The mechanisms of cardio-protective effects of desflurane and sevoflurane at the time of reperfusion: anaesthetic post-conditioning potentially translatable to humans?

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Abstract

Myocardial conditioning is actually an essential strategy in the management of ischaemia-reperfusion injury. The concept of anaesthetic post-conditioning is intriguing, its action occurring at a pivotal moment (that of reperfusion when ischaemia reperfusion lesions are initiated) where the activation of these cardio-protective mechanisms could overpower the mechanisms leading to ischaemia reperfusion injuries. Desflurane and sevoflurane are volatile anaesthetics frequently used during cardiac surgery. This review focuses on the efficacy of desflurane and sevoflurane administered during early reperfusion as a potential cardio-protective strategy. In the context of experimental studies in animal models and in human atrial tissues in vitro, the mechanisms underlying the cardio-protective effect of these agents and their capacity to induce post-conditioning have been reviewed in detail, underlining the role of reactive oxygen species generation, the activation of the cellular signalling pathways, and the actions on mitochondria along with the translatable actions in humans; this might well be sufficient to set the basis for launching randomized clinical studies, actually needed to confirm this strategy as one of real impact.

Key words: desflurane; mechanisms; mitochondria; myocardial reperfusion injury/prevention; sevoflurane
intervention may require precise, timed pulsations of ischaemia and reperfusion; 2) a training is needed of emergency medical professionals to provide timely intervention. Therefore, an alternative means of harnessing this protection might be by using pharmacological agents, such as anaesthetic agents, able to mimic the effect of ischaemic PreC or PostC which may provide a feasible and effective cardio-protective alternative.

Desflurane and sevoflurane are the volatile anaesthetics most widely used in cardiac surgery with CPB. Halogenated anaesthetics demonstrated their cardio-protective properties by biochemical mechanisms involving action on specific activation of signalling pathway and mitochondria, in addition they also have haemodynamic properties that improve myocardial oxygen balance during ischaemia, by reducing myocardial contractility and vasodilation. Clinical and experimental evidence support the concept of desflurane- and sevoflurane-induced preconditioning (PreC), and recently, multiple experimental studies focused on the cardio-protective effects of desflurane and sevoflurane when administered after ischaemia, corresponding to anaesthetic post-conditioning (PostC).

We concentrate here on current information on the effects of desflurane and sevoflurane, administered after ischaemia/hypoxia and the conferred protection against myocardial ischaemia-reperfusion injuries. The mechanisms underlying the cardio-protective effects of desflurane- and sevoflurane- induced PostC are reviewed in detail. The role of reactive oxygen species generation, activation of the cellular signalling pathways and the actions on mitochondria are discussed. Finally with the current review we aim to motivate the launch of clinical randomized studies that are desperately needed to demonstrate an appreciable value of anaesthetic PostC in clinical practice.

Myocardial reperfusion injury

During interventions such as percutaneous coronary angioplasty and cardiac surgery (Coronary artery bypass surgery (CABG), valve surgery) with or even without cardiopulmonary bypass (CPB), episodes of myocardial ischaemia are often expected. Cardiac surgery with CPB is associated with a prolonged global cardiac ischaemia. After an ischaemic episode, reperfusion, whether unpredicted (which corresponds to the majority of clinical cases) or expected could ‘save’ the myocardium. However, the cellular damage caused by the ischaemia-reperfusion sequence, the ‘reperfusion injury’, can induce dysfunction or cell death. Myocardial reperfusion is a paradoxical phenomenon: it is recognized as the only way to reduce infarct size in both experimental models and in clinical practice, provided it is carried out early enough, but it is accompanied by myocardial dysfunction, loss of viable myocardial tissue, via apoptosis and necrosis.4 Upon restoration of perfusion, the mitochondria produce a massive amount of reactive oxygen species (ROS) from the newly available oxygen going through the respiratory chain. The phenomenon of ‘ROS-induced ROS release’ is superimposed to the ROS production, which takes place at the respiratory chain and depends on the state (open or closed) of the pore of mitochondrial permeability transition (mPTP).5 The proposed mechanism is that the mPTP opening modifies the fluidity and rigidity of the inner mitochondrial membrane, which influences the transport of electrons, exacerbates mitochondrial dysfunction which leads to a vicious circle, including inhibition of neutrophil accumulation and inactivation of superoxide radicals.6

Calcium loading is initiated during ischaemia, which causes mitochondrial calcium loading. Upon reperfusion, ROS is produced from the respiratory chain, restoration of ionic balances aggravates calcium loading, which also impacts the mitochondrial calcium loading and the transition pore.7 This intracellular calcium overload, that in part results in the opening of the mPTP, could lead to the cardiomyocytes’ death.8 The direct consequence is a significant increase in intracellular [Ca2+] and cardiomyocytes hyper-contracture leading to reperfusion arrhythmia. The restoration of mitochondrial membrane potential leads to the entrance of calcium into the mitochondria, together with the loss of the inhibitory effect of the pH and the ROS production via mPTP, acting together to cause the mPTP opening and leading to dysfunction of oxidative phosphorylation, mitochondrial swelling and cardiomyocyte death.

Mitochondria are crucial in cardio-protective mechanisms. During ischaemia-reperfusion, the absence of the ATP synthesis accompanied by a stimulation of ATP hydrolysis, disruption of ionic homeostasis (especially calcium) and the generation of ROS are essential key events, consequence of the mitochondrial dysfunction, which can induce irreversible cell damage. At the time of reperfusion, the calcium overload, the generation of oxidative stress and the destruction of oxidative phosphorylation capacity, all increase the probability of mPTP opening. Myocardial ischaemia is accompanied by an acidosis that keeps the mPTP closed. It also decreases the ATP and inorganic phosphate accumulation or even the production (modest) of oxygen free radicals.9 It was really only during reperfusion that all conditions for the opening of the mPTP10 are met (calcium overload of the matrix, the burst of ROS, depletion of adenine nucleotides in the accumulation of inorganic phosphates, alkalization). Reperfusion, by combining optimal conditions to mPTP opening is a milestone that can truly transform the mitochondria into an initiator of cell death.

Cardio-protective effects of post-ischaemia administration of desflurane and sevoflurane

Myocardial post-conditioning

In some situations, myocardial ischaemia cannot be a foreseeable event. Myocardial PostC was first described by Zhao and colleagues11, as brief episodes of ischaemia immediately at the onset of reperfusion after a prolonged ischaemic insult, and was shown to reduce infarct size. This strategy provides a more clinically amenable approach to cardio-protection than ischaemic PreC, as the episode of long-lasting ischaemia is clearly and previously defined.12 The ability to reproduce the cardio-protective effects of PostC with pharmacological agents, raises the possibility that a drug may ultimately be introduced into clinical practice to treat hearts undergoing ischaemia/reperfusion. Although, multiple experimental studies investigated the effect of PostC by desflurane and sevoflurane, only few clinical trials investigated it, for the first time in 2004, De Hert and colleagues13 showed that sevoflurane PostC reduced postoperative troponin I concentrations and preserved stroke volume.

