Cardioprotection: Challenges and Possibilities

Derek J Hausenloy

Reader in Cardiovascular Medicine,
British Heart Foundation Senior Clinical Research Fellow,
The Hatter Cardiovascular Institute,
University College London, UK.

Adaptive Response in Biology and Medicine,
University of Massachusetts, Tue 22nd April 2014

Outline of talk

- The need for cardioprotection
  - Myocardial Reperfusion Injury.
- ‘Conditioning’ the heart to protect itself
  - Bench to Bedside in action.
- Challenges to cardioprotection
  - Confounders.

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The need for cardioprotection

- Ischemic heart disease is the leading cause of death and disability in the UK:

  124,000 heart attacks, 88,000 deaths per year.

  Costs UK £9.0 billion/year

  1 year death rate of 9% and heart failure 10%

- *Novel therapeutic interventions are required to protect the heart from acute IRI (cardioprotection) so as to reduce MI size, preserve LV function and increase patient survival.*

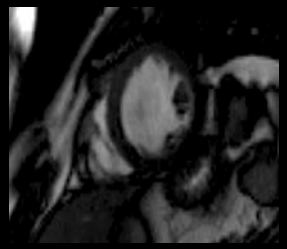
Acute ischemia-reperfusion injury

No effective therapy for preventing reperfusion injury.

STEMI patients undergoing PPCI

Chest pain
Start of cardiac bypass

PPCI
End of bypass



Acute myocardial ischemia

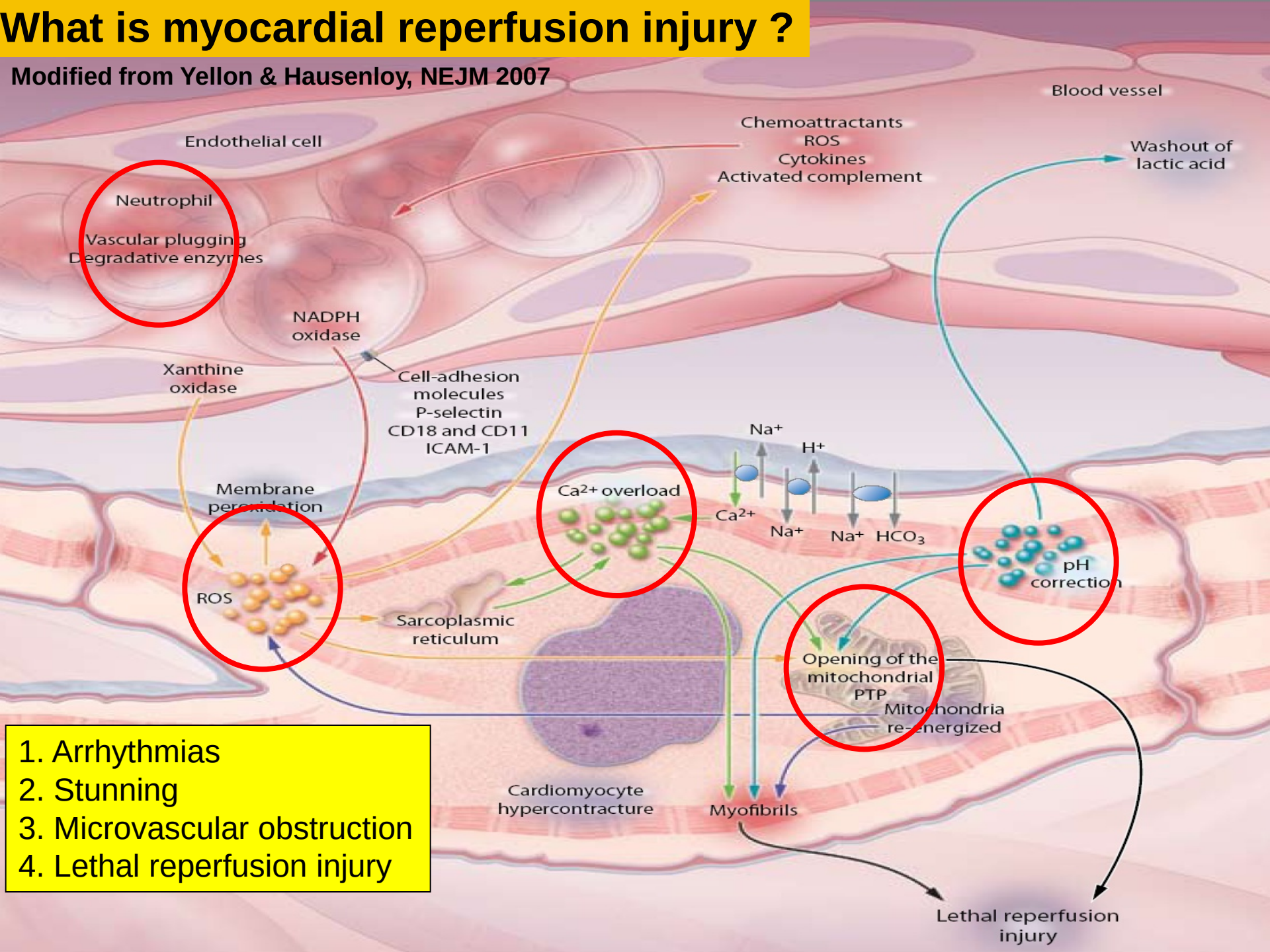
Reperfusion

Chest pain to PPCI time
Cardiac bypass time

Patients undergoing CABG surgery

What is myocardial reperfusion injury ?

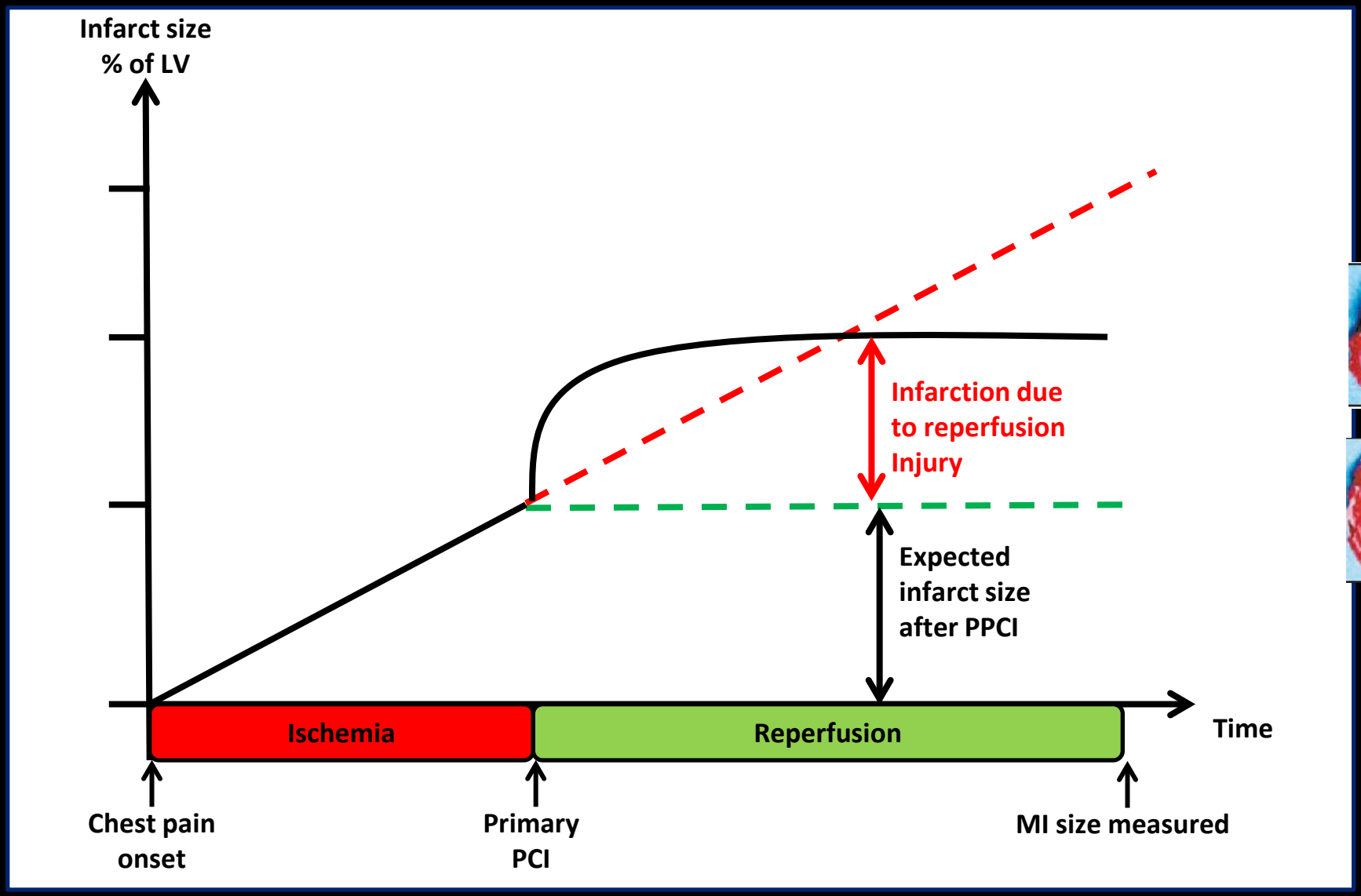
Modified from Yellon & Hausenloy, NEJM 2007

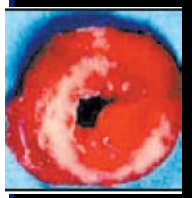


1. Arrhythmias
2. Stunning
3. Microvascular obstruction
4. Lethal reperfusion injury

How important is reperfusion injury?

