PERIOPERATIVE CARDIOPROTECTION

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Basic Science

SYSTEMATIC REVIEW ARTICLE

Perioperative Cardioprotection: General Mechanisms and Pharmacological Approaches

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Basic Science

SYSTEMATIC REVIEW ARTICLE

Perioperative Cardioprotection: Clinical Implications

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Anesth Analg 2020;131:1765–80

OUTLINE

- MECHANISMS OF CARDIOPROTECTION
- NONPHARMACOLOGICAL CONDITIONING
- PHARMACOLOGICAL CONDITIONING

INTRODUCTION

- Cardiovascular disease is one of the most common causes of death worldwide and is associated with significant impairment in quality of life
- Protecting the heart against the consequences of ischemia–reperfusion injury (IRI) will reduce cardiac complications, thereby potentially improving long-term outcome

INTRODUCTION

- Cardioprotection encompasses a variety of strategies protecting the heart against myocardial injury that occurs during and after inadequate blood supply to the heart during myocardial infarction

INTRODUCTION

- For acute myocardial injury (MI), early reperfusion through restored coronary blood flow is essential to rescue ischemic myocardium and reduce morbidity and mortality
- Reperfusion itself paradoxically leads to myocardial damage through release of intracellular enzymes, electrolyte shift, autophagy, and apoptosis

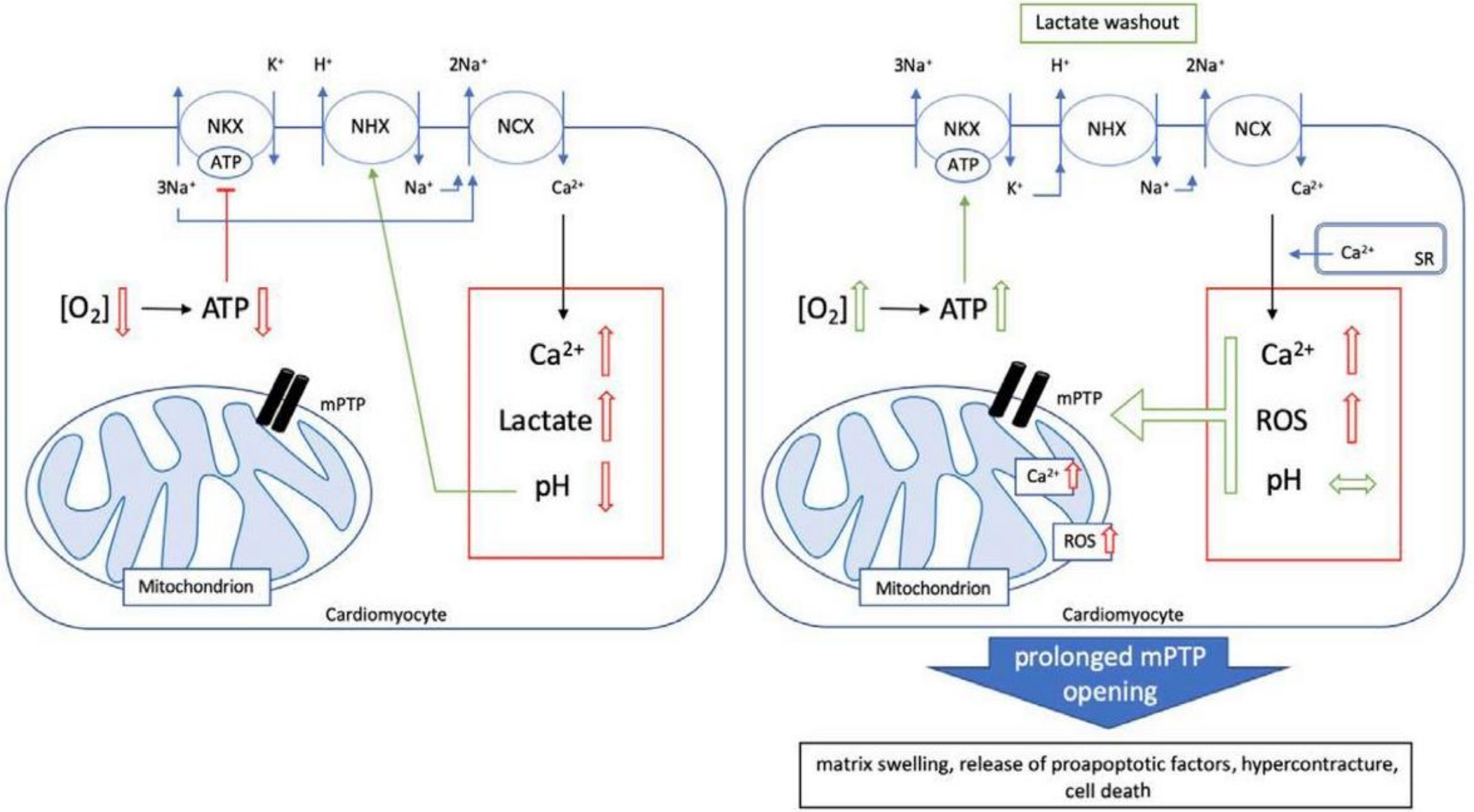


Figure 1. Lethal ischemia-reperfusion injury. Figure modified from Yellon and Hausenloy[4] and Hausenloy and Yellon.[5] ATP indicates adenosine triphosphate; mPTP, mitochondrial permeability transition pore; NCX, sodium (Na^+)-calcium (Ca^{2+})-exchanger; NHX, sodium (Na^+)-proton (H^+)-exchanger; NKX, sodium (Na^+)-potassium (K^+)-exchanger; O_2, oxygen; ROS, reactive oxygen species; SR, sarcoplasmic reticulum.

INTRODUCTION

- Even after survival of an acute MI, numerous patients develop severe myocardial remodeling that in many cases results in chronic heart failure
- Pharmacological strategies aiming at minimizing initial infarct size and I/R injury, improving outcome

