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<td>Author(s)</td>
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<tr>
<td>Citation</td>
<td>British Journal of Anaesthesia, 2016, v. 117 n. Suppl. 2, p. ii44-ii62</td>
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<tr>
<td>Issued Date</td>
<td>2016</td>
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<td>URL</td>
<td><a href="http://hdl.handle.net/10722/229096">http://hdl.handle.net/10722/229096</a></td>
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<td>Rights</td>
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Myocardial ischaemia reperfusion injury: the challenge of translating ischaemic and anaesthetic protection from animal models to humans

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Abstract

Myocardial ischaemia reperfusion injury is the leading cause of death in patients with cardiovascular disease. Interventions such as ischaemic pre and postconditioning protect against myocardial ischaemia reperfusion injury. Certain anaesthesia drugs and opioids can produce the same effects, which led to an initial flurry of excitement given the extensive use of these drugs in surgery. The underlying mechanisms have since been extensively studied in experimental animal models but attempts to translate these findings to clinical settings have resulted in contradictory results. There are a number of reasons for this such as dose response, the intensity of the ischaemic stimulus applied, the duration of ischaemia and lost or diminished cardioprotection in common co-morbidities such as diabetes and senescence. This review focuses on current knowledge regarding myocardial ischaemia reperfusion injury and cardioprotective interventions both in experimental animal studies and in clinical trials.

Key words: anaesthetic conditioning; diabetes; ischaemic conditioning; ischaemia-reperfusion injury

The recent VISION (The Vascular events In non-cardiac Surgery patients cOhort evaluatioN) study1 found that 8% of patients more than 45 yr of age suffered myocardial injury, based on troponin assay, after non-cardiac surgery, of which 84.2% were asymptomatic. This finding was significant because, amongst these, one in 10 died within 30 days. Ischaemic heart disease (IHD) is also one of the leading causes of death in economically developed countries worldwide. Increasing attention has been paid to the development of interventions to re-establish blood perfusion to ischaemic myocardium, to salvage tissue and protect against paradoxical reperfusion injury.7 This also decreases the risk of post-ischaemic complications such as heart failure and arrhythmia.7 Despite improvements in therapeutic strategies such as angioplasty, thrombolysis, percutaneous coronary intervention and coronary artery bypass surgery, recent studies indicate that post-ischaemic 30 day mortality and morbidity (about 8.5% after angioplasty and about 14% with thrombolysis) remains significant.1 The incident rate of IHD and post-ischaemic complications are significantly increased in patients with co-morbidities such as diabetes4 and/or hypertension. To make things worse, patients with diabetes are not responsive to cardioprotective strategies such as ischaemic preconditioning (IPC),5 postconditioning (IPo),7 and anaesthetic conditioning (APC)8 that are otherwise effective in non-diabetic subjects. This highlights the need to determine why hearts in patients with co-morbidities, in particular those with diabetes are susceptible to ischaemia and yet not sensitive to cardioprotective interventions. The answer to this question may facilitate the development of novel cardioprotective strategies that may also be applicable in other patients, such as the elderly.
Mechanism of ischaemia reperfusion injury

Myocardial infarction is usually caused by rupture of an atheroma-tous plaque in a coronary artery. Re-establishment of coronary blood flow (reperfusion) is mandatory to salvage the ischaemic myocardium but this is accompanied by dramatic changes in mitochondrial permeability transition pore (mPTP) opening, generation of reactive oxygen species (ROS), bioavailability of nitric oxide (NO), intracellular distribution of Ca²⁺ and Na⁺, and pH. Paradoxically, reperfusion itself can actually cause cardiomyocyte death and subsequent irreversible myocardial injury, a phenomenon termed ‘ischaemia reperfusion injury (IRI)’.9 (Fig. 1).

Mitochondrial dysfunction during myocardial ischaemia reperfusion

In order to meet the high energy demand for both contractility and diastolic relaxation, the heart needs a continuous energy supply, which depends on the synthesis of adenosine triphosphate (ATP). Approximately 95% of this ATP comes from mitochondrial oxidative phosphorylation.10 Thus, mitochondrial function has been considered as a key factor in the aetiology of myocardial ischaemia, a state of energy deficit in the heart. Mitochondrial dysfunction affects cell viability through a wide array of events including reduction or loss of ATP synthesis, increase in ATP hydrolysis,11 impairment in ionic homeostasis,12 and formation of ROS.13 All these suggest a critical role of mitochondria in myocardial IRI and, as such, mitochondria may act as critical triggers, mediators and effectors for protective strategies directed against myocardial IRI.

Under physiological conditions, the mitochondrial inner membrane is impermeable (except for a few selected metabolites and ions). However, under pathological conditions such as myocardial ischaemia, oxygen and nutrient deprivation causes a non-selective opening of the inner mPTP, resulting in depolarization and uncoupling/impairment of oxidative phosphorylation.14 This not only leads to ATP depletion but also causes the breakdown of any available ATP, which subsequently induces the hydrolysis of ATP and the enhancement of mitochondrial inorganic phosphate.15 On the other hand, during ischaemia (in the absence of oxygen) cellular metabolism switches to anaerobic glycolysis and the subsequent accumulation of lactate reduces intracellular pH (lower than 7.0).15 Depletion of ATP and acidosis impede the ability of the Na⁺/H⁺ antiporter to remove excess Na⁺ caused by the increase of intracellular proton accumulation-induced activation of Na⁺/H⁺ ion exchanger, resulting in intracellular Ca²⁺ overload and mitochondrial swelling.16 17 Influx of Ca²⁺ into the mitochondria and an increase in ROS production both favour mPTP opening, but the associated acidosis obstructs its opening. After reperfusion, a quick pH correction exacerbates the opening of the mPTP within a few min.16 This, in turn, leads to an abrupt increase in flow of accumulated electrons and an associated increase in electron leak which, together with the damaged electron transport chain, not only damages mitochondria but also promotes a burst production of superoxide anion and other ROS,18 19 eventually causing cell death (Fig. 1). Therefore, preventing mPTP opening at the time of reperfusion (mPTP remains closed during ischaemia) or timely removal of damaged mitochondria would serve as promising therapeutic avenues to protect the heart from myocardial IRI.

It has been shown that direct inhibition of mPTP opening by cyclosporine A, attenuated myocardial injury after reperfusion both in experimental studies in small20 and large animals21 and in patients with acute ST-elevation myocardial infarction.22 Treatments targeting inhibition of mPTP have been proved to be cardioprotective and are currently being evaluated for clinical use.23 24 As such, the mPTP provides an important therapeutic target for preventing lethal myocardial IRI. However, because of the complexity of mitochondrial metabolism and the fact that most experimental studies have been performed on isolated mitochondria which lack cellular context, further investigation...
is needed to reveal the whole picture of the role and mechanisms of mPTP in myocardial IRI and its application as a therapeutic target for cardioprotection.