Hausenloy & Yellon JCI 2012





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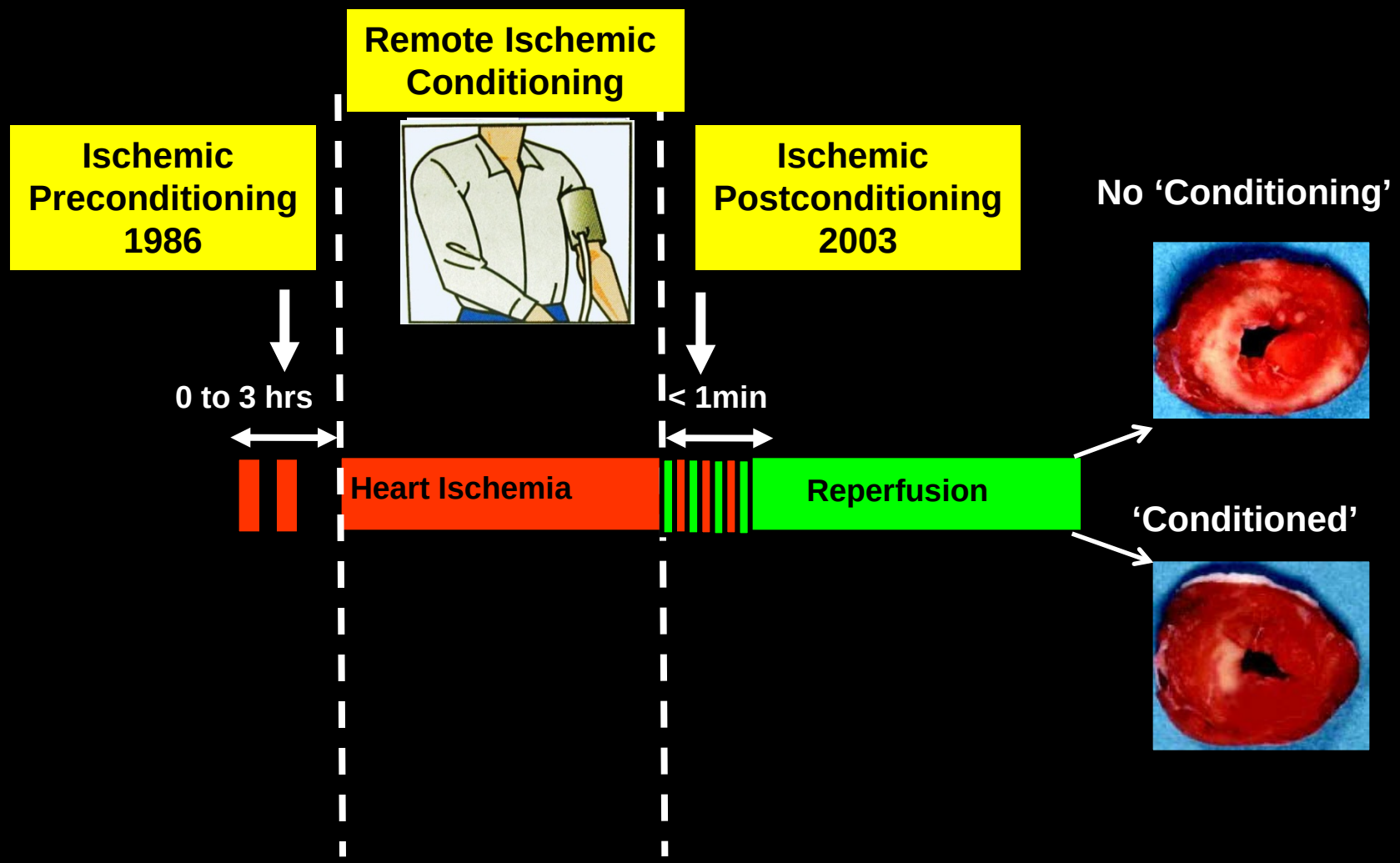
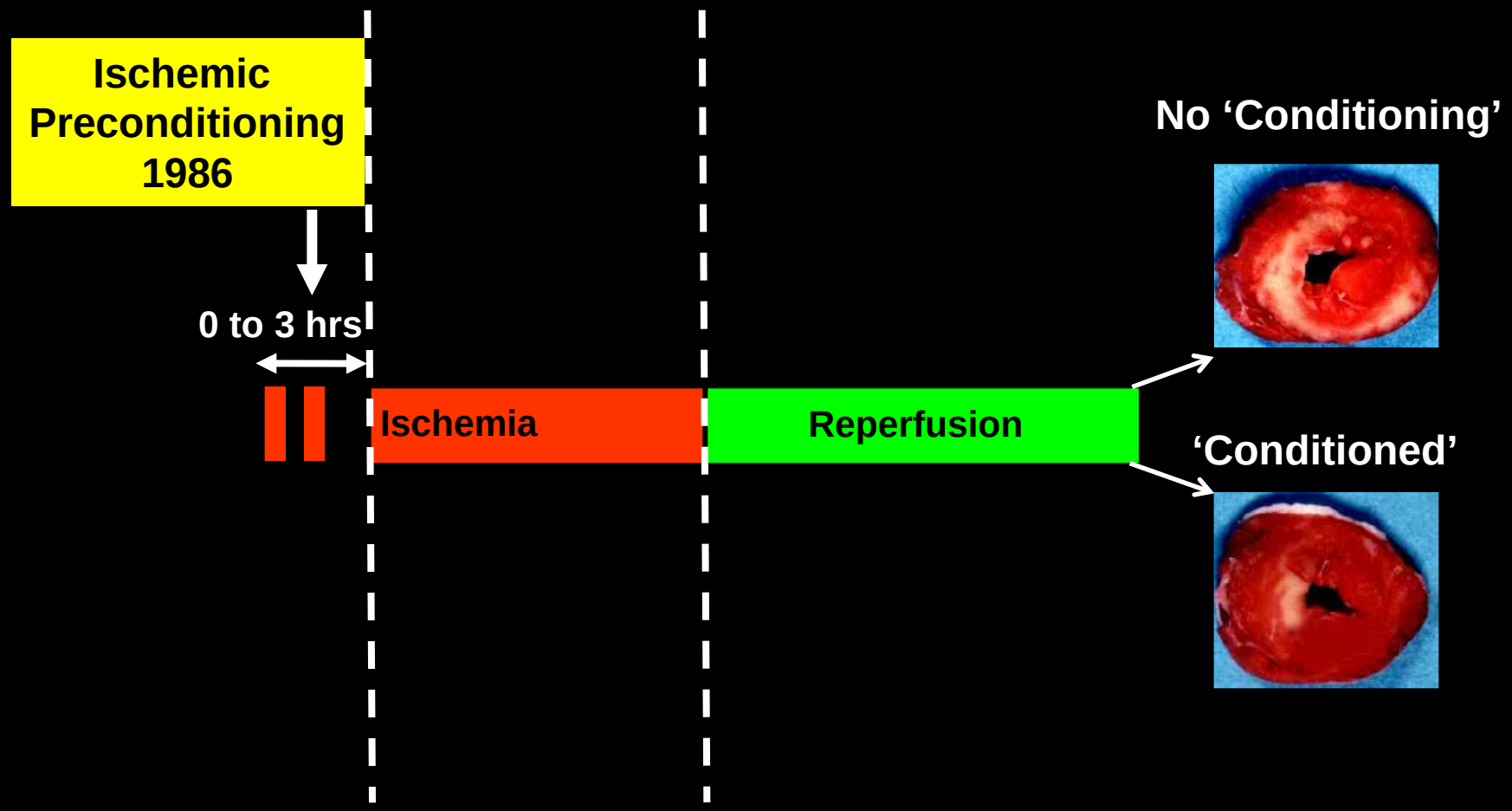
‘Conditioning’ the heart



