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REVIEW

Inflammatory response and cardioprotection during open-heart surgery: the importance of anaesthetics

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Open-heart surgery triggers an inflammatory response that is largely the result of surgical trauma, cardiopulmonary bypass, and organ reperfusion injury (e.g. heart). The heart sustains injury triggered by ischaemia and reperfusion and also as a result of the effects of systemic inflammatory mediators. In addition, the heart itself is a source of inflammatory mediators and reactive oxygen species that are likely to contribute to the impairment of cardiac pump function. Formulating strategies to protect the heart during open heart surgery by attenuating reperfusion injury and systemic inflammatory response is essential to reduce morbidity. Although many anaesthetic drugs have cardioprotective actions, the diversity of the proposed mechanisms for protection (e.g. attenuating Ca^{2+} overload, anti-inflammatory and antioxidant effects, pre- and post-conditioning-like protection) may have contributed to the slow adoption of anaesthetics as cardioprotective agents during open heart surgery. Clinical trials have suggested at least some cardioprotective effects of volatile anaesthetics. Whether these benefits are relevant in terms of morbidity and mortality is unclear and needs further investigation. This review describes the main mediators of myocardial injury during open heart surgery, explores available evidence of anaesthetics induced cardioprotection and addresses the efforts made to translate bench work into clinical practice.
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Keywords: cardiac surgery; inflammation; anaesthetics; ischaemia; reperfusion; cardiopulmonary bypass; cardioplegia; cytokine

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; IL, interleukin; K_{ATP}, channels ATP-dependent potassium channels; NO, nitric oxide; OPCAB, off-pump coronary artery bypass; PKC, protein kinase C; ROS, reactive oxygen species

Introduction

The predominant underlying cause of coronary heart disease is atherosclerosis, which can result in myocardial infarction. Clinical interventions used to reperfuse the acutely or chronically ischaemic myocardium, include thrombolysis, percutaneous coronary angioplasty and/or coronary bypass surgery (Verma *et al*., 2002; Bolli *et al*., 2004). However, reperfusion of the ischaemic heart can induce myocardial injury. This injury can be further exacerbated during open-heart surgery when the myocardium is exposed global ischaemic cardioplegic arrest (Verma *et al*., 2004). Myocardial reperfusion injury activates neutrophils (Petzelbauer *et al*., 2005), which trigger an inflammatory response resulting in generation of reactive oxygen species (ROS), cytokine release and complement activation, which further induce more cardiac injury (Jordan *et al*., 1999; Franke *et al*., 2005). In addition to the inflammatory response generated as a result of tissue reperfusion injury, there is a significant systemic inflammatory response that is triggered by cardiopulmonary bypass (CPB) during open-heart surgery. The CPB-induced inflammatory response could further contribute to myocardial injury, as surgery without CPB appears to be associated with reduced myocardial injury. Formulating strategies to protect the heart during open-heart surgery by attenuating reperfusion injury and systemic inflammatory response is essential to improve clinical outcome. The concept that selected anaesthetic drugs may provide additional cardioprotective effects during open-heart surgery is relatively new. This review summarizes the current literature and knowledge on triggers and mediators of myocardial injury during open-heart surgery, and different strategies to protect the heart, with special emphasis on the role of anaesthetics.

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Triggers of myocardial injury during open-heart surgery

Systemic inflammatory response

Open-heart surgery with CPB is associated with an acute inflammatory response, which has implications for

postoperative recovery and myocardial function (Freyholdt *et al*., 2003). Despite significant changes and improvements in surgical techniques, inflammation remains a significant problem. Therefore, the development of strategies to control the inflammatory response continues to be the focus of extensive experimental research and clinical studies (Raja and Dreyfus, 2005). In addition to CPB, reperfusion injury of the myocardium and the lungs, and surgical trauma are also important triggers of the inflammatory response (Wan *et al*., 2004; Franke *et al*., 2005; Prondzinsky *et al*., 2005). However, other factors such as temperature, anaesthesia, oxidative stress and genetic predisposal may also contribute. Recent and interesting evidence suggests that the inflammatory response during open-heart surgery is at least in part related to the genetic background of the individual (Lehmann *et al*., 2006).

Myocardial ischaemia and reperfusion

Myocardial ischaemia describes a condition of reduced coronary blood flow resulting in a decrease in the supply of oxygen and nutrients to the heart (reviewed in Suleiman *et al*., 2001). This in turn provokes a fall in energy production by the mitochondria, which is quickly followed by abnormal accumulation and depletion of several intracellular metabolites (for example, a fall in ATP and a rise in lactate). These metabolic changes lead to a decrease in intracellular pH and an increase in the intracellular concentrations of Na^+ and Ca^{2+}, which further consumes ATP. Several membrane ionic pumps and channels are disrupted, leading to membrane depolarization and loss of excitability. If coronary flow is restored quickly, then metabolic and ionic homeostasis are re-established, the plasma membrane repolarizes and recovery occurs. However, reperfusion following prolonged ischaemia can result in irreversible damage (death by necrosis or apoptosis). The main causes of reperfusion injury are cytosolic Ca^{2+} loading and generation of ROS, both of which exacerbate mitochondrial dysfunction and can result in opening of the mitochondrial permeability transition pore. Consequences of reperfusion injury include ventricular fibrillation, myocardial stunning and loss of intracellular proteins. Furthermore, cardiac generation of ROS and their release to the extracellular space can further compromise the cardiac function by, amongst other things, promoting an inflammatory response.

