Themed Section: Conditioning the Heart – Pathways to Translation

REVIEW

Anaesthetics as cardioprotectants: translatability and mechanism

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The pharmacological conditioning of the heart with anaesthetics, such as volatile anaesthetics or opioids, is a phenomenon whereby a transient exposure to an anaesthetic agent protects the heart from the harmful consequences of myocardial ischaemia and reperfusion injury. The cellular and molecular mechanisms of anaesthetic conditioning appear largely to mimic those of ischaemic pre- and post-conditioning. Progress has been made on the understanding of the underlying mechanisms although the order of events and the specific targets of anaesthetics that trigger protection are not always clear. In the laboratory, the protection afforded by certain anaesthetics against cardiac ischaemia and reperfusion injury is powerful and reproducible but this has not necessarily translated into similarly robust clinical benefits. Indeed, clinical studies and meta-analyses delivered variable results when comparing in the laboratory setting protective and non-protective anaesthetics. Reasons for this include underlying conditions such as age, obesity and diabetes. Animal models for disease or ageing, human cardiomyocytes derived from stem cells of patients and further clinical studies are employed to better understand the underlying causes that prevent a more robust protection in patients.

LINKED ARTICLES

This article is part of a themed section on Conditioning the Heart – Pathways to Translation. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2015.172.issue-8

Abbreviations

eNOS, endothelial nitric oxide synthase; GSK3β, glycogen synthase kinase 3β; iPSCs, induced pluripotent stem cells; K_{ATP} channel, ATP-sensitive potassium channel; ROS, reactive oxygen species

Tables of Links

TARGETS		
Enzymes[a]	**Ion channels**[b]	
eNOS, endothelial NOS	K_{ATP} channel, $K_{ir}6.2$	
Erk1/2	L-type calcium channels, $Ca_v1.2$	
GSK3β, glycogen synthase kinase 3β	**GPCRs**[c]	
MAPK	Adenosine receptors	
p38	β1-Adrenoceptors	
PI3K	**Transporter**[d]	
PKB/Akt	Adenine nucleotide carrier	
PKCδ		
PKCε		

LIGANDS
Adenosine
Desflurane
Glibenclamide
Halothane
Isoflurane
Morphine
Propofol
Sevoflurane
Vascular endothelial growth factor

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson et al., 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c,d]Alexander et al., 2013a,b,c,d).

Introduction

There is an increased risk of adverse cardiac events, such as ischaemia and infarction, congestive heart failure and arrhythmias, during and after cardiac and other surgery (Tuman, 1991; London, 2009). Early on it was reported that halothane, a volatile anaesthetic, decreased the severity of experimentally induced myocardial ischaemia in the non-failing canine heart whereby ischaemia was produced by repeated reversible occlusions of a coronary artery (Bland and Lowenstein, 1976). Volatile anaesthetic exposure was also associated with a mild depression of heart rate and systemic arterial pressure, suggesting decreased oxygen consumption. Similarly, the recovery of contractile function after a short period of ischaemia and reperfusion ('stunned' myocardium without tissue necrosis) was enhanced by isoflurane, along with preserved levels of ATP (Warltier et al., 1988; Kanaya et al., 1995). Later, it was discovered that volatile anaesthetics protect the heart in vivo and in vitro (Langendorff model) when applied shortly before a period of prolonged coronary artery occlusion (Cason et al., 1997; Cope et al., 1997; Kersten et al., 1997) and discontinued for occlusion, creating a memory effect similar to the very powerful endogenous cardioprotective mechanism of ischaemic preconditioning (Murry et al., 1986). This phenomenon was called anaesthetic preconditioning.

It was shown early on during the discovery of anaesthetic preconditioning, based on the effect of pharmacological inhibitors, that ATP-sensitive potassium (K_{ATP}) channels, PKC and adenosine receptors were involved in protection, again similarly to ischaemic preconditioning (Cope et al., 1997; Kersten et al., 1997). Volatile anaesthetics can also protect the heart when applied 24 to 72 h before a prolonged ischaemic event ('delayed' preconditioning or 'second window' of preconditioning) (Tonkovic-Capin et al., 2002; Pagel and Hudetz, 2011). Potentially clinically most relevant for non-surgery cardiac infarct patients, volatile anaesthetics decreased infarct size when administered immediately after the ischaemic event at the onset of reperfusion (Chiari et al.,

2005; Pagel, 2008). This phenomenon is named anaesthetic post-conditioning. Extensive research in various laboratories throughout the world has advanced our understanding of the mechanisms of cardioprotection by volatile anaesthetics. Many pathways are shared with ischaemic preconditioning and preconditioning by other pharmacological agents such as adenosine or opioids. Here, we will provide a summary of the mechanism involved in anaesthetic cardioprotection, review its translation into the clinical setting and discuss the limitations of anaesthetic-induced protection in the clinical practice.