Desflurane and sevoflurane-induced post-conditioning

During the last decade, several studies investigated the effect of desflurane and sevoflurane specifically administered at the time of myocardial reperfusion (Tables 1 and 2). Obal and colleagues26 in 2005 observed that a brief exposure to sevoflurane during the first two min of reperfusion, induced reduction of myocardial infarct size of isolated perfused rat hearts that had been subjected to 25 min of coronary artery occlusion, followed by...
by two h of reperfusion. Later, our group showed that sevoflurane and desflurane PostC enhanced the recovery of force of contraction of human atrial trabeculae, after prolonged hypoxia followed by reoxygenation. In Tables 1 and 2, we present the results from the experimental studies investigating the effect of myocardial post-ischaemic exposure to desflurane and

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<td>Rats and mice in vivo:</td>
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<td>Haeelewyn and colleagues Br J Anaesth 2004</td>
<td>n=10 Sprague-Dawley rats per group, a total of 50 rats included</td>
<td>30 min of coronary artery occlusion followed by 3 h of reperfusion</td>
<td>1 MAC during the first 15 min of reperfusion</td>
<td>Reduction of infarct size to 41(15%) vs 65(15%) in control group</td>
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<td>Redel and colleagues Exp Biol Med (Maywood) 2009; Stumpner and colleagues Acta Anaesthesiol Scand 2012; Stumpner and colleagues Br J Anaesth 2012</td>
<td>n=7–10 C57BL/6 mice per group, a total of 278 mice included</td>
<td>45 min of coronary artery occlusion followed by 3 h of reperfusion</td>
<td>1 MAC for 18 min, starting 3 min before the end of coronary artery occlusion</td>
<td>Reduction of infarct size to 15% vs 47% in control group. *</td>
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<td>New Zealand white rabbits in vivo:</td>
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<td>Preckel B. Br J Anaesth. 1998</td>
<td>n=10 per group, a total of 58 rabbits included</td>
<td>30 min of occlusion of coronary artery followed by 2 h of reperfusion</td>
<td>1 MAC during the first 30 min of reperfusion</td>
<td>Reduction of infarct size to 32(3%) vs 49(5%) in control group.</td>
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<td>Lange and colleagues. Anesthesiology 2009; Smul and colleagues. J Cardiothorac Vasc Anesth 2009</td>
<td>n=6 or 7 per group, a total of 144 rabbits included</td>
<td>30 min of coronary artery occlusion followed by 3 h of reperfusion</td>
<td>1 MAC during the first 30 min of reperfusion</td>
<td>Reduction of infarct size to 28% vs 53% in control group. *</td>
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<td>Human in situ:</td>
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<td>Lemoine and colleagues. Anesthesiology 2008</td>
<td>n=6 human atria trabeculae in desflurane group and n=10 in control, a total of 175 trabeculae included</td>
<td>30 min of hypoxia followed by 60 min of reoxygenation</td>
<td>0.5, 1 and 1.5 MAC during the first 5 min of reoxygenation</td>
<td>Enhanced the recovery of force after 60 min of reoxygenation with desflurane 0.5 MAC (76% of baseline), 1 MAC (87%), and 1.5 MAC (86%) vs 50% in Control.*</td>
</tr>
<tr>
<td>Lemoine and colleagues. Anesthesiology 2010;112:1355–63; Lemoine and colleagues. BMC Anesthesiol. 2010; Lemoine and colleagues. Br J Anaesth. 2011</td>
<td>n=6 human atria trabeculae in desflurane group and n=10 in control, a total of 226 trabeculae included</td>
<td>30 min of hypoxia followed by 60 min of reoxygenation</td>
<td>1 MAC during the first 5 min of reoxygenation</td>
<td>Enhanced the recovery of force after 60 min of reoxygenation with desflurane 1 MAC (81% of baseline) vs 51% in Control.*</td>
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<tr>
<td>Lemoine and colleagues. Diabetes Metab. 2010</td>
<td>n=6 diabetic insulin and non-insulin-dependent human atria trabeculae in desflurane group and n=9 in control, a total of 80 trabeculae included</td>
<td>30 min of hypoxia followed by 60 min of reoxygenation</td>
<td>0.5, 1 and 1.5 MAC during the first 5 min of reoxygenation</td>
<td>Desflurane 0.5 MAC has no effect; In diabetic insulin-dependent: desflurane 1 and 1.5 MAC [75(11%) and 81(8%) of baseline] enhanced the recovery of force compared with Control [54(6%)]. In non-insulin-dependent: desflurane 1 and 1.5 MAC [80(10%) and 79(7%)] enhanced the recovery of force compared with Control [52(10%)].</td>
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Table 1 Results from experimental works investigating the effects of desflurane given at the time of myocardial reperfusion. *The results of the study are presented as a mean of the results of all studies with the same experimental protocol.
Table 2 Results of experimental works investigating the effects of sevoflurane given at the time of myocardial reperfusion. *The results of the study are presented as a mean of the results of all studies with the same experimental protocol

