Key pathways to ischemia-reperfusion injury

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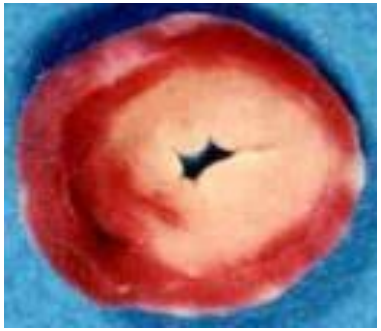
EUROPEAN SOCIETY OF CARDIOLOGY®

Outline

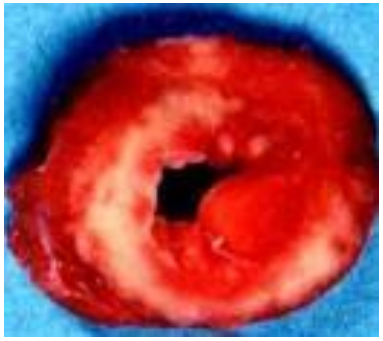
- What is ischaemia-reperfusion injury?
- What causes ischaemia-reperfusion injury?
  - Calcium
  - Reactive oxygen species (ROS)
  - The role of mitochondria
- How can we protect against ischaemia-reperfusion injury?

Cardiovascular disease – the leading cause of death

Ischaemia



Ischaemia Reperfusion

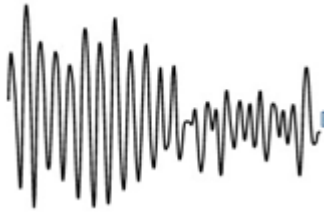


Reperfusion injury

What is reperfusion injury?

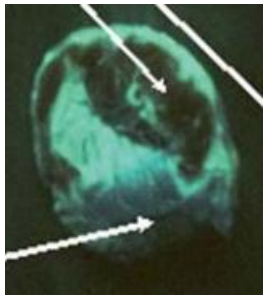
Four forms of reperfusion injury:

1) Arrhythmias

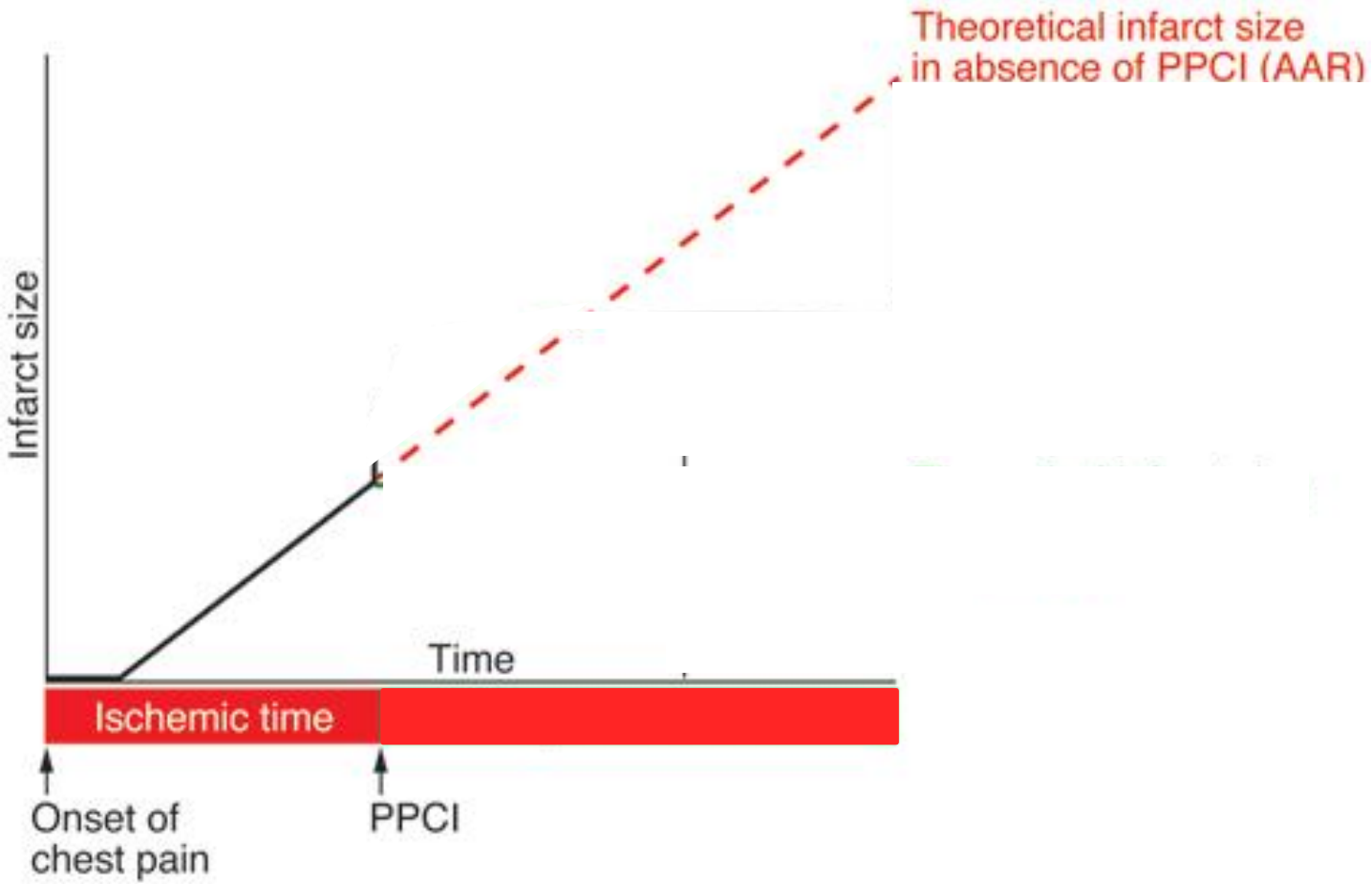


2) Myocardial stunning

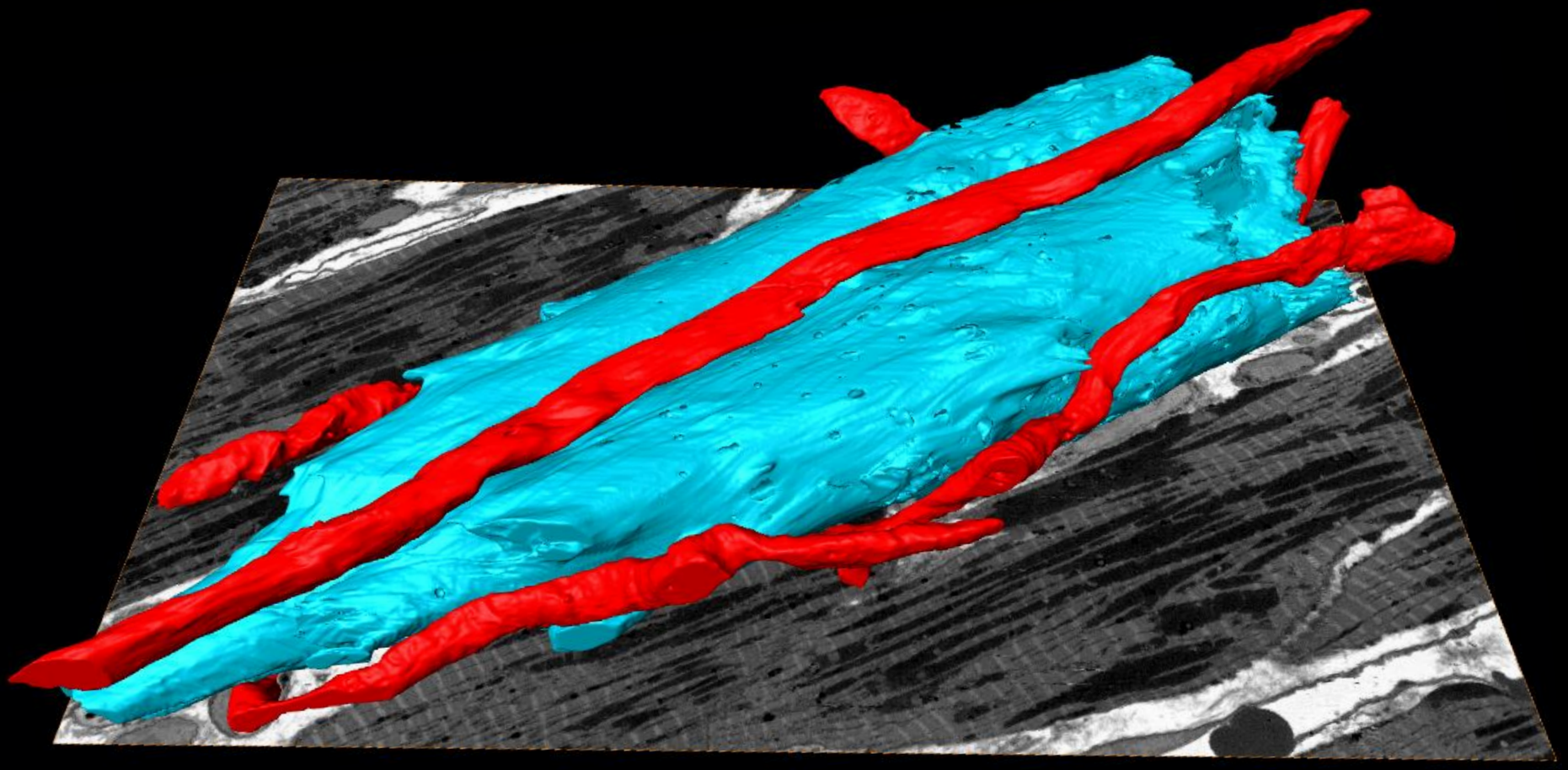
3) Microvascular injury

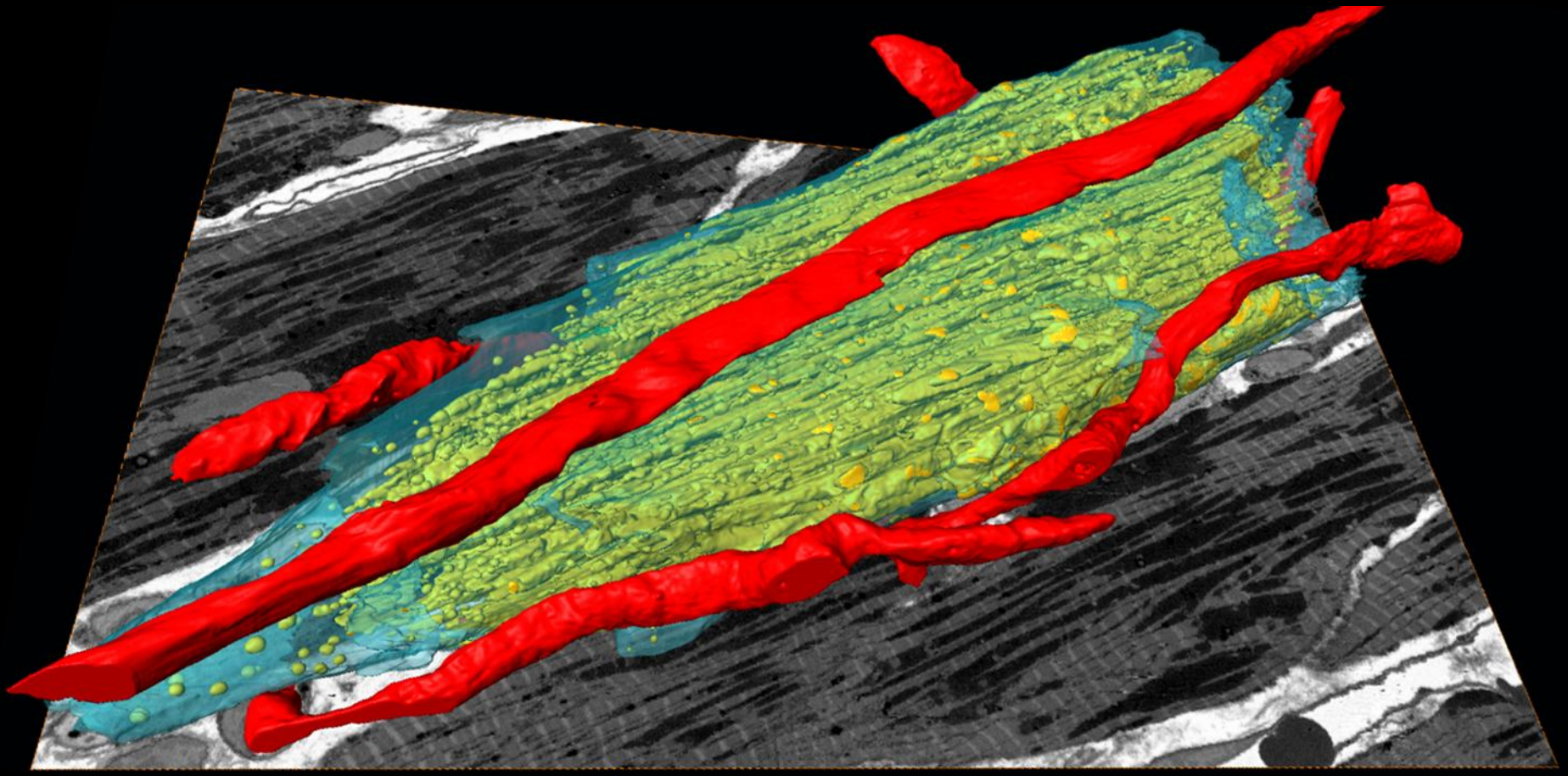


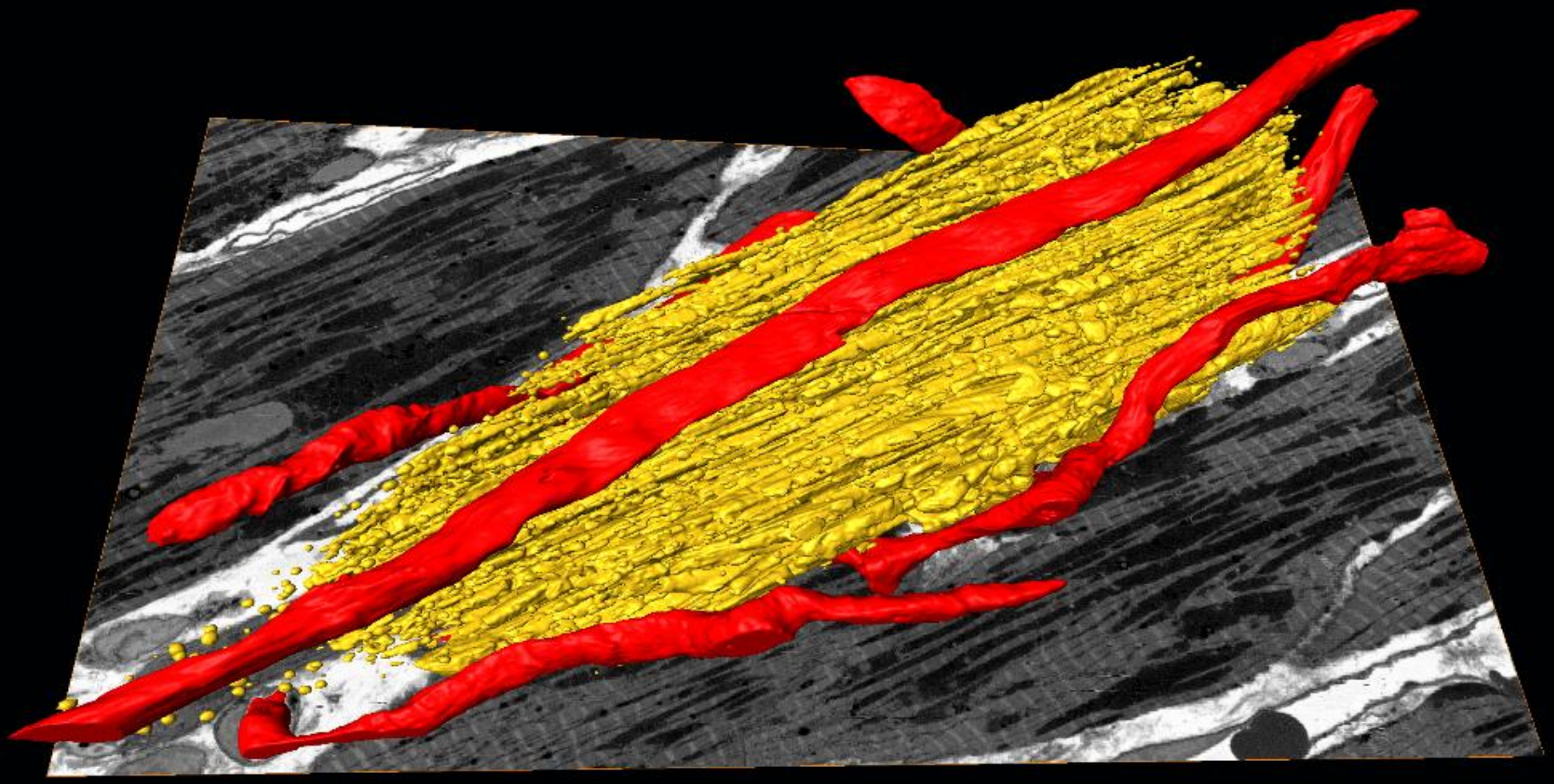
4) Myocardial Infarction



Hausenloy DJ and Yellon DM
Myocardial ischemia-reperfusion injury: a neglected therapeutic target
JCI 113(2013):92-100

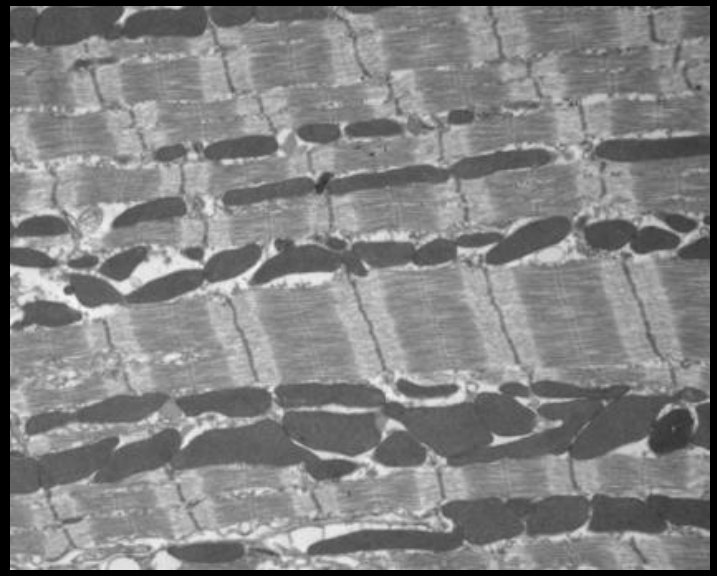




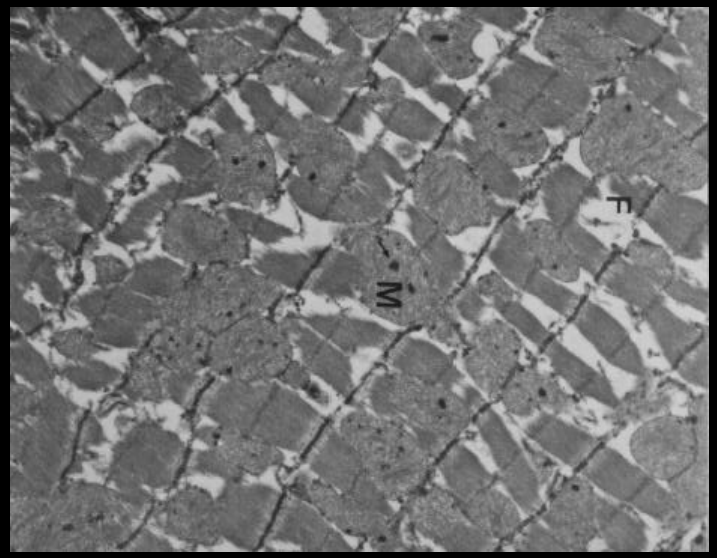


Mitochondrial damage occurs early during reperfusion

Control

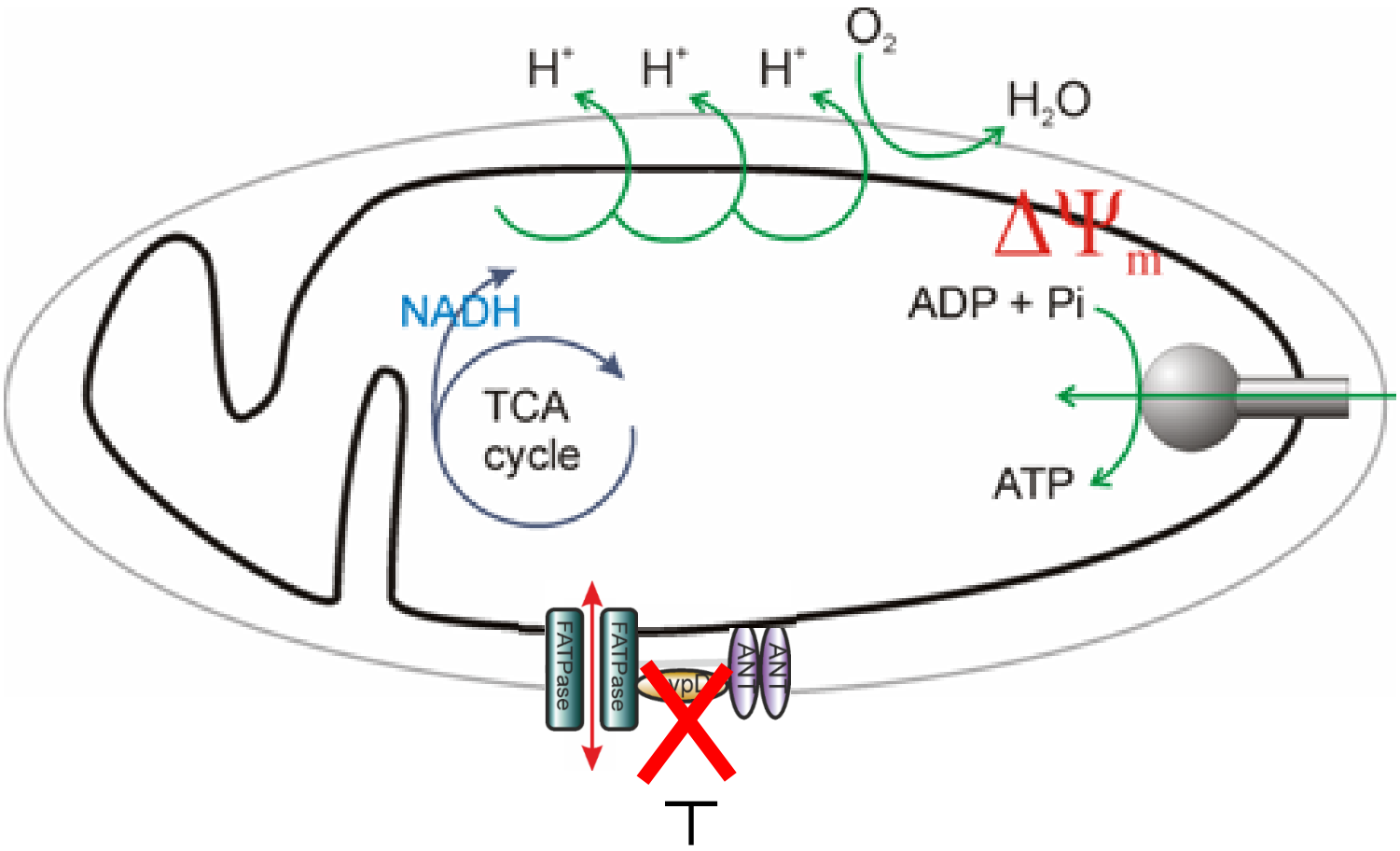


60 min ischaemia



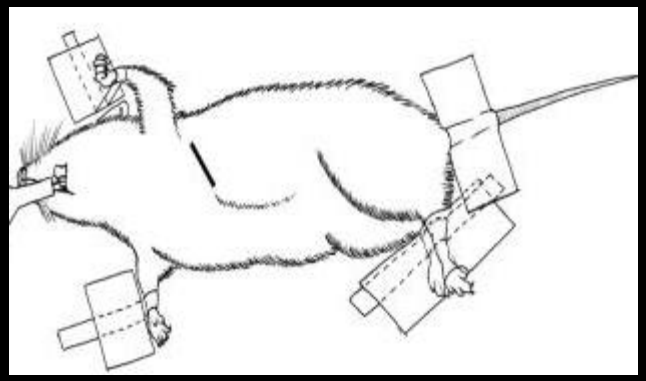
5 min after reperfusion

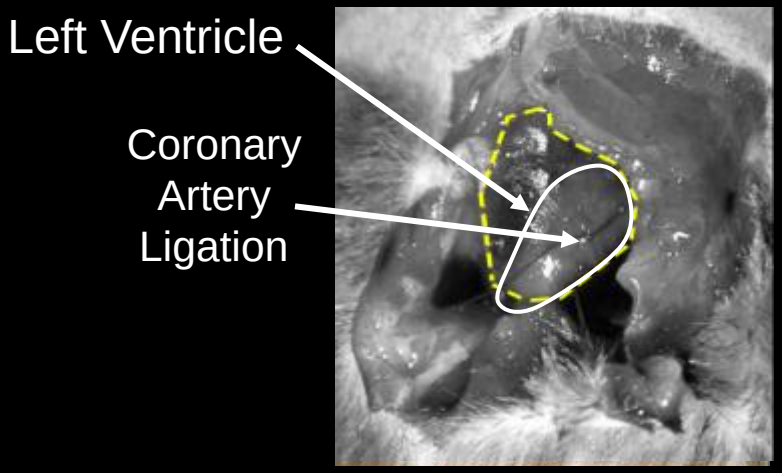
The mitochondrial permeability transition pore (mPTP, or PTP)