Protocols and mechanisms of anaesthetic-induced protection

The underlying mechanisms of anaesthetic-induced protection have been investigated on the level of isolated proteins, cellular organelles, cardiomyocytes, isolated hearts and whole animals. Proteins, organelles and cardiomyocytes have been isolated from various animal models and also from humans. In vivo models are utilized to establish the best choice, dosage, timing and frequency of anaesthetic administration for optimal protection against ischaemia and reperfusion injury. When tissue samples are obtained, punctual information about mechanisms, such as alterations of proteins or protein levels at a specific time point can be gathered. Studying the isolated heart or cardiomyocytes additionally allows following online parameters such as ion concentration, redox state or mitochondrial metabolism.

Choice and timing of anaesthetic agent

While volatile anaesthetics are most frequently studied, other anaesthetics have also been implicated in the protection against cardiac injury. As a general anaesthetic agent, propofol is used widely for induction and maintenance of anaesthesia because of its rapid onset and short recovery period. Due to its phenol-based structure, propofol has free radical

scavenging properties that might be beneficial against cardiac ischaemia and reperfusion injury. In addition, propofol acts as a Ca^{2+} channel antagonist by inhibition of cardiac L-type calcium channels which may prevent harmful cellular Ca^{2+} overload. Indeed, propofol improved functional and metabolic recovery in the ischaemic and reperfused isolated rat hearts when applied either before ischaemia and during reperfusion or only during reperfusion (Kokita et al., 1998). However, in an isolated rat heart model of regional ischaemia, propofol applied 5 min before reperfusion for 20 min provided no protective effect against myocardial reperfusion injury (Ebel et al., 1999). Similarly, propofol did not reduce the infarct size after 30 min coronary artery occlusion and 3 h reperfusion on the in vivo rabbit heart (Cope et al., 1997). Similarly, contradicting results were also found when propofol was administered in humans (Conzen et al., 2003; Xia et al., 2006; Ballester et al., 2011). While the beneficial effect of propofol particularly at the time of reperfusion is not firmly established and seems to depend on experimental model of injury and other variables, it seems clear that propofol has no preconditioning properties. When administered before ischaemia and followed by a memory period, the myocardial infarct size in rabbits was not reduced by propofol compared with its solvent intralipid alone. Moreover, propofol abolished the protection that was provided by the volatile anaesthetic desflurane (Smul et al., 2011). This might be explained by the radical scavenging properties as the presence of reactive oxygen species (ROS) is a necessary part of the preconditioning signalling cascade (see 'Mechanisms of anaesthetic-induced protection').

Less is known about the cardioprotective properties of other non-opioid i.v. anaesthetics. The short-acting barbiturate amobarbital reduces cardiac injury and improves mitochondrial function when present during ischaemia (Chen et al., 2006; Aldakkak et al., 2008). When administered during early reperfusion, amobarbital also decreased infarct size compared with untreated hearts (Stewart et al., 2009). The dissociative anaesthetic ketamine, on the other hand, has not been associated with cardioprotection but rather blocks ischaemic preconditioning in rabbit hearts in vivo (Mullenheim et al., 2001).

Opioids are widely used as analgesics alone and along with other agents such as i.v. non-opioid or inhalational anaesthetics. Morphine, through opioid receptor stimulation, causes a reduction in infarct size in rats similar to that produced by ischaemic preconditioning when applied intermittently before myocardial ischaemia (Schultz et al., 1996). These findings were confirmed and extended to other opioids, animal models, isolated heart and cardiomyocytes (Miki et al., 1998; Liang and Gross, 1999; Zhang et al., 2004). When applied 24 or 48 h before ischaemia, opioids also induced delayed cardioprotection in rats subjected to 30 min ischaemia and 2 h reperfusion (Fryer et al., 1999). Accumulating data demonstrate that opioids confer cardioprotection when applied at reperfusion as well (Weihrauch et al., 2005; Jang et al., 2008; Kim et al., 2010). This was extended to humans where morphine-induced post-conditioning reduced ischaemia and reperfusion injury in patients undergoing corrections of Tetralogy of Fallot (Zhang et al., 2013b).