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<tr>
<th>Studies</th>
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<tr>
<td>Obal and colleagues. Anesth Analg. 2005</td>
<td>n=10 Wistar rats in each group, a total of 79 rats included</td>
<td>25 min of coronary artery occlusion followed by 2 h of reperfusion</td>
<td>1 MAC during the first 2 min of reperfusion</td>
<td>Reduction of infarct size to 18(5%) vs 49(11%) in control group.</td>
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<tr>
<td>Deyhimy and colleagues. Anesth Analg. 2007</td>
<td>n=6 Fischer rats in each group, a total of 24 rats included</td>
<td>25 min of global ischaemia followed by 1 h reperfusion</td>
<td>1.25 MAC during the first 10 min of reperfusion</td>
<td>Reduction of infarct size to 16(8%) vs 44(8%) in the control group.</td>
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<tr>
<td>He and colleagues. J Zhejiang Univ Sci B. 2008</td>
<td>n=6 Sprague-Dawley rats, a total of 36 rats included</td>
<td>40 min of ischaemia followed by 1 h of reperfusion</td>
<td>1.5 MAC during the first 15 min of reperfusion</td>
<td>– Reduction of infarct size to 17(3%) vs 48(6%) in the control group.</td>
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<td>– Improvement in functional recovery during reperfusion.</td>
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<td>– Reduction of the lactate dehydrogenase and the creatine kinase-MB release.</td>
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<td>Chen and colleagues. Acta Pharmacol Sin 2008</td>
<td>n=12 Sprague-Dawley rats per group, a total of 84 rats included</td>
<td>30 min of ischaemia followed by 1 h reperfusion</td>
<td>1.5 MAC during the first 5 min of reperfusion</td>
<td>Reduction of infarct size to 23(5%) vs 39(6%) in control group.</td>
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<td>Zhang and colleagues. Eur J Anaesthesiol. 2009</td>
<td>n=8 Sprague-Dawley rats per group, a total of 80 rats included</td>
<td>40 min of global ischaemia followed by reperfusion</td>
<td>4 MAC for 2 min followed by 23 min of reperfusion</td>
<td>Regular beating was maintained by sevoflurane during the reperfusion (no arrhythmia was occurred).</td>
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<td>– Reduction of infarct size to 23(8%) vs 42(9%) in the control group.</td>
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<td>Yu and colleagues. J Zhejiang Univ Sci B. 2010</td>
<td>n=8 Sprague-Dawley rats, a total of 56 rats included</td>
<td>40 min of global ischaemia followed by 2 h of reperfusion</td>
<td>1.25 MAC during the first 10 min of reperfusion</td>
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<td>Yao and colleagues. Chin Med J (Engl) 2010; Yao and colleagues. Mol Biol Rep 2010</td>
<td>n=15 Sprague-Dawley rats per group, a total of more of 120 rats included</td>
<td>30 min of ischaemia followed by 60 min of reperfusion</td>
<td>1.5 MAC during the first 15 min of reperfusion</td>
<td>– Improvement in functional recovery during early reperfusion.</td>
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<td>– Reduction of the lactate dehydrogenase, the creatine kinase-MB release.</td>
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<td>– Reduction of apoptosis.</td>
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<td>– Reduction of infarct size to 17(4%) vs 37(5%) in the control group.*</td>
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<td>Dai and colleagues. J Zhejiang Univ Sci B 2010</td>
<td>n=8 Sprague-Dawley rats, a total of 24 rats included</td>
<td>20 min of global ischaemia followed by 40 min of reperfusion</td>
<td>4 MAC during the first 5 min of reperfusion</td>
<td>Sevoflurane reduces reperfusion arrhythmias without affecting the severity of myocardial stunning.</td>
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<td>– Significant reduction of infarct size</td>
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<td>– Improvement in functional recovery.</td>
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<tr>
<td>Fang and colleagues. Mol Biol Rep 2010</td>
<td>n=10 Male Wistar rats per group, a total of 60 rats included</td>
<td>40 min of ischaemia followed by 1 h of reperfusion</td>
<td>1 MAC during the first 15 min of reperfusion</td>
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<td>Zheng and colleagues. J Surg Res 2011</td>
<td>n=14 Sprague-Dawley rats per group, a total of 70 rats included</td>
<td>40 min of ischaemia followed by 2 h of reperfusion</td>
<td>1.5 MAC during the first 10 min of reperfusion</td>
<td>Sevoflurane PostC developed cardioprotection in male rats but not in female rats.</td>
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| Gong and colleagues. Mol Biol Rep 2012      | n=10 Sprague-Dawley rats per group, a total of 30 rats included | 25 min of ischaemia followed by 30 min of reperfusion | 1.5 MAC during the first 15 min of reperfusion | – Attenuation reperfusion-induced arrhythmia (duration and incidence of ventricular)  
– Regulation of lipid peroxidation and generation of reactive oxygen species. |
| Yao and colleagues. J Zhejiang Univ Sci B 2013 | n=7 Sprague-Dawley rats per group, a total of 42 rats included | 40 min of global ischaemia followed by 2 h reperfusion | 1 MAC during the first 5, 10, and 15 first min of reperfusion | Reduction of infarct size with sevoflurane exposure during 5, 10, and 15 min (respectively 19(6%), 18(6%), and 22(4%) vs 36(4%) in control group. |
| Rat in vivo: Huhn and colleagues. Br J Anaesth 2008 | n=11 Wistar rats in sevoflurane group and n=9 in control group, a total of 71 rats included | 25 min of coronary artery occlusion followed by 2 h of reperfusion | 1 MAC during the first 5 min of reperfusion starting 1 min before the onset of reperfusion | Reduction of infarct size to 33(13%) vs 51(5%) in control group. |
| Redel and colleagues. Exp Biol Med (Maywood) 2009 | n=10 C57BL/6 mice per group, a total of 88 rats included | 45 min of coronary artery occlusion followed by 3 h of reperfusion | 1 MAC for 18 min starting 3 min before the reperfusion | Reduction of infarct size to 27(6%) vs 50(4%) in control group. |
| Yao and colleagues. Biol Pharm Bull 2009 | n=10 Sprague-Dawley rats in each group, a total of 80 rats included | 30 min of coronary artery occlusion by 1 h of reperfusion | 1.5 MAC during the first 15 min of reperfusion | – Reduction of infarct size to 20(3%) vs 34(4%) in the control group.  
– Improvement in functional recovery during early reperfusion.  
– Reduction of the lactate dehydrogenase and the creatine kinase-MB release. |
| Drenger and colleagues. Anesthesiology 2011 | n=21–26 Sprague-Dawley rats in each group, a total of 157 rats included | 30 min of coronary artery occlusion followed by 3 h of reperfusion | 1.2 MAC during the first 5 min of reperfusion | – No reduction of infarct size was observed : 20% with sevoflurane and 19% in untreated diabetics rats.  
– In presence of diabetes no reduction of apoptosis was observed.  
– In non-diabetic rats : Reduction of infarct size to 10% vs 20% in control group and reduction of apoptosis. |
| Tai and colleagues. J Surg Res 2012 | n=8 or 9 Diabetic and non diabetic Sprague-Dawley rats for each group, a total of 56 rats included | 30 min of coronary artery occlusion followed by 2 h of reperfusion | 1 MAC during the first 5 min of reperfusion | – Reduction of infarct size to 35% (6%) vs 35(8%) in control group.  
– The infarct-sparing effect of sevoflurane PostC was completely abolished in the diabetic rats (compared with non diabetic rats). |
| Xu and colleagues. PLoS One. 2013 | n=8 Sprague Dawley rats in each group, a total of 133 rats included | 30 min of ischaemia and 2 h of reperfusion | 1.2 MAC during the first 5 min of reperfusion | – Reduction of infarct size to 27(6%) vs (44(5%), in the control group.  
– Anti-apoptotic effect of sevoflurane.  
– Absence of cardioprotection conferred by sevoflurane PostC in hypercholesterolemic rats. |
sevoflurane. However, although desflurane and sevoflurane were administered during reperfusion, there is some controversy about the term PostC, as it was determined as a 'brief' exposure of 30-min duration that some might also consider as a relatively prolonged exposure.

### Table 2 Continued

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<tr>
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<tbody>
<tr>
<td>Li and colleagues. Acta Anaesthesiol Scand 2013[^44^]</td>
<td>n=6 Sprague-Dawley rats in each group, a total of 100 rats included</td>
<td>30 min of global ischaemia, followed by 1 h of reperfusion</td>
<td>1.5 MAC during the first 5 min of reperfusion</td>
<td>– Reduction of infarct size to 35(4%) vs 56(3%) in control group in young rats. – Absence of cardioprotection conferred by sevoflurane PostC in old rats.</td>
</tr>
<tr>
<td>Zhang and colleagues. Acta Pharmacologica Sinica 2014[^15^]</td>
<td>n=7–13 Sprague-Dawley rats in each group, a total of 119 rats included</td>
<td>30 min of left anterior descending coronary artery ligation followed by 30 or 120 min of reperfusion</td>
<td>1.2 MAC during the first 5 min of reperfusion</td>
<td>– Reduction of infarct size to 20(5%) vs 45(2%) in control group, and decrease of Troponin. – Anti-apoptotic effect of sevoflurane.</td>
</tr>
<tr>
<td>Zhang and colleagues. Sci Rep. 2014[^15^]</td>
<td>n=10 Sprague-Dawley rats in each group, a total of 88 rats included</td>
<td>30 min of ischaemia and 2 h of reperfusion</td>
<td>1.2 MAC during the first 15 min of reperfusion</td>
<td>– Reduction of infarct size to 21 (9%) vs 51(4%) in control group – Inhibits myocardial apoptosis</td>
</tr>
<tr>
<td>Isolated perfused guinea pig hearts: Inamura and colleagues. Anesthesiology 2009[^7^]; Inamura and colleagues. J Anesth. 2010[^16^]</td>
<td>n=8 guinea pigs in sevoflurane and control groups, a total of 80 guinea pig included</td>
<td>30 min of global ischaemia followed by 2 h reperfusion</td>
<td>1 MAC during the first 2 min of reperfusion</td>
<td>– Reduction of infarct size to 15% in control group. – Improvement in functional recovery.</td>
</tr>
<tr>
<td>Rats in vivo: Preckel and colleagues. Br J Anaesth 1998[^18^]</td>
<td>n=10 New Zealand white rabbits per group, a total of 58 rabbits included</td>
<td>30 min of occlusion of a major coronary artery followed by 2 h of reperfusion</td>
<td>1 MAC during the first 15 min of reperfusion</td>
<td>Reduction of infarct size to 36(2%) vs 49(5%) in control group. – (1) Reduction of infarct size to 6(3%), 6(4%) respectively for 1 MAC sevoflurane and 2 MAC sevoflurane vs 20(7%) in control group. – (2) Reduction of infarct size to 23(5%), 21(6%) respectively for 1 MAC sevoflurane and 2 MAC sevoflurane vs 51(10%) in control group. – (3) No effect on infarct size</td>
</tr>
<tr>
<td>Chen and colleagues. Mol Biol Rep 2012[^15^]</td>
<td>n=8 Japanese White Rabbits per group, a total of 120 rabbits included</td>
<td>30 min of global ischaemia followed by 2 h reperfusion</td>
<td>0.5, 1, 1.5 and 2 MAC during the first 5 min of reperfusion</td>
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<td>Pigs, in vivo: Larsen and colleagues. Acta Anaesthesiol Scand 2012[^20^]</td>
<td>n=12 in sevoflurane group and n=10 in control group</td>
<td>45 min of regional coronary artery balloon occlusion and subsequent 2 h reperfusion</td>
<td>4 to 1.5 MAC during the reperfusion</td>
<td>Reduction of infarct size to 32(13%) vs 55(14%) in control group.</td>
</tr>
<tr>
<td>Human in situ: Zhu and colleagues. Acta Anaesthesiol Scand 2009[^11^]</td>
<td>n=6 human atria trabeculae in sevoflurane group and n=10 in control, a total of 75 trabeculae included</td>
<td>30 min of hypoxia followed by 60 min of reoxygenation</td>
<td>0.5, 1 and 1.5 MAC during the first 5 min of reoxygenation</td>
<td>Sevoflurane 0.5, 1 and 1.5 MAC [78(4%), 79(5%), and 85(4%) of baseline, respectively] enhanced the recovery of force compared with Control.</td>
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#### Mechanisms of desflurane and sevoflurane post-conditioning-induced cardio-protection

