Myocardial Protection

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Outline

- Introduction
- History
- Ischemia-Reperfusion Injury
- Non-Cardioplegic Techniques
- Cardioplegic Techniques
- Measuring pH and Efficacy of Protection
- Protection Strategies Under Investigation
Introduction
Myocardial Protection

- Involves strategies and methods used to reduce or prevent post-ischemic myocardial dysfunction during and after heart surgery

- Post-ischemic myocardial dysfunction ➔ ischemia-reperfusion induced injury
  - Manifests by low cardiac output and hypotension
Introduction

- Subdivided into two groups:
  - Reversible injury
  - Irreversible injury

- Groups are differentiated by:
  - Presence of EKG abnormalities
  - Elevations in specific enzymes (CK, troponin)
  - Presence of regional or global echocardiographic wall motion abnormalities
Introduction

- For CABG alone…
  - ~5% of patients may develop MI, severe ventricular dysfunction, heart failure, and/or death despite advances in surgical technique
  - Enormous impact on families and society
  - Initial hospital cost of CABG is ~$10 billion/year
  - Complications after CABG additional ~$2 billion/year
History
1950s

- Evolution of strategies ongoing over last 60 years

- 1950 – Bigelow et al. *Ann Surg.* on Hypothermia:
  - “A form of anesthetic” that could be used to expand the scope of surgery
  - Could be used as “a technique that might permit surgeons to operate on the bloodless heart without recourse to extracorporeal pumps and perhaps allotransplantation of organs.”
Hypothermia
1950s


- Reported method of stopping heart
- Injected potassium citrate into root of aorta at both normal and reduced body temperatures
- Potassium citrate concentration \( \sim 100 \text{ mmol/L} \)

Potassium citrate method was adopted by many centers

Interest waned when groups reported that potassium citrate arrest was associated with myocardial injury and necrosis
1950-60s

- Shortly thereafter, cardiac surgeons shifted to:
  1. Normothermic cardiac ischemia
     - Normothermic heart surgery performed with the aorta occluded while patient was on cardiopulmonary bypass
  2. Intermittent aortic occlusion
  3. Coronary artery perfusion

- Normothermic cardiac ischemia
  - Associated with metabolic acidosis, hypotension, and low cardiac output

Surgeons that got away with these strategies were FAST!
1970s

- Interest was renewed in discovering ways to achieve cardiac arrest

  - Cardiac arrest with low-sodium, calcium-free soln
1970s

  - Studied various components of cardioplegic solutions
  - Developed St. Thomas solution
    - Composition based on Ringer’s lactate soln + potassium chloride (16 mmol/L) and magnesium chloride (16 mmol/L)
1970s

  - Lower concentrations of potassium chloride could achieve chemical arrest and myocardial protection without associated myocardial necrosis reported earlier
  - Key paper: Proved why Melrose soln didn’t work

- 1977 – Roe *et al.* *JTCVS.*
  - Reported operative mortality of 5.4% for patients undergoing potassium-induced arrest as primary form of myocardial protection
1970-80s

- 1977 – Tyers *et al.* *JTCVS*.  
  - Reported that potassium cardioplegia provided *satisfactory protection in over 100 consecutive cardiac patients*

- 1980s – Normothermic aortic occlusion (for the most part) had been *replaced with cardioplegia to protect the heart during cardiac surgery*
Major Controversy

What are the ideal components of the solns?

Chief variants:

- Bretschneider → consisting of sodium, magnesium, and procaine (membrane stabilizer and antiarrhythmic)
- St. Thomas → consisting of potassium, magnesium, and procaine added to LR
- Potassium-enriched solns without magnesium or procaine
To complicate matters...

- Another variant → BLOOD CARDIOPLEGIA
  - Blood would be a superior delivery vehicle based on oxygenating and buffering capacity
    - 1978 – Follette et al. *JTCVS*
    - 1979 – Buckberg. *JTCVS*

Buffering – not so much oxygenation – is what makes blood cardioplegia useful.

Ironically, Melrose *et al.* had used blood as a vehicle to deliver potassium citrate more than 20 years earlier!
Today...

- Hypothermia and potassium infusions remain cornerstone of myocardial protection during on-pump heart surgery.

- Other cardioprotective techniques and methods are available.

- Ideal cardioprotective technique, solution, and method of administration have yet to be found.

