Myocardial Protection During Cardiac Surgery

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MYOCARDIAL PROTECTION DURING CARDIAC SURGERY

INTRODUCTION

- It is known that during cardiac surgery myocardial damage is cumulative.
- Cardiac surgery at some point will induce ischaemia to the myocardium, which may be global / local.
- Each patient’s myocardium will respond differently, unpredictably, and may/may not lead to immediate or delayed poor outcome.
- Myocardial protection refers to all interventions undertaken in the preoperative, intraoperative and postoperative periods that optimize myocardial $O_2$ supply and demand, therefore this definition incorporates all medical and interventional cardiology strategies and all manipulations of the determinants of $O_2$ supply and demand undertaken by the cardiac anaesthetist.
- While ischaemia is the most likely major factor inducing intraoperative myocardial damage, harmful mechanical and pharmacological factors must also be taken into account.
- This holistic approach is the basis to myocardial protection in cardiac surgery.

HISTORY

- The earliest cardiac surgical procedures used venous inflow occlusion techniques.
- However, time limitations precluded performing anything but the simplest procedures.
- With the development of Cardiopulmonary Bypass (CPB), hypothermia became the primary technique of tissue protection in general, and myocardial protection in particular.
- However, the limitations of this approach became evident quickly, and further advances in myocardial protection techniques (and the complexity of cardiac surgical procedures undertaken), awaited the introduction of cardioplegia by the St.Thomas group in 1975.
- Ironically, the use of high potassium ($K^+$) solutions to induce diastolic arrest was introduced 2 decades earlier (about the time that CPB was first described), but it was not pursued clinically because of the finding of focal myocardial necrosis probably resulting from very high concentrations of $K^+$.
- Blood cardioplegia was described as recently as 1978.
- Murray et al in 1986 were the first to describe the benefits of the cardioprotective effects of ischaemic preconditioning in a canine model.
- 14 years later (2000), Yellon and Dana demonstrated the same benefits of ischaemic preconditioning in humans.
- A novel concept of “post-conditioning” has also been a subject of research since discovery by Zhao et al (2003).
- Due to limitations of preconditioning in areas of unpredictable ischaemia, postconditioning holds better promise as a tool at reperfusion to reduce the reperfusion injury.
- Vinten-Johnson et al (2005) have shown that controlled reperfusion can improve contractility and post-ischaemia functional recovery.
- One of the greater discoveries of the 21st century for anaesthetists has been the discovery that some of the commonly used anaesthetic agents possess pre- and post – conditioning mimetic abilities (Halogenated agents, opioids, propofol?).

**AETIOLOGY OF MYOCARDIAL INJURY**
- **Mechanical**
- **Pharmacological**
- **Ischaemic**

**Mechanical Injury**
- Surgical incisions of the myocardium produces local myocardial necrosis.
- The incision and its subsequent closure may have more profound effects if coronary arteries are inadvertently divided, or if myocardial geometry is altered, thus decreasing efficiency of global contraction.
- Rough surgical handling – myocardial contusions / lacerations.
- Topical hypothermic injury
- Ventricular Distension:
- Stretch injury(cross-linking between actin–myosin filaments disrupted)
- Subendocardial ischaemia

**Pharmacological Injury**
- While certain pharmacological agents are used for their protective effect, they may also be injurious.
- Excessive doses of the so-called ‘protective agents’ can result in myocardial damage (ie. Certain cardioplegic regimens/solutions).
- Agents may be protective at certain times during surgery (beneficial effect of Glucose-Insulin-K⁺ pre-op and with respect to preconditioning), and deleterious other times (the effect of glucose on ischaemia).
- Inappropriate use of drugs (ie. Immediate post-ischaemia use of inotropic agents) may also increase myocardial damage.
- Agents ie. Sulphonylureas, which obliterate the beneficial effects of ischaemic preconditioning and Amiodarone, which has also been shown to be associated with increased operative morbidity and mortality due to hepatic, pulmonary and
cardiac dysfunction, are among drugs that are directly detrimental to cardiac and patient outcome.

**Ischaemic Injury of the Heart**

- Ischaemic injury during cardiac surgery may occur as a result of:
  - Progression of pre-existing disease,
  - Surgery itself, or
  - Relative ischaemia induced by altering the supply-demand ratio.

- Myocardial ischaemia exists whenever the energy demand of the myocardium exceeds supply.

- Anaerobic metabolism yielding potentially toxic end-products of metabolism, coupled with inadequate perfusion, further inhibits energy production and inadequate removal of toxic end-products.

- Should ischaemia not be reversed, ultimately energy-dependant systems begin to ‘shut down’ – electromechanical coupling and contractility declines, energy-dependant membrane pump functions cease with resultant changes to intracellular ionic concentrations, and damage occurs to the Sarcoplasmic Reticulum and Mitochondria. Finally, lipases and proteases are activated and cellular necrosis occurs.

- Initially, ischaemic-induced cellular changes are potentially reversible, but cell death eventually occurs if allowed to progress.

- By manipulating the ischaemic process, decreasing metabolic demands, stabilizing membranes and maintaining intracellular homeostasis, myocardial tolerance to ischaemia can be significantly increased and irreversible cell damage averted.

  a) The ultimate effect of ischaemia on the myocardium is determined by duration and degree of ischaemia (including stunning, hibernation and Reperfusion injury).
  b) Supply:Demand ratio of \( \text{O}_2 \) and substrates.
  c) The myocardium’s ability to withstand the ischaemic insult (cardiac preconditioning).

- Manipulation of the above 3, are the basis for providing myocardial protection in cardiac surgery.

  a) **The Duration and Severity of Ischaemia**
    - Are important determinants of the myocardial consequences of stunning, hibernation or necrosis.

  **Myocardial Stunning:**
  - The term “Myocardial Stunning” was coined by Braumwald and Kloner in 1982.
- It is defined as “Myocardial dysfunction that persists after reperfusion despite the absence of irreversible damage.”
- This transient contractile dysfunction is fully reversible with time (may take hours to days), although inotropic or mechanical circulatory support may be required.
- 3 main mechanisms are involved in the establishment of the stunned myocardium:
  - Formation of O$_2$-free radicals,
  - Accumulation of intracellular Ca$^{2+}$, and
  - Degradation of contractile proteins – collectively termed “Reperfusion Injury”.

**Mechanisms of Cell Death following Ischaemia – Reperfusion:**

- As much as ischaemia seems the obvious culprit in cell death, reperfusion actually contributes towards an increased infarct size.
- Cell death following ischaemia-reperfusion has features of necrosis, apoptosis and autophagy at various proportions depending on whether one is looking at adult / neonatal, or in-vivo / in-vitro cells.
- The release of troponin and creatine kinase during ischaemia is a result of cell rupture and extrusion of these intracellular components.
- Cell rupture is caused by:
  - Protease activation,
  - Loss of ATP, and
  - Ion dysregulation.
- The initiator of protease activation and ATP depletion is a rise in cytosolic free Ca$^{2+}$ during ischaemia.
- The rise in Ca$^{2+}$ causes:
  - Calpain activation, which then cleaves plasma membrane proteins leading to cell rupture. Calpains also activate pro-apoptotic proteins shifting the balance from autophagy to apoptosis.
  - In combination with increased Reactive O$_2$ Species (ROS), Ca$^{2+}$ causes activation of an inner mitochondrial large–conductance channel called “Mitochondrial Permeability Transition Pore (MPT)” Opening of this channel leads to loss of mitochondrial function and ATP, and eventually ion homeostasis.
- Cell death from ischaemia-reperfusion is a mixture of all 3 forms of cell death. Distinction between the various forms is not important as all of them are inter–related and can be manipulated.
- The important message is this one - Cell death during ischaemia-reperfusion:
  - Is an Active Process, which can be manipulated.
  - Mitochondria are the important mediators and regulators of all forms of cell death.
- MPT is a major regulator of both apoptosis and necrosis.
- \( \text{Ca}^{2+} \) and ROS are both activators of MPT during ischaemia and reperfusion.

