Myocardial Protection Principles

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Optimal conditions for cardiac surgery?

The ideal conditions required by a surgeon for a successful heart operation:

♥ bloodless field (good visualisation)

♥ non-beating heart (for operative ease)

These conditions can most easily be achieved by global ischemia
Ischemia causes myocardial injury

Onset of severe ischemia
- Reduced oxygen availability
- Contractile failure
- Reduced creatine phosphate
- Cyanosis
- Cellular potassium loss
- Disturbance of transmembrane ion gradients
- Depolarisation
- Accumulation of $P_i$
- Stimulation of anaerobic metabolism
- Depletion of intracellular GSH
- Increased free radical production
- Accumulation of GSSG
- Accumulation of reactive oxidised lipids
- ATP depletion
- Lactate accumulation
- Acidosis
- Leakage of metabolites
- Metabolic imbalance
- Glycogen utilisation
- Cell swelling
  - Inhibition of anaerobic glycolysis
  - Opening of $K_{ATP}$ channels
- Cellular Ca accumulation
  - Stress protein translocation
  - Cytoskeletal reorganisation
  - Ultrastructural changes

Onset of irreversible damage
- Mitochondrial depolarisation
- Lysosomal activation
- Opening of mitochondrial PTP
- Severe cell swelling
- Membrane blebbing
- Cytoskeletal disruption
- Loss of membrane integrity
- Protein leakage
- Cell autolysis

Cell death and necrosis
Optimal conditions for Cardiac surgery?

The ideal conditions required by a surgeon for a successful heart operation:

- bloodless field (so surgeon can see)
- non-beating heart (for ease of operation)

These conditions can most easily be achieved by global ischemia.

Ischemia is convenient for surgeon but damaging for heart.

Cardiac surgeons needed a means of delaying the onset of irreversible myocardial injury during the elective ischemia that is induced to correct the lesion.

Many techniques tried, but most successful has been Cardioplegia.
Cardioplegia

ocardiac surgery (CPB)

elective, rapid and reversible paralysis of the heart during cardiac surgery (CPB)
Cardioplegic Solutions

Two basic types:

♥ ‘intracellular-type’
  low Na\(^+\), low or zero Ca\(^{2+}\), (high K\(^+\))
  (Bretschneider HTK solution (Custodiol), UW solution)

♥ ‘extracellular-type’
  moderate K\(^+\) elevation, normal Na\(^+\), normal Ca\(^{2+}\)
  (St Thomas’ Hospital solutions (STH1 and Plegisol [STH2]),
   Celsior solution, blood solutions [Buckberg])
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St Thomas’ Hospital: Concept for Effective Cardioplegic Protection

3 factors of importance:

♥ Induction of rapid chemical arrest
   conserve energy and provide a still operating field

♥ Hypothermia
   reduce the rate of metabolism

♥ Addition of anti-ischemic agents
   enhance protection by combating specific deleterious ischemia-induced changes
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#### St Thomas' Hospital Cardioplegic Solutions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration (mmol/l)</th>
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<tr>
<td></td>
<td>STH1</td>
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<tr>
<td>Sodium chloride</td>
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<tr>
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<tr>
<td>Magnesium chloride</td>
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<td>Calcium chloride</td>
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<td>Sodium bicarbonate</td>
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<td>Procaine hydrochloride</td>
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<tr>
<td>Osmolarity (mOsmol/l)</td>
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<tr>
<td>pH</td>
<td>5.5-7.0</td>
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</table>
Effect of Cardioplegic Protection

Cardiac surgery and myocardial protection

Recovery (%) vs Duration of Ischemia (Time)

- Cardioplegia
- Cardioplegia + treatment
- Ischemia
Historical developments!

- 1952-53 - 1st open heart operation/cardio-pulmonary bypass
- 1955-60 - concept of cardioplegia by elevated K⁺-arrest
- [1960s - concept of Na⁺ poor/Ca²⁺-depletion arrest: Bretschneider/HTK solution]
- 1973-75 - revival of elevated K⁺-arrest [lab studies]
- 1975 - St Thomas’ Hospital cold crystalloid K⁺-cardioplegia
- 1979 - cold blood K⁺-cardioplegia
- 1991 - warm blood K⁺-cardioplegia

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Historical developments!

