

Anaesthetics and cardiac preconditioning. Part II.

Clinical implications

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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.

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Brief episodes of sublethal cardiac ischaemia protect against subsequent prolonged ischaemia. The phenomenon is termed ‘preconditioning’ and represents an endogenous protective mechanism inherent to all tissues with high-energy consumption. Preconditioning has been described in the kidney,⁹⁵ liver,⁷³ small intestine,⁶⁷ lung⁵² and brain.²⁷ It is tempting to speculate that this protective adaptive mechanism developed during the evolutionary process to increase cell survival within specialized tissues in response to temporal shortages of nutrient supply and repetitive noxious stimuli.

Part I of this review¹⁰⁸ focused on the important signalling steps and the cytoprotective mechanisms underlying ischaemic, pharmacological and anaesthetic-induced preconditioning in cardiac tissue. Particularly, it noted that volatile anaesthetics and opioids induce cardiac preconditioning. The signalling cascades involve alterations in nitric oxide and free oxygen radical formation and several G-protein-coupled receptors (adenosine and α/β -adrenergic receptors), and point to the key role of protein kinase C (PKC) as a signal amplifier and to the K_{ATP} channels as the main end-effectors in preconditioning. Laboratory investi-

gations also stress the concept that anaesthetics may precondition endothelial and smooth muscle cells, the main components of blood vessels.¹⁷ As blood vessels are responsible for the supply of nutrients and oxygen to all tissues, anaesthetic preconditioning might beneficially affect a much wider variety of organs, including the brain, spinal cord, liver and kidneys.

Part II of this review discusses experimental studies with clinical implications, and the clinical studies that provide evidence for perioperative cardiac preconditioning, particularly anaesthetic-induced preconditioning. In addition, the modulatory effects of anaesthetics and perioperative medication and the influence of disease states on cardiac preconditioning are reviewed.

Evidence of preconditioning in humans

Coronary angioplasty, unstable and ‘warm-up’ angina

The myocardial adaptation observed in patients undergoing percutaneous transluminal coronary angioplasty (PTCA)

strongly suggests that preconditioning also occurs in humans.¹⁸ Most, but not all,¹⁹ studies have demonstrated increased tolerance to ischaemia with repeated balloon inflations. A single 90-s balloon occlusion immediately before angioplasty markedly decreased periprocedural release of phosphocreatine kinase.⁴⁵ Unstable angina occurring in the 24 h before infarction can precondition the heart,⁶⁸ and preinfarct angina led to improved long-term survival compared with patients who were asymptomatic before the ischaemic insult.⁴² Both observations may reflect classic or delayed preconditioning. Recently, Leeser and colleagues⁵⁰ found that nitroglycerin infusion 24 h before PTCA with three 2-min balloon inflations interspersed with 5 min of reperfusion markedly enhanced tolerance of ischaemia, using ST-segment changes, ischaemic dysfunction and chest pain as the study end-points. This is the first study which provides evidence that delayed preconditioning also occurs in humans. It also showed that collateral vessel recruitment is not involved in the observed improvement and that early preconditioning effects, as assessed by ST-segment changes, occur after only two 2-min episodes of ischaemia. Another clinical correlate of preconditioning is so-called warm-up angina, a phenomenon which describes relief of anginal pain in response to increased duration of exercise.⁶⁵ Consistent with an early and delayed window of protection, patients with stable angina exhibit less stunning after exercise-induced myocardial ischaemia, or if a preceding exercise was performed, they had improved exercise tolerance 24 h after the exercise.¹⁵

Ischaemic preconditioning in coronary artery bypass surgery

On-pump procedures

Patients undergoing coronary artery bypass graft (CABG) surgery are an ideal model for studying the effects of preconditioning. Intermittent ischaemia achieved by aortic cross-clamping in a fibrillating heart during CABG surgery was used by Jenkins and colleagues³⁴ to evaluate the ischaemic preconditioning effect. Two cycles of 3-min ischaemic episodes (induced by intermittent aortic cross-clamping and pacing the heart at 90 beats min⁻¹), each followed by 2 min of reperfusion before a prolonged ischaemia of 10 min (induced by aortic cross-clamping), led to increased ATP preservation and decreased troponin T release compared with untreated patients. A 1-min episode of aortic cross-clamping before cold-blood cardioplegia followed by 5 min of reperfusion significantly improved heart function 1 h after surgery in another study, and decreased the need for inotropic support in patients undergoing open-heart surgery.³⁰ Similarly, improved cardiac function, and decreased release of phosphocreatine kinase MB isoenzyme was shown in patients undergoing valve replacement when receiving two cycles of 3 min of aortic cross-clamping, each followed by 2 min of