Overproduction of reactive oxygen species during myocardial ischaemia reperfusion

ROS such as superoxide anion, hydrogen peroxide, and hydroxyl radicals are generated as by-products of cellular metabolism. Under physiological conditions, small amounts of ROS are beneficial as they participate in normal cellular signaling and serve as an important mediator in the cardioprotection of IPC. However, under stress such as myocardial ischaemia reperfusion, after prolonged ischaemia, re-introduction of blood flow (reperfusion) leads to a massive burst of ROS production from damaged mitochondria. This exceeds the defensive capacity of the cells (e.g. catalase, glutathione peroxidase, and superoxide dismutase) and is detrimental to cardiomyocytes. Production of large quantities of ROS results in overload of Ca2+, breakdown of critical proteins as a result of protein oxidation, generation of peroxynitrite (ONOO-), disruption of cholesterol containing membranes as a result of lipid peroxidation, opening of the mPTP, and reduction of nitric oxide availability. This phenomenon is termed oxidative stress and ultimately causes cell death.

As increased generation of ROS during the first min of reperfusion is a major contributor to the pathogenic mechanisms underlying myocardial IRI, antioxidant therapy has been considered an appropriate option of preventive treatment. However, results from experimental and clinical studies are inconsistent. We and others have shown that antioxidant treatment with N-acetylcysteine and/or allopurinol attenuates post-ischaemic myocardial injury in a rat model of myocardial IRI and in patients undergoing coronary artery bypass surgery. However, others did not observe a beneficial antioxidant effect in patients with vascular disease. and long-term antioxidant (vitamin E) supplementation does not prevent major cardiovascular events and may even increase the risk of heart failure. A possible explanation for this contradiction may be the difference in timing and the choice of an antioxidant that targets specific ROS. It may also be because of the inability of the antioxidant to actually enter the cell. Given that mitochondria are considered as the primary site of ROS generation, discovery of mitochondrial-speciﬁc antioxidants may provide more effective therapy in combating myocardial IRI.

Reduction of nitric oxide bioavailable during myocardial ischaemia reperfusion

Nitric oxide (NO) is produced by NO synthases (NOS, with three isoforms respectively called endothelial (eNOS), neuronal (nNOS), and inducible NOS (iNOS)) through converting L-arginine to L-citrulline in the presence of oxygen. NO is a crucial signalling molecule in the cardiovascular system, acting as one of the most important defence mechanisms against myocardial IRI and as a mediator of cardioprotective interventions such as IPC and IPo. NO exerts its cardioprotective effect via distinct mechanisms: (1) activation of NO-sensitive guanylyl cyclase, (2) inhibition of mitochondrial Ca2+ influx and activation of the mitochondrial KATP channel, (3) activation of cGMP, (4) enhancement of cyclooxygenase-2, and (5) abrogation of ONOO- mediated lipid radical chain propagation. In the setting of prolonged myocardial ischaemia, the activity/activation of NOS (primarily eNOS and nNOS) is reduced concomitant with the reduced supply of oxygen that is required for the synthesis of NO from L-arginine. Thus, deprivation of oxygen during ischaemia leads to reduced or diminished NO release. Hence, enhancement of NOS activity/activation and NO bioavailability has been shown to be cardioprotective. Indeed, eNOS knockout exacerbates post-ischaemic myocardial injury in mice subjected to myocardial IRI, while overexpression of eNOS improves post-ischaemia cardiac functional recovery. Also, enhancing NO bioavailability by exogenous application of NOS and L-arginine, attenuates ischaemia reperfusion-induced microcirculatory alterations and post-ischaemic infarction. However, high concentration of NO in the presence of increased superoxide anion production may be detrimental as a consequence of increased formation of peroxynitrite (ONOO-), which exacerbates post-ischaemic myocardial injury. Interestingly, treatment with a NO donor in combination with an antioxidant, has been shown to reduce post-ischaemic myocardial infarct size and improve contractile function in the isolated rat heart model, indicating that maintaining a physiological concentration of NO is important for NO to confer its cardioprotective effects. Taken together, the cardioprotective effects of NO depend on its concentration/production, subcellular localization, and its bioavailability. Thus, further studies are needed to better understand the metabolism and dynamics of NO during myocardial IRI, in order to liberate the correct amount of NO in the correct place and at the correct time, under varying pathological conditions.

Other mechanisms of pre- and post-conditioning cardioprotection

Many of the endogenous signalling pathways that participate in anaesthetic-mediated cardioprotection have been identified. Mitochondrial oxidative phosphorylation is the main source of ATP production in the heart, providing the steady supply of ATP required to sustain cardiac contraction, and, as such, mitochondria have been the main focus in cardioprotection. Indeed, signalling pathways targeting cell factions other than mitochondria, such as the nucleus and membrane, also play important roles. For instance, sevoflurane preconditioning by activating Nrf2, upregulated antioxidant genes in the nucleus, resulting in attenuation of myocardial ischaemia reperfusion injury. The integrity and functionality of the cell membrane has also been proposed to mediate the cardioprotection of anaesthetics such as sevoflurane and isoflurane. Sevoflurane preconditioning has also been shown to confer delayed cardioprotection via inhibiting Beclin 1-mediated autophagic cell death, in cardiac myocytes subjected to hypoxia/reoxygenation injury after brief exposure to sevoflurane 24 h before inducing hypoxia, and is likely to involve both mitochondrial and non-mitochondrial mechanisms. Further in-depth investigation is needed to decipher their relative importance, timing of activation, and interactions, and to provide more insight into the mechanisms of volatile anaesthetic cardioprotection.

Protection against myocardial ischaemia reperfusion injury

Ischaemic conditioning

Ischaemic conditioning is achieved by intermittent occlusion of a coronary vessel either locally or remotely, by inducing reversible ischaemia of a distant organ (remote ischaemic conditioning), and limits myocardial infarct size. Ischaemic conditioning can be applied at different time points: before the induction of a period of prolonged ischaemia (IPc, ischaemic preconditioning) or immediately at the onset of reperfusion after prolonged ischaemia (IPo, ischaemic postconditioning). All these cardioprotective...
Ischaemic preconditioning

Ischaemic preconditioning (IPC) was first described by Murry and co-workers in a dog model. The first clinical evidence was provided by inducing several cycles of transient non-lethal ischaemia, using an aortic cross-clamp interspersed with reperfusion. This reduced post-ischaemic myocardial troponin T release and ATP depletion in patients undergoing cardiac bypass surgery. The protective effect of IPC is biphasic. The ‘first window’ or early phase arises immediately after ischaemic stress and lasts for two to three h. The ‘second window’ or late phase cardioprotection occurs 12–24 h after initial preconditioning and lasts for up to 48–72 h. Ischaemic preconditioning confers its early phase protection through the modification of existing pro-survival proteins in the heart, to protect against myocardial infarction, but it has no significant effect on limiting the degree of contractile dysfunction. The late phase of ischaemic preconditioning protection, is a result of the production of cytoprotective proteins in the myocardium and protects the heart from cardiomyocyte death while improving post-ischaemic cardiac functional recovery. Thus, the late phase of IPC cardioprotection is more clinically applicable for its more significant protection and longer duration.