In view of the fact that a reduction in myocardial infarct size improves myocardial function and reduces infarct-related acute mortality (Miller *et al*., 1998), the translation of diverse experimental cardioprotective interventions into clinical settings has been limited (Bolli *et al*., 2004; Cannon, 2005). Reasons like availability of relevant models and species-related differences may be responsible for this.

Cardiac cytokines and oxidative stress during ischaemia and reperfusion

The controversial views regarding the role of CPB in triggering an inflammatory and oxidative response during open-heart surgery have significantly shifted the focus away from the potential role of myocardial reperfusion injury as a source of inflammatory mediators.

Whether oxidative stress is a cause or an effect of myocardial injury during open-heart surgery is not known, but has been implicated in postoperative complications (Christen *et al*., 2005). The primary source of ROS during open-heart surgery on CPB is thought to be the neutrophils (Vinten-Johansen, 2004), which also release several proteolytic enzymes. Neutrophils are activated by agents derived from the systemic circulation, coronary vasculature and myocytes. Cytokines stimulate the upregulation of adhesion molecules on cardiomyocytes that allow neutrophils to adhere and release ROS and proteolytic enzymes (Ren *et al*., 2003). Neutrophils accumulate in the ischaemically damaged and/or reperfused area of the myocardium.

In addition to CPB, the myocardium generates inflammatory mediators and ROS during ischaemia–reperfusion, which would contribute to cardiac functional depression and apoptosis (Wang *et al*., 2005). In a variety of experimental models, cardiac myocytes, when exposed to ischaemia (hypoxia)-reperfusion have been shown to produce interleukin (IL)-6 (Sawa *et al*., 1998; Chandrasekar *et al*., 1999). This cytokine is also produced by the myocardium arrested using cold crystalloid cardioplegia in an experimental model of CPB (Dreyer *et al*., 2000), and in the coronary bed of patients undergoing coronary artery bypass graft (CABG) surgery (Zahler *et al*., 1999). Other inflammatory cytokines can be produced locally in the heart, including IL-8 that is released in the ischaemic myocardium, which would stimulate the upregulation of adhesion molecules on different cell types (Ren *et al*., 2003). This in turn allows neutrophils to adhere to the myocytes and release ROS and proteolytic enzymes. Other proinflammatory cytokines produced by the heart during cardiac insults include IL-18 and IL-1β (Matsumori *et al*., 1999; Pomerantz *et al*., 2001; Deten *et al*., 2003). In addition, heart cells produce IL-10, which is a potent anti-inflammatory cytokine (Jones *et al*., 2001). It is evident therefore that the myocardium is a source of cytokines particularly during ischaemia and reperfusion. What is not known, however, is whether the cytokines synthesized in heart cells are released and therefore could be involved in modulating the inflammatory response. More interestingly would be to know whether cytokines and their action on membrane receptors would alter the myocyte response to cardiac insults.

The cardiac actions of cytokines

It is evident from the above discussion that cytokines, depending on their type, can contribute to either myocardial injury or protection. This effect could be direct on the myocardium or via altering the levels of mediators of cardiac injury. In this respect, proinflammatory cytokines would influence the heart differently from anti-inflammatory ones. IL-6 production has been associated with negative inotropic effects (Finkel *et al*., 1992) and myocardial stunning (Zahler *et al*., 1999). It has been suggested that the acute cardiodepressant (negative inotropic) effect of cytokines is related to enhanced production of nitric oxide (NO) (Stangl *et al*., 2002). NO increases intracellular cyclic guanosine

monophosphate, which activates cyclic guanosine monophosphate-dependent protein kinase that inhibits L-type Ca^{2+} channels inducing negative inotropic effects (Kojda *et al*., 1999). In addition, IL-6 has been implicated in reperfusion injury, where its levels correlated with the extent of left ventricular dysfunction and poor clinical outcome in patients undergoing thrombolysis after myocardial infarction (Bennermo *et al*., 2004; Ikonomidis *et al*., 2005). An effect on neutrophil infiltration may underlie the action of IL-6 as mice deficient in IL-6 showed a reduced neutrophil infiltration in intestine (Cuzzocrea *et al*., 1999). IL-6 has also been shown to inhibit cardiac myocyte apoptosis (Dreyer *et al*., 2000). However this antiapoptotic effect was not confirmed by infusing IL-6 into rat heart but was seen upon infusing an IL-6/soluble IL-6 receptor complex (Matsushita *et al*., 2005). This complex stimulates several cell types not stimulated by IL-6 alone, a process called trans-signalling (Jones *et al*., 2005). Thus, based on currently available data, the role of IL-6 in reperfusion injury has to remain open, but several lines of evidence suggest that high IL-6 plasma levels positively correlate with myocardial damage following reperfusion. Contrary to all this is a proposal (Deten *et al*., 2003) suggesting that proinflammatory cytokines produced by the ischaemic myocytes may be involved in the initiation of wound healing of the necrotic area.

