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Anaesthesia and myocardial ischaemia/reperfusion injury

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Anaesthetists are confronted on a daily basis with patients with coronary artery disease, myocardial ischaemia, or both during the perioperative period. Therefore, prevention and ultimately adequate therapy of perioperative myocardial ischaemia and its consequences are the major challenges in current anaesthetic practice. This review will focus on the translation of the laboratory evidence of anaesthetic-induced cardioprotection into daily clinical practice.

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Prevention and adequate treatment of perioperative myocardial ischaemia and its consequences are the frequent challenges of current anaesthetic practice. The main goal in the therapy of myocardial ischaemia is to restore perfusion to the ischaemic tissue. However, reperfusion itself can induce additional cellular damage that can exceed that caused by the ischaemic injury, even resulting in death. This phenomenon is called lethal reperfusion injury.[25] Rosenkranz and colleagues[82] defined lethal reperfusion injury as an irreversible deterioration of the myocardium, which can be reduced by modifications of the conditions of reperfusion. However, not only modifications of reperfusion conditions but also the application of interventions before the occurrence of myocardial ischaemia may help to reduce the extent of ischaemic damage and subsequent reperfusion injury. Interestingly, the use of certain anaesthetic drugs seems to represent one such intervention.

There are three time frames in which protection against ischaemia–reperfusion injury can be induced: before ischaemia occurs, during ischaemia, and after the ischaemia at the onset of reperfusion. The first report that sublethal ischaemia before otherwise lethal ischaemia induces strong cardioprotection was published in 1986 by Murry and colleagues.[65] This preconditioning typically consists of two distinct phases: the early phase which starts immediately after the ischaemic stimulus and protects the myocardium for 2–3 h, followed by a late protection period occurring after 12–24 h and lasting for 2–3 days. The latter is called the late preconditioning phase. It has since been shown that the application of short ischaemic episodes interspersed by short periods of reperfusion after the longer period of myocardial ischaemia was also associated with a protective effect on the extent of myocardial damage and post-ischaemic dysfunction. This phenomenon was called post-conditioning.[112]

Evidence has now accumulated that anaesthetics and some narcotics may be cardioprotective. While experimental findings are increasingly being applied to clinical practice, continuing efforts are directed towards the unravelling of the underlying mechanisms. The understanding of the underlying signal transduction cascade is of special importance because there is conflicting clinical evidence concerning the relative contributions of early or late pre- and post-conditioning to clinical cardioprotection provided by anaesthetic agents. Several factors may be responsible for this conflicting evidence such as the differences in the extent and degree of myocardial ischaemia between different studies, possible interference by the use of other drugs, and the presence of co-existing disease such as diabetes. This review will focus on the translation of laboratory evidence of anaesthetic-induced cardioprotection into daily clinical practice.

Experimental evidence

Anaesthetic-induced early preconditioning

Besides the classical stimulus of short-term ischaemia, there are several stimuli that may induce a preconditioning-like effect. Physical interventions, such as rapid pacing[31] and hyperthermia,[108] and also several pharmacological agents may induce a preconditioning effect. Developments in the understanding of potential pharmacological approaches to preconditioning have emerged from studies investigating the signal transduction cascade involved in ischaemic preconditioning. Liu and colleagues[52] demonstrated that the adenosine A_1 receptor was involved in ischaemic preconditioning; this provided

evidence that preconditioning was induced by a receptor interaction, but also indicated that preconditioning could be modulated by pharmacological interventions.

In 1997, Kersten and colleagues[39] showed for the first time that a volatile anaesthetic (isoflurane) induces cardioprotection in a preconditioning protocol. This finding also triggered research into the mechanisms involved in anaesthetic preconditioning. Indeed, during the last decade, many studies have addressed the signal transduction cascade involved in anaesthetic-induced preconditioning. The first steps discovered were the activation of adenosine- and ATP-sensitive potassium (K_{ATP}) channels. Subsequently, the involvement of protein kinase C, mitogen-activated protein kinases, extracellular-regulated kinases (ERK), heat shock protein and their interaction with the cytoskeleton, and involvement of endothelial nitric oxide synthase were described (for a recent review, see Weber and Schlack).[102] In addition to the volatile anaesthetic agents, opioids have been shown to exhibit a preconditioning effect[85 86] as have the noble gases xenon and helium.[72 103]