reperfusion before cardioplegic arrest.⁵⁶ However, one trial with patients undergoing CABG surgery using one 3-min episode of aortic cross-clamping before the onset of warm-blood cardioplegic arrest failed to show beneficial effects, but rather exhibited exacerbated ischaemic damage.⁷⁴ Increased phosphocreatine kinase release and lactate production were observed in these patients. It is assumed that protective effects of preconditioning during CABG surgery may only become demonstrable if cardioplegic protection is inadequate⁸ or ischaemic times are long.¹² In addition, differences in surgical techniques (normothermic vs hypothermic, fibrillation vs cardioplegic arrest) and study end-points (haemodynamic vs metabolic vs cardiac enzymes vs clinical outcome variables) make a direct comparison between these studies impossible.

Off-pump procedures

In off-pump, beating-heart CABG surgery, temporary segmental occlusion of coronary arteries is required for successful suturing of the anastomosis. Ischaemic preconditioning may be used to preserve cardiac function during this critical time. Jacobson and colleagues³³ reported favourable effects of ischaemic preconditioning on pressure-area loops, as assessed by transoesophageal echocardiography, in patients undergoing minimally invasive CABG. A recent study in patients undergoing off-pump CABG surgery⁴⁶ investigated whether ischaemic preconditioning by occluding the left anterior descending coronary artery before bypass grafting would enhance myocardial performance. Decreased myocardial enzyme release and increased myocardial function was observed in preconditioned patients. Conversely, Malkowski and colleagues⁵⁸ did not observe functional improvement by ischaemic preconditioning during minimally invasive CABG surgery. Vigorous surgical manipulations and pharmacological stimulation by catecholamines with the potential to induce preconditioning may overwhelm any benefit from therapeutic ischaemia.⁵⁷

Volatile anaesthetic-induced preconditioning in CABG surgery

Volatile anaesthetics are well suited to preconditioning during the operative period as they can be administered via the ventilator or the cardiopulmonary bypass oxygenator. Only a few, small studies have investigated the preconditioning effects of volatile anaesthetics in human myocardium (Table 1). So far, three studies have evaluated the preconditioning effects of isoflurane^{3 25 93} and one the effects of enflurane⁷² on either post-ischaemic cardiac dysfunction or the release of cardiac injury markers in patients undergoing CABG surgery under cardioplegic arrest. A small study compared sevoflurane with propofol anaesthesia in CABG patients and found improved post-operative myocardial function in the sevoflurane patients.¹⁶ This study of only 20 patients further claimed that

Table 1 Clinical studies evaluating volatile anaesthetic-induced preconditioning. *0.5–2% isoflurane to maintain systolic arterial blood pressure within 20–25% of baseline values; **to reduce systolic blood pressure by 20–25%. ACC=aortic cross-clamping; CK-MB=phosphocreatine kinase MB isoenzyme; CPB=cardiopulmonary bypass; cTnI=cardiac troponin I; ecto-5'-NT=ecto-5'-nucleotidase; LVEF=left ventricular ejection fraction

