Perioperative myocardial protection

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Myocardial protection refers to all strategies that increase the heart’s ability to withstand ischaemic insult, which together with reperfusion injury are principally responsible for cardiac morbidity and mortality after high-risk surgery. The bloodless and motionless operating conditions required for cardiac surgery is an environment diametrically opposed to the metabolic demands of the heart.

Pathophysiology of myocardial reperfusion

Ischaemia of sufficient duration results in cell death. However, should the ischaemic insult be interrupted at an appropriate point, a patient will be left with viable myocardium while experiencing a spectrum of detrimental sequelae including arrhythmias and a low cardiac output state. This is directly consequent to the reperfusion injury. Should outright cell death be averted, there are two possible alternatives, that is, stunning and a state of hibernation.

In 1975, it was demonstrated that 15 min of coronary occlusion resulted in 6 h of left ventricular depression, leading Braunwald and Klomer to state that ‘transient ischaemia may interfere with normal myocardial function, biochemical processes, and ultra-structure for prolonged periods’.

Stunning is a commonly encountered phenomenon characterized by potentially life-threatening post-ischaemic myocardial impairment after coronary blood flow has been fully restored. It can be overcome by inotrope therapy or calcium infusions without negative consequences and has a duration of hours to days. Examples of stunning would be unstable angina or after aortic cross-clamping during cardiac surgery.

The mechanism underlying stunning is thought to be a combination of cytosolic calcium overload which, if prevented, abolishes this phenomenon and the development of oxygen free radicals. Severe cellular damage has been demonstrated when an anoxic heart preparation is re-exposed to oxygen. Calcium overload may damage the myocyte contractile apparatus in ways that impair its normal response to calcium.

Suggested sources of calcium include entry through voltage-sensitive calcium channels, decreased uptake into the sarcoplasmic reticulum, impaired sodium–calcium exchange due to decreased cytosolic pH, and activation of the calcium release channel of the ryanodine receptors. During a hypoxaemic episode, electrons form damaging free radicals instead of passing down the energy gradient of the electron transport chain. The hydroxyl group in particular is thought to play a significant role in the lipid peroxidation of cell membranes leading to increased permeability to calcium.

Hibernation was first described by Rahimtoola as ‘a state of persistently impaired myocardial and left ventricular function at rest due to reduced coronary blood flow that can be partially or completely restored to normal if the myocardial oxygen supply/demand relationship is favourably altered, either by improving blood flow and/or by reducing demand’. The ‘smart heart’ has down-regulated mechanical activity to a level at which aerobic metabolism functions normally. Current theories suggest that hibernation is the consequence of serial episodes of ischaemia, possibly silent, causing repeated stunning. Tumour necrosis factor-α signals structural changes that in part parallel disuse atrophy and include loss of myofibrils, accumulation of collagen and fibroblasts, and loss of mitochondria.

Hibernation is reversed by revascularization and the scope for potential improvement in ventricular function can be examined by a number of means including positron emission tomography (PET) and dobutamine stress echocardiography. Mismatch of myocyte utilization of labelled deoxyglucose relative to blood flow indicates hibernating tissue on PET scanning whereas a positive echocardiographic response to inotropy suggests viability with dobutamine stress examination.

Temperature and haemodynamic modulation

In addition to being the primary mode of cerebral protection, hypothermia also offers

Key points

Myocardial protection refers to all strategies that increase the heart’s ability to withstand an ischaemic insult.

Stunning is potentially life-threatening post-ischaemic myocardial impairment after blood flow is fully restored.

Hibernation is a prolonged state of reduced myocardial contractility in response to arterial insufficiency such that oxygen demand matches oxygen supply.

Volatile anaesthetic agents possess cardioprotective properties independent of their beneficial effect on myocardial oxygen balance.

There is good evidence that perioperative use of β-blockers, statins, and α1-agonists reduce perioperative myocardial mortality.

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Myocardial protection. It achieves this by promoting electromechanical inactivity, impeding the process that results in apoptosis, and perhaps most importantly by reducing oxygen consumption. The lowest oxygen demands occur when the heart is arrested and decompressed. At 22°C, myocardial oxygen consumption is reduced from 80 to 0.3 ml 100 g⁻¹ min⁻¹. Increases in wall tension, contractility, and heart rate all serve to increase myocardial oxygen demand. Laplace’s law for a sphere states that the wall tension (\( \sigma \)) is proportional to the internal pressure (\( P \)) and internal radius (\( r \)), and inversely proportional to the wall thickness (\( \eta \)) (Fig. 1).