Inhalational anaesthetics that have well-described cardioprotective properties include volatile anaesthetics and noble gases. In healthy, non-aged animal models, they protect against cardiac reperfusion injury as preconditioning, delayed preconditioning and post-conditioning agents. A notable exception is nitrous oxide (60%) that when administered for three 5 min periods before ischaemia and reperfusion in rats did not have an effect on infarct size (Weber et al., 2005a). In head-to-head comparisons of volatile anaesthetics, some differences in protective efficacy were found but those were minor and not consistent in different animals and protocols (Piriou et al., 2002; Redel et al., 2009). Overall, no 'favourite' volatile anaesthetic for cardioprotection has been identified. Noble gases with (Xe) (Weber et al., 2005b) and without (He, Ne, Ar) (Pagel et al., 2007) anaesthetic properties similarly reduce injury from ischaemic injury, suggesting that neither anaesthetic properties nor effects on haemodynamics are crucial for protective efficacy.

Dose-dependence has been described both for anaesthetic preconditioning (Riess et al., 2002) and post-conditioning (Ge et al., 2010). In general, clinically relevant anaesthetic concentrations were found to be protective. The duration of anaesthetic exposure in pre- and post-conditioning protocols varies between 5 and 30 min but no direct comparison between different exposure lengths has been reported so far. It is possible that anaesthetic preconditioning, similar to ischaemic preconditioning (Sandhu et al., 1997), can be enhanced by administering the volatile anaesthetic repeatedly interspersed with its washout. Data from the isolated guinea pig heart model suggest that this may be the case (Riess et al., 2004). A second in vivo administration of desflurane in rats accounted for more protein alterations in the myocardial proteome compared with only one (Dyballa-Rukes et al., 2014), and sevoflurane preconditioning is strengthened by multiple preconditioning cycles (Fradorf et al., 2010). Importantly, two periods of sevoflurane preconditioning were required to significantly reduce cellular damage in patients having coronary artery bypass, using troponin I as marker or cardiac damage (Frassdorf et al., 2009).