IPC confers cardioprotection by creating a cardiac ‘memory’ between the triggers and end-effectors in the signalling pathways in order to keep the heart in a ‘preconditioned’ state. Three major endogenous triggers of IPC are adenosine, bradykinin, and opioids, all of them are classified as G coupled protein receptor dependent triggers. There are others including ROS, the mitochondrial KATP channel and NO, which probably trigger IPC through the activation of G coupled proteins and protein kinases. After being stimulated by IPC, these triggers activate their downstream mediators, among which are mainly protein kinases, such as protein kinase C (PKC), Akt, tyrosine kinase, and the mitogen activated protein kinase (MAPK). PKC was one of the first mediators of IPC to be identified. Gene knock-out of PKC-δ cancels the cardioprotective effects of IPC in mice. However, in isolated ischaemic reperfused rat hearts, PKC-δ inhibition attenuates myocardial IRI, while PKC-ε activator (but not PKC-δ activator) mimics IPC, supporting the notion that PKC activation-mediated cardioprotection in IPC is isoform-specific. Further investigation is needed to provide a full picture of the beneficial or detrimental role of specific isoforms of PKC activation in the process of IPC. Numerous upstream activators (e.g. PI3K-Akt, NO, and mitochondrial KATP channel) or downstream targets (Sarcolemmal KATP channel, mitochondrial KATP channel, and p38 MAPK) of PKC have also been suggested as IPC mediators. There are others that work in parallel with the PKC pathway in IPC, including receptor tyrosine kinase, MEK1/2, the Jak-STAT pathways, GSK3β, and ROS.

The ultimate end-effector of IPC has not been determined, despite extensive research. The mitochondrion is where most signalling pathways governing IPC cardioprotection converge. The opening of the mitochondrial KATP channel by IPC inhibits mitochondrial Ca2+ overload and attenuates myocardial IRI. Other studies have shown that opening of the mitochondrial KATP channel facilitates the generation of small amounts of ROS and activates PKC, which in turn phosphorylates the mitochondrial KATP channel and keeps it in the open state. Inhibition of mPTP opening has also been considered as the final step in the process of IPC. It has been shown that IPC may inhibit mPTP opening through GSK3β, eNOS, or via the reperfusion injury salvage kinase (RISK) pathway. Of note, there are also other components that have been suggested as the end-effectors of IPC, for instance, the cytoskeleton, gap-junctions, and the Na+/H+ exchanger. Although IPC has been reported to be effective in both experimental and clinical studies, it needs to be performed before the onset of prolonged myocardial ischaemia (i.e. acute myocardial infarction (AMI)), which is neither predictable nor feasible in most clinical situations. Therefore, the majority of clinical investigations of IPC have been restricted to various cardiovascular surgical procedures, including both vascular and cardiac operations in which the ischaemia is predictable.

Ischaemic postconditioning

Recently, effort has focused on modifying events occurring at the time of myocardial reperfusion (ischaemic postconditioning, IPo). Applying transient brief interruptions of reperfusion by ischaemic episodes to reduce myocardial infarction, has higher clinical potential than IPC as, for example, it can be performed after myocardial infarction. IPo was first demonstrated by Zhao and his co-workers, in a rabbit model in which the investigators showed that three repeated cycles of 30 s reperfusion followed by 30 s of occlusion, after a prior 60 min of coronary occlusion, markedly reduced post-ischaemic myocardial infarct size and improved cardiac functional recovery. IPo has also shown considerable promise in clinical settings. In children undergoing corrective surgery for tetralogy of fallot, IPo, achieved by two cycles of unclamping the aorta for 30 s and then re-clamping the aorta for 30 s, reduced the concentrations of CK-MB and troponin T (two reliable markers of myocardial injury) 2 h after surgery. This has also been confirmed in a number of clinical studies including cardiac surgery for congenital heart disease, aortic valve replacement, and percutaneous coronary intervention.

It is now widely accepted that IPo confers its cardioprotective effects via two intracellular pathways, the RISK pathway which involves PI3K/Akt and the survival activating factor enhancement pathway (SAFE), which involves Jak/STAT3. These pathways converge in the mitochondrion which is, obviously, an integration point that is decisive for cardiomyocyte survival. As the experimental design of IPo mimics IPC and their cardioprotective effects are similar, it is not surprising that IPo and IPC share related cardioprotective signalling pathways. Indeed, elements of the RISK pathway, including PI3K, Akt, eNOS, and adenosine receptors have also been shown to be involved in IPo. In isolated rat hearts, IPo stimulation reduced post-ischaemic infarct size with associated elevations in Akt, eNOS, and p70S6K, while these beneficial effects of IPo were abolished by PI3K inhibition (either by LY294002 or wortmannin), indicating the involvement of PI3K-Akt in IPo. In addition, pharmacological inhibition of MEK1/2 abrogated IPo cardioprotection. Further, other components of the RISK pathway, such as PKC, Protein G, and p38 MAPK, are implicated in IPo cardioprotection. All these not only support the concept that cardioprotection of IPo shares a similar pathway (RISK) with IPC, but also suggest that the RISK pathway could be a common pathway mediating cardioprotection. However, the involvement of the RISK pathway in IPo has also been questioned. It was reported that Erk1/2 but not PI3K-Akt was involved in IPo cardioprotection in isolated rabbit hearts. Similarly, in vivo porcine hearts, IPo significantly increased Akt and Erk1/2 phosphorylation but failed to reduce post-ischaemic infarct size. The reason for these controversial results is not clear, but a possible explanation would be the difference of the models and the protocols used in each experiment. However, this may also suggest that IPo may confer...
Cardioprotective effects through RISK-independent pathways. Indeed, the more recently identified SAFE pathway has been shown to be essential and can be activated independent of the RISK pathway during IPo.88 The SAFE pathway is initiated by moderate elevation of tumour necrosis factor (TNF)-α (a pro-inflammatory cytokine). The cardioprotective effects of IPo were lost in TNF-α knockout mice94 and exogenous TNF-α given at the onset of reperfusion at a relative low dose can mimic the protective effects of IPo,94 indicating that low doses of TNF-α might serve as a trigger of IPo cardioprotection. Interestingly, administration of TNF-α to mimic the protective effects of IPo did not lead to the activation of Akt or Erk1/2,95 while inhibition of Erk1/2 (by PD98059) or PI3K (by wortmannin) aborted the protective effects mediated by TNF-α when applied at moderate dosage.94 These findings together with the fact that Akt and Erk1/2 are components of the RISK pathway, provide evidence that downstream signalling of the SAFE pathway is different from that of RISK and that the SAFE pathway can be activated independently in the setting of IPo. This concept has been further supported by a study showing that neither Akt nor Erk1/2 inhibition had significant impact on IPo-induced reduction of post-ischaemic infarct size in an in vivo pig myocardial IRI model.108 After initiation by IPo, TNF-α binds to its receptor (TNFR2 in myocardial IRI) and subsequently activates/phosphorylates signal transducer and activator of transcription 3 (STAT3), a transcription factor that has been shown to be an essential component of the SAFE pathway in IPo. Once phosphorylated/activated, tyrosine-phosphorylated STAT3 shuttles into the nucleus and initiates stress-responsive gene transcription,99 101 102 serine-phosphorylated STAT3 moves to mitochondria to regulate the mitochondrial respiratory chain97 98 (Fig. 3). The importance of STAT3 activation in the context of IPo has been demonstrated by both pharmacological inhibition99 and genetic deletion of STAT3.100 However, information regarding how IPo activates STAT3 is lacking. Moreover, although STAT3 is recognized as a transcription factor, its activation during myocardial IRI is much too rapid to assume that it works by modulating gene transcription. Of note, it has been shown that the RISK pathway is involved (but not essential) in IPo cardioprotection and cross-talk exists between the RISK and SAFE pathways.94 As Akt cannot be phosphorylated in STAT3 knockout mice subjected to IPC,101 it suggests that IPo may activate Akt via STAT3. IPo also activates STAT3 and increases its mitochondrial expression which subsequently improves mitochondrial function in pig hearts.99 Given that mitochondrial STAT3 co-localises with cyclophilin D, the target of the mPTP inhibitor,102 and that mPTP also works as the end-effector of the RISK pathway, it follows that the SAFE and RISK pathways may converge at the mitochondria.

