

**STEFAN G. DE HERT**

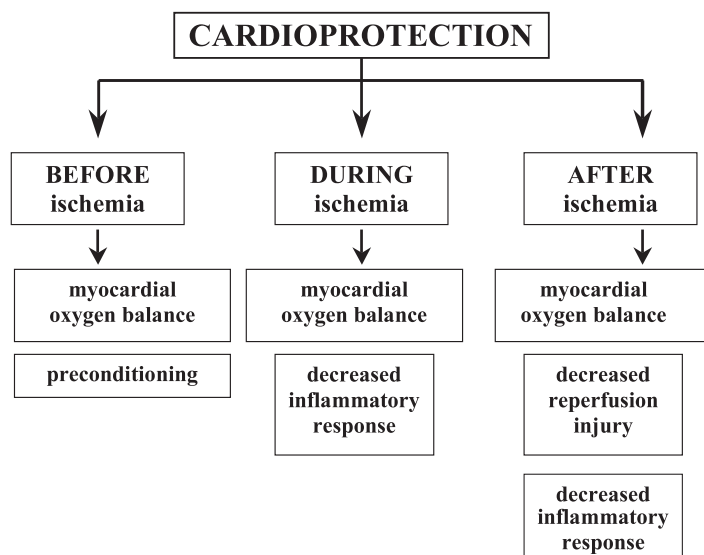
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11:30-12:15

Room: N113 & N114

The tissue damage caused during ischemia is termed ischaemic injury, and its extent is related to the duration of the ischaemic period. Reperfusion terminates the ischaemic episode and is essential for the tissue to survive and to resume its normal function. Nevertheless, this phase may be associated with severe functional disturbances which are referred to as reperfusion injury. Since myocardial ischaemia-reperfusion injury may lead to severe complications, part of the perioperative care of the patient will be directed towards the prevention and treatment of this type of complication. Cardioprotective strategies can be applied before ischaemia occurs, during myocardial ischemia or after the occurrence of any ischemia, during the reperfusion period (Figure 1). Recent evidence shows that anaesthetic agents may exert a cardioprotective effect. This property may provide anaesthesiologists with an additional tool to protect patients from the consequences of myocardial ischaemia during the perioperative period.



**Figure 1.** Mechanisms by which anaesthetic agents have been shown to exhibit a cardioprotective effect before, during, and after myocardial ischemia.

**CARDIOPROTECTIVE STRATEGIES WITH MYOCARDIAL ISCHEMIA: EFFECTS OF ANAESTHETIC AGENTS**

The heart can be protected by maintaining or optimizing myocardial oxygen balance, before myocardial ischemia occurs. In addition, the heart can also be preconditioned. The term preconditioning refers to the phenomenon that pre-treatment with a potentially noxious stress-stimulus can increase cellular tolerance to subsequent stress-stimuli. During ischemia, protection of the heart relies on an optimization of the myocardial oxygen balance. Additionally measures to provide leakage of high energy phosphates, or providing substrate for metabolism have been proposed. Finally, the heart can be protected by taking measures during the reperfusion period which may help to decrease the extent of reperfusion injury.

**MYOCARDIAL OXYGEN BALANCE**

Whenever myocardial oxygen demand exceeds myocardial oxygen supply, myocardial ischaemia will occur. Therapeutic strategies to prevent or to treat myocardial ischaemia are therefore based both on a preservation or restoration of myocardial supply and on a decrease in the myocardial oxygen demand. The first is obtained by maintaining or restoring blood flow to the ischaemic areas or the areas at risk of ischaemia, whereas the second can be achieved by decreasing the determinants of myocardial oxygen demand which are: heart rate, contractility and ventricular loading conditions. Numerous therapeutic approaches are available to obtain these effects. These include the anaesthetic agents, which by their effects on determinants of myocardial oxygen demand may have a myocardial oxygen sparing effect that may be beneficial in the heart at risk of ischemia.