Clinical study (study design)	No. of patients	Preconditioning: drug/dose/duration	Basal anaesthesia	No. of diseased vessels/grafts (mean)	Cross clamp time: treated/untreated (min)	Cardioplegia/core temperature	Outcome measures	Results
Tomai <i>et al.</i> ⁹² (randomized, unblinded)	40	Isoflurane 1.5% (ventilator), 15 min, 10 min washout before CPB	Diazepam, fentanyl, pancuronium	2–3/3.4–3.7	49/53	Antegrade, cold, with blood, intermittent, 32–33°C	Cardiac index	No change
Belhomme <i>et al.</i> ³ (randomized, unblinded)	20	Isoflurane 2.7% (2.5 MAC) (membrane oxygenator), 5 min, 10 min washout before ACC	Flunitrazepam, fentanyl, pancuronium	2/2.5–2.7	48/52	Retrograde, cold, with blood, intermittent, 33–34°C	LVEF before/after CPB cTnI/CK-MB preop-96 h postop cTnI/CK-MB preop-72 h postop	No change ↓ only patients with LVEF <50% Tendency to ↓ postop
Haroun-Bizri <i>et al.</i> ²⁵ (randomized, blinded?)	49	Isoflurane, 0.5–2%* (ventilator), whole pre-CPB time, discontinued before CPB (washout until ACC)	Thiopental, midazolam, sufentanil, cisatracurium	2/2.7–2.8	32/35	Antegrade, cold, no blood, intermittent, 28°C	Cardiac index before/after CPB ST changes before/after CPB Reperfusion arrhythmias after release of ACC	↑ after CPB ↓ after CPB No change
Penta de Peppo <i>et al.</i> ⁷² (randomized, unblinded)	21	Enflurane 1.3 (0.5–2)%** (ventilator), 5 min, before CPB, 1.5–1.8 min washout before ACC	Diazepam, fentanyl, pancuronium	2–3/3.7–4.2	111/125	Antegrade, cold, with blood, intermittent 26°C	Cardiac output preop/postop LV contractility (pressure-area relation) before/after CPB cTnI/CK-MB preop-96 h postop	No change ↑ after CPB No change

sevoflurane would decrease the release of cardiac troponin I, which is surprising considering the marked variability between patients and the large number of surgical techniques.¹⁶ Nonetheless, pharmacological induction of preconditioning, in contrast to classic ischaemic preconditioning, would be desirable, specifically in high-risk patients such as CABG surgery patients, in whom an ischaemic-type of preconditioning may further jeopardize diseased myocardium. Tomai and colleagues⁹³ gave isoflurane for 15 min at 1.5 vol/vol % through the ventilator followed by a washout period of 10 min before starting cardiopulmonary bypass. No differences in haemodynamic variables, such as cardiac index and left ventricular ejection fraction, were found between control and preconditioned groups. However, a decrease in postoperative phosphocreatine kinase MB and troponin I release could be detected in patients with a poor preoperative left ventricular ejection fraction (<50%) (Table 1). Conversely, when administering isoflurane 0.5–2 vol/vol % shortly before cardiopulmonary bypass through the ventilator, Haroun-Bizri and colleagues²⁵ demonstrated improved haemodynamic recovery and decreased ST-segment changes, but no reduction in dysrhythmias in the immediate reperfusion period. Administration of isoflurane 2.7 vol/vol % for 5 min on established cardiopulmonary bypass followed by a 10-min washout period before aortic cross-clamping only showed a tendency to lower phosphocreatine kinase MB isoenzyme and troponin I release (not statistically significant).³ Penta de Peppo and colleagues⁷² applied enflurane 1.3 vol/vol % over 5 min immediately before cardiopulmonary bypass. Preconditioning afforded increased left ventricular contractility, but no decrease in perioperative phosphocreatine kinase MB isoenzyme or cardiac troponin T release was noted. As raised concentrations of myocardial enzymes after CABG surgery can occur from cannulation of the right atrium, cardioplegia, inadequate delivery of cardioplegia in the presence of stenosis or hypertrophy, vigorous manipulations of the heart, prolonged surgery and differences in surgical techniques, they may not properly reflect the protection afforded by preconditioning. Collectively, these data provide some evidence that volatile anaesthetics may protect human hearts by anaesthetic preconditioning.

Preconditioning signal transduction pathways in human myocardium

Experimental studies on human tissue and clinical studies with patients support the concept that the signalling pathways that mediate preconditioning in humans are the same as those observed in animal models. The signalling steps and the cytoprotective mechanisms of ischaemic and anaesthetic preconditioning were described in detail in Part I of this review.¹⁰⁸

Human cardiomyocytes and myocardial tissue

The involvement of α_1 -adrenergic receptors, bradykinin B₂ receptors, adenosine 1, PKC and K_{ATP} channels (including mitochondrial channels) in human cardiomyocytes and myocardial tissue has been demonstrated.^{11–13} Cytosol-to-membrane translocation in response to adenosine stimulation was previously shown for the α isoform of PKC in human cardiomyocytes.²⁹ Many of these signalling components, including adenosine receptors, adrenergic receptors and the sarcolemmal and mitochondrial K_{ATP} channels, were also demonstrated to be related to the preconditioning elicited by volatile anaesthetics in human tissue.^{24–78}