It was initially considered that anaesthetic- and ischaemic-induced preconditioning shared the same signal transduction pathway. However, in 2004, Sergeev and colleagues[87] demonstrated that anaesthetic-induced preconditioning was associated with a more homogenous and predictable cardioprotective phenotype at the transcriptional level compared with ischaemic-induced preconditioning. Using a proteomic approach, it was shown that volatile anaesthetics induce long-lasting changes in the expression profile of 106 proteins, which are related to their cardioprotective effect.[36]

During the last few years, the focus of research has moved further down the signal transduction cascade leading to the theory that inhibition of the opening of the mitochondrial permeability pore is one of the key steps in preconditioning-induced cardioprotection. Although initially the opening of the K_{ATP} channel was considered to be the main step in the signal transduction of preconditioning, it has become increasingly obvious that this constitutes only one step among many others. A detailed description of the underlying signal transduction pathway is beyond the scope of this review and the reader is referred to a number of excellent review articles that have been published on the subject in recent years.[8 14 90 102] A schematic overview of the mechanisms involved in the cardioprotective effects of volatile anaesthetic agents is shown in Figure 1. The protection offered by anaesthetic preconditioning may be altered by the use of certain drugs or in the presence of certain diseases.

Drugs blocking preconditioning

Ketamine is known to be a blocker of the K_{ATP} channel, which constitutes a central step in the preconditioning cascade.[41] Mullenheim and colleagues[61 63] have demonstrated that only the *R*(−)-enantiomer of ketamine is responsible for the blocking of the early and late preconditioning effects. Thiopental also blocks K_{ATP} channels in isolated myocytes and attenuates cytoprotection induced by diazoxide, a K_{ATP} channel opener.[111] In rat hearts *in vitro*, however, thiopental did not abolish ischaemic preconditioning.[62]

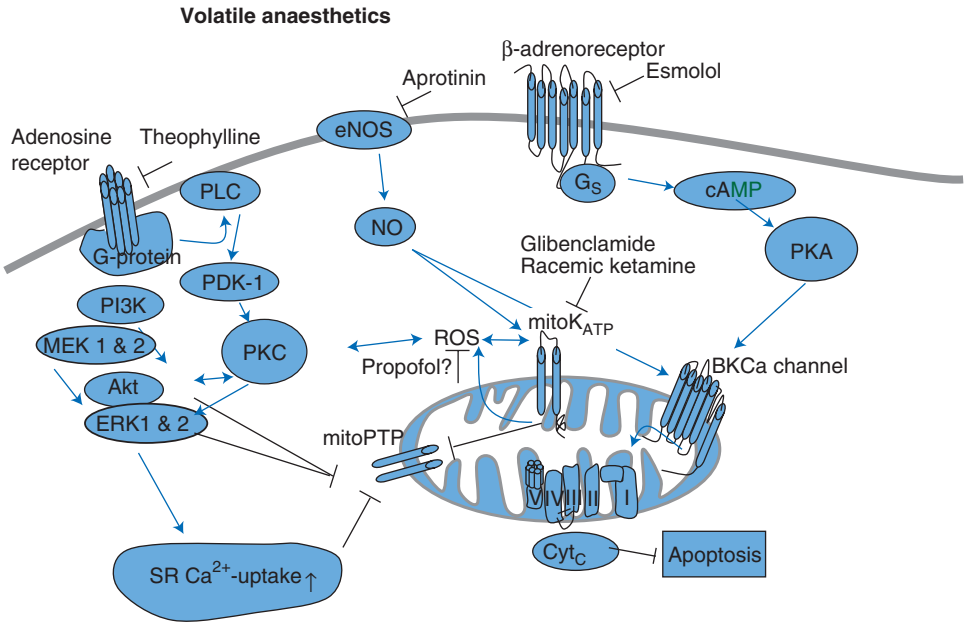

Fig 1 Schematic overview of the signal transduction of anaesthetic-induced cardioprotection and possible interactions through anaesthetic drugs or drugs used frequently in the perioperative period. Akt, protein kinase B; cAMP, cyclic adenosine monophosphate; ERK1, extracellular regulated kinase 1; mitoK$_{ATP}$ channels, mitochondrial adenosine triphosphate sensitive potassium channels; NO, nitric oxide; eNOS, endothelial nitric oxide synthetase; PKC, protein kinase C; PLC, phospholipase C; PKA, protein kinase A; mitoPTP, mitochondrial permeability transition pore; BKCa channel, large conductance Ca^{2+}-sensitive K^+ channel; Cyt, cytochrome C; I, II, III, IV, V, mitochondrial respiratory chain; SR, sarcoplasmatic reticulum; MEK 1, mitogen-activated protein kinase 1; PI3K, phosphoinositide 3-kinases; PDK-1, 3-phosphoinositide-dependent kinase 1; G_S, stimulatory G-protein.

