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Review Article

Peri-operative anaesthetic myocardial preconditioning and protection – cellular mechanisms and clinical relevance in cardiac anaesthesia

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Summary

Preconditioning has been shown to reduce myocardial damage caused by ischaemia–reperfusion injury peri-operatively. Volatile anaesthetic agents have the potential to provide myocardial protection by anaesthetic preconditioning and, in addition, they also mediate renal and cerebral protection. A number of proof-of-concept trials have confirmed that the experimental evidence can be translated into clinical practice with regard to postoperative markers of myocardial injury; however, this effect has not been ubiquitous. The clinical trials published to date have also been too small to investigate clinical outcome and mortality. Data from recent meta-analyses in cardiac anaesthesia are also not conclusive regarding intra-operative volatile anaesthesia. These inconclusive clinical results have led to great variability currently in the type of anaesthetic agent used during cardiac surgery. This review summarises experimentally proposed mechanisms of anaesthetic preconditioning, and assesses randomised controlled clinical trials in cardiac anaesthesia that have been aimed at translating experimental results into the clinical setting.

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Introduction

In the UK, about 34 760 adult cardiac surgical procedures were carried out in 2011, including 17 070 coronary artery bypass graft (CABG) procedures, and 17 690 valvular repairs or replacements, many of which also required concurrent CABG. Overall mortality was 2.97% (see http://bluebook.scts.org). The population requiring surgery is older than before, with more patients presenting with multiple co-morbidities, including obesity, diabetes, chronic renal failure, and peripheral vascular disease [1], which increase the risk of postoperative complications [2, 3].

Extensive evidence from experimental studies has shown that volatile anaesthetics protect the heart from ischaemic myocardial injury in animal models, and that they also have the potential to provide renal and cerebral protection. Clinical proof-of-concept studies and meta-analyses based on small clinical studies have supported these experimental results, but inconclusively. However, whereas surgical myocardial protec-

tion and cardioplegic strategies are routinely employed to improve organ protection during cardiac surgery [4], management of general anaesthesia has remained basically unchanged over the last 20 years, with some anaesthetists using intravenous propofol only for maintenance, and others volatile anaesthetics alone, or volatile anaesthetics plus propofol in combination. This variation in clinical practice stems from a lack of evidence as to which type of anaesthetic is superior, and it demonstrates the potential for more protective anaesthesia if best practice could be conclusively demonstrated.

This article will provide a review of the current literature on mechanisms of anaesthetic protection by preconditioning in cardiac anaesthesia, and an overview of clinical trials assessing potentially protective anaesthetic regimens.

Methods

We performed a comprehensive literature review using MEDLINE and EMBASE, accessed via the National Health Service Healthcare Databases Advanced Search (HDAS) link. Articles from 2004 until 2014 were accessed with the following terms: volatile anaesthetics OR inhalation anaesthetics OR isoflurane OR sevoflurane OR desflurane AND myocardial protection OR preconditioning OR myocardial reperfusion injury OR cardiac protection OR myocardial ischaemia. Only studies written in the English language were considered. A total of 886 studies were identified, and based on their relevance to cellular mechanisms and clinical applications of myocardial conditioning by volatile anaesthetics in cardiac anaesthesia, we selected 97 for inclusion in this review.

Experimental evidence

Myocardial preconditioning describes the experimentally observed phenomenon that an intervention or a trigger, before a prolonged ischaemic insult to the myocardium, results in a reduction in the infarcted area. The preconditioning trigger can either be an ischaemic intervention or a pharmacological stimulus, such as volatile anaesthetics. Ischaemic preconditioning was first described in 1986 by Murry et al., who demonstrated in a dog model that four short episodes of 5 min of myocardial ischaemia, followed by 5 min of reperfusion, before a prolonged ischaemic period of 40 min, produced a 'memory' effect in the myocytes, that led to a 75% reduction in infarct size [5]. The pathophysiology of this phenomenon has subsequently been well described [6].

In addition to an immediate window of protection 1–2 h after the preconditioning stimulus, a delayed phase of protection from preconditioning, that persists for 2–3 days, has been described as late preconditioning [7]. Furthermore, the myocardium can also be protected by a stimulus that is applied after ischaemia–reperfusion injury [8]; this phenomenon is called postconditioning, and has been reviewed elsewhere in this journal [9]. If the ischaemic stimulus for myocardial protection is applied at a distant organ or tissue such as a limb, the technique is called remote preconditioning, and is included in this thematic series [10].

The first experimental evidence of myocardial protection from ischaemia–reperfusion injury by volatile anaesthetics was obtained using halothane in a dog model, in the 1970s [11]. This protective effect was subsequently confirmed in the 1980s using halothane [12], enflurane [13] and isoflurane [14]. Volatile anaesthetic agents, however, have also been shown to induce the harmful phenomenon of 'coronary steal' in experimental models [15]. This describes the phenomenon where by vasodilation results in the shunting of blood flow away from the ischaemic myocardium, which then worsens myocardial ischaemia. Conflicting results in subsequent studies meant that by the early 1990s, the proposed phenomenon of coronary steal had been largely refuted [16]. More than 10 years after the first experimental description of preconditioning by an ischaemic trigger, preconditioning by an anaesthetic stimulus was described in 1997 by three independent groups, in rabbit models [17, 18] and in a dog model [19].