In addition to IL-6, other inflammatory cytokines that originate locally or from the systemic circulation, particularly IL-8, that would also exacerbate cardiac injury by enhancing leukocyte activation and accumulation. In fact, postoperative levels of cardiac troponin-I have been shown to correlate with IL-8 levels in patients undergoing CABG surgery (Wan and Yim, 1999). Another cytokine, IL-18 has been shown to activate proapoptotic signalling pathways and induces endothelial cell death (Chandrasekar *et al*., 2004). In addition to the effects of proinflammatory cytokines, the heart is also influenced by anti-inflammatory ones. For example IL-10 deficiency augments reperfusion injury possibly by enhancing the infiltration of neutrophils into the myocardium (Jones *et al*., 2001).

Cardioprotective strategies during open-heart surgery

The anti-inflammatory approach

Several anti-inflammatory techniques and pharmacological agents (largely aimed at coping with CPB) have been used in recent years in cardiac surgery. These include leukocyte filtration, corticosteroids, aprotinin, heparin and NO donor compounds (Harig *et al*., 2001; Paparella *et al*., 2002; Asimakopoulos and Gourlay, 2003; Goudeau *et al*., 2007). Despite the relatively small number of studies investigating the effects of reducing the inflammatory response on myocardial reperfusion injury, majority of these studies have shown evidence of myocardial protection. For example, aprotinin (serine protease inhibitor) pretreatment has been shown to reduce reperfusion injury in patients undergoing cardiac surgery (CABG and valvular) on CPB (Goudeau *et al*., 2007). The administration of sodium nitroprusside (NO donor compound) at a non-vasodilatory dosage in patients undergoing CABG on CPB reduces the myocardial inflammatory response and improves postoperative cardiac pump function (Freyholdt *et al*., 2003). Reducing the inflammatory response by leukocyte filtration has also been shown to improve clinical and biochemical indices of myocardial reperfusion injury after elective coronary revascularization with CPB (Matheis *et al*., 2001; Palatianos *et al*., 2004). Heparin-coated circuits were found to reduce inflammatory responses to CPB and myocardial injury in patients undergoing heart or heart–lung transplantation (Wan *et al*., 1999), and in patients undergoing elective CABG with CPB (Harig *et al*., 1999). More recently, this technique was found to reduce reperfusion injury in patients undergoing cardiac surgery on CPB (Goudeau *et al*., 2007). Corticosteroids are used during cardiac surgery to reduce CPB-induced systemic inflammatory response (for example, Harig *et al*., 2001). in children undergoing open-heart surgery on CPB and pretreated with dexamethasone, this anti-inflammatory response has been associated with a reduction in cardiac reperfusion injury (Checchia *et al*., 2003). Although major reviews of clinical studies have indicated that such intervention has little clinical benefit (Chaney, 2002; Asimakopoulos and Gourlay, 2003), a recent randomized, multicentre trial demonstrated that intravenous hydrocortisone significantly reduces atrial fibrillation after cardiac surgery (Halonen *et al*., 2007).

Whether the cardiac actions of these techniques and pharmacological agents are directly due to a reduction in inflammatory response remains to be determined, as this issue is complicated by the fact that there are several myocardial factors (changes) that could influence reperfusion injury following on-pump cardiac surgery. For example there are haemodynamic and osmotic changes that can result in oedema in the heart (Simonardottir *et al*., 2006).

Off-pump coronary artery bypass surgery

It has been proposed for many years that excluding CBP circuit and avoiding cardioplegic ischaemic arrest would significantly reduce the stress response associated with open-heart surgery. It is now widely accepted that beating heart surgery performed without the aid of CPB significantly attenuates cytokine and stress response (Ganapathy *et al*., 2001; Raja, 2004; Yamaguchi *et al*., 2005; Lehmann *et al*., 2006). The reduced inflammatory response has been associated with improvement in organ function (Ascione *et al*., 2000, 2001, 2002a, b; Caputo *et al*., 2002b) and postoperative bleeding (Raja and Dreyfus, 2006). However, as the inflammatory response is only reduced and not prevented, it is likely to continue to influence cardiac function and clinical outcome (Quaniers *et al*., 2006). The main source is likely to be surgical trauma, which will continue to trigger a stress response mediated by the release of various cytokines and stress hormones. Therefore, not employing CPB and cardioplegic arrest does not necessarily mean the absence of inflammatory response.

Although the relationship between inflammation and clinical outcome after off-pump coronary artery bypass (OPCAB) has been addressed (Aljassim *et al*., 2006; Raja and Dreyfus, 2006), little work has investigating the relationship

between inflammatory response and cardiac function been done. The use of a miniature bypass system (beating-heart surgery) was not effective in improving haemodynamic performance or reducing myocardial injury compared to on-pump surgery (Rex *et al*., 2006). However, an early study investigating the safety of OPCAB revascularization demonstrated that this procedure also reduced myocardial injury (Ascione *et al*., 1999).