Mechanisms of anaesthetic-induced protection

Overall, the mechanisms responsible for anaesthetic-induced conditioning of the heart closely resemble those implicated in ischaemic conditioning. However, gene expression profiles in cardiac preconditioning demonstrated partly distinct genetic programmes in ischaemic and anaesthetic preconditioning (Sergeev et al., 2004). For example, there appears to be a divergent role for MAPKs in the signal transduction underlying ischaemic and anaesthetic preconditioning. MAPKs may act as triggers and mediators in ischaemic preconditioning, while they do not trigger, but may have mediator effects in anaesthetic preconditioning (da Silva et al., 2004). There are several excellent older and more recent articles that review various aspects related to the mechanisms of anaesthetic-induced cardioprotection, particularly in respect of the relevant signalling pathways (Zaugg et al., 2003; De Hert et al., 2005; Pagel, 2008; Weber and Schlack, 2008; Pagel and Hudetz, 2011; Van Allen et al., 2012; Alvarez et al., 2014). Up to now, how and where small pharmacologic agents such as the practically inert volatile anaesthetics or noble gases exert their direct action that lead to protection against ischaemia and reperfusion injury remains largely unresolved. It is unclear whether the agents interact with proteins directly or, through
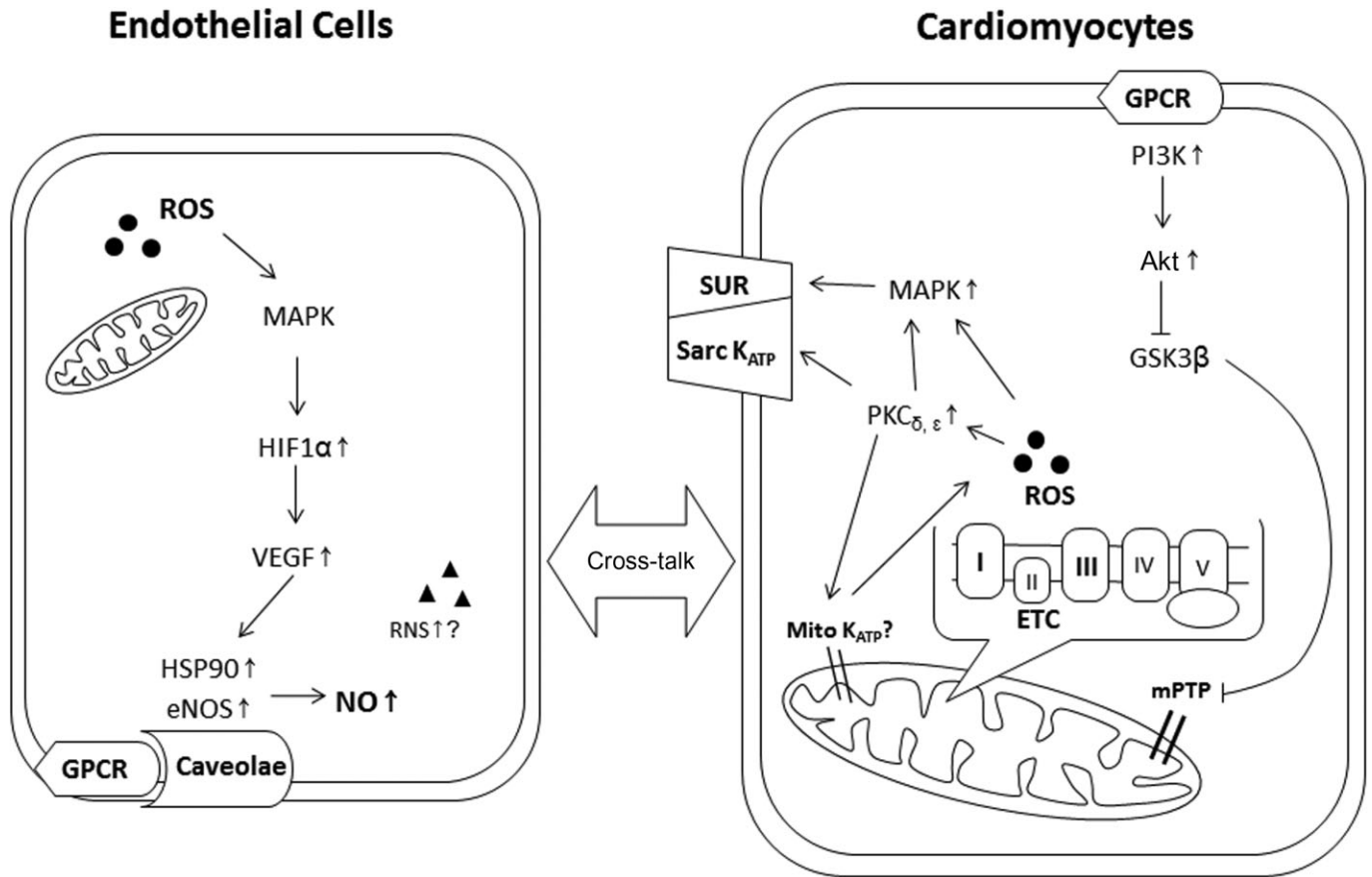
Endothelial Cells

Cardiomyocytes

Figure 1

Scheme depicting key elements of the pathways activated in anaesthetic-induced protection as described in the text. ETC, electron transport chain; HIF1α, hypoxia-inducible factor 1α; HSP90, heat shock protein 90; Mito K_{ATP} , mitochondrial ATP-sensitive potassium channels; mPTP, mitochondrial permeability transition pore; RNS, reactive nitrogen species; Sarc K_{ATP}, sarcolemmal ATP-sensitive potassium channels; SUR, sulfonylurea receptor.

their lipophilic nature, indirectly through membranes. For example, the effect of isoflurane on sarcolemmal K_{ATP} channels could be well mediated through direct interaction with the sulfonylurea receptor, the regulatory subunit of this channel. Single amino acid mutations in the nucleotide binding domain of the sulfonylurea receptor blunted the activation of K_{ATP} channels that was observed in a patch-clamp study on excised patches at a mildly acidic pH, comparable to that achieved during ischaemia (Bienengraeber *et al.*, 2006). While an indirect effect involving changes in K_{ATP} channel regulating nucleotides cannot be entirely ruled out, these results point towards a direct effect of isoflurane on the channel.