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## PRECONDITIONING

At the level of the myocardium, ischaemic preconditioning represents an adaptive endogenous response to brief sublethal episodes of ischaemia leading to a pronounced protection against subsequent lethal ischaemia. The protective effects offered by the ischaemic preconditioning are of limited duration and can typically be divided into two phases. The early phase occurs immediately and induces a strong protection but has a limited duration of 1 to 3 hours, whereas the late phase occurs about 24 hours after the initial stimulus, induces less protection, but lasts for as long as 3 days.

Although the underlying mechanisms still are not definitively elucidated, the main pathways involve the activation of receptors, which then trigger a number of intracellular signalling pathways that ultimately activate one or more end-effectors, which finally results in protection against prolonged ischaemia. This ischaemic preconditioning can be either abolished or mimicked by the use of pharmacological compounds that either block or stimulate certain steps in the intracellular cascade of events. This has led to the concept of pharmacological preconditioning. From a clinical point of view, preconditioning with pharmacological agents is to be preferred above ischaemic preconditioning, because it is devoid of the risk of jeopardizing a diseased myocardium by making it transiently ischaemic. However, the clinical use of such "preconditioning" compounds is limited by the occurrence of important side-effects.

Over the last few years, an important number of experimental studies have indicated that volatile anaesthetic agents protect against ischaemic myocardial dysfunction. This cardioprotective effect could not be related to the effects on the myocardial oxygen balance. Instead it appears that one of the mechanisms by which the volatile anaesthetics induce protection in the myocardium is pharmacological preconditioning. The mechanisms involved in anaesthetic preconditioning strongly resemble those involved in ischaemic preconditioning, and have been the subject of recent reviews [1, 2]. The signal transduction pathway involved in anaesthetic preconditioning has indeed been shown to involve among others; the adenosine receptor, the inhibitory guanine nucleotide-binding proteins, protein kinase C, protein tyrosine kinase, and sarcolemmal and mitochondrial  $K_{ATP}$  channel activity. The relative importance of the different proposed intracellular pathways is still to be established. The final target of anaesthetic preconditioning is the opening of the mitochondrial  $K_{ATP}$  channels resulting in the depolarization of the mitochondrial membrane potential with an improvement of mitochondrial bioenergetics. The ultimate result would be a reduction in cytosolic and mitochondrial calcium loading, with better structural and functional preservation.

In addition, to any direct effects on myocytes, both ischaemic and anaesthetic preconditioning protect the endothelial cells of the coronary (and other) vasculature. One of the major features of this endothelial protection seems to be the ability to generate nitric oxide and mediate vasodilation.

## EXTENT OF REPERFUSION INJURY

Decreasing the extent of reperfusion injury is one of the prime goals in the prevention and treatment of ischaemic myocardial problems. Over the years, numerous techniques and pharmacological compounds have been proposed that may decrease the extent of any myocardial damage during ischaemia. It is beyond the scope of this review to discuss these approaches but it is worthwhile mentioning that volatile anaesthetic agents seem to have an inhibitory effect, among others, on ischaemia-induced adhesion of polymorphonuclear neutrophils in the coronary system.

Other experimental studies have indicated that the administration of volatile anaesthetic agents early during reperfusion decreased the extent of reperfusion injury. The underlying mechanisms for this effect are poorly understood. It has been suggested that one of the main protective mechanisms involves the prevention of reoxygenation-induced cellular contraction. Other possible effects include actions on activated leucocytes and upon reactive oxygen species. Neutrophil activation, adherence and release of oxygen free radicals are known to play a major role in reperfusion injury.