- 1952-53 - 1st open heart operation/cardiopulmonary bypass

The basic concept of K\(^+\) arrest has been universal in cardiac surgery since mid-70’s ~ 35 years

These trends, although important, involve relatively minor changes.

- 1979 - cold blood K\(^+\)-cardioplegia
- 1991 - warm blood K\(^+\)-cardioplegia
The “Blue Book”
Published in 2009

n = 400,394 patients
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Crude survival and mortality rates by procedure (n=269,610)

- Isolated CABG
- All CABG
- Isolated valve
- CABG & valve

Crude mortality rate

2001 2002 2003 2004 2005 2006 2007 2008
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Rises in the numbers of elderly cardiac surgery patients (n=53,266)

- 76-80 years old
- 81-85 years old
- >85 years old

Financial year ending

Number of patients
Current practice is to operate on patients who are:

- Older, sicker with more diffuse and severe ischemic heart disease.
- Hypertrophy and heart failure.
- Rapid revascularisation after ACS/NSTEMI.
- Likely to have a reduced tolerance to ischemia/reperfusion (I/R) injury, and thus require enhanced protection.
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The Society for Cardiothoracic Surgery in Great Britain & Ireland
Sixth National Adult Cardiac Surgical Database Report

Isolated CABG: Crude mortality and age category (n=112,612)

- <56 years
- 56-60 years
- 61-65 years
- 66-70 years
- 71-75 years
- 76-80 years
- >80 years

Crude mortality rate

Financial year ending

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Relationship Between Postoperative Cardiac Troponin I Levels and Outcome of Cardiac Surgery

Bernard L. Croal, MB, ChB, MD; Graham S. Hillis, MB, ChB, PhD; Patrick H. Gibson, BM, BCh; Mohammed T. Fazal, MB, ChB; Hussein El-Shafei, MB, ChB, MD; George Gibson, MB, ChB; Robert R. Jeffrey, MB, ChB; Keith G. Buchan, MB, ChB; Douglas West, MB, ChB; Brian H. Cuthbertson, MB, ChB, MD

Circulation 2006; 14: 1468
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Current patients undergoing cardiac surgery

♥ These data suggest that increased myocardial injury during surgery has implications for post-operative mortality and morbidity.

♥ It is likely that inadequate myocardial protection (especially in the aged or high risk patient) is one of the factors that contribute to this increased myocardial injury!
Mechanism of $K^+$-based arrest?

Elevated extracellular $K^+$ concentration induces a ‘depolarisation’ of the resting membrane potential.
Excitation-Contraction Coupling and Targets for Arrest

-50mV (depolarised arrest)

- High $K^+_e$
- Fast Na$^+$ Channels
- SR
- L-type Ca$^{2+}$ Channels
- Cardiac myocyte

Action potential $E_m$ (mV)
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Principles of K⁺ Arrest: depolarisation

Calculated resting membrane potential ($E_m$)

Threshold potential for Ca channel activation

Threshold potential for Na channel inactivation

$STH2 = 16 \text{ mM } K^+$
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**Effect of elevated K$^+$ on membrane potential**

*5 h global ischemia (7.5°C)*

Membrane potential measured by sharp electrode during ischemia

![Graph showing the effect of elevated K$^+$ on membrane potential during ischemia. The graph plots resting membrane potential (mV) against ischemic duration (min). The data points indicate that 16 mM K$^+$ maintains a more negative membrane potential throughout the ischemic period compared to control.](image-url)

Snabaitis et al. Circulation 1997;96:3148
Ischemia and hypothermia inhibits Na/K-ATPase

Limitations of K^+-induced depolarised membrane potential

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- Na^+ window current
- K^+>>16mM
- Na/Ca exchange reverse mode
- Na^+/H^+ exchange
- K^+>>16mM
- Ca^2+ window current

Na^+ loading

Ca^2+ loading

Maintained energy (ATP) utilisation, contracture, reperfusion injury, cell death
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2013

– how can protection for all patients be optimised?
Polarised Arrest

Myocardial cell membrane potential is maintained at or near the resting membrane potential and leads to:

- balanced ionic gradients
- few channels or pumps activated
- little metabolic demand

❤ should lead to cardioprotection from cellular perspective

❤ should also attenuate adverse effects of I/R in higher risk patients
Excitation-Contraction Coupling and Targets for Arrest