- Fortunately, majority of strategies allow patients to undergo operations with an operative mortality rate of less than 2-4%. 
Ischemia-Reperfusion Injury
Ischemia-Reperfusion Injury

- Occurs as result of attenuation or cessation of coronary blood flow

- Oxygen delivery to myocardium is insufficient to meet basal myocardial oxygen requirements

- May induce reversible or irreversible cellular injury
Ischemia-Reperfusion Injury

- Reversible injury is manifested as stunning or hibernation

- Irreversible injury is manifested as necrosis or apoptosis

- Stunning:
  - Mechanical dysfunction that persists after reperfusion
  - Despite absence of myocellular damage
  - Despite return of normal or near-normal perfusion
Ischemia-Reperfusion Injury

- Hibernation:
  - Syndrome of reversible, chronically reduced contractile function
  - Result of one or more recurrent episodes of acute or persistent ischemia (referred to as chronic stunning)
  - Hibernating myocardium is viable but not functional, and is reversible with coronary revascularization.
Ischemia-Reperfusion Injury

- All patients undergoing cardiac surgery have varying degrees of myocardial stunning

- Evidence
  - Requirement of inotropic support for separation from bypass
  - Support may last from hours to days after surgery
  - Patients are eventually weaned from these drugs as the stunning abates, without objective evidence of MI
Ischemia-Reperfusion Injury
Calcium Hypothesis

- Inability of myocyte to modulate intracellular and intraorganellar calcium homeostasis

- Cascade of events culminating in cell injury and death is induced
Calcium

- Inotropic agent

- If given as patients come off of bypass, it can lead to contracture of heart (maximally contracted heart)

- Therefore, it is desirable to avoid calcium when heart is recovering from arrest
Free Radical Hypothesis

- Accumulation of reactive oxygen species (ROS) – during early stages of reperfusion – causes myocardial cellular damage and cell death through microsomal peroxidation of cellular phospholipid layer

- Leads to loss of cellular integrity and function
Ischemia-Reperfusion Injury

Diagram showing the process of ischemia and reperfusion, including key physiological changes such as calcium and pH levels, leading to reversible and irreversible injuries with associated outcomes like hibernation, stunning, necrosis, and apoptosis.
Non-Cardioplegic Techniques

Advantageous to surgeons who were fast! (Cooley reportedly only poured a bucket of ice water on the heart and went to work…)
Intermittent Cross-Clamping with Fibrillation and Moderate Hypothermic Perfusion (32° to 36°)

- CABG can be performed on unarrested heart with:
  - ascending aorta cannulation
  - two-stage single venous cannula
Intermittent Cross-Clamping with Fibrillation and Moderate Hypothermic Perfusion (32° to 36°)

- During fibrillation, distal anastomoses are performed.

- After completion of last distal graft, heart is defibrillated, and proximal graft anastomoses are created with a beating heart using partial occlusion clamp

Not preferable because without a single-clamp technique, risk of stroke increases dramatically.
Intermittent Cross-Clamping with Fibrillation and Moderate Hypothermic Perfusion (32° to 36°)

- 1992 – Bonchek et al. JTCVS.
  - 3000 pts undergoing CABG with technique
    - 29% > 70 years, 27% women, 9.7% had EF < 30%, 13% had MI 1 week pre-op, 31% had pre-infarction angina in hospital.
    - 26% were purely elective.
  - Operative mortality: elective 0.5%, urgent 1.7%, emergency 2.3%
  - Postop inotropc support used in 6.6% of patients
  - 1% used IABP
Intermittent Cross-Clamping with Fibrillation and Moderate Hypothenmic Perfusion (32° to 36°)

  - 800 consecutive CABG operations
  - Mean age | # of distal grafts | mortality
    - Elective: 61.5 years, 3.2 grafts, 0.6%
    - Urgent: 63.1 years, 3.2 grafts, and 3.1%
    - Emergent: 63.8 years, 2.9 grafts, and 5.6%

- Technique is safe and effective in elective and non-elective patients
Systemic Hypothermia and Elective Fibrillatory Arrest

- For protection during CABG, mainstays are:
  - Systemic hypothermia (28 °C)
  - Elective fibrillatory arrest
  - Maintenance of systemic perfusion pressure at 80-100 mm Hg

- On fibrillatory arrest, vessel is isolated and anastomosis is performed
Systemic Hypothermia and Elective Fibrillatory Arrest

- Limitations of technique:
  - Not applicable for intracardiac procedures
  - Field may be obscured by blood during revascularization
  - Ventricular fibrillation is associated with increased muscular tone (can limit surgeon’s ability to position the heart for optimal exposure)
Cardioplegic Techniques
Methods of Delivery