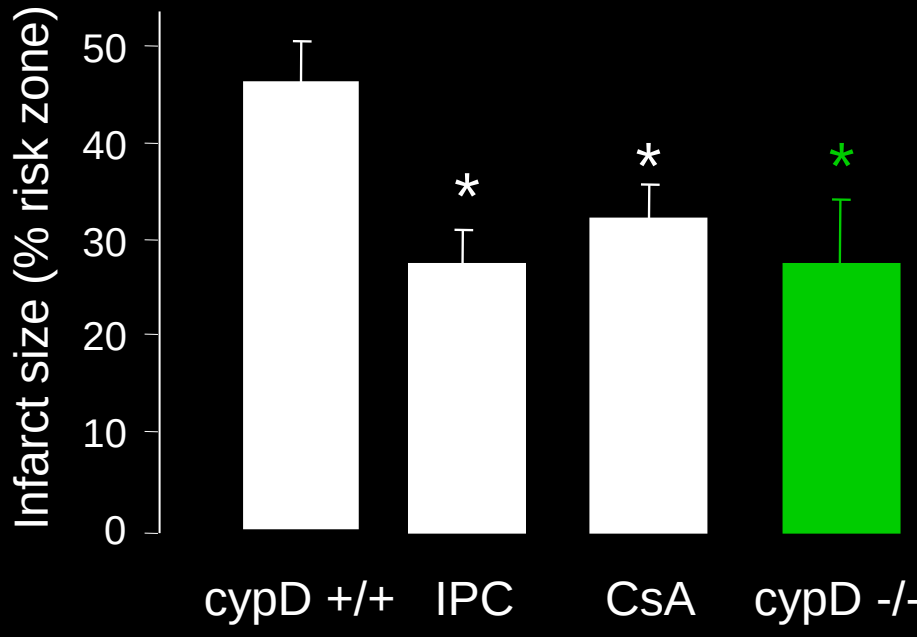


Cyclosporine A

mPTP opening contributes to IR injury

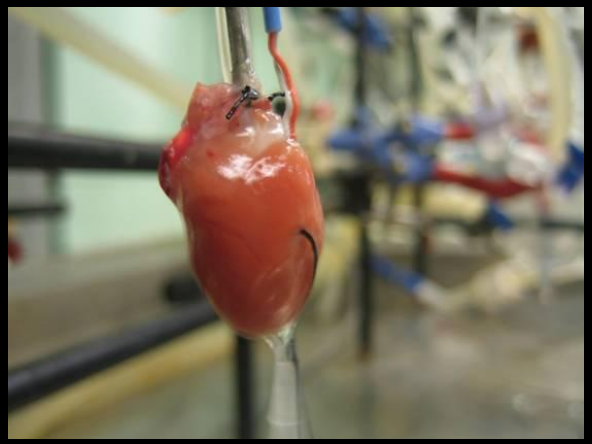


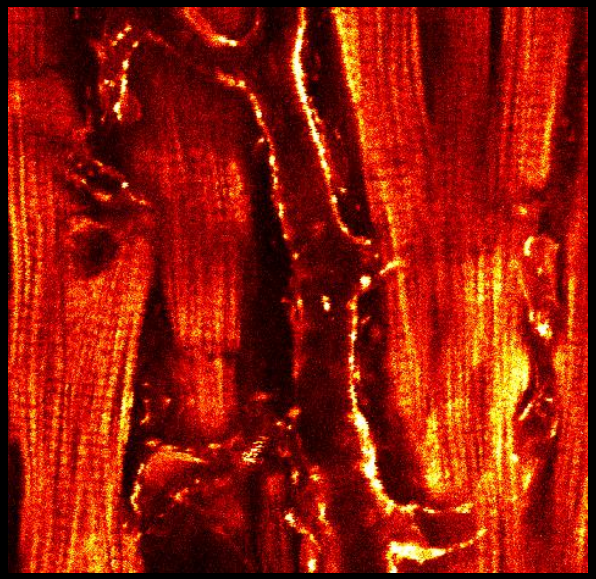


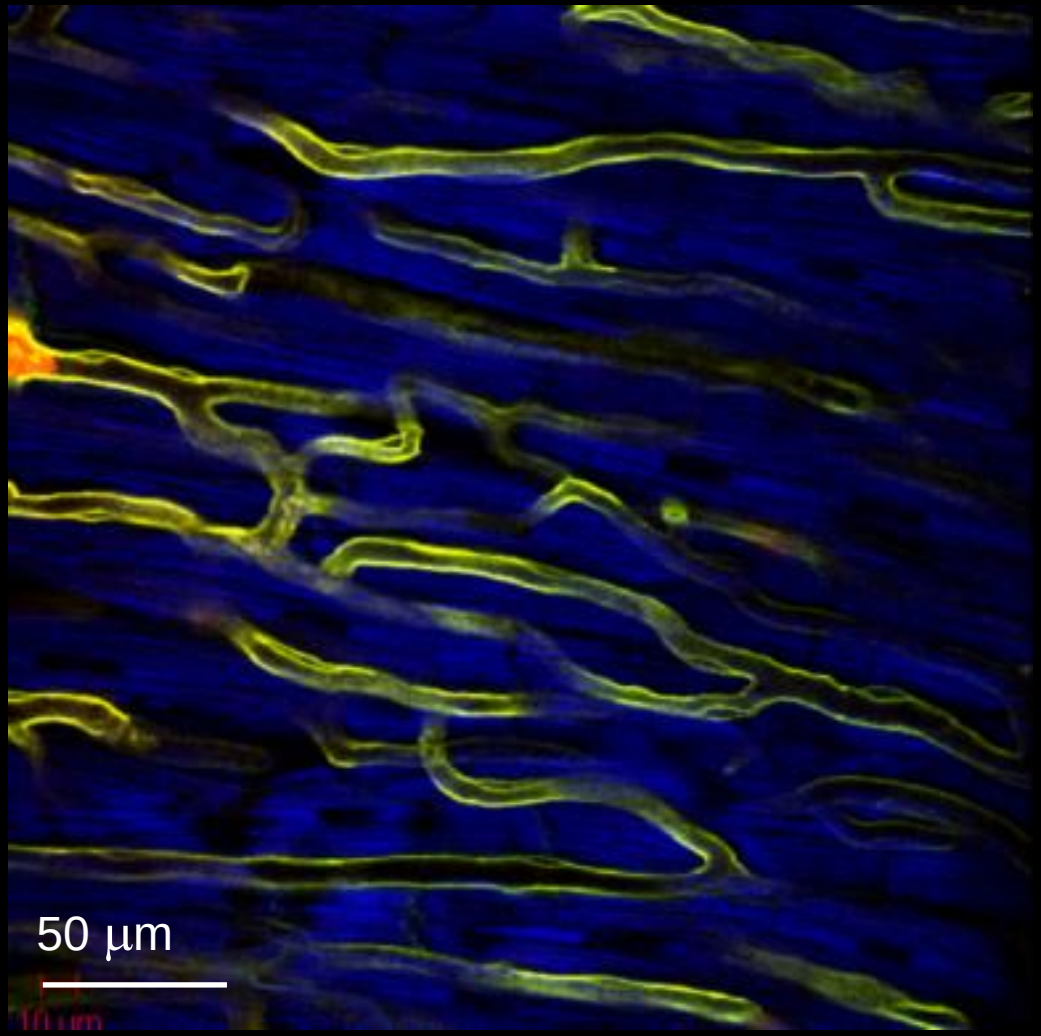


Lim, Davidson, Hausenloy, Yellon Cardiovasc Res, 07

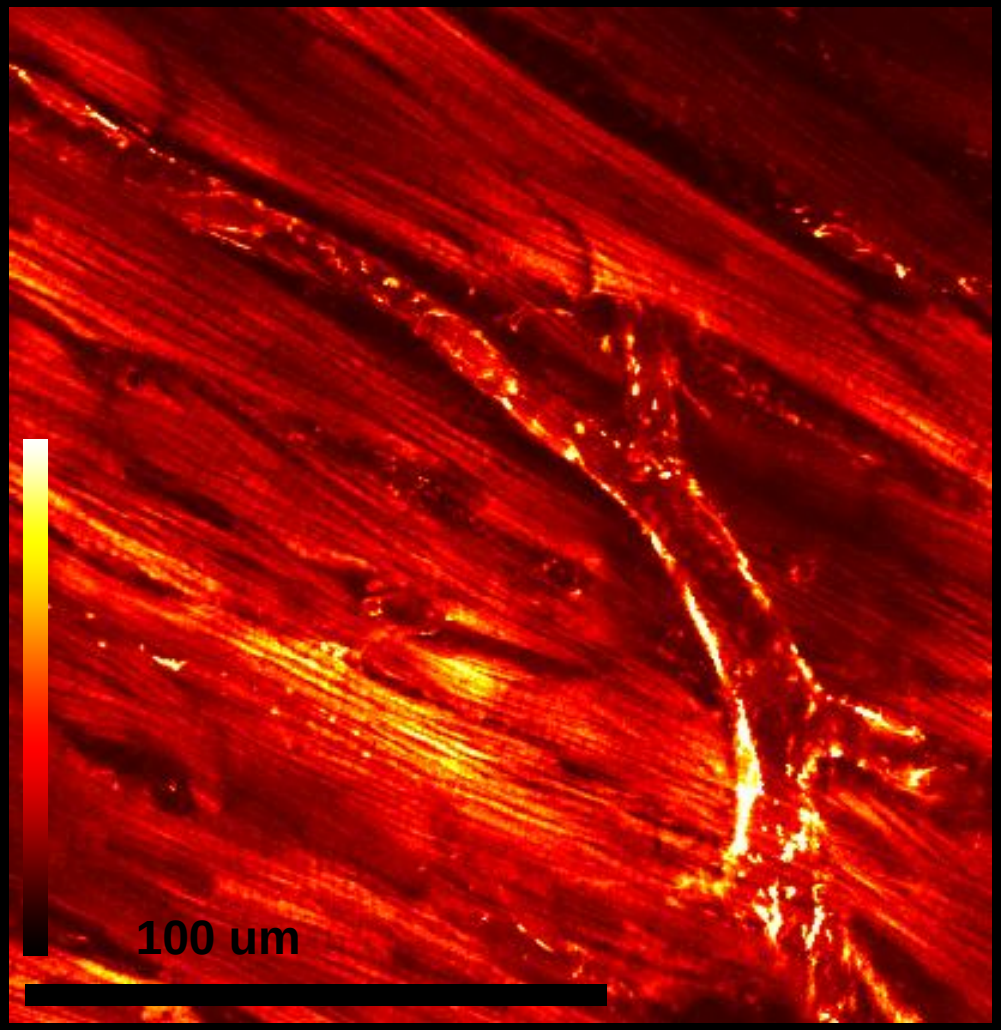
Multiphoton microscopy







Mitochondria in the myocardium

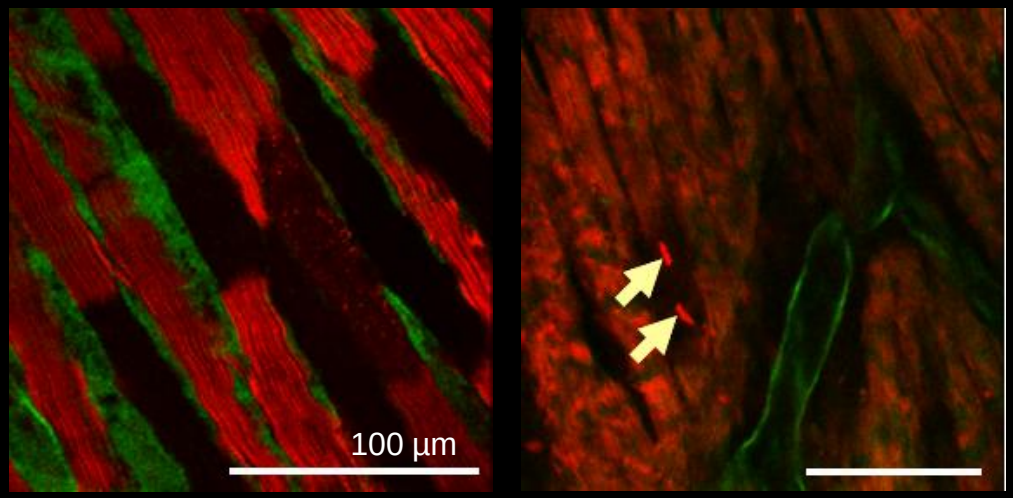


TMRM