Clinical studies

Adenosine antagonists such as aminophylline and bambipylline can prevent adaptation to ischaemia during repeated balloon inflation,⁹⁰ and intracoronary adenosine and bradykinin administration was as effective as ischaemic preconditioning.^{49–51} Also, adaptation to ischaemia can be induced by morphine and abrogated by naloxone⁹² or phentolamine,⁹¹ suggesting that opioid and α -adrenergic receptors play an important role in human myocardium. Involvement of PKC and K_{ATP} channels was shown in some clinical studies. Ecto-5'-nucleotidase, a marker of PKC activity, was increased in response to isoflurane administration in patients undergoing CABG surgery.³ Nicorandil, a mitochondrial K_{ATP} channel opener, reduces ST-segment changes in patients undergoing PTCA, and perioperatively in patients undergoing abdominal surgery.³⁶ Clinically used oral sulfonylurea agents, used to treat type II diabetes mellitus and potent blockers of the K_{ATP} channels, effectively abolish cardiac preconditioning.⁴¹

Modulatory effects of anaesthetics and perioperative medication on cardiac preconditioning

Anaesthetics

Many anaesthetics have profound effects on sarcolemmal and mitochondrial membranes, the putative sites of the end-effectors for preconditioning, at concentrations as low as those known to produce general anaesthesia. It is therefore not surprising that cardiac preconditioning can be prevented by different anaesthetics. Anaesthetics with mostly inhibitory or no effects on K_{ATP} channels are listed in Table 2. Inhibition of this important endogenous protective mechanism may be a hazard. To date, there are only sparse clinical data addressing this important topic.¹⁰⁰ In rabbit hearts, racemic ketamine, but not the stereoisomer *S*-ketamine, was found to block early and late preconditioning.^{63–64} Racemic ketamine and the stereoisomer of ketamine were also shown to block both types of K_{ATP} channel in isolated rat cardiomyocytes.^{43–107} Similarly, the barbiturate thiamylal,⁹⁹ which closely

Table 2 Intravenous anaesthetics with inhibitory effects or no effects on mitochondrial and sarcolemmal K_{ATP} channels. \longleftrightarrow =no effect; \uparrow =increased effect; \downarrow =decreased effect. #Only at high concentrations

Anaesthetic drug	Mitochondrial K_{ATP} channel activity	References	Sarcolemmal K_{ATP} channel activity	References
R-ketamine	\downarrow	63, 64, 107	\downarrow	43, 63, 64
S-ketamine	\longleftrightarrow	107	?	
Propofol	\longleftrightarrow (\downarrow #)	37, 44, 107	\longleftrightarrow (\downarrow #)	37
Etomidate	\longleftrightarrow	107	?	
Thiopental	\downarrow	107	?	
Midazolam	\longleftrightarrow	107	?	
Pentobarbital (used in the laboratory)	\downarrow	44, 107	\downarrow	23
Thiamylal (used in the laboratory)	?		\downarrow	100
Xylazine (used in the laboratory)	\longleftrightarrow	107	?	

resembles thiopental in its chemical structure, inhibits sarcolemmal K_{ATP} channels. Two laboratories independently showed that commonly used barbiturates inhibit mitochondrial K_{ATP} channel activity.^{44 107} No inhibitory effects on mitochondrial K_{ATP} channels were found for xylazine, an α_2 -adrenergic agonist similar to clonidine, dexmedetomidine and mivazerol.¹⁰⁸ Similarly, propofol, etomidate and midazolam did not have any effect on K_{ATP} channels or ischaemic myocyte survival in a rat model.^{37 107} Taken together, these studies support the concept that certain anaesthetics may antagonize the protective effects of preconditioning.