Thus, we see a direct relationship between radius and wall tension that provides the rationale behind several haemodynamic interventions available to the surgical team all aimed at reducing ventricular wall tension. Venting of the left side of the heart via a catheter is an effective technique for cardiac decompression and air removal and has the added advantage of providing a dry operative field. The left ventricular vent catheter can be inserted during the surgical procedure via various routes such as the ascending aorta, a right-sided pulmonary vein, or the left ventricular apex. The aim is to maintain a low ventricular wall tension. Separation from cardiopulmonary bypass while the heart is relatively empty offers the same advantage but requires careful observation and incremental filling to maintain an adequate preload.

**Cardioplegic techniques**

Cardioplegic diastolic arrest and hypothermia currently form the foundation of protective practice for on-pump cardiac surgery. Other interventions such as anaesthetic preconditioning (APC) and several novel strategies are worthy of discussion. Widespread in use, cardioplegia was introduced as a concept by Lamb in 1958. Cardioplegia may be blood or crystalloid, warm or cold, and continuous or intermittent. The main component of cardioplegic solutions responsible for inducing diastolic cardiac arrest is potassium, and concentrations in the order of 20 mmol litre are required. Blood is superior at preserving myocyte and endothelial function resulting in reduced incidence of mortality, myocardial infarction, and left ventricular failure in high-risk patients. A recent meta-analysis demonstrated reduced incidence of low cardiac output syndrome in the blood cardioplegia arm. Compared with crystalloid cardioplegia, blood offers several attributes that may contribute to the above clinical findings. In addition to the potential oxygen carrying ability, blood offers delivery of other nutrients, and also an inherent buffering ability and scavenging of oxygen free radicals. Note that the haemoglobin content of blood used for cardioplegia is diluted to around 5 g dl⁻¹ and its p50 on the oxygen haemoglobin dissociation curve is displaced to the left. This will decrease potential oxygen delivery to the myocardium significantly.

Cardioplegia can be delivered in antegrade or retrograde fashion. The former provides quick arrest and good left ventricular protection and is undertaken by infusing the solution into the aortic root proximal to the aortic cross-clamp. A competent aortic valve is required in order for the cardioplegia to perfuse the coronary arteries and to prevent detrimental left ventricular dilation. Retrograde cardioplegia is applied through a specific cannula into the coronary sinus and requires venting of the aortic root. This may reach parts of the myocardium inadequately perfused by the coronary arteries but may be insufficient for right ventricular protection as a sole technique.

The optimal composition for cardioplegia is a subject of continued research. It should be slightly hyperosmolar to limit oedema, alkallotic to attenuate subsequent pH changes, and have a low calcium concentration. The basic recipe can be complemented by a variety of substances aiming to provide metabolic substrates and enhanced cellular protection. Addition of aspartate and glutamate improves left ventricular stroke work index, increases myocardial oxygen consumption, and improves metabolic recovery. Metabolic enhancement with insulin and glucose has recently demonstrated trends towards improved functional recovery in patients undergoing coronary artery bypass grafting (CABG). Adding the vasodilator and metabolic precursor adenosine has also demonstrated promising trends in a variety of clinically relevant endpoints. Other possible additives include magnesium, the nitric oxide precursor L-arginine, N-acetylcysteine, nicorandil, and bupivacaine.

The temperature at which cardioplegia is administered can be divided into cold (5–10°C), tepid (27–30°C), and warm (37–38°C). Low temperatures may be conducive to ischaemic protection but may accentuate the reperfusion injury. Evidence exists to suggest that warm cardioplegia is associated with reduced postoperative CK-MB increase (12.3% vs 17.7%) and a reduced hospital stay (6 vs 9 days). The authors of this study did, however, warn that interruption to the continuous administration of warm cardioplegia renders the myocardium susceptible to warm ischaemic injury. Surgeons who prefer intermittent administration of cardioplegia might adopt a regimen consisting of inducing arrest with warm cardioplegia and then providing maintenance with cold. Alternatively, an infusion of warm cardioplegia or warm blood only, via the cardioplegia cannula towards the end of the procedure (hot shot), has its advocates. Evidence to date suggests that, on
balance, tepid cardioplegia provides the best overall protection and recovery.

**Ischaemic preconditioning**

Preconditioning describes the remarkable phenomenon whereby exposure to a physical or pharmacological stimulus reduces subsequent injury from ischaemia. This is analogous to the reduced infarct size seen in a myocardial infarct after frequent angina. Postconditioning is similar, but the stimulus occurs at the end of the insult. Remote ischaemic preconditioning (RIPC) happens after reperfusion of a limb or organ, distant from the myocardium, which underwent a period of ischaemia. The concept of preconditioning can be broadly divided into ischaemic preconditioning (IPC) and APC.

