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Perioperative Myocardial Preconditioning: definitions and opportunities

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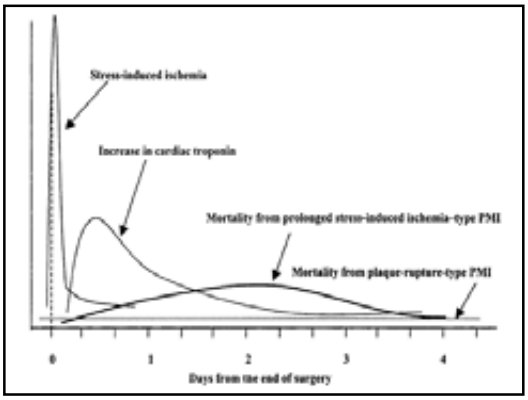

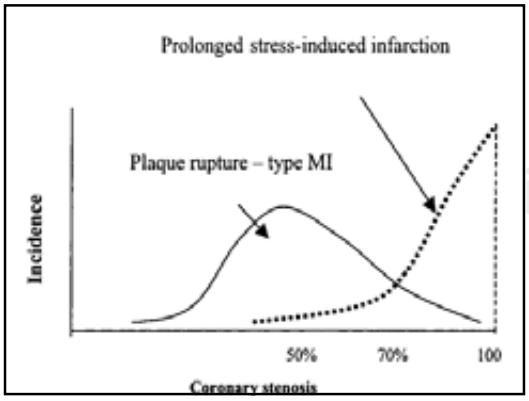

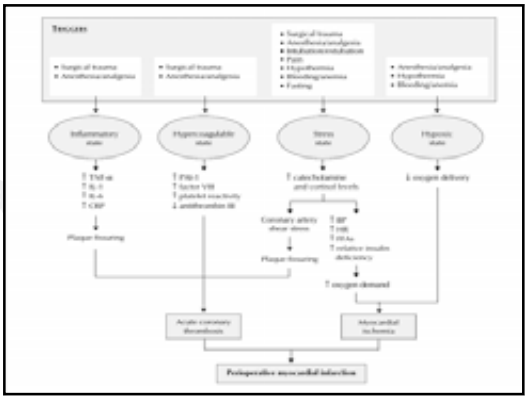


ACC/AHA Guideline

ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery)

Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery

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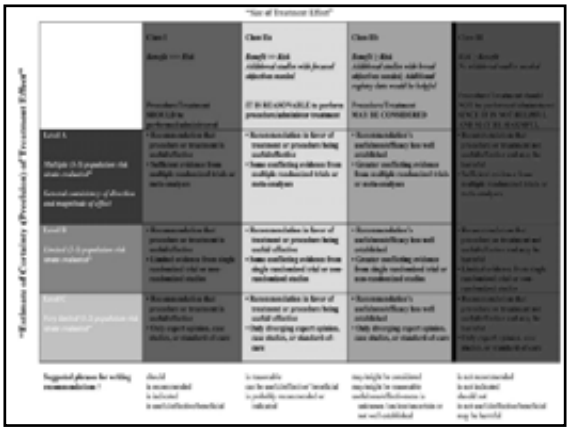

"Size of Treatment Effect"

"Estimate of Certainty (Precision) of Treatment Effect"

Class I

Class IIa

Class IIb

Class III

Level A

Level B

Level C

Suggested phrase for writing recommendations*

should

is recommended

is indicated

is useful/effective/beneficial

is reasonable

can be useful/effective/beneficial

is probably recommended or indicated

may/might be considered

may/might be reasonable

usefulness/effectiveness is unknown/unclear/uncertain or not well established

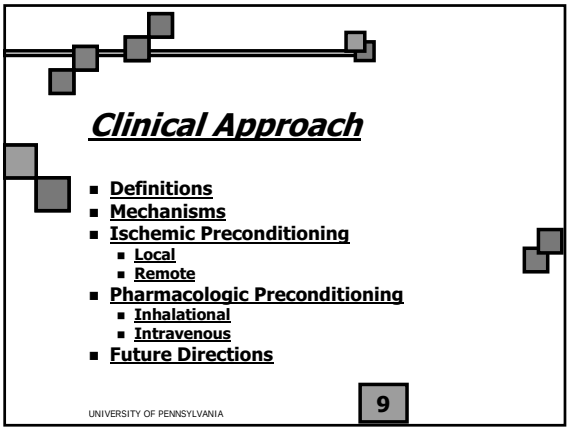
is not recommended

is not indicated

should not

is not useful/effective/beneficial

may be harmful


Clinical Approach

- Definitions
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- Future Directions

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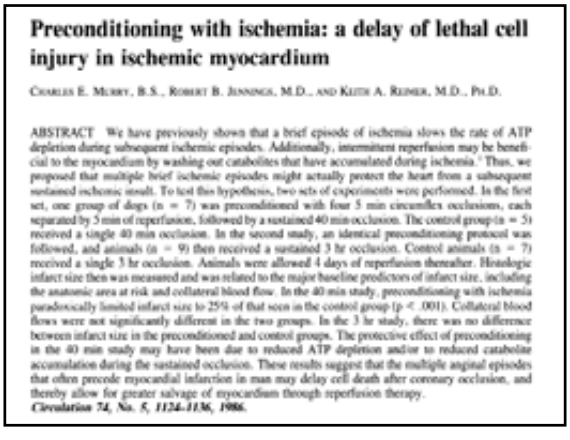
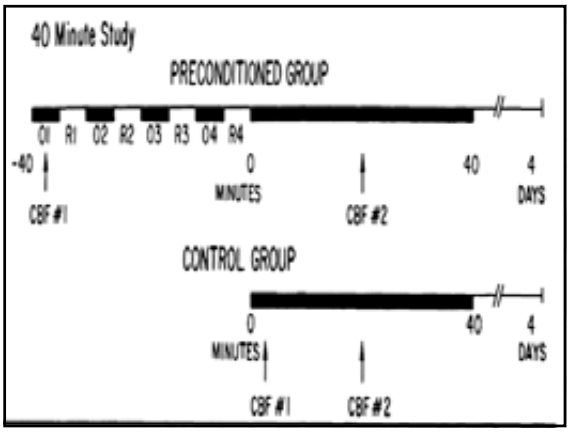

Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium

CHARLES E. MURRY, B.S., ROBERT B. JENNINGS, M.D., AND KEITH A. REIMER, M.D., PH.D.

ABSTRACT We have previously shown that a brief episode of ischemia slows the rate of ATP depletion during subsequent ischemic episodes. Additionally, intermittent reperfusion may be beneficial to the myocardium by washing out catabolites that have accumulated during ischemia.[1] Thus, we proposed that multiple brief ischemic episodes might actually protect the heart from a subsequent sustained ischemic insult. To test this hypothesis, two sets of experiments were performed. In the first set, one group of dogs (n = 7) was preconditioned with four 5 min circumflex occlusions, each separated by 5 min of reperfusion, followed by a sustained 40 min occlusion. The control group (n = 5) received a single 40 min occlusion. In the second study, an identical preconditioning protocol was followed, and animals (n = 9) then received a sustained 3 hr occlusion. Control animals (n = 7) received a single 3 hr occlusion. Animals were allowed 4 days of reperfusion thereafter. Histologic infarct size then was measured and was related to the major baseline predictors of infarct size, including the anatomic area at risk and collateral blood flow. In the 40 min study, preconditioning with ischemia paradoxically limited infarct size to 25% of that seen in the control group ($p < .001$). Collateral blood flows were not significantly different in the two groups. In the 3 hr study, there was no difference between infarct size in the preconditioned and control groups. The protective effect of preconditioning in the 40 min study may have been due to reduced ATP depletion and/or to reduced catabolite accumulation during the sustained occlusion. These results suggest that the multiple anginal episodes that often precede myocardial infarction in man may delay cell death after coronary occlusion, and thereby allow for greater salvage of myocardium through reperfusion therapy.

Circulation 74, No. 5, 1124–1136, 1986.



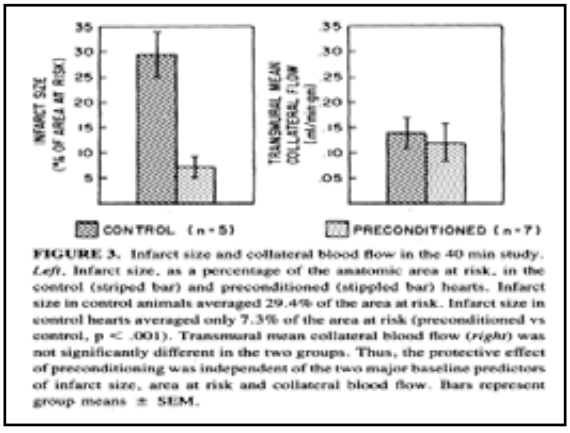


FIGURE 3. Infarct size and collateral blood flow in the 40 min study. *Left*, Infarct size, as a percentage of the anatomic area at risk, in the control (striped bar) and preconditioned (stippled bar) hearts. Infarct size in control animals averaged 29.4% of the area at risk. Infarct size in control hearts averaged only 7.3% of the area at risk (preconditioned vs control, $p < .001$). Transmural mean collateral blood flow (*right*) was not significantly different in the two groups. Thus, the protective effect of preconditioning was independent of the two major baseline predictors of infarct size, area at risk and collateral blood flow. Bars represent group means ± SEM.

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Myocardial injury and its prevention in the perioperative setting

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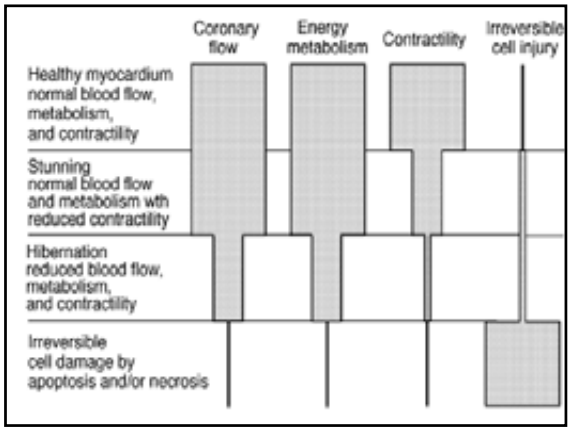
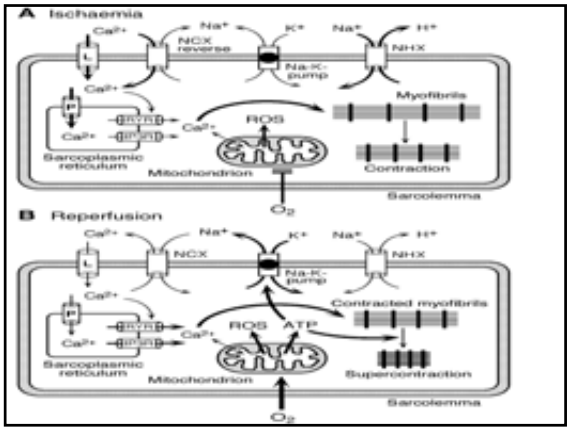
Br J Anaesth 2004; 93: 21–33

Keywords: anaesthetic techniques, inhalation; complications, myocardial ischaemia; heart, cardioprotection; hibernation; stunning





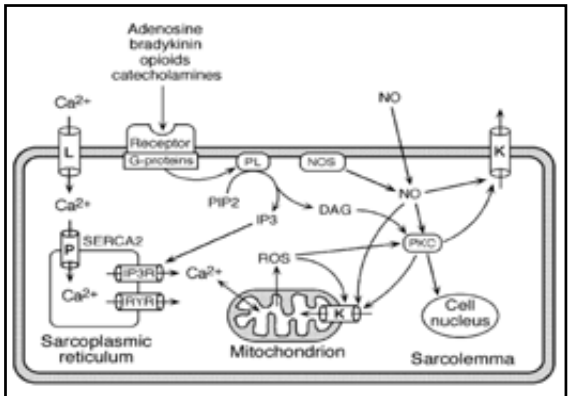


Fig 3 Main signalling pathways in ischaemic preconditioning.