Ca\(^{2+}\) causes cell death in 3 ways during reperfusion:
- A transient increase in intracellular Ca\(^{2+}\) triggers arrhythmias, which are a major cause of death.
- Intracellular [Ca\(^{2+}\)] decreases rapidly to normal in the absence of arrhythmias in the cells that survive, but oscillations in the intracellular [Ca\(^{2+}\)] can occur causing cell hypercontracture and ATP depletion leading to further cell death.
- In some cells, high intracellular Ca\(^{2+}\) persists causing irreversible cell injury.

- Role of Reactive O\(_2\) Species during ischaemia:
- Low levels are produced during ischaemia, the significance of which is uncertain.
- A burst of ROS production occurs at reperfusion, thought to be a product of damaged Electron Transport Chain components generating Superoxide. This is a major activator of MPT and cardiomyocyte death.
- They play a pivotal role in triggering early and delayed cardioprotection.

Myocardial Hibernation:
- Later, in 1985, Rahimtoola put forward the concept of “Hibernation”.
- The “hibernating myocardium” refers to the presence of “persistent myocardial dysfunction at rest associated with cardiac ischaemia”, (ie. Reperfusion has not yet occurred).
- Ventricular function is diminished as a consequence of insufficient coronary blood flow.
- This adaptive function of the myocardium at the expense of worsening effort tolerance and possible CCF, is suspected to be a somewhat protective mechanism of the myocardium.
- Cardiac metabolism is down-regulated.
- It has been proposed that the abolition of contractility of hibernating cardiac tissue is attributable to chronic stunning caused by multiple episodes of severe ischaemia followed by repetitive reperfusion.
- An improved balance of supply and demand to the hibernating myocardium will eventually result in recovery of myocardial function.
- The issue of hibernation is clinically important because the risk of adverse cardiac outcome increases with decrease in ejection fraction (and effort tolerance).
- If coronary revascularization increases the ejection fraction, the risk of adverse cardiac outcome is likely to be reduced.
The likelihood of improved function after coronary reperfusion can be predicted by the result of a Dobutamine Stress Echo. If Dobutamine worsens ventricular function (reversible ischaemia), coronary revascularization is likely to improve cardiac function, ie. Likely to be hibernating, rather than infarcted.

Schematic characterization of cardiac ‘stunning’ and ‘hibernation’ (Ref 7)

- In stunning, normal blood flow and energy metabolism are accomplished by reduced contractility, designated as ‘Flow-Contractility Mismatch’. The impaired contractile function seems to be caused primarily by increased IC Ca\textsuperscript{2+}, activation of Ca\textsuperscript{2+}-dependant non-lysosomal cysteine proteinases (calpain), and degradation of sarcomere-associated proteins including Troponin-I. Hibernation is characterized by reduced contractility accompanied by reduced VO\textsubscript{2} as a consequence of reduced blood flow. Partially damaged cardiomyocytes can be rescued to full function after stunning as well as after hibernation, provided normal blood flow is restored after the latter within the critical time period before irreversible cell damage has occurred. Despite their distinct definition, stunning and hibernation may merely represent intermediary states in a continuum extending from unimpaired functional myocytes to necrosis.

b) O\textsubscript{2} Supply and Demand Ratio:
- Ischaemia occurs if myocardial O\textsubscript{2} supply does not meet the demand of the cardiac myocytes required to perform work. This ‘work’ varies with HR, rhythm, contractility, preload and afterload.
- Delivery of O\textsubscript{2} is achieved during diastole. As the coronary arteries are located epicardially, systolic flow is almost non-existent due to the force of
the contracting myocardium. In 1975, Buckberg proposed the **Buckberg Index / Endocardial Viability Ratio**. He plotted aortic and Lt ventricular BP against time and matched this with coronary blood flow. (Ref 7)

- The area beneath the LV systolic pressure curve constitutes the **Tension Time Index** (TTI = Energy Demand), and the area between the aortic and LV pressure curves in diastole constitutes the **Diastolic Pressure Time Index** (DPTI = Energy Supply).
- He proposed that if the ratio of DPTI(supply): TTI(demand) <0.8, subendocardial ischaemia is very likely. (Normal ratio > 1).
- Therefore, any pathology or cause that:
  - ↑es HR (↓ Diastolic Time = ↓ DPTI)
  - ↑es the LV Diastolic pressure – wall tension (↓ area between aortic and LV pressure curves as LV pressure is ↑ed), or
  - Any ↑es in systolic pressure (↑ed TTI).
- Will lead to a ↓ in DPTI: TTI ratio.
- It is this concept that allows the perioperative physician to manipulate the physiological variables to provide cardiac protection.
c) CARDIAC PRECONDITIONING
   i) Definition and Time Course:
   - The heart possesses a remarkable ability to adapt to stress by changing its phenotype in a manner that makes it more resistant to further damage.
   - Hibernation and stunning may be examples of this ability.
   - Ischaemic Preconditioning (IPC) [as described by Murray et al in 2006 (in a canine model)] - ‘4 brief periods of coronary artery occlusion followed by 5 minute reperfusion intervals before a prolonged (40 min) occlusion, dramatically reduced infarct size by 70 – 80%.’
   - This has been shown to be applicable in all species, including humans.
   - IPC has 2 phases:
     ➢ Early (Classic) Phase:
       - The early window of protection lasts 1-2 hours after IPC.
       - It is a state of marked protection against subsequent prolonged ischaemia.
       - Disappears after 2 – 3 hours.
     ➢ Late Phase:
       - A second delayed window of protection 12–24 hours after initial preconditioning, and lasts up to 72 hours.
       - It is thought to depend on gene up-regulation and reduces further myocardial risk to ischaemia.
       - Protects against stunning.

   - While multiple, brief ischaemic episodes may have additive effects, too many repetitive stimuli abolish the protection.
   - Of note, preconditioning itself, does not prevent myocardial cell death, but significantly delays its occurrence during the first 2–3 hours of sustained ischaemia.

ii) Mechanisms Cardiac Preconditioning:
   - Most importantly, a multitude of additional stressful stimuli (apart from ischaemia), can induce the same early and late protective response in cardiac tissue, ie.
     ➢ Oxidative (hyperoxia),
     ➢ Mechanical (stretch),
     ➢ Electrical (rapid pacing),
     ➢ Thermal
     ➢ Chemical (hormonal), Ionic (Ca^{2+}), and
     ➢ Pharmalogical stressors.
   - Modulatory effects of various drugs on IPC have been studied, and are listed in the table below.
- It would therefore be prudent to avoid drugs that inhibit preconditioning and promote the use, where possible, of those drugs that promote preconditioning in the setting of cardiac surgery, where ischaemia and its consequences are almost guaranteed.