Two main intracellular signal transduction pathways, directing cardioprotection from cell surface receptors to convergent targets in the mitochondria, have been proposed as models to explain preconditioning: the reperfusion injury salvage kinases (RISK) pathway [20] via G-protein-coupled cell surface receptors; and the survivor-activating factor enhancement (SAFE) pathway [21]. The latter operates mainly through the tumour necrosis factor (TNF)-alpha receptor and signal transducer, and activator of transcription

(STAT)-3. In the mitochondria, protection is triggered by inhibition of the opening of the mitochondrial permeability transition pore (mPTP) [22], and by activating the opening of the ATP-dependent potassium (KATP) channel [23]. Mitochondria supply ATP to cardiomyocytes, but they have also recently been identified as activators of cell death pathways; cell death can be inhibited by mitochondrial autophagy and pro-survival pathways, and mPTP plays an important role in modulating the balance of pro-survival over cell death pathways [24]. A recent study demonstrated that drug-induced activation of autophagy in rabbits before ischaemia, or during reperfusion, protected the myocardium from ischaemia–reperfusion injury [25].

The intracellular signal transduction proteins and molecules that are candidates for interactions with volatile anaesthetic agents are listed in Table 1 [26–57]. These interactions have been demonstrated in a number of experimental models in animals, in isolated perfused hearts (the so-called Langendorff heart apparatus), and also in human atrial myocardium and human embryonic stem cells. This body of evidence demonstrates that all three volatile anaesthetics currently in use (isoflurane, sevoflurane and desflurane), have the ability to protect myocardium not only in vivo in mammals, but also in vitro in human and animal myocardial tissue and cells.

In addition to protection in cardiac myocytes, direct endothelial protection by volatile anaesthetic agents has also been described, which may be of relevance for myocardial protection (Table 2 [58–64]).

It has been recently demonstrated that isoflurane (and also morphine) provides endothelial protection by preventing TNF-alpha-induced adhesion molecule expression in human umbilical vein endothelial cells [60], and more recently in volunteers anaesthetised with sevoflurane [61]. More detailed interactions and the individual signal transduction pathways of anaesthetic conditioning have been reviewed previously [8, 65–70].

Experimental investigations suggest that the ability of volatile anaesthetics to protect the myocardium by anaesthetic preconditioning significantly increases from isoflurane to sevoflurane to desflurane [71]. Not only the type of volatile anaesthetic, but also the duration and frequency of exposure to the volatile anaesthetic before ischaemia, have been shown to be of potential relevance in in-vitro experiments. In guinea pig hearts, exposure to sevoflurane for two periods of 5 min before a period of ischaemia, with a 5-min washout period in-between, showed improved protection compared with one single 15-min exposure to sevoflurane before ischaemia [72].

In addition to volatile anaesthetic agents, other drugs used in the peri-operative period may have an effect on anaesthetic preconditioning. In-vivo experiments in rabbits suggest that propofol may block preconditioning attributed to desflurane [73]. On the other hand, propofol may protect rat myocardium from ischaemia–reperfusion injury by up-regulation of nitric oxide synthase activity [74]. Interestingly, the combination of isoflurane preconditioning before cardiopulmonary bypass (CPB), and propofol during and after CPB, provided significantly improved myocardial protection in a dog model, compared with either agent alone [75]. Experimental data show that morphine enhances pharmacological preconditioning of isoflurane [76]. In addition, opioid infusions of remifentanil and sufentanil have been shown to protect human right atrial muscle from ischaemia–reperfusion injury in vitro [77]. Sulfonylureas are KATP channel blockers, and prevent myocardial preconditioning [78], and the beta-blocker metoprolol has been shown to block desflurane-induced preconditioning [79].

Experimental data have also suggested that co-morbidities such as diabetes/hyperglycaemia and obesity may attenuate the protective effects of volatile anaesthetics. Hyperglycaemia prevents isoflurane preconditioning in dogs in vivo, and also in human cardiomyocytes derived from induced pluripotent stem cells [80]. Sevoflurane-induced preconditioning was prevented by obesity [81] and reduced in isolated hypercholesterolaemic hearts from rats exposed to a high cholesterol diet, and in hypertrophied rat hearts, induced by transverse aortic constriction [82, 83]. Advanced age reduces myocardial protection provided by volatile anaesthetic agents, as demonstrated in guinea pig hearts [84] and also in human atrial cardiomyocytes [85].

The experimental evidence supports several hypotheses of molecular interactions by volatile anaesthetics resulting in potential myocardial protection;

Table 1 Effects of volatile anaesthetic preconditioning on signal transduction proteins in cardiomyocytes.