Perioperative medication

Frequently used drugs that may inhibit or enhance ischaemic preconditioning are listed in Table 3. Sulfonylurea hypoglycaemic agents prevent ischaemic preconditioning¹³ and are thought to be responsible, in part, for the reported increase in cardiovascular mortality in patients treated with these agents.^{20 61} However, this has been questioned recently.²² Importantly, recent observations in type-2 diabetes patients suggest that glibenclamide-induced inhibition of preconditioning-related cardioprotection can be prevented by changing the antidiabetic treatment to insulin.⁸² Because β -blockers are thought to have beneficial perioperative effects^{109 110} and to reduce early⁷⁶ and late⁶⁰ perioperative cardiovascular morbidity and mortality, the suggested inhibitory effects of β -blockers on cardiac preconditioning (Table 3) appear somewhat conflicting, with their strong perioperative cardioprotection. However, metoprolol, a pure β -blocking agent, did not neutralize the favourable effects of preconditioning in pigs.¹⁰³ In addition, β -adrenergic receptors represent only one signalling pathway by which preconditioning can be triggered, and specific alterations in the diseased heart, such as downregulation of G-protein-coupled receptors, may diminish the protective effects of preconditioning.

Effects of preconditioning in the aged and diseased heart

Most experimental studies have evaluated the phenomenon of preconditioning in healthy juvenile hearts. This approach is far from clinical reality, as diseased myocardium would benefit most from this protection. Some clinical and experimental studies provide evidence that diseased myocardium may be less amenable to the protective effects of preconditioning (Table 4).

Ageing

Preconditioning protection may be lost in aged myocardium. Even worse, increased deleterious effects of ischaemia were reported in preconditioned aged rat hearts.⁸⁸ This effect appears to be due to the insufficient translocation of PKC isoforms in response to the preconditioning stimulus.⁸⁷ These experimental findings are supported by two clinical studies in which the anti-arrhythmic and infarct-limiting effects of prodromal angina were lost in elderly patients with myocardial infarction.^{1 32} In contrast, Jiménez-Navarro and colleagues³⁵ found that the occurrence of angina 1 week before myocardial infarction still conferred protection against in-hospital adverse outcomes in patients aged >70 yr. However, a more recent clinical study in patients undergoing PTCA, comparing ischaemic preconditioning in younger (45 (SD 5) yr) and elderly patients (71 (3) yr), also suggests that ischaemic preconditioning is attenuated in the aged human myocardium, most probably as a result of age-related inhibitory effects upstream of the mitochondrial K_{ATP} channels.⁴⁸

Metabolic dysfunction: hypercholesterolemia and diabetes

Rabbit myocardium loses its preconditioning-induced protection when exposed to a cholesterol-enriched diet for more than 4 weeks,⁸⁵ and markedly increased serum glucose concentrations (>500 mg dl⁻¹) can inhibit K_{ATP} channel

Table 3 Modulatory effects of medication on cardiac preconditioning. NSAIDs=non-steroidal anti-inflammatory drugs; COX-2=cyclooxygenase 2

Preconditioning ↑	Preconditioning ↓
Adenosine receptor agonists ⁴⁹ Including nucleotide transporter inhibitors (acadesine, ⁷ ⁵⁹ dipyrindamol ⁷⁰)	Adenosine receptor antagonists ⁹⁰ Theophylline, aminophylline
K _{ATP} channel openers (Nicorandil, ⁷¹ diazoxide, cromakalim, levosimendan, ³⁹ minoxidil, benzocaine, p-diethylaminoethylbenzoate), including the uncoupler of oxidative phosphorylation: bupivacaine, ropivacaine, most NSAIDs ⁸⁴	K _{ATP} channel blockers Sulfonylurea agents, including antidiabetic drugs: glibenclamide, glyburide. Much less: glimepiride, ⁴¹ and anticancer drugs (diarylsulfonylurea), ⁸⁴ lidocaine, mexiletine ⁹⁸
Opioid agonists (probably via δ ₁) Morphine, ⁸⁰ pentazocine, fentanyl	Opioid antagonists Naloxone ⁹²
β-Adrenergic receptor agonists ¹⁰⁴ Isoproterenol, norepinephrine, epinephrine. Some β-blockers with auxiliary effects may enhance preconditioning, ¹⁰⁹ such as carvedilol, ⁶⁶ nipradilol ²⁸ and nebivolol	β-Adrenergic receptor antagonists ⁵⁵ Including drugs which deplete myocardial tissue of catecholamines, such as reserpine ⁹⁴
α ₁ -Adrenergic receptor agonists ¹⁰² Phenylephrine, norepinephrine	α ₁ -Adrenergic receptor antagonists Phentolamine
M ₂ -muscarinic receptor agonists ⁵ Acetylcholine esterase inhibitors	M ₂ -muscarinic receptor antagonists Atropine
Nitric oxide releasers Nitroglycerin, ⁵⁰ nitroprusside, L-arginine	Nitric oxide scavengers Vitamin E?
Ca ²⁺ ⁶²	Ca ²⁺ channel blocker Nifedipine ¹⁰¹
B ₂ -bradykinin receptor agonists ⁵¹ ⁸¹ Angiotensin converting enzyme inhibitors: captopril, lisinopril, enalapril	
AT ₁ -receptor antagonists ⁹ Statins Lovastatin, pravastatin, via activation of ecto-5'-nucleotidase ⁴⁷	
Flumazenil ¹⁰⁶ Amrinone ⁷⁹	Digoxin ²⁶ Gadolinium ⁷⁵ Aprotinin ⁶ COX-2 inhibitors ⁴