MECHANISMS OF CARDIOPROTECTION

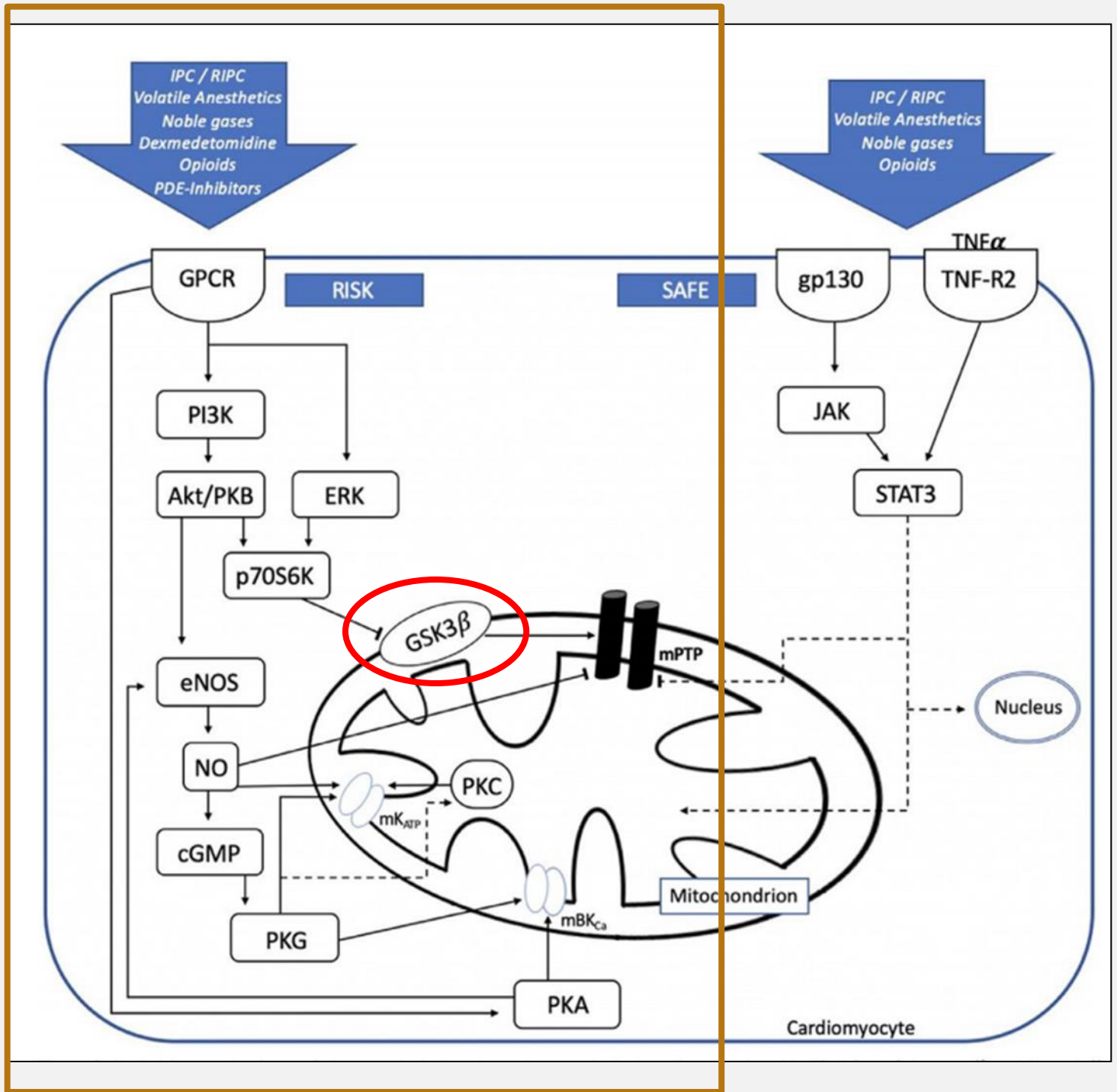
MECHANISMS OF CARDIOPROTECTION

- 2 main signaling pathways
  - reperfusion injury salvage kinase (RISK)
  - survivor activating factor enhancement (SAFE)

THE RISK PATHWAY

- Activated through binding of various substances to G protein–coupled receptors

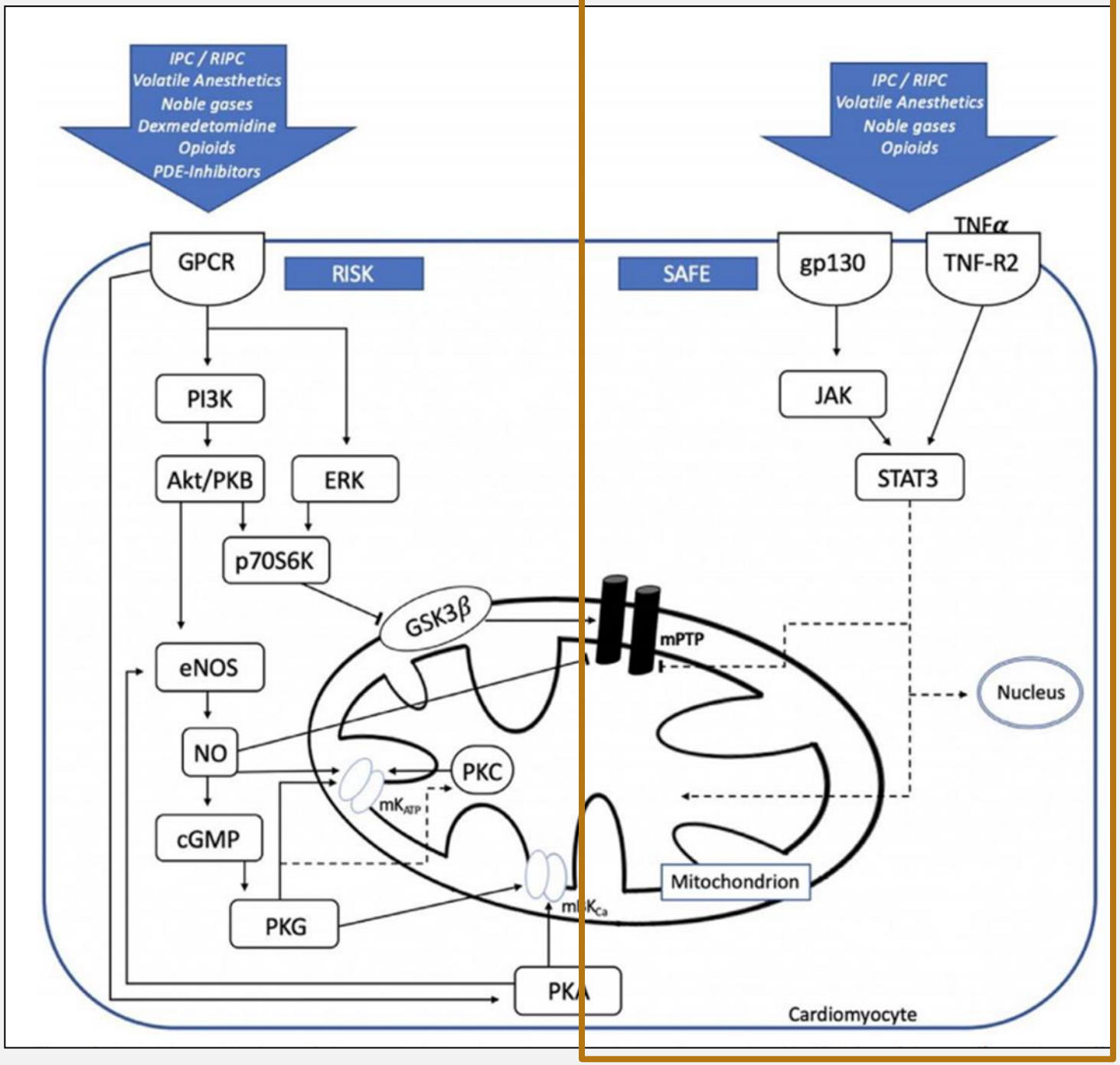
The RISK Pathway



THE SAFE PATHWAY

- Independent alternative to the RISK pathway

The SAFE Pathway



MECHANISMS OF CARDIOPROTECTION

- Signal transduction of conditioning strategies is clearly described in animal tissues, data from human tissue are scarce and do not allow for definitive unraveling of protective mechanisms

NONPHARMACOLOGICAL CARDIOPROTECTION

NONPHARMACOLOGICAL CONDITIONING

- Ischemic preconditioning (IPC)
- Remote ischemic preconditioning (RIPC)
- Ischemic postconditioning (IPostC)
- Remote ischemic postconditioning (RIPostC)