Remote ischaemic conditioning
Remote conditioning is a strategy whereby application of one or more cycles of non-lethal ischaemia reperfusion to an organ or
tissue, distant from the heart either before inducing prolonged ischaemia (remote ischaemic preconditioning, RIPC), or at the onset of reperfusion (remote ischaemic postconditioning) protects against myocardial IRI. It was first discovered in 1997 when it was shown that repeated occlusions to a lower limb of rabbits could attenuate myocardial infarct size after myocardial IRI, and it was initially called ‘ischaemic preconditioning at a distance’. This simple and effective technique has subsequently been translated into clinical use. The first clinical application of RIPC in humans was in 2006 in children undergoing cardiac surgery, where RIPC (four 5 min cycles of lower limb ischaemia and reperfusion using a blood pressure cuff) significantly reduced postoperative troponin I release and inotrope requirement. However, negative results have also been reported in cardiac bypass surgery. The possible explanation for this contradiction is not clear but may be as a result of: (1) the use of anaesthetics such as sevoflurane, opioids and propofol, which can exert cardioprotective effects themselves during cardiac bypass surgery; (2) differences in protocol and the timing of RIPC application; and (3) differences in patient population and type of cardiac surgery. Thus, large multi-centre, randomized, controlled clinical trials are needed to confirm the cardioprotective effects of RIPC. Indeed, a recent large-scale trial has shown that RIPC is cardioprotective in patients undergoing elective CABG under ischaemic cardioplogic arrest, in which medication with β-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) was not interrupted for the CABG, while the use of propofol was discontinued and diabetes was an exclusion criterion. The efficacy of RIPC mediated cardioprotection was reflected in a reduction in serum troponin release, assessed by the area under the curve values for serum troponin I from baseline to 72 h after surgery. Aortic cross-clamp time was the major independent variable that impacted efficacy of RIPC. However, two recent large-scale, prospective, randomized, sham-controlled trials of RIPC in cardiac surgery with cardiopulmonary bypass, have shown that RIPC was not effective when utilized in anaesthetised patients immediately before surgery. This may be related to the use of propofol, which induces cardioprotection via different mitochondrially related molecular mechanisms. In contrast, RIPC applied some time before surgery, increases myocardial salvage-index in patients with acute myocardial infarction. Experimentally, we and others have demonstrated that RIPC repeated for three consecutive days, reduced myocardial infarction in rats with chronic heart failure after myocardial infarction and in rats with diabetes, two main cofounders that impact the efficacy of RIPC cardioprotection. These suggest that RIPC initiated at a remote time may allow the second-window of cardioprotection to develop and, thereby, improve tolerance to ischaemia during cardiac surgery. Thus, RIPC should not be abandoned but merits further clinical trials concerning optimal timing of application.

Although RIPC currently has been extensively investigated, the underlying mechanism remains unclear. Three inter-related
events have been proposed: (1) RIPC-induced generation of endogenous autocrines (e.g. encephalin, endorphin) in the remote organ, (2) transmission of the protective signal from the remote organ to the target organ; (3) events occurring in the target organ which ultimately confer the protective effect. Several signalling mediators have been proposed to be involved in RIPC including PKC, ROS, NO, Akt, Erk1/2, p38 MAPK, and STAT3, which are also the mediators of IPC and Ipo. Further studies are needed to identify potential triggers, clarify the downstream targets, and explore the end-effectors of RIPC.

Cardioprotection by anaesthetics

Application of certain drugs used in anaesthesia (e.g. isoflurane, sevoflurane, propofol, and opioids) before or during the early phase of reperfusion can also reduce myocardial ischaemia-reperfusion injury, a phenomenon that is termed anaesthetic pre-conditioning (APreC) and postconditioning (APoC), or collectively referred to as anaesthetic pre- or post-conditioning (APC).

Mechanisms of APoC cardioprotection conferred by volatile anaesthetics, propofol or opioids

Similar to ischaemic preconditioning, volatile anaesthetics and opioids provide protection against myocardial IRI by stimulating the generation of a small amount of ROS, which triggers and enhances the production of endogenous antioxidant enzymes and activates mitochondrial KATP channels, limiting myocardial infarction. In contrast, propofol protects against myocardial IRI mainly via its ROS scavenging properties, which enhances endogenous cardiac antioxidant capacity and ultimately attenuates myocardial IRI. Opioids play an important role in mammalian hibernation. Endogenous and exogenous (e.g. remifentanil and morphine) opioid agonists reduce myocardial oxidative stress and Ca overload and attenuate myocardial IRI both in animal models and in patients undergoing cardiac surgery. Most recent study shows that remifentanil preconditioning confers cardioprotection in rats, primarily via activation of JAK2/STAT3 signalling, that can function independent of PI3K/Akt activation.

However, it should be noted that application of high doses of opioid receptor agonists such as morphine may cause significant increases in ROS production in the vascular endothelium and myocardium and subsequently impair vascular endothelial function and exacerbate myocardial ischaemia-reperfusion injury, although the doses of remifentanil required to do this are much higher than those used clinically.

Major randomized clinical trials of anaesthetic conditioning are listed in Table 1 which includes cardiac surgeries conducted under either on-pump or off-pump conditions. It should be mentioned that only the on-pump surgery provides typical ischaemia-reperfusion injury and that the duration of ischaemia time may be one of the determinants of the effectiveness of conditioning protection.

Similarity in mechanism and potential advantages of APC vs ischaemic conditioning

The concept of APC was evolved from IPC and Ipo, and the mechanisms governing their cardioprotective effects are similar. APC confers cardioprotection mainly via the RISK and SAFE pathways (Fig. 4). APC activates the RISK pathway via a G-protein-coupled cell surface receptor and activates the SAFE pathway through the TNFα receptor, which all inhibit IRI-induced mPTP opening and activate the opening of the KATP channel, thereby protecting cardiomyocytes from IRI-induced cell death. However, unlike IPC and Ipo, anaesthetic application during APC is to the whole body and it is possible, therefore, that APC may also exert protection to other organs and other types of cells rather than just cardiomyocytes. We have recently shown that sevoflurane pre-treatment protects against TNFα-induced vascular endothelial dysfunction, through activation of the eNOS/NO pathway and inhibition of NF-κB. Sevoflurane may also protect against liver injury in patients undergoing cardiac surgery.

Exogenous opioids have also been shown to confer systemic multi-organ protection. Remifentanil pre-treatment ameliorated liver injury in rats subjected to hepatic ischaemia reperfusion and attenuated intestinal ischaemia reperfusion injury in mice.