The underlying mechanisms whereby desflurane and sevoflurane may induce cardio-protection are only partly elucidated.
Nevertheless, several studies have analysed the mechanisms involved in desflurane and sevoflurane PostC.

**Role of the coupled G proteins receptors in desflurane- and sevoflurane - induced post-conditioning**

The main receptors involved in cardio-protection, include a receptor coupled to G-proteins, whose activation induces a change in the structure of the receptor. These G-proteins, activate different intracellular effectors in the cell membrane or cytosol (Fig. 1). These effectors can modulate the intracellular second messengers, such as 3'-5'-cyclic adenosine monophosphate (cAMP), inositol triphosphate (IP3), calcium and diacyl glycerols.

The contribution of beta-adrenergic receptors in desflurane-induced PostC was recently demonstrated. Lange and colleagues showed that co administration of esmolol or ICI 118551, respectively beta(1)- and beta(2)-adrenergic receptor blockers, with desflurane during the initial reperfusion blocked desflurane-induced PostC.

Ligands such as adenosine and bradykinin which accumulate during PreC and PostC manoeuvres may initiate the cascade that lead to cardio-protection. In isolated human myocardium, we have reported that inhibition of adenosine receptors and bradykinin B2 receptors with SPT (one adenosine receptor antagonist) and HOE140 (a bradykinin B2 receptors antagonist) administered in presence of desflurane PostC, antagonized the improved recovery of contraction induced by desflurane.

**Impact of desflurane and sevoflurane post-conditioning on calcium metabolism**

Lange and colleagues have observed that desflurane elaborated PostC via the phosphorylation of phospholamban that was mediated by beta(1) and beta(2) adrenergic and CaMK II.
Signaling pathways involved in cardio-protection with post-conditioning by desflurane and sevoflurane

Protein kinase C (PKC) plays a major role in the signalling pathway of myocardial PreC and PostC, because it activates many signalling pathways and many mitochondrial targets including mitochondrial adenosine triphosphate–sensitive potassium (K<sub>AATP</sub>) channels (Fig. 1). There is evidence identifying PKC as a mediator rather than a trigger of the PostC by desflurane: specific blockade of PKC by calphostin C abolishes desflurane-induced PostC of the diabetic and non-diabetic human heart in situ. In isolated guinea pig hearts, PostC by sevoflurane induced an enhanced phosphorylation of PKC-delta and no modification of the expression of phospho-PKC epsilon, thus suggesting that sevoflurane PostC is specifically mediated by the activation/phosphorylation of PKC-delta.

‘Reperfusion Injury Salvage Kinase’ signalling pathway in desflurane and sevoflurane induced post-conditioning

The activation of the Reperfusion Injury Salvage Kinase pathway (RISK pathway) plays a key role in cardio-protection induced by PostC (Fig. 2). This pathway is defined as a kinases cascade activated at reperfusion, which leads to cardio-protection, with two main molecular signalling pathways, the phosphatidylinositol-3 kinase (PI3 K) and the extracellular signal regulated kinase 1/2 (MEK/ERK1/2), responsible at reperfusion for relaying the cardio-protective effect from the receptor in the myocardium to a downstream end effector. These pathways converge to cause inhibition of glycogen synthase kinase-3 beta (GSK-3 beta). Desflurane-induced PostC protects the human myocardium through the activation of PI3 K/protein kinase B (Akt) and MEK/ERK1/2 pathways. In rat hearts, cardio-protective effects induced by post-ischaemia administration of sevoflurane were mediated by the PI3 K/Akt and MEK/ERK1/2 pathways. In addition, PostC by sevoflurane induced an enhanced phosphorylation of Akt and ERK1/2, as compared with a control group, in rat hearts and in isolated guinea pig hearts.

Our group reported that the activation of 90-kDa ribosomal protein S6 kinase (p70S6 K), in early re-oxygenation period, mediated desflurane-induced cardio-protection. In Langendorff-perfused rat hearts, at 15 min of reperfusion, the expression of phospho-p70S6 K in the sevoflurane PostC groups further increased. The p70S6 K plays an essential role in ischaemic and anaesthetic PostC and is activated by the PI3 K/Akt pathway. The GSK-3 beta, strongly activated in the basolateral membrane, participates in many cellular processes including cell division and transcription. Upstream regulators of GSK-3 beta include the PI3 K/Akt pathway. PKC, the mammalian target of rapamycin (mTOR) and Mitogen-activated protein kinase (MAPK) proteins. Non-mitochondrial cell lines have also shown that ERK primes GSK-3 beta to allow for phosphorylation and inhibition at the Ser9 site. PostC by sevoflurane of guinea pig hearts and PostC by desflurane of isolated human myocardium induced an enhanced phosphorylation of GSK-3 beta.

Relationship between desflurane and sevoflurane post-conditioning-induced cardio-protection and apoptosis factors

Some studies have shown that desflurane and sevoflurane could reduce the occurrence of myocardial apoptosis induced by ischaemia-reperfusion (Fig. 3). In mouse heart in vivo, phosphorylation of the pro-apoptotic molecule Bcl-2-associated death (Bad), mediates desflurane-induced PostC via the Pim-1 kinase activation. Pim-1 kinase, a proto-oncogene serine/threonine-protein kinase, was recently identified as a downstream mediator of protein Akt activity in cardiomyocytes: it reduces myocardial infarct size and cardiomyocyte apoptosis and phosphorylates several downstream targets, including Bad. The isolated perfused rat hearts exposed to sevoflurane, in early reperfusion, showed that the expression of Bcl-2 and phospho-Bad increased, and the expression of Bcl-2-associated X protein (Bax: a pro-apoptotic protein) decreased. In isolated perfused guinea pig hearts, PostC by sevoflurane prevents activation of caspase 3 and 9, both mediators of apoptosis in ischaemia-reperfusion injury and this anti-apoptotic effect was mediated by PI3 K and ERK1/2 activation. In isolated perfused rat hearts, in early reperfusion, the content of cytochrome c in the group exposed to sevoflurane in early reperfusion significantly decreased in cytosol and obviously increased in mitochondria; this effect could be attributed to the inhibition of the mPTP opening induced by sevoflurane. Recently, it was demonstrated, in rat in vivo, that sevoflurane induced PostC restore autophagic flux in myocardial tissues exposed to ischaemia-reperfusion, by preventing the increase of levels of LC3B-II, beclin-1 and p62 and improved the lysosomal function in ischaemia-reperfusion myocardial tissues.