GPCRs, intracellular signalling kinases, ROS and nitrogen species, caveolae, sarcolemmal and mitochondrial potassium channels and mitochondrial metabolism are some of the main players in the mechanism of anaesthetic-induced protection (Figure 1). Originally, pharmacological inhibition was the main method for determining the molecular components required for protection. However, the non-specific action of some inhibitors may have led to a misplaced emphasis on, for example, the role of mitochondrial K_{ATP} channels in anaesthetic-induced protection (Hanley and Daut, 2005). In a more general approach, the impact of anaesthetic precondi-

tioning on the myocardial proteome has been studied. Particularly, proteins associated with stress and mitochondrial metabolism were found to be up- or down-regulated after early and delayed anaesthetic preconditioning (Xiao *et al.*, 2011; Bienengraeber *et al.*, 2013; Dyballa-Rukes *et al.*, 2014). In future studies, proteomics will serve as a useful tool to study post-translational modifications associated with anaesthetic-induced protection. Phosphorylation of signalling proteins, such as PKB/Akt (Chiari *et al.*, 2005), glycogen synthase kinase 3β (GSK3β) (Feng *et al.*, 2005) or endothelial nitric oxide synthase (eNOS) (Lamberts *et al.*, 2009) but also of the adenine nucleotide carrier in mitochondria (Feng *et al.*, 2008), have already been discovered. Most certainly, there are many more post-translational modifications, such as nitrosation of cysteine residues, that are waiting to be identified.

The mechanistic endpoints of the different protocols of anaesthetic-induced protection (early and delayed preconditioning, post-conditioning) are similar: decreased cell death from necrosis and apoptosis along with prevention or delay of permeability transition pore opening (Piriou *et al.*, 2004; Pravdic *et al.*, 2009) and preserved mitochondrial function (Riess *et al.*, 2002; Mio *et al.*, 2009). There is ample evidence that mitochondria are not only endpoints but also act as

triggers of protection and are direct targets of the anaesthetic agents. During preconditioning, low levels of ROS are generated, probably through direct or indirect interaction of the anaesthetic agent with complex I and/or III of the electron transport chain (Sedlic *et al.*, 2010; Hirata *et al.*, 2011; Agarwal *et al.*, 2014). A moderate activation of ROS is required for activation of protective intracellular signalling pathways (Ludwig *et al.*, 2004). The burst of ROS generated at the onset of reperfusion contributes to myocardial injury. Nevertheless, anaesthetic post-conditioning also depends on the presence of ROS as protection is abolished in the presence of radical scavengers (Tsutsumi *et al.*, 2007; Yao *et al.*, 2010). Whether there is a specific source and species of ROS that is required during anaesthetic post-conditioning is so far not known. Anaesthetics may have other direct effect on mitochondria during post-conditioning that contribute to protection, such as decreasing toxic ROS generation by reversible inhibition of complex I and decreasing mitochondrial matrix pH that could directly inhibit opening of the permeability transition pore (Hirata *et al.*, 2011; Pravdic *et al.*, 2012).

Aside from mitochondria, GPCRs (specifically, adenosine and opioid receptors) (Weihrauch *et al.*, 2005; Bonney *et al.*, 2014) participate in anaesthetic-induced protection and activate multiple protective signalling pathways. The participation of specific PK isoforms, their role (trigger or effector) and temporal relationship are dependent on species, experimental protocol and detection method (e.g. pharmacological inhibitors vs. Western blotting). Activation and/or translocation of PKs that were firmly associated with anaesthetic-induced protection include PKs Cδ and Cε, members of the MAPK family (Erk1/2 and p38) and the PI3K–Akt–GSK3β cascade (Uecker *et al.*, 2003; Toma *et al.*, 2004; Feng *et al.*, 2005). Downstream of PK activation, there is up-regulation of hypoxia-inducible factor 1α, vascular endothelial growth factor, heat shock protein 90 and eNOS whereby a cross-talk between endothelial cells and cardiomyocytes enhances the protection (Wang *et al.*, 2006; Amour *et al.*, 2009; Leucker *et al.*, 2011). Targeted intracellular signalling, for example towards mitochondria, is supported by spatially organized complexes of signalling molecules in lipid-rich microdomains of the plasma membrane known as caveolae. The number of caveolae and the interaction of signalling proteins with the scaffolding domain of caveolin are enhanced by volatile anaesthetics (Roth and Patel, 2011).

Translation to human tissues

Although most studies on mechanisms related to anaesthetic-induced protection of the heart were performed in animals, it seems likely that the same or similar pathways are involved in protection of the human heart as well. Trabeculae, cardiomyocytes and mitochondria were isolated from human right atrial appendages to confirm the presence and underlying mechanisms of anaesthetic-induced protection (Mio *et al.*, 2008; Lemoine *et al.*, 2011). Those studies confirmed the presence of anaesthetic-induced protection in human tissue. However, obvious obstacles are associated with the investigation of patient tissue, particularly when studying the mechanisms that are involved in protection and also those that may blunt protection. Among those obstacles are technical ones

such as unpredictability of tissue availability and variable time lapse from tissue harvest to laboratory experiment and patient-related ones such as variations in age, underlying disease and medication history.