Compared with IPC and Ipo, APC is more clinical feasible as anaesthetic agents are being used in surgery anyway. The beneficial effects of APC in a clinical setting was first demonstrated by Belleromme and colleagues, who reported that isoflurane pre-conditioning (5 min isoflurane exposure followed by 10 min washout) reduced the release of cardiac troponin I (Tnl) and creatine kinase MB (CKMB), markers of cardiac injury, in patients undergoing coronary artery bypass graft (CABG) surgery. Subsequently, the effects of APC in patients undergoing on-pump and off-pump CABG surgery have been examined with conflicting results. Exposure to isoflurane at 1-1.5 MAC end-tidal throughout surgery, reduced postoperative plasma TnI and CKMB release in patients undergoing CABG surgery with cardiopulmonary bypass. While in patients undergoing off-pump CABG surgery, sevoflurane at 1 MAC provided optimal myocardial protection as increasing sevoflurane concentration to 1.5 MAC did not further attenuate myocardial injury and sevoflurane did not confer cardioprotection when being used at 0.75 MAC.

We also showed that treatment with propofol (120 mcg kg⁻¹ min⁻¹ for 10 min before the onset of CPB until 15 min after aortic unclamping and then decreased to 60 mcg kg⁻¹ min⁻¹ until the end of surgery) significantly attenuated cardiac injury in patients undergoing CABG, as compared with isoflurane or low dose propofol. Continuous administration of 1 MAC desflurane induced cardioprotection in patients undergoing CABG surgery evidenced as reduced cardiac Tnl release. However, administration of isoflurane at 1 MAC for 5 min followed by a 5 min washout before CPB, did not reduce troponin I concentrations in patients undergoing CABG with CPB. Similarly, a double-blind trial showed that there was no difference among patients receiving propofol or sevoflurane during surgery in terms of postoperative recovery in the cardiac intensive care unit. Thus, currently it is premature to draw a firm conclusion as to whether APC is beneficial in the clinical settings of CABG surgery, when patients are elderly with co-morbidities such as diabetes and hypertension.

A recent meta-analysis of 2578 patients where on pump and off pump patients were analysed separately, compared peak postoperative cardiac Tnl between volatile and i.v. anaesthesia. Volatiles reduced postoperative peak serum cardiac Tnl enzyme concentrations by ~8% on-pump with no difference seen in off pump cardiac surgery. An accompanying editorial stated ‘So how much longer do we need to keep repeating that the use of a volatile anaesthetic regimen during on-pump coronary artery surgery is associated with a lower post-operative cardiac troponin release compared with an intravenous anaesthetic regimen?’ and suggested that ‘authors must stop designing and performing this type of study; ethical committees must stop approving such trials and editors must stop publishing over and over again data that simply confirm what is already known’. However, all we can discern from such data is that although volatile anaesthetics
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<td>Liu169</td>
<td>36</td>
<td>Institutional standard general anaesthesia</td>
<td>Sevoflurane, 1–8%</td>
<td>Propofol 2–4 mg kg⁻¹</td>
<td>Off-pump CABG</td>
<td>Reduced cTnI, CK-MB, and LDH</td>
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<td>30</td>
<td>Induction: Sufentanil 0.5–1 μg kg⁻¹, pancuronium 0.1 mg kg⁻¹, Maintain: Sufentanil 0.5–1 μg kg⁻¹ h⁻¹</td>
<td>Dexmedetomidine 0.3 μg kg⁻¹ h⁻¹</td>
<td>Propofol 4 μg ml⁻¹</td>
<td>On-pump CABG surgery under mini-CPB</td>
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<td>Rogers171</td>
<td>101</td>
<td>Institutional standard general anaesthesia</td>
<td>Propofol in cardioplegia solution 6 μg ml⁻¹</td>
<td>Intralipid in cardioplegia solution</td>
<td>On-pump CABG or AVR surgery</td>
<td>Reduced cTnI</td>
</tr>
<tr>
<td>Jia172</td>
<td>105</td>
<td>Induction: Midazolam (2 mg), propofol (2 mg kg⁻¹) and fentanyl (2–3 μg kg⁻¹)</td>
<td>Propofol 3–4 μg ml⁻¹, or Sevoflurane 0.7 MAC + propofol 1 μg ml⁻¹</td>
<td>Sevoflurane 1-1.3 MAC</td>
<td>Off-pump CABG</td>
<td>Reduced postoperative lymphopenia</td>
</tr>
<tr>
<td>Sirvinskas173,174</td>
<td>72</td>
<td>Induction: A bolus injection of 20 mg of etomidate and 0.2–0.3 μg kg⁻¹ of fentanyl, 1 mg kg⁻¹ of rocuronium</td>
<td>Sevoflurane 2–3 vol%</td>
<td>Propofol 2–3 mg kg⁻¹</td>
<td>On-pump CABG</td>
<td>Protected the mitochondrial outer membrane, reduced cTnI</td>
</tr>
<tr>
<td>Jerath174</td>
<td>141</td>
<td>Induction: 5 μg kg⁻¹ fentanyl, 0.05–0.1 mg kg⁻¹ midazolam, 1 mg kg⁻¹ propofol, and 0.5 mg kg⁻¹ rocuronium. Maintain: volatile group using isoflurane or sevoflurane</td>
<td>Isoflurane or sevoflurane. The choice of volatile agent was left to the discretion of the attending anaesthetist</td>
<td>Propofol 50–75 μg kg⁻¹ min⁻¹</td>
<td>On-pump CABG</td>
<td>Faster extubation times, higher prevalence of vasodilation with hypertension and higher cardiac outputs necessitating greater use of vasoconstrictors</td>
</tr>
<tr>
<td>Landoni175</td>
<td>200</td>
<td>Induction:Midazolam (0.15–0.25 mg kg⁻¹) or thioental (3–6 mg kg⁻¹), opioid (fentanyl 5–10 μg kg⁻¹), and rocuronium (0.6–1.2 mg kg⁻¹). Maintain: fentanyl (3–5 μg kg⁻¹ h⁻¹), rocuronium (10 μg kg⁻¹ min⁻¹)</td>
<td>Sevoflurane 0.5–2 MAC, 4–6 h, from induction of anaesthesia to transport to ICU and including cardiopulmonary bypass-CPB</td>
<td>Propofol 2–3 mg kg⁻¹ h⁻¹ for the same 4–6 h period</td>
<td>Combined valvular and coronary surgery</td>
<td>No difference in composite of death, prolonged intensive care unit stay, and mortality</td>
</tr>
<tr>
<td>Kim176</td>
<td>153</td>
<td>Institutional standard general anaesthesia</td>
<td>Lidocaine 2 mg kg⁻¹ h⁻¹ after bolus 1.5 mg kg⁻¹, or Desmedetomidine 0.3–0.7 μg kg⁻¹ h⁻¹, or Lidocaine+ dexmedetomidine</td>
<td>Isoflurane 0.8–1.0 MAC</td>
<td>Off-pump CABG</td>
<td>Lower cTnI and CK-MB in lidocaine and the combination group</td>
</tr>
<tr>
<td>Yilmaz177</td>
<td>86</td>
<td>Institutional standard general anaesthesia</td>
<td>Lidocaine 1.5 mg kg⁻¹, 2 min before aortic declamping, Amiodarone 300 mg, intravenously 15 min before release of the aortic cross clamp Placebo</td>
<td>CABG (On-pump or off-pump not stated)</td>
<td>Lower incidence of ventricular fibrillation</td>
<td></td>
</tr>
<tr>
<td>Mrozinski178</td>
<td>60</td>
<td>Fentanyl 0.2 mg, etomidate 0.3 mg kg⁻¹, vecuronium bromide 0.1 mg kg⁻¹</td>
<td>Desflurane 3–9% throughout the procedure, 1 MAC for at least 15 min before coronary artery clamping</td>
<td>Propofol, continuous infusion 2–4 mg kg⁻¹ h⁻¹</td>
<td>Off-pump CABG</td>
<td>No difference in cardiac function, CK-MB, and cTnI</td>
</tr>
</tbody>
</table>

