Key pathways to ischemia-reperfusion injury

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Outline

• What is ischaemia-reperfusion injury?
• What causes ischaemia-reperfusion injury?
  – Calcium
  – Reactive oxygen species (ROS)
  – The role of mitochondria
• How can we protect against ischaemia-reperfusion injury?
Cardiovascular disease – the leading cause of death

37%
What is reperfusion injury?

Four forms of reperfusion injury:

1) Arrhythmias
2) Myocardial stunning
3) Microvascular injury
4) Myocardial Infarction
Hausenloy DJ and Yellon DM
Myocardial ischemia-reperfusion injury: a neglected therapeutic target
JCI 113(2013):92-100
Mitochondrial damage occurs early during reperfusion.

5 min after reperfusion
The mitochondrial permeability transition pore (mPTP, or PTP)
mPTP opening contributes to IR injury

Lim, Davidson, Hausenloy, Yellon Cardiovasc Res, 07
Multiphoton microscopy
Mitochondria in the myocardium
Ischaemia and reperfusion model

<table>
<thead>
<tr>
<th>STABILIZE</th>
<th>ISCHAEMIA</th>
<th>REPERFUSION</th>
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<tbody>
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<td>time</td>
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TMRM

+PI

100 µm
Cardiomyocyte-specific, inducible expression of GCaMP2
Calcium and TMRM during reoxygenation

Calcium and TMRM during reoxygenation

Cell death

mPTP opening

$[\text{Ca}^{2+}]_c$
The role of mitochondrial Ca\textsuperscript{2+} in IR injury
The Mitochondrial Calcium Uniporter (MCU)

The role of mitochondrial Ca\(^{2+}\) in IR injury
Inducible cardiac NCLX deletion

Luongo TS et al. The mitochondrial Na⁺/Ca²⁺ exchanger is essential for Ca²⁺ homeostasis and viability Nature 545(2017):93-97
Inducible cardiac NCLX overexpression

Luongo TS et al. The mitochondrial Na⁺/Ca²⁺ exchanger is essential for Ca²⁺ homeostasis and viability. Nature 545(2017):93-97
What about Reactive oxygen species (ROS)?
What is the source of ROS in reperfusion?


Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS.
What is the source of ROS in reperfusion?

Dihydroethidium (DHE) = fluorescent detection of ROS
Dimethyl malonate = competitive inhibitor of SDH

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Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS.
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Oxidative stress

$\text{[Ca}^{2+}]_\text{c}$
Ischaemic preconditioning (IPC)

No Conditioning  Conditioned

Cardioprotective pathways

Ischaemic preconditioning (IPC)

Insulin
Bradykinin
Gliptins
Stromal derived factor (SDF-1α)
Adipocytokines (leptin, adiponectin)
Erythropoietin
Urocrortin

Reperfusion
Injury
Salvage
Kinase pathway

Reduced Infarct size
BUT Ischaemic conditioning is:
- invasive
- impractical
- potentially dangerous – (thrombo-embolic risk)

Is there a non-invasive way to “condition” the animal & human heart?
Brief ischaemia-reperfusion in a distal organ or tissue can render the heart resistant to a myocardial infarction.


Kharbanda et al, Circ 2002

Gou et al, Circ, 1996

Gustafsson et al, Circ, 2006

Remote Conditioning
Remote Ischaemic Conditioning protects the rat heart from IR injury

Doppler blood flow of hind limb

A. Subject  B. Baseline  C. Ischaemia  D. Reperfusion

Graph showing IS/AAR (%) comparison between IR + Vehicle and RIPC + Vehicle groups.
Further reading


Ischaemic conditioning and targeting reperfusion injury: a 30 year voyage of discovery.

9th Hatter Biannual Meeting: position document on ischaemia/reperfusion injury, conditioning and the ten commandments of cardioprotection.
Bell RM et al, Basic Res Cardiol. 2016 Jul;111(4):41
Inhibition of SDF-1α binding prevents RIC

Davidson et al Basic Res Cardiol 108(2013):377