Modulatory Effects of Medication on Cardiac Preconditioning: Ref 12

<table>
<thead>
<tr>
<th>PRECONDITIONING ↑</th>
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<tr>
<td><strong>Adenosine Rec Agonists</strong></td>
<td><strong>Adenosine Rec Antagonists</strong></td>
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<tr>
<td>- Adenosine, Dipyridamole</td>
<td>- Theophylline, Aminophylline</td>
</tr>
<tr>
<td><strong>K&lt;sub&gt;ATP&lt;/sub&gt; Channel Openers</strong></td>
<td><strong>K&lt;sub&gt;ATP&lt;/sub&gt; Channel Blockers</strong></td>
</tr>
<tr>
<td>- Nicorandil, Diazoxide, Levosimendan, Bupivacaine, Lignocaine</td>
<td>- Sulphonylureas, Glibenclamide</td>
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<td><strong>Opioid Agonists (51)</strong></td>
<td><strong>Opioid Antagonists</strong></td>
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<tr>
<td>- Morphine, Fentanyl, Pentazocine</td>
<td>- Naloxone</td>
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<tr>
<td><strong>β-adrenergic Agonists</strong></td>
<td><strong>β-blockers</strong></td>
</tr>
<tr>
<td>- Isoproterenol, NA, Adrenaline, Some β-blockers - Carvedilol</td>
<td>- Incl drugs that deplete myocytes of catecholamines - Reserpine</td>
</tr>
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<td><strong>α-agonists</strong></td>
<td><strong>α-antagonists</strong></td>
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<tr>
<td>- Phenylephrine, NA</td>
<td>- Phentolamine</td>
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<tr>
<td><strong>M&lt;sub&gt;2&lt;/sub&gt;-Rec Agonists</strong></td>
<td><strong>M&lt;sub&gt;2&lt;/sub&gt;-Rec Antagonists</strong></td>
</tr>
<tr>
<td>- AchE inhibitors</td>
<td>- Atropine</td>
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<td><strong>NO Releasers</strong></td>
<td><strong>NO Scavengers</strong></td>
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<tr>
<td>- Nitroglycerine, SNP, L-arginine</td>
<td>- vitamin E?</td>
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<tr>
<td><strong>Ca&lt;sup&gt;2+&lt;/sup&gt;</strong></td>
<td><strong>Ca&lt;sup&gt;2+&lt;/sup&gt; Channel Blocker</strong></td>
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<tr>
<td></td>
<td>- Nifedipine</td>
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<tr>
<td><strong>β-2 Bradykinin Rec Agonists</strong></td>
<td><strong>AT&lt;sub&gt;1&lt;/sub&gt;-Rec Antagonists</strong></td>
</tr>
<tr>
<td>- ACE-I: Captopril, Lisinopril, Enalapril</td>
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<tr>
<td><strong>Statins</strong></td>
<td><strong>Statins</strong></td>
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<tr>
<td>- Lovastatin, Pravastatin</td>
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<tr>
<td><strong>Other</strong></td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>- Flumazenil, Amrinone</td>
<td>- Digoxin, Gadolinium, Aprotinin, COX-2 Inhibitors.</td>
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- The concept that brief renal, mesenteric or skeletal muscle ischaemia of remote origin can effectively precondition the heart is consistent with humoral induction of the preconditioned state (‘remote preconditioning’).
- Also consistent with this notion is the fact that regional cardiac ischaemia can initiate global protection and render remote myocardium resistant to infarction (‘preconditioning at a distance’).
- IPC is mediated via several sarcolemmal receptors, which are mostly linked to inhibitory G-protein (Gi) which couple to a highly complex network of kinases, namely:
  - Adenosine (A-1, A-3)
- Purinoreceptors (P2Y)
- Endothelin (ET1)
- Ach (M2)
- α1 & β adrenoreceptors.
- Angiotensin II (AT1)
- Bradykinin (B2)
- Opioid (δ1, κ) receptors.

- The importance of the individual receptor depends heavily on the species
  and the preconditioning stimulus itself.
- The main signalling steps and components of early and late preconditioning
  are summarized schematically in: (Ref 11)

- **Adenosine:**
  - Is considered to be one of the most relevant triggers of early and late
    preconditioning.
  - Released from cells in the ischaemic zone by upregulation of membrane –
    associated nucleotidase and activates the respective receptors on
    cardiomyocytes.

- **Reactive O₂ Species:**
  - Are important intracellular signalling molecules and are increased during
    sublethal oxidative stress (preconditioning stimulus).
  - They play a pivotal role in triggering early and delayed cardioprotection, and
    are probably derived from mitochondria.
- Activates Phospholipase C and Protein Kinase C, which in turn, amplify the preconditioning stimulus.

**Nitric Oxide:**
- Able to induce a cardioprotective effect against myocardial stunning and infarction.
- Recent studies provided direct evidence of enhanced biosynthesis of NO in the myocardium subjected to brief episodes of ischaemia and reperfusion, probably via increased NOS activity (endogenous constitutive).
- Although most studies indicate that endogenous NO is not necessary for ischaemia-induced early preconditioning, exogenous or pharmacologically increased endogenous NO production elicits an early preconditioning effect (ie. NO is sufficient but not necessary for early preconditioning).
- Conversely, NO has an obligatory role in late preconditioning.
- The most likely cardioprotective effects of NO in late preconditioning are:
  - Inhibition of Ca\(^{2+}\) influx,
  - Antagonism of β - adrenergic stimulation,
  - Reduced contractility and myocardial O\(_2\) consumption.
  - Opening of K\(_{ATP}\) channels,
  - Antioxidant actions,
  - Activation COX-2 with the synthesis of prostanoids.

### iii) K\(_{ATP}\) Channels:
- Cardiomyocytes have 2 distinct types of K\(_{ATP}\) channels - one located in the surface membrane and another in the inner mitochondrial membrane. (Ref 11)

- Preconditioning can be pharmacologically mimicked by K\(_{ATP}\) channel openers and abolished by K\(_{ATP}\) channel inhibitors.
- Sarcolemmal $K_{ATP}$ channels are physically bound with the creatine PO$_4$ – creatine kinase system and provides a direct link between the metabolic state and cellular excitability.
- Mitochondrial $K_{ATP}$ channels regulate mitochondrial volume state, mitochondrial membrane potential, formation of ROS and energy production.
- Toyoda and colleagues suggested that infarct size reduction is mediated largely by mitochondrial $K_{ATP}$, and functional recovery (in which HR plays a pivotal role) is mediated by sarcolemmal $K_{ATP}$ channels.
- Mitochondrial $K_{ATP}$ channels also play a impot role in the prevention of cardiomyocyte apoptosis and in delayed preconditioning protection.

**$K_{ATP}$ modulation of infarct size:** (Ref 11)

B. During ischaemia-reperfusion injury, the ↑ cytosolic [Ca$^{2+}$] induces high metabolic activity with accumulation of inorganic phosphate and ROS. This is accompanied by swelling of the intermembrane space, with subsequent shrinkage of the mitochondrial matrix and disruption of the Supramolecular Complex (SMC). This impairs energy production and nucleotide transport, resulting in cellular ATP depletion. The Mitochondrial Permeability Transition Pore (PTP) opens and induces dissipation of the inner membrane potential, leading to cell death.