Myocyte	Protein	Experimental model	Volatile anaesthetic
Cytosol			
PKC	PKC-delta activation preceded by ROS release	Rat myocardial trabeculae in vitro	Isoflurane [26]
	PKC-delta and PKC-epsilon translocation, and Src PTK activation	Rat heart in vivo	Isoflurane [27]
	PKC-epsilon and ERK1/2	Rat heart in vivo	Desflurane [28]
	PKC-delta activation depends on modulation of Na^+/Ca^{2+} exchanger	Right ventricular rat trabeculae in vitro	Sevoflurane [29]
	PKC-epsilon activation	Rat cardiomyocytes	Isoflurane [30]
	PKC-alpha and -epsilon translocation and activation	Guinea pig hearts in vitro	Sevoflurane [31]
	PKC-delta, and -alpha activation, phosphorylation of Akt and GSK-3 beta, ERK1/2 activation	Human right atrial appendages, 3 cycles of preconditioning in vivo	Isoflurane and sevoflurane [32]
ERK1/2	ERK1/2 triggered HIF-1alpha and VEGF up-regulation	Rat hearts in vivo	Isoflurane [33]
PI3K/Akt	PI3K/Akt activation and attenuation of myocardial apoptosis	Rabbit heart in vivo	Isoflurane [34]
5'AMP PK	5'AMP-activated protein kinase, ROS induced	Rat hearts in vitro	Sevoflurane [35]
Cyclooxygenase	Cyclooxygenase-2: critical mediator	Dog hearts in vivo	Isoflurane [36]
Caveolin-3	Caveolin-3 expression and caveolae are critical mediators	Caveolin-3-knockout mice, hearts in vivo and cardiomyocytes in vitro	Isoflurane [37]
	Caveolin-3-dependent cyclooxygenase-2 inhibition	Caveolin-3-knockout mice in vivo	Sevoflurane [38]
NO	NO release mediated protection	Rabbit hearts in vivo	Desflurane [39]
NOS	Activation of NOS	Rabbit hearts in vivo	Desflurane [40]
ROS	ROS generation from electron transport chain complex III	Rabbit hearts in vivo	Isoflurane [41]
	ROS mediates attenuation of mitochondrial respiration complex I	Guinea pig myocardial mitochondria	Sevoflurane [42]
	ROS generated PKC-alpha activation	Rat right ventricular trabeculae in vitro	Sevoflurane [43]
	ROS generation	Human atrial trabeculae	Sevoflurane and desflurane [44]
	ROS generation, and ROS dependent protection	Adult ventricular rat cardiomyocytes	Sevoflurane and desflurane [45]
	ROS generation	Cardiomyocytes from hESC	Isoflurane [46]
	attenuation of complex I activity and ROS generation	Rat hearts in vitro	Isoflurane [47]
Mitochondrium			
mPTP	Improved resistance of mPTP to Ca^{2+} induced opening	Rabbit hearts in vivo	Desflurane [48]
	mKATP activation induced mPTP inhibition	Rabbit hearts in vivo	Isoflurane [49]
	Delayed opening of mPTP	Cardiomyocytes from hESC	Isoflurane [46]
	Delayed opening of mPTP	Rat cardiomyocytes	Isoflurane [30]
	O-GlcNAc modification of mitochondrial voltage-dependent anion channel inhibits opening of mPTP	Mouse myocytes	Isoflurane [50]
mKATP	Activation of mKATP channels	Rabbit hearts in vivo	Isoflurane [49]
	Activation of human cardiac mKATP channels	Lipid bilayers	Isoflurane [51]
BK_{Ca}	Activation of BK_{Ca} (PKA mediated)	Mouse hearts in vivo	Desflurane [52]

Table 1 (*continued*)

Myocyte	Protein	Experimental model	Volatile anaesthetic
Cell nucleus			
NF-kappa B	Attenuation of NF-kappa B activation at the end of I-R	Rat hearts in vitro	Sevoflurane [53]
	Activation of NF-kappa B, up-regulation of autophagy, decreased apoptosis before I/R	Rat hearts in vitro	Sevoflurane [54]
	Inhibition of NF-kappa B during I/P	Rat hearts in vivo	Sevoflurane [55]
	Up-regulation of NF-kappa B and anti-apoptosis factors before I-R	Rat hearts in vivo	Sevoflurane [56]
HIF-1 alpha	Activation of HIF-1 alpha	Rabbit hearts in vivo	Isoflurane [57]

PKC, protein kinase C; ROS, reactive oxygen species; Src PTK, sarcoma protein tyrosine kinase; ERK, extracellular signal regulated kinase; Akt, protein kinase B; GSK, glycogen synthase kinase; HIF, hypoxia inducible factor; VEGF, vascular endothelial growth factor; PI3K, phosphoinositide 3-kinase; AMP, adenosine monophosphate; NO, nitric oxide; NOS, nitric oxide synthase; mPTP, mitochondrial permeability transition pore; mKATP channel, mitochondrial ATP-sensitive potassium channel; hESC, human embryonic stem cells; O-GlcNAc, O-linked beta-N-acetylglucosamine; BK_{Ca}, large-conductance calcium-activated K^+ channel; PKA, protein kinase A; NF, nuclear factor; I-R, cardiac ischaemia-reperfusion.

Table 2 Effects of volatile anaesthetic preconditioning on signal transduction proteins in endothelium.