- Intermittent antegrade
- Antegrade via the coronary bypass grafts
- Continuous antegrade
- Continuous retrograde
- Intermittent retrograde
- Antegrade followed by retrograde
- Simultaneous antegrade and retrograde
Retrograde Perfusion


- Reported use of retrograde perfusion to protect heart during aortic valve surgery
Retrograde Perfusion

Pros:

- Advantage of ensuring a more homogeneous distribution of cardioplegic solution to regions of heart that are poorly collateralized

- Effective in setting of AR and valve surgery

- Effective in reducing risk of embolization from SVGs that could occur during antegrade perfusion during re-op CABG

- Effective in delivering cardioplegia in continuous manner
Retrograde Perfusion

Limitations:

- Soln can be poorly distributed to the right ventricle due to the variable venous anatomy of the heart
- Best and most continuous perfusion of the anterior left and right ventricles is achieved using antegrade and retrograde routes simultaneously
Cardioplegic Solutions

Crystalloid Cardioplegia

Cold

Blood Cardioplegia

Cold

Warm

Tepid
Cold Crystalloid Cardioplegia
Cold Crystalloid Cardioplegia

- Patients are first placed on CPB
- Cooled to between 28-33 °C
- Soln infused after cross-clamping aorta through cardioplegic catheter inserted into aorta proximal to cross-clamp
Cold Crystalloid Cardioplegia

- Cold hyperkalemic soln is infused (antegrade) up to 1000 mL

- One or more infusions of 300-500 mL of soln may be given if:
  - there is evidence of electrical activity resumption
  - if prolonged ischemic time is anticipated
Cold Crystalloid Cardioplegia

- If CABG is performed:
  - Aortic cross-clamp can be removed after completing distal anastomoses
    - Heart can be reperfused while proximal anastomoses are completed using partial occlusion clamp
  - OR, proximal grafts can be performed after distal grafts have been completed with cross-clamp still in place (single-clamp technique)
Cold Crystalloid Cardioplegia

- If CABG is performed (cont’d):
  - OR, perform proximal anastomoses first, then cross-clamp aorta and infuse soln

- For valve repair/replacement:
  - Soln can be instilled directly into coronary arteries via cannulation of ostia or retrograde via coronary sinus catheter
Cold Crystalloid Cardioplegia

- Results

  - Controversy exists about “ideal” soln
  - Excellent myocardial protection can be achieved
  - Perioperative MI rate is < 4%
  - Operative mortality rate is < 2%
Cold Blood Cardioplegia
Cold Blood Cardioplegia

- Technique most commonly used in US today

- Prepared by combining autologous blood from extracorporeal circuit (while patient is on CPB) with a crystalloid soln of:
  - citrate-phosphate-dextrose (CPD) \( \rightarrow \) lowers ionic calcium
  - tris-hydroxymethyl-aminomethane (tham) or bicarbonate buffers \( \rightarrow \) maintains alkaline pH of \( \sim 7.8 \)

  pH = 7.4 is physiologic, but pH is temp dependent, and optimal buffering occurs when pKa is 7.8.

- potassium chloride \( \rightarrow \) arrests heart at 30 mmol/L
Cold Blood Cardioplegia

- Soln characteristics:
  - Temperature 4-12 °C
  - Ratio of blood-to-crystalloid can vary

- If hematocrit of blood is 30:
  - 8:1 ratio $\rightarrow$ Hct 27
  - 4:1 ratio $\rightarrow$ Hct 24
  - 2:1 ratio $\rightarrow$ Hct 20

4:1 ratio is used at BMC
Using blood...

- Reasons to use blood for hypothermic potassium-induced cardiac arrest:
  - Provides oxygenated environment
  - Provides method for intermittent reoxygenation of heart during arrest
  - Can limit hemodilution when large volumes of cardioplegia are used
  - Has excellent buffering capacity
Using blood…

- Reasons to use blood for hypothermic potassium-induced cardiac arrest:
  - Has excellent osmotic properties
  - The electrolyte composition and pH are physiologic
  - Contains endogenous antioxidants and free-radical scavengers
  - Is less complex than other solns to prepare
Warm Blood Cardioplegia
Warm Blood Cardioplegia

- Concept introduced in 1980s

  - In canines
  - Warm induction with normothermic blood cardioplegia – with multidose cold blood cardioplegia for maintenance of arrest – led to better recovery of function than using cold blood induction
Warm Blood Cardioplegia

1986 – Teoh et al. *JTCVS*.
- Terminal infusion of warm blood cardioplegia before removing cross-clamp (“hot shot”) accelerated myocardial metabolic recovery.