A block of cardiac sympathetic activity is an interesting route to reduce inflammation and myocardial injury during OPCAB surgery (Ganapathy *et al*., 2001). In fact it has been suggested that differences in the changes in plasma catecholamines may explain why outcome during an inflammatory response is different. Catecholamines increase intracellular cyclic adenosine monophosphate (cAMP), which in rat cardiac myocytes induces IL-6 production (Briest *et al*., 2003). In humans, adrenaline infusions have been shown to stimulate plasma IL-6 production both in healthy adult volunteers and in HIV-infected patients (Sondergaard *et al*., 2000; Keller *et al*., 2004).

Cardioplegic solutions

Major advances have been made in the preservation of myocardial function during open-heart surgery since the introduction of cardioplegic arrest (Melrose *et al*., 1955). However, despite variation in the composition of cardioplegia, myocardial protection has been based primarily on high-potassium cold cardioplegic solution. Although cardioplegia does confer protection, human hearts still suffer damage. This is because under these conditions the heart is rendered ischaemic and therefore susceptible to reperfusion injury. More recent strategies for myocardial protection include one or more combinations of warm- versus cold-blood cardioplegia, antegrade versus retrograde delivery, intermittent versus continuous perfusion, and the inclusion of various additives that aim at reducing Ca^{2+} overload, provide energy substrates and remove harmful ROS (Demmy *et al*., 1994; Buckberg, 1995; Caputo *et al*., 1998a, b, 2002a; Liebold *et al*., 1999; Thourani *et al*., 1999; Matsuda *et al*., 2000; Imura *et al*., 2001; Ascione *et al*., 2002; Lotto *et al*., 2003; Ji *et al*., 2006; Kacila *et al*., 2006; Pouard *et al*., 2006; Susumu *et al*., 2006).

Ischaemic conditioning (pre- and post-conditioning)

Hearts can be protected from reperfusion injury by subjecting them to brief ischaemia/reperfusion cycles before (preconditioning) or after (post conditioning) starting the prolonged period of ischaemia (see recent reviews, Bolli, 2007; Hausenloy and Yellon, 2007). The mechanisms responsible for this protection are not fully understood, but several processes have been implicated (Tsang *et al*., 2004, 2005; Hausenloy *et al*., 2005; Vinten-Johansen *et al*., 2005; Yellon and Hausenloy, 2005; Hausenloy and Yellon, 2006, 2007; Yellon and Opie, 2006; Bolli, 2007). The signal transduction pathways underlying classical preconditioning involve 'triggers' that activate 'mediators' (for example, protein kinases), which in turn activate effectors. In addition, heart cells appear to have a memory so that several days later the protection is still detectable. This delayed preconditioning involves the stimulation of transcription of distal mediators and effectors. More recently, the concept of conditioning has been extended to post-conditioning, which describes the cardioprotection resulting from brief ischaemia/reperfusion cycles during reperfusion (Hausenloy and Yellon, 2007). Conditioning (pre and post) are potentially useful in cardiological and cardiac surgical settings (Hausenloy and Yellon, 2007). In addition to ischaemia-related protective conditioning, other conditioning-type interventions (for example, pharmacological, temperature) before or after prolonged ischaemia have also been reported (Bolli, 2007; Khaliulin *et al*., 2007).

Ischaemic conditioning has strong clinical implications both in cardiology and during cardiac surgery. The human myocardium can be preconditioned (reviewed in Yellon and Downey, 2003) as shown *in vitro* (for example, muscle preparations) and *in vivo* (for example, angioplasty and surgical studies). There is also evidence that the human myocardium can undergo remote and post-conditioning (Hausenloy and Yellon, 2007). However, despite the potential benefits of these phenomena and an array of conditioning agents, clinical applications and use remains controversial.

Anaesthetics as cardioprotective agents

A large number of anaesthetic agents have been implicated in protecting the heart against ischaemia and reperfusion injury. Several mechanisms have been proposed to explain their cardioprotective action, which include preconditioning, antioxidant and anti-inflammatory activities (Kato and Foex, 2002; Kevin *et al*., 2005; Riess *et al*., 2005).

Cardioprotection with inhalation anaesthetics

Volatile anaesthetics to various degrees have been shown to decrease myocardial contractility and myocardial oxygen demand, a property that has been suggested to explain cardioprotection against ischaemia and reperfusion (Coetzee *et al*., 1993; Mattheussen *et al*., 1993; Schlack *et al*., 1998). However, these anaesthetics were also found to induce cardioprotection via mechanisms that are similar to pathways involved in ischaemic preconditioning (Cope *et al*., 1997). It is, however, a combination of alteration in contractility and metabolism, as well as a preconditioning-like effect, that appears to be responsible for the protective properties against ischaemia and reperfusion damage (reviewed in De Hert, 2006).

Isoflurane. The use of isoflurane during cardiac surgery has been complicated by a controversial issue associated with isoflurane-induced coronary steal. This phenomenon describes a redistribution of collateral blood flow away from ischaemic regions, thus suggesting that isofluarne would exacerbate the ischaemic insult in an already compromised myocardial region. Although isoflurane has been shown to cause coronary steal in experimental models of chronic coronary occlusion (for example, Buffington *et al*., 1987), most clinical studies did not (reviewed in Agnew *et al*., 2002).