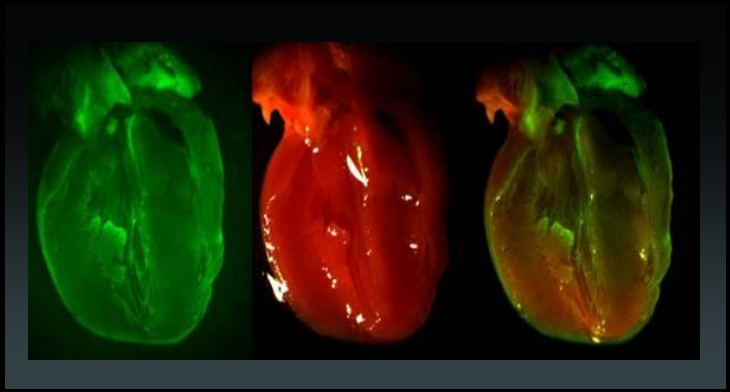
Ischaemia and reperfusion model

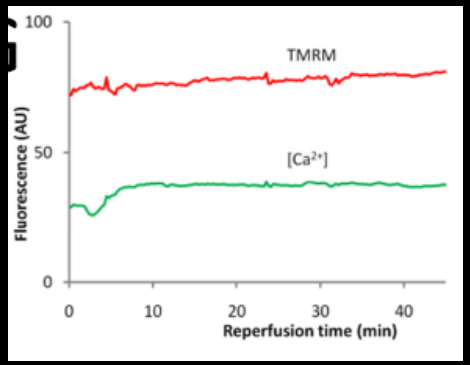
TMRM

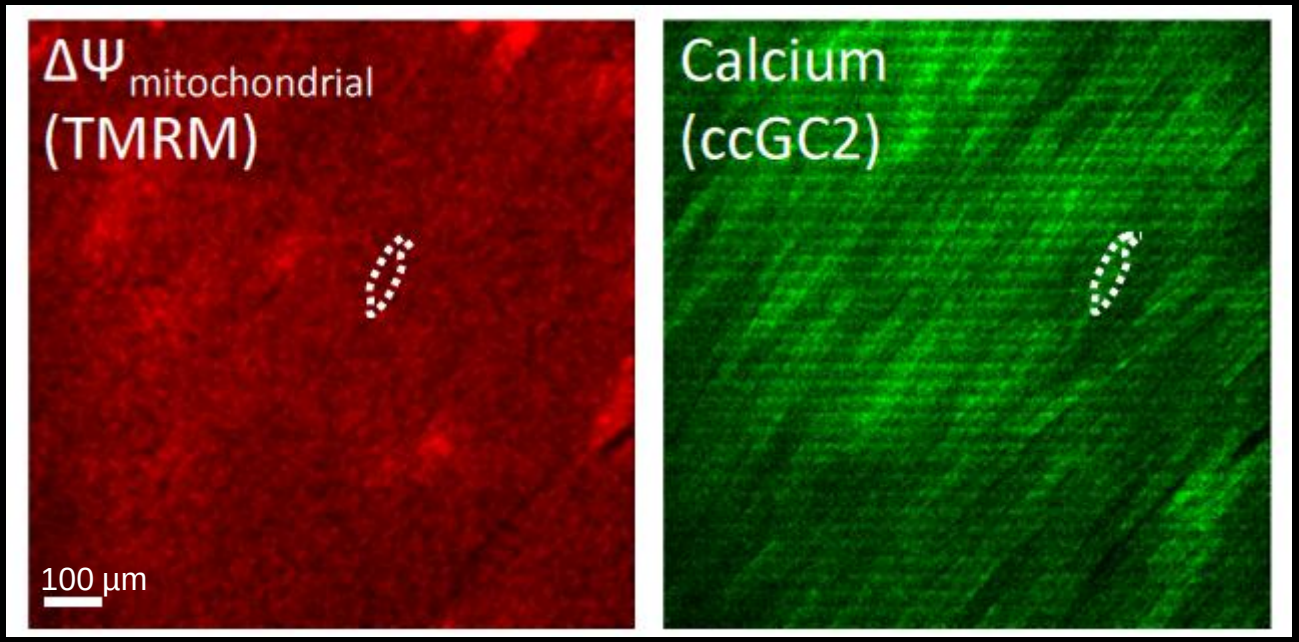
+PI



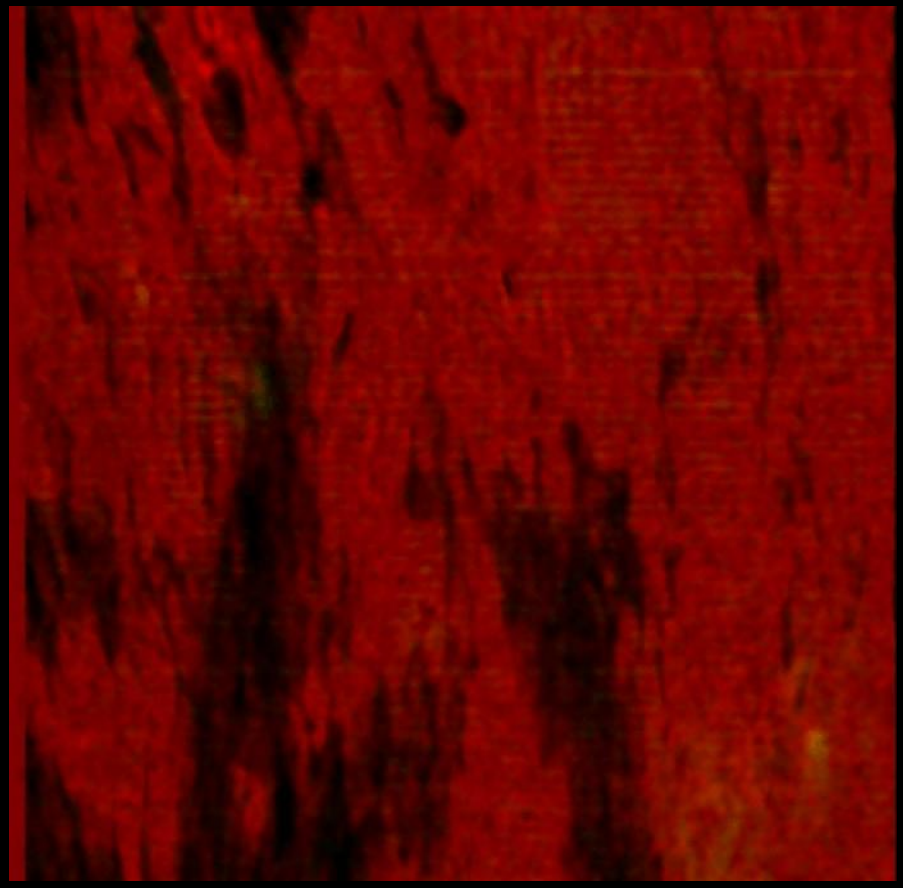
Cardiomyocyte-specific, inducible expression of GCaMP2





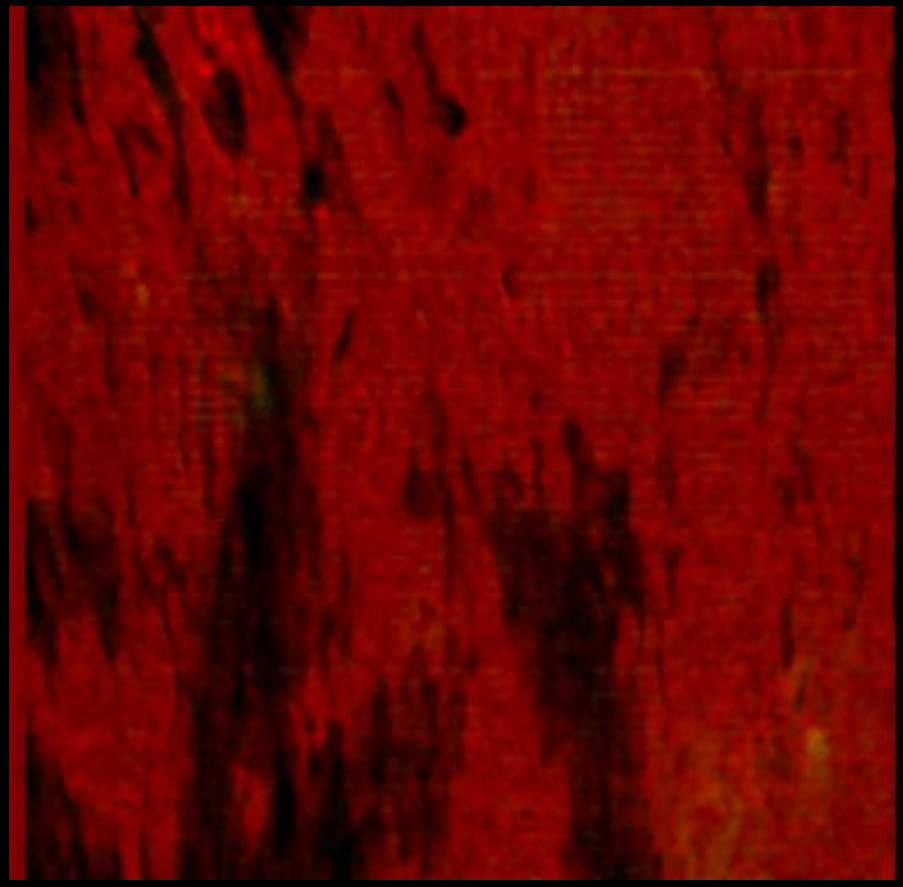


Calcium and TMRM during reoxygenation



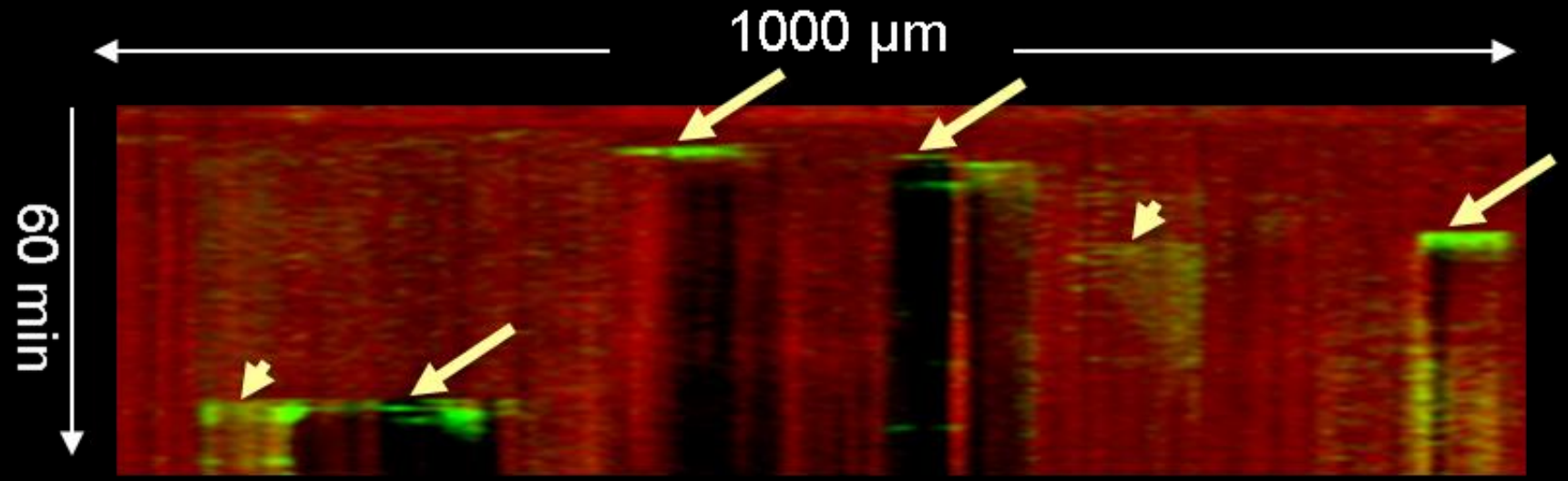
Davidson SM et al., Cardiovasc Res 93(2012):445-53