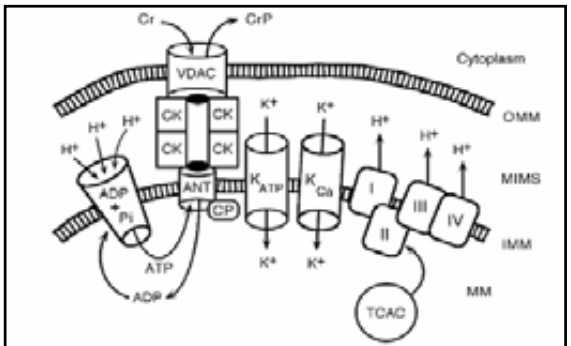


Fig 4 Functional connections between the mitochondrial permeability transition pore (mPTP) and the oxidative energy production during ischaemia-reperfusion and pharmacological preconditioning (PC). The

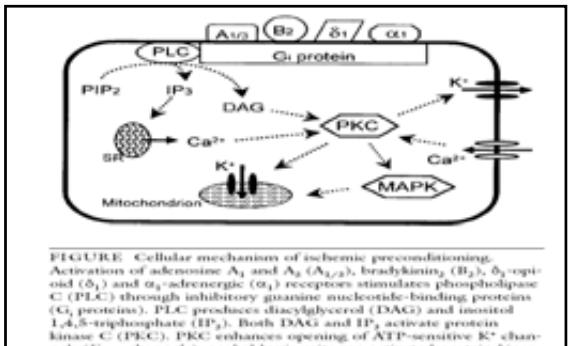


FIGURE Cellular mechanism of ischemic preconditioning. Activation of adenosine A_1 and A_3 ($A_{1/3}$), bradykinin$_2$ (B_2), δ_1-opioid (δ_1) and α_1-adrenergic (α_1) receptors stimulates phospholipase C (PLC) through inhibitory guanine nucleotide-binding proteins (G_i proteins). PLC produces diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3). Both DAG and IP_3 activate protein kinase C (PKC). PKC enhances opening of ATP-sensitive K^+ channels (K_{ATP} channels), probably via mitogen-activated protein kinases (MAPK). The K_{ATP} channel seems to be the end-effector for inducing protection, though the downstream process is still unknown. Recently mitochondrial K_{ATP} channels have been considered more important than sarcolemmal K_{ATP} channels. PIP_2 = phosphatidyl inositol; SR = sarcoplasmic reticulum.

British Journal of Anaesthesia 91 (4): 551–65 (2003)
DOI: 10.1093/bja/aeg205

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REVIEW ARTICLES

Anaesthetics and cardiac preconditioning. Part I.

Signalling and cytoprotective mechanisms

M. Zaugg[1,2]*, E. Lucchinetti[1], M. Uecker[1], T. Pasch[1] and M. C. Schaub[1]

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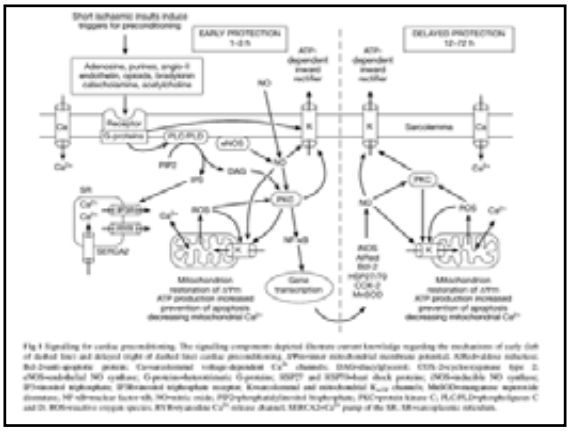
Cardiac preconditioning represents the most potent and consistently reproducible method of rescuing heart tissue from undergoing irreversible ischaemic damage. Major milestones regarding the elucidation of this phenomenon have been passed in the last two decades. The signalling and amplification cascades from the preconditioning stimulus, be it ischaemic or pharmacological, to the putative end-effectors, including the mechanisms involved in cellular protection, are discussed in this review. Volatile anaesthetics and opioids effectively elicit pharmacological preconditioning. Anaesthetic-induced preconditioning and ischaemic preconditioning share many fundamental steps, including activation of G-protein-coupled receptors, multiple protein kinases and ATP-sensitive potassium channels (K_{ATP} channels). Volatile anaesthetics prime the activation of the sarcolemmal and mitochondrial K_{ATP} channels, the putative end-effectors of preconditioning, by stimulation of adenosine receptors and subsequent activation of protein kinase C (PKC) and by increased formation of nitric oxide and free oxygen radicals. In the case of desflurane, stimulation of α_1- and β-adrenergic receptors may also be of importance. Similarly, opioids activate δ_1- and κ-opioid receptors, and this also leads to PKC activation. Activated PKC acts as an amplifier of the preconditioning stimulus and stabilizes, by phosphorylation, the open state of the mitochondrial K_{ATP} channel (the main end-effector in anaesthetic preconditioning) and the sarcolemmal K_{ATP} channel. The opening of K_{ATP} channels ultimately elicits cytoprotection by decreasing cytosolic and mitochondrial Ca^{2+} overload.

Br J Anaesth 2003; **91**: 551–65

Keywords: anaesthesia, perioperative; hours, cardiac preconditioning; cardioprotection



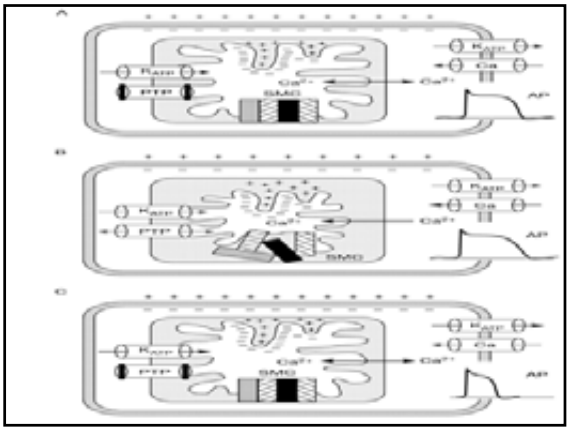
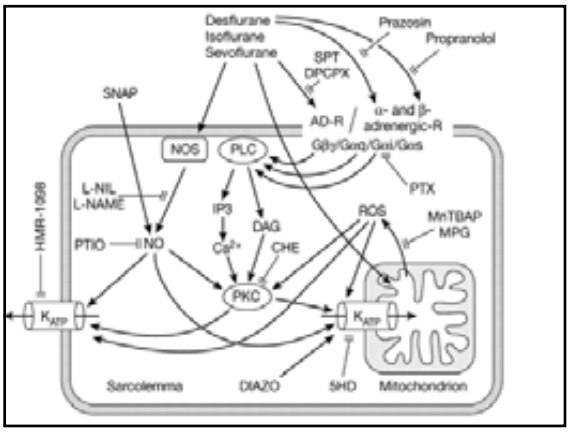


Table 1 Pharmacology of mitochondrial and sarcolemmal K_{ATP} channels. ATP=adenosine triphosphate; CoA=coenzyme A; GDP=guanosine diphosphate; GTP=guanosine triphosphate; UDP=uridine diphosphate

Selectivity	Agonists	Antagonists
Sarcolemmal	Long-chain CoA esters	HMR-1098
	P-1075	
	ADP	
Mitochondrial	GTP	ADP
	GDP	Long-chain-CoA esters
	UDP	5-Hydroxydecanoate
	Superoxide anions	
	Diazoxide	
	Nicorandil	
	BMS-191095	
Non-selective	Cromakalim	ATP
	Bimakalim	Glibenclamide
	Aprikalim	Glyburide
	Diethylaminoethylbenzoate	
	Pinacidil	



British Journal of Anaesthesia 91 (4): 566–76 (2003)
DOI: 10.1093/bja/aeg204

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Anaesthetics and cardiac preconditioning. Part II.

Clinical implications

M. Zaugg[1,2]*, E. Lucchinetti[1], C. Garcia[1], T. Pasch[1], D. R. Spahn[2] and M. C. Schaub[1]

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There is compelling evidence that preconditioning occurs in humans. Experimental studies with potential clinical implications as well as clinical studies evaluating ischaemic, pharmacological and anaesthetic cardiac preconditioning in the perioperative setting are reviewed. These studies reveal promising results. However, there are conflicting reports on the efficacy of preconditioning in the diseased and aged myocardium. In addition, many anaesthetics and a significant number of perioperatively administered drugs affect the activity of cardiac sarcolemmal and mitochondrial K_{ATP} channels, the end-effectors of cardiac preconditioning, and thereby markedly modulate preconditioning effects in myocardial tissue. Although these modulatory effects on K_{ATP} channels have been investigated almost exclusively in laboratory investigations, they may have potential implications in clinical medicine. Important questions regarding the clinical utility and applicability of perioperative cardiac preconditioning remain unresolved and need more experimental work and randomized-controlled clinical trials.

Br J Anaesth 2003; **91**: 566–76

Clinical Approach

- Definitions
- Mechanisms
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  - Local
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Catheterization and Cardiovascular Interventions 65:361–367 (2005)

Brief Repetitive Balloon Occlusions Enhance Reperfusion During Percutaneous Coronary Intervention for Acute Myocardial Infarction: A Pilot Study

Warren K. Laskey* MD, FSCAI

The objective of this study was to determine whether acutely ischemic myocardium may be conditioned during percutaneous coronary intervention for acute myocardial infarction. Ischemic preconditioning is a powerful cardioprotective mechanism that limits infarct size in animal investigations and ischemic sequelae during percutaneous coronary intervention in man. However, the conditioning stimulus in all these studies has been applied prior to the defining episode of ischemia. Seventeen patients undergoing percutaneous coronary intervention for acute myocardial infarction were randomly assigned to a standard ischemic preconditioning protocol (n = 10) or a usual-care control group (n = 7). ST segment shift response and Doppler-derived distal coronary velocity data were compared. Despite similar degrees of baseline ST segment elevation, the magnitude of final ST segment elevation in the conditioning group was less than that in controls at the protocol conclusion (conditioning, 1.60 ± 0.8 mV; control, 4.0 ± 0.5 mV; $P = 0.001$). The rate of ST segment resolution was greater in the conditioning group (conditioning, 0.26 ± 0.1 mV/min; control, 0.12 ± 0.1 mV/min; $P = 0.05$). Distal coronary velocimetry indicated significant improvement in coronary flow velocity reserve in the conditioning group at the protocol conclusion (conditioning, 1.6 ± 0.2; control, 1.1 ± 0.1; $P = 0.009$). Brief periods of occlusion and reperfusion during percutaneous intervention for acute myocardial infarction mitigate the extent of ischemic injury and improve distal myocardial perfusion. Each ischemic conditioning represents a potentially useful adjunct to strategies for enhancing reperfusion during acute myocardial infarction. © 2005 Wiley-Liss, Inc.

Key words: ischemia; reperfusion; preconditioning

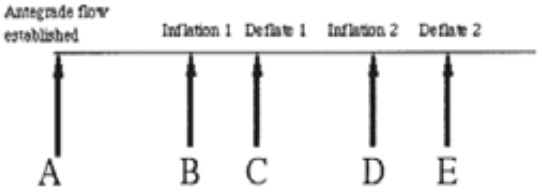


Fig. 1. The study protocol. Point A indicates the time at which antegrade flow was initially established with guidewire passage. Point B indicates the time of onset of the initial 90-sec balloon occlusion. Point C represents the point of balloon deflation and the beginning of the first reperfusion interval. Point D represents the onset of the second 90-sec balloon occlusion and point E the time of balloon deflation and the onset of the second reperfusion interval.

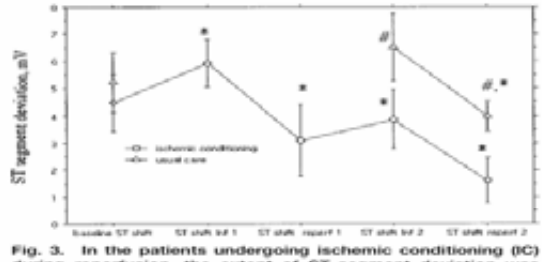


Fig. 3. In the patients undergoing ischemic conditioning (IC) during reperfusion, the extent of ST segment deviation was significantly different across the various points (P for ANOVA < 0.0001). The asterisks represent statistically significant differences ($P < 0.01$) in ST segment deviation from baseline. In the control patients (UC), although the magnitude of ST segment deviation significantly decreased following the single balloon inflation (asterisk, $P < 0.001$), the ST segment deviation in the UC group exceeded that of the IC group during both balloon inflation and the final determination (UC, 4.0 ± 0.5 mV; IC, 1.6 ± 0.8 mV; number symbol, $P = 0.002$).

Heart Failure

Long-Term Benefit of Postconditioning

Hélène Thibault, MD; Christophe Piot, MD, PhD; Patrick Staat, MD; Laurence Bontemps, MD; Catherine Sportouch, MD; Gilles Rioufol, MD, PhD; Thien Tri Cung, MD; Eric Bonnefoy, MD, PhD; Denis Angoulvant, MD; Jean-François Aupetit, MD, PhD; Gérard Finet, MD, PhD; Xavier André-Fouët, MD; Jean Christophe Macia, MD; Franck Raczka, MD; Rolland Rossi, MD; Rolland Ini, MD, PhD; Gilbert Kirkorian, MD, PhD; Geneviève Derumeaux, MD, PhD; Michel Ovize, MD, PhD

Background—We previously demonstrated that ischemic postconditioning decreases creatine kinase release, a surrogate marker for infarct size, in patients with acute myocardial infarction. Our objective was to determine whether ischemic postconditioning could afford (1) a persistent infarct size limitation and (2) an improved recovery of myocardial contractile function several months after infarction.