C. Ischaemic and pharmacological preconditioning are thought to exert cardioprotection, first by activation of the sarcolemmal $K_{ATP}$ channel, which reduces the IC [Ca$^{2+}$] by stabilization of the resting membrane potential below -80mV and shortening of the AP. Secondly, activation of the mitochondrial $K_{ATP}$ channel leads to an increase in the mitochondrial matrix volume and concomitantly reduces the intermembrane space, which leads to reassembly of
the SMC, closure or maintenance of the closed state of the PTP, and restoration of mitochondrial energy production.

iv) **Effects of Preconditioning:**
- Reduced infarct size.
- Reduced generation of lactate
- Reduced rate of fall in ATP
- Reduced arrhythmias
- Reduced contractile dysfunction.

v) **Postconditioning:**
- This describes the benefits of intermittent reperfusion after ischaemia on infarct size (Zhao et al, 2003).
- There are a number of caveats about postconditioning:
  - Species – specific (number of ischaemic and reperfusion episodes and time duration between episodes.)
  - The time limit for benefit is 10 minutes from beginning of reperfusion.
  - Of benefit only in coronary occlusion < 45 minutes.
  - Effects of preconditioning and postconditioning are not additive.
- Volatile anaesthetics can also induce myocardial protection during reperfusion, when administered after ischaemia.

**CLINICAL APPLICATIONS OF PROTECTION**
- Cardiac surgery is dependant upon:
  - A compromise between the needs of the surgeon,
  - Surgical exposure and sufficient time to complete the necessary procedure,
  - And the needs of the myocardium for a continuous supply of O₂ and substrate.
- The intraoperative objective during cardiac surgery should therefore be 2-fold:
  - Correction of the pathological entity necessitating the operation.
  - Limiting the amount of additional myocardial damage.

**APPROACH TO MYOCARDIAL PROTECTION**
1) Pre-op technique
2) Intraop technique:
   - Anaesthetic and pharmacological factors.
   - Effects of CPB.
   - Surgical incisions and handling of the heart.
   - Adjuvant techniques used to decrease the effects of myocardial ischaemia.
3) Postop care.
Myocardial Protection in the Pre-Op Period

- The aim of protection preop is to establish a myocardium with the best possible supply demand ratio of O₂ (ie. Highest possible endocardial viability ratio), and the best possible energy stores to cope with periods of ischaemia.
- Drugs associated with negative outcomes with respect to cardiac surgery should be discontinued.

Possible Pre-Operative Interventions (Ref 7)

<table>
<thead>
<tr>
<th>↑ O₂ SUPPLY</th>
<th>↓ O₂ DEMAND</th>
<th>METABOLIC</th>
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<tbody>
<tr>
<td>↑FiO₂</td>
<td>Optimize HR</td>
<td>↑ Cellular Glycogen - GIK</td>
</tr>
<tr>
<td>Optimize Cor Bld Flow</td>
<td>Optimize Preload and Afterload</td>
<td>Inhibit FFA Metabolism</td>
</tr>
<tr>
<td>- Vasodilator Therapy - Vasodilators - β-Blockers - IABP</td>
<td>Afterload - β-Blockers - IABP</td>
<td>- Nicotinic Acid</td>
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<td>- Intra-AorticBallonPump (IABP)</td>
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<td>- IABP</td>
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<tr>
<td>↓ Catech</td>
<td>Prevent Free Radical</td>
<td></td>
</tr>
<tr>
<td>- β-blockers</td>
<td>Generation</td>
<td></td>
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<tr>
<td>- Premed - anxiolytics</td>
<td></td>
<td>- Allopurinol</td>
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i) **Supply:**
- \( DO₂ = \) Coronary flow \( \times \) CaO₂
- Increasing FiO₂, vasodilator therapy, maximizing vessel diameter => decreases resistance to flow.
- IABP ensures maximal flow during diastole by increasing the area between aortic pressure and LV pressure during diastole (increased DPTI).

ii) **Demand:**
- Optimal HR for the condition presented (↓HR in IHD to ↓ demand, but may not be appropriate for regurgitant lesions).
- Decreasing demand through the use of vasodilators, β-blockers (non-selective to ↓ afterload and inotropic demand), and IABP.
- IABP ↓es afterload and therefore demand, as it deflates at the end of diastole, giving the heart an ‘empty aorta’ to contract against in systole.
- ↓ing catecholamines thro’ the use of β-blockers, premedication and anxiolytics (incl. psychological counselling), ensures the least possible utilization of O₂ and energy substrates preop.
  - Adequate preop β−blockade (as demonstrated in various studies), ↓es peri-op ischaemia by approximately 50%.
  - Because β-blockers are thought to have beneficial peri-op effects, and to ↓ early late peri-op CVS morbidity and mortality, the suggested inhibitory effects of β-blockers on cardiac preconditioning appear somewhat conflicting.
As the evidence points towards benefit, β-blocker use is encouraged where indicated. Their possible inhibition may be negated by the fact that they block only one signalling pathway by which preconditioning is triggered, or due to specific alteration of the diseased myocardium, ie. Down-regulation of G-protein coupled receptors, diminishing the protective effects of preconditioning.

iii) **Metabolic:**
- Sodi-Polares in 1963 first reported the benefits of Glucose–Insulin–K⁺ (GIK) infusions in patients with IHD.
- Further currently convincing studies conducted by Van den Berg suggesting the deleterious effects of glucose, and possible beneficial effects of Insulin within a narrow range, make the use of GIK (if appropriately applied) attractive.
- Mechanisms of benefit include:
  - Increases in cellular K⁺
  - Promotion of glycolysis and gluconeogenesis.
  - Improved SR Ca²⁺ uptake.
  - Inhibition of lipid metabolism
  - Decreased accumulation of potentially harmful fatty acyl CoA.
  - Increased PG production.
  - Immune–modulation, and
  - Possibly scavenging of free radicals.
- Even a short period of 'metabolic enhancement', from induction of anaesthesia until aortic x-clamping has been shown to be beneficial.
- Higher pre-ischaemic myocyte glycogen levels are associated with improved tolerance to ischaemia and fewer complications after open heart surgery.
- It is imp to note that certain ‘free-radical scavengers’ ie. Allopurinol may inhibit cardiac preconditioning, altho’ evidence that they abolish the multiple other pharmacological promoters of preconditioning is lacking, and therefore, their administration is probably beneficial, thro’ the buildup of oxypurinol and allo-xanthine, which inhibits xanthine oxidase and scavenges hydroxyl radicals.

iv) **Drugs That Should Be Discontinued Prior To Surgery:**
- Certain therapeutic agents should be discontinued preop if possible, because of their possible detrimental effects during subsequent ischaemia.
- Including:
  - **Amiodarone:**
    - Preop use has been associated with increased operative morbidity and mortality - hepatic, pulmonary and cardiac dysfunctions are increased after open heart surgery.
    - Ideally it should be stopped for 6 months before surgery, because of its long half-life.
- **Digitalis:**
  - Possibly increases cytosolic Ca$^{2+}$ during ischaemia, which impairs post-ischaemic myocardial function and should therefore be discontinued if possible.
- **Sulphonylureas:**
  - Directly inhibits cardiac preconditioning, and has been associated with increased morbidity and mortality when used preop for cardiac surgery.

**Myocardial Protection During Surgery:**

i) Pre – bypass.
ii) Off – pump surgery.
iii) Cardiopulmonary bypass.
iv) Aorta x–clamping.
v) Reperfusion of ischaemic heart.

i) **PRE – BYPASS:**
- The principles of supply and demand and the maintenance of a favourable endocardial ratio remain throughout the anaesthetic and is particularly important pre–bypass.
- Pharmacological preconditioning may afford real benefit and is often applied through ‘routine’ drugs used in anaesthesia.