Propofol, on the other hand, does not interact with the K_{ATP} channels *in vitro*,[111] but its structure is similar to that of the free-radical scavenger vitamin E (tocopherol). Small amounts of radical oxygen species are necessary to induce volatile anaesthetic-induced preconditioning,[60] and therefore, it is possible that propofol can interfere with this type of cardioprotection. Smul and colleagues[89] demonstrated in rabbit hearts *in vivo* that propofol blocks anaesthetic-induced preconditioning, whereas it has no influence on ischaemic preconditioning.

It is important to note that β-blockers may adversely affect anaesthetic-induced preconditioning. In human right atrial tissue, desflurane-induced preconditioning is abolished by the non-selective β-blocker propranolol.[28] Lange and colleagues[49] have demonstrated that anaesthetic-induced preconditioning (induced by desflurane or sevoflurane) is abolished in the presence of esmolol (a β_1-blocker) and that desflurane-induced preconditioning is blocked by a β_2-blocker.[48]

Finally, aprotinin that is a well-known protease inhibitor has been shown to abolish ischaemic- and anaesthetic-induced preconditioning in *in vivo* animal models.[5 20]

Pathophysiological and experimental conditions interacting with preconditioning

The K_{ATP} channels play a pivotal role in signal transduction of ischaemic- and anaesthetic-induced preconditioning. These channels are not only present in the myocardium, but also in the pancreas. Blockade of these channels stimulates insulin secretion. Therefore, K_{ATP} channel blockers such as the sulphonylurea gliblenclamide are widely used in diabetic patients. Of note, glibenclamide is also used in experimental studies to block K_{ATP} channels in order to demonstrate their crucial role in the signalling pathway of preconditioning. Diabetes itself[92] and also hyperglycaemia[37] in the non-diabetic myocardium have been shown to abolish anaesthetic-induced preconditioning.

Most studies investigating ischaemic- or anaesthetic-induced preconditioning have used healthy young animals. Whereas in hypertrophic myocardium, preconditioning seems to be preserved, in the failing heart, this powerful endogenous cardioprotection is not present (reviewed in Pantos and colleagues).[73] In the aged heart, preconditioning is also abolished,[1] but can be restored by exercise and food restriction.[2]

The first studies of ischaemic preconditioning were performed using a protocol of multiple short-term ischaemia episodes interspersed by reperfusion. Later, it was concluded that one cycle of ischaemia and reperfusion induced the same cardioprotection as multiple cycle protocols.[35 51] However, Sandhu and colleagues demonstrated that the efficacy of multiple cycle ischaemic preconditioning protocols seemed to depend on the stabilization period after preparation of the experimental animals. With a 30 min stabilization period, they demonstrated that three cycles of short-term ischaemia and reperfusion before the index ischaemia of 30 min led to stronger cardioprotection compared with the one-cycle protocol of ischaemic preconditioning. Additionally, they were able to show that the one-cycle preconditioning protocol could be blocked by inhibiting protein kinase C or activating cAMP activity, whereas three-cycle preconditioning required both interventions to be blocked.[83] Multiple-cycle preconditioning with sevoflurane increases the cardioprotection in guinea pig hearts *in vitro*.[80] Desflurane-induced preconditioning has a threshold between 0.5 and 1 MAC in a single-cycle protocol with 30 min desflurane exposure time. Increasing the concentration of desflurane to 1.5 MAC or the time of application to 90 min does not increase the observed cardioprotection. While once cycle of 0.5 MAC was not protective, with repetitive administration (three cycles of 10 min interspersed with 10 min wash-out) cardioprotection was induced.[48]

Anaesthetic-induced late preconditioning

In 1993, two separate groups reported that the cardioprotection through ischaemic preconditioning reappeared after 12–24 h and lasted for 72 h.[44 58] There is some conflicting evidence regarding the existence of anaesthetic-induced late preconditioning. Initially, Kehl and colleagues[38] could not demonstrate late preconditioning with isoflurane in dog hearts. In contrast, in neonatal rabbits, isoflurane did induce delayed cardioprotection.[98] This finding was later confirmed in adult rabbits by Tanaka and colleagues.[93] Sevoflurane was also shown to induce delayed cardioprotection.[57] Apart from the halogenated volatile anaesthetics, the noble gas xenon[101] and opioids, including the experimental selective δ-opioid receptor agonist TAN-67[22] and also morphine[21] and remifentanil,[110] seem to induce delayed cardioprotection.