Methods and Results—Patients presenting within 6 hours of the onset of chest pain, with suspicion for a first ST-segment–elevation myocardial infarction, and for whom the clinical decision was made to treat with percutaneous coronary intervention, were eligible for enrollment. After reperfusion by direct stenting, 38 patients were randomly assigned to a control (no intervention; n=21) or postconditioned group (repeated inflation and deflation of the angioplasty balloon; n=17). Infarct size was assessed both by cardiac enzyme release during early reperfusion and by ^{99m}thallium single photon emission computed tomography at 6 months after acute myocardial infarction. At 1 year, global and regional contractile function was evaluated by echocardiography. At 6 months after acute myocardial infarction, single photon emission computed tomography rest-redistribution index (a surrogate for infarct size) averaged 11.8±10.3% versus 19.5±13.3% in the postconditioned versus control group ($P=0.04$), in agreement with the significant reduction in creatine kinase and troponin I release observed in the postconditioned versus control group (−40% and −47%, respectively). At 1 year, the postconditioned group exhibited a 7% increase in left ventricular ejection fraction compared with control ($P=0.04$).

Conclusions—Postconditioning affords persistent infarct size reduction and improves long-term functional recovery in patients with acute myocardial infarction. (*Circulation*. 2006;117:1037-1044.)

Key Words: infarction ■ ischemia ■ myocardial infarction ■ postconditioning ■ reperfusion

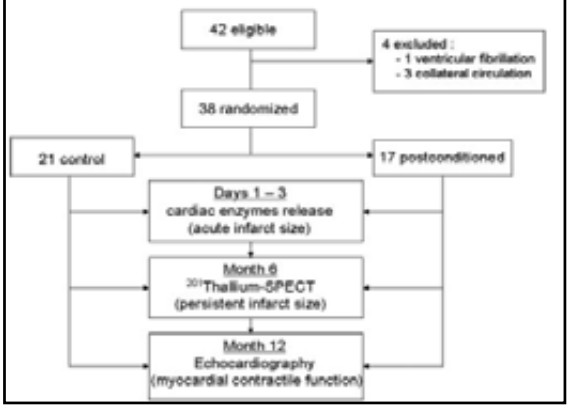


Table 2. Infarct Size and LV Function

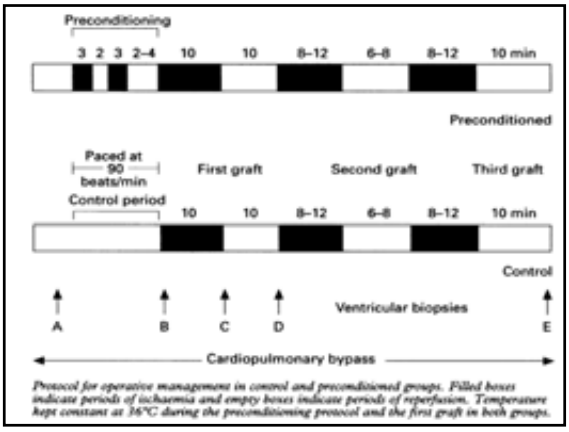
	Control Group (n=21)	Postconditioned Group (n=17)	*P*
Cardiac enzyme infarct size (at days 1 to 3)			
CK release (AUC $\times 10^6$)	37.9±19.5	22.7±9.3*	0.01
TnI release (AUC $\times 10^6$)	24.6±20.6	13.0±7.0*	0.02
SPECT infarct size (at 6 months)			
Perfusion defect index (%)	19.5±13.3	11.8±10.3*	0.04
LV function by echocardiography (at 12 months)			
LV ejection fraction, %	49±13	56±8*	0.04
Wall motion score index	1.6±0.4	1.4±0.4*	0.04
Strain rate, s^{-1}	0.6±0.4	1.2±0.6*	0.0002

Data are presented as mean±SD. AUC indicates area under the curve. Infarct size was assessed early (cardiac enzyme release) and at 6 months by SPECT imaging. LV function was evaluated at 12 months by echocardiography.
*$P<0.05$ vs control.

Heart 1997;77:314–318

Ischaemic preconditioning reduces troponin T release in patients undergoing coronary artery bypass surgery

David P Jenkins, Wilf B Pugsley, Abdul M Alkhulaifi, Michael Kemp, James Hooper, Derek M Yellon



Protocol for operative management in control and preconditioned groups. Filled boxes indicate periods of ischaemia and empty boxes indicate periods of reperfusion. Temperature kept constant at 36°C during the preconditioning protocol and the first graft in both groups.

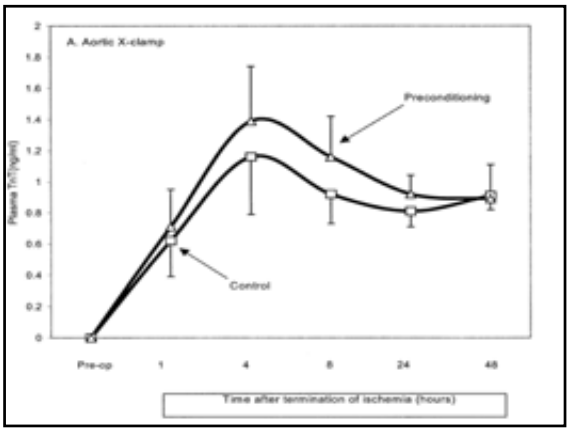
Table 2 Troponin T in serum

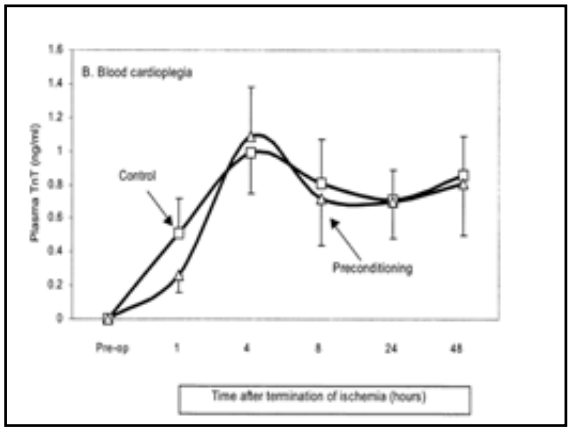
TnT, µg/l	Pre CPB	1 h post CPB	6 h post CPB	24 h post CPB	72 h post CPB
Control	<0·1	1·0 (0·4 to 1·5)	1·9 (0·8 to 3·5)	1·4 (0·5 to 2·2)	1·4 (0·7 to 3·9)
IPC	<0·1	1·4 (0·5 to 1·4)	1·1 (0·5 to 3·3)	0·4 (0·3 to 1·7)	0·3 (0·2 to 2·0)*

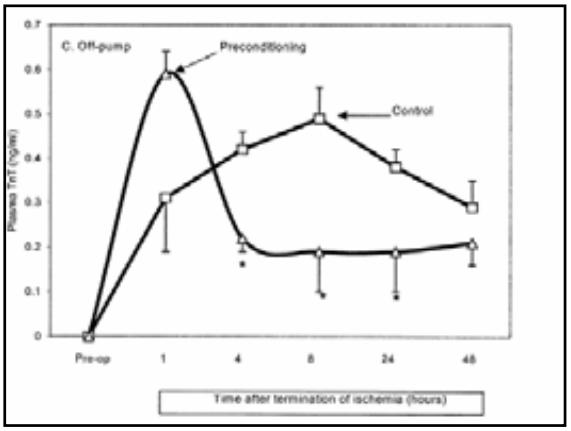
Median and (interquartile range) of serum troponin T.
CPB, cardiopulmonary bypass; IPC, ischaemic preconditioning; TnT, troponin T.
*P = 0·05, Mann–Whitney U test.

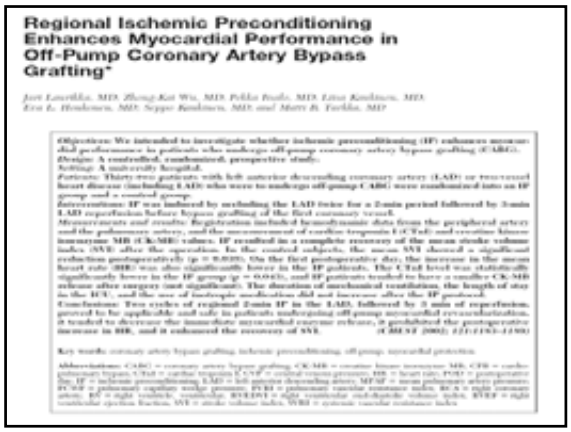
Protection of the human heart with ischemic preconditioning during cardiac surgery: Role of cardiopulmonary bypass

Sidi Ghosh, MD
Manuel Galiñanes, MD, PhD, FRCS









Regional Ischemic Preconditioning Enhances Myocardial Performance in Off-Pump Coronary Artery Bypass Grafting*

Jani Laurikka, MD, Zhong-Kai Wu, MD, Pekka Tarkka, MD, Liisa Kauhanen, MD, Eva L. Hendricus, MD, Seppo Rankinen, MD, and Matti K. Turkka, MD

Objectives: We intended to investigate whether ischemic preconditioning (IP) enhances myocardial performance in patients who undergo off-pump coronary artery bypass grafting (CABG).
Design: A controlled, randomized, prospective study.
Setting: A university hospital.
Patients: Thirty-two patients with left anterior descending coronary artery (LAD) or proximal heart disease (including LAD) who were to undergo off-pump CABG were randomized into an IP group and a control group.
Interventions: IP was induced by occluding the LAD twice for a 2-min period followed by 2-min LAD reperfusion before bypass grafting of the first coronary vessel.
Measurements and results: Registration included hemodynamic data from the peripheral artery and the pulmonary artery, and the measurement of cardiac troponin I (cTnI) and creatine kinase isoenzyme MB (CK-MB) values. IP resulted in a complete recovery of the mean stroke volume index (SVI) after the operation. In the control subjects, the mean SVI showed a significant reduction postoperatively ($p = 0.035$). On the first postoperative day, the increase in the mean heart rate (HR) was also significantly lower in the IP patients. The cTnI level was statistically significantly lower in the IP group ($p = 0.045$), and IP patients tended to have a smaller CK-MB release after surgery (not significant). The duration of mechanical ventilation, the length of stay in the ICU, and the use of inotropic medication did not increase after the IP protocol.
Conclusions: Two cycles of regional 2-min IP in the LAD, followed by 2 min of reperfusion, proved to be applicable and safe in patients undergoing off-pump myocardial revascularization. It tended to decrease the immediate myocardial enzyme release, it prohibited the postoperative increase in HR, and it enhanced the recovery of SVI.

Key words: coronary artery bypass grafting, ischemic preconditioning, off-pump, myocardial protection.

Abbreviations: CABG = coronary artery bypass grafting, CK-MB = creatine kinase isoenzyme MB, CPB = cardiopulmonary bypass, CTnI = cardiac troponin I, CVP = central venous pressure, HR = heart rate, POD = postoperative day, IP = ischemic preconditioning, LAD = left anterior descending artery, MPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PVRI = pulmonary vascular resistance index, RCA = right coronary artery, RV = right ventricle, ventricular, RVEDVI = right ventricular end-diastolic volume index, RVEF = right ventricular ejection fraction, SVI = stroke volume index, SVRI = systemic vascular resistance index.

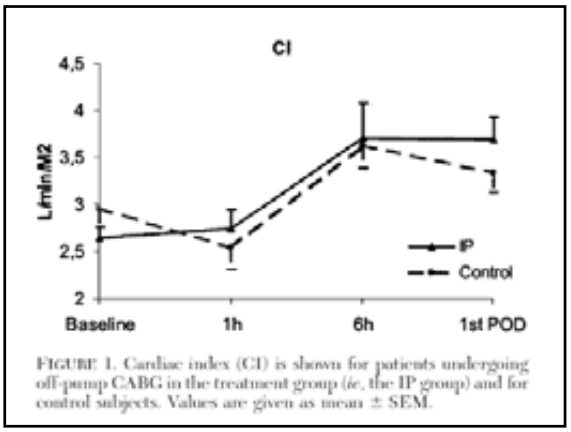


FIGURE 1. Cardiac index (CI) is shown for patients undergoing off-pump CABG in the treatment group (*ie*, the IP group) and for control subjects. Values are given as mean ± SEM.