Ischemic Preconditioning

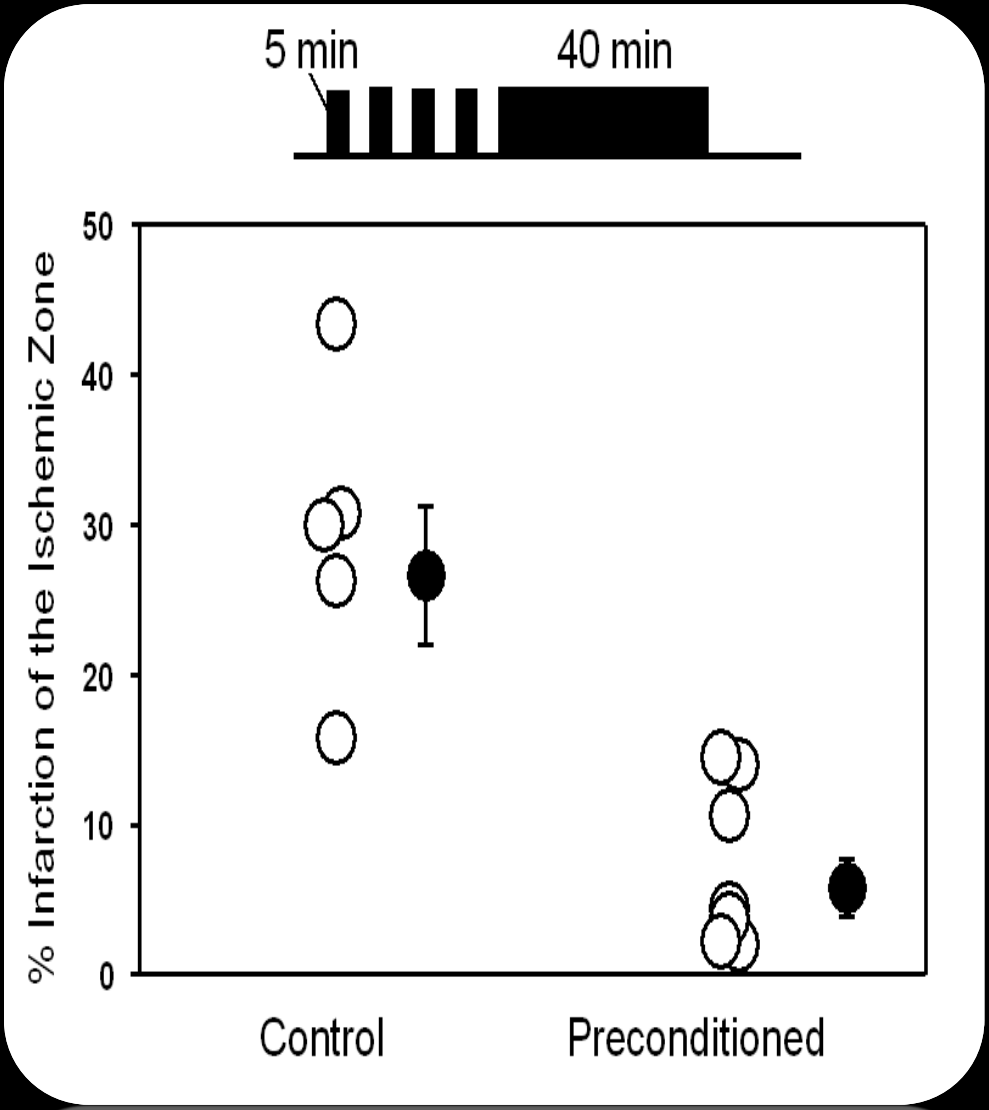


Ischemic Preconditioning

Murry et al Circ 1986:74;1124.

- Canine hearts:
  40 min LAD occlusion
  72 hrs reperfusion.

- IPC: 4x5 min LAD occlusion.



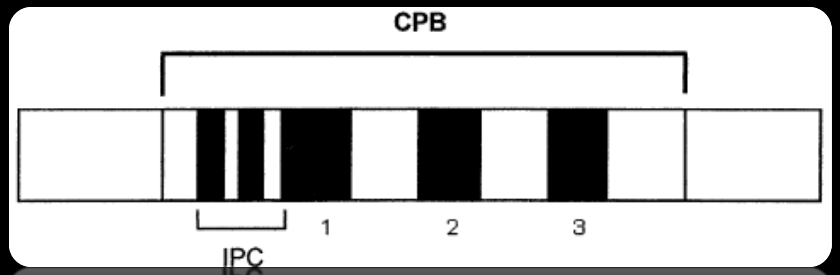
Ischemic Preconditioning in Surgery

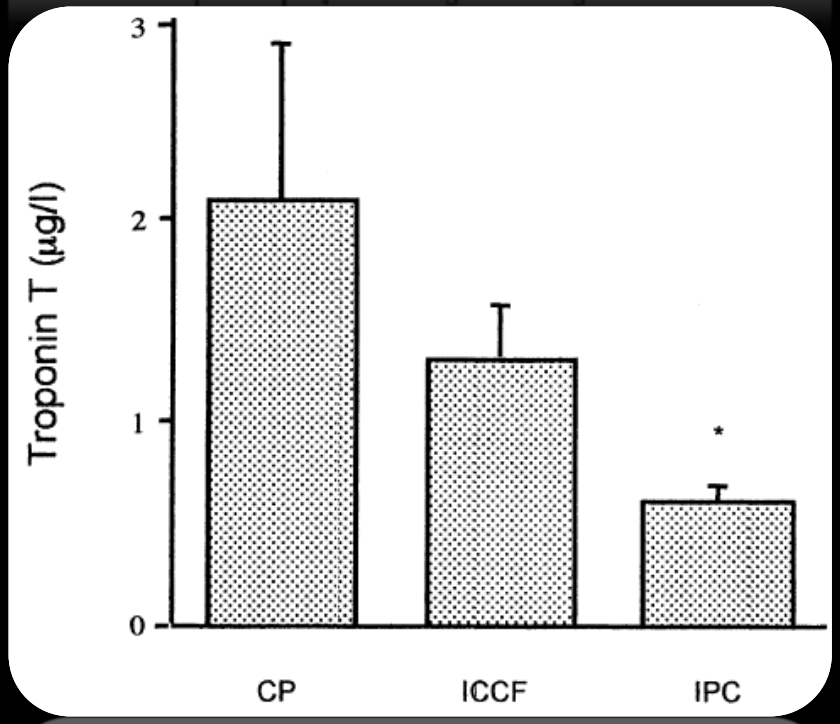
Teoh et al Cardiovasc Surg 2002:10;251.
Walsh et al Eur J Cardiothorac Surg. 2008:34;985.

- 30 CABG patients:
  Control or IPC.
- IPC- 2x3 min episode of aortic cross-clamping
- Meta-analysis of 22 trials, 933 on-pump CABG patients.
- IPC reduced the following:

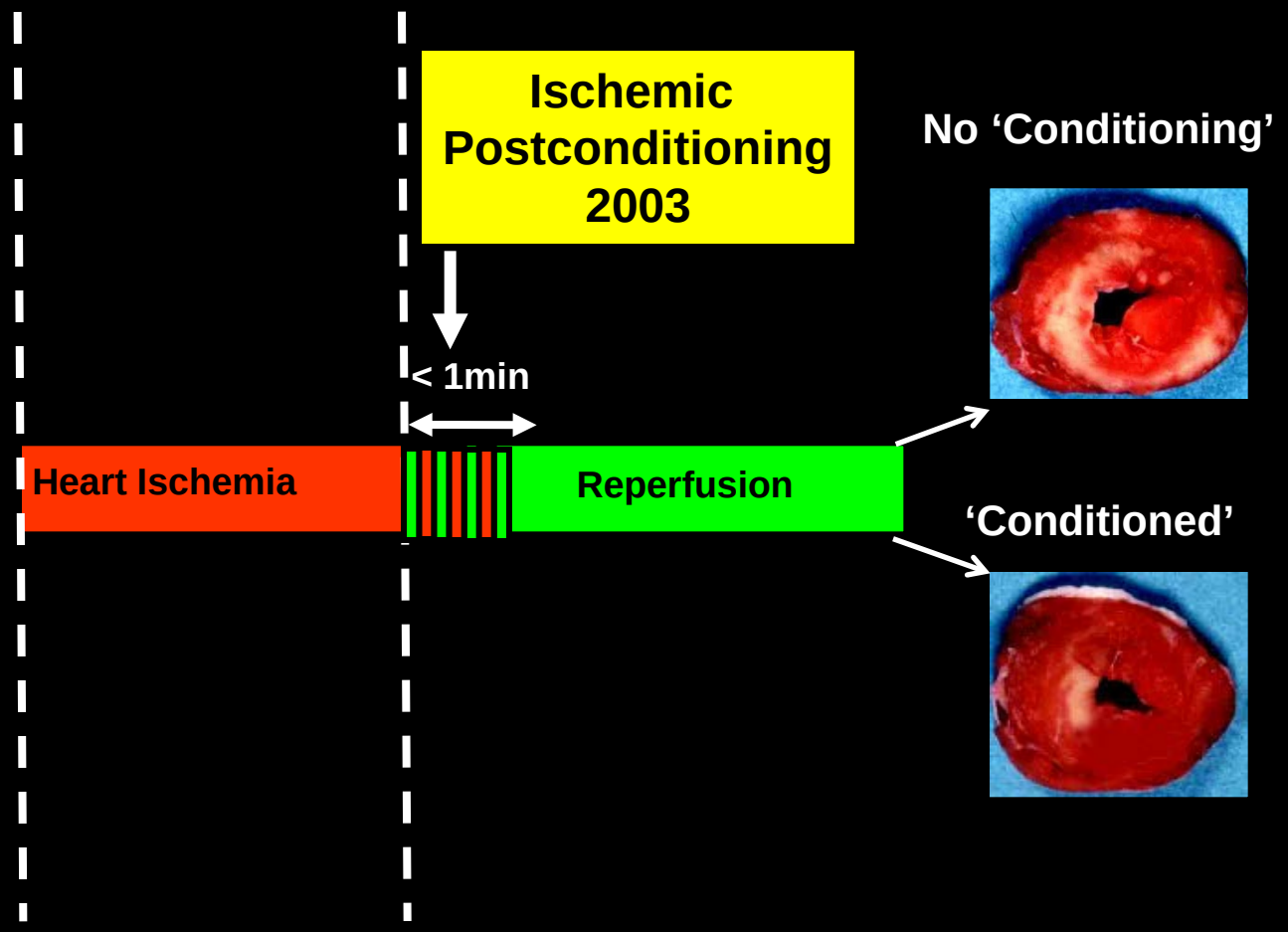
1. ventricular arrhythmias
2. inotrope requirements
3. intensive care unit stay