**Anaesthetic Preconditioning:**

a) **Volatile Anaesthesia:**
- The potential cardiac protective effects of volatile anaesthesia were already recognized before the introduction of the concept of ‘Anaesthetic Preconditioning’.
- Warltier et al described a better recovery of myocardial function after a 15 minute coronary artery occlusion when a volatile anaesthetic was administered before occlusion.
- Identifying the mechanism by which volatile agents mediate these anti-ischaemic events, is the subject of intense research.
- This objective has been difficult to accomplish because volatile agents also profoundly affect CVS function, by:
  - Decreasing arterial and coronary perfusion pressure.
  - Cause dose-related depression of myocardial contractility.
  - Produce coronary vasodilatation.
  - Affect electrophysiologic function, and
  - Modify autonomic nervous system acitivity to varying degrees.
Therefore the anti-ischaemic effects of volatile anaesthetics may be mediated, in part, by favourable alterations in myocardial O₂ supply-demand relations, preserving energy-dependant cellular functions and increasing coronary blood flow. However, it seems unlikely that these effects are solely responsible for protection against ischaemic damage.

Instead, several endogenous signal transduction pathways, acting through the ATP–sensitive K⁺ (Kₐ₅₆) channels and involving the generation of ROS, have been implicated in mediating the anti-ischaemic actions of volatile agents, including, activation/translocation of PKC, Tyrosine Kinases and p38-mitogen – activated kinases.

These mechanisms decrease cytosolic and mitochondrial Ca²⁺ loading.

Volatile agents may also suppress neutrophil activation and the neutrophil-endothelial interactions that cause myocardial dysfunction.

The absence of clinically straightforward data from anaesthetic preconditioning studies has prompted some centres to examine whether the choice of anaesthetic regimen during the entire surgical procedure would really have an impact on myocardial outcome.

A study by De Hert and colleagues in 2002, compared the effects of Sevoflurane and Propofol on myocardial function during and after CABG surgery. Before CPB, haemodynamic variables were similar between the 2 anaesthetic treatment groups.

However, after CPB, patients who received the volatile anaesthetic regimen had reserved cardiac performance, which was evident from a preserved SV, dP/dTmax, and length–dependant regulation of myocardial dysfunction.

In addition, need for inotropic support in the early postop period was significantly less with the volatile group, and postop plasma concentrations of cardiac Troponin I were consistently less than after total IV anaesthetic regimens.

The above graphs show cardiac Troponin I concentrations in Propofol-treated and Sevoflurane-treated patients before and after cardiac surgery. Time points shown are before surgery (control), at arrival in the ICU (T0), and after 3 (T3), 12 (T12), 24 (T24) and 36 (T36) hours later. The lines show the median values with 95% CI. Concentrations were significantly larger with Propofol. (15)
These data therefore suggested that volatile anaesthesia provided a cardioprotective effect that was not observed with IV anaesthetic regimen. This was confirmed in a subsequent study by the same authors in a group of elderly, high-risk patients with documented impaired myocardial function. Isoflurane was thought to be capable of directly producing myocardial ischaemia in susceptible patients with “steal-prone” coronary artery anatomy, under certain haemodynamic conditions. This implication was dispelled by several investigations conducted in animal models and humans with CAD. Subsequent investigations with the newer volatiles (Sevo and Des), showed that these drugs also did not decrease or abnormally redistribute coronary collateral blood flow. Halothane was also shown to preserve contractile function and ultrastructural integrity during cardioplegic arrest. This study was of particular interest because these data indicated that Halothane was capable of exerting a cardioprotective effort completely independent of improvements in myocardial O₂ supply demand balance. In addition, Halothane, Enflurane, Desflurane and Sevoflurane have been shown to decrease myocardial damage when administered during reperfusion after prolonged coronary occlusion or cardioplegic arrest. Halothane and Isoflurane markedly decreased myocardial infarct size in dogs, and this beneficial effect was found to persist despite discontinuation of the volatile agent before coronary artery occlusion. The myocardium acted as if it “remembered” the previous exposure to the volatile agent. This phenomenon was termed “Anaesthetic Preconditioning”, and was characterized by a short-term memory phase similar to that observed during IPC. Recent findings showed that Isoflurane decreased myocardial damage when administered 24 hours before coronary artery occlusion and reperfusion in rabbit heart’s in vivo. Pre-treatment with Isoflurane also preserved endothelial and vascular smooth muscle cell viability 12–48 hours after cytokine injury. Therefore volatiles produce a “late phase” (ie, a 2ⁿᵈ window) of myocardial protection similar to IPC. The evidence collected to date implies that volatile anaesthetics do not necessarily directly open Kₐ₅P channels, but instead, prime the activation of these channels in both sarcolemmal and mitochondrial membranes. Volatile anaesthesia may activate parallel or redundant signalling pathways that involve Kₐ₅P channel opening to generate a physiologically meaningful cellular response.
- Eg. Administration of Isoflurane in the presence of the $K_{ATP}$ channel openers, Nicorandil or Diazoxide, markedly enhanced protection against ischaemic injury beyond that observed with either drug alone.
- Administration of Isoflurane immediately before aortic x-clamping in patients undergoing CABG was shown to decrease the severity of subsequent ST segment changes and preserve cardiac index to a greater extent than that observed in patients who did not receive pre-treatment with a volatile.
- Differences in the efficiency of APC and the timing of administration among volatile anaesthetic agents alone and in combination with other cardioprotective drugs remain to be fully distinguished.

**Signalling pathways involved in volatile anaesthetic-induced preconditioning:**

(Ref 11)

![Diagram](image)

Multiple signalling cascades prime the sarcolemmal and mitochondrial $K_{ATP}$ channels, allowing prompt opening at the initiation of ischaemia. Arrows indicate positive activity and lines with blunted ends indicate inhibition.

b) **Intravenous Agents:**
- IV agents confer less protection than volatile anaesthesia.
  
  b.1) **Propofol:**
  - Decreases postischaemic myocardial mechanical dysfunction, infarct size, and histological degeneration.
- It has a chemical structure similar to that of phenol–based free radical scavengers, ie. Vitamin E, and reduces free radicals.
- It attenuates intracellular [Ca^{2+}] and suppresses the activity of neutrophils.
- These features suggest that Propofol may directly intervene at the critical phase of reperfusion injury by decreasing free radicals, Ca^{2+} influx and neutrophil activity, but does not act as a preconditioning–inducing agent.
- Protection was observed when the heart was treated with Propofol solely during reperfusion.
- Addition of Glibenclamide, a K_{ATP} channel blocker, did not abolish the protection of Propofol.

b.2) Ketamine:
- In rabbit hearts, racemic Ketamine, but not the stereoisomer S-Ketamine, was found to block early and late preconditioning.
- Both types of Ketamine were shown to block mitochondrial and sarcolemmal K_{ATP} channels in isolated rat cardiomyocytes.

b.3) Barbiturates:
- Thiamylal, which closely resembles Thiopental in its chemical structures, inhibits sarcolemmal K_{ATP} channels.
- 2 laboratories independently showed that commonly used barbiturates inhibited mitochondrial K_{ATP} channel activity.

b.4) Other:
- No inhibitory effects on mitochondrial K_{ATP} channels were found for Xylazine, an α2 adrenergic agonist similar to Clonidine and Dexmedetomidine.
- Etomidate and Midazolam did not have any effect on K_{ATP} channels or ischaemic myocyte survival in rat models.

** Taken together, these studies support the concept that certain anaesthetics may antagonize the protective effects of preconditioning.

b.5) Opioids:
- The existence of κ & δ receptors (but not μ rec), has been reported in rat atrial and ventricular tissue.
- In addition, cardiomyocytes constantly release opioids into the circulation, particularly during stressful stimuli and therefore serves as an endocrine organ.
- Activation of opioid receptors results in potent cardio-protective effects similar to classical and late preconditioning.
Currently, it is thought that selective activation of δ1opioid agonists exert this protection via interaction with Gi–protein and activation of PKC, Tyrosine Kinases and ultimately K\text{ATP} channels.