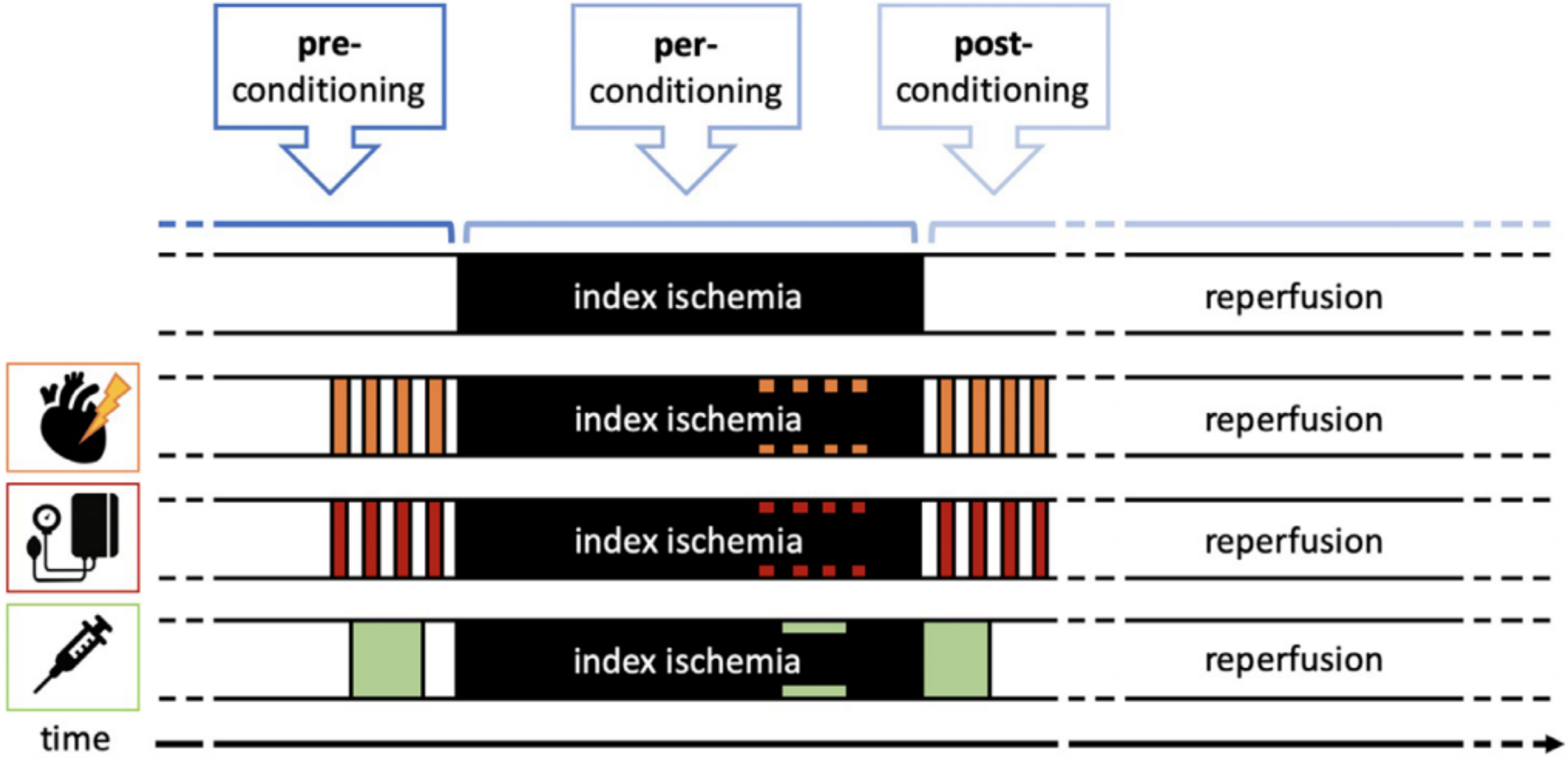


Figure 2. Schematic diagram demonstrating the different time windows for conditioning strategies. Treatments before index ischemia are called preconditioning. Perconditioning describes treatments used during index ischemia and postconditioning comprises all strategies applied after index ischemia during the reperfusion phase. Second row = ischemic conditioning directly at the heart. Third row = remote ischemic conditioning. Fourth row = pharmacological conditioning.

ISCHEMIC PRECONDITIONING

- Short periods of nonlethal myocardial ischemia and reperfusion protect the heart against the detrimental consequences of a following ischemic event
- Induce the release of endogenous ligands
  - activates both the RISK and the SAFE pathway
  - preventing mPTP opening
  - reducing mitochondrial damage and cell death

REMOTE ISCHEMIC PRECONDITIONING

- This measure seems to mediate the same cardioprotective effect as IPC but is realized via short cycles of noninvasive ischemia–reperfusion interventions
- limbs are most commonly used as RIPC sites
- No evidence on whether arm versus leg ischemia is superior with regard to outcome

ISCHEMIC POSTCONDITIONING

- Activates both the RISK and the SAFE pathway
- Brief episodes of ischemia/reperfusion performed at the onset of reperfusion protect against further organ

Table 1. Important Clinical Trials of Remote Ischemic Preconditioning

Clinical Studies on Nonpharmacological Cardioprotection								
Study Title	**Authors**	**Journal/Year**	**Design**	**Sample Size**	**Population**	**Intervention**	**End Points**	**Results**
Effect of remote ischemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery	Hausenloy et al[45]	*Lancet*, 2007	Single-center RCT	57	CABG	RIPC versus placebo	Troponin T at 6, 12, 24, 48, and 72 h after CABG	RIPC significantly reduced troponin T release at 6, 12, 24, and 48 h after surgery
Cardioprotective and prognostic effects of remote ischemic preconditioning in patients undergoing coronary artery bypass surgery	Thielmann et al[46]	*Lancet*, 2013	Single-center RCT	329	CABG	RIPC versus placebo	Troponin I in the first 72 h after CABG + all-cause mortality	RIPC significantly reduced troponin I release and significantly reduced all-cause mortality
Does remote ischemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery?	Hong et al[14]	*Eur Heart J*, 2014	Multicenter RCT	1280	Elective cardiac surgery	RIPC + RIPostC versus placebo	Composite of major adverse outcomes, including death, myocardial infarction, arrhythmia, and stroke	RIPC + RIPostC did not improve clinical outcome
Remote ischemic preconditioning and outcomes of cardiac surgery	Hausenloy et al[13]	*N Engl J Med*, 2015	Multicenter RCT	1612	Adults at increased surgical risk who were undergoing on-pump CABG (with or without valve surgery) with blood cardioplegia	RIPC versus placebo	Combined primary end point of death from cardiovascular causes, nonfatal myocardial infarction, coronary revascularization, or stroke, assessed 12 mo after randomization	RIPC did not improve clinical outcomes
A multicenter trial of remote ischemic preconditioning for heart surgery	Meybohm et al[12]	*N Engl J Med*, 2015	Multicenter RCT	1403	Elective cardiac surgery requiring cardiopulmonary bypass	RIPC versus placebo	Composite of death, myocardial infarction, stroke, or acute renal failure up to hospital discharge	RIPC did not show a relevant benefit (no significant differences)
Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery	Zarbock et al[47]	*JAMA*, 2015	Multicenter RCT	240	Patients undergoing cardiac surgery with high risk for acute kidney injury	RIPC versus placebo	Rate of acute kidney injury within the first 72 h after cardiac surgery	Significant reduction of the rate of acute kidney injury and use of renal replacement therapy
Effect of remote ischemic conditioning on clinical outcomes in patients with acute myocardial infarction	Hausenloy et al[48]	*Lancet*, 2019	Multicenter RCT	5401	ST elevation myocardial infarction	RIC before primary PCI versus placebo	Combined end point of cardiac death or hospitalization for heart failure at 12 mo	Remote ischemic conditioning did not improve clinical outcomes

PHARMACOLOGICAL CARDIOPROTECTION

PHARMACOLOGICAL CARDIOPROTECTION

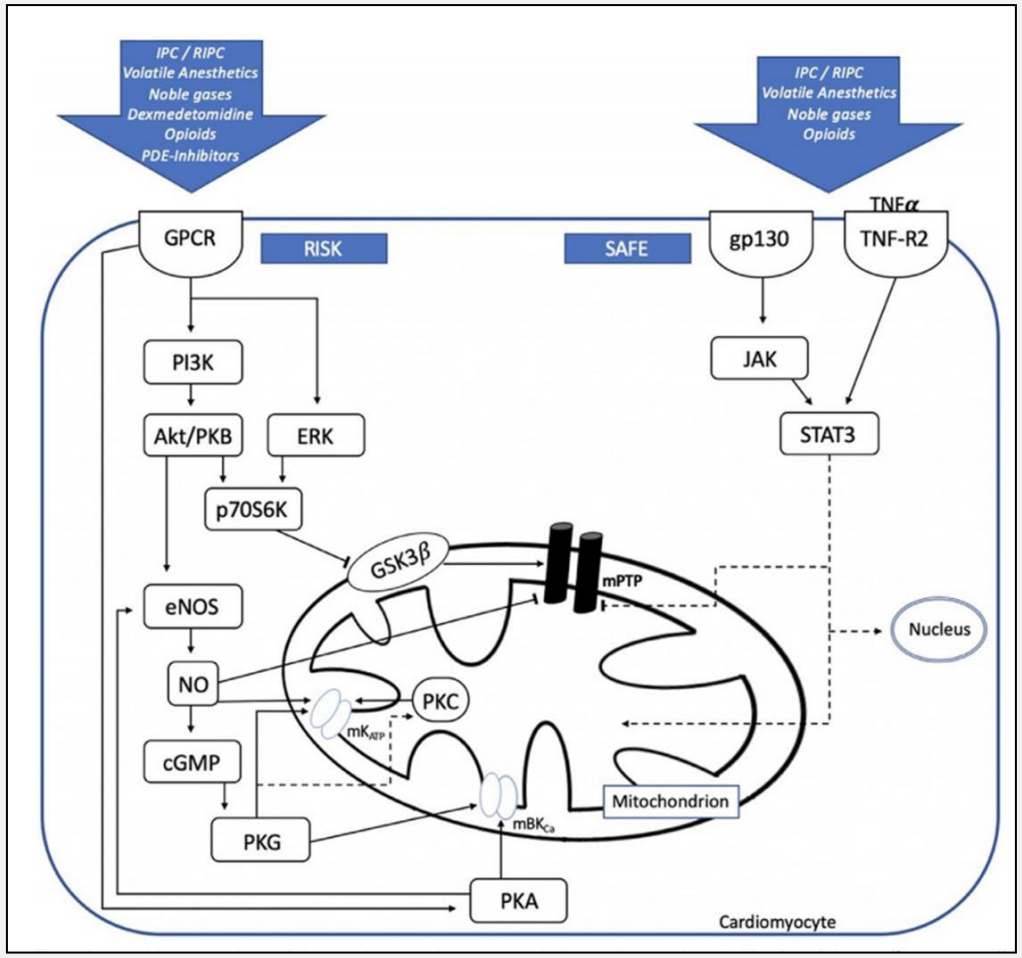
- a concept that is based on the administration of specific drugs mimicking the effect of IPC
- Pharmacological postconditioning seems to be the most promising candidate for clinical use
  - Not invasive and fairly practicable