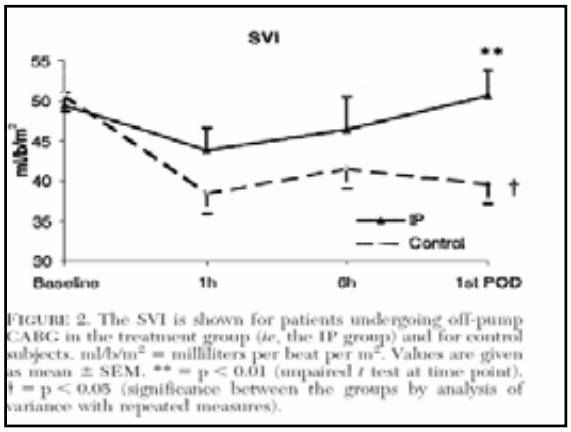


FIGURE 2. The SVI is shown for patients undergoing off-pump CABG in the treatment group (*ie*, the IP group) and for control subjects. ml/b/m^2 = milliliters per beat per m^2. Values are given as mean ± SEM. ** = $p < 0.01$ (unpaired *t* test at time point). † = $p < 0.05$ (significance between the groups by analysis of variance with repeated measures).

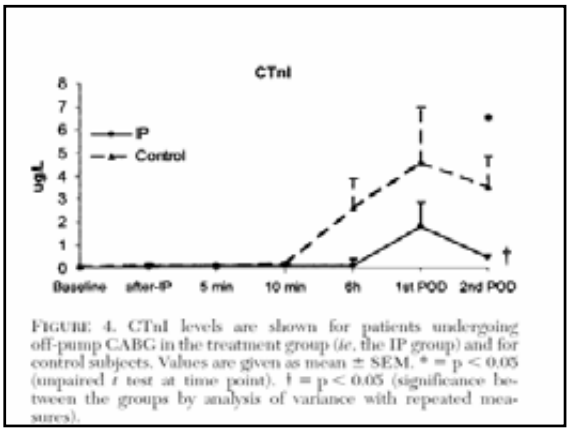


FIGURE 4. CTnI levels are shown for patients undergoing off-pump CABG in the treatment group (*ie*, the IP group) and for control subjects. Values are given as mean ± SEM. * = $p < 0.05$ (unpaired *t* test at time point). † = $p < 0.05$ (significance between the groups by analysis of variance with repeated measures).

Clinical Approach

- Definitions
- Mechanisms
- Ischemic Preconditioning
  - Local
  - Remote
- Pharmacologic Preconditioning
  - Inhalational
  - Intravenous
- Future Directions

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BJA

REVIEW ARTICLE

Cardioprotection by remote ischaemic preconditioning

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Perioperative myocardial infarction is a leading cause of morbidity and mortality after major non-cardiac surgery. Pharmacological agents such as beta-blockers may reduce the risk but are associated with side-effects and may be contra-indicated in some patients. Basic scientific experiments and preliminary clinical trials in humans suggest that remote ischaemic preconditioning (RIPC), where brief ischaemia in one tissue confers resistance to subsequent sustained ischaemic insults in another tissue, may provide a simple, cost-effective means of reducing the risk of perioperative myocardial ischaemia. The Medline and Pubmed databases were searched for articles concerning RIPC. The mechanism may be humoral, neural, or a combination of both, and involves adenosine, opioids, bradykinins, protein kinase C, and K-ATP channels, although the precise end-effector remains unclear. Small randomized trials in humans undergoing major surgery suggest that RIPC induced by brief lower limb ischaemia significantly reduces myocardial injury. It may also reduce other ischaemic complications of surgery and anaesthesia. Small studies provide some evidence that RIPC could reduce myocardial injury and other ischaemic complications of surgery. However, large-scale clinical trials to assess the effect of RIPC on mortality and morbidity are required before RIPC can be recommended for routine clinical use.

Br J Anaesth 2007; **99**: 611–16

Keywords: complications, myocardial infarction; heart, ischaemic; surgery, postoperative care

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Randomized Controlled Trial of the Effects of Remote Ischemic Preconditioning on Children Undergoing Cardiac Surgery

First Clinical Application in Humans

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Toronto, Canada

OBJECTIVES We conducted a randomized controlled trial of the effects of remote ischemic preconditioning (RIPC) in children undergoing repair of congenital heart defects.

BACKGROUND Remote ischemic preconditioning reduces injury caused by ischemia-reperfusion in distant organs. Cardiopulmonary bypass (CPB) is associated with multi-system injury. We hypothesized that RIPC would modulate injury induced by CPB.

METHODS Children undergoing repair of congenital heart defects were randomized to RIPC or control treatment. Remote ischemic preconditioning was induced by four 5-min cycles of lower limb ischemia and reperfusion using a blood pressure cuff. Measurements of lung mechanics, cytokines, and troponin I were made pre- and postoperatively.

RESULTS Thirty-seven patients were studied. There were 20 control patients and 17 patients in the RIPC group. The mean age and weight of the RIPC and control patients were not different (0.9 ± 0.9 years vs. 2.2 ± 3.6 years, $p = 0.4$, and 8.9 ± 2.9 kg vs. 11.5 ± 10 kg, $p = 0.06$). Bypass and cross-clamp times were not different (90 ± 24 min vs. 88 ± 25 min, $p = 0.3$, and 55 ± 13 min vs. 59 ± 13 min, $p = 0.4$). Levels of troponin I postoperatively were greater in the control patients compared with the RIPC group ($p = 0.04$), indicating greater myocardial injury in control patients. Postoperative inotropic requirement was greater in the control patients compared with RIPC patients at both 3 and 6 h (7.9 ± 4.7 vs. 10.9 ± 3.2, $p = 0.04$, and 7.3 ± 4.9 vs. 10.6 ± 3.9, $p = 0.03$, respectively). The RIPC group had significantly lower airway resistance at 6 h postoperatively ($p = 0.009$).

CONCLUSIONS This study demonstrates the myocardial protective effects of RIPC using a simple noninvasive technique of four 5-min cycles of lower limb ischemia and reperfusion. These novel data support the need for a larger study of RIPC in patients undergoing cardiac surgery. © Am Coll Cardiol 2006;47:2277–82) © 2006 by the American College of Cardiology Foundation

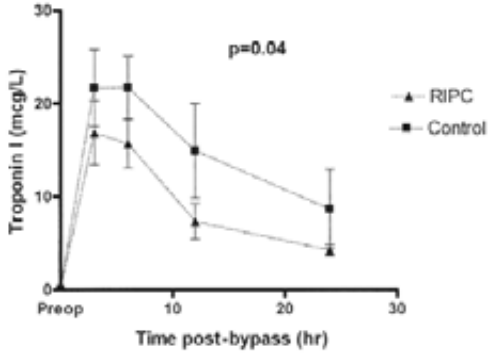


Figure 1. Pre- and postoperative levels of troponin I in remote ischemic preconditioning (RIPC) and control groups.

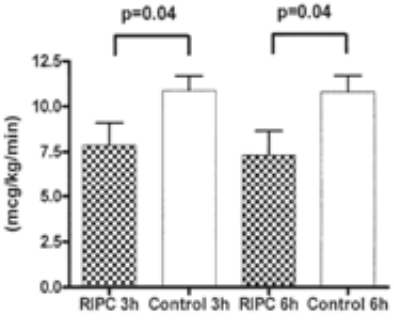


Figure 2. Postoperative inotrope scores in remote ischemic preconditioning (RIPC) and control groups.

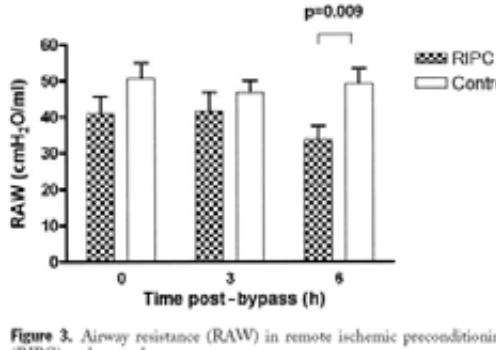


Figure 3. Airway resistance (RAW) in remote ischemic preconditioning (RIPC) and control groups.

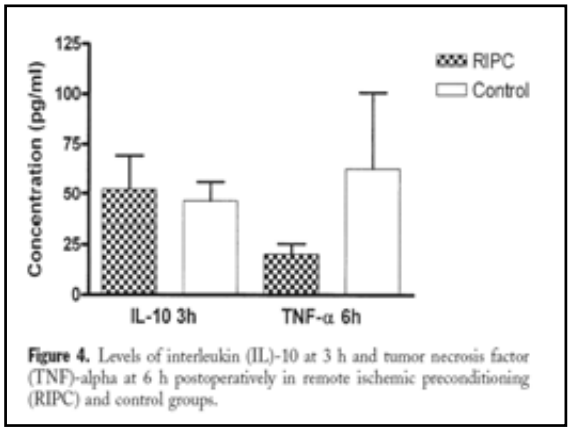
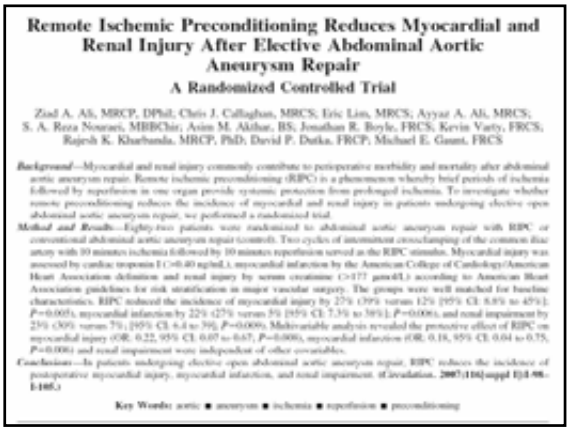


Figure 4. Levels of interleukin (IL)-10 at 3 h and tumor necrosis factor (TNF)-alpha at 6 h postoperatively in remote ischemic preconditioning (RIPC) and control groups.



Remote Ischemic Preconditioning Reduces Myocardial and Renal Injury After Elective Abdominal Aortic Aneurysm Repair

A Randomized Controlled Trial

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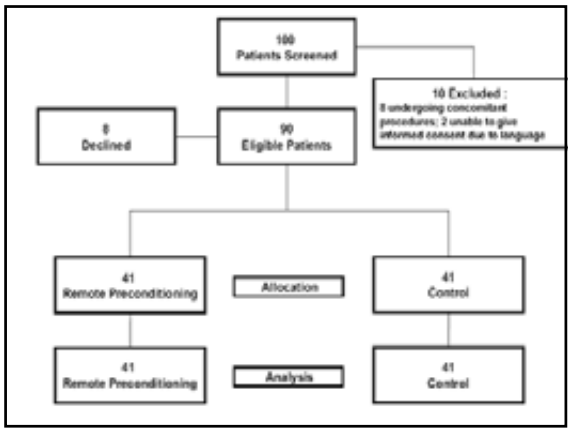
Background—Myocardial and renal injury commonly contribute to perioperative morbidity and mortality after abdominal aortic aneurysm repair. Remote ischemic preconditioning (RIPC) is a phenomenon whereby brief periods of ischemia followed by reperfusion in one organ provide systemic protection from prolonged ischemia. To investigate whether remote preconditioning reduces the incidence of myocardial and renal injury in patients undergoing elective open abdominal aortic aneurysm repair, we performed a randomized trial.

Method and Results—Eighty-two patients were randomized to abdominal aortic aneurysm repair with RIPC or conventional abdominal aortic aneurysm repair (control). Two cycles of intermittent cross-clamping of the common iliac artery with 10 minutes ischemia followed by 10 minutes reperfusion served as the RIPC stimulus. Myocardial injury was assessed by cardiac troponin I (>0.40 ng/mL), myocardial infarction by the American College of Cardiology/American Heart Association definition and renal injury by serum creatinine (>177 μmol/L) according to American Heart Association guidelines for risk stratification in major vascular surgery. The groups were well matched for baseline characteristics. RIPC reduced the incidence of myocardial injury by 27% (39% versus 12% [95% CI: 8.8% to 45%]; $P=0.005$), myocardial infarction by 22% (27% versus 5% [95% CI: 7.3% to 38%]; $P=0.006$), and renal impairment by 23% (30% versus 7% [95% CI: 6.4 to 39]; $P=0.009$). Multivariable analysis revealed the protective effect of RIPC on myocardial injury (OR: 0.22, 95% CI: 0.07 to 0.67; $P=0.008$), myocardial infarction (OR: 0.18, 95% CI: 0.04 to 0.75; $P=0.006$) and renal impairment were independent of other covariables.

Conclusions—In patients undergoing elective open abdominal aortic aneurysm repair, RIPC reduces the incidence of postoperative myocardial injury, myocardial infarction, and renal impairment. (Circulation. 2007;116[suppl I]:I-98–I-105.)