Key factors responsible for this controversy have been poor control of haemodynamics and lack of evidence supporting steal-prone anatomy. For example, in patients undergoing CABG, adequate control of haemodynamics was not associated with isoflurane-induced coronary artery steal (Leung *et al*., 1991, 1992).

The role of isoflurane in myocardial protection has been extensively studied. Earlier studies have attributed its protective action to improving metabolism possibly by blocking L-type Ca^{2+} channels (Coetzee *et al*., 1993), preserving energy-rich phosphates (Mattheussen *et al*., 1993), vasodilation of coronary vessles (Crystal *et al*., 1996) and to reduce expression of the adhesion molecules (Heindl *et al*., 1999b). However, there were reports that isoflurane offered no protection against reperfusion injury *in vivo* (Preckel *et al*., 1998a).

In recent years there has been a shift in interpreting the mechanisms underlying the cardioprotective action of isoflurane and other halogenated anaesthetics as triggers of a preconditioning-like phenomenon. This started from work showing that isoflurane activates ATP-dependent potassium channels (K_{ATP}) channels (Kersten *et al*., 1996) and its cardioprotection appears to involve the opening of mitochondrial K_{ATP} channels and generation of ROS that are upstream of protein kinase C activation (Shimizu *et al*., 2001; Dworschak *et al*., 2004; Ludwig *et al*., 2004). Isoflurane cardioprotection triggers partial mitochondrial uncoupling and reduces mitochondrial Ca^{2+} uptake (Ljubkovic *et al*., 2007). Interestingly, the pro-survival signalling pathways seen during classical ischaemic preconditioning are also involved in this cardioprotection (reviewed in Pratt *et al*., 2006). Activation of these pathways and modulation of the expression of pro- and antiapoptotic proteins may play a role in isoflurane (and other volatile anaesthetics)-induced myocardial protection (Raphael *et al*., 2006). The differences between classical ischaemic preconditioning and isoflurane-induced preconditioning-like cardioprotection are not well understood. For example, the combination of ischaemic preconditioning and isoflurane did not improve haemodynamic recovery, but did increase preservation of ATP (Boutros *et al*., 1997). Cardioprotection by isoflurane can be augmented by adenosine and NO donor possibly involving mitochondrial K_{ATP} channel (Wakeno-Takahashi *et al*., 2004). Interestingly, isoflurane cardioprotection has an additive protective effect when used with cardioplegia or with Na^+/Ca^{2+} exchanger inhibition (Preckel *et al*., 1998b; An *et al*., 2006). Cardioplegia protects by arresting the heart and preserving metabolites, thus delaying Ca^{2+} overload, which is essentially similar to what happens as a result of inhibiting Na^+/Ca^{2+} exchanger.

In addition to its preconditioning-like effect, isoflurane has been shown to produce a second window of preconditioning in mice *in vivo* (Tsutsumi *et al*., 2006). This effect could be mediated by cyclooxygenase-2 (Tanaka *et al*., 2004), or through overexpression and activation of iNOS (Wakeno-Takahashi *et al*., 2005). There are, however, reports that isoflurane does not produce a second window of preconditioning in dogs *in vivo* (Kehl *et al*., 2002). An interesting and clinically relevant effect (for example, infarct-remodelled myocardium) is the finding that isoflurane is cardioprotective when present during reperfusion (Chiari *et al*., 2005; Tessier-Vetzel *et al*., 2006). The mediators involved in this protection include NO, activation of phosphatidylinositol-3-kinase signal transduction and phosphorylation of protein kinase B/Akt (Feng *et al*., 2006; Tessier-Vetzel *et al*., 2006). Finally, availability of gene chips has enabled researchers to show that ischaemic preconditioning and isoflurane cardioprotection appear to differentially modulate gene expression in rat hearts suggesting trigger-dependent transcriptome variability (Sergeev *et al*., 2004).

Sevoflurane. Although there are reports that sevoflurane does not induce preconditioning-like cardioprotection (Piriou *et al*., 2002), others have reported that it does and the effect is mediated by mitochondrial K_{ATP} channel opening (Hara *et al*., 2001; Riess *et al*., 2002). This type of preconditioning occurs after long-term hypothermic ischaemia (Chen *et al*., 2002), and is independent of the cardioplegic solution used (Ebel *et al*., 2002). It has also been suggested that this protection is triggered by ROS/nitrogen species (Novalija *et al*., 2002), and like ischaemic preconditioning, it reduces Ca^{2+} loading (An *et al*., 2001).

Myocardial protection by sevoflurane could also be related to its anti-inflammatory effect. For example, pretreatment of hearts with sevoflurane reduces intracoronary platelet adhesion most likely via an endothelial mechanism (Heindl *et al*., 1999a). During cardiac surgery, sevoflurane was found to suppress the production of IL-6 and IL-8, but not IL-10 and IL-1Ra, indicating that sevoflurane protects the heart by modulating the levels of pro- and anti-inflammatory cytokines (Kawamura *et al*., 2006). Furthermore, the addition of sevoflurane to cardioplegia has been associated with an inhibition of neutrophils activity after CPB (Nader *et al*., 2006).