Thus, in the search for alternative source of human tissue, the use of cardiomyocytes that were derived from human embryonic stem cells and induced pluripotent stem cells (iPSCs) presents a novel approach. These cardiomyocytes can be generated without limit and carry the patient's genetic information. This is of particular interest in the case of iPSCs as these cells offer a model to dissect the roles of environmental factors and individual genetic background on the efficacy of anaesthetic-induced protection. Indeed, anaesthetic preconditioning protects human embryonic stem cell-derived cardiomyocytes against oxidative stress, triggers ROS generation and delays permeability transition pore opening, suggesting the feasibility to use these cells as a model for studying anaesthetic preconditioning (Sepac *et al.*, 2010). When using cardiomyocytes derived from iPSCs from healthy and type 2 diabetic patients, elevated glucose levels disrupted anaesthetic-mediated protection present at normal glucose level for both cell lines (Canfield *et al.*, 2012). Eventually, cardiomyocytes derived from healthy donors and patients with a specific disease open possibilities in studying genotype- and phenotype-related pathologies in a human-relevant model. However, challenges remain in regard to reproducibility and efficiency, as well as variability in maturity and cardiac subpopulations when generating cardiomyocytes either from the same or from different iPSC lines. For progressive complex multifactorial diseases such as diabetes, the disease phenotype may not be present in cardiomyocytes differentiated from iPSCs from a type 1 or type 2 diabetic donor. A large number of cell lines from both disease and healthy donors will be required to account for line-to-line and intra-line variability.

Apart from mechanistic studies, one of the main goals is to use stem cells and/or stem cell-derived cardiomyocytes for therapy, specifically for the infarcted heart, by injecting cells in or around the infarcted area. One great challenge for stem cell therapy of an infarcted heart is the limited survival of injected or endogenously activated cells in and around the ischaemic zone of the infarct. While sevoflurane inhalation did not increase the number of circulating endothelial progenitor cells in volunteers, *in vitro* sevoflurane preconditioning promoted proliferation of human endothelial progenitors (Lucchinetti *et al.*, 2009). In this way, anaesthetic exposure may be used to promote perioperative vascular healing and to support cell replacement therapies. Being more resistant against ischaemic stress, stem cell-derived cardiomyocytes may exhibit better survival when injected into the infarcted zone.

Clinical studies

Anaesthetics, and in particular, volatile anaesthetics appear to evoke powerful protection in various injury models. This includes human tissue as well as cardiomyocytes derived from human tissue or stem cells. Obviously, of most relevance is the question whether those findings from the laboratory translate into significant improvement in the clinical

outcome in patients that are either at risk for myocardial ischaemia or actually suffer from it. The American Heart Association stated in its guideline for coronary artery bypass graft surgery that volatile-based anaesthesia can be useful in reducing the risk of perioperative myocardial ischaemia and infarction (Hillis *et al.*, 2012). Recent excellent reviews summarized clinical studies related to anaesthetic-induced protection during surgery (Pagel, 2013; Ishii, 2014); so we will only provide a short summary and report on the most recent studies. Overall, the outcome of clinical studies is highly variable and sometimes contradictory. Frequently, improvements in secondary endpoints such as cardiac troponin I release were detected but not in primary clinical outcome (such as mortality, heart function, myocardial infarction). Even meta-analyses where the outcome of cardiac surgery with volatile versus i.v. anaesthesia was compared and that included largely the same clinical studies sometimes lead to different conclusions. In two of the earlier meta-analyses analysing coronary artery bypass graft surgery, 2979 patients in 27 clinical trials (Symons and Myles, 2006) and 2841 patients in 32 clinical trials (Yu and Beattie, 2006) were examined. In both analyses, volatile anaesthetics reduced postoperative troponin I release when compared with i.v. anaesthetics. However, while sevoflurane-mediated reduction in cardiac troponin was associated with improved long-term outcomes in individual studies, these meta-analyses were not able to confirm that positive effects on troponin were translated into improved clinical outcomes. In contrast, in another meta-analysis, a year later, that included 22 studies with a total of 1922 patients undergoing cardiac surgery, a significant reduction of myocardial infarctions and mortality was found (Landoni *et al.*, 2007).