In contrast to early preconditioning,[96] late preconditioning requires de-novo synthesis of proteins.[81] This may explain the gap in time between myocardial protection by early and by late preconditioning that occurs after the initial stimulus.

Interventions during ischaemia

Interventions applied during ischaemia to reduce the extent of myocardial damage typically aim to shift the balance between oxygen consumption and oxygen supply in favour of the oxygen supply. It has long been recognized that volatile anaesthetic agents have negative inotropic and chronotropic properties, and thus decrease the oxygen consumption–supply ratio and improve the capability to maintain myocardial energy stores.[84] Tarnow and colleagues[94] demonstrated in 1986 that patients receiving isoflurane during coronary artery bypass procedures were less susceptible to pacing-induced myocardial ischaemia. Compared with other strategies known to protect against

ischaemia–reperfusion injury, the contribution of this direct anti-ischaemic effect is small.[84]

During ischaemia and reperfusion, reactive oxygen species cause lipid peroxidation. As propofol has antioxidant properties, it is thought that propofol may reduce ischaemic injury. Propofol given before, during, and after the index ischaemia reduces lipid peroxidation and improves functional recovery in rat hearts *in vitro*. However, this cardioprotection was observed at a propofol concentration of 12 μg ml^{-1} but not of 5 μg ml^{-1}.[106]

Intervention after ischaemia at the onset of reperfusion

In 1996, Schlack and colleagues[84] described the protective effects of halothane against reperfusion injury. These findings were later confirmed for sevoflurane, desflurane, and xenon[79 78] and for opioid receptor agonists such as morphine.[24]

This idea of limiting the extent of reperfusion injury by a treatment during early reperfusion was re-introduced in 2003 when Zhao and colleagues published their observation that episodes of short-term ischaemia and reperfusion at the end of a period of longer term ischaemia reduced infarct size similar to ischaemic preconditioning. This phenomenon was named post-conditioning.[112]

The underlying mechanisms of anaesthetic-induced post-conditioning are the subject of intensive research. In 1997, Siegmund and colleagues[88] demonstrated that halothane prevented hypercontracture of myocytes during early reperfusion via an interaction with the ryanodine receptor (calcium release channel) of the sarcoplasmic reticulum. Neutrophils contribute to the reperfusion injury and volatile anaesthetics have inhibitory effects on neutrophil adhesion in the coronary arteries after ischaemia.[32] A third major factor accounting for lethal reperfusion injury is activation of apoptotic cell death.[23] Several pro-survival, anti-apoptotic kinases are activated at the time of reperfusion. These pro-survival protein kinases are called reperfusion injury salvage kinases (RISK) and include protein kinase B, ERK1/2, c-Jun N-terminal kinase, protein kinases C and G, p70s6 kinase, and glycogen synthase kinase 3 beta.[30] The RISK pathway is also activated by volatile anaesthetics and opioids. Interestingly, it can also be activated through pre-ischaemic administration of volatile anaesthetics, opioids, or ischaemic preconditioning. Therefore, it is likely that pre- and post-conditioning share some final steps in signal transduction.[71] However, it is not clear if activation of the RISK pathway and consequent interaction with the mitochondrial permeability pore is really the final step in signalling of myocardial pre- and or post-conditioning.