Endothelium	Inhibition of endothelial NF-kappa B activation	Human umbilical vein, endothelial cells	Desflurane [58]
	Inhibition of TNF-alpha-stimulated expression of adhesion molecules ICAM-1, VCAM-1 and E-selectin	Human umbilical vein, endothelial cells	Desflurane [59]
	Prevention of TNF-alpha-induced adhesion molecule expression	Human umbilical vein, endothelial cells	Isoflurane [60]
	Inhibition of endothelial leucocyte adhesion	Human volunteers	Sevoflurane [61]
	Preservation of glycocalix from I-R-induced degradation by attenuation of lysosomal cathepsin B release	Guinea pig hearts in vitro	Sevoflurane [62]
	Endothelial protection against ischaemia mediated by PKCs and mKATP channels	Bovine pulmonary arterial endothelial cells	Isoflurane [63]
	NOSs (endothelial NOS and inducible NOS)	NOSs knockout mice	Desflurane [64]

NF, nuclear factor; TNF, tumour necrosis factor; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1; I-R, cardiac ischaemia–reperfusion; PKC, protein kinase C; mKATP channel, mitochondrial ATP-sensitive potassium channel; NOSs, nitric oxide synthases.

however, the limitations of the experimental set-ups do need to be considered. For example, in-vivo animal models may experience variable collateral blood flow, which can potentially interfere with the infarct size, and is difficult to control for. This issue is avoided in tissue models such as human atrial trabeculae, and also in single cardiomyocytes. However, human atrial muscle has different subtypes of contractile and metabolic proteins compared with ventricular myocytes, which may alter the response to ischaemia of atrial muscle cells compared with those of ventricular myocytes. Isolated adult cardiomyocytes lose important pathophysiological aspects of myocardial ischaemia–reperfusion injury. In the whole heart, hyper-contracture of myocytes, causing sarcolemmal and cytoskeletal disruption, results in massive enzyme release, influx of calcium ions into broken cells, and interstitial oedema during reperfusion, after an ischaemic insult. Both hyper-contracture and interstitial oedema do not occur during reperfusion in isolated adult cardiomyocytes [86].

On the other hand, embryonic cells (including human embryonic stem cell-derived cardiomyocytes), which have the advantage of a non-animal model, and

elimination of collateral blood flow and maintenance of contractility, have a completely different energy metabolism compared with adult cardiomyocytes. One feature is that the fetal heart relies on carbohydrate substrates such as lactate and glucose, thus tolerating a low oxygen environment much better than adult cardiomyocytes [87]. Membrane preparations with membrane proteins and applied patch-clamp techniques can measure and quantify interactions and modulation from volatile anaesthetic agents; however, these interactions cannot be shown to have a causal relationship with myocardial protection from ischaemia–reperfusion injury.

Clinical evidence of anaesthetic preconditioning

The very low incidence of hard clinical endpoints such as mortality and myocardial infarction in the postoperative period means that surrogate endpoints, such as postoperative troponin concentrations, are commonly used in proof-of-concept trials. While serum markers may reflect clinical outcome, their clinical importance as an appropriate endpoint remains open to debate [88].

Raised levels of troponin postoperatively have been shown to correlate strongly with worse clinical outcome [89]. In addition, postoperative troponin I correlates well with the mass of myocyte necrosis diagnosed by serial cardiac magnetic resonance imaging (MRI) after CABG surgery [90].

We have identified a number of small-to-medium-sized, prospective, randomised controlled proof-of-concept trials in which volatile anaesthetics induced a significant reduction in postoperative troponin levels in cardiac surgery [91–103], summarised in Table 3, and other, similarly-sized trials that did not demonstrate reduced postoperative troponin levels with volatile anaesthetics (Table 4 [104–117]).

In coronary surgery, Lee et al. demonstrated that isoflurane, if given at the beginning of CPB at 2.5 minimum alveolar concentration (MAC) before aortic cross-clamping, and with a 5-min washout period after its administration, significantly reduced the postoperative ischaemic marker troponin I at 24 h [92]. However, dose-related effects and application patterns, including several cycles of volatile anaesthetic preconditioning with washout intervals, were not investigated. Amr and Yassin used the same anaesthetic preconditioning protocol with the application of 2% isoflurane followed by a 5-min washout period, to show that anaesthetic preconditioning reduced postoperative cardiac troponin I as much as the protection conferred by ischaemic preconditioning, and significantly more than in the control group, that received midazolam and no volatile anaesthetic agent [100]. In another small proof-of-concept trial by Meco et al., desflurane, given before CPB, resulted in myocardial protection and reduced cardiac troponin I postoperatively [96]. In contrast to the three trials mentioned above, where volatile anaesthetic agents were administered before placement of the aortic cross-clamp, De Hert et al. described significant reductions in postoperative cardiac troponin I after continuous administration of sevoflurane during surgery [91]. In the same study, sevoflurane was also administered only pre- or post-CPB, and this did not result in significant postoperative troponin changes compared with patients receiving propofol only. These results are confounding when compared with those described by Lee et al., Amr and Yassin and Meco et al., where the volatile anaesthetic was only given before CPB. However, all patients in De Hert et al.'s trial underwent CABG surgery with CPB and intermittent aortic cross-clamping, which potentially provided an additional ischaemic preconditioning stimulus, as well as adding additional reperfusion episodes. The improved myocardial protection may therefore have been a result of the combination of anaesthetic preconditioning during CPB, and ischaemic preconditioning caused by intermittent aortic cross-clamping [91].