Key Words: aortic ■ aneurysm ■ ischemia ■ reperfusion ■ preconditioning



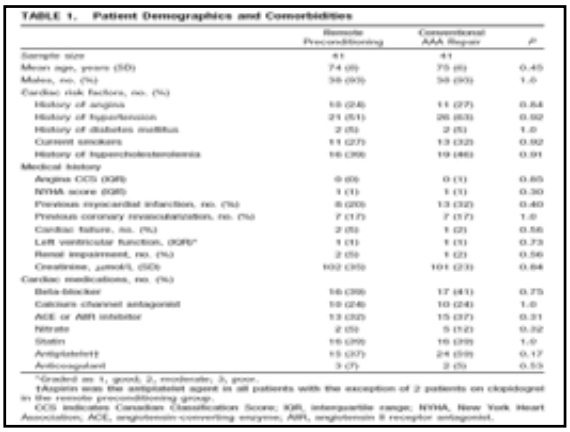


TABLE 1. Patient Demographics and Comorbidities

	Remote Preconditioning	Conventional AAA Repair	*P*
Sample size	41	41	
Mean age, years (SD)	74 (6)	75 (6)	0.45
Males, no. (%)	38 (93)	38 (93)	1.0
Cardiac risk factors, no. (%)			
History of angina	10 (24)	11 (27)	0.84
History of hypertension	21 (51)	26 (63)	0.32
History of diabetes mellitus	2 (5)	2 (5)	1.0
Current smokers	11 (27)	13 (32)	0.62
History of hypercholesterolemia	16 (39)	19 (46)	0.51
Medical history			
Angina CCS (IQR)	0 (0)	0 (1)	0.65
NYHA score (IQR)	1 (1)	1 (1)	0.30
Previous myocardial infarction, no. (%)	8 (20)	13 (32)	0.40
Previous coronary revascularization, no. (%)	7 (17)	7 (17)	1.0
Cardiac failure, no. (%)	2 (5)	1 (2)	0.56
Left ventricular function, (IQR)*	1 (1)	1 (1)	0.73
Renal impairment, no. (%)	2 (5)	1 (2)	0.56
Creatinine, μmol/L (SD)	102 (35)	101 (23)	0.84
Cardiac medications, no. (%)			
Beta-blocker	16 (39)	17 (41)	0.75
Calcium channel antagonist	10 (24)	10 (24)	1.0
ACE or ARB inhibitor	13 (32)	15 (37)	0.31
Nitrate	2 (5)	5 (12)	0.22
Statin	10 (25)	10 (25)	1.0
Antiplatelet†	15 (37)	24 (59)	0.17
Anticoagulant	3 (7)	2 (5)	0.53

*Graded as 1, good; 2, moderate; 3, poor.
†Aspirin was the antiplatelet agent in all patients with the exception of 2 patients on clopidogrel in the remote preconditioning group.
CCS indicates Canadian Classification Score; IQR, interquartile range; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist.

TABLE 2. Operative Characteristics and Postoperative Outcomes

	Remote Preconditioning	Conventional AAA Repair	*P*
Median AAA diameter, cm (IQR)	6.5 (2.3)	6.4 (1.4)	0.33
Median ASA score (IQR)	3 (1)	3 (1)	0.96
Median POSSUM Physiology Score, (IQR)	19 (10)	22 (9)	0.16
Median POSSUM Operative Score, (IQR)	20 (4)	20 (4)	0.77
Suprarenal clamp, no. (%)	3 (7)	5 (12)	0.46
Median blood loss, mL (IQR)	1200 (1125)	1426 (1219)	0.51
Median blood transfusion, mL (IQR)	250 (500)	0 (500)	0.36
Median intravenous fluid infusion, mL (IQR)	3750 (1702)	3982 (1093)	0.74
Median crossclamp time, minutes (IQR)	55 (18)	55 (19)	0.54
Median operating time, minutes (IQR)	202 (71)	180 (52)	0.75
ICU stay, days (IQR)	1 (1)	3 (3)	0.03
Postoperative stay, days (IQR)	9 (6)	11 (7)	0.23

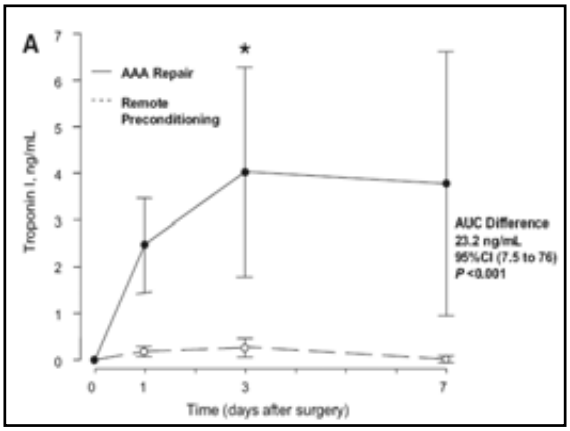
IQR indicates interquartile range; ASA, American Society of Anesthesiologists; POSSUM, physiological operative severity score for the enumeration of mortality and morbidity; ICU, intensive care

TABLE 3. Major Adverse Outcomes After Open AAA Repair

	Remote Preconditioning	Conventional AAA Repair	*P*
Sample size	41	41	
In-hospital			
Myocardial injury, no. (%)	5 (12)	16 (39)	0.005
Myocardial infarction, no. (%)	2 (5)	11 (27)	0.006
Renal impairment, no. (%)	3 (7)	12 (30)	0.009
In-hospital death, no. (%)	2 (5)	3 (7)	0.77

TABLE 4. Incidence and Timing of Postoperative Injury

	Remote Preconditioning	Conventional AAA Repair	*P*
Myocardial injury			
Day 1–new TnI elevation, no. (%)	5 (24)	12 (57)	0.05
Day 3–new TnI elevation, no. (%)	0 (0)	4 (19)	0.04
Day 7–new TnI elevation, no. (%)	0 (0)	0 (0)	…
Renal impairment			
Day 1–new renal impairment, no. (%)	3 (20)	8 (53)	0.10
Day 3–new renal impairment, no. (%)	0 (0)	4 (27)	0.04
Day 7–new renal impairment, no. (%)	0 (0)	0 (0)	…



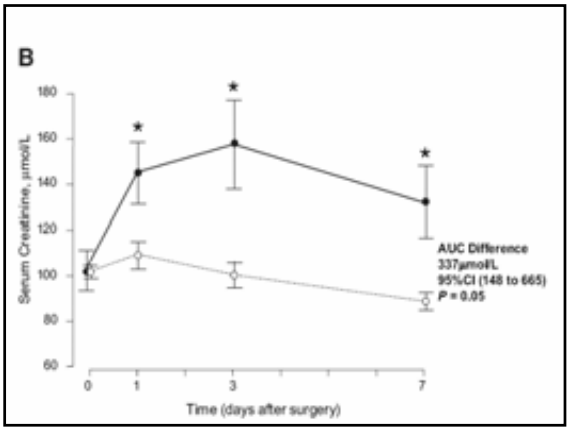


TABLE 5. Logistic Regression Analysis of Predictors of Myocardial Injury in Patients Undergoing AAA Repair

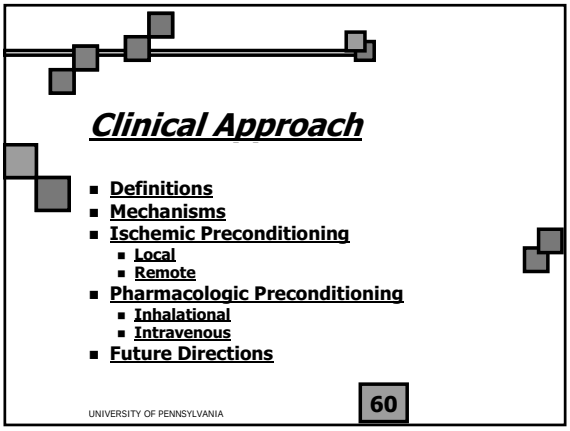
Variable	OR	95% CI	*P*
Univariable predictors of myocardial injury			
Remote preconditioning	0.22	0.07 to 0.67	0.008
Age, per year	1.3	0.87 to 1.8	0.23
Previous MI	3.1	1.0 to 9.3	0.05
Angina	2.5	0.82 to 7.7	0.10
New York Heart Association III/IV	5.1	0.75 to 35	0.10
Diabetes mellitus	0.72	0.06 to 8.4	0.79
Hypertension	0.74	0.24 to 2.3	0.60
Smoking	0.47	0.14 to 1.6	0.24
Hypercholesterolemia	1.4	0.48 to 4.1	0.53
Antiplatelet therapy	4.0	1.2 to 14	0.03
POSSUM Risk Score, per unit	1.1	0.99 to 1.2	0.13
Total operative time, per minute	1.0	0.99 to 1.0	0.49
Total crossclamp time, per minute	0.97	0.93 to 1.0	0.16
Aneurysm size, per cm	1.3	0.87 to 1.8	0.23
Postoperative renal impairment	3.2	1.0 to 10	0.05
Multivariable predictors of myocardial injury			
Remote preconditioning	0.22	0.07 to 0.67	0.008

POSSUM indicates physiological operative severity score for the enumeration of mortality and morbidity.

TABLE 6. Logistic Regression Analysis of Predictors of Renal Impairment in Patients Undergoing AAA Repair

Variable	OR	95% CI	*P*
Univariable predictors of renal impairment			
Remote preconditioning	0.18	0.05 to 0.71	0.01
Suprarenal aortic crossclamp	5.5	1.5 to 21	0.01
Preoperative creatinine levels	1.0	1.0 to 1.1	0.06
Previous MI	2.0	0.60 to 6.6	0.26
Angina	1.2	0.37 to 4.2	0.72
New York Heart Association III/IV	25	2.4 to 267	0.007
Diabetes mellitus	1.3	0.37 to 4.2	0.72
Hypertension	1.1	0.32 to 3.5	0.93
Smoking	0.25	0.05 to 1.2	0.09
Hypercholesterolemia	1.3	0.45 to 4.0	0.68
POSSUM Risk Score, per unit	1.1	1.0 to 1.3	0.08
Total operative time, per minute	1.0	0.99 to 1.0	0.73
Total crossclamp time, per minute	1.0	0.97 to 1.0	0.99
Aneurysm size, per cm	1.4	0.94 to 2.1	0.10
Multivariable predictors of renal impairment			
Remote preconditioning	0.18	0.05 to 0.71	0.01
Suprarenal aortic crossclamp	5.8	1.3 to 26	0.02
Preoperative creatinine levels	1.0033	1.0023 to 1.0660	0.04

POSSUM indicates physiological operative severity score for the enumeration of mortality and morbidity.



ACC/AHA Guideline

ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery)

Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery

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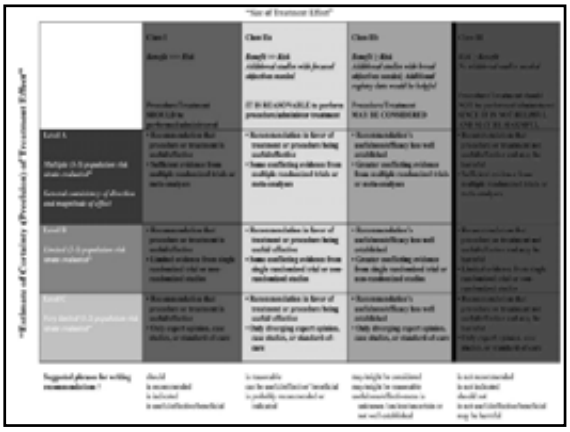


"Size of Treatment Effect"

"Estimate of Certainty (Precision) of Treatment Effect"

	Class I Benefit >>> Risk Procedure/Treatment SHOULD be performed/administered	Class IIa Benefit >> Risk additional studies with focused objectives needed IT IS REASONABLE to perform procedure/administer treatment	Class IIb Benefit ≥ Risk additional studies with broad objectives needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	Class III Risk ≥ Benefit No additional studies needed Procedure/Treatment SHOULD NOT BE PERFORMED/ADMINISTERED SINCE IT IS NOT BELIEVED TO BE BENEFICIAL
Level A Multiple (3-5) populations risk/ strata evaluated* General consistency of direction and magnitude of effect	• Recommendation that procedure or treatment is useful/effective • Sufficient evidence from multiple randomized trials or meta-analyses	• Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from multiple randomized trials or meta-analyses	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from multiple randomized trials or meta-analyses	• Recommendation that procedure or treatment not useful/effective and may be harmful • Sufficient evidence from multiple randomized trials or meta-analyses
Level B Limited (2-3 populations risk/ strata evaluated* Some inconsistency of direction and magnitude of effect	• Recommendation that procedure or treatment is useful/effective • Limited evidence from single randomized trial or non-randomized studies	• Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from single randomized trial or non-randomized studies	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from single randomized trial or non-randomized studies	• Recommendation that procedure or treatment not useful/effective and may be harmful • Limited evidence from single randomized trial or non-randomized studies
Level C Very limited (1 population risk/ strata evaluated* Not applicable	• Recommendation that procedure or treatment is useful/effective • Only expert opinion, case studies, or standard-of-care	• Recommendation in favor of treatment or procedure being useful/effective • Only divergent expert opinion, case studies, or standard-of-care	• Recommendation's usefulness/efficacy less well established • Only divergent expert opinion, case studies, or standard-of-care	• Recommendation that procedure or treatment not useful/effective and may be harmful • Only expert opinion, case studies, or standard-of-care
Suggested phrase for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