IPC was first described in dog hearts in 1986. In these experiments, hearts were subjected to four short episodes of ischaemia separated by 5 min of perfusion before being subjected to a 40 min ischaemic insult. Preconditioning reduced the size of the resultant infarct from 30% to 7%. IPC is divided into early (classical) and late, with differing mechanisms that explain the different chronology. Early preconditioning starts within 15 min and lasts for several hours. It protects against myocardial infarction but not stunning. The speculative mitochondrial hypothesis for preconditioning proposes adenosine as one of several possible triggering agents that activates phospholipase C leading to increased expression of protein kinase C. This subsequently phosphorylates and hence activates the final target, that is, mitochondrial ATP-sensitive potassium channels (K\textsubscript{ATP}). Drugs such as the sulphonylureas, which act by blocking K\textsubscript{ATP} channels, may inhibit the preconditioning effect. Recent evidence suggests that patients with non-insulin-dependent diabetes mellitus and coronary heart disease may benefit from changing their medication leading to opening of mitochondrial K\textsubscript{ATP} channels. Production of mitochondrial reactive oxygen species (ROS) is increased via partial inhibition of complex III of the electron transport chain, which activates signalling pathways for preconditioning resulting in less ROS production on reperfusion. Mitogen-activated protein kinase and adenosine receptor activation are also involved. In a recent meta-analysis involving slightly <3000 patients undergoing CABG surgery, APC significantly lowered troponin I concentrations, reduced inotrope requirement, reduced duration of hospital stay, and was associated with 20% greater cardiac indices. However, it did not reduce the incidence of perioperative myocardial infarction or mortality.

Halogenated volatile agents are not the only pharmacological agents capable of eliciting pharmacological preconditioning. Xenon, adenosine, nicorandil, and norepinephrine among others also have preconditioning properties. Morphine is a preconditioning agent, which in addition has synergistic activity with volatiles. As this effect is mediated via the delta receptor, other opioids used in anaesthesia do not demonstrate this property. Ageing, diabetes, and hypercholesterolemia all attenuate APC.

**Anaesthetic preconditioning**

Over a quarter of a century ago, reduced ST segment elevation was demonstrated in dog hearts exposed to brief ischaemic episodes in the presence of halothane. Unfortunately, subsequent concerns regarding the risk of ‘coronary steal’ with isoflurane anaesthesia took precedence. Coronary steal is postulated to occur in the presence of coronary vasodilators acting on normal vasculature and depriving tissue supplied by atherosclerotic vessels of blood, as these are less able to dilate. It was thought to be a particular risk in ‘steal-prone’ anatomy, defined as being the complete occlusion of one coronary artery that is supplied distally by collateral flow from another coronary artery with >50% occlusion. In clinically relevant concentrations, this has been shown not to be the case. It is now appreciated that all currently used volatile agents are cardioprotective and that this property extends to ischaemic tissue. In addition to the indirect cardioprotective properties of negative inotropy and chronotropy that result in a beneficial effect on myocardial oxygen balance, volatile anaesthetic agents have a direct cardioprotective effect that strongly resembles IPC (Fig. 2).

APC involves exposure of the myocardium to halogenated inhalation anaesthetics in order to attenuate the subsequent injury due to ischaemia and reperfusion. As low as 0.25 minimum alveolar concentration (MAC) may be protective, but the maximum effect is achieved at 1.5–2 MAC. It is also associated with an early and a late or memory effect. This technique avoids the risk and practical difficulty of exposing diseased myocardium to transient ischaemia. Evidence now exists suggesting that volatile agents also exert a renal, cerebral, and hepatic preconditioning effect. The extracellular signalling pathways responsible for this effect are very similar to those seen in IPC and involve signalling substances binding to inhibitory G-protein-coupled receptors to trigger several intracellular pathways. Intracellular protein kinase C plays a central role in the mechanism leading to opening of mitochondrial K\textsubscript{ATP} channels. Production of mitochondrial reactive oxygen species (ROS) is increased via partial inhibition of complex III of the electron transport chain, which activates signalling pathways for preconditioning resulting in less ROS production on reperfusion. Mitogen-activated protein kinase and adenosine receptor activation are also involved. In a recent meta-analysis involving slightly <3000 patients undergoing CABG surgery, APC significantly lowered troponin I concentrations, reduced inotrope requirement, reduced duration of hospital stay, and was associated with 20% greater cardiac indices. However, it did not reduce the incidence of perioperative myocardial infarction or mortality.