Involvement of mitochondria (opening of mitochondrial permeability transition pore) in damages related to myocardial ischaemia-reperfusion

Multiple studies showed that the mPTP has a major role in PostC; administration of the inhibitors of mPTP given at reperfusion limited infarct size, equivalently to that observed during ischaemic PostC.

The mechanisms by which desflurane protects the myocardium against ischaemia, seen at a molecular level, may involve preservation of the integrity/function of the mitochondrial electron transport chain. Desflurane-induced PostC was blocked by concomitant administration of atractyloside, a mPTP opener, in mice hearts and human myocardium in vitro, suggesting that desflurane-induced PostC prevented the mPTP opening in early re-oxygenation period. The major components of the ‘RISK’ pathway (Fig. 2) may influence the state of mPTP opening; moreover the cardio-protective effect of desflurane, seems to be dependent on the inhibition of GSK-3 beta. According to the majority of studies, the state of mPTP opening is governed by...
different parameters including calcium overload, also considered to be responsible for the opening of mPTP. Piriou and colleagues showed, in mitochondria isolated from in vivo rabbit hearts, that desflurane improved the resistance of mPTP to calcium-induced opening, when exposed to calcium overload, moreover, a link between mitochondrial KATP channels and mPTP has been suggested. In isolated perfused rat hearts, exposure of sevoflurane PostC, maintained the myocardial content of nicotinamide adenine dinucleotide (NAD+) decreased by ischaemia-reperfusion, thus suggesting that sevoflurane inhibits the opening of mPTP and this effect was dependent of PI3 K and MEK/ERK. Finally, cardio-protective effects of haemodynamic recovery and infarct size reduction by sevoflurane was completely abolished by atractylloside. Moreover atractylloside could abrogate the anti-apoptotic effects of sevoflurane induced postC.

**Mitochondrial adenosine triphosphate–sensitive potassium channels**

The importance of K<sub>ATP</sub> channels in cardio-protection is usually demonstrated using inhibitor of the opening of K<sub>ATP</sub> channels: 5-hydroxydecanoate (a selective mitochondrial K<sub>ATP</sub> channel.
antagonist) and HMR-1098 (a selective sarcolemmal K<sub>ATP</sub> channel antagonist) (Fig. 1). We have shown that desflurane-induced PostC of non-diabetic and non-insulin-dependent diabetic human myocardium in vitro, was mediated by the opening of mitochondrial K<sub>ATP</sub> during the early period of reoxygenation.21 24 Concerning sevoflurane-induced PostC, all the experimental data show the implication of mitochondrial K<sub>ATP</sub> channels: in rat heart, 5-hydroxydecanoate antagonized the reduction of infarct size and haemodynamic recovery induced by sevoflurane PostC.26 41 The role of the mitochondrial K<sub>ATP</sub> channel as an effector mechanism in cardio-protection can be explained by the following: 1) The decrease in mitochondrial membrane potential resulting in decreased matrix calcium overload thus resulting in a lower probability of mPTP opening; 2) The opening of mitochondrial K<sub>ATP</sub> allowed volume regulation of the mitochondrial matrix, which would lead to the maintenance of chain electron transport and preserve the architecture of the inter-membrane, allowing a transfer of more efficient energy between mitochondria and cellular ATPases;67 69 3) ROS may also be involved, with decreased production during reperfusion, after the activation/opening of mitochondrial K<sub>ATP</sub> channels; 4) The mitochondrial K<sub>ATP</sub> opening in early reperfusion also promote the inhibition of mPTP opening, allowing the ischaemic and anaesthetic PostC.70 71

Relationship between desflurane, sevoflurane and reactive oxygen species generation

Under ischaemia-reperfusion conditions, the formation of ROS can quickly exceed the antioxidant defences and causes cellular damage, in particular during early reoxygenation.72 73 The natural defence systems being very active in the ‘ischaemic cells’, re-admission of oxygen during reperfusion will cause oxidative stress, caused by: 1) The increase in the production of superoxide anion at the mitochondrial respiratory chain from the newly available oxygen, 2) the activation of neutrophils accumulated in the ischaemic area itself, linked to the production (which contribute to the genesis of reperfusion arrhythmias)74 and diffusion of extracellular free radicals, 3) the reaction of certain products of anaerobic metabolism, hypoxanthine and xanthine oxidase, which form the xanthine and the superoxide anion in the presence of oxygen. The involvement of ROS in the pathogenesis of post-ischaemic necrosis, apoptosis and vascular dysfunction has been demonstrated in several studies.75 76

One paradigm that presently seems to exist in cardio-protective signalling is the benefit of ROS generation, that could also be included among the triggers of PostC, or may act as a second messenger system. Indeed, it is now known that ROS act as important mediators in signal transduction processes, involved in multiple...
aspects of cardio-protection and decrease mitochondrial calcium overload preventing mPTP from opening. Decreased intracellular ROS levels induced by sevoflurane PostC have led to the reduction of the incidence of ventricular tachycardia and ventricular fibrillation and decreased reperfusion arrhythmia scores, in isolated perfused rat hearts model.57 In consequence, it is important to do a distinction: the ROS that trigger protection, and that causing the cellular damage. The difference could be as a result of the amount of ROS produced at the time of reperfusion: a small amount of ROS could trigger the cardio-protection while excessive amounts will induce a large part of the reperfusion injuries. In isolated human myocardium, the cardio-protective effects of PostC by desflurane were abolished in the presence of a ROS scavenger, mercaptopropionylglycine, suggesting that (moderate) ROS generation could trigger desflurane-induced PostC.68 Moreover, an increase in ROS production precedes oxidation of flavoproteins (i.e. mitochondrial KATP channel opening), in response to desflurane exposure in rat ventricular cardiomyocytes.57

Nitric oxide
Nitric Oxide (NO) plays an essential role in cardio-protection: the major roles of endothelial nitric oxide synthase (eNOS)70 and inducible nitric oxide synthase (iNOS) have been documented.79 The beneficial and deleterious effects of NO and nitrite in physiological conditions and in cardio-protective strategies during reperfusion have also been well documented.50 81 There is evidence that NO was involved in desflurane-induced PostC, as the N-omega-nitro-L-arginine (L-NAME), a NOS inhibitor, concomitantly administered with desflurane abolished its cardio-protective effect.72 In isolated human myocardium and in the rabbit heart in vivo, desflurane-induced PostC depends on ROS activation in the first min of reperfusion;52 20 In isolated guinea pig hearts, NO production after reperfusion was higher in hearts exposed to PostC with sevoflurane than in untreated hearts.47 Altogether, these data showed that the release of NO plays a role in desflurane and sevoflurane PostC. The exact mechanism whereby NO is involved in cardio-protection remains however uncertain. It is known that NO exerts a number of beneficial actions on the myocardium submitted to ischaemia-reperfusion; in particular: 1) inhibition of calcium influx via its action on L-type calcium channels, 2) activation of mitochondrial KATP channels, 3) an antioxidant and anti-apoptotic effect, 4) the availability of NO could limit the opening of the mPTP.81 Taken together, these speculated mechanisms suggest what future experimental studies need to concentrate on to understand the exact role of NO in halogenated anaesthetics induced-PostC.

