

# Remote Ischemic Conditioning: Bench to Bedside in Action!

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Joint meeting of Coronary Revascularization

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**The Hatter Cardiovascular Institute**



- The need for cardioprotection.
- Remote ischemic conditioning as a cardioprotective strategy.
- Ongoing clinical outcome studies.

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# Ischemia-reperfusion injury as a target

*No effective therapy for preventing reperfusion injury*

STEMI patients undergoing PPCI



Chest pain



Start of cardiac bypass



PPCI

End of bypass



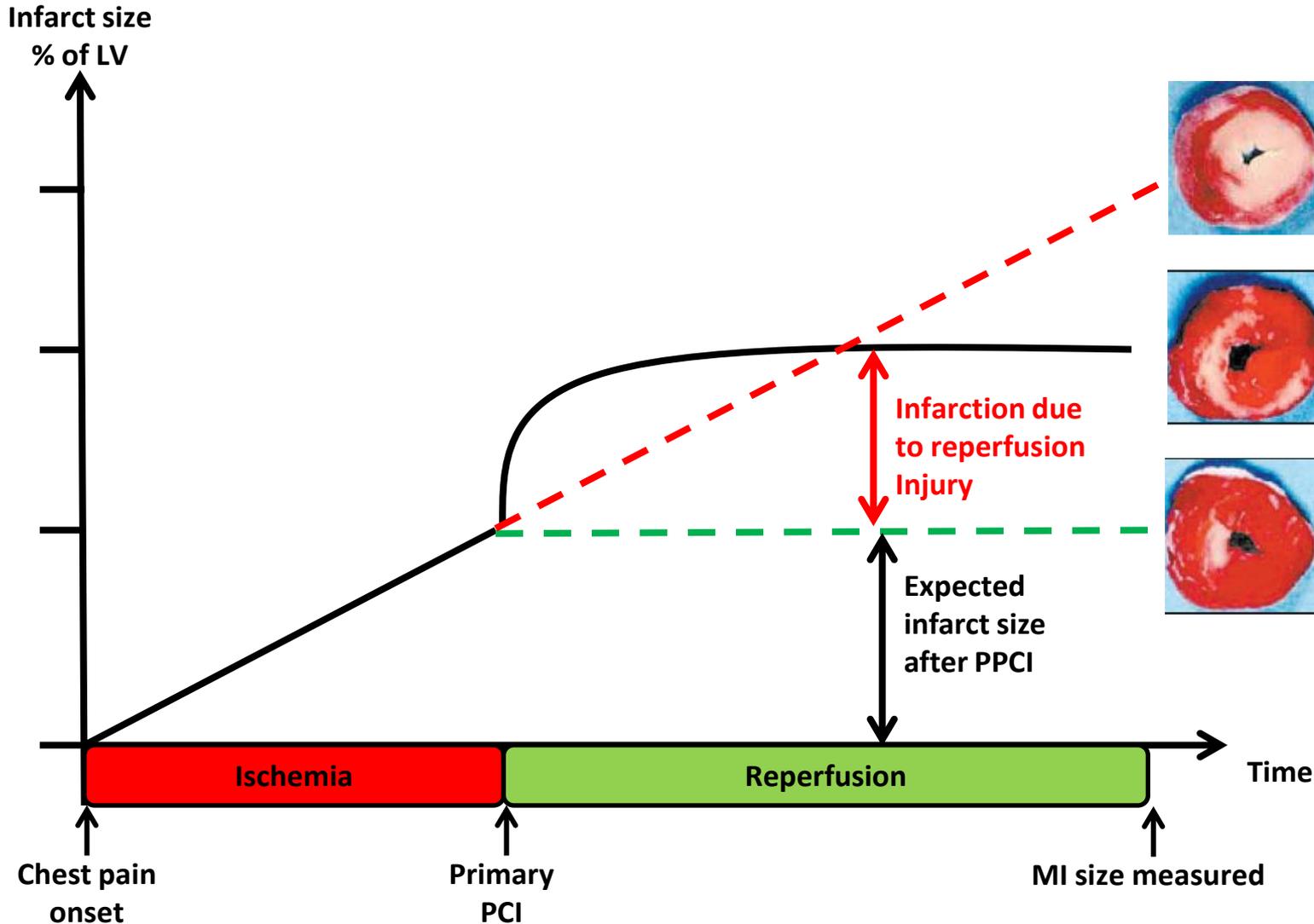
**Higher risk patients**

**Age, DM, HT, CRF, Valve surgery**

**Worse clinical outcomes**

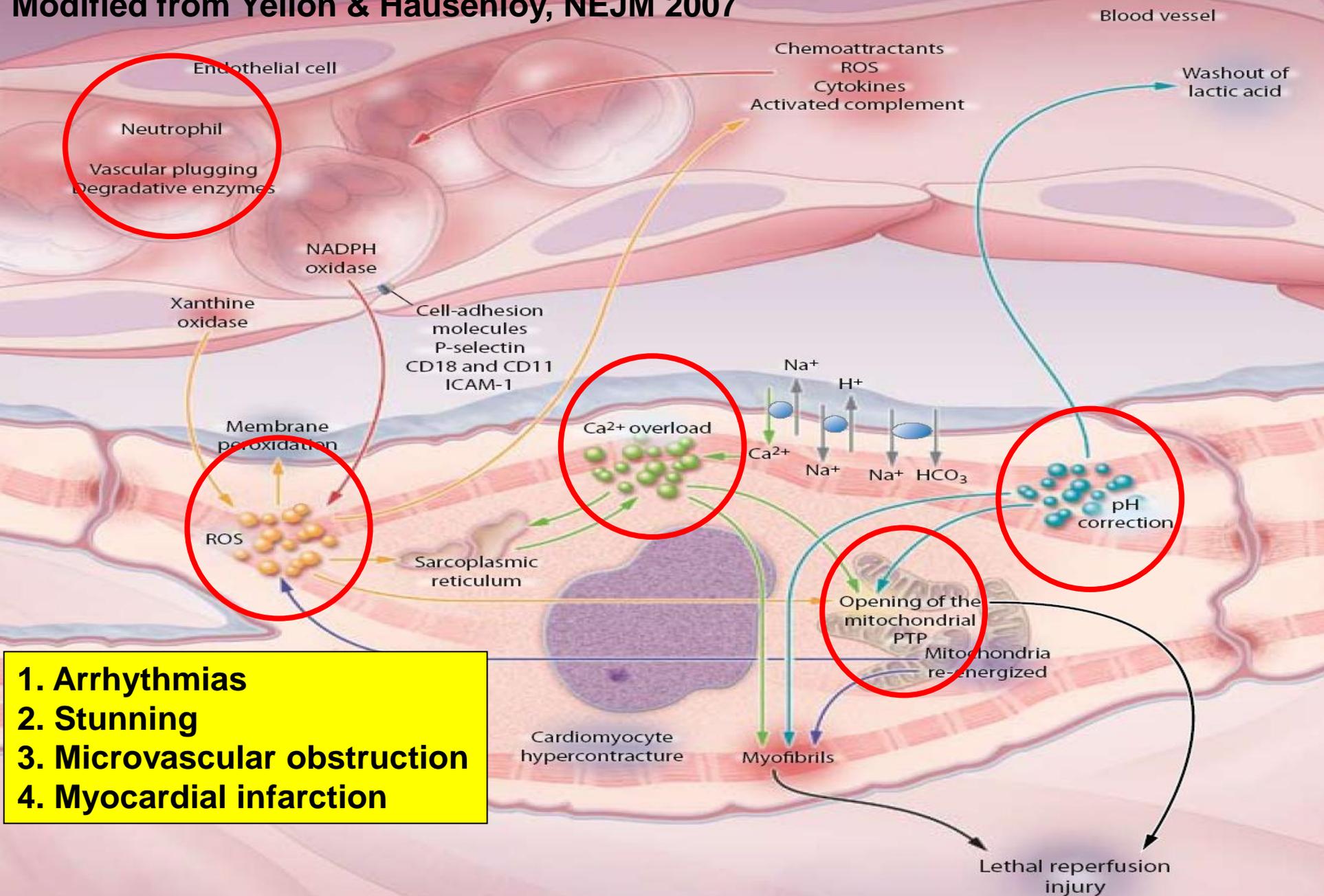
# How important is reperfusion injury?