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**Postconditioning and remote ischaemic preconditioning**

Ischaemic postconditioning is the interruptive reperfusion at completion of cardiac surgery. This might consist of repeated
sequences of perfusion for 30 s followed by re-occlusion for 30 s. It has been found to significantly reduce infarct size in patients undergoing angioplasty for complete coronary artery occlusion. Volatile agents also have a postconditioning effect possibly mediated by inhibition of the neutrophil-mediated ROS generation responsible for reperfusion injury.

RIPC involves inducing ischaemia distant to the myocardium in tissues such as the mesentery, kidney, or lower limb in order to obtain a myocardial protective effect after reperfusion of the remote tissue. An example is 5 min of renal artery occlusion before coronary artery reperfusion; this also has demonstrated reduction in the extent of infarct. A recent study of RIPC in patients undergoing elective abdominal aortic aneurysm repair found a 27% reduction in myocardial injury, a 22% reduction in myocardial infarction, and a 23% reduced incidence of renal impairment. Both remote conditioning and postconditioning are mediated by adenosine which reduces inotropic requirement, ICU stay, and significant reductions in troponin I release. Volatile anaesthetic agents also possess postconditioning properties which, as in preconditioning, results in the opening of ATP-sensitive potassium channels preventing mitochondrial calcium overload.

**Pharmacotherapy**

Postoperative myocardial infarction has a mortality of ~10%. It is often silent, non-Q-wave, and preceded by ST depression. It normally occurs within a few hours of completion of surgery and is associated with tachycardia and hypertension, which, as previously discussed, are factors contributing to increased myocardial oxygen demand. β-blockade reduces mortality after myocardial infarction in proportion to the reduction in heart rate. The influential Mangano and colleagues, and Poldermans and colleagues trials have demonstrated reduced myocardial infarction and mortality after major non-cardiac surgery in β-blocked patients. However, for a variety of reasons, these trials have courted criticism. A meta-analysis of six randomized controlled trials found that β-blockade was associated with a 75% reduction in the risk of perioperative cardiac death. The benefits of β-blockers are not confined to non-cardiac surgery as their use has also been shown to reduce 30 day mortality after CABG. The benefits of perioperative β-blockade may be more pronounced in patients with risk factors for ischaemic events.

The α2-agonists clonidine and mivazerol have demonstrated perioperative myocardial protective properties. In patients with known coronary artery disease, mivazerol reduces the incidence of myocardial infarction and overall mortality rate in general surgical and vascular patients. Clonidine after operation significantly reduces myocardial ischaemia in vascular patients.

The statin family of drugs offers both lipid lowering and a complex collection of unrelated or ‘pleotropic’ benefits, including increased plaque stability, decreased platelet activity, decreased inflammatory markers, and improved arterial blood flow. Patients receiving statins at the time of surgery enjoy a reduction in all-cause mortality, myocardial infarction, and cardiovascular mortality. The reduced mortality has been shown to extend up to 5 yr after operation. Like β-blockers, the benefit may be greater in higher risk patients.

**Other strategies**

Meta-analysis has demonstrated that despite the sound theoretical reasoning of improved analgesia and reduced stress response to surgery, thoracic epidural analgesia and intrathecal analgesia do not reduce the incidence of mortality or myocardial infarction. It
has recently been shown that a glucose–insulin–potassium infusion in non-diabetics reduces myocardial damage and inotrope requirements. The potential antioxidant properties of propofol remain controversial with a recent study comparing large-dose propofol (100 μg kg⁻¹ min⁻¹) with isoflurane and finding a reduced inotrope requirement and myocardial injury. Antibody therapy to prevent P-selectin and intercellular adhesion molecule-1 activation may attenuate leucocyte-mediated reperfusion injury and is associated with reduced infarct size in animal models.

**Conclusion**

The ageing and more expectant population with increasing morbidity provides continued impetus to develop the practice of a myocardial preservation management system. The role of hypothermia is increasingly controversial in the light of the fact that diastolic arrest provides the majority of protection derived from reduced oxygen demand. An increased understanding of the mechanisms involved in myocardial injury will lead to an increased application of pharmacotherapy to prevent them. Volatile anaesthetic agents and morphine possess direct and synergistic cardioprotective effects, independent of their beneficial effects on myocardial oxygen balance. The American College of Cardiology and American Heart Association recommend that patients with a requirement for β-blockers to manage angina or hypertension and patients at risk for ischaemic heart disease should be titrated to a heart rate of 50–60 beats min⁻¹. This may protect against ischaemic events. It also suggests that the α₂-agonists may offer similar protection.

**References**


Please see multiple choice questions 22–26