VOLATILE ANESTHETICS

- Volatile anesthetics :
  (sevoflurane, isoflurane, desflurane)
  have been proposed to provide cardioprotective effects as they activate or prime the same cellular pathways as IPC and RIPC
- Improvement of secondary end points and surrogate parameters of organ injury, reduction of troponin release

VOLATILE ANESTHETICS

- Volatile-induced pre- and postconditioning is triggered via several key pathways
  - Akt/PI3K
  - ERK1/2
  - eNOS—as well as mKATP activation and modulation of mPTP



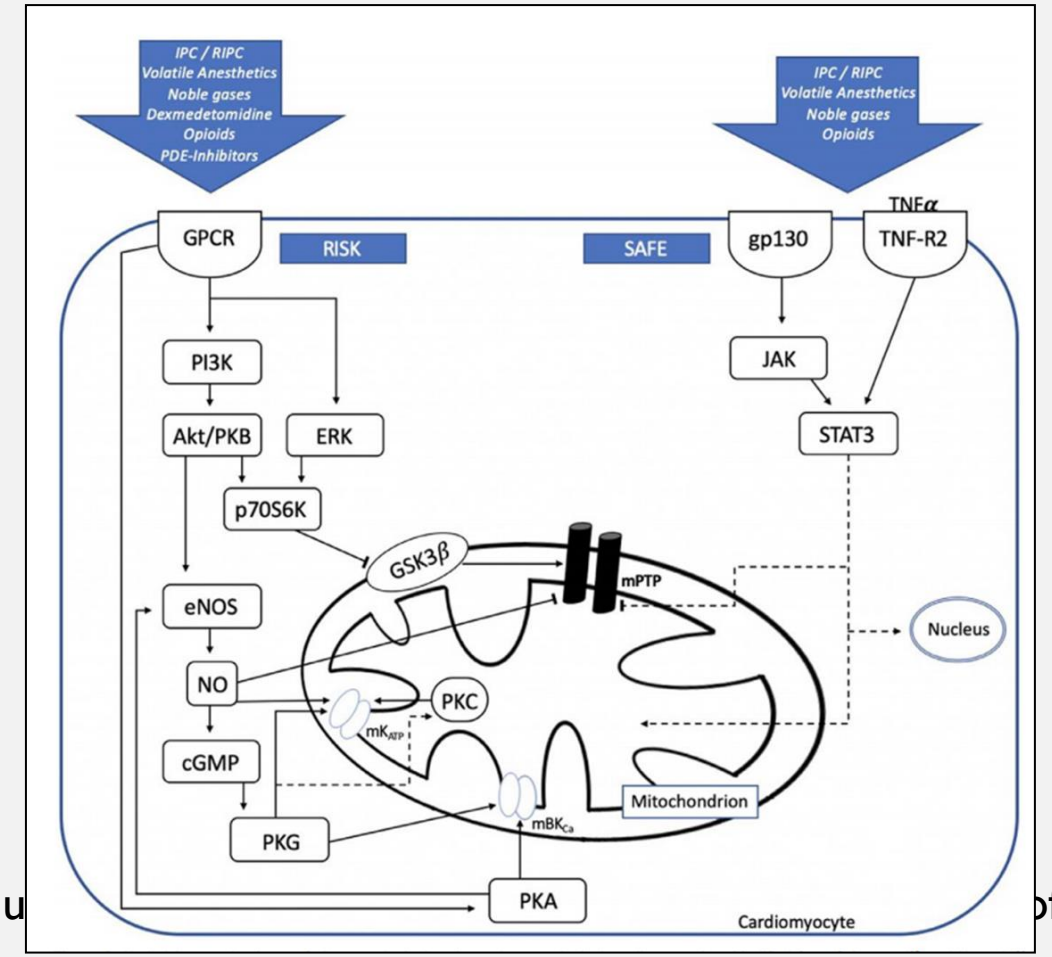
SEVOFLURANE

- treatment with sevoflurane results in an increase of VEGFR-1 expression and a decrease in markers of inflammation in a rat model
- 2.5% sevoflurane preconditioning alleviates heart I/R injury, which is probably mediated by the anti-inflammatory property and upregulation of VEGFR-1

Qian B, Yang Y, Yao Y, Liao Y, Lin Y. Upregulation of vascular endothelial growth factor receptor-1 contributes to sevoflurane preconditioning-mediated cardioprotection. Drug Des Devel Ther. 2018 ;12:769–776.

SEVOFLURANE

- sevoflurane-induced postconditioning in rats modulates apoptosis via the JAK-STAT3 pathway



Wu J, Yu J, Xie P, et al. Sevo!urane postconditioning protects the myocardiu of the JAK2-STAT3 pathway. PeerJ. 2017;5:e3196.

DESFLURANE

- commonly used volatile anesthetic in clinical practice
- experimental research on its cardioprotective properties is scarce

RESEARCH ARTICLE Open Access

Meta-analysis of the cardioprotective effect of sevoflurane versus propofol during cardiac surgery

Feng Li[1*] and Yuan Yuan[2]

sevoflurane anesthesia significantly improved

- postoperative CI
- postoperative 12 hour CI
- postoperative cardiac output
- reduced postoperative 24 hour cardiac troponin I
- postoperative inotropic , vasoconstrictor drug usage

Sevoflurane anesthesia has a better cardioprotective effect on patients undergoing cardiac surgery according to several indicators than propofol anesthesia

Li F, Yuan Y. Meta-analysis of the cardioprotective effect of sevoflurane versus propofol during cardiac surgery. BMC Anesthesiol. 2015;15:128.

Effects of Volatile Anesthetics on Mortality and Postoperative Pulmonary and Other Complications in Patients Undergoing Surgery

A Systematic Review and Meta-analysis

- General anesthesia with volatile anesthetics in cardiac surgery may be associated with reduced mortality, lower incidence of pulmonary and other complications
- No benefits were seen in noncardiac surgical patients

Uhlig C, Bluth T, Schwarz K, et al. Effects of volatile anesthetics on mortality and postoperative pulmonary and other complications in patients undergoing surgery: a systematic review and meta-analysis. Anesthesiology. 2016;124:1230–1245.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Volatile Anesthetics versus Total Intravenous Anesthesia for Cardiac Surgery

Table 3. Clinical Outcomes.