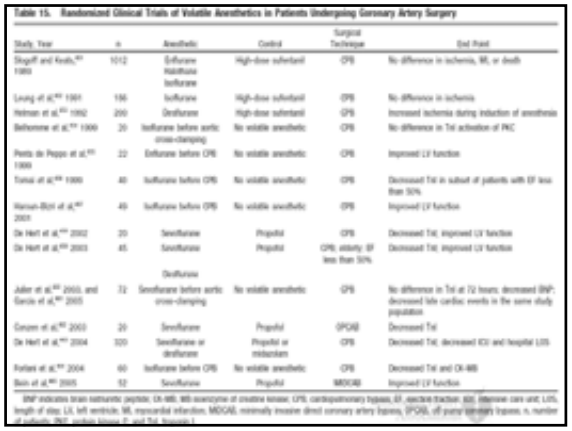
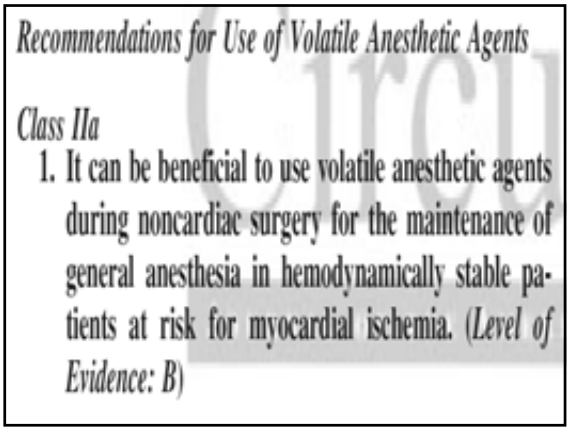


Table 15. Randomized Clinical Trials of Volatile Anesthetics in Patients Undergoing Coronary Artery Surgery

Study, Year	n	Anesthetic	Control	Surgical Technique	End Point
Shapiff and Kraft,[43] 1999	1012	Enflurane Halothane Isoflurane	High-dose sufentanil	CPB	No difference in ischemia, MI, or death
Leung et al,[44] 1991	156	Isoflurane	High-dose sufentanil	CPB	No difference in ischemia
Hetman et al,[45] 1992	200	Desflurane	High-dose sufentanil	CPB	Increased ischemia during induction of anesthesia
Belhomme et al,[46] 1999	20	Isoflurane before aortic cross-clamping	No volatile anesthetic	CPB	No difference in TnI activation of PKC
Pretta de Peppo et al,[47] 1999	22	Enflurane before CPB	No volatile anesthetic	CPB	Improved LV function
Tomai et al,[48] 1999	40	Isoflurane before CPB	No volatile anesthetic	CPB	Decreased TnI in subset of patients with EF less than 50%
Hansen-Bizzi et al,[49] 2001	40	Isoflurane before CPB	No volatile anesthetic	CPB	Improved LV function
De Hert et al,[50] 2002	20	Sevoflurane	Propofol	CPB	Decreased TnI; improved LV function
De Hert et al,[51] 2003	45	Sevoflurane Desflurane	Propofol	CPB; elderly; EF less than 50%	Decreased TnI; improved LV function
Julier et al,[52] 2003, and Garcia et al,[53] 2005	72	Sevoflurane before aortic cross-clamping	No volatile anesthetic	CPB	No difference in TnI at 72 hours; decreased BNP; decreased late cardiac events in the same study population
Conzen et al,[54] 2003	20	Sevoflurane	Propofol	OPCAB	Decreased TnI
De Hert et al,[55] 2004	320	Sevoflurane or desflurane	Propofol or midazolam	CPB	Decreased TnI; decreased ICU and hospital LOS
Forlani et al,[56] 2004	60	Isoflurane before CPB	No volatile anesthetic	CPB	Decreased TnI and CK-MB
Bein et al,[57] 2005	52	Sevoflurane	Propofol	MIDCAB	Improved LV function

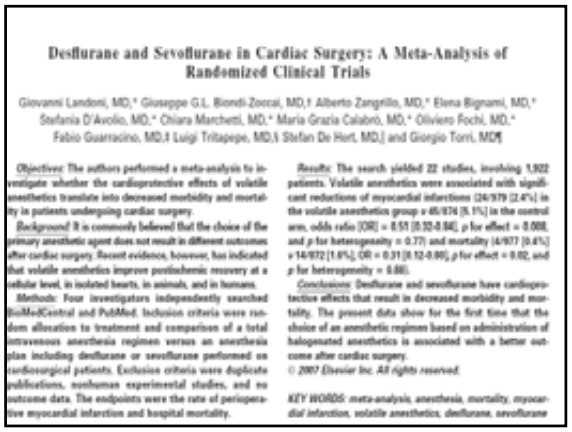
BNP indicates brain natriuretic peptide; CK-MB, MB isoenzyme of creatine kinase; CPB, cardiopulmonary bypass; EF, ejection fraction; ICU, intensive care unit; LOS, length of stay; LV, left ventricle; MI, myocardial infarction; MIDCAB, minimally invasive direct coronary artery bypass; OPCAB, off-pump coronary bypass; n, number of patients; PKC, protein kinase C; and TnI, troponin I.



Recommendations for Use of Volatile Anesthetic Agents

Class IIa

1. It can be beneficial to use volatile anesthetic agents during noncardiac surgery for the maintenance of general anesthesia in hemodynamically stable patients at risk for myocardial ischemia. (*Level of Evidence: B*)



Desflurane and Sevoflurane in Cardiac Surgery: A Meta-Analysis of Randomized Clinical Trials

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Objectives: The authors performed a meta-analysis to investigate whether the cardioprotective effects of volatile anesthetics translate into decreased morbidity and mortality in patients undergoing cardiac surgery.

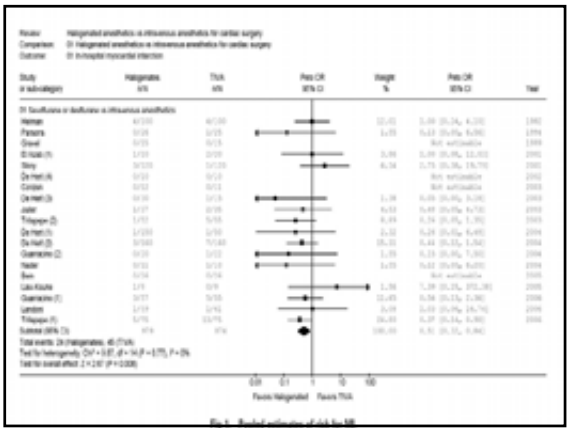
Background: It is commonly believed that the choice of the primary anesthetic agent does not result in different outcomes after cardiac surgery. Recent evidence, however, has indicated that volatile anesthetics improve postischemic recovery at a cellular level, in isolated hearts, in animals, and in humans.

Methods: Four investigators independently searched BioMedCentral and PubMed. Inclusion criteria were random allocation to treatment and comparison of a total intravenous anesthesia regimen versus an anesthesia plan including desflurane or sevoflurane performed on cardiosurgical patients. Exclusion criteria were duplicate publications, nonhuman experimental studies, and no outcome data. The endpoints were the rate of perioperative myocardial infarction and hospital mortality.

Results: The search yielded 22 studies, involving 1,932 patients. Volatile anesthetics were associated with significant reductions of myocardial infarctions (24/979 [2.4%] in the volatile anesthetics group v 65/974 [6.1%] in the control arm, odds ratio [OR] = 0.51 [0.32-0.84], *p* for effect = 0.008, and *p* for heterogeneity = 0.77) and mortality (4/977 [0.4%] v 14/972 [1.6%], OR = 0.31 [0.12-0.80], *p* for effect = 0.02, and *p* for heterogeneity = 0.88).

Conclusions: Desflurane and sevoflurane have cardioprotective effects that result in decreased morbidity and mortality. The present data show for the first time that the choice of an anesthetic regimen based on administration of halogenated anesthetics is associated with a better outcome after cardiac surgery.

KEY WORDS: meta-analysis, anesthesia, mortality, myocardial infarction, volatile anesthetics, desflurane, sevoflurane



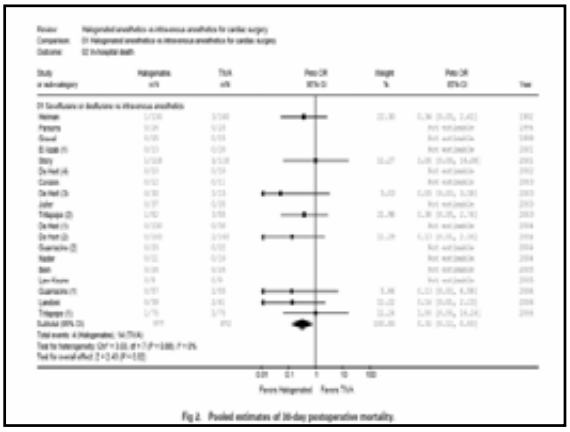


Fig 2. Pooled estimates of 30-day postoperative mortality.

BJA

CARDIOVASCULAR

Sevoflurane preconditioning at 1 MAC only provides limited protection in patients undergoing coronary artery bypass surgery: a randomized bi-centre trial

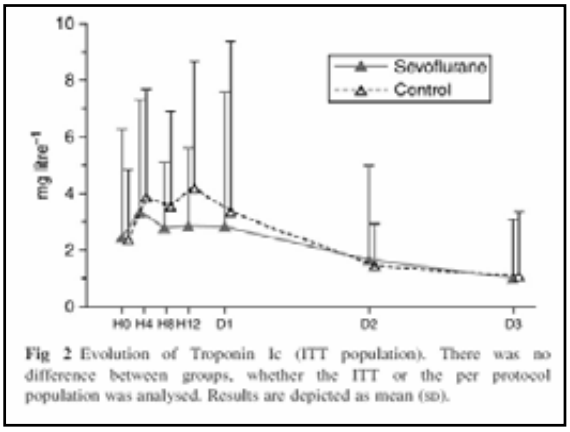
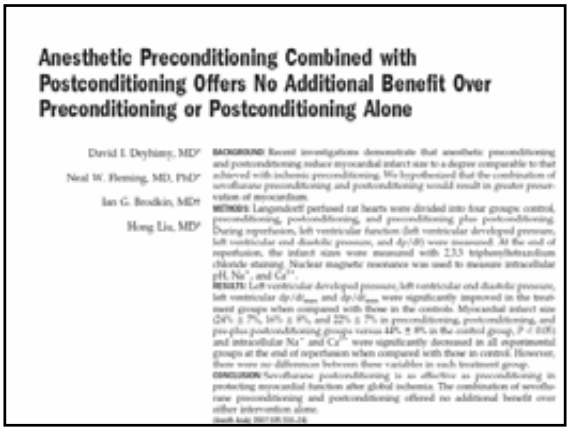


Fig 2 Evolution of Troponin Ic (ITT population). There was no difference between groups, whether the ITT or the per protocol population was analysed. Results are depicted as mean (SD).



Anesthetic Preconditioning Combined with Postconditioning Offers No Additional Benefit Over Preconditioning or Postconditioning Alone

David I. Deyhimy, MD*
Neal W. Fleming, MD, PhD*
Ian G. Brodkin, MD†
Hong Liu, MD*

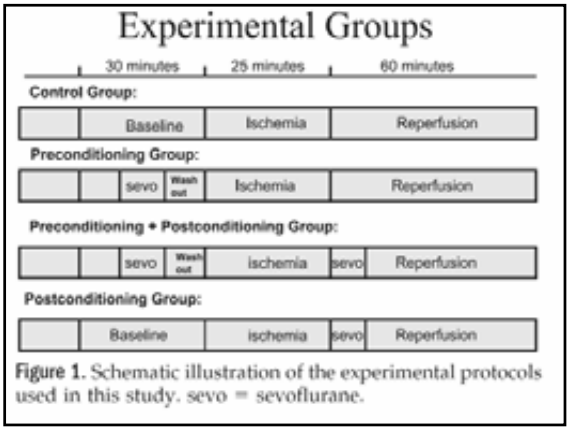
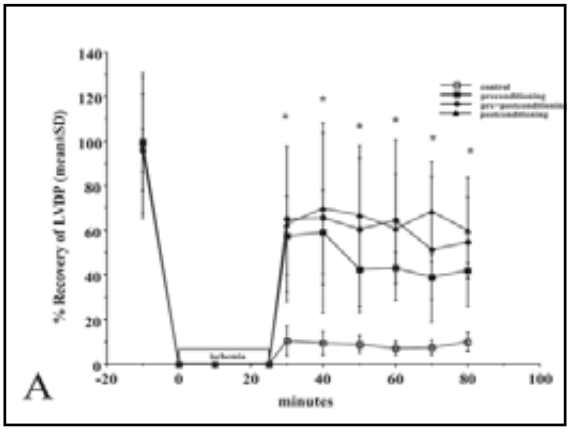


Figure 1. Schematic illustration of the experimental protocols used in this study. sevo = sevoflurane.