-70mV (polarised arrest)

**Channels**
- L-type Ca$^{2+}$
- K$^+$
- Na$^+$
- Fast Na$^+$
- SR

**Drugs**
- TTX
- Lidocaine
- Procaine

Cardiac myocyte
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Effect of elevated K\(^+\) on membrane potential

5 h global ischemia (7.5°C)

Membrane potential measured by sharp electrode during ischemia

Snabaitis et al Circulation 1997;96:3148
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Depolarised vs polarised arrest

Isolated working rat hearts: 5h global ischemia (7.5°C)

Snabaitis et al. Circulation 1997;96:3148
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**Depolarised vs polarised arrest**

High-energy phosphate content at the end of ischemia (5h; 7.5°C)

- **KH (Control)**
- **Depolarised (K⁺: 16 mM)**
- **Polarised (TTX: 22µM)**

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Snabaitis et al Circulation 1997;96:3148
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Depolarised vs polarised arrest: 8h global ischemia (7.5°C)

Snabaitis et al JTCVS 1999;118:123
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Summary

♥ Polarised arrest can be achieved with a variety of agents that target the fast Na\(^+\)-channel [and the ATP-dependent K\(^+\)-channel].

♥ Compared to depolarised arrest, polarised arrest improved protection.
Excitation-Contraction Coupling and Targets for Arrest

-80 -60 -40 -20 0 +20

Action potential $E_m$ (mV)

Esmolol

L-type Ca$^{2+}$ Channels

K$^+$ Channels

Fast Na$^+$ Channels

Cardiac myocyte

SR

Ca$^{2+}$

Cardiac myocyte
Esmolol

♥ Ultra-short-acting cardioselective β-blocker: half-life ~9 min.
♥ Rapid systemic clearance: esterase hydrolysis.
♥ High concentrations (~1mM) induce arrest!
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Esmolol as Cardioplegic Agent: Dose-response

![Graph showing the effect of Esmolol concentration on atrial and ventricular rates and LVDP as a percentage of baseline value.](image)

Bessho and Chambers JTCVS 2001;122:993
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**Esmolol cardioplegia vs STH**

- Langendorff-perfused rat hearts
- Global (37°C) ischemia (40 min), multidose infusion - 2 min every 10 min

![Graph showing recovery of LVDP (%)](image)

- Control
- STH2
- EA (1mM)

*Bessho and Chambers JTCVS 2001;122:993*
Myocardial Protection Principles

**Esmolol Blood Cardioplegia vs STH**

- Langendorff-perfused rat hearts
- Global (37°C) ischemia (60 min), multidose infusion - 3 min every 15 min

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Myocardial Protection Principles

**Esmolol cardioplegia vs STH: Hypothermic (32°C) ischemia**

- Langendorff-perfused rat hearts
- Global (32°C) ischemia (multidose infusion - 3 min every 30 min)

![Graph showing LVDP recovery over ischemic time](image)

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Summary

♥ High-dose esmolol (1 mM) arrests the heart, and can be used as an effective cardioplegic agent with similar (at least) efficacy to St Thomas’ Hospital cardioplegia.

♥ Esmolol cardioplegia is effective when used as a blood cardioplegic solution, with improved protection compared to St Thomas’ Hospital cardioplegia.

♥ Esmolol cardioplegia is effective when used during hypothermic (32°C) ischemia. Extended infusion durations are effective, with improved protection compared to St Thomas’ Hospital cardioplegia.

♥ Esmolol cardioplegia may be an effective alternative to hypothermic K+-based cardioplegia.
Esmolol is an effective cardioplegic agent
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Esmolol Cardioplegia: Characterisation studies

- Isolated rat ventricular myocytes
- Voltage clamped using the ruptured patch technique
Esmolol dose-response on Ca-current in voltage clamped cells

Inhibition of Ca$^{2+}$ channels
Esmolol dose-response on Ca-current in voltage clamped cells

Inhibition of L-type Ca\(^{2+}\) channels

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IC\(_{50}\) = 0.449 mM

\(n=5\)
New concepts for improving myocardial protection

Esmolol dose-response on Na-current in voltage clamped cells

Inhibition of fast Na⁺ channels

![Graph showing Esmolol dose-response on Na-current in voltage clamped cells. The graph plots Esmolol concentration against Na⁺ current (% control). The IC₅₀ is 0.17±0.03 mM.](image)
Excitation-Contraction Coupling and Targets for Arrest

Action potential $E_m$ (mV)

-80
-60
-40
-20
0
+20

Cardiac myocyte

Esmolol

Fast Na$^+$ Channels

K$^+$ Channels

Ca$^{2+}$ Channels

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Question mark
Esmolol has pronounced inhibitory effects on the L-type Ca\(^{2+}\)-channel and the Na\(^{+}\)-channel. This explains its negative inotropic and arresting effect, independent from its β-blocking effect.