- Not practical and potentially dangerous.





Ischemic Postconditioning



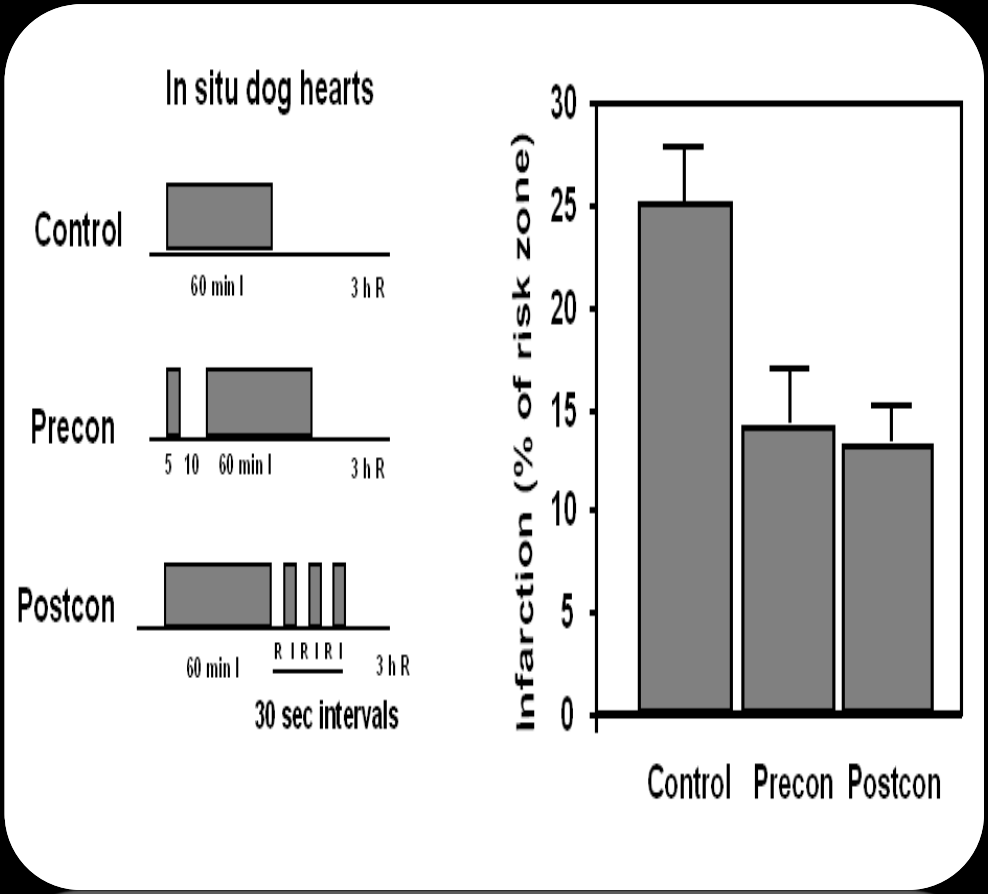
Ischemic Postconditioning

Zhao et al AJP 2003 285;H579.

- Canine hearts:

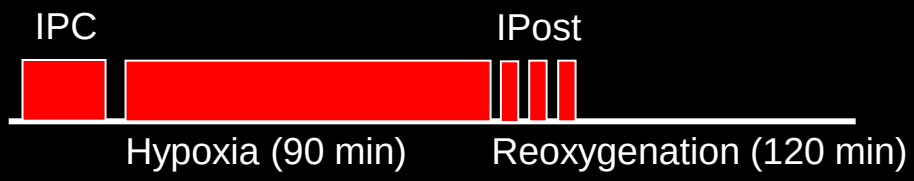
  LAD occlusion for 60 min
  3 hrs reperfusion.

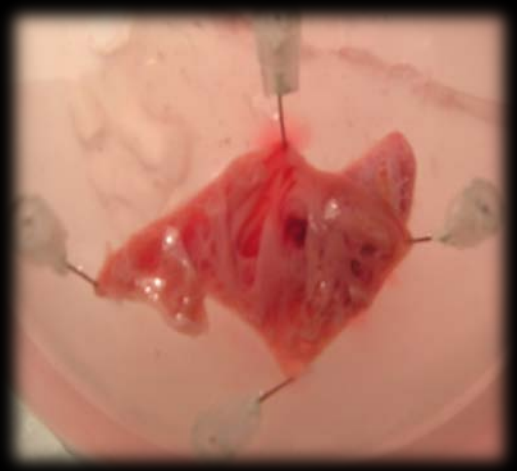
- Interrupting myocardial reperfusion with 3x30 sec episodes of LAD re-occlusions.

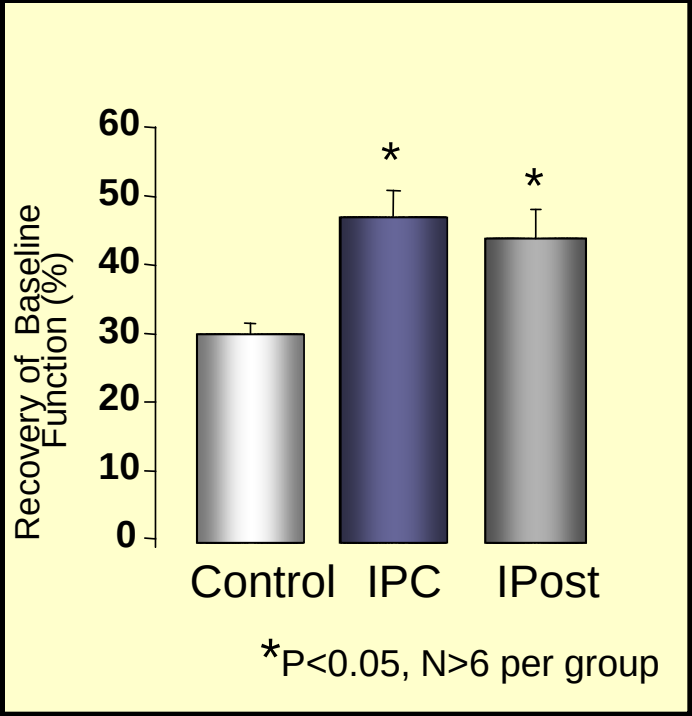


Human atrial tissue SIRI model

Sivaraman, Hausenloy, et al 2005 AJP







Ischemic Postconditioning in STEMI

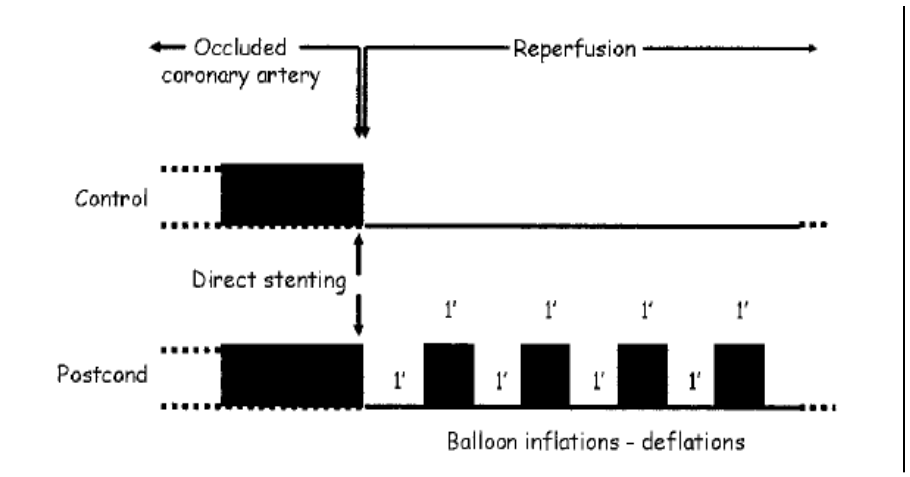
Staat et al Circ 2005:112;2143.