1991 – Lichtenstein et al. *JTCVS*
- 121 consecutive patients who received antegrade normothermic blood cardioplegia during MR operations compared to 133 pts who received antegrade hypothermic cold blood cardioplegia
- Operative mortality: warm 0.9%, cold (historical) 2.2%
Warm Blood Cardioplegia

  - 113 consecutive patients
  - Warm blood cardioplegia administered via coronary sinus
  - 96% had spontaneous return of rhythm on reperfusion
  - 7% needed transient IABP circulatory support
  - 6% had evidence of perioperative MI
  - 3% did not recover
Warm Blood Cardioplegia

- Still concerns abound with approach
  - Unclear how long warm heart will tolerate an ischemic event
    - When infusion is interrupted, flow rates are reduced, or soln is not distributed evenly
  - Warm blood cardioplegia is associated with increased incidence of neurologic deficits
    - Up to three-fold higher when compared with cold crystalloid cardioplegia
Tepid Blood Cardioplegia
Tepid Blood Cardioplegia

- Both cold blood and warm blood solns have temperature related advantages and disadvantages

  - 72 patients undergoing CABG randomized to receive blood cardioplegia:
    - Cold (8 °C) antegrade or retrograde
    - Tepid (29 °C) antegrade or retrograde
    - Warm (37 °C) antegrade or retrograde
Tepid Blood Cardioplegia


- Protection was adequate for all three groups
- Tepid antegrade cardioplegia was most effective in reducing anaerobic lactic acid release during arrest period

Other studies have demonstrated that tepid blood cardioplegia is safe and effective

No studies exist to determine if it is better than any other strategy
Measuring pH and Efficacy of Protection
Clinical Surgery-American

Impact of intraoperative myocardial tissue acidosis on postoperative adverse outcomes and cost of care for patients undergoing prolonged aortic clamping during cardiopulmonary bypass

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Measuring pH and Efficacy of Protection

- 162 patients with cross-clamp time of 119 minutes or longer
  - 100 pts underwent valve + CABG
  - 22 pts underwent valve surgery
  - 17 pts underwent CABG alone
  - 23 pts underwent reoperations

- Impact of intraoperative myocardial acidosis and adverse post-op outcomes on cost of cardiac surgical care assessed
**Discussion Notes:**

pH determination is useful, but did not become mainstream.

Utility of temp monitoring of myocardium is key because you can infuse >1000cc of cardioplegia without a significant drop in temp in patients with left main dz, significant CAD, or hypertrophy.

Tx by giving more cardioplegia.
<table>
<thead>
<tr>
<th></th>
<th>Adverse event and/or death</th>
<th>n = 46</th>
<th>No adverse event or death</th>
<th>n = 101</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69.7 ± 6.9</td>
<td>45</td>
<td>70.3 ± 9.3</td>
<td>99</td>
<td>.7101</td>
</tr>
<tr>
<td>Preoperative EF, %</td>
<td>48.9 ± 13.0</td>
<td>44</td>
<td>50.1 ± 11.9</td>
<td>98</td>
<td>.5825</td>
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<tr>
<td>Cardioplegia given, mL</td>
<td>5,268.0 ± 4,882.4</td>
<td>42</td>
<td>5,083.8 ± 5,601.5</td>
<td>98</td>
<td>.8515</td>
</tr>
<tr>
<td>XC time, min</td>
<td>161.8 ± 32.7</td>
<td>45</td>
<td>148.4 ± 29.2</td>
<td>99</td>
<td>.0143</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>265.7 ± 89.2</td>
<td>45</td>
<td>212.9 ± 45.8</td>
<td>99</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean pH&lt;sub&gt;37°C&lt;/sub&gt; during XC</td>
<td>6.95 ± .31</td>
<td>45</td>
<td>6.30 ± .31</td>
<td>99</td>
<td>.0510</td>
</tr>
<tr>
<td>pH&lt;sub&gt;37°C&lt;/sub&gt; at 10 minutes of reperfusion</td>
<td>6.66 ± .40</td>
<td>38</td>
<td>6.83 ± .30</td>
<td>93</td>
<td>.0167</td>
</tr>
<tr>
<td>pH&lt;sub&gt;37°C&lt;/sub&gt; at end of reperfusion</td>
<td>6.85 ± .36</td>
<td>41</td>
<td>6.98 ± .31</td>
<td>97</td>
<td>.0359</td>
</tr>
<tr>
<td>No. of surgical service days</td>
<td>21.3 ± 14.8</td>
<td>12</td>
<td>12.3 ± 6.0</td>
<td>45</td>
<td>.0018</td>
</tr>
<tr>
<td>No. of hospital days</td>
<td>26.5 ± 20.6</td>
<td>12</td>
<td>15.9 ± 9.5</td>
<td>45</td>
<td>.0118</td>
</tr>
<tr>
<td>Surgical service cost</td>
<td>$93,595 ± $43,491 ($93,163)</td>
<td>12</td>
<td>$44,806 ± $13,136 ($41,273)</td>
<td>45</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total hospital cost</td>
<td>$119,376 ± $70,578 ($95,685)</td>
<td>12</td>
<td>$56,723 ± $19,137 ($52,856)</td>
<td>45</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, cost data are expressed as mean ± SD (median).