Desflurane. Desflurane does not induce coronary steal in experimental models (Hartman *et al*., 1991; Warltier and Pagel, 1992). However, desflurane, like other volatile anaesthetics, has been shown to be cardioprotective (Preckel *et al*., 1998a, b). Furthermore, the onset of functional recovery following ischaemia and reperfusion in isolated rat heart was much earlier with desflurane than with other anaesthetics (Schlack *et al*., 1998). There is also strong recent evidence demonstrating that desflurane confers a preconditioning-like cardioprotection (Toma *et al*., 2004; Tsai *et al*., 2004; Smul *et al*., 2006). This protection appears to involve both sarcolemmal and mitochondrial K_{ATP} channels (Toller *et al*., 2000) and mediated by NO (Smul *et al*., 2006), but does not involve tyrosine kinase activation (Ebel *et al*., 2004). Recently it has been suggested that signal transduction pathways associated with β1-adrenergic receptor mediate anaesthetic preconditioning for desflurane and sevoflurane (Lange *et al*., 2006). Such signalling involves an increase of intracellular cyclic adenosine monophosphate, which is likely to improve contractility and Ca^{2+} cycling. In addition to its preconditioning effect, desflurane also has a post-conditioning-like effect, as the drug is protective when administered before, during or after ischaemia, or throughout the experiment (Haelewyn *et al*., 2004).

An interesting observation was made while investigating whether desflurane can be used to augment cardioplegic protection (Preckel *et al*., 1999). Addition of desflurane (or sevoflurane) during the early reperfusion period confers additional protection against reperfusion injury in isolated rat heart.

The administration of desflurane to human volunteers can lead to substantial activation of the neurohumoral axis (sympathetic activation and hypertension), which can be reduced by propofol induction (Lopatka *et al*., 1999). However, in multicentre randomized controlled study in which OPCAB patients received either desflurane or propofol in addition to an opiate-based anaesthesia, desflurane significantly reduced myocardial damage and improved clinical outcome (Guarracino *et al*., 2006).

Other volatile anaesthetics. Several other volatile anaesthetics have been implicated in myocardial protection. These include nitrous oxide (N_2O), halothane and xenon. However, these are hardly used in cardiac surgery and appear to have diverse and different cardiac actions. N_2O is without preconditioning effect on the heart and it does not alter isoflurane-induced preconditioning (Weber *et al*., 2005a).

Halothane is cardioprotective and this effect has been initially attributed to its antiarrhythmic (depressant) effect (Deutsch *et al*., 1990; Oguchi *et al*., 1995), possibly by reducing Ca^{2+} loading (Drenger *et al*., 1994). In addition, it has been shown to inhibit the production of hydroxyl radicals (Glantz *et al*., 1997), which could in turn prevent disruption in intracellular Ca^{2+} mobilization during reperfusion (re-oxygenation) (Siegmund *et al*., 1997). The relevance of its post-ischaemic effect has been confirmed using an *in vivo* model, which was independent of the haemodynamic effect of halothane (Schlack *et al*., 1997). The link to intracellular Ca^{2+} mobilization has been recently highlighted by data suggesting that at low ATP levels the ryanodine receptor sensitivity increases in the presence of halothane (Yang *et al*., 2005). Like other volatile anaesthetics, halothane has also been shown to induce preconditioning (Piriou *et al*., 2002) and to reduce post-ischaemic adhesion of neutrophils in the coronary system (Kowalski *et al*., 1997).

The chemically inert and anaesthetic gas xenon induces preconditioning of the heart possibly by eliciting partial mitochondrial uncoupling and reducing mitochondrial Ca^{2+} uptake (Weber *et al*., 2005b, 2006). In addition to its preconditioning-like effect, xenon is protective when administered during early reperfusion in the rabbit heart *in vivo* (Preckel *et al*., 2000).

Cardioprotection with intravenous anaesthetics

Examples of injected drugs that are used during anaesthesia are barbiturates, propofol, ketamine and etomidate, as well as larger doses of opioids (for example, fentanyl) and benzodiazepines. In contrast to inhalation anaesthetics, some of theses anaesthtics (for example, pentobarbital, ketamine–xylazine or propofol) are not as effective at protecting the heart against reperfusion injury, and their action is not related to ischaemic preconditioning. Etomidate (carboxylated imidazole) is a popular choice for the induction of anaesthesia in cardiac compromised patients, as it does not alter cardiovascular activity (Bovill, 2006).

Ketamine. A number of earlier experimental studies have indicated that ketamine is not cardioprotective, and there has been suggestions that ketamine itself contributes to generation of radicals (Reinke *et al*., 1998). Ketamine inhibits the K_{ATP} channel activity in a concentration-dependent manner in rat heart, thus raising the possibility that ketamine may attenuate the cardioprotective effects of the K_{ATP} channel during ischaemia and reperfusion (Ko *et al*., 1997). In fact, ketamine has been shown to attenuate the cardioprotective effects of ischaemic preconditioning in an enantiomer-specific manner, with R(−), and not S(+), being the isomer responsible for this blockade (Molojavyi *et al*., 2001; Mullenheim *et al*., 2001a, b).