BJA

CARDIOVASCULAR

Preconditioning with sevoflurane decreases PECAM-1 expression and improves one-year cardiovascular outcome in coronary artery bypass graft surgery

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Background. Cardiac preconditioning is thought to be involved in the observed decreased coronary artery reocclusion rate in patients with angina preceding myocardial infarction. We prospectively examined whether preconditioning by sevoflurane would decrease late cardiac events in patients undergoing coronary artery bypass graft (CABG) surgery.

Methods. Seventy-two patients scheduled for elective CABG surgery were randomized to preconditioning by sevoflurane (10 min at 4 vol%) or placebo. For all patients, follow-up of adverse cardiac events was obtained 6 and 12 months after surgery. Transcript levels for platelet–endothelial cell adhesion molecule-1 (PECAM-1/CD31), cardiac and heat shock protein 70 (Hsp70) were determined in atrial biopsies after sevoflurane preconditioning.

Results. Pharmacological preconditioning by sevoflurane reduced the incidence of late cardiac events during the first year after CABG surgery (sevoflurane 3% vs 17% in the placebo group, log-rank test, $P=0.038$). One patient in the sevoflurane group and three patients in the placebo group experienced new episodes of congestive heart failure and three additional patients had coronary artery reocclusion. Perioperative peak concentrations for myocardial injury markers were higher in patients with subsequent late cardiac events (NT-proBNP, 9031 (4133) vs 3049 (1706) ng litre^{-1}, $P=0.001$; cTnT, 1.91 (0.88) vs 0.46 (0.29) μg litre^{-1}, $P=0.001$). Transcript levels were reduced for PECAM-1 and increased for cardiac but unchanged for Hsp70 in atrial biopsies after sevoflurane preconditioning.

Conclusions. This prospective randomized clinical study provides evidence of a protective role for pharmacological preconditioning by sevoflurane in late cardiac events in CABG patients, which may be related to favourable transcriptional changes in pro- and antiapoptotic proteins.

Br J Anaesth 2005; **94**: 159–65

Keywords: cell adhesion molecules; heart, cardiac preconditioning; surgery, perioperative outcome

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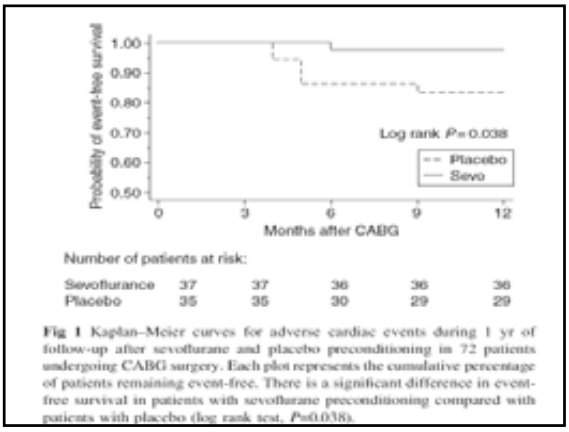

Fig 1 Kaplan–Meier curves for adverse cardiac events during 1 yr of follow-up after sevoflurane and placebo preconditioning in 72 patients undergoing CABG surgery. Each plot represents the cumulative percentage of patients remaining event-free. There is a significant difference in event-free survival in patients with sevoflurane preconditioning compared with patients with placebo (log rank test, $P=0.038$).

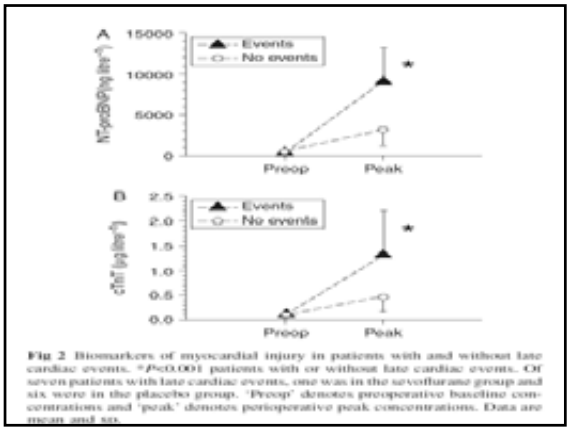

Fig 2 Biomarkers of myocardial injury in patients with and without late cardiac events. *$P<0.001$ patients with or without late cardiac events. Of seven patients with late cardiac events, one was in the sevoflurane group and six were in the placebo group. 'Preop' denotes preoperative baseline concentrations and 'peak' denotes perioperative peak concentrations. Data are mean and SD.

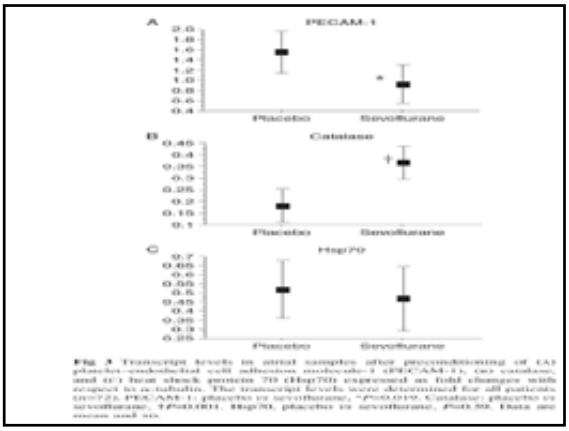

Fig 3 Transcript levels in atrial samples after preconditioning of (A) platelet–endothelial cell adhesion molecule-1 (PECAM-1), (B) catalase and (C) heat shock protein 70 (Hsp70) expressed as fold changes with respect to α-tubulin. The transcript levels were determined for all patients ($n=72$). PECAM-1: placebo vs sevoflurane, *$P=0.019$. Catalase: placebo vs sevoflurane, †$P=0.001$. Hsp70, placebo vs sevoflurane, $P=0.59$. Data are mean and SD.

Desflurane preconditioning in coronary artery bypass graft surgery: a double-blinded, randomised and placebo-controlled study

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Abstract

Background: Recent clinical and experimental data indicate that volatile anesthetics may precondition myocardium against ischaemia and infarction. The present clinical trial was designed to verify the cardioprotective effects of desflurane in patients undergoing elective coronary artery bypass surgery. It was hypothesized that desflurane preconditioning would decrease perioperative release of troponin I and brain natriuretic peptide (NT-proBNP). Besides, we have hypothesized that desflurane preconditioning would preserve the myocardium from the dysfunction following cardioplegic arrest. **Methods:** Twenty-eight patients were randomly divided into two groups: Control group (14 patients) and Desflurane group (14 patients). In Desflurane group (Des) patients, preconditioning was elicited after the onset of cardiopulmonary bypass via a 5-min exposure to desflurane (2.5 minimum alveolar concentration), followed by a 10-min washout before aortic cross-clamping and cardioplegic arrest. The control group (C) patients underwent an equivalent period (15 min) of pre-arrest desflurane-free bypass. Haemodynamic measurements were obtained at six different times. The biochemistry markers of cellular damage and myocardial dysfunction (troponin I, NT-proBNP) were determined. Left ventricular (LV) function was assessed using tissue Doppler imaging (TDI) of mitral annulus. Two-factor repeated-measures analysis of variance was used to evaluate differences over time between groups for all parameters determined in plasma samples and for all TDI derived variables. **Results:** After surgery, both the troponin I values (2.64 ± 1.09 ng/ml vs 1.46 ± 0.77 ng/ml, $p < 0.01$ after 24 h and 1.42 ± 0.96 ng/ml vs 1.00 ± 0.34 ng/ml, $p < 0.01$ after 72 h respectively) and those of the NT-proBNP (2167 ± 282.9 ng/l vs 885.4 ± 117.35 ng/l, $p < 0.01$ after 24 h and 3097.9 ± 226.2 vs 1310.6 ± 312.67 ng/l, $p < 0.01$ after 72 h respectively) were less in the desflurane-treated patients. The values of TDI of mitral annulus were constantly better in desflurane-treated patients. **Conclusions:** We can conclude that the use of desflurane in these patients provides a pharmacological preconditioning so as to reduce myocardial necrosis and improve the cardiac performance in the postoperative period.

Keywords: Heart; Coronary artery bypass; Myocardial preservation; Anaesthetics volatile; Desflurane

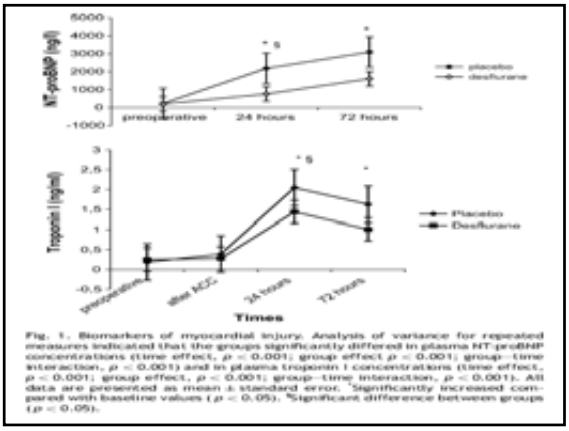
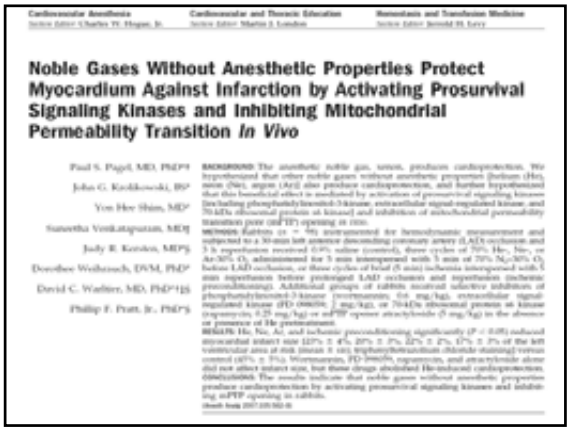


Fig. 1. Biomarkers of myocardial injury. Analysis of variance for repeated measures indicated that the groups significantly differed in plasma NT-proBNP concentrations (time effect, $p < 0.001$; group effect $p = 0.001$; group–time interaction, $p = 0.001$) and in plasma troponin I concentrations (time effect, $p < 0.001$; group effect, $p < 0.001$; group–time interaction, $p < 0.001$). All data are presented as mean ± standard error. *Significantly increased compared with baseline values ($p < 0.05$). §Significant difference between groups ($p < 0.05$).



Cardiovascular Anesthesia | Cardiovascular and Thoracic Education | Hemostasis and Transfusion Medicine

Noble Gases Without Anesthetic Properties Protect Myocardium Against Infarction by Activating Prosurvival Signaling Kinases and Inhibiting Mitochondrial Permeability Transition *In Vivo*

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Philip F. Pratt, Jr., PhD*§

BACKGROUND: The anesthetic noble gas, xenon, produces cardioprotection. We hypothesized that other noble gases without anesthetic properties [helium (He), neon (Ne), argon (Ar)] also produce cardioprotection, and further hypothesized that this beneficial effect is mediated by activation of prosurvival signaling kinases [including phosphatidylinositol-3-kinase, extracellular signal-regulated kinase, and 70 kDa ribosomal protein s6 kinase] and inhibition of mitochondrial permeability transition pore (mPTP) opening in vivo.

METHODS: Rabbits (n = 94), instrumented for hemodynamic measurement and subjected to a 30-min left anterior descending coronary artery (LAD) occlusion and 3 h reperfusion received 0.9% saline (control), three cycles of 70% He-, Ne-, or Ar-30% O_2 administered for 5 min interspersed with 5 min of 70% N_2-30% O_2 before LAD occlusion, or three cycles of brief (5 min) ischemia interspersed with 5 min reperfusion before prolonged LAD occlusion and reperfusion (ischemic preconditioning). Additional groups of rabbits received selective inhibitors of phosphatidylinositol-3-kinase (wortmannin, 0.6 mg/kg), extracellular signal-regulated kinase (PD 098059, 3 mg/kg), or 70-kDa ribosomal protein s6 kinase (rapamycin, 0.25 mg/kg) or mPTP opener atractyloside (5 mg/kg) in the absence or presence of He pretreatment.