The key clinical question, however, is when to instigate the intervention designed to limit reperfusion injury. Kin and colleagues investigated whether ischaemic post-conditioning has to be started immediately with the beginning of reperfusion or 1 min after reperfusion. Post-conditioning by three cycles of 10 s reperfusion and 10 s ischaemia reduced infarct size from 52% in controls to 40%. Delaying the post-conditioning protocol by only 1 min abolished the protective effects. Increasing the stimulus to six cycles of ischaemia and reperfusion did not further increase the protection.[40] Obal and colleagues investigated in sevoflurane-induced post-conditioning the effect of the sevoflurane concentration and the timing of administration. In a first set of experiments, sevoflurane was administered for 15 min starting with the onset of reperfusion. In these experiments, 0.75 MAC did not induce cardioprotection, whereas 1 MAC did. Further increases in concentration up to 2 MAC did not decrease infarct size in rat hearts *in vivo*.[69] In a second set of experiments, the time of administration of 1 MAC sevoflurane was investigated. It was observed that after 2 min of sevoflurane administration with the onset of reperfusion, cardioprotection was present, which could not be enhanced by a longer administration up to 10 min.[70]

Propofol as a free-radical scavenger[43] with calcium channel blocking properties[7] might be anticipated to reduce ischaemia–reperfusion injury if given during reperfusion. However, application of propofol during early reperfusion results in conflicting evidence.[17 42 105] Studies demonstrating protective properties of propofol used supra-therapeutic concentrations (30–120 μmol $litre^{-1}$) in Langendorff-perfused hearts, whereas free plasma concentrations of propofol are usually <1 μmol $litre^{-1}$.[74]

Like preconditioning, post-conditioning is altered in pathological conditions. Hyperglycaemia blocks sevoflurane-induced post-conditioning.[33] The cardioprotection induced by sevoflurane can be restored by blocking the mitochondrial permeability transition pore.[33] Rho-associated kinases (ROCKs) appear to have the opposite effect to the RISK group.[27 104] ROCKs are activated in vasospastic angina, ischaemic stroke, and atherosclerosis.[68] However, there is no direct evidence that cardioprotection through post-conditioning is altered in these circumstances.

Clinical evidence

Anaesthetic-induced early preconditioning

Although a number of clinical studies have aimed to investigate anaesthetic-induced preconditioning, it appears that the protocols used did not, in fact, constitute a genuine preconditioning intervention. Indeed, by definition preconditioning requires that the stimulus is followed by a so-called washout period before the actual ischaemic insult occurs. Another methodological concern is the continued presence of slowly cleared drugs, such as morphine or β-adrenoreceptor blockers, in the myocardium during the index ischaemia after their intended use as a preconditioning stimulus. As such, these interventions cannot be regarded as preconditioning stimuli.

A further prerequisite for clinical research in this field is the availability of a suitably predictable and reproducible ischaemic insult. Such a predictable and comparable setting of myocardial ischaemia is only seen during cardiac surgery, and this is why most of the clinical studies have been performed during coronary surgery. One problem is that these procedures themselves may influence preconditioning and confound the extent of anaesthetic preconditioning. For instance, cardiopulmonary bypass can induce cardioprotection,[6] and most patients undergoing coronary surgery have co-existing diseases and are taking medications that may interfere with anaesthetic-induced preconditioning.

Belhomme and colleagues were the first to present evidence that isoflurane could induce anaesthetic-induced preconditioning in patients undergoing coronary surgery. Exposure to isoflurane (2.5 MAC for 5 min) 10 min before aortic cross-clamping and cardioplegic arrest increased ecto-5′-nucleotidase, an indirect marker of protein kinase C, activation in right atrial samples. Furthermore, they observed a trend towards lower troponin I and creatine kinase-MB in isoflurane-treated patients. Other studies demonstrated improved cardiac function with lower troponin release after coronary surgery[50 59 97] whereas some demonstrated only improved function.[29 75] Morphine, compared with fentanyl, improves functional recovery after coronary surgery but has no influence on biochemical markers of myocardial necrosis.[64] Once again, most of these studies do not comply with the strict definition of preconditioning.

Of special interest is the study by Julier and colleagues who demonstrated that administration of 2 MAC sevoflurane before aortic cross-clamping induced a translocation of protein kinase C in right atrial samples. This was the first study to demonstrate such an effect in the clinical setting. However, a number of methodological issues should be kept in mind. The authors had to administer phenylephrine to treat the haemodynamic consequences of 4% sevoflurane in patients on cardiopulmonary bypass. Both phenylephrine[3 100] and cardiopulmonary bypass[6] were shown to induce cardioprotection in experimental studies. On the other hand, all patients received aprotinin, which can block anaesthetic-induced preconditioning.[20]