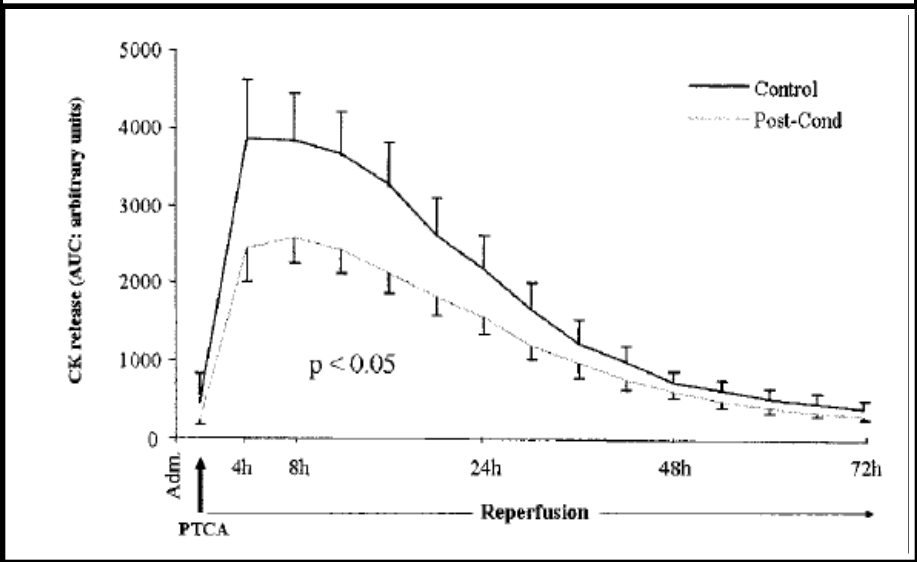
- 30 STEMI pts:

  Control- Normal PPCI

  IPost- 4x1 min inflations/deflation
- 40% MI size reduction confirmed using SPECT and cardiac MRI in larger studies.

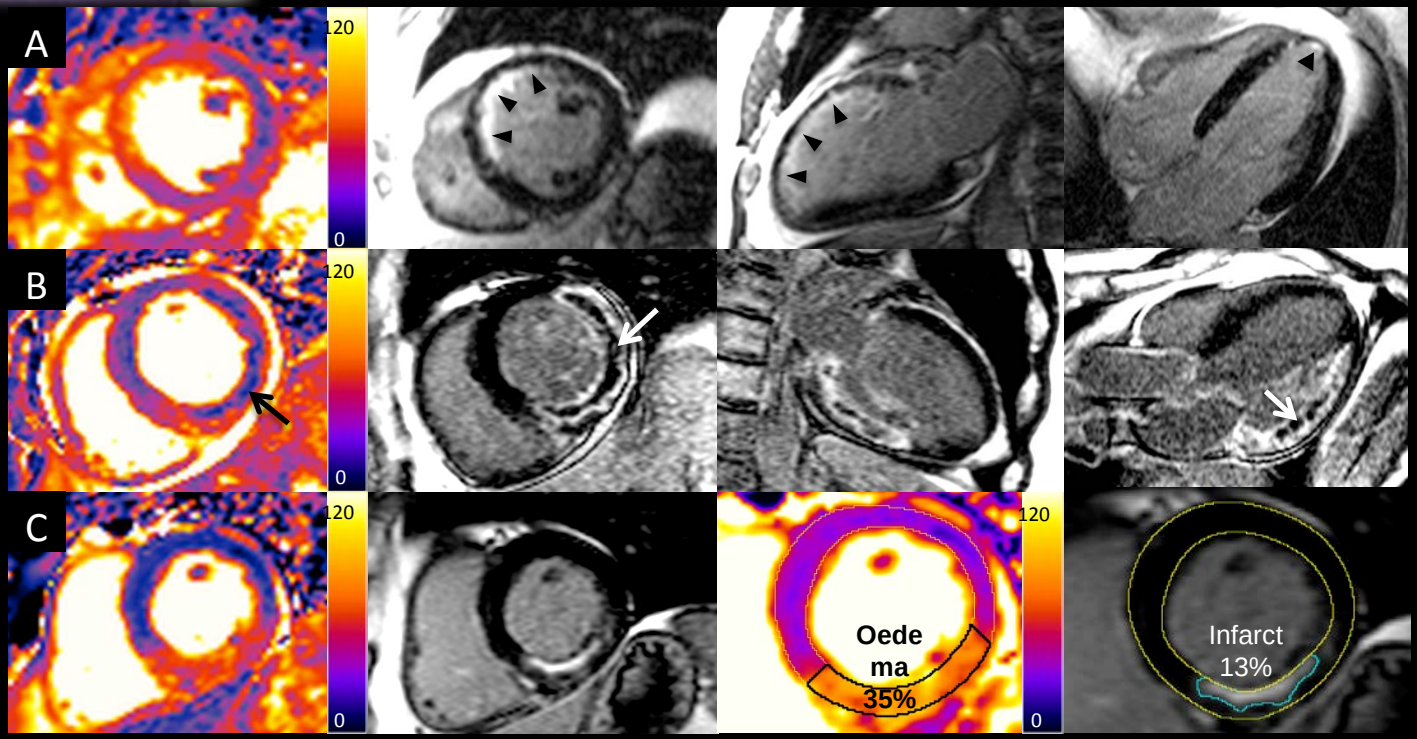
- Some negative studies.
- Difficult to implement protocol
- DANAMI-3 clinical outcome study underway.





ERIC-STEMI trial

White, Yellon, Hausenloy et al (JACC Intervention 2014 In Press)