Calcium and TMRM during reoxygenation

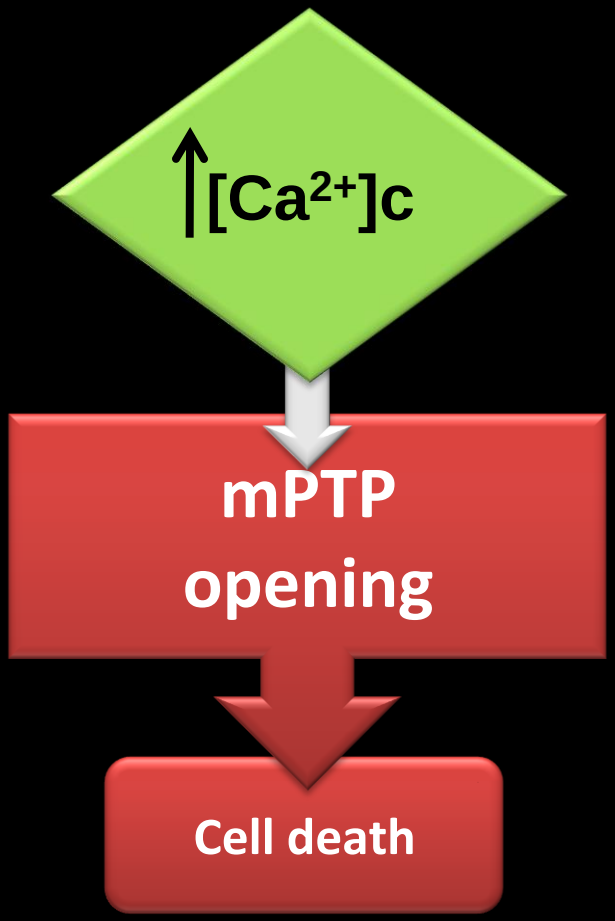


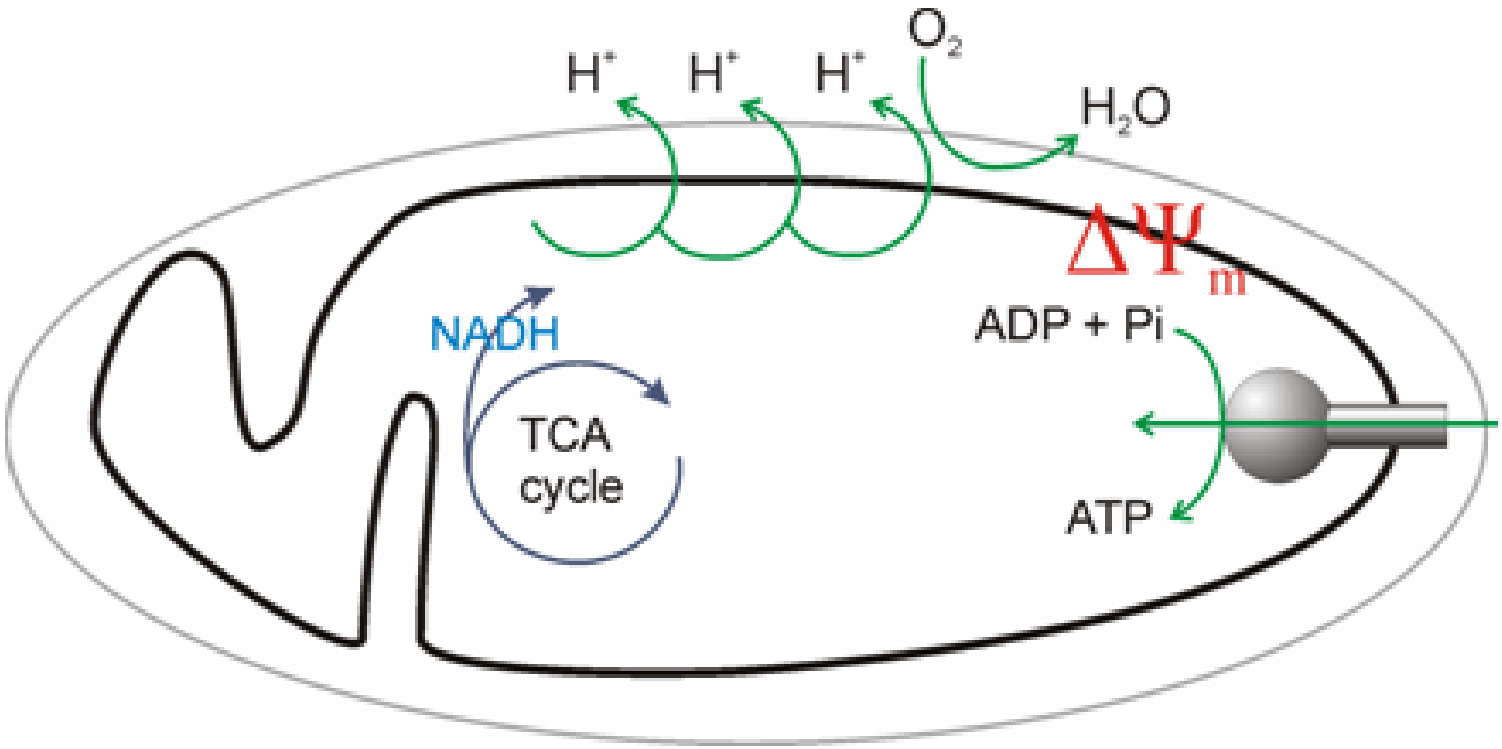
Davidson SM et al., Cardiovasc Res 93(2012):445-53

Linescan

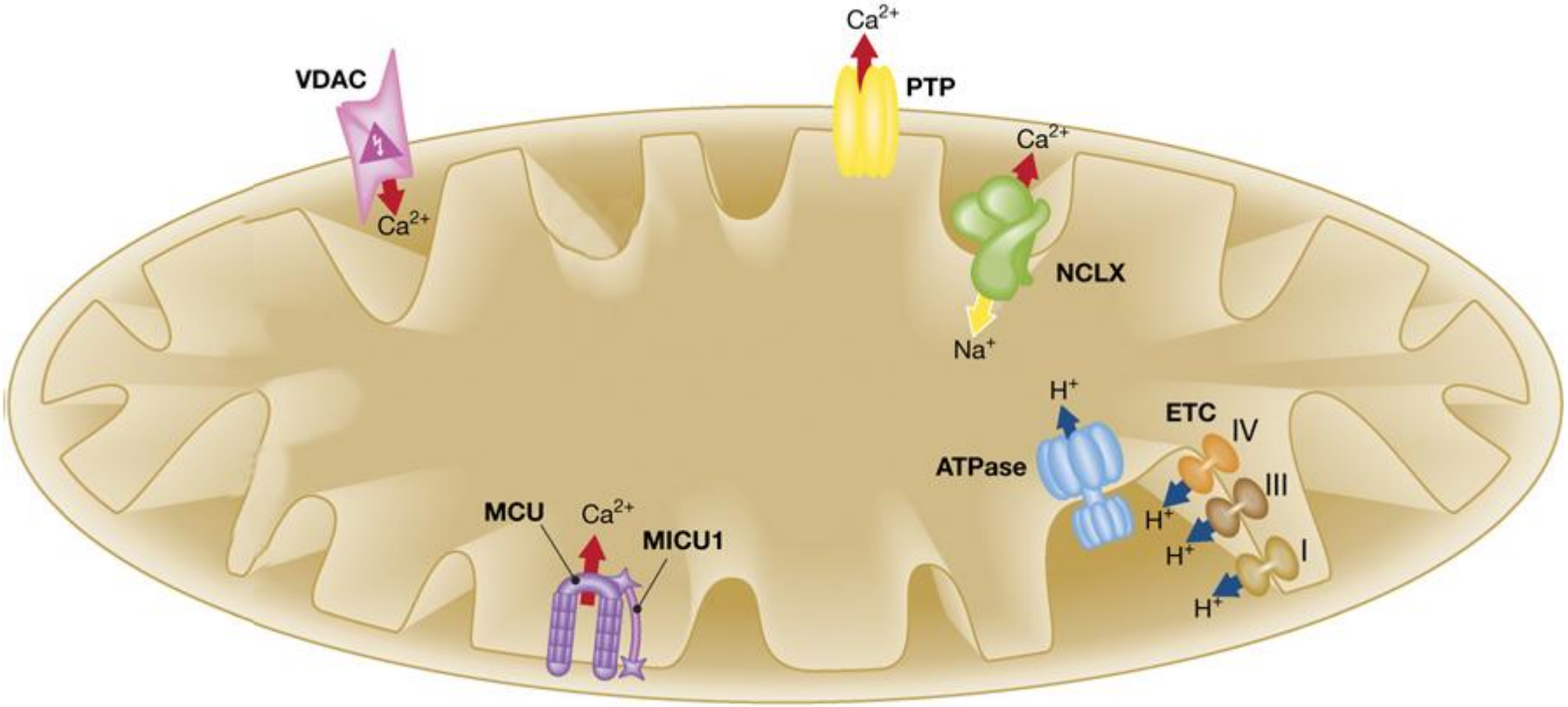


Davidson SM et al., Cardiovasc Res 93(2012):445-53

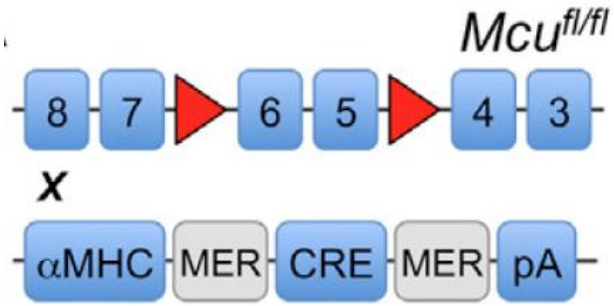

↑[Ca2+]c
mPTP opening
Cell death

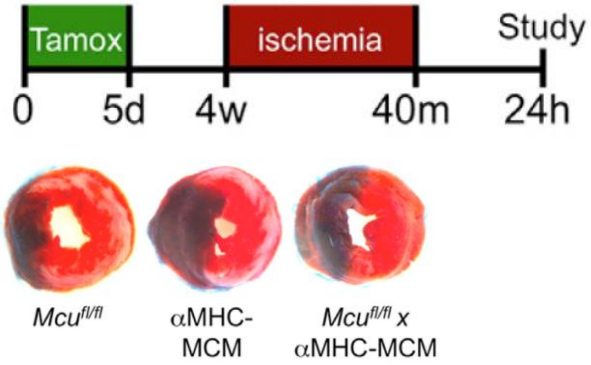

H+
H+
H+
O2
H2O
ΔΨm
NADH
TCA
cycle
ADP + Pi
ATP

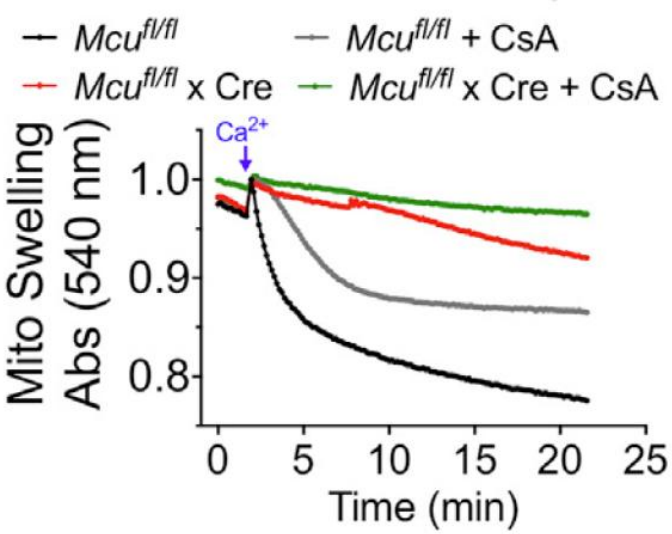
The role of mitochondrial Ca^{2+} in IR injury

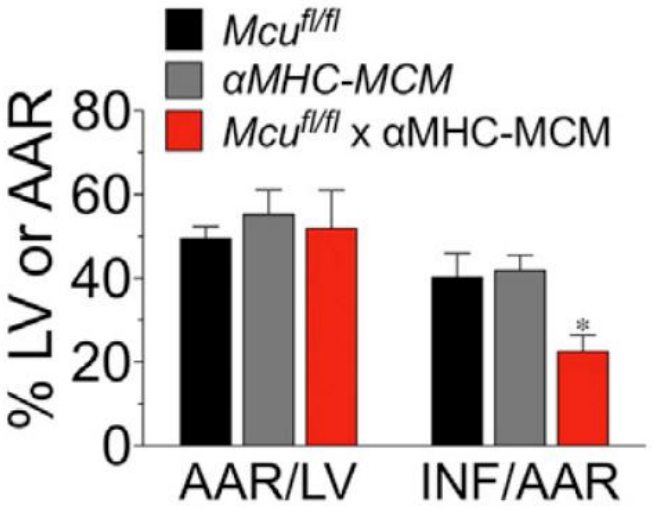


The Mitochondrial Calcium Uniporter (MCU)