Outcome	Volatile Anesthetics Group (N=2709)		Total Intravenous Anesthesia Group (N=2691)		Relative Risk (95% CI)*
	Value	No. with Missing Data	Value	No. with Missing Data	
Primary outcome					
Death from any cause at 1 year — no. (%)	75 (2.8)	24	79 (3.0)	23	0.94 (0.69 to 1.29)†
Secondary outcomes					
Death from any cause at 30 days — no. (%)	38 (1.4)	0	34 (1.3)	2	1.11 (0.70 to 1.76)
Death from cardiac causes — no. (%)					
At 30 days	20 (0.7)	0	24 (0.9)	2	0.83 (0.46 to 1.49)
At 1 year	33 (1.2)	25	43 (1.6)	23	0.76 (0.49 to 1.20)
Composite of nonfatal myocardial infarction or death at 30 days — no. (%)	134 (5.0)	27	127 (4.7)	11	1.05 (0.83 to 1.34)

- No significant reduce mortality at 1 year after surgery
- No significant differences with regard to secondary outcomes such as myocardial infarction or other adverse events

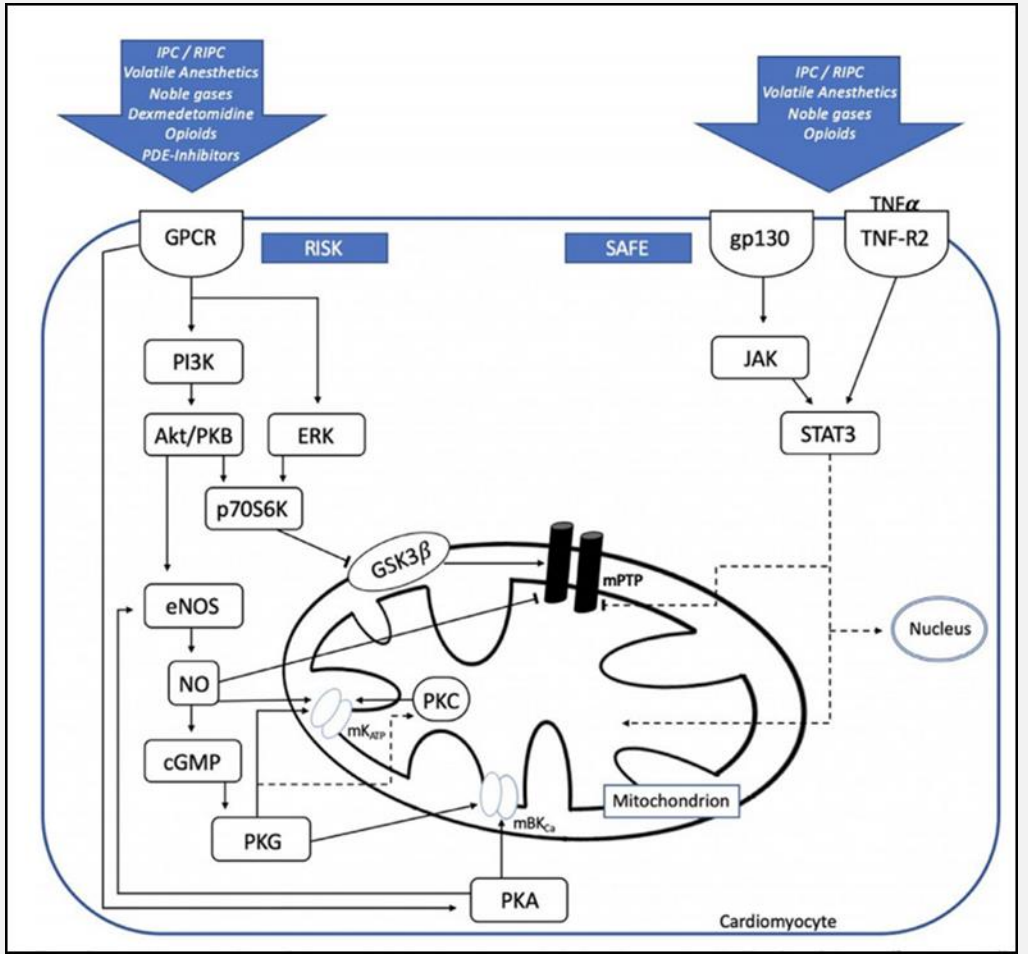
Landoni G, Lomivorotov VV, Nigro Neto C, et al; MYRIAD Study Group. Volatile anesthetics versus total intravenous anesthesia for cardiac surgery. N Engl J Med. 2019;380:1214–1225.

VOLATILE ANESTHETICS

- No final answer regarding cardioprotective effects of volatile anesthetics
- According to different guideline volatile anesthetics should be favored over propofol in cardiothoracic anesthesia
  - hypothesis that propofol counteracts cardioprotection

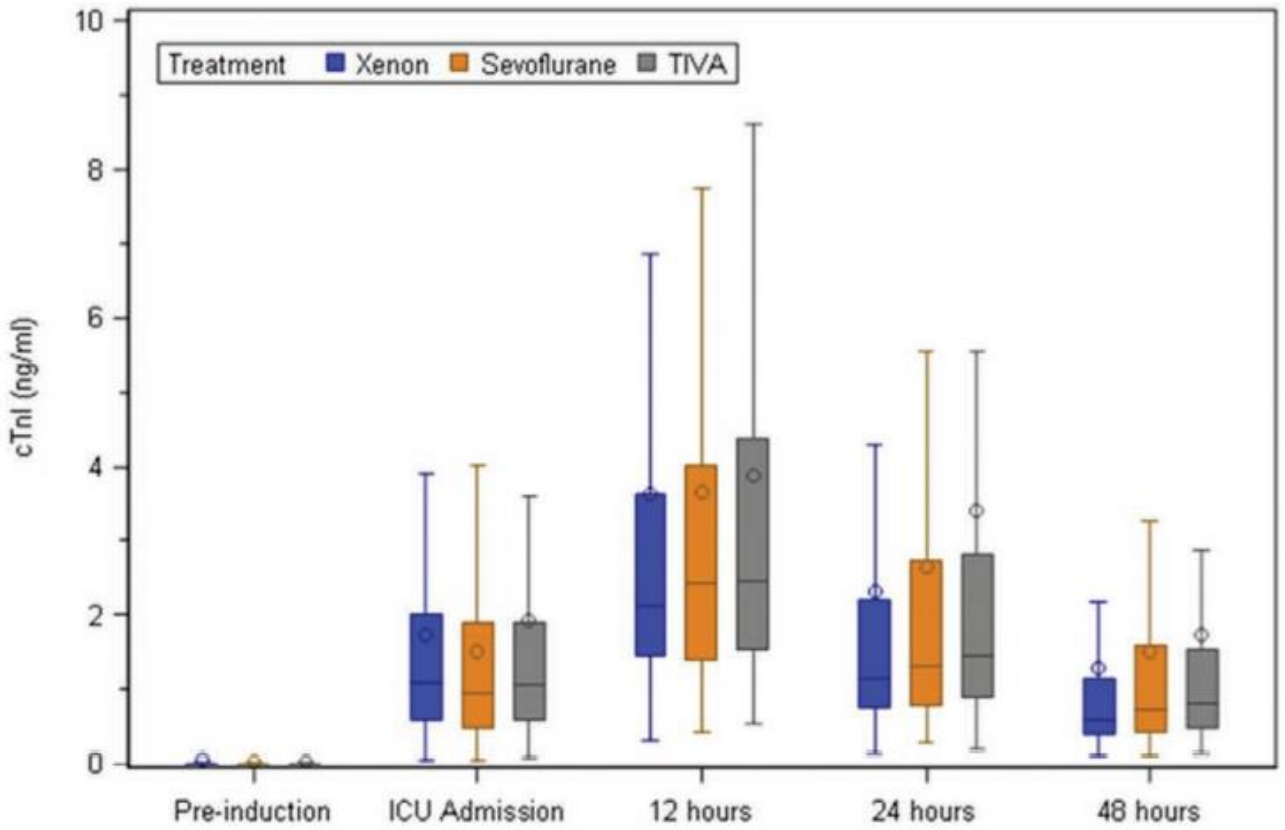
XENON

- xenon-induced cardioprotection resemble those of volatile anesthetics
- Phosphorylation and translocation of PKC-Ɛ and its downstream targets p38 MAPK and MAPK-activated protein kinase 2 (MAPKAPK-2)



Effect of Xenon Anesthesia Compared to Sevoflurane and Total Intravenous Anesthesia for Coronary Artery Bypass Graft Surgery on Postoperative Cardiac Troponin Release

An International, Multicenter, Phase 3, Single-blinded, Randomized Noninferiority Trial