EF = ejection fraction; CPB = cardiopulmonary bypass.
Strategies Under Investigation
Strategies Under Investigation

- Ischemic Preconditioning
- Remote Preconditioning
- Postconditioning
- Sodium-Hydrogen Exchange Inhibition
- Molecular Manipulation
Ischemic Preconditioning

- Adaptive biologic phenomenon

- Heart becomes more tolerant to a period of prolonged ischemia if it is first exposed to prior episode of brief ischemia (3-5 min) and reperfusion

- Increased tolerance to ischemia is associated with a reduction in infarct size, apoptosis, and reperfusion-associated arrhythmias
Ischemic Preconditioning

- After acute phase of preconditioning disappears, 2\textsuperscript{nd} phase of protection appears 24 hours later and is sustained for up to 72 hours

- “Late-phase preconditioning” or “Delayed preconditioning”

- Protects against BOTH infarction and myocardial stunning

- Applicability of ischemic preconditioning as adjunct to conventional cardioplegia remains to be determined
Remote Preconditioning

- Transient ischemia and reperfusion in an organ remote from the heart (i.e. extremities)

- Demonstrated to protect the heart after surgically induced myocardial ischemia in both children and adults
  - Decreases postop serum troponin T release by protecting mitochondria

- Mechanisms conferring cardioprotection are believed to involve neural and humoral pathways, or systemic responses that interact with known IPC effectors
Postconditioning

- Consists of repeated ischemia and reperfusion episodes, resulting in an interrupted or stuttering reperfusion that improves the effects of reperfusion injury

- Mechanisms still under investigation, but appear similar to IPC

- Efficacy is questionable
Sodium-Hydrogen Exchangers

- Play a central role in regulation of intracellular sodium and calcium concentrations, pH homeostasis, and volume regulation

- Facilitate exchange of intracellular hydrogen ions for extracellular sodium ions across cell membrane
Sodium-Hydrogen Exchangers

- Normally, sodium-calcium exchanger moves calcium out of cell to maintain normal intracellular $[\text{Ca}^{2+}]$.

- During ischemia, intracellular $[\text{Na}^+]$ accumulates because of inactivation of ATP dependent Na-K exchanger.
Sodium-Hydrogen Exchangers

- Increased intracellular \([\text{Na}^+]\) slows Na-Ca exchanger, increasing \([\text{Ca}^{2+}]\)

- Inhibiting sodium-hydrogen exchanger decreases intracellular \([\text{Na}^+]\), and thus decreases intracellular \([\text{Ca}^{2+}]\) and is cardioprotective
Sodium-Hydrogen Exchangers

- Administration of sodium-hydrogen pump antagonists before ischemia or both before ischemia and during reperfusions:
  - Shown to provide significantly greater cardioprotection compared with administration during reperfusion alone.
Molecular Manipulation

- **During normal temporal development of myocardium**
  - There is phenotypic induction, expression, and synthesis of a defined number of genes

- **During stress, disease, and induction resulting from insults:**
  - There is adaptive remodulation of gene synthesis often not initially apparent at gross anatomic or histologic level.
Molecular Manipulation

- Recent advantages in gene-based technologies allow these events and altered genes and gene products to be identified.
- May aid in new therapeutic interventions.
- Apoptosis inhibitors represent a potential therapeutic approach to limit cell death.
  - Apoptosis has been partially alleviated under experimental conditions.
  - Not in studies involving humans.
A few final notes…
Know Myocardial Protection Strategies for Managing the Following Scenarios

- Diffuse CAD with proximal stenotic disease
- Hypertrophic heart
- Aortic regurgitation
- Anomalous venous return (such as persistent left SVC)
Maximum tolerable cross-clamp time for heart surgery

- No more than 180 minutes (3 hours)!!!
Great Equalizers in Cardiac Surgery
Among Fast and Slow Surgeons

- Cardioplegia

- Intra-aortic balloon pump circulatory support
Myocardial Protection

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