RESULTS: He, Ne, Ar, and ischemic preconditioning significantly ($P < 0.05$) reduced myocardial infarct size [(27% ± 4%, 25% ± 3%, 22% ± 2%, 17% ± 3% of the left ventricular area at risk (mean ± sd); triphenyltetrazolium chloride staining] versus control (45% ± 5%). Wortmannin, PD 098059, rapamycin, and atractyloside alone did not affect infarct size, but these drugs abolished He-induced cardioprotection.

CONCLUSIONS: The results indicate that noble gases without anesthetic properties produce cardioprotection by activating prosurvival signaling kinases and inhibiting mPTP opening in rabbits.

(Anesth Analg 2007;105:562–9)

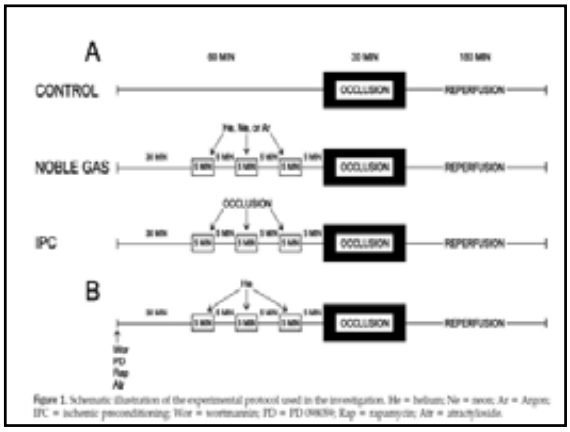
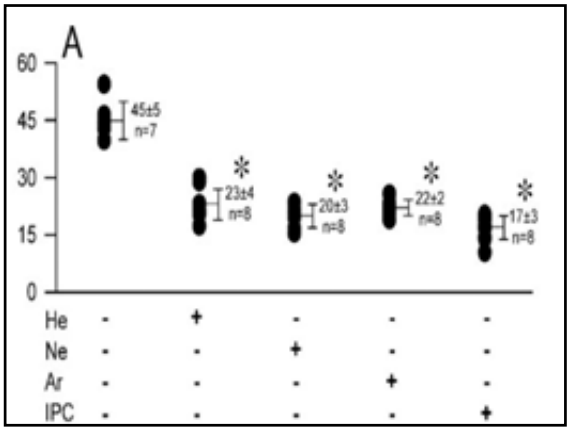
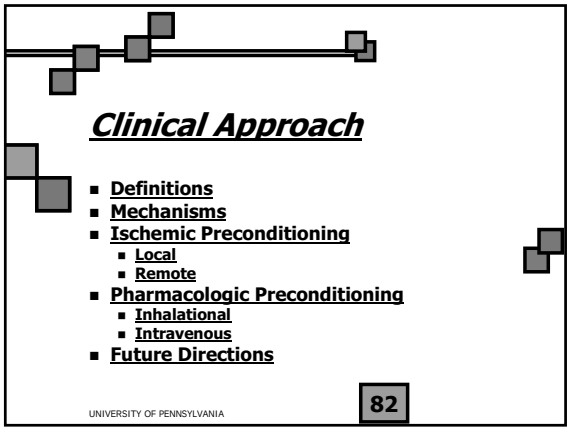


Figure 1. Schematic illustration of the experimental protocol used in the investigation. He = helium; Ne = neon; Ar = Argon; IPC = ischemic preconditioning; Wor = wortmannin; PD = PD 098059; Rap = rapamycin; Atr = atractyloside.





BJA

Remifentanil preconditioning confers delayed cardioprotection in the rat[1]

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Background. Preconditioning with remifentanil (RPC) provides immediate cardioprotection in rats via all three types of opioid (OP) receptor. This study sought to investigate whether remifentanil also confers delayed cardioprotection via OP receptors.

Methods. Male rats received preconditioning either by ischaemia (IPC; 5 min occlusion, 5 min reperfusion ×3) or with remifentanil (RPC, 1, 5, 10, and 20 μg kg^{-1} min^{-1}, 20 min infusion). After 30 h, all animals were subjected to 30 min occlusion of the left coronary artery and 3 h of reperfusion. Subsequently, the time-course effect of RPC (10 μg kg^{-1} min^{-1}, 20 min infusion) was determined at 12, 16, 24, 32, 36, and 48 h intervals, using the same experimental procedure. The effect of RPC (10 μg kg^{-1} min^{-1}, 20 min infusion) and IPC in the presence of selective OP receptor antagonists was evaluated at the 24 h interval. Infarct size (IS), as a percentage of the area at risk (AAR), was determined.

Results. Pre-treatment with remifentanil at 1, 5, 10, and 20 μg kg^{-1} min^{-1} significantly reduced the IS/AAR at 24 h with the maximum effect at 10 μg kg^{-1} min^{-1}. Remifentanil at 10 μg kg^{-1} min^{-1} significantly reduced the IS at 12 h [20.5 (sd 9.1)%], 24 h [16.1 (3.6)%], 36 h [19.5 (3.6)%], 32 h [21.2 (9.1)%], and 36 h [26.0 (9.6)%] after drug administration. The maximal reduction in IS was seen at 24 h and the effect completely disappeared at 48 h [34.4 (9.6)%]. The protective effect of RPC was abolished or significantly attenuated by blockade of any of the three OP receptors with selective antagonists.

Conclusions. Like IPC, remifentanil produces delayed cardioprotection in anaesthetized rats 12–36 h after administration. The protective effect is mediated via all three OP receptors.

Br J Anaesth 2007; 99: 631–8

Keywords: analgesics, opioid; remifentanil; hearts; ischaemia; rat; receptors, opioid

Accepted for publication: June 13, 2007

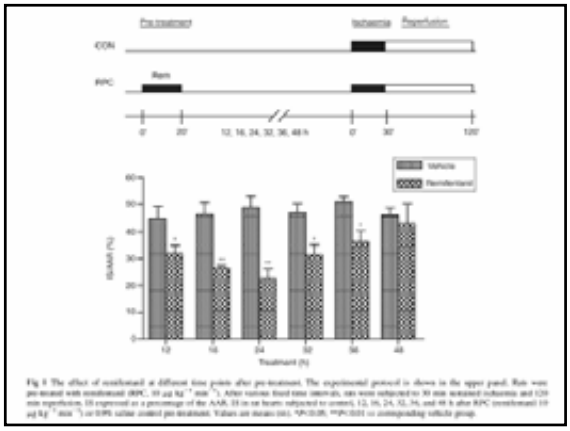

Fig 1 The effect of remifentanil at different time points after pre-treatment. The experimental protocol is shown in the upper panel. Rats were pre-treated with remifentanil (RPC, 10 μg kg^{-1} min^{-1}). After various fixed time intervals, rats were subjected to 30 min sustained ischaemia and 120 min reperfusion. IS expressed as a percentage of the AAR. IS in rat hearts subjected to control, 12, 16, 24, 32, 36, and 48 h after RPC (remifentanil 10 μg kg^{-1} min^{-1}) or 0.9% saline control pre-treatment. Values are means (SD). *P<0.05, **P<0.01 vs corresponding vehicle group.

BJA

Preconditioning effects of levosimendan in coronary artery bypass grafting—a pilot study

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Background. The calcium sensitizer levosimendan protects against myocardial ischaemia and reperfusion injury in animal models.

Methods. The present pilot study investigated whether a short infusion before coronary artery bypass grafting (CABG) would protect the myocardium and improve postoperative haemodynamics. Twenty-four patients with stable angina undergoing elective CABG surgery were randomized to receive either placebo or levosimendan (0.4 μg kg^{-1}) infused i.v. over a 10 min period just before placing the patient on cardiopulmonary bypass.

Results. Perioperative haemodynamic variables, concentrations of cardiac troponin I over the 48 h postoperative period, and clinical outcomes were assessed. There were no adverse effects related to levosimendan. Compared with control patients, levosimendan-treated patients had lower postoperative troponin I concentrations ($P<0.05$) and a higher cardiac index ($P<0.05$).

Conclusion. Patients receiving a short infusion of levosimendan before CABG showed evidence of less myocardial damage, suggestive of a preconditioning effect. Larger outcome studies are thus indicated to confirm benefit.

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Keywords: anaesthesia, cardiac; complications, myocardial infarction; heart, ischaemia; heart, myocardial function; muscle cardiac, contractility

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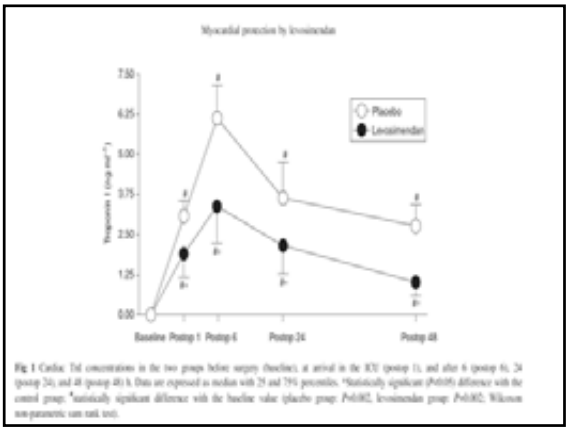

Fig 1 Cardiac Tnl concentrations in the two groups before surgery (baseline), at arrival in the ICU (postop 1), and after 6 (postop 6), 24 (postop 24), and 48 (postop 48) h. Data are expressed as median with 25 and 75% percentiles. *Statistically significant ($P<0.05$) difference with the control group. †Statistically significant difference with the baseline value (placebo group: $P<0.002$, levosimendan group: $P<0.002$, Wilcoxon non-parametric rank test).

The Influence of Propofol Versus Sevoflurane Anesthesia on Outcome in 10,535 Cardiac Surgical Procedures

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Objective: The purpose of this study was to evaluate the possible cardioprotective effect of sevoflurane versus propofol anesthesia in patients undergoing cardiac surgery.

Methods: Ten thousand five hundred thirty-five consecutive single cardiac surgical procedures from 3 cardiac centers were reported to a common registry from 1999 to 2005. The registry was established by the National Board of Health, and reporting was obligatory for all public heart centers in Denmark. The patients were stratified according to preoperative risk factors (EuroSCORE parameters). The outcome parameters were 30-day mortality, the incidence of postoperative myocardial infarction, and the incidence of postoperative arrhythmias.

Results: Overall, the 30-day mortality was lower after sevoflurane (2.04%) versus propofol (3.30%), although not significantly so ($p = 0.16$). No difference was found in the incidence of postoperative myocardial infarction (sevoflurane, 7.76%/propofol, 7.47%). Patients with preoperative unstable angina and/or recent myocardial infarction, and thus already "preconditioned," did not show any difference in mortality between anesthetic groups, whereas patients without these predictors showed a lower postoperative mortality after sevoflurane (2.28% v 3.14%, $p = 0.015$), which can at least partly be explained by a preconditioning-like effect. The data suggest that patients suffering relatively severe preoperative ischemic stress benefited from propofol anesthesia, which can be related to the antioxidant effects of propofol. Patients in the sevoflurane group had a higher incidence of postoperative atrial fibrillation (28.75% v 24.67%, $p < 0.001$), whereas patients in the propofol group showed a higher incidence of all other arrhythmias.

Conclusion: Sevoflurane and propofol both possess some, although different, cardioprotective properties. Sevoflurane appears to be superior to propofol in patients with little or no ischemic heart disease, such as nonconsonary artery bypass graft (CABG) surgery and CABG surgery without severe preoperative ischemia, whereas propofol seems superior in patients with severe ischemia, cardiovascular instability, or in acute/urgent surgery.

KEY WORDS: risk assessment, risk factors, anesthetic techniques, sevoflurane, propofol, mortality, arrhythmias

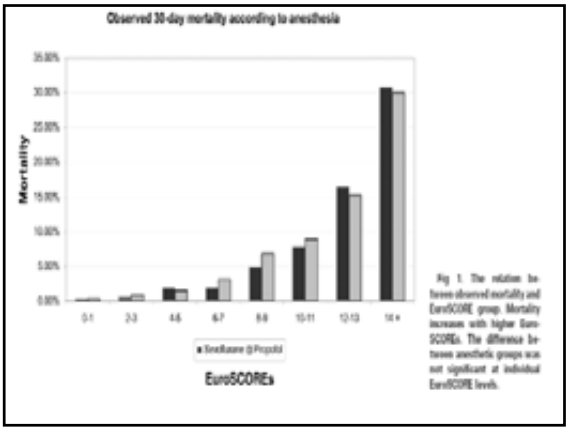

Fig 1 The relation between observed mortality and EuroSCORE group. Mortality increases with higher EuroSCOREs. The difference between anesthetic groups was not significant at individual EuroSCORE levels.