Tritapepe et al., in a relatively large trial with 150 patients, demonstrated that the continuous administration of 1 MAC desflurane during CABG surgery, except during CPB, induced significant cardioprotection, as assessed by reduced postoperative cardiac troponin I levels, compared with propofol infusion [97]. In contrast to the study by de Hert et al., anterograde or retrograde cold blood cardioplegia was used to immobilise the myocardium during grafting, thus excluding an additional protective effect by cross-clamp defibrillation. Kawamura et al. showed a similar effect on postoperative myocardial ischaemic markers in a small cohort of 23 patients after continuous

Table 3 Clinical trials comparing volatile anaesthesia with propofol anaesthesia in cardiac surgery that indicated less myocardial injury with volatile anaesthetics, demonstrated by statistically significant reductions in postoperative ischaemic markers.

Procedure	Anaesthetic intervention	Control group	Analgesia	n	Cardiac marker	Findings and effect sizes (reduction in cardiac marker)	Reference
CABG	Sevoflurane 0.5–2% pre/post-CPB or continuously	TCI propofol	Remifentanil infusion	200	CTnI	Significantly lower increase in cTnI in the sevoflurane continuous group compared with the propofol group	[91]
CABG	Isoflurane 2.5 MAC at onset of CPB for 15 min before CC, 5-min washout	Propofol	Fentanyl	40	CTnI	Significant reduction in cTnI at 24 h after the surgery in the isoflurane group	[92]
AVR	Sevoflurane 0.5–1%	TCI propofol	Remifentanil infusion	30	CTnI	Significant reduction in cTnI up to 24 h postoperatively in the sevoflurane group	[93]
OPCAB	Desflurane 0.5–2 MAC during surgery	TCI propofol	Fentanyl	112	CTnI	Significant reduction of the cTnI AUC up to 24 h postoperatively	[94]
CABG	Sevoflurane 0.5–1.0% during surgery	Propofol	Fentanyl	23	CTnT	Significant reduction in peak cTnT up to 3 h after aortic declamping in the sevoflurane group	[95]
CABG	Desflurane 2.5% for 5 min during CPB before CC, 10-min washout	Propofol	Fentanyl	28	CTnI	Significant reduction in peak cTnI at 24 h and 72 h after surgery in the desflurane group	[96]
CABG	Desflurane 1 MAC during surgery, except during CPB time	TCI propofol	Fentanyl	150	CTnI	47% reduction of the cTnI AUC in the desflurane group	[97]
CABG	Sevoflurane 1 MAC continuous vs intermittent (10-min washout) before CPB	Propofol	Sufentanil	42	CTnT	Significant reduction in peak cTnI at 24 and 48 h postoperatively in the intermittent sevoflurane group	[98]
CABG	Sevoflurane 1 MAC × 5 min vs 2 MAC × 5 min with 10-min washout before CPB	TCI propofol	Sufentanil	30	CTnI	Significant reduction in peak cTnT up to 72 h postoperatively in the 2 × 5 min sevoflurane group	[99]
CABG	Isoflurane 2.5% 10 min before CC	Midazolam	Sufentanil	45	CTnI	Significant reduction in peak cTnI up to 36 h postoperatively in the isoflurane group	[100]
OPCAB	1–2.5% Isoflurane during surgery	Propofol	N_2O	45	CTnT	Significant reduction in peak cTnT at 6 and 24 h after surgery in the isoflurane group	[101]
CABG	Isoflurane 1-1.5 MAC until CPB and propofol during and after CPB; or isoflurane only	Propofol or midazolam	Fentanyl	120	CTnI	Isoflurane plus propofol reduced the cTnI AUC by 33% compared with iso only, and 35% compared with propofol only	[102]
OPCAB	Sevoflurane 0.75/1.0/1.5 MAC	Midazolam	Fentanyl	48	CTnI	Significant reduction of cTnI peak levels at 24, 48 and 72 h after surgery in the 1.0 and 1.5 MAC groups	[103]

CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; TCI, target controlled infusion; CTnI, cardiac troponin I; MAC, minimal alveolar concentration; CC, aortic cross-clamp; AVR, aortic valve replacement surgery; OPCAB, off-pump coronary artery bypass graft surgery; AUC, area under the curve; CTnT, cardiac troponin T.

administration of sevoflurane during CABG surgery, where patients received anterograde cold blood cardioplegia [95].

The washout period of the preconditioning trigger before the episode of critical ischaemia is part of the classical preconditioning protocol [5]. This technique was assessed by Frassdorf et al. and Bein et al. in patients undergoing CABG surgery with CPB [98, 99]. Their studies showed that only intermittent administration of sevoflurane induced statistically relevant reductions in postoperative ischaemic markers, compared with one single episode of volatile anaesthetic administration before CPB. Bein et al. compared intermittent sevoflurane before CPB, with continuous administration of sevoflurane before CPB, and Frassdorf et al. compared intermittent sevoflurane with a single 5-min period of sevoflurane before CPB. Both trials also included a control group receiving propofol only. However, the intermittent sevoflurane regimen was not compared with sevoflurane-only during the whole procedure, particularly during CPB. Clinical limitations of intermittent sevoflurane applications, with washout periods in-between, include natural limits on the number of these washout periods before CPB, as the beginning of CPB should not be delayed. In addition, during the interruption of sevoflurane, the administration of a different non-volatile anaesthetic regimen needs to be considered.