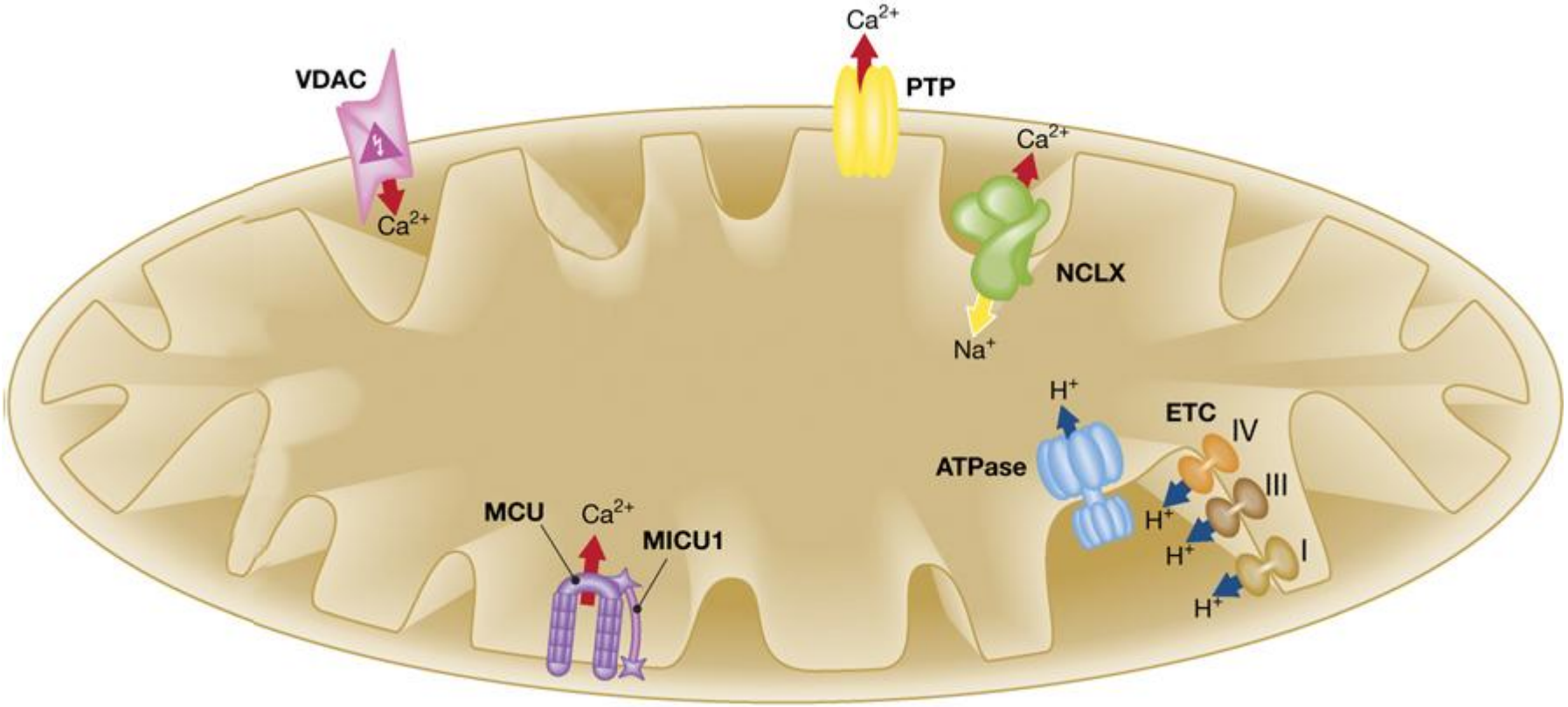




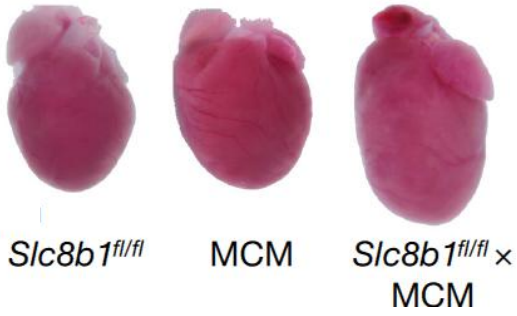


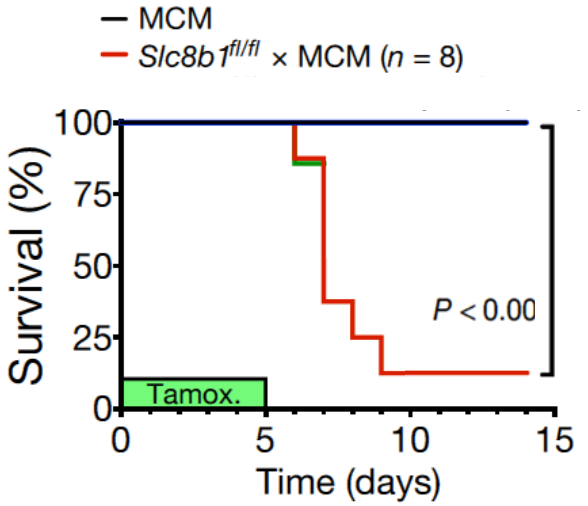
Luongo TS et al. The Mitochondrial Calcium Uniporter Matches Energetic Supply with Cardiac Workload during Stress and Modulates Permeability Transition
Cell Reports 12(2015):1-12

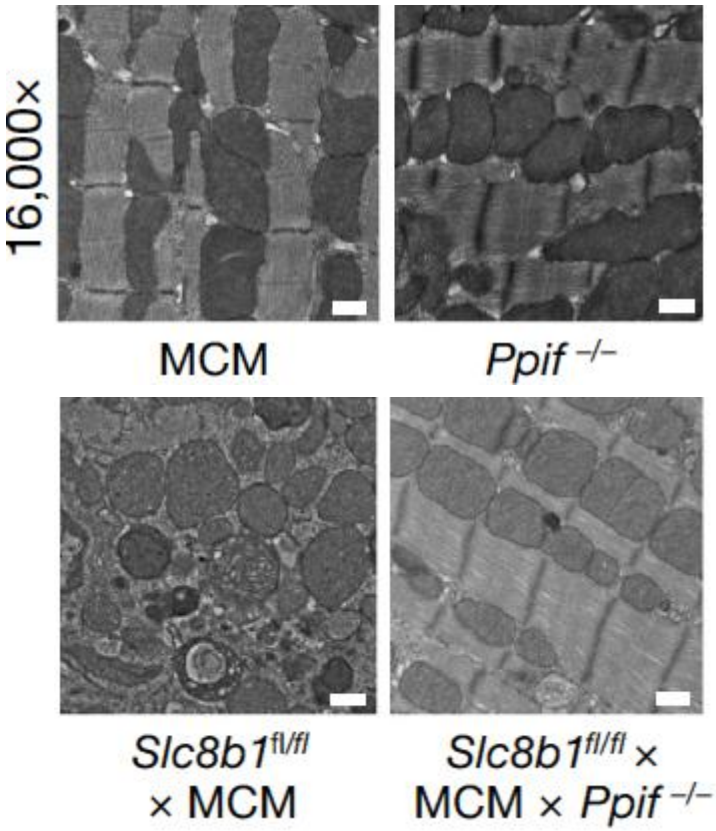
The role of mitochondrial Ca^{2+} in IR injury



Inducible cardiac NCLX deletion

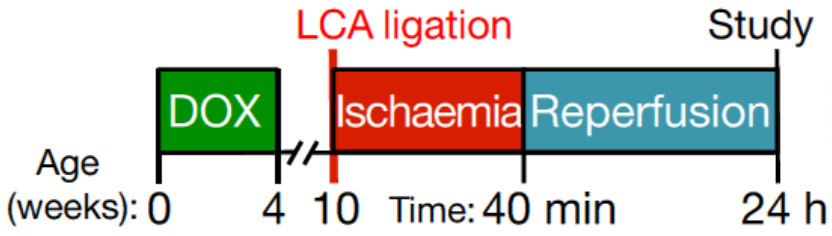


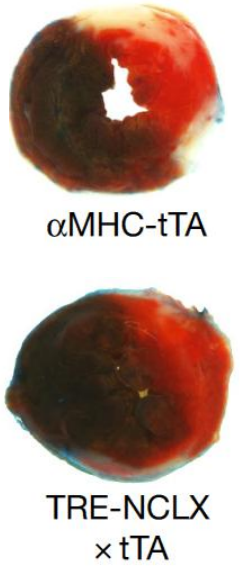


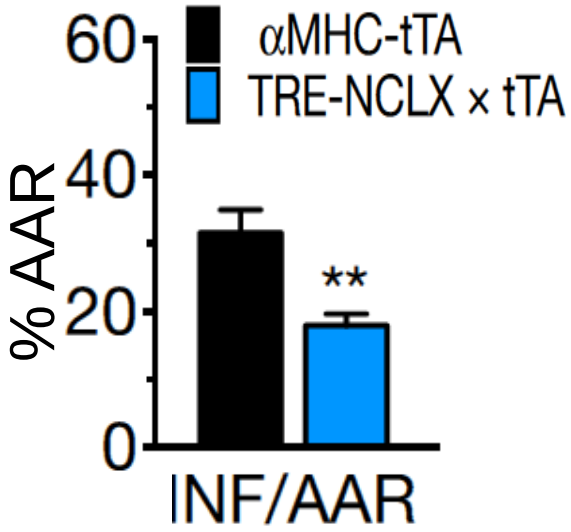


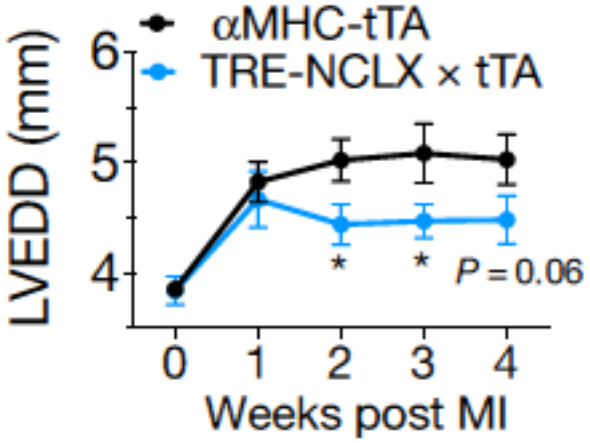
Luongo TS et al. The mitochondrial Na^+ /Ca^{2+} exchanger is essential for Ca^{2+} homeostasis and viability Nature 545(2017):93-97

Inducible cardiac NCLX overexpression









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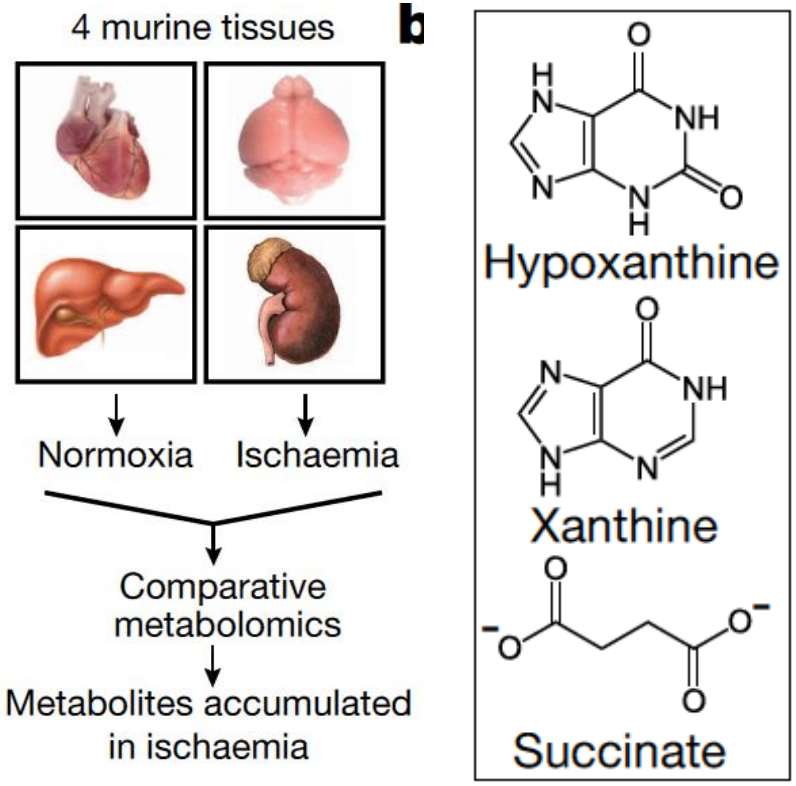
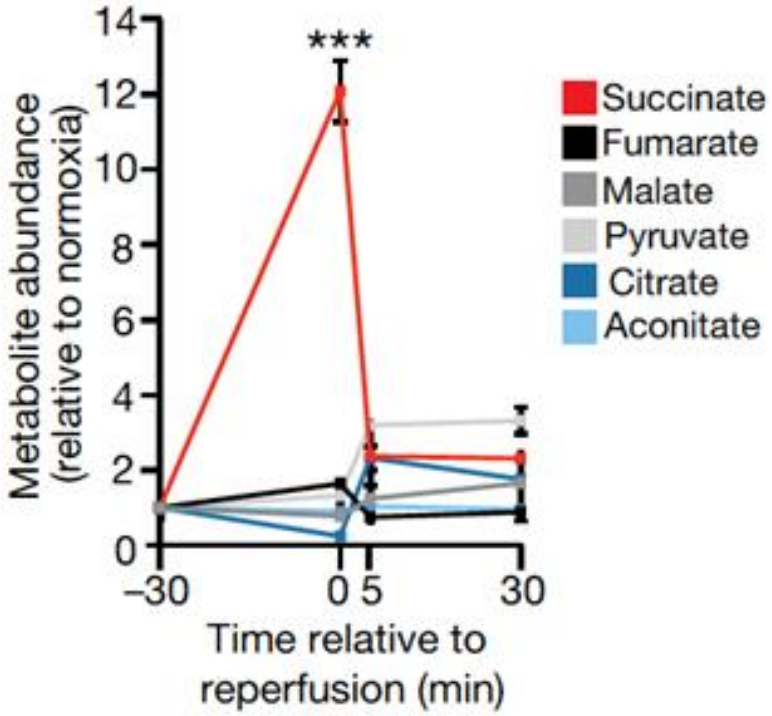
What about Reactive oxygen species (ROS)?

What is the source of ROS in reperfusion?





Chouchani ET, Nature. 2014 Nov 20;515(7527):431-5.

Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS.