Anaesthetic pre- and post-conditioning: from bench to bedside
There has recently been great clinical expectation with volatile anaesthetic agents and two phenomena have been observed:55 86 a) myocardial infarct size reduction when they are given transiently before prolonged ischaemia (an effect whose size was comparable to ischaemic PreC) and b) a small increase of reactive oxygen species after anaesthetics might in turn trigger the conditioning action, through secondary messenger pathways.57 88 However, PostC despite numerous experimental studies on animals and on isolated myocardial cells as reviewed above, has not been applied in clinical practice such as ischaemic PostC during angioplasty.89 However, it is important to understand that when comparing clinical studies performed in diverse types of surgery, it is essential to define the exact anaesthetic protocol used and under these circumstances CABG surgery with on-pump vs off-pump and non-cardiac surgery categories might utilize quite different anaesthetic techniques. Studies performed within these categories should be interpreted accordingly and the relative amount of ischaemia-reperfusion injury and protection interpreted along with it. Clearly, further in-depth reviews should be performed along these interpretation lines. Table 3 is presented as a tentative effort to rationalize the interpretation of existing clinical data on this subject.

Myocardial conditioning with desflurane and sevoflurane : meta analyses
There has been a series of meta-analyses performed with the aim of providing a global overview of results obtained in randomized clinical trials with desflurane or sevoflurane: one showed that the incidence of perioperative myocardial infarction was twice lower and mortality rate fourfold lower than in patients anaesthetized with propofol.91 When anaesthesia with volatile and i.v. anaesthetics during CABG were compared, involving in total over 34 000 patients, 30-day mortality was lower in patients receiving volatile anaesthetics.117 However, this was a risk adjusted analysis in patients undergoing CABG surgery. The authors found a weak (r²=0.07) correlation between use of volatile anaesthetics and 30-day mortality. Also, this was an uncontrolled, retrospective design and statistical methods were used to estimate 30-days mortality instead of directly quantifying it. Moreover, it was demonstrated that longer use of volatile anaesthetics was the factor correlating with lower mortality.118 Prolonging the observation period to one-year post-cardiac surgery, the incidence of severe cardiac complications was 8.3% in desflurane or sevoflurane patients and 24.4% in propofol patients. Nevertheless, some limitation of the interpretation exist, as these may be considered as quite high complication rates.89 It has to be pointed out however, that the results of clinical studies vary widely and the outcomes are extremely different. Apart from reduction of enzymes release indicating myocardial necrosis, the most important goals such as mortality, and myocardial infarction with low cardiac output, were rarely investigated. The largest meta-analyses sometimes reach different conclusions. In two previous meta-analyses of about 6000 patients including more than 59 clinical trials of CABG patients56 86 volatile anaesthetics were able to reduce the postoperative troponin I release, when compared with i.v. anaesthetics. Although single studies showed a clear-cut reduction of troponin I, in the meta-analyses, it was not possible to associate troponin reduction to a better clinical outcome. This may in turn be interpreted as a cosmetic effect and not one of real impact. Another meta-analysis including 22 studies (total of 1922 patients undergoing cardiac surgery) obtained extraordinary results, such as myocardial infarction decrease and mortality reduction.91 However, in that meta-analysis, several studies were single-centred with few patients included and varied methodologies such as different cardiopulmonary techniques, different definitions of myocardial infarction and on- and off-pump procedures. No evidence for a dose-response effect was found. In contrast, the same authors have not observed any beneficial effect in cardiac surgery when anaesthesia included sevoflurane and desflurane compared with i.v. anaesthesia, on the composite end-point of prolonged ICU stay, mortality, or both in patients undergoing high-risk cardiac surgery (PreC and PostC study, On-pump CABG).106 In a recent meta-analysis, in which different protocols of anaesthesia patients in cardiac and non-cardiac surgery were included, only sevoflurane showed a reducing effect in myocardial infarction incidence and mortality, thanks to its cardio-protective effect.
Table 3 Pre- and post-conditioning by desflurane and sevoflurane: clinical trials. CABG, Coronary artery bypass surgery; CPB, cardiopulmonary bypass; BNP, Brain Natriuretic Peptide; ICU, Intensive care unit; NA, Not Applicable; NS, not significant

<table>
<thead>
<tr>
<th>Studies</th>
<th>Type of bypass pump</th>
<th>Type of surgery</th>
<th>Drugs</th>
<th>Type of Conditioning</th>
<th>Number of patients</th>
<th>Effects of conditioning (desflurane or sevoflurane) tested</th>
<th>Mortality – length of stay in ICU</th>
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<tr>
<td>Meta-analyses</td>
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<tr>
<td>Symons and colleagues. Br J Anaesth. 2006</td>
<td>On pump</td>
<td>CABG</td>
<td>+</td>
<td>PreC PostC continuous</td>
<td>27 trials (2979 patients)</td>
<td>+</td>
<td>NA</td>
</tr>
</tbody>
</table>
| - No significant difference with respect to MI, mortality, myocardial ischaemia or ICU length of stay.  
- Lesser requirement for inotropic support.  
- A 1 day decrease in hospital length of stay | |
| Yu CH, Beattie W. Can J Anaesth. 2006 | On-pump and off-pump | CABG | +   | +                      | 32 studies (2841 patients) | + | NA | NA |
| - Decrease of morbidity and mortality |
| Landoni and colleagues. J Cardiothorac Vasc Anesth. 2007 | On-pump and off-pump | CABG | +   | +                      | 22 studies (1922 patients) | + | NA | NA |
| - Lower incidence of myocardial ischemia  
- Shorter ICU and hospital stay length  
- No significant difference in postoperative mechanical ventilation time, inotropic support, mortality, myocardial infarction | |
| Yao YT, Li LH. Chin Med Sci J 2009 | On-pump and off-pump | CABG | -  | PreC PostC continuous | 13 studies (836 patients) | + | NA | - |
| - Preservation of LV function after CPB |
| Landoni and colleagues. British Journal of Anaesthesia 2013 | On-pump and off-pump | Cardiac surgery | +  | PreC PostC continuous | 38 trials (3996 patients) | NA | NA | NA |
| - Reduction of mortality |
| Randomized studies. |                      |                 |       |                      |                    |                                                        |                                 |
| De Hert and colleagues. Anesthesiology 2002 | On-pump | CABG | –   | +                      | 32 | NA | NA | Preservation of LV function after CPB |
| - No change in ST-segment changes |
| Julier and colleagues. Anesthesiology 2003 | On-pump | CABG | –   | +                      | 72 | – | + | Decrease of duration in ICU |
| - Preservation of stroke volume after CPB |
| De Hert and colleagues. Anesthesiology 2004 | On-pump | CABG | –   | +                      | 200 | + | NA | Decreased the incidence of late adverse cardiac events |
| Garcia and colleagues. 2005 Br J Anaesth | On-pump | CABG | –   | +                      | 72 | NA | NA | |