Not all clinical preconditioning studies, however, have shown cardioprotective effects in terms of either better preservation of myocardial function or less postoperative myocardial damage.[18 76 77] This underscores the fact that the clinical preconditioning protocol may be critical to the demonstration of protective effects. This question was recently addressed by Bein and colleagues,[4] who demonstrated that interrupted administration of sevoflurane before cardiopulmonary bypass induced cardioprotection in coronary artery bypass graft patients, whereas continuous administration did not. Similarly, we observed that in coronary surgery patients, a preconditioning protocol with only one cycle of sevoflurane (1 MAC for 5 min 10 min before cardiopulmonary bypass and aortic cross-clamping) did not decrease postoperative tropinin I release, whereas the application of two cycles of sevoflurane administration for 5 min, interspersed by 5 min wash-out, significantly reduces troponin I levels.[19]

Myocardial ischaemia also occurs on a regular basis during coronary artery stenting procedures. Treatment with 0.5 MAC sevoflurane for 20 min in patients before a stenting procedure did not reduce post-procedural plasma troponin levels.[47]

Anaesthetic-induced late preconditioning

There is only indirect evidence that anaesthetic-induced late preconditioning might occur in humans. Lucchinetti and colleagues[53] investigated if a subanaesthetic dose of sevoflurane-induced changes in gene expression in white blood cells of volunteers. They observed markedly altered gene expression of rapid onset and reduced expression of the proinflammatory L-selectin, concluding that these findings were consistent with a 'second window of protection' in humans.[53]

Interventions during ischaemia

To investigate the direct anti-ischaemic properties of volatile anaesthetics is complicated. Nader and colleagues added sevoflurane (2 vol%) into the cardioplegia solution during coronary artery bypass graft procedures. They observed a better functional recovery and lower plasma troponin levels and a decrease of the inflammatory response after cardiopulmonary bypass and myocardial reperfusion.[66 67] High-dose propofol (120 $\mu g\ kg^{-1}\ min^{-1}$, plasma total propofol concentration $\sim$4.2 $\mu g\ ml^{-1}$) during cardiopulmonary bypass attenuated indices of oxidant stress and reduced the release of troponin after coronary surgery compared with 'low'-dose (60 $\mu g\ kg^{-1}\ min^{-1}$) propofol anaesthesia or isoflurane-based anaesthesia.[107]

Intervention after ischaemia with the onset of reperfusion

As timing seems to be crucial in post-conditioning,[40] volatile anaesthetics should be present with the onset of reperfusion to achieve clinically relevant cardioprotection. To date, little is known of the clinical relevance of this type of cardioprotection. De Hert and colleagues[15] could not detect a significant reduction in cellular damage in terms of postoperative plasma troponin levels with sevoflurane given only during reperfusion. However, postoperative recovery of myocardial function seemed to occur earlier than in the control group. A similar phenomenon was observed in an anaesthetic-induced preconditioning group. Only when sevoflurane was administered during the whole procedure was there a significant reduction in postoperative troponin I release and a better preservation of post-cardiopulmonary bypass myocardial function. The fact

that in this study sevoflurane administration was started only with the release of the aortic cross-clamp might imply that the volatile anaesthetic was not present in the myocardium during early reperfusion.

In contrast, there is good clinical evidence that ischaemic post-conditioning protects the myocardium during early reperfusion. Patients undergoing coronary stenting as treatment for myocardial infarction who received a post-conditioning protocol had reduced troponin I and creatine kinase-MB release, smaller infarct size after 6 months, and a better long-term functional recovery after 1 yr.[95] Additionally, Luo and colleagues[56] demonstrated that in children undergoing correction of a tetralogy of Fallot, post-conditioning reduced the need for inotropes in the first 24 h after operation, and it was associated with a 50% reduction in troponin I and a 34% reduction of creatine kinase-MB compared with controls. These findings were later confirmed in adult valve replacement surgery, where post-conditioning was induced by three cycles of reperfusion and ischaemia (each 30 s).[55] However, a major concern with regard to ischaemic post-conditioning in humans is the increased risk of embolic events with every new aortic cross-clamping.