One recent small proof-of-concept trial by Huang et al. investigated the concept of whether isoflurane plus propofol anaesthesia would result in less myocardial damage during CABG surgery, compared with isoflurane, propofol or midazolam alone [102]. Isoflurane was administered before CPB, and propofol 100 $\mu g.kg^{-1}.min^{-1}$ was given during CPB, and until 15 min after aortic declamping, followed by propofol 60 $\mu g.kg^{-1}.min^{-1}$ after CPB. The results indicated that a combination of isoflurane preconditioning before CPB, and propofol protection during and after CPB, resulted in a significant reduction in postoperative markers of myocardial ischaemia, in contrast to the effects of either isoflurane or propofol anaesthesia alone. Propofol may protect the myocardium from ischaemia–reperfusion injury by scavenging peroxynitrite [118]. This effect can potentially be synergistic with the preconditioning effect of isoflurane, which generates small amounts of peroxynitrate before bypass that at low levels provides myocardial protection.

During CABG surgery without the use of CPB, isoflurane, desflurane or sevoflurane administered during the whole procedure have been shown to reduce postoperative troponin concentrations [94, 101, 103], while during aortic valve replacement surgery, sevoflurane has also been shown to reduce postoperative troponin levels [93]. Wang et al. investigated different doses of isoflurane during CABG surgery without CPB, and demonstrated that 1 MAC of sevoflurane induced a significant reduction in postoperative troponin levels, whereas a lower dose of 0.75 MAC provided no protection, and a higher dose conferred no additional myocardial protection [103].

In contrast to the evidence presented up to now, there are a number of trials showing that volatile anaesthetic agents in cardiac surgery do not reduce postoperative troponin levels. Xia et al. demonstrated a protective effect of propofol in the clinical setting, when compared with isoflurane alone. High doses of propofol (120 $\mu g.kg^{-1}.min^{-1}$), from 10 min before CPB until 15 min after aortic unclamping, resulted in a significant reduction in postoperative troponin I, suggesting that a continuous infusion of high-dose propofol is more protective than either isoflurane or a lower-dose infusion of propofol [106]. One explanation for this confounding finding may be the long aortic cross-clamp time in all groups, which exceeded 80 min. Experimental data have shown previously that the therapeutic timeframe for anaesthetic preconditioning lies between 25 and 40 min [119]. Therefore, protection by the volatile anaesthetic agent may not have been observed in the study conducted by Xia et al. owing to the prolonged CPB and ischaemic time.

Flier et al. investigated a protocol with isoflurane given during the whole procedure [112]. Their results did not reveal any differences in postoperative troponin levels after maintenance of anaesthesia with propofol, in comparison with isoflurane. However, patients taking the K_{ATP} channel blocker sulphonylurea were not excluded from the study, and sulphonylureas are known to block the potentially cardioprotective effect of volatile anaesthetic agents. In addition, the intervention had to be discontinued in 13% of patients, and three patients were from the isoflurane group, which led to a potential

Table 4 Clinical trials comparing volatile anaesthesia with propofol anaesthesia in cardiac surgery that indicated the same amount of myocardial injury with volatile anaesthetics and propofol, with similar peri-operative troponin serum concentrations, or less myocardial injury and lower postoperative cardiac serum markers with propofol.

Procedure	Anaesthetic intervention	Control group	Analgesia	n	Cardiac marker	Other findings apart from no difference between postoperative biomarkers	Reference
CABG	Isoflurane 1 MAC for 5 min before CPB plus 5-min washout	Propofol	Sufentanil	34	CTnI	No difference between groups in postoperative CTnI peak values	[104]
MIDCAB	Sevoflurane 1 MAC during surgery	Propofol	Remifentanil	50	CTnT	No difference in postoperative cTnT values. After LAD occlusion. Preserved myocardial function with sevoflurane	[105]
CABG	Isoflurane 1–1.5% after induction during surgery	Propofol: 60 $\mu g.kg^{-1}.min^{-1}$, 120 $\mu g.kg^{-1}.min^{-1}$ during CPB	Fentanyl	54	CTnT and cTnI	Significantly lower cTnI and cTnT levels at 8, 24 and 48 h after surgery in the high-dose propofol group compared with the other groups	[106]
OPCAB	Sevoflurane during surgery	Propofol	Remifentanil	18	CTnI	Similar AUC of postoperative cTnI in sevoflurane and propofol groups (up to 36 h)	[107]
OPCAB	Sevoflurane during surgery	Propofol	Remifentanil	20	CTnT	Similar postoperative cTnT release in sevoflurane and propofol groups. Different transcriptional response in sevoflurane group	[108]
CABG	Sevoflurane 1 MAC 15 min before CPB	Propofol	Sufentanil	72	CTnI	Similar AUC for postoperative cTnI concentrations (up to 12 h)	[109]
MVR	Desflurane 0.5–2 MAC pre-CPB	Propofol	Fentanyl	120	CTnI	Similar postoperative cTnI release in both groups. Significant difference in subgroup of patients with CAD (n = 20) with reduced cTnI peak levels postoperatively	[110]
CABG	Desflurane/ sevoflurane > 0.5 MAC at least 30 min before CC until at least 10 min after CC	Propofol	Not defined	414	CTnI	No difference in postoperative cTnI peak levels and AUC between groups	[111]
CABG	Isoflurane 0.5–1 MAC during surgery	Propofol	Sufentanil	84	CTnI	Similar postoperative cTnI peak levels in both groups	[112]
OPCAB	Sevoflurane during surgery	Propofol	Remifentanil	94	CTnI	Similar postoperative cTnI levels in both groups	[113]
OPCAB	Sevoflurane 1.5–2.5%	Propofol	Fentanyl	38	CTnI	Similar postoperative cTnI peak levels in both groups. Increased oxidative stress markers in propofol group	[114]