As with IPC, activation of δ opioid receptors also protects the heart from arrhythmias.

Combined administration of Isoflurane and Morphine, a μ receptor agonist with a δ1 receptor agonist properties, also reduced the extent of myocardial infarction to a greater degree than either drug alone.

Zaugg and colleagues demonstrated that Fentanyl enhanced Diazoxide-induced mitochondrial K\text{ATP} channel activity.

This is consistent with the priming effect of Fentanyl on mitochondrial K\text{ATP} channels.

Conversely, in an isolated perfused rat model, Sufentanyl did not improve post-ischaemic recovery, but produced an increase in Lt ventricular end-diastolic pressure during reperfusion.

### Factors that Affect the Efficacy of Cardiac Preconditioning: (Ref 12)

<table>
<thead>
<tr>
<th>Factors/Disease States</th>
<th>Ischaemic Preconditioning</th>
<th>Anaesthetic Preconditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>↓/←→/↑</td>
<td>↓</td>
</tr>
<tr>
<td>Medication</td>
<td>↓/←→/↑</td>
<td>↓/←→/↑</td>
</tr>
<tr>
<td>↑ Plasma Cholesterol</td>
<td>↓</td>
<td>?</td>
</tr>
<tr>
<td>CAD (Ischaemic cardiac remodeling)</td>
<td>↓/←→</td>
<td>?</td>
</tr>
<tr>
<td>Arterial Hypertension (Hypertrophic remodeling)</td>
<td>↓/←→</td>
<td>?</td>
</tr>
<tr>
<td>↑ Age</td>
<td>↓/←→</td>
<td>?</td>
</tr>
</tbody>
</table>

### Ageing:

- A recent clinical study in patients undergoing PTCA, comparing IPC in younger (45yrs; SD 5) and elderly (71yrs; SD 3), suggests that IPC is attenuated in the aged human myocardium, most probably as a result of age-related inhibitory effects upstream of the mitochondrial K\text{ATP} channels.

### Metabolic Dysfunction: - Increased Cholesterol and DM:

- Rabbit myocardium loses its preconditioning–induced protection when exposed to a cholesterol enriched diet for >4 weeks, and markedly increased serum [gluc] (>500mg/dl) can inhibit K\text{ATP} channel activation.
- Some of the experimental result are consistent with clinical observations in which prodromal angina did not limit infarct size, enhance recovery of
myocardial function, or improve survival in diabetic patients with MI, as opposed to non-diabetic patients.

Remodelled Heart:

- In a dog model of ventricular hypertrophy (2° to AS), there was no evidence of cardioprotection with IPC.
- Results from muscle slices of human Rt Atrial Appendages of patients with a LV EF <30%, indicate the failing human myocardium is much less amenable to IPC.

Clinical Benefits Of Anaesthetic Pre-/Post-Conditioning:

- In preconditioning protocols, volatiles (cf to TIVA):
  - Decreased CK-MB and cTnI release post–ischaemia => ↓ myocardial damage.
  - Preservation of global haemodynamics and LV function.
  - Shorter ICU and total hospital stays.
  - Faster weaning from mechanical ventilation.
  - Trend towards decreased MI and death.
  - Decreased incidence of long–term cardiac events.
- The benefits of APC are pronounced when volatiles are used throughout surgery, and not just before x-clamp or reperfusion.
- An APC protocol with volatiles and morphine (instead of Fentanyl) has been shown to yield better cardiac function Following CABG surgery.
- Taken together, these observations sugges that the benefits of APC and APoC depend upon factors ie:
  - Administration protocols
  - The choice of agent (Des > Sevo > Iso > Hal in RCT’s)
  - Concomitant use of other drugs with preconditioning properties (eg. Morphine).

II) MYOCARDIAL PROTECTION DURING OFF-PUMP PROCEDURES:

- In off–pump, beating heart CABG surgery, temporary segmental occlusion of the coronary artery is required for successful suturing of anastomoses.
- Ischaemic and pharmacological preconditioning may be used to preserve cardiac function during this critical time.
- It is important to be aware that vigorous surgical manipulations and pharmacological stimulation by catecholamines with the potential to induce preconditioning, may overwhelm any benefit from therapeutic ischaemia.
III) MYOCARDIAL PROTECTION DURING CPB:

There are many sources of myocardial injury during coronary surgery:

- The inflammatory response to CPB is a source of visceral (incl. myocardial) injury, inherent in the standard techniques of surgery using extra-corporeal circulation.
- Overdistension, retraction, athero-embolism, inadequate coronary perfusion and excessive work demands in the peri-op period are other sources of injury.
- Generally these latter influences are well understood and are minimized by:
  - Appropriate care in handling and retracting the heart,
  - Careful monitoring and manipulation of HR, filling pressure and SVR.
  - Limiting the duration of CPB whenever possible. Longer bypass times equate to increased M and M, 2° to organ damage and dysfunction (CNS, Kidney, Pulmonary and Myocardium), due to damage and destruction of all blood components. The consequence of which is the generation of macro and micro emboli, release of vaso-active substances, catecholamine release, Complement activation, leucocyte sequestration, FFA and denatured protein.
  - This can also be decreased by Pulsatile flow during CPB, which is considered more physiological, as the pulsatile energy ensures the patency of the vascular bed and mechanical motion of tissue fluid around the cell membrane, improves microcirculation and enhances diffusion. It also provides a lower SVR and higher O2 consumption.
  - Despite theoretical advantages, pulsatile CPB has not been widely accepted due to lack of clear objective data on organ metabolism and fear of increased haemolysis because of platelet destruction.
  - In a “Comparative Study of Pulsatile and Non-Pulsatile Flow During CPB”, by Pradeep Poswal et al, published in the Annals of Cardiac Anaesthesiology 2004, found that there was no significant difference between pulsatile and non-pulsatile flow with respect to platelet count, bleeding, coagulation profile, Liver and Kidney function and haemodynamic parameters in patients undergoing CABG surgery; except that creatinine clearance and urine output were better in the pulsatile group, which may be beneficial in patients with pre–existing renal dysfunction.

- Systemic perfusion pressure is easily controlled, and should be maintained at adequate levels throughout CPB (50–70 mmHg). Requirements are decreased during hypothermia.
- Ventricular fibrillation leads to a supply: demand mismatch, by:
  - Decreasing supply through compressive forces on the subendocardium and therefore perfusion; and
Increasing demand through increased electrical and physical activity and increased myocardial wall tension.

- This myocardial injury will be aggravated if:
  - Perfusion pressures are low/unequally distributed throughout the arterial system.
  - Fibrillation is electrically maintained.
  - There is ventricular hypertrophy (larger mass of at-risk myocardium and outgrowth of supply).
  - Normothermic fibrillation consumes 190% more O₂ than at 28°C.
  - Ventricular distension occurs.
- Therefore monitoring for VF is vital for prompt treatment - Rapid cardioversion is preferred.

- Ventricular Distension: Results in increased wall tension, therefore increased myocardial O₂ consumption.
  - Prevented by insertion of a Lt ventricular vent. LVEDP should be maintained at < 15 mmHg during hypothermic cardioplegic arrest.
  - This “relative” distension can be used to “protective” advantage by using cold distending solution, employing the protective effects of hypothermia on metabolism.
  - Factors associated with a greater risk of ventricular distension during CPB incl:
    - Aortic Regurgitation
    - Inadequate systemic venous drainage
    - Ventricular Fibrillation
    - Increased bronchial blood flow

- Systemic / Topical Hypothermia:
  - Defined as lowering of the entire body temperature.
  - Hypothermia decreases O₂ demand of all organs, and increases tissue energy stores.