More recently, the cardioprotective properties of isoflurane versus any non-volatile anaesthetics were investigated in both cardiac (16 studies) and non-cardiac (21 studies) surgery with a total of 3539 patients in terms of the rate of myocardial infarction and overall mortality. While mortality was reduced in the isoflurane group when only studies with a low risk of bias were included in the analyses, overall no differences in the rates of mortality and myocardial infarction were noted (Bignami *et al.*, 2013). The same research group reported later that specifically desflurane and sevoflurane reduce mortality after cardiac surgery when compared with i.v. anaesthesia (Landoni *et al.*, 2013). Similarly mixed are the results of the more recent individual clinical studies. In a prospective, randomized study with 193 patients, sevoflurane-based anaesthesia did not even reduce troponin T release after elective abdominal aortic surgery, compared with total i.v. anaesthesia (Lindholm *et al.*, 2013). On the other hand, a small proof-of-concept study suggested that intramyocardial or systematic delivery of sevoflurane attenuated the systemic inflammatory response after cardiopulmonary bypass but without reducing postoperative markers of myocardial cell damage such as troponin T (Kortekaas *et al.*, 2014). Some clinical studies result in a follow-up discussion in regard of data evaluation. In a randomized three-centre study, 385 patients with cardiovascular risk that underwent non-cardiac surgery received either sevoflurane or propofol for anaesthesia. Sevoflurane did not reduce the incidence of myocardial ischaemia in high-risk patients undergoing major non-cardiac surgery (Lurati Buse *et al.*, 2012). However, the

study was considered underpowered by others and the endpoints as well as the timing of endpoint measurements were criticized (Zaugg and Lucchinetti, 2013; Zhang *et al.*, 2013a).

In the majority of clinical studies that investigate potential protective effects of anaesthetics against cardiac injury, the agent was present throughout injury. Fewer studies with low participant numbers investigated pre- and post-conditioning effects of anaesthetics on the outcome of surgery. In one direct comparison between only propofol anaesthesia, continuous sevoflurane exposure and sevoflurane pre- and post-conditioning (50 patients each), troponin I exposure was decreased in all sevoflurane groups, but hospital length of stay was only decreased when sevoflurane was administered throughout the operation (De Hert *et al.*, 2004). Children seem susceptible to anaesthetic preconditioning: 80 children that underwent ventricular septal defect closure were assigned to preconditioning for 5 min with either isoflurane, sevoflurane, desflurane or placebo (oxygen-air mixture). Volatile anaesthetics were associated with significantly decreased postoperative release of creatine kinase (MB isoform) and with a trend towards shorter duration of inotropic support, mechanical ventilation and length of intensive care unit stay (Singh *et al.*, 2013). Thus, compared with the cardioprotection by volatile anaesthetics unequivocally found in laboratory settings, the findings are more variable in the clinical setting. More studies will be required to find a more definitive answer whether and in what setting certain anaesthetics are more useful than others in providing protection against myocardial injury.

Underlying conditions

The reasons why reproducible cardioprotection for various anaesthetics observed in the laboratory setting does not translate into robust and reproducible clinical benefits are likely to be multifaceted. By and large, patients that are undergoing cardiac or non-cardiac surgery are elderly and/or suffer from underlying conditions such as obesity and diabetes. Indeed, in a study with 784 patients scheduled for arterial vascular surgery and a history of at least three of risk factors such as age, diabetes, prior myocardial infarction and hypertension, inhalational anaesthetics failed to reduce the incidence of postoperative cardiac events and troponin I release when compared with non-inhalational anaesthetics (De Hert *et al.*, 2008). In the laboratory, anaesthetic-induced preconditioning with isoflurane decreases stress-induced cell death and preserves mitochondrial respiratory function to a greater degree in cardiomyocytes isolated from right atrial appendages from middle-aged patients than in those isolated from elderly patients (Mio *et al.*, 2008). In aged rats, the lack of preconditioning was associated with disruption of well-described protective pathways such as volatile anaesthetic-induced ROS generation (Nguyen *et al.*, 2008), activation and translocation of GSK3β and delay of permeability transition pore opening (Zhu *et al.*, 2013).