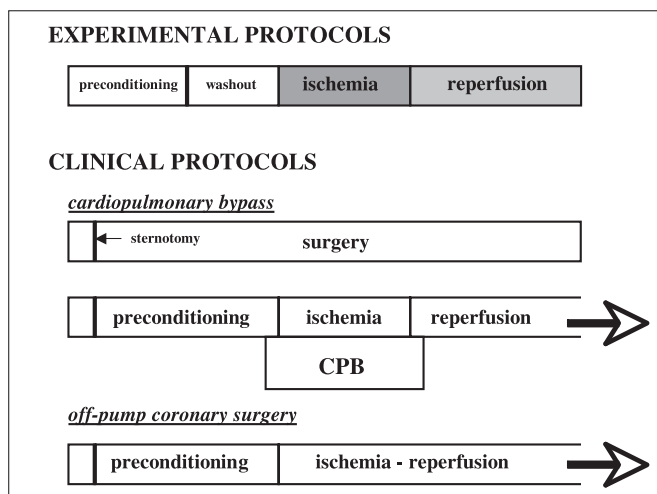
Direct cardioprotective effects related to either a preconditioning action and / or an effect when administered only during ischemia and / or the reperfusion period have mainly been demonstrated for the volatile anaesthetic agents and opioids. The evidence for a cardioprotective effect by other intravenous anaesthetic drugs is less straightforward. In isolated adult rat ventricular myocytes it was demonstrated that anaesthetics exhibit a differential effect on mitochondrial  $K_{ATP}$  channel activity and cardiac myocyte protection [3]. Several studies have shown that propofol may have an antioxidant action and this property has been claimed to protect the myocardium. The possible implication of this antioxidant action for real preservation of tissue function however remains to be demonstrated.

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## CLINICAL IMPLICATIONS ON MYOCARDIAL FUNCTION

The implementation of the cardioprotective effects of anaesthetic agents during clinical anaesthesia might provide an additional tool in the treatment and / or prevention of cardiac dysfunction in the perioperative period. In clinical practice, these effects should be associated with improved cardiac function, ultimately resulting in a better outcome in patients with coronary artery disease.

To address this issue in the clinical setting is not straightforward since it requires the occurrence of myocardial ischemia in a standardized and reproducible way. However, the setting of cardiac surgical procedures might provide such a situation in which myocardial ischemia during aortic cross clamping is part of the integral procedure. This implies that the different possible protocols of the experimental settings (preconditioning – ischemia – reperfusion) might also be applied in a clinical setting (Figure 2). However, whereas the cardioprotective effects in experimental protocols were clearly present and straightforward, the results of clinical studies are disappointing.



**Figure 2.** Different experimental and clinical protocols used in the research on cardioprotective effects of anaesthetic agents. Experimental protocols on preconditioning involve various modalities (continuous vs. intermittent) time periods of the preconditioning stimulus, which may or may not be followed by a washout period. The reperfusion protocols involve administration of the anaesthetic agents for various time periods early during the reperfusion period. In the clinical protocols the duration of the cardiac operation can be divided in a period of ischemia which is preceded by a period during which a preconditioning stimulus can be applied, and which is followed by a period during which reperfusion occurs. In the clinical setting of coronary surgery, it may be difficult to clearly delineate the period of ischemia from the period of reperfusion because episodes of ischemia are frequently alternated by periods of reperfusion. This is especially the case in off-pump coronary surgery. (CPB = cardiopulmonary bypass).

Several clinical studies have analyzed the effects of anaesthetic agents during the preconditioning phase (Table 1) [4 – 8]. To date the largest study (72 patients) has been performed by Julier et al [9]. In this study, sevoflurane 4% was administered during the first 10 min of CPB before aortic cross-clamping. Compared to the control group, a lower postoperative release of brain natriuretic peptide, a biochemical marker of myocardial contractile dysfunction, was observed. However, no differences were found between both groups for perioperative ST-segment changes, arrhythmias, creatine kinase MB, and cardiac troponin T release. This latter study did not report on haemodynamic data but demonstrated that sevoflurane preconditioning seemed to be associated with translocation of protein kinase C to specific sub-cellular targets as was observed in the experimental studies.

Taken together, the results of these different clinical “preconditioning” protocols give a very variable result on the different outcome variables. Although this may be in part related to the different administration protocols, it seems that the cardioprotective properties of an anaesthetic preconditioning protocol, which seem very straightforward in the experimental setting have only minor implications in the clinical setting.

Clinical reports on the potential cardioprotective effects of volatile anaesthetic agents when administered only during ischemia or only during the reperfusion period are even more scarce than the preconditioning protocols. In one study, the administration of sevoflurane with the cardioplegic solution during ischemia was reported to be associated with a decreased inflammatory response, a lower postoperative release of troponin I and a better regional myocardial function compared to the control group [10].