**Myocardial Vo₂ (at 37°C) for Different Work and Electrical Conditions** (Ref 1)

<table>
<thead>
<tr>
<th>Condition</th>
<th>VO₂ (ml/100g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beating (full, perfused)</td>
<td>10.0</td>
</tr>
<tr>
<td>Beating (empty, perfused)</td>
<td>5.5</td>
</tr>
<tr>
<td>Fibrillating (empty,perfused)</td>
<td>6.5</td>
</tr>
<tr>
<td>K⁺ cardioplegia (empty, x-clamp)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

- Total body consumption at 28°C is decreased by 50–60% and at 18°C by 85–90%.
- Normothermic flow rates for adults (2.2 – 2.5 l/min/m²) can be decreased to 1.6 – 2.2 l/min/m², if systemic temperature is decreased to < 28°C.
Influence of Temperature on Myocardial Vo2 for Different Work and Electrical Conditions  (Ref 1)

<table>
<thead>
<tr>
<th></th>
<th>MYOC VO2 (ml / 100g min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37°C</td>
</tr>
<tr>
<td>Beating (empty)</td>
<td>5.5</td>
</tr>
<tr>
<td>Fibrillating (empty)</td>
<td>6.5</td>
</tr>
<tr>
<td>K+ Cardioplegia</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Advantages and Disadvantages of Systemic Hypothermia  (Ref 7)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑es safe circulatory arrest time:</td>
<td>Lt shift of oxyHb dissociation curve</td>
</tr>
<tr>
<td>- 3-5 min @ 37°C</td>
<td>- Less O2 released at lower temps.</td>
</tr>
<tr>
<td>- 10-15 min @ 28°C</td>
<td>(but there is ↑ dissolved plasma O2)</td>
</tr>
<tr>
<td>- 45-60 min @ 18 – 20°C</td>
<td>* Optimize PO2:250mmHg (30-35kPa)</td>
</tr>
<tr>
<td>CPB flow rates can be ↓ed:</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>↓ non-coronary collateral flow prevents</td>
<td>- ↑ SVR and Pulm VR</td>
</tr>
<tr>
<td>- Obscuring of the operative field</td>
<td>- Coronary vasoconstriction</td>
</tr>
<tr>
<td>- Rewarming the myocardium</td>
<td>- ↓ coronary autoregulation</td>
</tr>
<tr>
<td>↓ pump- oxygenator induced damage</td>
<td>* Maintain adequate perfusion pressure</td>
</tr>
<tr>
<td>Helps maintain myoc hypothermia</td>
<td>↑ blood viscosity</td>
</tr>
<tr>
<td>- ↓ conducted from adjacent organs</td>
<td>* Haemodilute at hypothermia (aim for HCT 0.2 – 0.25 @ 25°C)</td>
</tr>
<tr>
<td>- ↓ heat gain from systemic perfusate</td>
<td>Positive inotropic effect</td>
</tr>
<tr>
<td></td>
<td>- Due to ↑ IC Ca^{2+}</td>
</tr>
<tr>
<td></td>
<td>Change in pH of neutrality</td>
</tr>
<tr>
<td></td>
<td>* α stat pH management</td>
</tr>
<tr>
<td></td>
<td>Inhibition of insulin release</td>
</tr>
<tr>
<td></td>
<td>↑ time taken to rewarm pt intraop (↑ CPB time):</td>
</tr>
<tr>
<td></td>
<td>- ‘After-drop’ Following adequate rewarming</td>
</tr>
<tr>
<td></td>
<td>* Pharmacologic vasodilation during rewarming.</td>
</tr>
<tr>
<td></td>
<td>↑ VO2 by shivering postop.</td>
</tr>
<tr>
<td></td>
<td>* ?Neuromuscular blockade</td>
</tr>
</tbody>
</table>

* Measures suggested to prevent deleterious effects of hypothermia.

- Note: The temperature difference between the blood entering the patient and the patient’s actual temperature, should not be >10-14°C during systemic cooling, in order to prevent bubbles coming out of solution. (Well oxygenated cooled blood is rapidly warmed on contacting the warmer body.)
- Maintenance of uniform myocardial hypothermia is essential throughout the x-clamp period to preserve energy. This is best achieved through:
  - Maintenance of systemic hypothermia,
  - Infusion of multidose cold (4°C) cardioplegic solutions,
  - Topical myocardial hypothermia, and
  - Use of Lt Ventricular vent, with the accumulation of warm systemic blood in the heart.

IV) MYOCARDIAL PROTECTION DURING AORTIC X-CLAMP:

- The attraction to the surgeon of immobile, bloodless coronary arteries obtained with CPB and aortic x-clamp is obvious.
- The objectives of the surgeon utilizing a x-clamp are:
  - A still, bloodless field.
  - The heart is soft and can be retracted more easily.
  - Microvascular anastomoses can be more accurately constructed.
  - Cerebral air embolism can be prevented.
  - Certain cardiac abnormalities can only be corrected with prolonged x-clamping of the aorta.
- The most widely used method of arresting myocardial electrical activity is the administration of K⁺-rich crystalloid or blood.
- Numerous cardioplegic techniques have evolved to protect the myocardium from the effects of global ischaemia.
- Broadly there are varieties of crystalloid solutions, or blood with various additives, designed to induce and maintain safe cardiac arrest.
- Ongoing attempts to improve the efficacy of cardioplegia represents efforts to attenuate ischaemia–reperfusion injury:
  - Eg:
    - Manipulating tonicity to attenuate cellular swelling,
    - Altering buffering capacity to decrease acidosis,
    - Optimizing Ca²⁺ levels to limit IC Ca²⁺ overload, yet maintain contractile function, and
    - Adding free radical scavengers to decrease oxyradical injury.
- Although these are important and ongoing areas of study, the original rationale for using cardioplegic solutions was based on the profound influence of:
  - Diastolic arrest (vs a beating heart).
  - Temperature, and a full vs empty heart, on myocardial O₂ requirements.
Therefore, diastolic arrest, by increasing extracellular K⁺, making repolarization impossible, preserves energy and prevents expenditure.

Diastolic arrest can be produced pharmacologically by a number of mechanisms, but only 5 primary mechanisms are used in present cardioplegic solutions, either singly or in combination:

- High concentration of K⁺ or Mg²⁺ (Prevent efflux during repolarization.)
- Depletion of extracellular Ca²⁺ or Na⁺ (Prevent Na⁺/Ca²⁺ influx at depolarization).
- Local anaesthetic agents ie. Lignocaine / Prilocaine.

- Profound myocardial hypothermia used in conjunction with cardioplegic arrest further decreases basal metabolism, assists in maintaining electromechanical arrest and provides additional myocardial protection.

**Delivery of Cardioplegic Solutions:**

- In order to obtain optimal myocardial protection during the aortic x-clamp period, of importance is:
  - Composition of cardioplegic solution,
  - Ensuring uniform delivery of the solution, and
  - Maintenance of cardioplegic arrest.

- While delivery of these solutions is the domain of perfusionists, of importance in cardiac protection is vigilance with respect to pressures used to deliver the solution.
Moreover, cardioplegia can be delivered antegrade or retrograde, or in combination, and through saphenous vein grafts after the completion of distal anastomoses.