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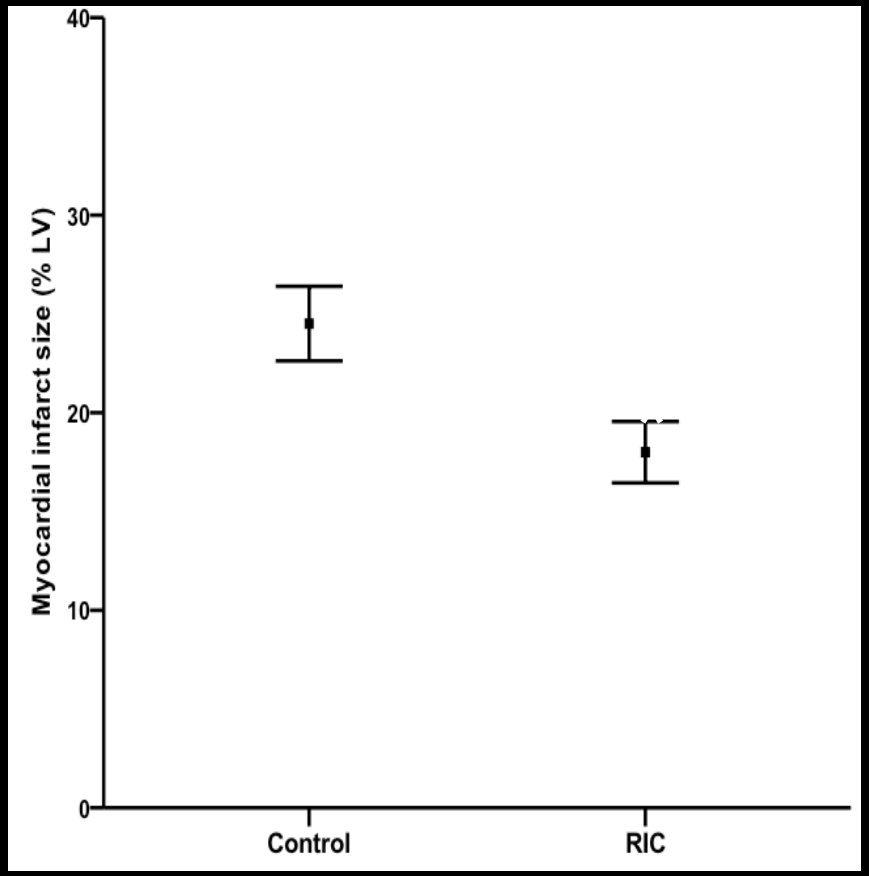
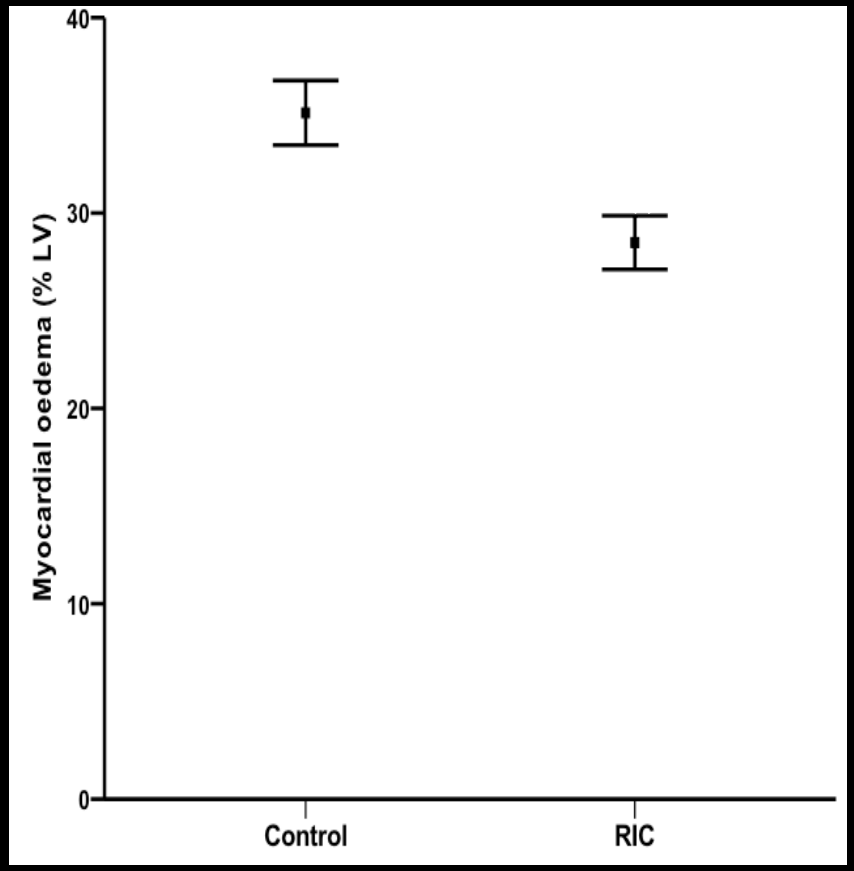
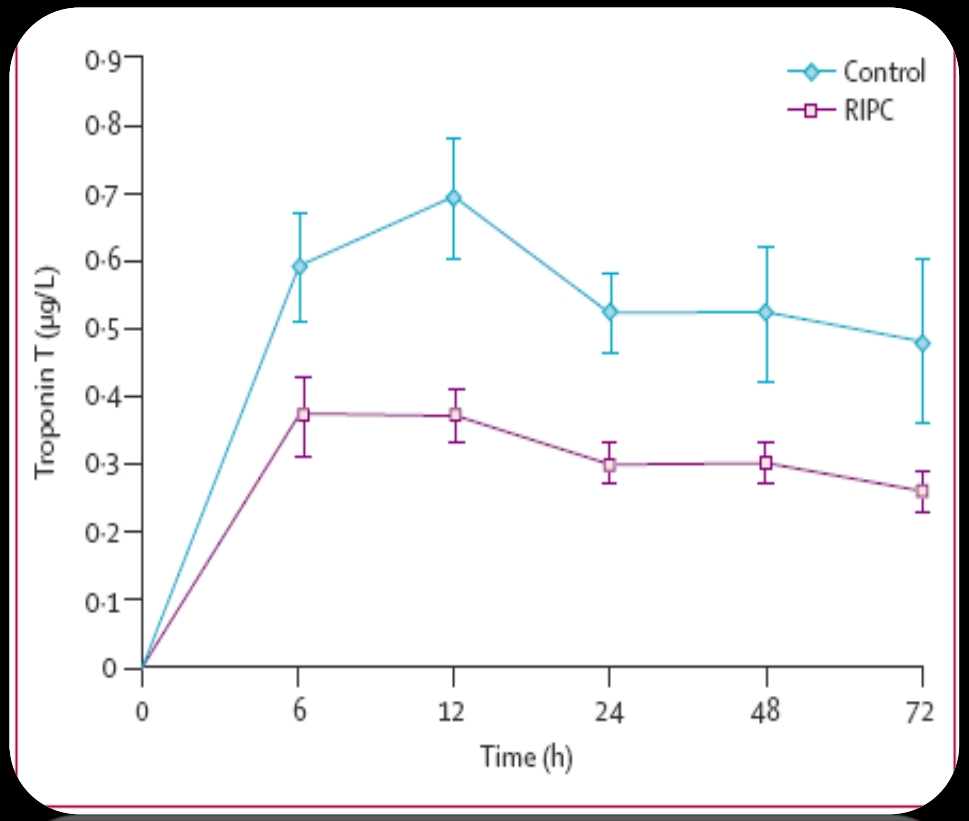




RIC in CABG surgery

Hausenloy et al Lancet 2007

- Higher risk patients undergoing CABG surgery.
- During CABG surgery PMI (CK-MB/Trop) linked to worse outcomes.
- 57 adult CABG patients:
  RIPC- 3x5 min cuff inflation
  Control- 30 min deflated cuff
- RIPC reduced myocardial injury by 43% (AUC 72hr Trop T).



RIC in CABG surgery

Candilio, Hausenloy, Yellon et al (unpublished)

- Several negative studies with 3x5 min RIC cycles.
- Increase the strength of the RIC stimulus but shorten it- simultaneous arm/leg IR (only 20 min protocol).
- RIC improved short-term clinical outcomes.

1. *Reduced 72 hr AUC hsTrop-T by 27%*
2. *Decreased incidence of post-operative AF (11% RIC versus 24% control)*
3. *Less AKI (7% RIC versus 17% control)*
4. *Shortened ICU stay (2.0 days RIC versus 3.0 days control).*

ERICCA trial

30 UK centres 1610 patient study

CABG±valve surgery/ Euroscore≥5/ blood cardioplegia

Randomization/allocation

RIC: 4 x 5 min cuff Inflation 200mmHg/deflation

Sham RIC: 4 x 5 min simulated Inflations/deflations

<u>Primary outcome at one year</u>

CV death, Myocardial Infarction, Revascularisation, Stroke

1612 patients recruited - outcomes Mar 2015

Efficacy and Mechanism Evaluation programme

MRC Medical Research Council

NHS National Institute for Health Research

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Challenges of cardioprotection

- *Translation of cardioprotective therapies for patient benefit has been disappointing.*

- Pre-clinical assessment of cardioprotective therapies (animals, models).

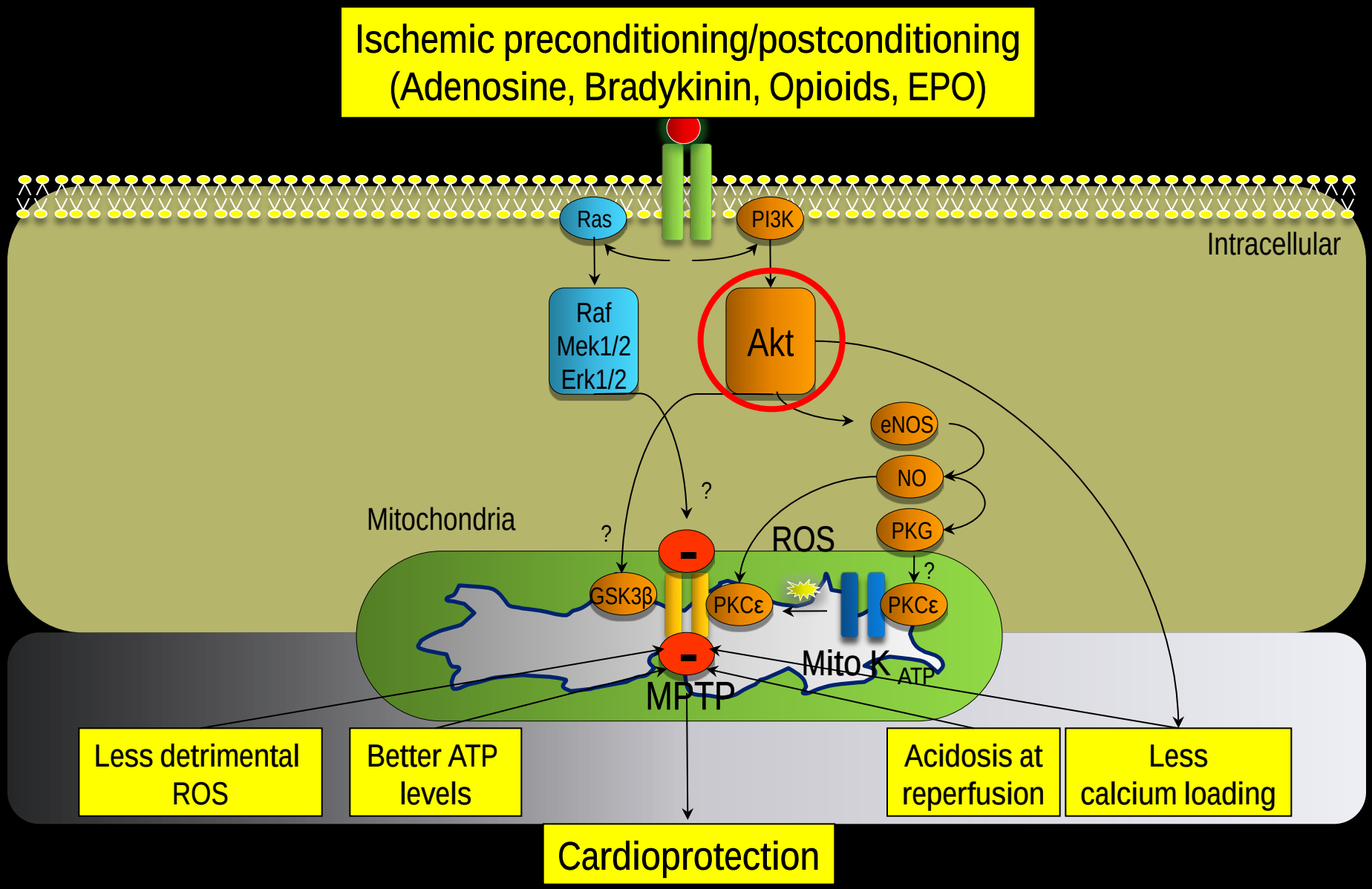
- Confounding factors (age, DM, chol, HT, gender)