Table 4 (*continued*)

Procedure	Anaesthetic intervention	Control group	Analgesia	n	Cardiac marker	Other findings apart from no difference between postoperative biomarkers	Reference
MVR	Sevoflurane 0.5–2 MAC pre- + post-CPB	Propofol	Fentanyl	100	CTnI	Similar postoperative cTnI peak levels in both groups	[115]
CABG	Sevoflurane during surgery and postoperatively, not during CPB	Propofol	Remifentanil	73	CTnI	Similar postoperative cTnI peak levels in both groups	[116]
OPCAB	Sevoflurane 1–2% or desflurane 4–6% during surgery	Propofol	Fentanyl	139	CTnT	Similar postoperative cTnT levels in all three groups up to 96 h after surgery	[117]

CABG, coronary artery bypass graft surgery; MAC, minimal alveolar concentration; CPB, cardiopulmonary bypass; CTnI, cardiac troponin I; MIDCAB, minimally invasive direct coronary artery bypass surgery; CTnT, cardiac troponin T; LAD, left anterior descending artery; OPCAB, off-pump coronary artery bypass graft surgery; AUC, area under the curve; MVR, mitral valve replacement; CAD, coronary artery disease; CC, aortic cross-clamp.

problem with statistical power [112]. Soro et al. compared three groups of patients, with one group receiving propofol only, the second group sevoflurane during surgery and the third receiving sevoflurane during surgery and postoperatively in the cardiac intensive care unit before tracheal extubation [116]. This study was designed as a double-blind trial, with sevoflurane administered using an infusion pump. There was no difference between the groups with regard to postoperative myocardial ischaemic markers. However, nearly half of the patients were diabetic, which might have blocked potential cardioprotective effects, and relatively low doses of sevoflurane (1 MAC) were used postoperatively, which may not have been high enough to induce significant myocardial protection [116]. Wang et al. reported that the administration of 1 MAC of isoflurane for 5 min, plus a 5-min washout before CPB, did not result in reduced postoperative troponin levels [104]. However, only a single application/washout period was included, which may have reduced the effect of the intervention. Similarly, Piriou et al. showed that 1 MAC of sevoflurane for 15 min before CPB had no effect compared with propofol [109]. Potential causes of the negative outcome of this trial include: the dose, which may have been too low; the administration pattern, which was not intermittent; and the administration time, which may have been too short and/or the washout period too long [109].

De Hert et al. assessed a large cohort of patients (n = 414) in a multicentre randomised trial; interestingly, they did not observe a change in postoperative troponin I peak levels in patients receiving volatile anaesthetics, compared with propofol anaesthesia. However, the protocol in this trial allowed the centres to administer sevoflurane or desflurane in different patterns. All patients received the volatile anaesthetic during CPB, and some patients in addition both before and/or after CPB. The type of analgesia was not fixed [111]. In contrast to the troponin I results, however, they observed trends in clinical outcomes in favour of volatile anaesthetics; the 1-year mortality was 12.3% in the propofol group, but only 3.3% in the sevoflurane and 6.7% in the desflurane groups, and the hospital length of stay was reduced in the group receiving volatile anaesthetics.

In contrast to Wang et al., who demonstrated a cardioprotective effect of sevoflurane during CABG without CPB [103], five other study groups did not observe a similar effect [107, 108, 113, 114, 117]. Three of these trials recruited small numbers of patients with n = 18, [107], n = 20 [108] and n = 38 [114], which may have contributed to the negative results, as they are likely to have been statistically underpowered. In addition, the relatively short duration of ischaemia during CABG without CPB, and the low doses of sevoflurane used, may have contributed to the confounding results. Ballester et al. assessed levels of oxidative stress

during CABG without CPB, by analysing lipid peroxidation and nitrosative stress biomarkers from the coronary sinus. These remained constant in the sevoflurane group, but were significantly increased in the control group receiving propofol, suggesting that oxidative stress is reduced with sevoflurane [114]. Suryaprakash et al. studied 139 patients undergoing CABG without CPB, randomly allocated to anaesthesia using sevoflurane, desflurane or propofol [117]. Postoperative troponin levels were similar in all study groups, possibly owing to insufficient statistical power [117].

It is hard to draw firm conclusions from these results, with some studies showing beneficial effects of volatile anaesthetics, others demonstrating beneficial effects of propofol, and one recent study showing that a combination of volatile anaesthetics plus propofol provides optimal myocardial protection. Similarly, different administration patterns of volatile anaesthetics during surgery, and only before CPB, have been shown to be beneficial. This variability may be a result of different anaesthetic and surgical techniques, operations, patient co-morbidities and peri-operative drug administration. Another issue to consider is that troponin release after cardiac surgery does not always indicate irreversible myocardial damage, as has been demonstrated recently by Pegg and colleagues, using delayed enhancement cardio-MRI after CABG surgery [90]. The release pattern of troponin from myocardial tissues occurs in two phases: an initial troponin peak between 1 h and 6 h postoperatively, with non-necrotic/reversible myocardial injury and troponin release from the cytoplasmic compartment, due to CPB; and a delayed and sustained secondary release pattern with a peak after 24 h, caused by degradation of the contractile myofibril apparatus, inducing necrosis. Pegg et al. concluded that either several postoperative troponin measurements resulting in a washout curve (area under the curve), or equally a 24-h post-surgery single measurement of troponin I, correlate best with new postoperative myocyte necrosis. This differential picture of troponin release may further explain contradictory results in the assessment of preconditioning using volatile anaesthetics, with troponin levels as the primary outcome measure.