**Mechanism of Action of Cardioplegia:**

- Following initiation of CPB, induction of hypothermia, and aortic x-clamping, the coronary circulation is perfused with cold cardioplegia. The resulting increase in extracellular \([K^+]\) decreases the transmembrane potential. This progressively interferes with the normal \(Na^+\) current during depolarization, decreasing the rate of rise, amplitude and conduction velocity of subsequent action potentials.
- Eventually the \(Na^+\) channels are completely inactivated, AP’s are abolished and the heart is arrested in diastole.
- Usually cold cardioplegia must be repeated several times (about every 30 min), because of gradual washout and rewarming of the myocardium.
- Washout occurs as a result of the persistence of non-collateral coronary blood flow derived from pericardial vessels, which are branches of intercostal arteries.
- Moreover, multiple doses of cardioplegia may improve myocardial preservation by preventing the excessive build-up of metabolites that inhibit anaerobic metabolism.
- Preferential warming of the posterior ventricular wall can also occur as a result of direct contact with warmer blood in the descending aorta.
- Although exact composition of cardioplegia varies from centre to centre, the essential composition is the same:

  - **K**\(^+\) 10–40 meq/l – \([K^+]\) kept below 40meq/l because higher levels can be associated with a paradoxical increase in myocardial energy requirements and excessive \(K^+\) loads.
  - **[Na\(^+\)] < plasma [Na\(^+\)] (< 140 meq/l) -** because ischaemia tends to increase intracellular \(Na^+\) content.
  - Small amount of \(Ca^{2+}\) (0.7–1.2 mmol/l) is needed to maintain cellular integrity.
  - **Mg\(^{2+}\) (1.5–15 mmol/l) -** usually added to control excessive intracellular influxes of \(Ca^{2+}\).
  - **A buffer -** Most commonly Bicarbonate - necessary to prevent excessive buildup of acid metabolites. Alternative buffers include Histidine and Tromethamine (aka THAM)
  - **Other components may include:**
    - Procaine, Hypertonic agents to control cellular oedema (Mannitol).
    - Lignocaine or Glucocorticoids (for their membrane-stabilizing effect).
    - Energy substrates are provided as glucose, glutamate or aspartate.
Antegrade vs Retrograde Cardioplegia:

- **Antegrade Cardioplegia:**
  - The perfusion pressure should be 80–100 mmHg.
  - Excessive perfusion pressures will injure the endothelium, but higher pressures may be needed in the presence of CAD (130mmHg).
  - A lower pressure of 50 mmHg is recommended during maintenance reinfusions in the arrested heart - prevents the formation of oedema.

- **Retrograde Cardioplegia:**
  - The solution is delivered via the Rt Atrium or Coronary Sinus in the presence of coronary artery stenoses.
  - Venous injury is prevented provided infusion pressures never exceed 50mmHg.
  - Retrograde cardioplegia is technically more difficult, should be delivered at low pressures, does not necessarily deliver cardioplegia to the same capillary bed as antegrade cardioplegia does, and may be the victim of variable venous anatomy, eg. The Lt SVC draining into the coronary sinus, or the tip of the cardioplegia cannula proximal to the great cardiac vein.
  - Nevertheless, it may be the preferred technique in Aortic Regurgitation or severe coronary obstruction.

  - Sanjay et al from St John’s Medical College Hospital in Bangalore evaluated the effects of antegrade vs antegrade with retrograde delivery of cardioplegic solutions in a prospective study of 60 patients who underwent myocardial revascularization.
  - All patients had triple vessel disease.
  - Myocardial protection consisted of the administration of St.Thomas Hospital Cardioplegic Solution, topical slushed ice and systemic hypothermia (28 – 30°C).
  - They concluded that the use of a combined antegrade and retrograde technique facilitates early recovery of Lt ventricular function after CABG.

- **Crystalloid vs Colloid:**
  - The question of whether to use crystalloid or blood as a vehicle for achieving cardioplegia remains somewhat controversial.
  - Evidence suggests that at least some groups of high-risk patients may do better with blood cardioplegia.
  - Certainly, oxygenated blood cardioplegia has the added benefit of delivering more O₂ than crystalloid cardioplegia.
  - Several recent studies have demonstrated either the superiority of blood over crystalloid, or failed to show a difference between them.
Intuitively we would predict that in patients with well-perfused myocardial function who are subjected to less protected and complex procedures, the type and route of cardioplegia delivery would probably make little difference. The converse may be true.

- In 2 studies by Ibrahim et al in 1999, it was illustrated that in patients with well preserved myocardial function, the type of cardioplegia made no difference, as assessed by the magnitude of enzyme leak.
- In contrast, in patients with EF < 40%, blood cardioplegia was superior to crystalloid as determined by enzyme leak, function parameters and conduction abnormalities.

**Multidose Cardioplegia:**

Intermittent re-infusions of cardioplegic solutions:

- Corrects metabolic acidosis
- Washes out lactate,
- Allows reactivation of glycolysis.
- Continuous myocardial rewarming and washout of cardioplegia by non-coronary flow is counteracted.
- Metabolic end-products are removed, and
- Substrates resupplied to the myocardium.

**V) REPERFUSION OF THE ISCHAEMIC MYOCARDIUM:**

- Reperfusion should be controlled at a lower pressure (<50mmHg) which prevents oedema formation, decreases endothelial cell damage and improves recovery, and should in addition be pulsatile.
- Premixed solutions (eg. THAM) are mixed in a 4:1 ratio with blood and infused in place of cardioplegic solution just prior to the release of the aortic x-clamp.
- In the early post-ischaemic period, haemodynamic stresses should be avoided.
- Allowing the heart to remain asystolic in the immediate reperfusion period is beneficial by preventing energy from being “wasted” on electromechanical contraction, provided ventricular distention does not occur.
- Thereafter, while remaining on CPB, myocardial energy demands should be maintained as low as possible, in order to allow available energy to be channelled to reparative processes.
- The heart should be allowed to beat in a non–working state (not ejecting), which decreases O₂ demand by more than 40%, while perfusion pressure, venous volume, Temperature, metabolic and electrolyte components and oxygenation are optimized.
- A period of 15–30 min of optimal reperfusion Following the release of the x-clamp should be allowed prior to introducing inotropic agents, as premature use
of Ca$^{2+}$ and inotropic agents accentuates myocardial damage and impairs functional recovery.
- HR should first be optimized with external pacemakers, and preload and afterload optimized by the use of volume expanders and vasodilators.

**Postoperative Considerations:***
- Cardiac protection extends into the postop period.
- All patients undergoing cardiac surgery will be admitted to a postop ICU.
- Protective measures incl:
  - Appropriate lung protective ventilatory strategies
  - Ensuring all parameters affecting O$_2$ delivery are optimized (SPO$_2$, Hb, PaO$_2$, CO).
  - Optimising rate, rhythm, contractility, preload and afterload - are essential to maintaining a favourable supply:demand ratio.
  - GIK infusions, monitoring for ongoing/new ischaemia and pain management, are all important in the continuation of “cardiac and organ protection” into the postop period.
  - Intra-aortic Balloon Pump Counter Pulsation should be considered in most patients who have pre-existing poor LV function or those with persistent poor LV function post surgery. This will assist in increasing myocardial energy supply and decreasing myocardial energy demand.

**CONCLUSION**
- It is important to identify and eliminate those agents causing harm or preventing good.
- ‘However, meticulous anaesthesia, understanding, application and manipulation of physiological variables through using tried and tested drugs, and incorporating proven protective techniques that are most often not unique to the heart, but beneficial to most organ systems and the patient as a whole, ensure that cardiac “protection” is actually the practice of good medicine.’

  ‘Lasersohn’
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