- Concomitant medication (GTN, sulphonylureas, nicorandil, Statins).

- Poorly designed clinical studies.

Cardioprotective signaling in diabetes

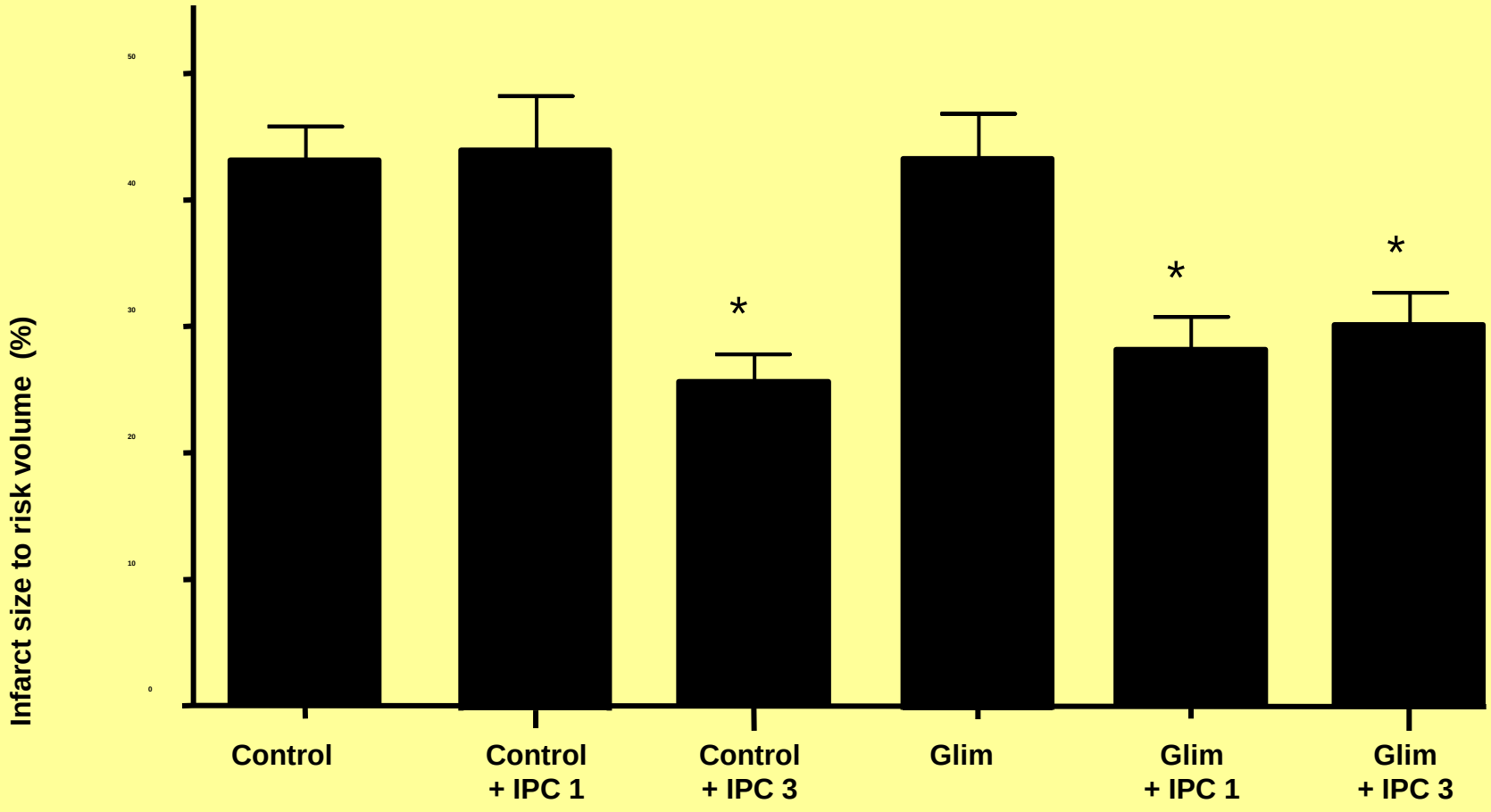
Hausenloy & Yellon Basic Res Cardiol. 2009 104(2):189-202