Similarly, hyperglycaemia and diabetes in various animal and cell models attenuated or abolished anaesthetic-induced protection against myocardial injury. Isoflurane-induced pre- and post-conditioning was abolished in animal models of type 1 and 2 diabetes as well as hyperglycaemia (Tanaka *et al.*,

2002; Huhn *et al.*, 2008; Matsumoto *et al.*, 2009; Muravyeva *et al.*, 2014). While signalling kinase pathways seem to be at least partially intact after sevoflurane-induced preconditioning during hyperglycaemia (Weber and Schlack, 2008; Weber *et al.*, 2008), coupling of eNOS through its interaction with heat shock protein 90 was disrupted after anaesthetic exposure (Amour *et al.*, 2010). It is likely that diabetes-induced alterations in metabolism such as a switch in substrate preference affect anaesthetic-induced protection (van den Brom *et al.*, 2013). However, desflurane was able to post-condition the right atrial trabeculae isolated from diabetic human myocardium (Lemoine *et al.*, 2010). Factors such as glucose level and length of hyperglycaemia, degree of insulin insensitivity, obesity and hyperlipidaemia are all likely to affect the cardioprotective capacity of anaesthetics.

In addition to underlying disease, medications may influence the cardioprotective action of anaesthetics. As a case in point, patients with coronary artery disease that undergo surgery are frequently treated with β-adrenoceptor antagonists (β-blockers) for perioperative cardioprotection. In an *in vivo* rabbit model, the protection afforded by desflurane and sevoflurane was blunted upon inhibition of the $β_1$-adrenoceptor pathway (Lange *et al.*, 2006). Similarly, the glucose-lowering drug and K_{ATP} channel inhibitor glibenclamide, blocks anaesthetic-induced protection (Toller *et al.*, 2000). Interestingly, a perioperative shift from glibenclamide to insulin restores reduction in troponin I release in diabetic patients undergoing coronary artery bypass surgery in the presence of isoflurane (Forlani *et al.*, 2004). It will be interesting to further assess the ability of interventions with other glucose-lowering drugs such as metformin to restore or improve protection in patients. Metformin alone provides cardioprotection against ischaemic injury in hearts from diabetic *db/db* mice (Calvert *et al.*, 2008), but the combination of volatile anaesthetics and metformin has not been systematically studied yet.

Outlook

Similar to ischaemic pre- and post-conditioning, certain anaesthetics provide powerful protection in defined models of ischaemia and reperfusion injury. As it avoids any mechanical intervention, the use of volatile anaesthetics is considered safer for clinical application as compared with the short ischaemic episodes during ischaemic conditioning. Nevertheless, anaesthetic-induced pre- and post-conditioning is currently met with scepticism at funding agencies, pointing out that the research had made little progress in regard of clinical implementation of over the last years. In order to see robust clinical benefits, conditions that hamper preconditioning, such as underlying diseases, and how to overcome them require further laboratory investigations and clinical studies. The rather high severity of ischaemia and reperfusion injury in experimental models may not compare well with the area of risk during coronary artery bypass graft surgery that is frequently examined in clinical studies of anaesthetic-induced protection (Pagel, 2013). In this regard, one potentially interesting application of anaesthetic-induced post-conditioning might be during cardiopulmonary resuscitation. Out-of-hospital cardiac arrests have a very low, regionally variable

survival rate (Nichol *et al.*, 2008; Hasegawa *et al.*, 2013). In a recent study on rats, cardiopulmonary resuscitation was performed after electrically induced ventricular fibrillation. Rats received sevoflurane for 5 min either before resuscitation, during resuscitation or after resuscitation. While sevoflurane treatment did not affect the survival rate, all treatment protocols resulted in an improved contractility 24 h after restoration of spontaneous circulation, together with a higher ejection fraction (Knapp *et al.*, 2013). In a pig model of cardiopulmonary resuscitation, sevoflurane post-conditioning reduced myocardial damage and dysfunction after cardiopulmonary resuscitation in the early post-resuscitation period, along with reduced apoptosis and myocardial proinflammatory cytokine expression (Meybohm *et al.*, 2011). Sevoflurane did not improve the neurological recovery which might be explained by the rather late start of sevoflurane administration after recovery of spontaneous circulation. Ischaemic post-conditioning (two 20 s breaks during cardiopulmonary resuscitation) after 15 min of untreated cardiac arrest in pigs was neuroprotective and improved 48 h survival dramatically (Yannopoulos *et al.*, 2013). Potential applications like this suggest that further research in anaesthetic-induced protection is warranted and clinically relevant. Understanding and overcoming obstacles related to concomitant conditions of ischaemia and reperfusion injury and a well-targeted patient population seem to be the key for successfully implementing anaesthetic-induced protection further into the clinical practice.

Acknowledgements

Conflict of interest

None.

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