Table 4 Factors affecting the efficacy of cardiac preconditioning. ←→=no effect; ↑=increased effect; ↓=decreased effect

Factors/disease states	Ischaemic preconditioning	References	Anaesthetic preconditioning	References
Diabetes	↓/←→/↑	31, 38, 54, 96	↓	86
Medication	↓/←→/↑	(Table 3 in present paper)	↓/←→/↑	(Table 3 in present paper)
Increased age	↓/←→	1, 32, 35, 48, 87, 88	?	
Raised plasma cholesterol	↓	85	?	
Coronary artery disease (ischaemic cardiac remodelling)	↓/←→	48, 53	?	
Arterial hypertension (hypertrophic cardiac remodelling)	↓/←→	5, 69, 77, 83	?	

activation *per se*.³⁸ Tosaki and colleagues⁹⁶ reported a loss of protection by preconditioning in streptozotocin-induced diabetic rat hearts. Conversely, Liu and colleagues⁵⁴ demonstrated that preconditioning reduces infarct size in non-insulin-dependent diabetic rats to the same extent as in normal hearts. One study found less pronounced release of cardiac enzymes in preconditioned isolated perfused hearts of streptozotocin-treated diabetic rats compared with preconditioned hearts of normal rats.⁸⁹ More recently, isoflurane-induced preconditioning was found to be attenuated in diabetic dogs.⁸⁶ Some of these experimental results

are consistent with clinical observations in which prodromal angina did not limit infarct size, enhance recovery of myocardial function or improve survival in diabetic patients with myocardial infarction, as opposed to non-diabetic patients.³¹

Remodelled heart

The effects of preconditioning have been shown to be operative in three rat models of hypertrophied myocardium (deoxycorticosteroid-treated and salt-fed rats,⁸³ spon-

taneously hypertensive rats⁵ and transgenic hypertensive rats⁷⁷). Conversely, in a dog model of hypertrophy (aortic stenosis), there was no evidence of cardioprotection with preconditioning.⁶⁹ Results from muscle slices of human right atrial appendages of patients with a left ventricular ejection fraction <30% indicate that failing human myocardium is much less amenable to ischaemic preconditioning.²¹ In contrast, successful preconditioning can be established in severely atherosclerotic knockout mice (ApoE/LDLr^{-/-}).⁵³