Anaesthetic agents and clinical cardioprotection

Although the relative contributions of pre- and post-conditioning to clinical cardioprotective effects of volatile anaesthetics are unclear, the best available clinical evidence to date suggests that the effects of volatile anaesthetics are most evident when given throughout the entire surgical procedure. De Hert and colleagues[13] demonstrated that sevoflurane reduced cellular damage and preserved post-bypass cardiac function compared with a propofol-based anaesthetic regimen in patients undergoing coronary surgery. This cardioprotective effect was also observed in high-risk elderly patients with sevoflurane and desflurane[11] and also in aortic valve replacement procedures.[10] In contrast, no protection was observed in patients undergoing isolated mitral valve replacement, whereas patients undergoing mitral valve replacement plus coronary surgery had lower troponin plasma concentrations.[46] The observed cardioprotection seemed to be associated with a shorter length of stay in the intensive care unit, a shorter length of stay in hospital, and a reduced incidence of prolonged (>48 h) intensive care stay.[16] These findings were subsequently confirmed by other groups, not only in surgery involving cardiopulmonary bypass[99] but also in off-pump surgery.[26]

Sevoflurane also attenuates transcripts involved in activation of the granulo-colony stimulating factor cell survival pathway and DNA damage signalling. These pathways are predictors of postoperative cardiac index and diastolic heart function. These data were collected by using gene microarray screening.[54] However, the interpretation of data from gene microarray screening experiments seems to be complicated and could be associated with a high risk of false positive data.[9]

Another clinical setting with a high incidence of myocardial ischaemia is major vascular surgery. De Hert and colleagues retrospectively analysed if the use of volatile anaesthetics or an i.v. anaesthetic regimen affected postoperative troponin release in vascular surgery patients. No differences were observed but the subgroup of patients undergoing aortic surgery who received volatile anaesthetics (n=62) tended to have lower postoperative troponin levels compared with those who received an i.v. anaesthesia (n=43).[12]

Effects on outcome

An important question remains whether the choice of the anaesthetic regimen may affect major postoperative outcomes. Unfortunately, none of the studies performed to date is sufficiently powered to address this question.

In a retrospective analysis of a Danish complication registry with more than 10 000 patients,[34] possible cardioprotective properties of sevoflurane were investigated. The authors observed no difference in 30 day mortality compared with patients who received propofol anaesthesia (sevoflurane 2.84% *vs* propofol 3.3%, P=0.18). In a subgroup analysis the authors could demonstrate that patients with no history of unstable angina, myocardial infarction, or both and, therefore, most likely not preconditioned before the operation, benefited from sevoflurane anaesthesia in terms of a reduced mortality (sevoflurane 2.28% *vs* propofol 3.14%, P=0.015). On the other hand, propofol-based anaesthesia was associated with a lower mortality in emergency procedures. Of note, there are a number of limitations with this study that should be kept in mind. Since this was a retrospective database analysis, there was no randomization: all propofol-based anaesthetics were given in one of the three participating centres. The other two centres used only sevoflurane-based anaesthesia. Secondly, the centres used different types of cardioplegia. The propofol centre used only crystalloid cardioplegia, whereas one of the sevoflurane centres used only blood cardioplegia, and the last centre used both types of cardioplegia. Therefore, the differences observed are possibly biased through these circumstances.

Several meta-analyses have tried to answer the question whether the use of a volatile anaesthetic during cardiac surgery is superior to a propofol-based anaesthetic.[45 91 109] In the most recent meta-analysis (22 studies including 1922 patients) including only studies comparing i.v. anaesthesia with either desflurane or sevoflurane, Landoni and colleagues[45] found a reduction of myocardial infarctions [volatile anaesthetics 2.4% *vs* propofol 5.1%, OR=0.51 CI (0.32–0.84), P for effect=0.008] and a reduced mortality

[volatile anaesthetics 0.4% *vs* propofol 1.6%, OR=0.31 CI (0.12–0.80), *P* for effect=0.02]. Neither the observational study from Jakobsen and colleagues[34] nor the meta-analysis from Landoni and colleagues[45] investigated the possible influence of co-existing diseases or other co-administered drugs.

Conclusion

Volatile anaesthetics offer cardioprotective effects by different mechanisms, i.e. pre- and post-conditioning. A clinical benefit of volatile anaesthetics has been clearly demonstrated in patients undergoing heart surgery, reducing morbidity, and perhaps mortality. However, to what extent the concepts of either pre- or post-conditioning contribute to the observed myocardial protection remains unclear. A more detailed knowledge of involvement of different mechanisms and of the efficiency of different administration protocols might allow a more tailored administration of cardioprotective anaesthetic protocols.

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