The diabetic heart and IPC

Tsang et al Diabetes 2005; Hausenloy et al CPT 2013

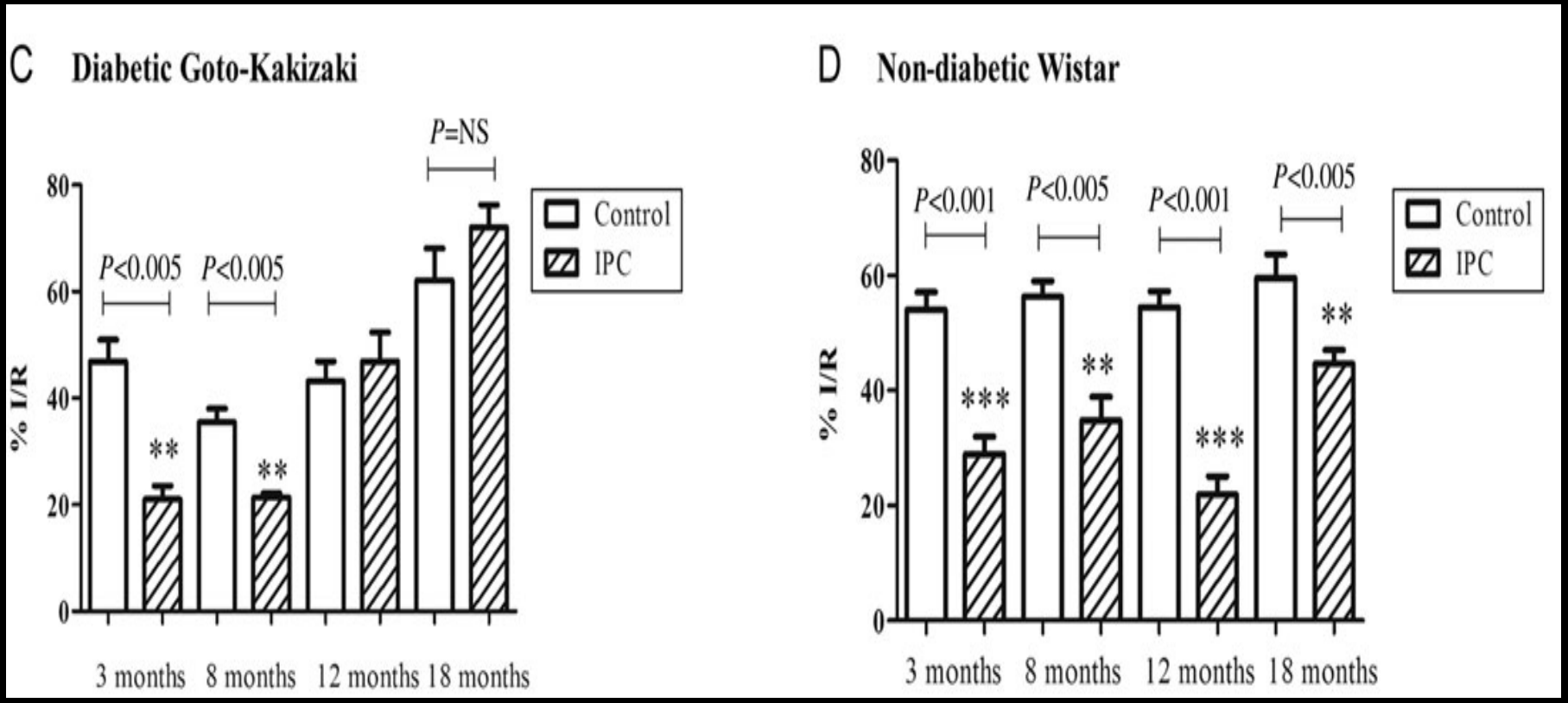
24 hours pre-treatment with glimepiride



Mean±SEM. *P<0.05. N>6/group

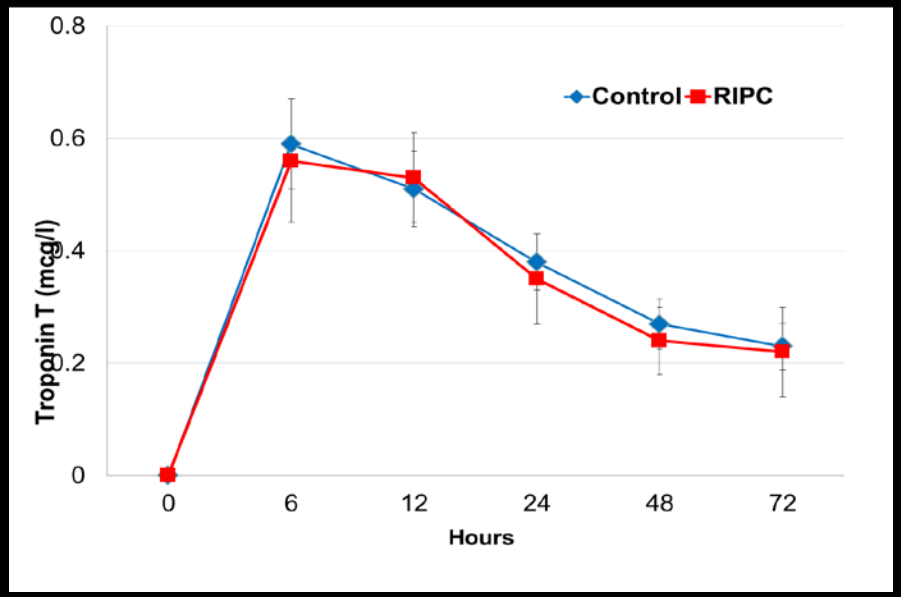
The diabetic aged heart and IPC

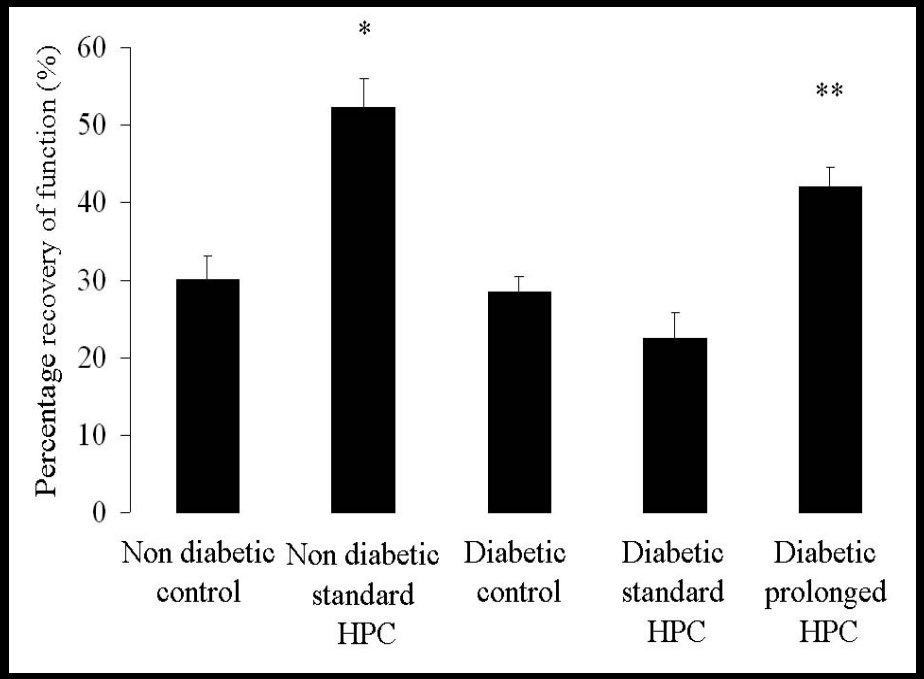
Whittington et al CVR 2013

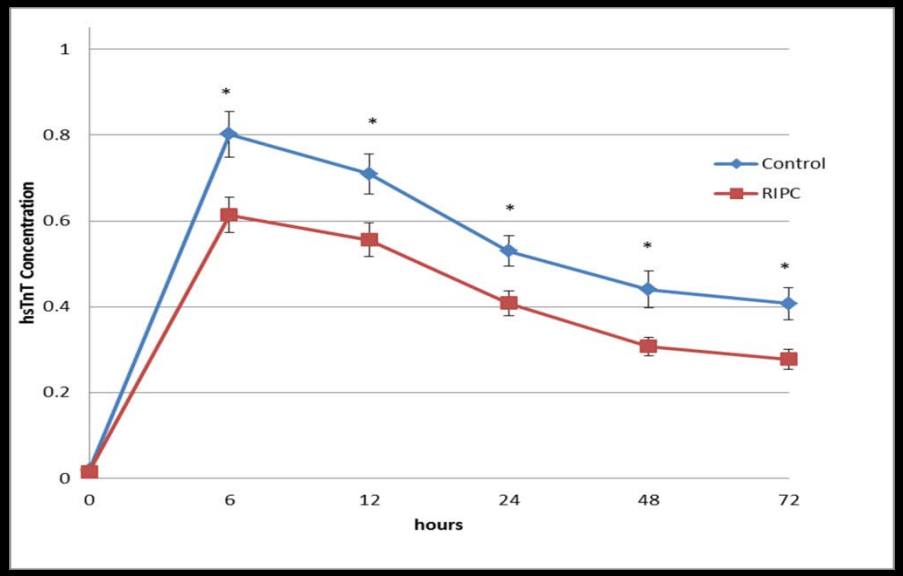


Cardioprotection in diabetic patients

Sivaraman, Candilio, Babu, Hausenloy Yellon







Improve pre-clinical studies

Hausenloy, Lecour et al (unpublished)

Model of I/R → *Complexity of the model*

↓ *Bench-to-bedside*

Cell culture	Cardiac cell lines	Neonatal cardiomyocytes	Adult cardiomyocytes	
Ex vivo	Isolated heart perfusion Human heart tissue	Confounders Co-morbidities Co-medication		
In vivo	Small animal Non recovery	Small animal recovery	Large animal Non recovery	Large animal recovery
	Confounders Co-morbidities Co-medication			
	Multi-centre randomized controlled studies			
Humans	Clinical testing of cardioprotective strategy			

Improve clinical study design

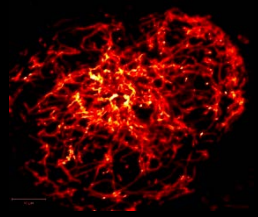
Hausenloy, Ovize et al CVR 2014

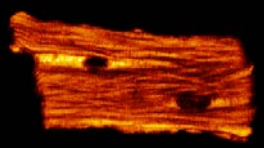
Table 6 Recommendations for designing MI-limiting studies in STEMI patients

Patient selection
• Select patients with a large area at risk (AAR) (>30% of the left ventricle)
• Select patients with no significant coronary collateralization to the AAR (Rentrop grade <1)
• Select patients with an occluded culprit artery at the time of study intervention administration (TIMI flow grade 0 or 1)
The study intervention
• Select a study intervention which has shown conclusive cardioprotection in pre-clinical studies
• Administer the study intervention as an iv or intracoronary bolus *prior* to myocardial reperfusion
Choose MI-limiting-related study endpoints
• MI size (48 h AUC cardiac enzymes or late gadolinium enhancement cardiac MRI)
• Myocardial salvage index (AAR-MI size/AAR)
• Incidence and extent of microvascular obstruction (cardiac MRI)
• Indexed left ventricular end systolic/diastolic dimensions (echocardiography or cardiac MRI)
• Left ventricular systolic function (echocardiography or cardiac MRI)
• Hospitalization for heart failure
• Cardiac death

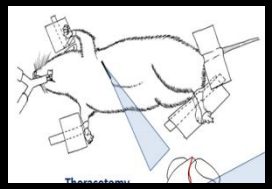
Translational pathway for cardioprotection

Identification of novel therapeutic targets





Test in ex-vivo and in vivo small animal IRI models



Test in ex-vivo human heart tissue IRI models

Test in proof of concept clinical studies

Test in large multicentre clinical outcome studies

ERICCA

Conclusions

- Myocardial reperfusion injury:
  - neglected target for cardioprotection.
- Proof-of-concept clinical studies have shown that ischemic conditioning can benefit patients
  - clinical outcomes studies now underway
- Many challenges to cardioprotection translation.
  - better pre-clinical assessment of intervention
  - better design clinical studies

Acknowledgements

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Efficacy and Mechanism Evaluation programme

MRC Medical Research Council

NHS National Institute for Health Research