Questions and perspectives

Preconditioning by anaesthetics represents a promising new therapeutic strategy in patients undergoing PTCA, CABG surgery (including off-pump procedures) or valve replacement, and in the preservation of donor hearts.⁴⁰ Pharmacological preconditioning may even exert better protection than ischaemic preconditioning.⁹⁷ However, in short surgical procedures with optimal cardioplegic protection or short ischaemic periods, loss of function and cell death may be negligible. Furthermore, it remains to be established whether diseased and aged myocardium can be preconditioned in the same manner as healthy myocardium. Although it is possible to re-initiate preconditioning once it has worn off,¹⁰⁵ there is currently sparse experimental evidence indicating that cardiac tissue can be constantly maintained in a protective preconditioned state. Dana and colleagues¹⁴ showed in a rabbit model that repeated administration of an adenosine receptor agonist, with a 48-h interval schedule, can maintain the heart in a protective state against myocardial infarction with no evidence of tachyphylaxis. However, continuous stimulation of the preconditioning mechanism may lead to tachyphylaxis. In this regard, late preconditioning may be more attractive, though less effective. Late preconditioning has been demonstrated for opioids, but not for volatile anaesthetics. Moreover, silent ischaemia, overt angina or warm-up angina may already precondition high-risk cardiac patients and thereby abrogate the beneficial effects of pharmacological interventions. Recently, Aitchison and colleagues² presented experimental evidence that there may exist an 'anti-preconditioned' state of the myocardium. By means of pre-ischaemic transient κ_1 -opioid receptor stimulation in isolated perfused rat hearts, a sizeable increase in infarct size compared with ischaemia alone was achieved. This observation implies that transient receptor stimulation may make the heart more vulnerable to necrosis ('death memory' vs 'survival memory' by preconditioning). The discovery of pro-injurious anti-preconditioning effects opens up a fascinating field for future studies in experimental and clinical cardioprotection. Some of the commonly used perioperative medications may induce anti-preconditioning in cardiac tissue and thereby affect outcome. Prophylactic treatment with pharmacological preconditioning should be used with extreme care. The combination of ischaemic precondition-

ing and antecedent prophylactic treatment with nicorandil can abolish the protection afforded by ischaemia in human trabeculae,¹⁰ and halothane can inhibit the effects of hypoxic preconditioning.⁷⁸ No direct extrapolation should be made from theoretical experimental knowledge, and the effects of each preconditioning protocol need to be evaluated in randomized controlled trials.

Conclusions

Cardiac preconditioning is an area of basic research with clinical relevance. Human myocardium is amenable to this form of protection. Although the key signalling steps and ultimate cellular protective mechanisms underlying cardiac preconditioning have been unravelled, many questions remain unresolved, particularly with respect to the aged and diseased myocardium. The concept that many anaesthetics interact with the endogenous cardioprotection elicited by preconditioning should be considered carefully in experimental and clinical medicine. Although there is some promising evidence that anaesthetic preconditioning may improve the perioperative cardiovascular outcome in patients at high risk of cardiovascular complications, its definitive role in clinical practice needs to be established in randomized controlled clinical trials.

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Addendum

Anaesthetic-induced preconditioning in humans

During the review process of this article, a double-blinded, placebo-controlled study on the protective effect of sevoflurane preconditioning in 72 patients undergoing CABG surgery was published by Julier and colleagues.¹¹¹ Sevoflurane preconditioning significantly decreased postoperative release of NT-proBNP (*N*-terminal pro-brain natriuretic peptide), a sensitive biochemical marker of myocardial contractile dysfunction. Pronounced PKC δ and ϵ translocation was observed in sevoflurane-preconditioned myocardium. In addition, the postoperative cystatin C plasma concentration (a more sensitive marker of subtle changes in renal glomerular filtration rate than plasma creatinine) increased significantly less in sevoflurane-preconditioned patients. No differences between groups (sevoflurane vs placebo) were found for perioperative ST-segment changes, arrhythmias or phosphocreatine kinase-MB and cardiac troponin T release. In summary,

sevoflurane preconditioning preserves myocardial and renal function, as assessed by biochemical markers in patients undergoing CABG surgery. This suggests that anaesthetic preconditioning may elicit more global protection. In contrast, Pouzet and colleagues,¹¹² assessing the activation of PKC, p38 mitogen-activated protein kinase and tyrosine kinase in atrial biopsies of 20 sevoflurane-preconditioned patients undergoing CABG surgery, did not observe significant differences in enzyme activities compared with control patients. However, all kinases were significantly activated, probably as a result of the stimulus by the cardiopulmonary bypass. No decrease in cardiac troponin I release was reported in patients preconditioned with sevoflurane.

Preconditioning-inducing drugs

Lee and colleagues¹¹³ demonstrated that administration of oestrogen in women undergoing coronary angioplasty diminishes signs of myocardial ischaemia, as assessed by ECG. Another study showed infarct size-limiting effects by sildenafil (Viagra) mediated by mitochondrial K_{ATP} channels in a rabbit model of regional ischaemia.¹¹⁴

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