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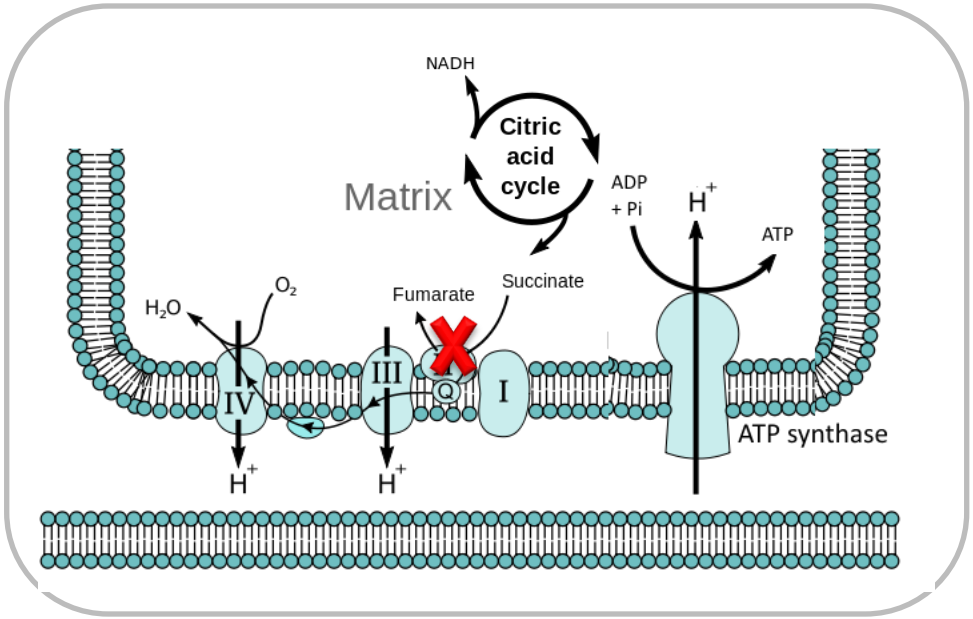

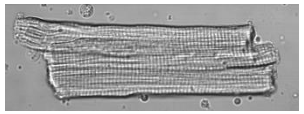

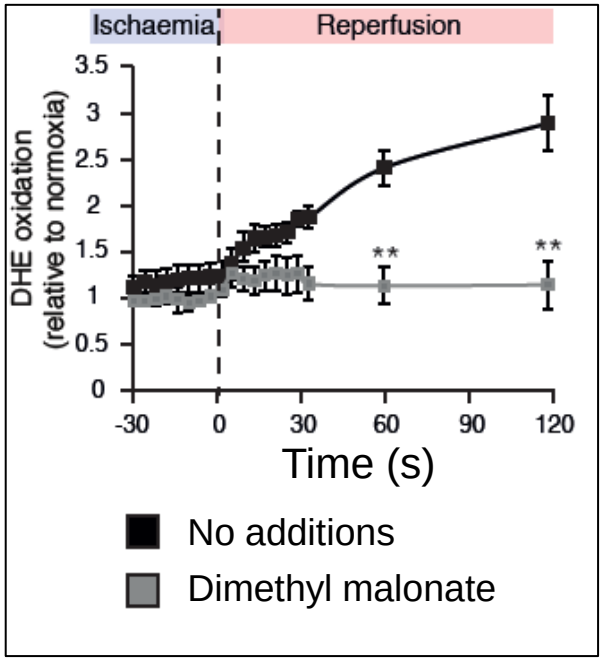

Dihydroethidium (DHE) = fluorescent detection of ROS
Dimethyl malonate = competitive inhibitor of SDH

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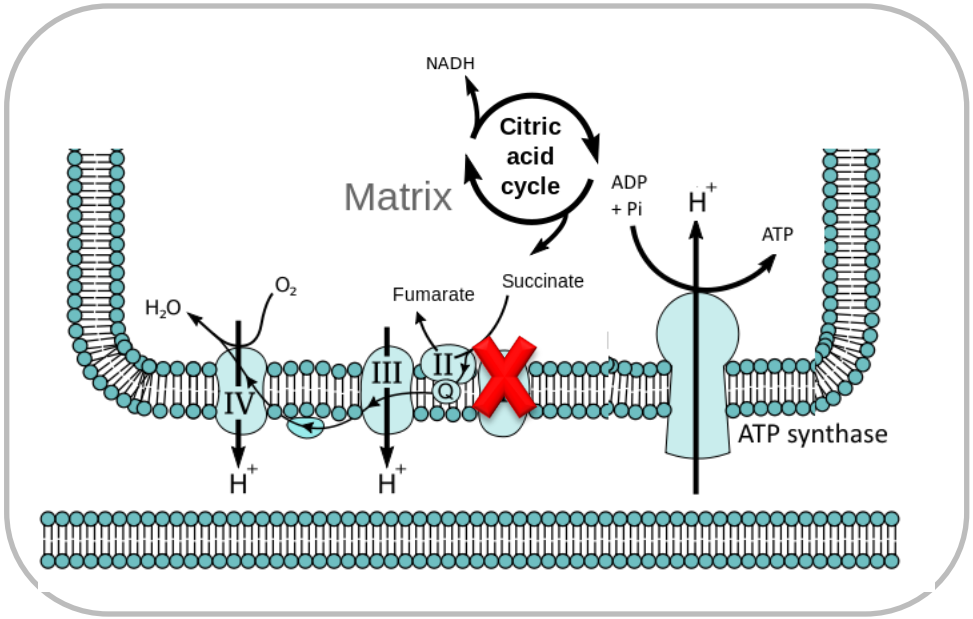

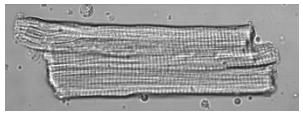

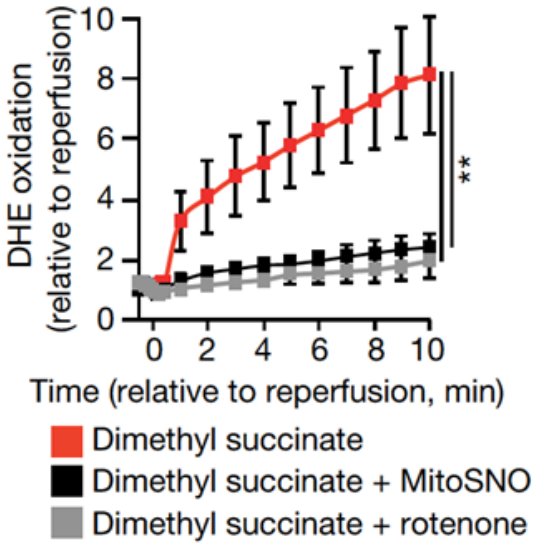

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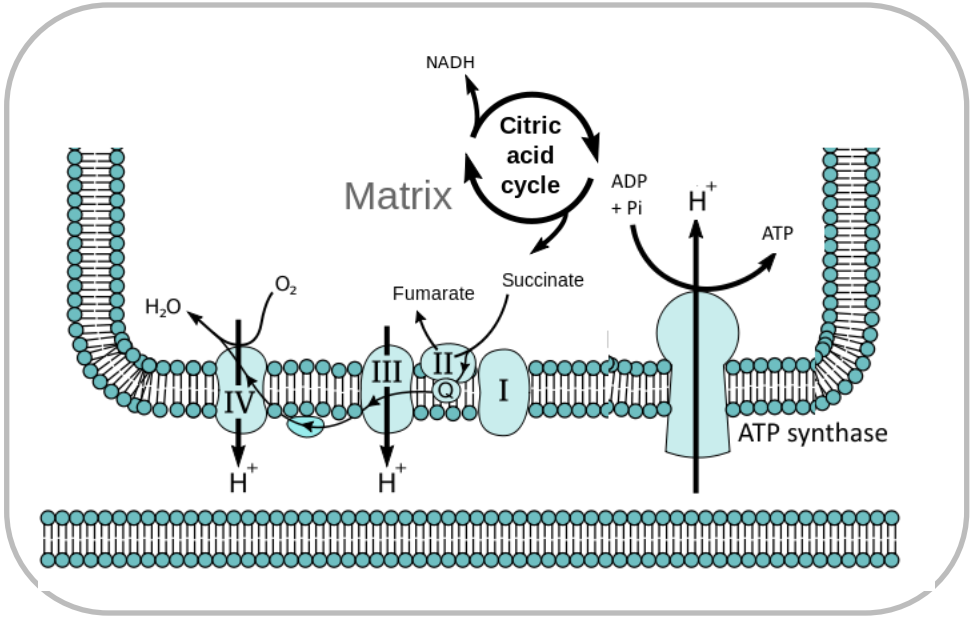

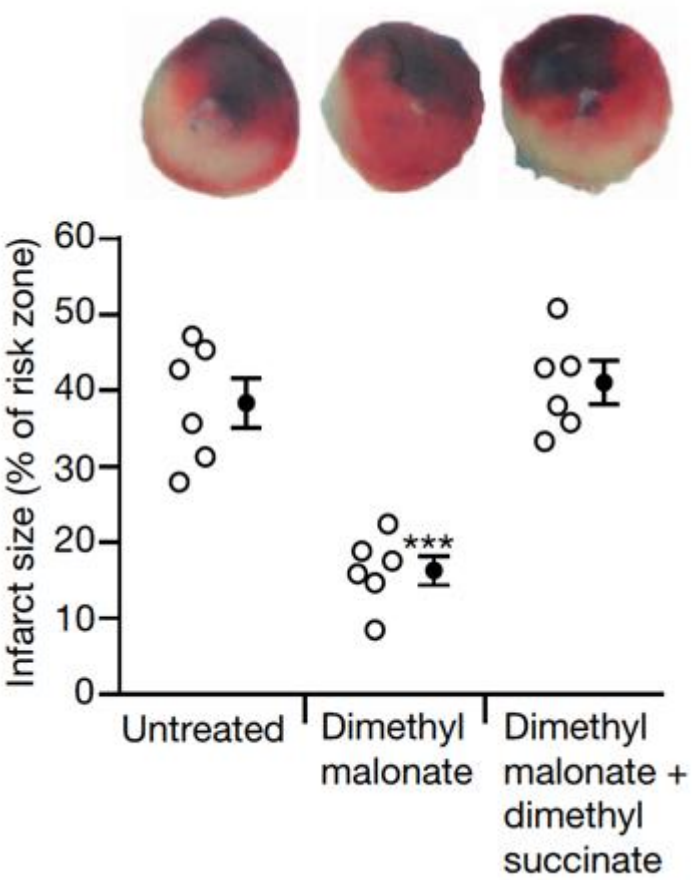

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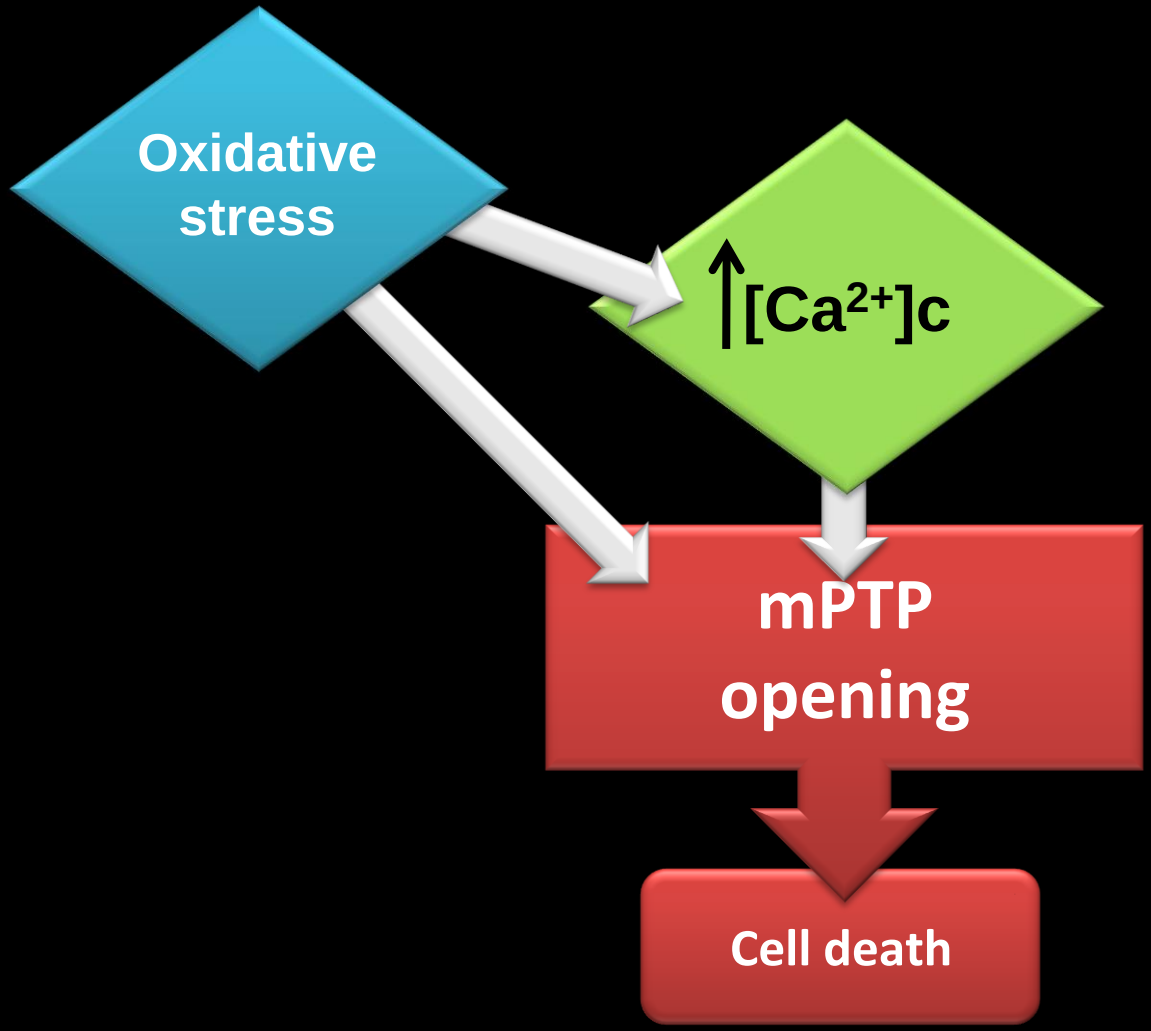
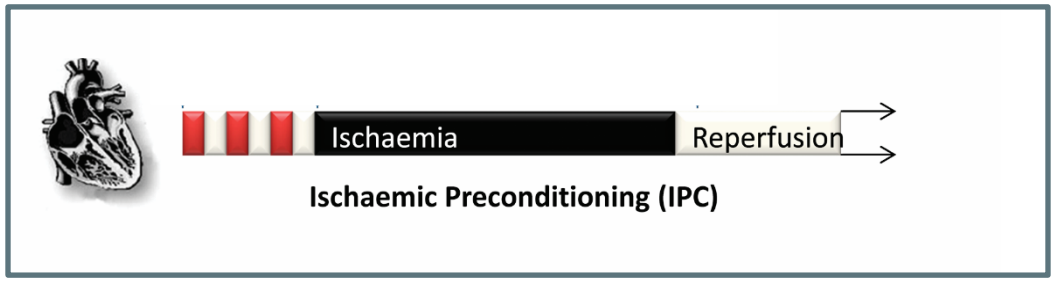
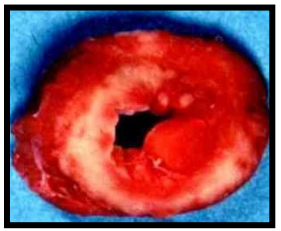