More recently, work on isolated human atrial myocardium has shown that ketamine confers preconditioning-like protection that is similar to inhalation anaesthetics (Hanouz *et al*., 2005). Ketamine has an anti-inflammatory effect and has been shown to reduce ROS generation by neutrophils and to decrease endotoxin-stimulated IL-6 production in human whole blood (Weigand *et al*., 2000). Although it does not impair neutrophil function (Nishina *et al*., 1998), ketamine reduces post-ischaemic adhesion of neutrophils in the coronary system of isolated perfused guinea pig hearts at clinically relevant concentrations (Szekely *et al*., 2000).

Propofol. Propofol is a general anaesthetic used widely for induction and maintenance of anaesthesia during cardiac surgery and in postoperative sedation (reviewed in Bryson *et al*., 1995; Kato and Foex, 2002; Bovill, 2006). It has also been shown to protect the heart against cardiac insults in a variety of experimental models (Kokita and Hara, 1996; Kokita *et al*., 1998; Javadov *et al*., 2000). These effects were attributed to its ability to act as a free-radical scavenger (Stratford and Murphy, 1998), enhancing tissue antioxidant capacity (Xia *et al*., 2003a, b), and through inhibition of plasma membrane calcium channels (Buljubasic *et al*., 1996; Li *et al*., 1997). Some of these effects (for example, antioxidant) could be responsible for its inhibitory action of mitochondrial permeability transition pore opening in the Langendorff perfused rat heart (Javadov *et al*., 2000), and its antiapoptotic properties (Roy *et al*., 2006). Cardioprotection by propofol could also be due to its ability to increase protein kinase C activity in cardiomyocytes (Wickley *et al*., 2006).

Although there is extensive evidence that propofol provides cardioprotection against ischaemia and reperfusion, its benefits when used in models of cardiac surgery have not been demonstrated (Coetzee, 1996; Thompson *et al*., 2002). Reports of the benefits of its use in cardiac surgery are conflicting (De Hert *et al*., 2002; Sayin *et al*., 2002). It has been suggested that its use in cardiac surgery could be beneficial when used after the onset of ischaemia (Kato and Foex, 2002). More recently however, a pig model of cardiopulmonary bypass and cardioplegic arrest demonstrated the cardioprotective action of propofol when used

at clinically relevant concentrations (Lim *et al*., 2005). However, the clinical benefits appear to be more evident at higher doses of propofol as shown by Ansley *et al*. (1999), who demonstrated that propofol's antioxidant capacity is enhanced and maintained during CPB when using relatively high dose of the drug. The group later demonstrated that such a dose (plasma levels of approx $4.2\,\mu g\,ml^{-1}$) used as maintenance anaesthesia during CPB in patients undergoing CABG surgery attenuated postoperative myocardial cellular damage, improved cardiac pump function and clinical outcome compared with isoflurane or small-dose propofol anaesthesia (Xia *et al*., 2006).

Fentanyl. Fentanyl is one opioid that has been closely linked to inflammatory mediators and myocardial protection. It reduces the CPB-induced inflammatory response and ischaemic reperfusion injury during cardiac surgery (Liu *et al*., 2005). Its analogues were shown to reduce the inflammatory response during surgery (Elena *et al*., 2006) and oppose the negative inotropic effect induced by inflammatory mediators on rat ventricular myocytes (Duncan *et al*., 2007). These effects are related to improvement in intracellular Ca^{2+} mobilization and do not seem to be related to adhesion of neutrophils in the coronary system (Szekely *et al*., 2000).

Thiopental. It is a commonly used injected barbiturate anaesthetic. Thiopental protects the myocardium during hypoxia and low-flow ischaemia only when the pH is kept at 7.4 (Ruigrok *et al*., 1985). However, in isolated rat heart–lung preparation, thiopental was not cardioprotective, and at high doses it aggravated injury (Kashimoto *et al*., 1987). Thiopental inhibits the inward and delayed rectifier K^+ currents in myocytes and therefore increases the action potential duration (Martynyuk *et al*., 1999). These changes could increase Ca^{2+} loading and would explain the reported deleterious effects. Paradoxically, thiopental has an anti-inflammatory response, as it reduces post-ischaemic adhesion of neutrophils in the coronary system of isolated perfused guinea pig hearts (Szekely *et al*., 2000), and at clinically relevant concentrations, it impairs neutrophil-induced ROS production (Nishina *et al*., 1998).

Anaesthetics, the inflammatory response and cardioprotection
As already discussed, several anaesthetics appear to alter the systemic inflammatory response. This is likely to be a direct effect on the inflammatory mediators or indirectly by reducing myocardial reperfusion injury and associated inflammatory response or both. Unfortunately this issue is likely to remain controversial for the time being, as clinical studies investigating different anaesthetic regimen on systemic inflammatory response and myocardial injury during CPB cardiac surgery are few. In one study comparing sevoflurane and propofol in patients undergoing CABG surgery, Kawamura *et al*. (2006) showed that sevoflurane was associated with less production of cytokines and reduced myocardial injury. The beneficial effects of sevoflurane are also seen when the drug is added to the cardioplegia, where it decreases the inflammatory response and improves myocardial function after CPB in CABG patients (Nader *et al*., 2004, 2006). On the other hand, propofol controlled infusion (compared with saline) immediately before aortic cross-clamp release and during reperfusion in patients undergoing CABG was found to reduce systemic inflammatory response without attenuating myocardial injury (Corcoran *et al*., 2006).

