume >> impair organ perfusion
     - Backward failure : pulmonary edema, salt water retension
  2. Minimize cardiac work load
     - Tachycardia from hypovolemia

Special consideration

- Heart failure : practical approach
  - Careful preoperative assessment fluid status
    - Cardiac output monitoring : TEE, PAC
  - Infuse large volume of any fluid >> evidence of intravascular volume loss
  - Multidrug : [eg.loop diuretic, ACEI, digoxin] check electrolyte

Special consideration

- Kidney disease : dialysis dependent
  - Reduce to absent urine production
  - Target “dry weight” >> represent euvolemia
  - Suggest dialysis 1 day before surgery
    - Allow fluid equilibrium, dialysis anticoagulant metabolite
    - Check electrolyte morning of surgery
  - Invasive monitoring : assessment volume status

Special consideration

- Kidney disease : dialysis dependent
  - Type of fluid
    - Avoid large volume isotonic saline >> acidosis, move K+ from cell
    - K+ containing balance crystalloid >> did not cause hyper K+
    - Colloids for volume replacement >> potential toxicity
  - Blood transfusion
    - Patient waiting for renal transplant : communicate with nephologist

Special consideration

- Sepsis
  - Cardiovascular instability >> endothelial dysfunction, IVF loss
  - Goal >> maintain adequate end organ perfusion
- Goal for septic patient with evidence of tissue hypoperfusion
  - At least 30 ml/kg of crystalloid in first 3 hour of resusitation
  - Frequent reassessment of hemodynamic status >> HR, BP, urine
  - Dynamic test fluid responsive : SV response
  - Less positive fluid balance >> improve outcome

Special consideration

- Burn
  - IV fluid therapy : % burn > 15 % in adult , > 10 % in children
  - Parkland formula
    - Excessive fluid >> “fluid creep” >> more complication
    - Titration for urine output : 0.5-1 ml/kg/hr
  - Modified broke
    - Use lower volume
  - Colloid is controversial : severe capillary leak

Special consideration

- Pediatrics
  - Holliday and Segar : maintenance fluid >> hypotonic crystalloid containing glucose
  - Perioperative phase
    - glucose base solution >> high risk hypoglycemia
    - Risk for preoperative dehydration : fasting time
      - Replenishment : isotonic salt solution
      - 25 ml/kg in 3 years of age and younger
      - 15 ml/kg in 4 years of age and older

Special consideration

- Obstetric : Preeclampsia
  - Reduce plasma volume, endothelial dysfunction, hypoalbuminemia
  - Positive fluid balance : pulmonary edema 5-30%
  - Should receive restricted volume of IV crystalloid [80 ml/hr]
    - Replace appropriate volume from blood loss
    - Invasive monitor in severe preeclampsia

Special consideration

- Neurosurgery
  - Goal : 1. maintain baseline blood volume 2. cerebral perfusion 3. avoid significant ⬇ serum Na+, osmolality and oncotic pressure
  - Increase ICP : Mannitol and hypertonic saline
  - Cerebral vasospasm : [hypervolemia, hemodilution, hypertension]
    - Now hypervolemia is not recommend : pulmonary edema
  - Not clear for crystalloid or colloid
    - Albumin associate with increase mortality in TBI

Special consideration

- Trauma
  - Fluid infusion : target normal CO, O_2 delivery, lactate level and blood clotting
    - Large volume of iv fluid >> hemodilution, dilute clotting factor
    - Saline-based fluid >> induce acidosis
    - GDT perioperative
    - Massive blood transfusion suggest high ratio
    - Control of bleeding

Special consideration

- Free tissue flap surgery
  - Conservative fluid strategy : improve flap outcome
  - Avoid large volume of crystalloid : increase capillary filtration
  - Colloid use for blood volume expansion
  - Dextran to improve blood flow : not currently recommend

Special consideration

- Hepatic resection
  - Blood loss >> worse outcome
  - Conservative fluid management
  - Low CVP technique >> CVP < 5 cmH_2O
  - Liver resection is finished >> more fluid to adequate circulating volume

Special consideration

- Renal transplant
  - Goal >> adequate renal perfusion to support early graft function , avoid fluid side effect
  - Conservative >> Limit crystalloid infusion to 15 ml/kg/hr
    >> CVP 7-9 mmHg with no apparent increase graft failure
  - Renal failure >> develop acidosis >> hyperkalemia [saline infusion]
    - Balanced crystalloid should be use