The absence of an unequivocal and reproducible clinical protective effect on the different variables in these clinical protocols has initiated the question whether the choice of an anaesthetic regimen is of any importance to postoperative cardiac function. This issue was addressed in several recent clinical papers comparing - in coronary surgery patients - the effects on cardiac function and myocardial damage of a total intravenous anaesthetic regimen to a volatile anaesthetic regimen. In all these studies, the use of a volatile anaesthetic regimen seemed to be associated with a better early postoperative myocardial function and a lower postoperative release of troponin indicating better preservation of myocardial function after ischemia [11 – 15].

The straightforward results of these studies is in contrast with the absence of obvious clinical beneficial effects in the protocols where the volatile agent was administered only as a preconditioning stimulus. Discrepancies observed in the importance of the cardioprotection afforded by these different protocols could therefore be related to the fact that the duration and timing of administration of volatile anaesthetics is one of the factors contributing to the extent of myocardial protection. In a recent study, it was hypothesized that the postoperative release of biochemical markers of myocardial damage would be lower and that immediate postoperative myocardial function would be better when the agent was administered throughout the entire procedure, than when administered only during a limited period before ischemia or after completion of the coronary anastomoses [16]. In this study, postoperative levels of troponin I and indexes of myocardial function were analyzed in patients undergoing coronary surgery with cardiopulmonary bypass (CPB) under four different anaesthetic protocols: an intravenous regimen with propofol throughout, sevoflurane only before CPB, sevoflurane only after completion of the coronary anastomoses, and sevoflurane throughout. The results of this study indicated that the cardioprotective effects of an anaesthetic regimen with sevoflurane were clinically most apparent when the volatile anaesthetic was administered throughout the entire surgical procedure. This was evident from a lower postoperative troponin I release and preservation of postoperative cardiac function when compared to a total intravenous anaesthetic regimen. When administered only during the period before CPB, or only after completion of the coronary anastomoses, postoperative recovery of stroke volume occurred earlier but the postoperative release of troponin I was not significantly different from the pattern observed with the intravenous anaesthetic regimen.

**TABLE 1. CLINICAL PRECONDITIONING (PC) PROTOCOLS IN PATIENTS UNDERGOING CORONARY ARTERY SURGERY**

<b>Anaesthetic Agent</b>	<b>Protocol</b>	<b>Effect</b>	<b>Reference</b>
Isoflurane 2.5 MAC on CPB with heart totally decompressed before aortic cross clamping	<ul style="list-style-type: none"> <li>▪ study group: n = 10 <i>5 min PC followed by 10 min washout</i></li> <li>▪ control group: n = 10</li> </ul>	<ul style="list-style-type: none"> <li>▪ lower TnI and CK-MB release in study group (not significant)</li> <li>▪ higher 5' nucleotidase activity (~ PKC activation)</li> <li>▪ no functional data</li> </ul>	4
Enflurane before CPB	<ul style="list-style-type: none"> <li>▪ study group: n = 8 <i>5 min PC before start CPB</i></li> <li>▪ control group: n = 8</li> </ul>	<ul style="list-style-type: none"> <li>▪ preserved cardiac function in study group</li> <li>▪ TnI and CK-MB not different between groups</li> </ul>	5
Isoflurane before CPB	<ul style="list-style-type: none"> <li>▪ study group: n = 20 <i>15 min PC followed by 10 min washout</i></li> <li>▪ control group: n = 20</li> </ul>	<ul style="list-style-type: none"> <li>▪ myocardial function not different between groups</li> <li>▪ TnI and CK-MB not different between groups</li> </ul>	6
Isoflurane before CPB	<ul style="list-style-type: none"> <li>▪ study group: n = 28 <i>isoflurane discontinued at initiation CPB</i></li> <li>▪ control group: n = 21</li> </ul>	<ul style="list-style-type: none"> <li>▪ better cardiac index in study group</li> </ul>	7
Sevoflurane 2.5 MAC on CPB before aortic cross clamping	<ul style="list-style-type: none"> <li>▪ study group: n = 10 <i>10 min PC without washout</i></li> <li>▪ control group: n = 10</li> </ul>	<ul style="list-style-type: none"> <li>▪ increased TK activity in study group</li> <li>▪ increased PKC and p38 MAPK in both groups</li> <li>▪ no functional data</li> </ul>	8
Sevoflurane 2 MAC on CPB with heart totally decompressed before aortic cross clamping	<ul style="list-style-type: none"> <li>▪ study group: n = 37 <i>10 min PC without washout</i></li> <li>▪ control group: n = 35</li> </ul>	<ul style="list-style-type: none"> <li>▪ decreased BNP release in study group</li> <li>▪ TnT and CK-MB not different between groups</li> <li>▪ activation of PKC <math>\delta</math> and <math>\epsilon</math> isoforms</li> <li>▪ no functional data</li> </ul>	9