An earlier study investigating the effect of anaesthesia on inflammatory response during CABG surgery has shown no difference in cytokine production using high-dose fentanyl or low-dose opioid anaesthesia (Brix-Christensen *et al*., 1998). More recently, the administration of morphine, but not fentanyl, as part of standardized opioid–isoflurane anaesthetic technique suppressed the inflammatory response to CABG surgery and CPB (Murphy *et al*., 2007)

The effects of volatile anaesthetics have also been associated with preventing the neutrophil-induced coronary endothelial dysfunction. This relationship has been demonstrated in a series of experimental studies by Crystal and co-workers (Hu *et al*., 2003, 2004, 2005a, b). More recently, a clinical study on patients undergoing CABG surgery on CPB has shown that the addition of sevofluarne to cardioplegia reduces neutrophils activity (Nader *et al*., 2006). The finding that desflurane induces greater systemic proinflammatory response than sevoflurane during anaesthesia for ear surgery (Koksal *et al*., 2005), suggests that the latter would be a better choice in clinical settings like OPCAB surgery.

Anaesthetics and cardioprotection: clinical implications

Experimental research described thus far supports the view that most of the anaesthetics used during open- heart surgery are cardioprotective against cardiac insults like ischaemia and reperfusion. However, it is also evident that the efficacy of these anaesthetics is different with some providing significant protection. In contrast, little evidence comes from clinical research, and the extensive experimental research has not been translated to clinical settings. The diversity of the proposed mechanisms for protection by anaesthetics (for example, ischaemic preconditioning-like effect, interference in the neutrophil/platelet–endothelium interaction, blockade of Ca^{2+} overload and antioxidant effect) may have contributed to the slow adoption/utilization of certain anaesthetics as cardioprotective agents during open-heart surgery. However, volatile anaesthetics are widely selected in clinical practice for being cardioprotective.

A recent extensive systematic overview and meta-analysis of randomized trials comparing volatile with non-volatile anaesthesia in CABG surgery has shown that volatile anaesthetics are associated with better myocardial protection compared with intravenous anaesthetics (Symons and Myles, 2006), as shown by improvement in cardiac index and a reduced level in troponin I release. The anti-inflammatory effect of volatile anaesthetics (for example, sevoflurane) seen during CABG surgery is likely to be an important cardioprotective characteristic and supports its use (Kawamura *et al*., 2006). Sevoflurane when used to

induce and maintain anaesthesia was associated with better haemodynamic stability and relatively less cardiac injury compared with propofol (De Hert *et al*., 2002; Samarkandi and Mansour, 2004; Bein *et al*., 2005). Furthermore, using sevoflurane in patients undergoing minimally invasive direct CABG surgery conferred better cardiac protection than propofol (Conzen *et al*., 2003; Bein *et al*., 2005). Even though clinical research suggests that sevoflurane is cardioprotective in patients with ischaemic disease, several factors (for example, old age, diabetes and duration of myocardial ischaemia) may limit the benefits under clinical conditions (Riess *et al*., 2004) and therefore more clinical research is needed before recommending it as an anaesthetic of choice. An additional aspect that adds support to its use is the finding that sevoflurane is not influenced by the type of cardioplegia used (Ebel *et al*., 2002), and that patients undergoing valve surgery had better cardioprotection when sevoflurane was used (Xu *et al*., 1998; Van Der Linden *et al*., 2003; Cromheecke *et al*., 2006).

Propofol protects the myocardium against ischaemia–reperfusion injury, due to its antioxidant effect and inhibition of the mitochondrial permeability transition pore. A recent review focusing on the use of anaesthesia during surgery on a failing heart suggests that the most commonly used intravenous anaesthesia is a combination of propofol and an opioid (Bovill, 2006). Unlike propofol, opioids do not cause myocardial depression and protect the heart by preconditioning-like mechanism and therefore both agents can have an additive effect.

Conclusions

Anti-inflammatory interventions during cardiac surgery are likely to be incorporated into strategies aimed at reducing myocardial injury. The experimental literature suggests that most of the anaesthetic drugs used during open-heart surgery are cardioprotective against ischaemia and reperfusion injury. Although there has been significant progress in selecting anaesthetic drugs that are also cardioprotective, this issue remains controversial. The diversity of the proposed mechanisms for protection by anaesthetics and whether they have anti-inflammatory effects may have contributed to this controversy. Clinical trials have suggested that volatile anaesthetics in general and sevoflurane in particular are good cardioprotective and anti-inflammatory agents when used during open-heart surgery. Whether this is relevant in terms of morbidity and mortality is unclear and needs further investigation.

Conflict of interest

The authors state no conflict of interest.

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