**Table 1** Major randomized clinical trials of anaesthetics in patients undergoing coronary artery surgery. CABG: coronary artery bypass surgery; CPB: cardiopulmonary bypass; AVR: aortic valve replacement; MAC: minimum alveolar concentration; BNP: brain natriuretic peptide; cTnI: cardiac troponin I; cTnT: cardiac troponin T; CK-MB: creatine kinase-MB; LDH: lactate dehydrogenase.
<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Background anaesthesia</th>
<th>Anaesthetic</th>
<th>Control</th>
<th>Surgery</th>
<th>Endpoint</th>
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<tbody>
<tr>
<td>Guerrero[179]</td>
<td>60</td>
<td>Etomidate 0.2 mg kg⁻¹, fentanyl 4 μg kg⁻¹, cisatracurium 0.15 mg kg⁻¹</td>
<td>Sevoflurane-sevoflurane, 0.7–1 MAC</td>
<td>Sevoflurane-propofol Propofol-propofol 2–4 μg ml⁻¹</td>
<td>Off-pump CABG</td>
<td>Lower N-terminal pro-BNP and cTnl and lower number of inotropic drugs</td>
</tr>
<tr>
<td>Wang[180]</td>
<td>48</td>
<td>Midazolam 0.05–0.1 mg kg⁻¹, fentanyl 15 μg kg⁻¹, vecuronium 0.1 mg kg⁻¹</td>
<td>Sevoflurane 0.75, 1, or 1.5 MAC</td>
<td>Midazolam 0.1–0.15 mg kg⁻¹ h⁻¹, fentanyl ≤ 30 μg kg⁻¹, 0.1 mg kg⁻¹ h⁻¹ vecuronium</td>
<td>Off-pump CABG</td>
<td>Sevoflurane 1.0 MAC decreased cTnl</td>
</tr>
<tr>
<td>Suryaprakash[180]</td>
<td>139</td>
<td>Induction: Fentanyl 5–10 μg kg⁻¹, midazolam 0.02 mg kg⁻¹, and vecuronium 1 mg kg⁻¹.</td>
<td>Sevoflurane 1–2% or Desflurane 4–6% in a mixture of air and oxygen.</td>
<td>Propofol 2–4 mg kg⁻¹ h⁻¹</td>
<td>Off-pump CABG</td>
<td>No difference in cTnl</td>
</tr>
<tr>
<td>Soro[181]</td>
<td>73</td>
<td>Midazolam 0.1–0.3 mg kg⁻¹, etomidate 0.2–0.4 mg kg⁻¹, fentanyl 2–40 μg kg⁻¹, cisatracurium 0.1 mg kg⁻¹</td>
<td>Sevoflurane 0.7–1.5%</td>
<td>Propofol 1–4 mg kg⁻¹ h⁻¹</td>
<td>On-pump CABG</td>
<td>No difference in cTnl, CK-MB, NT-proBNP, haemodynamic events and lengths of stay in the intensive care unit and hospital</td>
</tr>
<tr>
<td>Bassuoni[181]</td>
<td>126</td>
<td>Fentanyl 0.5 μg kg⁻¹, rocuronium 0.2 μg kg⁻¹</td>
<td>Induction with sevoflurane 8% and maintained with sevoflurane 1–1.5 MAC</td>
<td>Induced by 1–2 mg kg⁻¹ and maintained with continuous infusion of 2–3 mg kg⁻¹ h⁻¹ of propofol</td>
<td>Off-pump CABG</td>
<td>Reduced cTnl, less in duration, cumulative duration, and magnitude of ST-segment depression of ischaemic events</td>
</tr>
<tr>
<td>imantalab[182]</td>
<td>60</td>
<td>Sufentanil 1 μg kg⁻¹, etomidate 0.2 mg kg⁻¹, cisatracurium 0.15 mg kg⁻¹</td>
<td>Propofol 6–8 mg kg⁻¹ h⁻¹, isoflurane</td>
<td>Midazolam 0.2 μg kg⁻¹ h⁻¹</td>
<td>CABG (On-pump or off-pump not stated)</td>
<td>Lowest cTnl in isoflurane groups and highest in midazolam group</td>
</tr>
<tr>
<td>Riha[183]</td>
<td>38</td>
<td>Institutional standard general anaesthesia</td>
<td>Induction: midazolam 0.1 mg kg⁻¹, dexmedetomidine 1 μg kg⁻¹, ketamine 1 μg kg⁻¹</td>
<td>Induction: midazolam 0.05 mg kg⁻¹</td>
<td>On-pump CABG</td>
<td>Reduced cTnl and CK-MB</td>
</tr>
<tr>
<td>Ceyhan[184]</td>
<td>40</td>
<td>Etomidate 0.3 mg kg⁻¹, pancuronium 0.1 mg kg⁻¹, remifentanil 1 μg kg⁻¹</td>
<td>Sevoflurane 2–4%</td>
<td>Sevoflurane 1–2%</td>
<td>On-pump CABG</td>
<td>Lower cTnl and CK-MB</td>
</tr>
<tr>
<td>Lee[185]</td>
<td>99</td>
<td>Induced with a bolus of 0.2 mg kg⁻¹, etomidate followed by 0.8 mg kg⁻¹ rocuronium and a continuous infusion of remifentanil and propofol using a target-controlled infusion pump</td>
<td>1.5 mg kg⁻¹ bolus at induction of lidocaine followed by 2.0 mg kg⁻¹ h⁻¹ infusion intraoperatively</td>
<td>An equal volume of saline</td>
<td>Off-pump CABG</td>
<td>Reduced cTnl and CK-MB</td>
</tr>
<tr>
<td>Tempe[186]</td>
<td>45</td>
<td>Fentanyl 5–30 μg kg⁻¹, along with thiopental, 1–2 mg kg⁻¹, and pancuronium, 0.1 mg kg⁻¹</td>
<td>Isoflurane 1.0–2.5%</td>
<td>Propofol 1.5–3.5 mg kg⁻¹ h⁻¹</td>
<td>Off-pump CABG</td>
<td>Lower cTnT and CK-MB</td>
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<tr>
<td>Reference</td>
<td>Study Type</td>
<td>Anaesthetic Protocol</td>
<td>Outcome</td>
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<tr>
<td>Wong 122</td>
<td>40</td>
<td>Induction: Fentanyl 5 μg kg⁻¹, pancuronium 0.15 mg kg⁻¹. Maintain: Propofol 60 μg kg⁻¹ min⁻¹. Remifentanil 1 μg kg⁻¹ followed by a 0.5 μg kg⁻¹ min⁻¹ infusion for 30 min after induction but before sternotomy. Normal saline. On-pump CABG. Lower CK-MB, cTnl, h-FABP.</td>
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<td>Arm 59</td>
<td>45</td>
<td>Sufentanil 1.0 μg kg⁻¹ h⁻¹, midazolam 0.12 mg kg⁻¹ h⁻¹, pancuronium 0.01 mg kg⁻¹ every 30 min. A 10-min exposure to isoflurane 2.5% followed by 5 min of washout. No isoflurane. On-pump CABG. Improvement of haemodynamic data, less need for inotropic support and lower CK-MB and cTnl.</td>
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<tr>
<td>Frassdorff 188</td>
<td>30</td>
<td>Sufentanil 0.3 mg kg⁻¹ h⁻¹ and propofol as target controlled infusion 2.5 mg ml⁻¹. 10 min before establishing the extracorporeal circulation, patients of the sevoflurane I group received 1 MAC of sevoflurane for 5 min. Patients of the sevoflurane-II group received (2 times) 5 min of sevoflurane, interspersed by 5-min washout 10 min before extracorporeal circulation. No further intervention. On-pump CABG. Two periods of sevoflurane preconditioning reduced cTnl.</td>
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<tr>
<td>Cho 189</td>
<td>50</td>