- Noninferior to sevoflurane
- Superior to TIVA with propofol

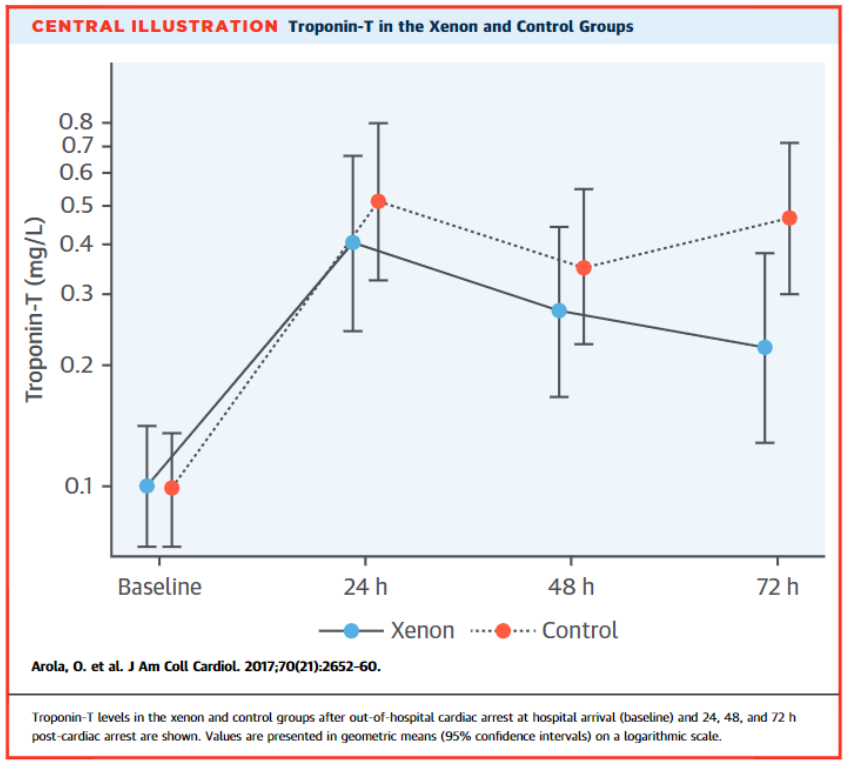
in lowrisk CABG surgery patients

- Only with xenon was cardiac troponin I release less than with total intravenous anesthesia

Hofland J, Ouattara A, Fellahi JL, et al; Xenon-CABG Study Group.. Anesthesiology. 2017;127:918

Inhaled Xenon Attenuates Myocardial Damage in Comatose Survivors of Out-of-Hospital Cardiac Arrest

The Xe-Hypotheca Trial



- Inhaled xenon combined with hypothermia suggested a less severe myocardial injury as demonstrated by the significantly reduced release of troponin-T

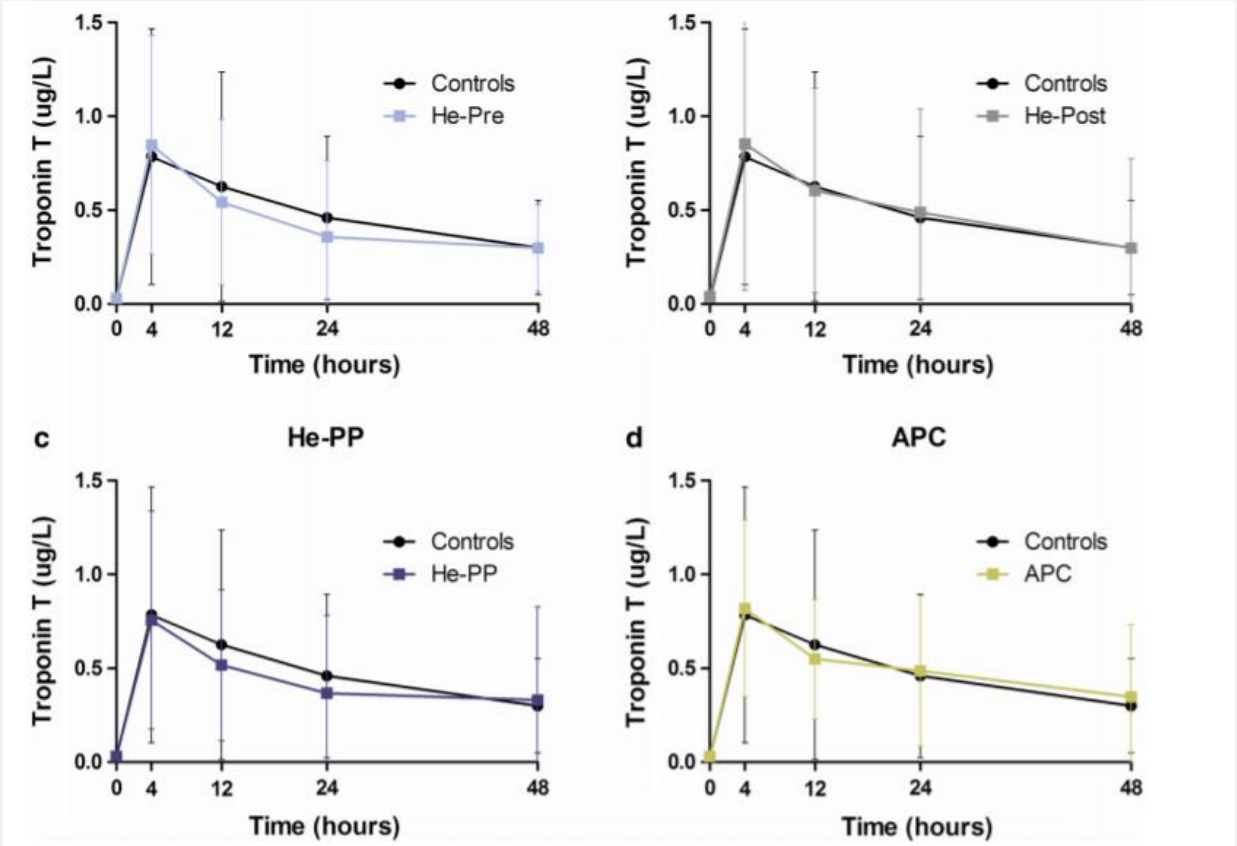
Arola O, Saraste A, Laitio R, et al; Xe-HYPOTHECA Study Group. Inhaled xenon attenuates myocardial damage in comatose survivors of out-of-hospital cardiac arrest: the Xe-hypotheca trial. J Am Coll Cardiol. 2017;70:2652–2660

HELIUM

- No anesthetic properties
- Helium inhalation leads to a release of caveolins from the cell membrane into the blood stream where they convey protection to different organs

RESEARCH Open Access

Effect of helium pre- or postconditioning on signal transduction kinases in patients undergoing coronary artery bypass graft surgery



Investigating cardioprotection had no effect on postoperative troponin release

Smit KF, Brevoord D, De Hert S, et al. Effect of helium pre- or postconditioning on signal transduction kinases in patients undergoing coronary artery bypass graft surgery. J Transl Med. 2016;14:294.

OPIOIDS

- Activation of κ and δ opioid receptors is directly involved in protective strategies
- In cardiac surgery : sufentanil , remifentanil
  ↓ infarct size defined as decreased release of cardiac biomarkers

Tanaka K, Kersten JR, Riess ML. Opioid-induced cardiopro tection. Curr Pharm Des. 2014;20:569

Original Article

Effect of the Aortic Root Infusion of Sufentanil on Ischemia-Reperfusion Injury in Patients Undergoing Coronary Artery Bypass Grafting: A Randomized Clinical Trial

Table 2. Serum levels of CK-MB in the sufentanil and control groups over time*

	Sufentanil Group	Control Group	P value
CK-MB at induction time (U/L)	18.30±8.25	19.50±7.13	0.489
CK-MB 4 h after unclamping (U/L)	65.25±15.63	95.75±22.55	<0.001
CK-MB 8 h after unclamping (U/L)	45.58±13.91	73.78±18.77	<0.001
CK-MB 24 h after unclamping (U/L)	27.83±11.45	41.63±12.51	<0.001

*Data are presented as mean±SD

Table 3. Serum levels of troponin in the sufentanil and control groups over time*

	Sufentanil Group	Control Group	P value
Troponin at induction time (μg/L)	0.10±0.28	0.17±0.33	0.468
Troponin 4 h after unclamping (μg/L)	1.73±0.79	3.24±1.29	<0.001
Troponin 8 h after unclamping (μg/L)	1.26±0.68	2.49±1.18	<0.001
Troponin 24 h after unclamping (μg/L)	0.77±0.55	1.23±0.66	<0.001

*Data are presented as mean±SD

single dose of sufentanil into the aortic root prior to aorta cross-clamp removal diminished the release of cardiac biochemical markers and myocardial injury during on-pump CABG

Zuo Y, Cheng X, Gu E, Liu X, Zhang L, Cao Y. Effect of aortic root infusion of sufentanil on ischemia-reperfusion injury in patients undergoing mitral valve replacement. J Cardiothorac Vasc Anesth. 2014;28:1474–1478

MORPHINE

- Cardioprotection induced by morphine is partly mediated by NO
- During reperfusion , suppression of NO synthesis leads to reduced contraction , while systolic and diastolic function was restored in the presence of morphine

Kunecki M, Roleder T, Biernat J, et al. Opioidergic conditioning of the human heart muscle in nitric oxide-dependent mechanism. Adv Clin Exp Med. 2018;27:1069–1073.