CPB = cardiopulmonary bypass; MAC = minimal alveolar concentration; Tn = troponin; CK = creatine kinase; PKC = protein kinase C; TK = tyrosine kinase; MAPK = mitogen-activated protein kinase; BNP = brain natriuretic peptide

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## IMPLICATIONS FOR CLINICAL OUTCOME

Although all these clinical observations clearly indicate that volatile anaesthetics protect the myocardium during coronary surgery, the impact of this phenomenon on postoperative morbidity and clinical recovery remains to be established. Only very recently, this issue was addressed in a larger study population [17]. Three hundred and twenty coronary surgery patients were randomly assigned to receive either a total intravenous anaesthetic regimen or an anaesthetic regimen with a volatile anaesthetic agent. Surprisingly, the group of patients who had received a volatile anaesthetic regimen demonstrated a significant lower intensive care and hospital length of stay. Multiple regression analysis revealed that prolonged length of stay in the intensive care unit in this particular study was related to the following independent variables: occurrence of atrial fibrillation, an increase in postoperative troponin I levels in excess of 4 ng/ml, and the need for prolonged postoperative inotropic support during more than 12 hours. Whereas the incidence of atrial fibrillation seemed not significantly different among the groups, the number of patients with an increase in postoperative troponin I > 4 ng/ml, and the number of patients necessitating prolonged postoperative inotropic support was significantly lower in the volatile anaesthetic groups. This was associated with better myocardial function during the first postoperative hours. The authors attributed the shorter intensive care and hospital length of stay with the volatile anaesthetic regimen to this better early postoperative haemodynamic profile, resulting in better organ and tissue perfusion in the first postoperative hours.

There is indeed some evidence that the use of a volatile anaesthetic regimen may have beneficial effects on other organ systems. In a study of 20 coronary surgery patients El Azab et al [18] found that the use of sevoflurane during coronary surgery was associated with a lower postoperative release of tumour necrosis factor  $\alpha$  and a shorter length of stay in the intensive care unit. Julier et al. [7] observed that the use of a sevoflurane preconditioning protocol in coronary surgery patients was associated with a lower release of cystatin C (a marker of renal dysfunction). The same group recently reported on the one year follow-up of these patients showed some evidence of a protective role for pharmacological preconditioning by sevoflurane and the occurrence of late cardiac events [19]. Finally, another study recently demonstrated that the incidence of postoperative atrial fibrillation, which also affects outcome after surgery, seemed to be lower in the presence of a sevoflurane-based anaesthesia [20].

## CONCLUSIONS

During the last decade, increasing experimental evidence has demonstrated that anaesthetic agents have direct cardioprotective effects. Although parts of the underlying pathways have been identified, the exact mechanisms of any cardioprotection are still not definitively elucidated. Recently, research has been focused on the possible implementation of this experimentally observed cardioprotection in clinical patient care. Initial observations are encouraging, indicating that in the clinical setting, anaesthetic agents may exhibit direct cardioprotective effects. This data has been obtained in the specific setting of cardiac surgery and is mainly related to better early postoperative cardiac function and less release of biochemical markers of myocardial damage. The possible impact on clinical outcome in other areas however, remains to be demonstrated.

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