<td>Induction: Midazolam 0.03-0.05 mg kg⁻¹ after ketamine 1% (0.5 mg kg⁻¹) or the same volume of normal saline. Sufentanil 1.5-2.0 μg kg⁻¹ and vecuronium bromide 50 mg were administered and tracheal intubation was performed. Maintain: Sevoflurane 1.5-2.5%, and continuous infusion of sufentanil 0.2-0.3 μg kg⁻¹ h⁻¹ and vecuronium 1-2 μg kg⁻¹ min⁻¹. Ketamine 0.5 mg kg⁻¹ during induction of anaesthesia. Normal saline. Off-pump CABG. No effect on pro-inflammatory cytokines release.</td>
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<tr>
<td>Winterhalter 190</td>
<td>42</td>
<td>Institutional standard general anaesthesia. Remifentanil infusion rate 0.25 mg kg⁻¹ min⁻¹. Fentanyl total fentanyl dose 2.6 (0.3) mg. CABG (On-pump or off-pump not stated). Reduced pro-inflammatory cytokines release.</td>
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<tr>
<td>Piriou 191</td>
<td>72</td>
<td>Anaesthesia was induced and maintained with propofol, cisatracurium, and sufentanil. Before the CPB, anaesthesia was maintained with a continuous infusion of propofol and boluses or infusion of sufentanil as clinically indicated. Sevoflurane 1 MAC administered via the ventilator for 15 min followed by a 15 min washout before CPB. No sevoflurane. On-pump CABG. No benefit.</td>
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<tr>
<td>Meco 192</td>
<td>28</td>
<td>A combination of fentanyl, midazolam, propofol and pancuronium. Desflurane preconditioning was elicited after the onset of cardiopulmonary bypass via a 5 min exposure to desflurane 2.5 MAC, followed by a 10 min washout before aortic cross-clamping and cardioplegic arrest. An equivalent period (15 min) of pre-arrest desflurane-free bypass. On-pump CABG. Reduced cTnl and NT-proBNP.</td>
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<tr>
<td>Author</td>
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<tr>
<td>Murphy193</td>
<td>30</td>
<td>Standardized opioid-isoflurane anaesthetic</td>
<td>Morphin (40 mg)</td>
<td>Fentanyl (1000 microg)</td>
<td>On-pump CABG</td>
<td>Reduced inflammatory response</td>
</tr>
<tr>
<td>Corcoran194</td>
<td>27</td>
<td>Fentanyl 15 μg kg⁻¹ and inhalation of isoflurane 0.5%, with pancuronium 0.1 mg kg⁻¹</td>
<td>Target-controlled infusion propofol immediately before aortic cross-clamp release until 4 h after reperfusion</td>
<td>Saline</td>
<td>Impaired left ventricular function ongoing CABG</td>
<td>Attenuated free-radical-mediated lipid peroxidation and systemic inflammation</td>
</tr>
<tr>
<td>Lee195</td>
<td>40</td>
<td>Institutional standard general anaesthesia</td>
<td>Isoflurane 2.5 MAC was administered for 15 min followed by a 5 min washout period before aortic cross-clamping</td>
<td>A time-matched period of isoflurane-free cardiopulmonary bypass</td>
<td>On-pump CABG</td>
<td>Improved cardiac index and stroke volume index, lower cTnI</td>
</tr>
<tr>
<td>Xia140</td>
<td>44</td>
<td>Midazolam 0.1 mg kg⁻¹, fentanyl 15 μg kg⁻¹, pancuronium 0.1 mg kg⁻¹</td>
<td>Propofol 60 mg kg⁻¹ min⁻¹; or dose of propofol was increased to 120 mg kg⁻¹ min⁻¹ for 10 min before the onset of CPB until 15 min after aortic unclamping and then decreased to 60 mg kg⁻¹ min⁻¹ until the end of surgery</td>
<td>Isoflurane 1%-3.5%</td>
<td>On-pump CABG</td>
<td>Reduced cTnI and oxidative stress markers</td>
</tr>
<tr>
<td>Cromheecke196</td>
<td>30</td>
<td>Induction: Remifentanil 0.4 μg kg⁻¹ min⁻¹</td>
<td>Sevoflurane 0.5–1%</td>
<td>Target-controlled infusion of propofol 2 µg ml⁻¹ to stabilize mean arterial pressure and heart rate within 20% of baseline values, with opioids, and neuromuscular blocking agents, as required</td>
<td>On-pump AVR</td>
<td>Improved cardiac function and lower cTnI</td>
</tr>
<tr>
<td>Garcia197</td>
<td>72</td>
<td>Propofol or etomidate, opioids and neuromuscular blocking agents and maintained with a target-controlled infusion of propofol 2–5 µg ml⁻¹ to stabilize mean arterial pressure and heart rate within 20% of baseline values, with opioids, and neuromuscular blocking agents, as required</td>
<td>Sevoflurane (10 min at 4 vol%) during CPB</td>
<td>Placebo</td>
<td>On-pump CABG</td>
<td>Reduced the incidence of late cardiac events during the first year after CABG. Lower NT-proBNP, cTnT</td>
</tr>
<tr>
<td>Conzen198</td>
<td>20</td>
<td>Sufentanil 0.025 μg kg⁻¹ min⁻¹</td>
<td>Sevoflurane 1 MAC</td>
<td>Propofol 2–3 µg ml⁻¹</td>
<td>Off-pump CABG under cardioplegic arrest</td>
<td>Lower cTnI</td>
</tr>
<tr>
<td>Julier199</td>
<td>72</td>
<td>Maintain: propofol infusion, continuous infusion or repeated doses of opioids, and pancuronium or vecuronium administration as required.</td>
<td>First 10 min of complete CPB with sevoflurane 4 vol% (2 MAC)</td>
<td>First 10 min of complete CPB with placebo (oxygen-air mixture only)</td>
<td></td>
<td>Reduced BNP, No difference in ST-segment changes, arrhythmias, CK-MB, and cTnT</td>
</tr>
</tbody>
</table>
do seem to reduce cTnl concentrations in I/R injury, the clinical significance of cTnl reduction is unclear (although likely to be good). I.V. anaesthesia in the above meta-analysis was not homogeneous, with midazolam and even etomidate included in that cohort, and, in our opinion, this does not mean that volatiles are preferable to propofol in patients with cardiovascular disease as both possess some, although different, cardioprotective properties. For example a large trial suggested that sevoflurane appears to be superior to propofol in patients with little or no ischaemic heart disease, such as non-coronary artery bypass graft (CABG) surgery and CABG surgery without severe preoperative ischaemia, whereas propofol seems superior in patients with severe ischaemia, and/or cardiovascular instability, possibly because myocardial ischaemia has already preconditioned the heart and propofol exerts it’s protection differently.146