Apart from ischaemic markers, inflammatory markers may be reduced in patients receiving volatile anaesthetic agents, which may have a beneficial effect on postoperative morbidity and mortality. For example, sevoflurane reduced interleukin (IL)-6 and IL-8 concentrations in patients undergoing CABG surgery compared with propofol [95]. In another clinical trial, sevoflurane 2% was added to the cardioplegia, which resulted in a reduced postoperative inflammatory response, indicated by lower IL-6, CD11b/CD18, and TNF-alpha serum levels postoperatively, compared with a control group receiving only propofol [120].

In summary, it is evident from the above clinical proof-of-concept trials that all three volatile anaesthetics (isoflurane, desflurane and sevoflurane) have the potential to provide myocardial protection, and also that some patterns of administration, e.g. during the whole surgical procedure and intermittently before CPB, may increase the potential protection from volatile anaesthetics. In addition, recent data have suggested that a combination of volatile anaesthetics and a high dose of propofol during bypass and reperfusion might increase myocardial protection [102].

So far, clinical trials have been too small to investigate the effects of volatile anaesthetics on clinical outcomes such as postoperative myocardial infarction and mortality. Nevertheless, clinical outcome has been addressed by two retrospective longitudinal studies and by recent meta-analyses. In the longitudinal studies, a total of 34 310 patients undergoing CABG in 64 Italian cardiac surgery centres, and 10 535 consecutive patients undergoing cardiac surgery in three Danish centres, were studied; both suggested that the use of volatile anaesthetic agents is associated with a decline in 30-day mortality [121, 122]. One meta-analysis of 2979 patients in 27 trials showed that the protective intracellular effects of volatile anaesthetic agents on the myocardium in patients undergoing CABG surgery resulted in reduced postoperative troponin I levels, higher cardiac indices and a lower requirement for inotropic support [123]. However, the authors were unable to demonstrate a significant clinical benefit from volatile anaesthetics on other outcome variables such as myocardial infarction or mortality, predominantly because the studies were small, with low statistical power for clinical endpoints. In another meta-analysis, including 2841 patients from 32 clinical trials, Yu and Beattie found no difference in

postoperative myocardial infarction or in-hospital mortality [124]. Similarly, Yao and Li, who assessed the potential beneficial effects of sevoflurane on clinical outcome in 696 patients, did not find any differences in postoperative myocardial infarction or mortality [125].

In contrast, another meta-analysis of 1922 patients from 22 clinical trials showed a reduction in postoperative myocardial infarction and mortality with the use of volatile anaesthetics [126]. Only proof-of-concept studies investigating sevoflurane or desflurane were included, and the volatile anaesthetics were mainly administered throughout the cardiac surgery, or before CPB. Recently, Landoni et al. published another meta-analysis with the largest number of patients so far, assessing clinical outcomes and anaesthetic preconditioning [127]. A total of 3642 patients from 38 trials were included. Postoperative mortality was doubled in patients receiving total intravenous anaesthesia, compared with those receiving volatile anaesthetics in cardiac surgery, from 25/1994 (1.3%) in the volatile anaesthetic group to 43/1648 (2.6%) in the group of patients receiving intravenous anaesthesia. Despite the relatively large number of patients, the authors commented that the number of patients enrolled in clinical trials investigating the potential benefits of volatile anaesthetics in cardiac surgery is still low, and that there is a need for large randomised trials. Limitations of the above meta-analyses include the potentially suboptimal quality and heterogeneity of the proof-of-concept trials that were included, as well as the different secondary endpoints.

Conclusions

There is evidence from experimental in-vitro and in-vivo trials that volatile anaesthetics have a beneficial effect, by inducing myocardial protection. This body of evidence includes not only animal studies, but also in-vitro analysis of human myocardial muscle tissue or cells. The translation of the experimental evidence into clinical practice has, to date, resulted in many small- to medium-sized proof-of-concept trials, with only surrogate myocardial ischaemic markers as the primary outcome measure. The results of these trials are promising, with many studies indicating a beneficial effect of volatile anaesthetics in patients undergoing cardiac surgery. However, they remain inconclusive. The evidence has not been convincingly translated from experimental studies into the clinical setting, and there is still a high degree of variability in anaesthetic techniques, with different administration patterns, including volatile anaesthetics and/or propofol [128, 129]. Larger pragmatic, multicentre trials are therefore required to investigate whether volatile anaesthetic agents in cardiac surgery have the potential to reduce the incidence and severity of major adverse clinical endpoints, such as peri-operative cardiac events, or postoperative mortality [130]. The results of these multicentre clinical outcome trials will be necessary to inform the evidence base, and change our clinical practice.

Competing interests

AAK is an Editor of *Anaesthesia* and this paper has undergone an additional external review as a result. No external funding declared.

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