OPIOIDS

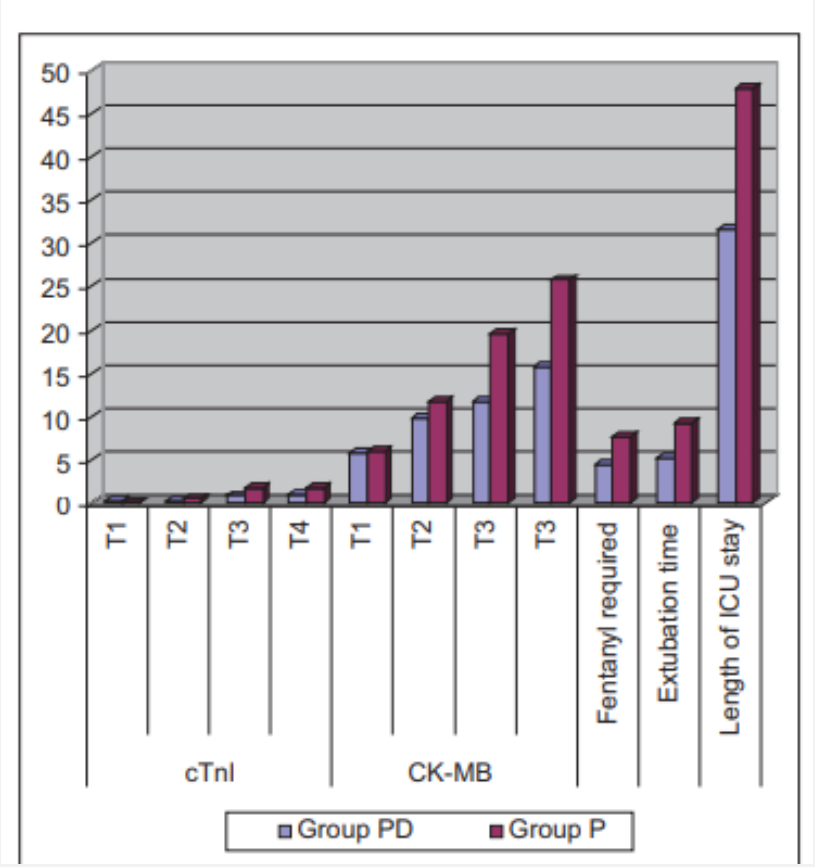
- Cardioprotective doses are much higher than opioid doses routinely used for general anesthesia

DEXMEDETOMIDINE

- Selective α-2 receptor agonist
- Cardioprotective effects via pre and postconditioning using RISK pathway and by activation of mK channels

Original Article

Cardioprotective Effects of Propofol-Dexmedetomidine in Open-Heart Surgery: A Prospective Double-Blind Study



The use of propofol-dexmedetomidine in CPB surgeries offers more cardioprotective effects than the use of propofol alone

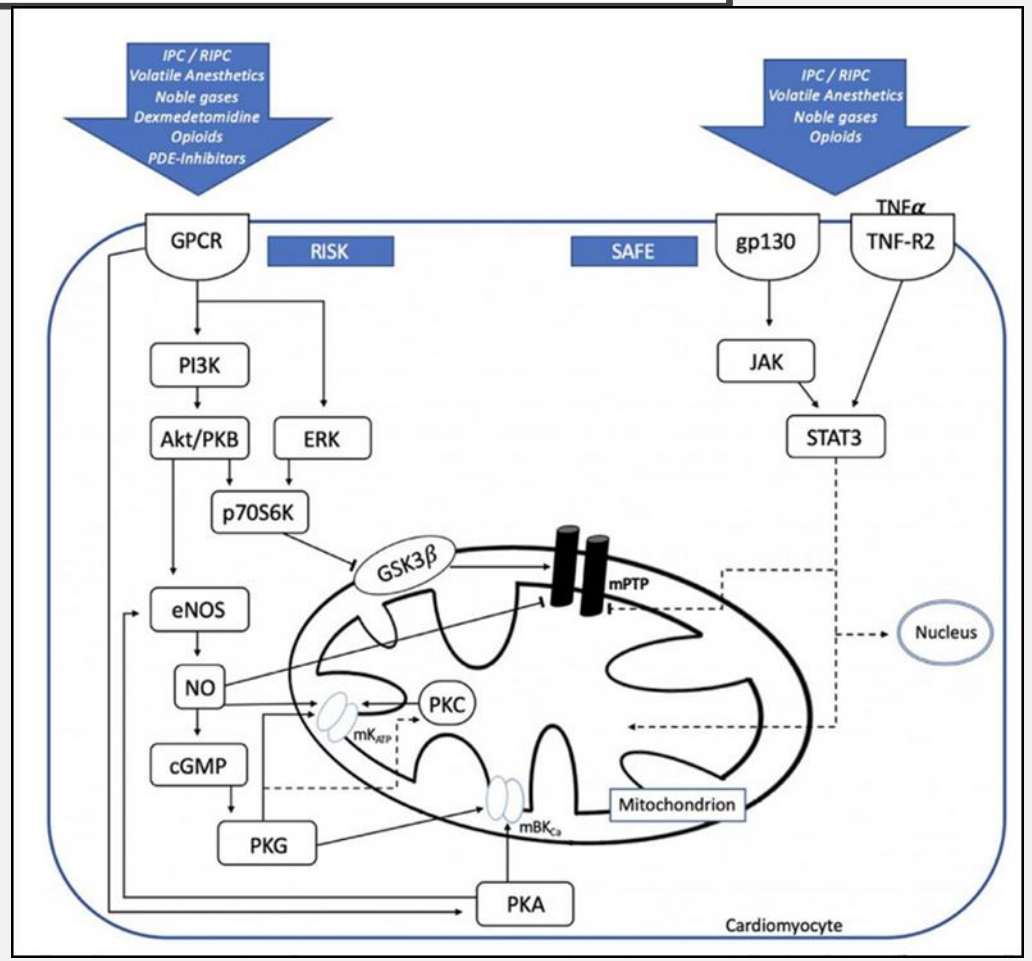
- -lower levels of cardiac enzymes
- -stable hemodynamics
- -less fentanyl requirements
- -earlier postoperative extubation
- -shorter ICU stay

Elgebaly AS, Fathy SM, Sallam AA, Elbarbary Y. Cardioprotective effects of propofol-dexmedetomidine in open-heart surgery: a prospective double-blind study. Ann Card Anaesth. 2020;23:134–141.