Oxidative stress
↑[Ca2+]c
mPTP opening
Cell death

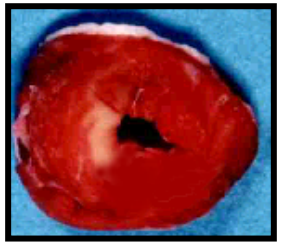
Ischaemic preconditioning (IPC)

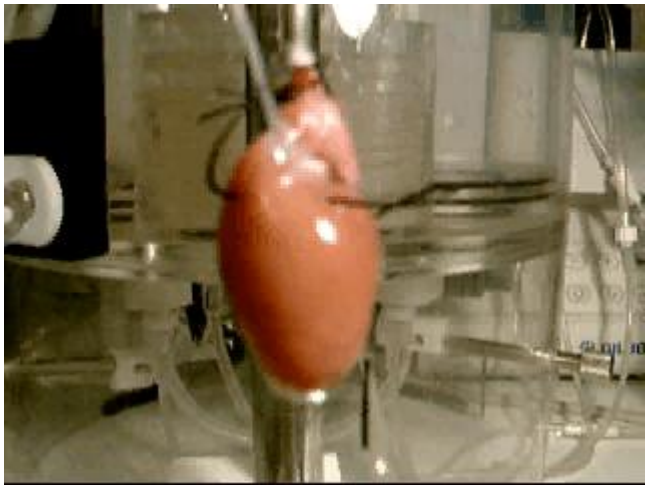


No Conditioning



Conditioned





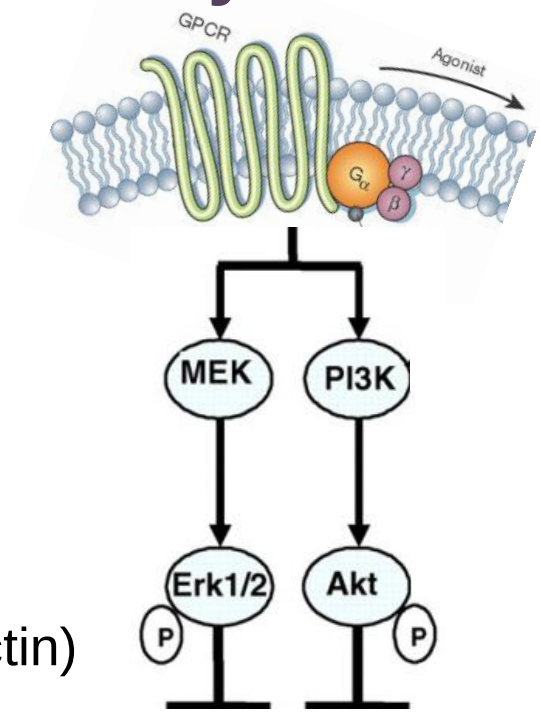
Control Preconditioned

Murry et al. Circulation 74 (1986): 1124–1136.

Cardioprotective pathways

Ischaemic preconditioning (IPC)

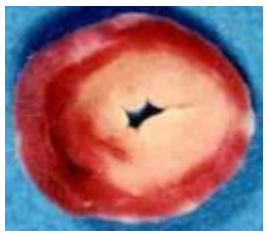
Insulin
Bradykinin
Gliptins
Stromal derived factor (SDF-1α)
Adipocytokines (leptin, adiponectin)
Erythropoietin
Urocortin



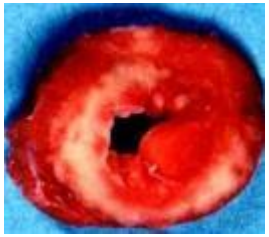
Reperfusion
Injury
Salvage
Kinase
pathway

Reduced Infarct size

Control



Treated



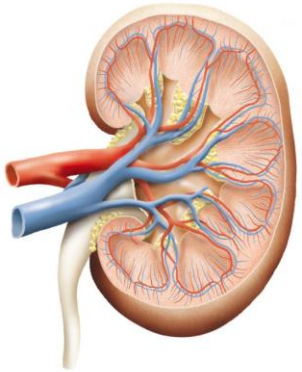
BUT Ischaemic conditioning is:

- invasive
- impractical
- potentially dangerous – (thrombo-embolic risk)

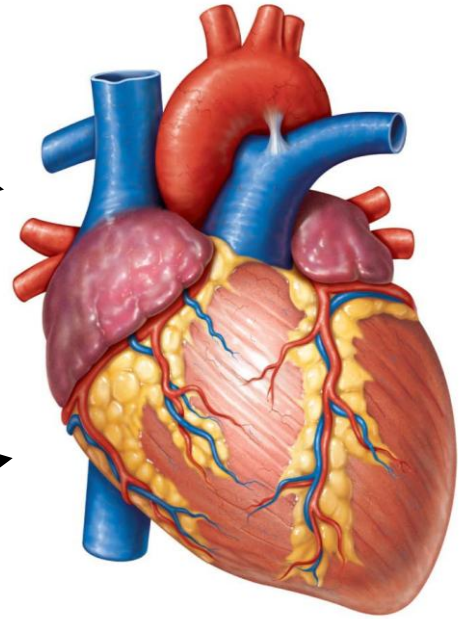
Is there a non-invasive way to “condition” the animal & human heart?

Brief ischaemia-reperfusion in a distal organ or tissue can render the heart resistant to a myocardial infarction.

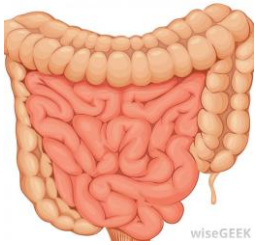
Pell et al, Am J Physiol, 1998



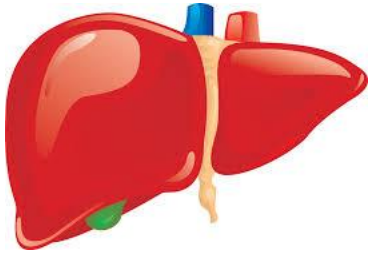
Kharbanda et al, Circ 2002



Gou et al, Circ, 1996

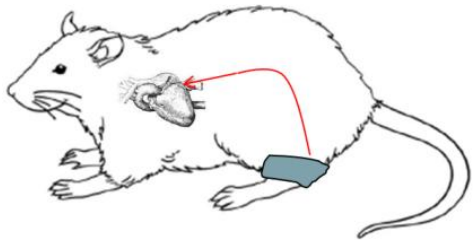


Gustafsson et al, Circ, 2006

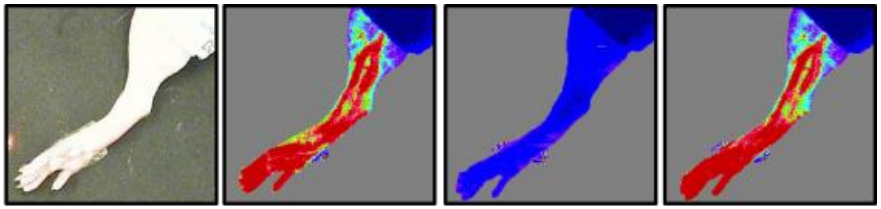


Remote Conditioning

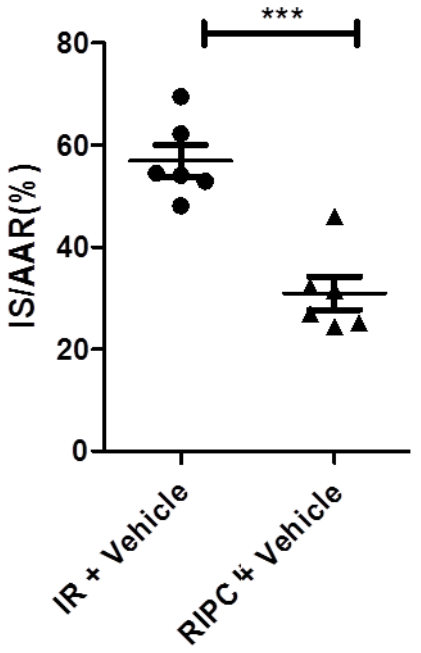
Remote Ischaemic Conditioning protects the rat heart from IR injury



Doppler blood flow of hind limb



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



Further reading

Novel targets and future strategies for acute cardioprotection: Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart.

Hausenloy DJ, et al. Cardiovasc Res. 2017 May 1;113(6):564-585. doi: 10.1093/cvr/cvx049

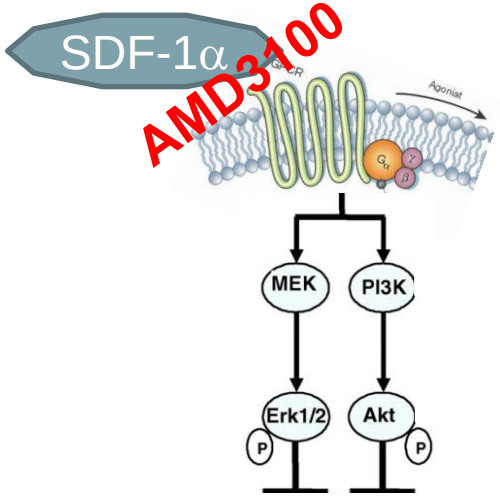
Ischaemic conditioning and targeting reperfusion injury: a 30 year voyage of discovery.

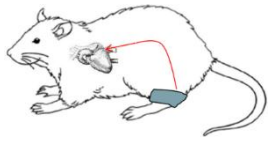
Hausenloy DJ, et al Basic Res Cardiol. 2016 Nov;111(6):70

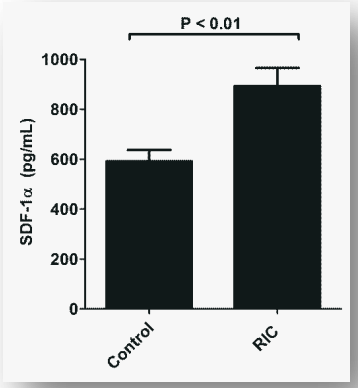
9th Hatter Biannual Meeting: position document on ischaemia/reperfusion injury, conditioning and the ten commandments of cardioprotection.

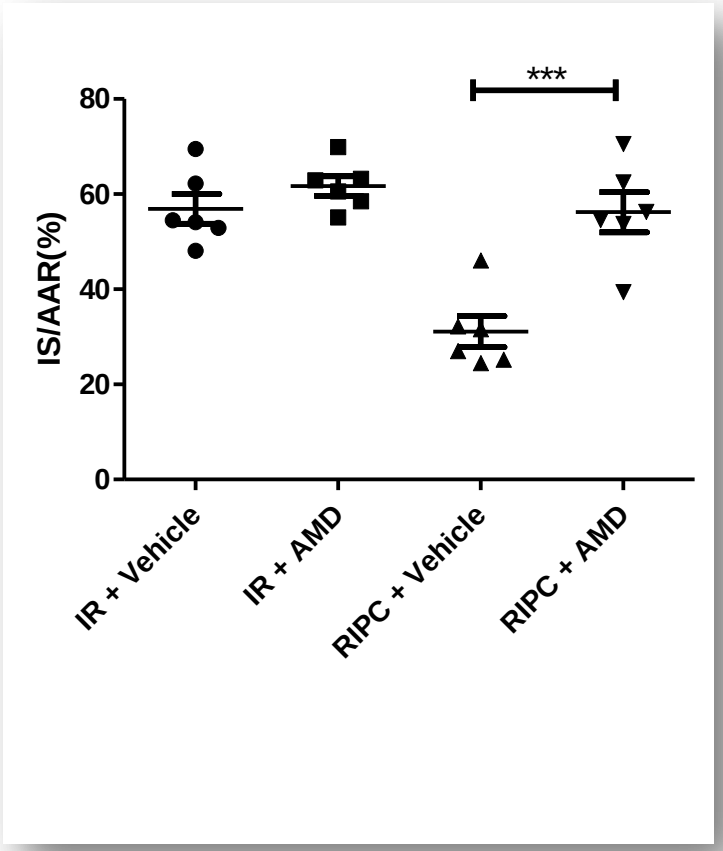
Bell RM et al, Basic Res Cardiol. 2016 Jul;111(4):41

Inhibition of SDF-1α binding prevents RIC









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