The inhibitory effect of esmolol on the Na\(^{+}\)-channel suggests induction of polarised arrest, and hence beneficial advantages over depolarised (high K\(^{+}\)) cardioplegia.
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Criteria for an Optimum Clinical Cardioplegic Solution

- Rapid diastolic arrest.
- Delay onset of irreversible ischemic injury.
- Rapid reversibility of arresting agent.
- No prolonged systemic toxic effect of arresting agent.
### Cardioplegia criteria

- **Rapid diastolic arrest.**
- **Delay onset of irreversible injury.**
- **Rapid reversibility.**
- **No prolonged systemic toxic effect.**

<table>
<thead>
<tr>
<th>Cardioplegia criteria</th>
<th>TTX</th>
<th>Lidocaine</th>
<th>Verapamil</th>
<th>BDM</th>
<th>Adenosine</th>
<th>Esmolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid diastolic arrest.</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Delay onset of irreversible injury.</td>
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<td>Rapid reversibility.</td>
<td>✔️</td>
<td>✔️</td>
<td>✗</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>No prolonged systemic toxic effect.</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✔️</td>
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**Myocardial Protection Principles**

- **Rapid diastolic arrest.**
- **Delay onset of irreversible injury.**
- **Rapid reversibility.**
- **No prolonged systemic toxic effect.**
Myocardial Protection Principles

Esmolol + Adenosine Cardioplegia

♥ Langendorff-perfused rat hearts
♥ Global ischemia (4h), room temperature (23°C), 30 min re-infusion

![Graph showing LVDP (%) control vs Reperfusion Time (min) for different treatments: Esmolol (0.6mM)+Adenosine (0.25mM), Lidocaine (0.6mM)+Adenosine (0.25mM), STH2. * p<0.05 vs STH]
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Esmolol + Adenosine Cardioplegia: effect of additives

![Bar graph showing the effect of BDM and Mg²⁺ on final recovery.](Image)
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Pig Study (Vienna)

♥ STHPol (Es-Ad-Mg) versus STH2, in pigs on CPB (6/group)
♥ 60 min ischemia, 180 min reperfusion (60 min on-pump, 120 min off-pump)
**Summary**

**Esmolol-based Cardioplegia:**

- was at least equal to, and probably superior to, St Thomas’ Hospital cardioplegia as crystalloid or blood-based solutions and at normothermia or hypothermia.
- esmolol blocks the fast Na\(^+\) and L-type Ca\(^{2+}\)-channels, initiating polarised arrest; a combination of esmolol and adenosine (a K\(^+\)-channel opener) synergistically improves function.
- both agents have short half-lives, metabolised independently from the liver or kidney, improving clinical feasibility.
- adding anti-ischemic agents improves protection.
- studies evaluating efficacy of esmolol-adenosine cardioplegia in pigs undergoing CPB suggest similar (at least) efficacy to STH2.
Cardioplegic arrest during cardiac surgery can be induced by ‘intracellular-type’ or ‘extracellular-type’ solutions.

During the past ~35 years, cardioplegia solutions have changed only minimally despite huge surgery criteria changes in patients.

Current K⁺-based cardioplegic solutions (depolarised arrest) are probably not optimal for the current older and sicker patients requiring cardiac surgery.

Alternative protection concepts, such as the use of agents that induce polarised arrest, are likely to provide improved protection.

Optimal protection should be the aim for all cardiac surgery patients.

Esmolol-based cardioplegia may fulfill this role.
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Acknowledgements

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<th>St Thomas’ Hospital</th>
<th>Nippon Medical School</th>
<th>University of Vienna</th>
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<tr>
<td>Dr Andrew Snabatis</td>
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<td>Dr Bruno Podesser</td>
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<td>Dr Omal Walgama</td>
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