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<table>
<thead>
<tr>
<th>Studies</th>
<th>Type of bypass pump</th>
<th>Type of surgery</th>
<th>Drugs</th>
<th>Type of Conditioning</th>
<th>Number of patients</th>
<th>Effects of conditioning (desflurane or sevoflurane) tested</th>
<th>Cardiac function</th>
<th>Mortality – length of stay in ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tritapepe and colleagues. Eur J Anaesthesiol. 200726</td>
<td>On-pump</td>
<td>CABG</td>
<td>+</td>
<td>–</td>
<td>150</td>
<td>+</td>
<td>Reduction in number of Q-wave myocardial infarction (NS)</td>
<td>Reduction of intensive care unit (NS)</td>
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<tr>
<td>Piriou and colleagues. Br J Anaesth 200725</td>
<td>On-pump</td>
<td>CABG</td>
<td>–</td>
<td>+</td>
<td>72</td>
<td>–</td>
<td>No difference in incidence of peri-operative myocardial infarction and new onset atrial fibrillation</td>
<td>The one-year mortality was decreased</td>
</tr>
<tr>
<td>De Hert and colleagues. Anaesthesia. 2009;64:953-60.</td>
<td>On-pump</td>
<td>CABG</td>
<td>+</td>
<td>–</td>
<td>414</td>
<td>–</td>
<td>No difference in incidence of peri-operative myocardial infarction and new onset atrial fibrillation</td>
<td>– shorter wake-up times and quicker cooperation – No differences were seen in ICU-stay, adverse memories or recovery events in the short-term sedation – No difference in the length in ICU stay – No difference in hospitalization time No difference in 1-year mortality</td>
</tr>
<tr>
<td>Hellström and colleagues. Scand Cardiovasc J. 2012212</td>
<td>On-pump</td>
<td>CABG</td>
<td>–</td>
<td>+</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Steurer and colleagues. Crit Care. 2012213</td>
<td>On-pump</td>
<td>CABG and valve replacement</td>
<td>+</td>
<td>–</td>
<td>100</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Landoni and colleagues. Br J Anaesth. 2014216</td>
<td>Off and on-pump</td>
<td>Cardiac surgery</td>
<td>–</td>
<td>+</td>
<td>200</td>
<td>–</td>
<td>NA</td>
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<tr>
<td>Conzen and colleagues. Anesthesiology 2003217</td>
<td>Off-pump</td>
<td>CABG</td>
<td>–</td>
<td>+</td>
<td>20</td>
<td>–</td>
<td>Had less myocardial injury during the first 24 postoperative hours</td>
<td>No difference in ICU stays</td>
</tr>
</tbody>
</table>

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<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparison</th>
<th>N</th>
<th>Outcome 1</th>
<th>Outcome 2</th>
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<tr>
<td>Rein and colleagues. Anesth Analg 2005</td>
<td>Off-pump Minimally Invasive Direct CABG</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
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<tr>
<td>Lucchinetti and colleagues. Anesthesiology 2007</td>
<td>Off-pump CABG</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Guerrero Orriach and colleagues. J Crit Care 2013</td>
<td>Off-pump CABG (+sedation protocol)</td>
<td>−</td>
<td>+</td>
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<td>−</td>
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<td>Randomized non cardiac surgery studies:</td>
<td></td>
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<tr>
<td>Zangrillo and colleagues. J Cardiothorac Vasc Anaesth 2011</td>
<td>Off-pump non cardiac surgery</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Bassuoni and colleagues. Saudi J Anaesth 2012</td>
<td>Off-pump elective peripheral vascular surgery</td>
<td>−</td>
<td>+</td>
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<tr>
<td>Lurati Buse and colleagues. Circulation 2012</td>
<td>Off-pump Major non cardiac surgery</td>
<td>−</td>
<td>+</td>
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<tr>
<td>Lindholm and colleagues. Anesthesiology 2013</td>
<td>Off-pump Abdominal Aortic Surgery</td>
<td>−</td>
<td>+</td>
<td>−</td>
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<tr>
<td>Lindholm and colleagues. Anaesthesia. 2014</td>
<td>Off-pump Abdominal aortic surgery</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

Significant decrease of ST depression
Significant decrease in duration, cumulative duration of ischemic events
No difference in duration of ICU stays
No difference in duration of ICU stays
Preservation of postoperative cardiac function
No difference in major adverse cardiac events
No difference on mortality at 1yr
No differences in postoperative complications, non-fatal coronary events or mortality
Improved indices of cardiac function
properties. This important result seems to be related to a few well-conducted and statistically comparable studies, and cannot be generalized to all the remaining studies. Finally the biggest meta-analysis of Landoni and colleagues included 38 cardiac surgery studies with 3966 patients, observed that mortality was doubled in patients receiving i.v. anaesthesia compared with volatile anaesthetics. But still the authors admit that the statistical significance was reached exclusively when combining all volatile agents. Also, they only looked at the all-cause mortality, not that of cardiac origin only.

On pump CABG - preconditioning studies pre- and post-conditioning studies

Only few clinical studies investigated the effects of both PreC and PostC. Overall, De Hert and colleagues showed that the decrease of troponin release was linked to a reduction of ICU/in-hospital length of stay and also showed a marked reduction in the use of inotropes in cardiac patients who had undergone CABG, but only when sevoflurane was administered during the whole duration of surgery. In this case, the coupled actions of PreC and PostC effects of sevoflurane might have been evident. However, this might also be questioned, as if during continuous application of volatile anaesthetic during surgery, the result observed would be from the coupled actions of PreC and PostC, the protective action might become clinically detectable, irrespective of the mechanism that may have contributed to condition the myocardium, a quite improbable situation. This study including 200 post-CABG patients (actually the only human PostC study) showed that sevoflurane treatment (throughout the intervention) reduced postoperative troponin I concentrations vs propofol and preserved stroke volume. Comparison of anaesthesia with sevoflurane, desflurane (PreC and PostC protocol) and propofol for CABG with CPB, despite the lack of significant differences in the concentration of troponin T, showed the following differences in mortality within one year after surgery: 12.3, 6.7 and 3.3% in propofol, desflurane and sevoflurane patients, respectively. However it is of some importance to note that in this study a ‘disproportionately’ high one-year mortality rate was seen in the propofol group compared with other CABG surgery studies. Tritapepe and colleagues randomly assigned 75 patients to propofol and 75 patients to desflurane (PreC and PostC protocol) for CABG. Patients receiving propofol (5.5 ng dl−1) when compared with those receiving desflurane (2.5 ng dl−1) had a significantly (P<0.001) higher postoperative median peak of troponin I and the median (interquartile) troponin I area under the curve analysis confirmed these results: 68 (30.5–104.8) vs 36.3 (17.9–86.6) h ng dl−1 (P=0.002). Moreover, patients who received desflurane had less postoperative inotropic support (24/75, 32.0% vs 31/75, 41.3%, P=0.04), and tended toward a reduction in number of Q-wave myocardial infarction, time on mechanical ventilation and intensive care unit (ICU) and overall hospital stays. Thus desflurane was effective to reduce myocardial damage in CABG surgery, when administered during the entire duration of the procedure. The effects of sevoflurane PreC were investigated by Julier and colleagues who measured brain natriuretic peptide (BNP) released postoperatively, and found it to be significantly decreased and concluded that myocardial and renal functions as the consequence of sevoflurane PreC were preserved. Nevertheless the authors have not observed differences in other secondary outcomes, such as troponin release and ST-segment changes. Meco and colleagues observed lower levels of troponin T and pro-BNP in the group receiving desflurane (PreC protocol) before aorta clamping during CABG with CPB and improved diastolic left ventricular function, expressed in increased mobility of the mitral ring in the initial phase of diastole. Garcia and colleagues investigated 72 patients undergoing elective CABG surgery randomized to sevoflurane 2 MAC for 10 min (PreC protocol) vs placebo. Atrial biopsies were obtained to show that sevoflurane reduced transcript levels for platelet-endothelial cell adhesion molecules and increased catalase levels. The concept of PreC by volatile halogenated agent is difficult to define in clinical practice, because this strategy require a wash-off period, which is not systematically applicable, especially when the volatile anaesthetic is administered continuously throughout the procedure or re-administered as a PostC. A recent study in rats shows that the combination of PreC and PostC by sevoflurane induced a more powerful protection against myocardial ischaemia reperfusion lesions than that observed with a single treatment (PreCor PostC).