Although experimental animal studies have consistently shown effective cardioprotection and have identified the specific cellular signalling involved, only a few studies have attempted to identify and confirm the specific cellular signalling of IPC, IPO, and APC in humans. More importantly, attempts to translate the findings regarding the mechanism and effectiveness of IPC, IPO, and APC from experimental animals into the clinical setting have largely failed. The reason for these failures might be: (1) many of the patients have comorbidities such as diabetes, aging, dyslipidemia, and hypertension which have been shown to influence the protective effects of IPC, IPO, and APC; (2) poor experimental design and no allowance for the use of concomitant medication such as anaesthetics. Some of the confounding factors such as age, diabetes and myocardial remodelling that may cause conflicting results in clinical trials have been discussed elsewhere147 148 and summarized below.

**Cardioprotection in diabetes and the impact of diabetes on anaesthetic cardioprotection**

Higher rates of cardiovascular disease and mortality after AMI are observed in patients with diabetes. These patients are not only vulnerable to myocardial IRI but also not sensitive to cardioprotective strategies such as ischaemic conditioning and anaesthetic conditioning, that are effective in non-diabetic animal models of myocardial ischaemia/reperfusion or in non-diabetic patients undergoing CABG surgery. Clinically, diabetes is considered as an independent risk factor for cardiac injury during and after cardiac surgery.149 Poorer recovery and higher mortality rates (two to
four-fold higher than in non-diabetic subjects) after acute myocardial ischaemia/infarction (AMI) have also been reported.\textsuperscript{110} Infarct size was 30–70% larger after reperfusion therapy (either thrombolytic therapy or percutaneous coronary intervention) in diabetic than in non-diabetic patients,\textsuperscript{111} 112 and worse short and long-term progression after AMI was observed.\textsuperscript{105} 114

Multiple factors have been proposed to contribute to the disparate outcomes regarding the susceptibility of diabetic hearts to myocardial IRI including: (1) the duration and the severity of the diabetic status; (2) the experimental protocols (e.g. type of animal species, severity of ischaemia and reperfusion); (3) the metabolic profiles of diabetic subjects at the time the experiment was conducted. Enhanced oxidative stress, which is mainly because of the burst production of ROS and/or depleted endogenous antioxidant system in diabetes, has been suggested as a major factor.\textsuperscript{115} Increased oxidative stress has been shown to increase mPTP opening\textsuperscript{116} and induce Ca\textsuperscript{2+} overload,\textsuperscript{117} factors that are attributable to myocardial IRI as discussed earlier. More importantly, enhanced oxidative stress may also impair endogenous cardioprotective signalling, which not only increases post-ischaemic myocardial injury in diabetic hearts but also diminishes or abolishes the protective effects of cardioprotective interventions such as ischaemic conditioning.

With a few exceptions, the cardioprotection of IPC, IPo, and APC has been shown to be compromised or even abolished in the hearts of diabetics. The effectiveness of sevoflurane postconditioning in reducing post-ischaemic myocardial infarct size and apoptosis in non-diabetic rats, was completely abrogated in streptozotocin-induced diabetic rats and diabetes blockade of sevoflurane postconditioning could not be restored by insulin,\textsuperscript{117} although it could be restored by treatment with the antioxidant N-Acetylcysteine, which attenuated or restored diabetes induced reductions in cardiac p-STAT3 and adiponectin.\textsuperscript{118} Defects in the RISK and SAFE pathways in diabetes have also been considered as a reason.\textsuperscript{119} 120 However, the exact role and the mechanism of reduced cardiac p-STAT3 activation in diabetes is not clear and needs further investigation, in order to facilitate the development of novel interventions to restore myocardial sensitivity to IPo in diabetes.

Major cardiovascular co-morbidities that may affect ischaemic or anaesthetic conditioning effects

Ischaemic, anaesthetic preconditioning and postconditioning, trigger endogenous cardioprotective mechanisms that render the heart more resistant to lethal ischaemia-reperfusion injury. However, in addition to diabetes and senescence as aforementioned, certain major cardiovascular co-morbidities such as hyperlipidaemia,\textsuperscript{141} 142 cardiomyocyte hypertrophy,\textsuperscript{143} 144 hypertension,\textsuperscript{144} 145 and myocardial remodelling,\textsuperscript{146} and many of their associated medications (e.g. β-blockers, glibenclamide, glitazides) may interfere with the mechanisms of conditioning cardioprotection, thereby limiting the efficacy of ischaemic or anaesthetic conditioning in clinical settings. The exact mechanisms by which these co-morbidities and medications interfere with conditioning cardioprotection are not well understood. Glibenclamide abolishes the protective effect of mitochondrial K\textsubscript{ATP} channel opening\textsuperscript{146} and is one of the worst drugs in this regard. Statins may actually increase the effect of mitochondrial K\textsubscript{ATP} channel opening\textsuperscript{146} and induce Ca\textsuperscript{2+} overload,\textsuperscript{117} factors that are attributable to myocardial IRI as discussed earlier. More importantly, enhanced oxidative stress may also impair endogenous cardioprotective signalling, which not only increases post-ischaemic myocardial injury in diabetic hearts but also diminishes or abolishes the protective effects of cardioprotective interventions such as ischaemic conditioning.

Summary and future perspectives

Anaesthetic and ischaemia-induced myocardial protective effects are fascinating phenomena that have been extensively studied in various animal models with several mechanisms now elucidated. Clinically, beneficial effects, in terms of reduction in markers of cardiac injury, have also been demonstrated in patients undergoing heart surgery. Remote ischaemic conditioning, as a relatively simple and safe technique, may have particular clinical application (not only in protecting the heart but many other organs), however, many studies have been hampered by small sample sizes and lack of hard and more long-term clinical outcome data, with many relying on surrogate markers of cardiac injury. Certain patients that are particularly vulnerable to vascular complications (e.g. those with diabetes, hypertension and senescence), are particularly resistant to cardiac conditioning of all forms and this may be further complicated by adjuvant pharmacotherapy. Despite some ‘proof of concept’, large randomized clinical trials are still needed to determine whether this is just a healthy heart phenomenon or whether it’s something that we can routinely use to protect our increasingly high-risk patients undergoing cardiac and vascular surgery.

Authors’ contributions

Writing paper: all authors

Revising paper: all authors

Declaration of interest

None declared.

Funding

The work of the authors was supported in part by the Hong Kong Research Grants Council (RGC) general research fund grants (17121315M to M.G.I. and 17123915M to Z.X.).

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Handling editor: J. G. Hardman