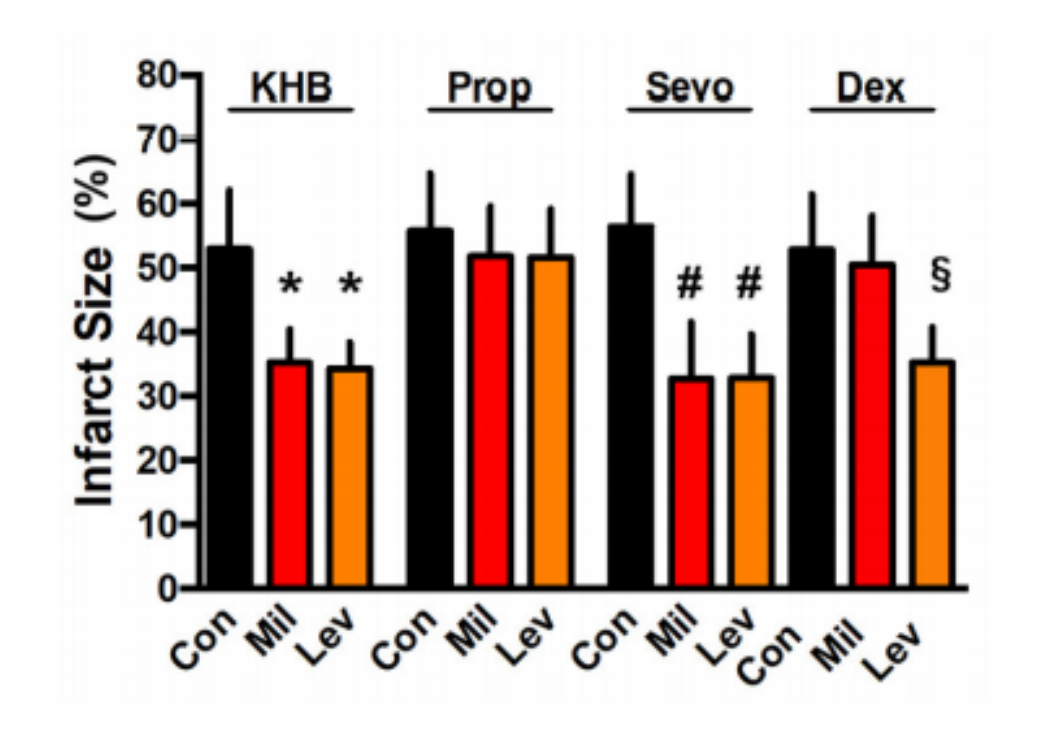
PDE INHIBITORS

- milrinone (PDE3)
- sildenafil (PDE5)

- cGMP/PKG/ERK/GSK3β signaling, leading to an activation of mKATP channels and blocking of mPTP opening



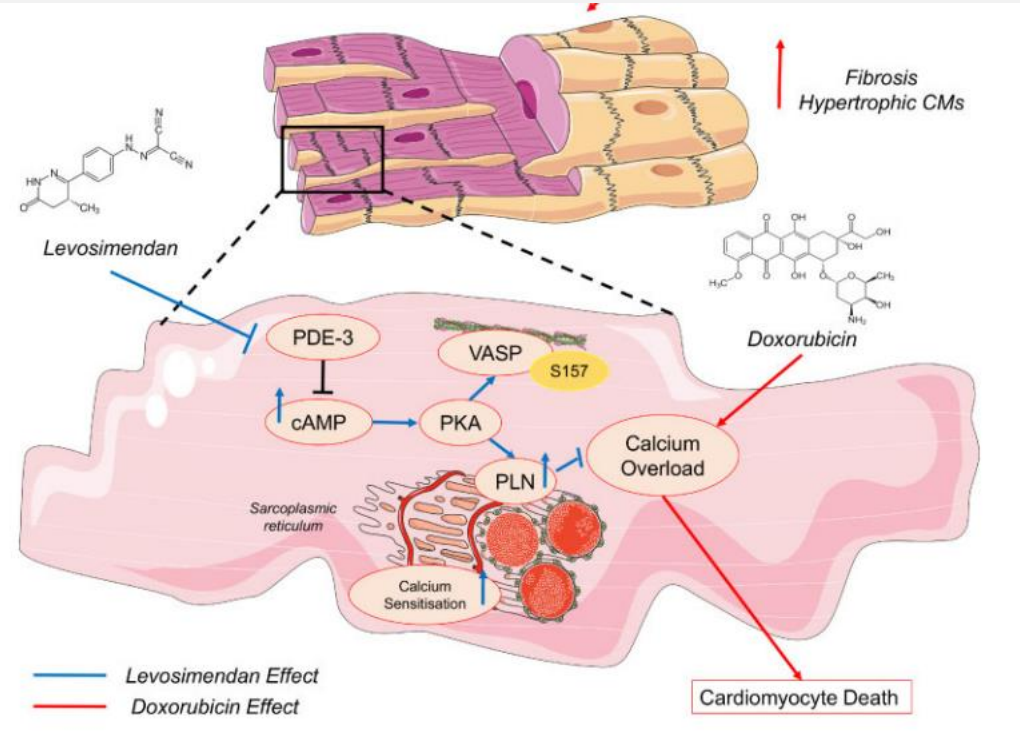
PDE INHIBITORS



- Milrinone or levosimendan was completely abolished under propofol
- Milrinone and levosimendan showed significant infarct size reduction under sevoflurane
- Dexmedetomidine blocked protection of milrinone, but did not affect levosimendan-induced preconditioning.

Bunte S, Lill T, Falk M, et al. Impact of anesthetics on cardioprotection induced by pharmacological preconditioning. J Clin Med. 2019;8:396.

LEVOSIMENDAN



- Levosimendan reduced myocardial dysfunction and oxidative stress induced by doxorubicin, through PDE3 inhibition resulting in an activation of the cAMP-PKA-phospholamban axis and reducing Ca2+ overload in rat cardiomyocytes

Efentakis P, Varela A, Chavdoula E, et al. Levosimendan prevents doxorubicin-induced cardiotoxicity in timeand dose-dependent manner: implications for inotropy. Cardiovasc Res. 2020;116:576–591.

CYCLOSPORINE A

- Cyclosporine A inhibits opening of the MPTP

Table 2. Important Clinical Trials of Pharmacological Conditioning

Clinical Studies on Pharmacological Cardioprotection

Study Title	Authors	Journal/Year	Design	Sample Size	Population	Intervention	End Points	Results
Volatile anesthetics versus total intravenous anesthesia for cardiac surgery	Landoni et al[16]	*N Engl J Med*, 2019	Multicenter RCT	5400	Elective CABG	Volatile anesthetic versus total intravenous anesthesia	Death from any cause at 1 y	Anesthesia with a volatile agent did not result in significantly fewer deaths at 1 y than total intravenous anesthesia
Cyclosporine A in reperfused myocardial infarction	Ottani et al[15]	*J Am Coll Cardiol*, 2016	Multicenter RCT	410	Patients with STEMI, TIMI flow grade 0 to 1, and committed to primary PCI	Cyclosporine A versus placebo	Incidence of ≥70% ST segment resolution 60 min after TIMI flow grade 3, troponin T, and clinical outcome parameters	No effect on ST segment resolution or troponin T; no improvement of clinical outcomes up to 6 mo
NO for inhalation in ST elevation myocardial infarction	Janssens et al[52]	*Eur Heart J*, 2018	Multicenter RCT	250	STEMI	NO versus oxygen	Infarct size assessed by delayed enhancement contrast magnetic resonance imaging	Inhalation of NO in STEMI patients was safe but did not reduce infarct size at 48–72 h
Clonidine in patients undergoing noncardiac surgery	Devereaux et al[53]	*N Engl J Med*, 2014	Multicenter RCT	10,010	Patients at risk for atherosclerotic disease undergoing noncardiac surgery	Clonidine versus placebo	Composite end point of death or nonfatal myocardial infarction at 30 d	Clonidine did not reduce the rate of the composite outcome but increase risk of hypotension and cardiac arrest
Effect of xenon anesthesia compared to sevoflurane and total intravenous anesthesia for coronary artery bypass graft surgery on postoperative cardiac troponin release	Hofland et al[54]	*Anesthesiology*, 2017	Multicenter RCT	492	Low-risk, on-pump CABG	Xenon versus sevoflurane and TIVA	Cardiac troponin I concentration in the blood 24 h postsurgery	In postoperative troponin I release, xenon was noninferior to sevoflurane in CABG patients
Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery	Mehta et al[55]	*N Engl J Med*, 2017	Multicenter RCT	882	Left ventricular ejection fraction of ≤35% and cardiac surgery with cardiopulmonary bypass	Levosimendan versus placebo	Composite of death, renal replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device	Levosimendan did not result in a rate of the composite end point
Effect of early metoprolol on infarct size in ST segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention	Ibanez et al[56]	*Circulation*, 2013	Multicenter RCT	270	Patients with STEMI undergoing PCI within 6 h of symptoms onset	Metoprolol versus placebo	Infarct size on magnetic resonance imaging performed 5–7 d after STEMI	Early intravenous metoprolol before reperfusion reduced infarct size and increased left ventricular ejection fraction with no excess of adverse events