Off pump CABG

Guerrero Orriach and colleagues showed that sevoflurane administration in patients undergoing off-pump CABG, in the operating room and ICU, showed lower myocardial injury as compared with when sevoflurane was just given during the intraoperative period, although the sevoflurane option was better than the propofol one. Also these results are in favour of a prolonged effect of sevoflurane, enhancing cardio-protection in the postoperative period (late PostC). However off-pump CABG studies have drawn conflicting conclusions, showing no benefit on the duration of ICU stays in patients exposed to sevoflurane during CABG. However, ischaemia-reperfusion injury is not so prominent such as on CPB, therefore volatile anaesthetic might have smaller effect.

Heart valve surgery

Cromheecke and colleagues randomly assigned 30 patients undergoing aortic valve surgery (continuous protocol) to receive sevoflurane (continuous protocol). Patients receiving sevoflurane expressed a reduction of concentration of cardiac necrosis markers and faster restoration of systolic and diastolic ventricular functions, after CPB compared with patients receiving propofol. This may be particularly important in patients with severe hypertrophy of the heart, in whom optimal cardio-protection against ischaemia might be difficult to obtain. Despite negative results in relation to troponin T release, Kortekaas and colleagues speculated that intra-myocardial or systematic delivery of sevoflurane administered during aortic cross-clamping in 11 patients undergoing valve surgery was capable of modulating the systemic inflammatory response after CPB, with important consequences on myocardial function.

Sedation protocols with sevoflurane in cardiac surgery

Steurer and colleagues (on-pump CABG and valve replacement surgery) investigated whether volatile anaesthetics administered for postoperative sedation, may have a beneficial effect on myocardial injury, after on-pump valve replacement surgery. Anaesthesia was performed with propofol and 117 patients were randomized to be sedated for at least four h with either propofol or sevoflurane, when they were transferred to the ICU. Sevoflurane was administered by using the anaesthetic conserving device. Injury markers on the first postoperative day (POD1) were the primary end-points whereas oxygenation, postoperative pulmonary complications, and hospital stays were the secondary end-points. Troponin T at POD1 was significantly lower in the
sevolfrurane group compared with the propofol group. Thus, late PostC with sevolfrurane was effective to stimulate myocardial protection after brief and low-dose application. However, Hellström and colleagues observed, in a study on on-pump CABG, no differences between sevolfrurane sedation and propofol after cardiac surgery concerning the ICU-stay. Guerrero Orriach and colleagues maintained the early postoperative sedation with halogenated agents, after its intra-operative administration, aimed at increasing their benefits. There were 60 patients undergoing CABG surgery divided into three groups: sevolfrurane alone, sevolfrurane plus propofol, and propofol alone. The group sevolfrurane had significant differences as compared with the other two groups in the levels of pro-BNP and troponin I and lower use of inotropic drugs. Another study described a case-series of patients in ICU sedated with volatile anaesthetics during therapeutic hypothermia after cardiac arrest. The authors used the anaesthetic conserving device to give isoflurane, considering this technique as a feasible short-acting option with potential PostC effects, to protect vital organs from ischaemia-reperfusion injury. Its measurability and insignificant drug accumulation could facilitate early neurological assessment. Encouraging results were associated to PostC effects of volatile anaesthetics. Delayed ischaemic PostC confers significant cardio-protection appears to rely on a different mechanism as compared with those of early ischaemic PostC. We can speculate that delayed anaesthetic PostC share the same mechanism with late ischaemic PostC. Finally, it is important to stress that among anaesthetic agents, volatile ones have comparatively lower cost and carry very few risks during cardiac surgery.

Non cardiac surgery

Non-cardiac surgery is far more frequent performed type of surgery compared with cardiac surgery, however, the results from the clinical trials are not particularly encouraging. A randomized trial of 385 patients with high cardiovascular risk undergoing non-cardiac surgery, compared with a regimen of anaesthesia with sevolfrurane or propofol, showed no difference in the incidence of myocardial ischaemia injuries. A prospective randomized study with 193 patients, in whom sevolfrurane anaesthesia was done for abdominal aortic surgery, showed the same results in terms of clinical outcome and troponin release as compared with the group of i.v. anaesthesia. Finally, in a randomized controlled trial, including patients undergoing non-cardiac surgery, sevolfrurane did not significantly reduce postoperative median peak troponin I release, compared with the total i.v. anaesthesia group. There were criticisms about the sampling of the study, considering it underpowered, and the end points, and the timing of measurements of the peak troponin. Nevertheless, patients with coronary artery disease receiving sevolfrurane during elective peripheral vascular surgery, had significantly lower release of cardiac troponin I at six h postoperatively and lasting for 48 h than patients receiving propofol with significant decrease in duration, decrease cumulative duration of ischaemic events, and degree of ST depression.

Limitations in anaesthetic post-conditioning use

There are also practical limits to show the effectiveness of anaesthetic-related PostC, as perioperative complications of anaesthetic protocols are rare events: the statistical power needed to show a 50% reduction (which is a quite large difference in relative terms) requires to enroll more than 4000 patients, if cardiac-related perioperative death rate should be reduced from 1.2 to 0.6%, and more than 1000 patients if the incidence of perioperative cardiac infarction should be lowered from 4 to 2%. A further limit to the clinical anaesthetic-related PostC development is related to its application as it may take quite some time to achieve acceptable levels of volatile anaesthetics, while remote ischaemic PostC with repeated unclamping/clamping may be more direct and/or more efficacious: why bother to use anaesthetics while repeated inflation of a blood pressure cuff around a limb may provide protection just as well? Moreover, there are also problems related to the way volatile anaesthesia is performed, as in order to be effective, at least a relatively high 1 MAC concentration should be present at the time of reperfusion, which may be sometimes difficult to obtain in practice. Then, as shown for the ischaemic PostC, importance of having early PostC (at the exact beginning of reperfusion) signal for observing cardio-protection, so anaesthetic should be applied through CPB circle or directly intra-myocardially. The last limitation of anaesthetic PostC is its application to patients going through PCI procedure or in the ICU after reanimation. Finally, patient selection should also be extremely important as diabetic patients might be less sensitive to clinical PostC with anaesthetics, if one considers experimental observations with human atrial tissues, although clinical studies in general do not exclude insulin-treated diabetics.

Conclusions

The full translation of a large body of experimental evidence with halogenated anaesthetics into clinical practice was not properly done until now. And, the cumulative conclusions of several studies showed that using a volatile anaesthetic in cardiac surgical patients potentially reduced long-term cardiovascular complications and mortality, compatible with its strong anti-inflammatory and potentially plaque-stabilizing actions. It is important to note that many studies on the ischaemic PostC showed the effectiveness in cardio-protection in cardiac surgery; animal studies indicated that PostC by desflurane/sevolfrurane and ischaemic PostC share the same signalling pathway (see the section D): taken together these arguments open the way for human studies on PostC by desflurane and sevolfrurane in cardiac surgery. Clinical trials are therefore clearly required to assess the potential benefit of anaesthetic PostC in patients, for three majors reasons: 1) the efficacy of desflurane-sevolfrurane-induced PostC has been shown in human myocardium studied in vitro; 2) anaesthetic PostC is mediated by the same cardio-protective signalling pathway (including its effect on mitochondria) mediating ischaemic PostC; 3) unlike ischaemic PostC, anaesthetic PostC is a completely non-invasive manoeuvre.

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