Hausenloy & Yellon JCI 2012



# What causes myocardial reperfusion injury ?

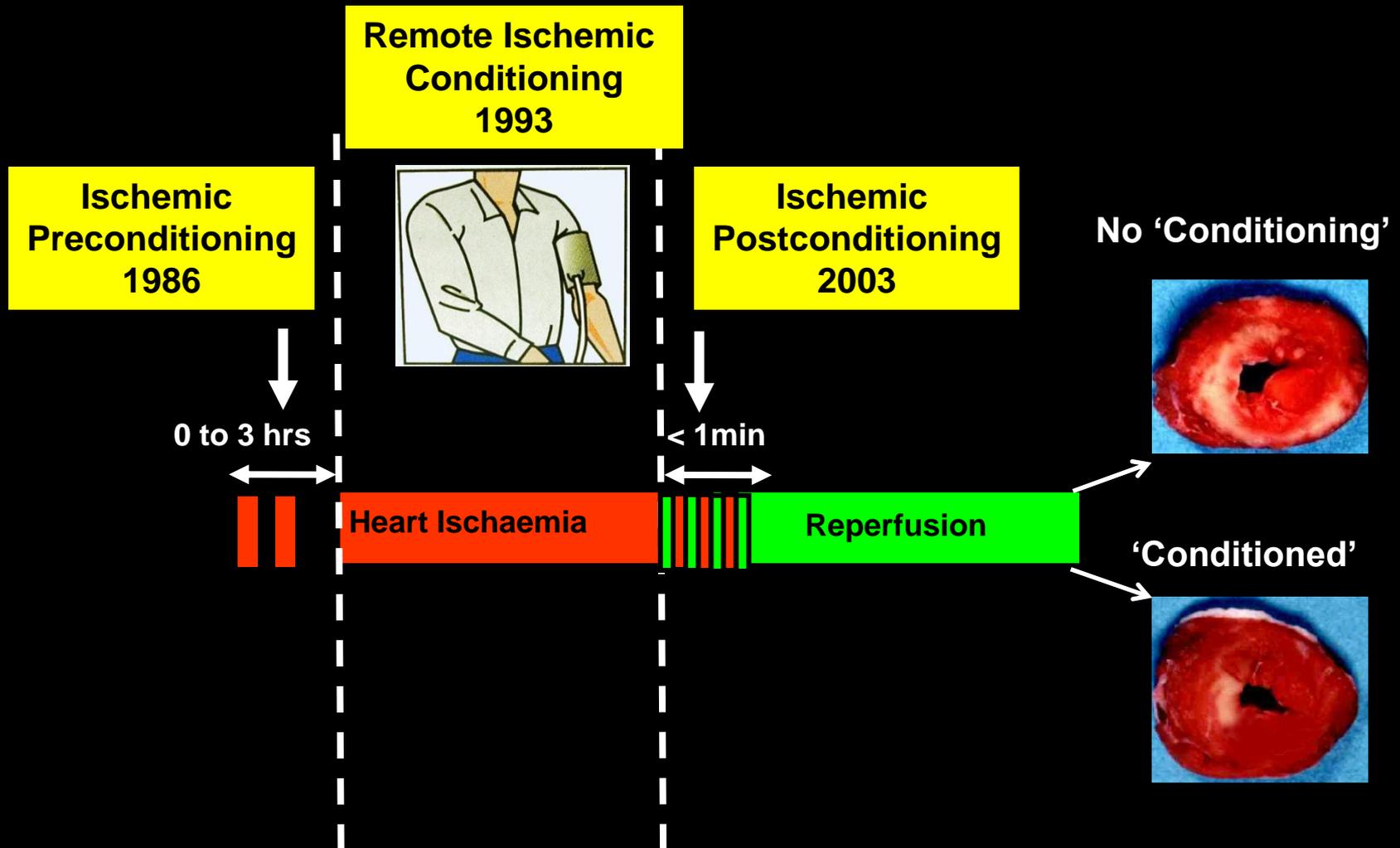
Modified from Yellon & Hausenloy, NEJM 2007



- The need for cardioprotection.
- Remote ischemic conditioning as a cardioprotective strategy.
- Ongoing clinical outcome studies.

# 'Conditioning' the heart

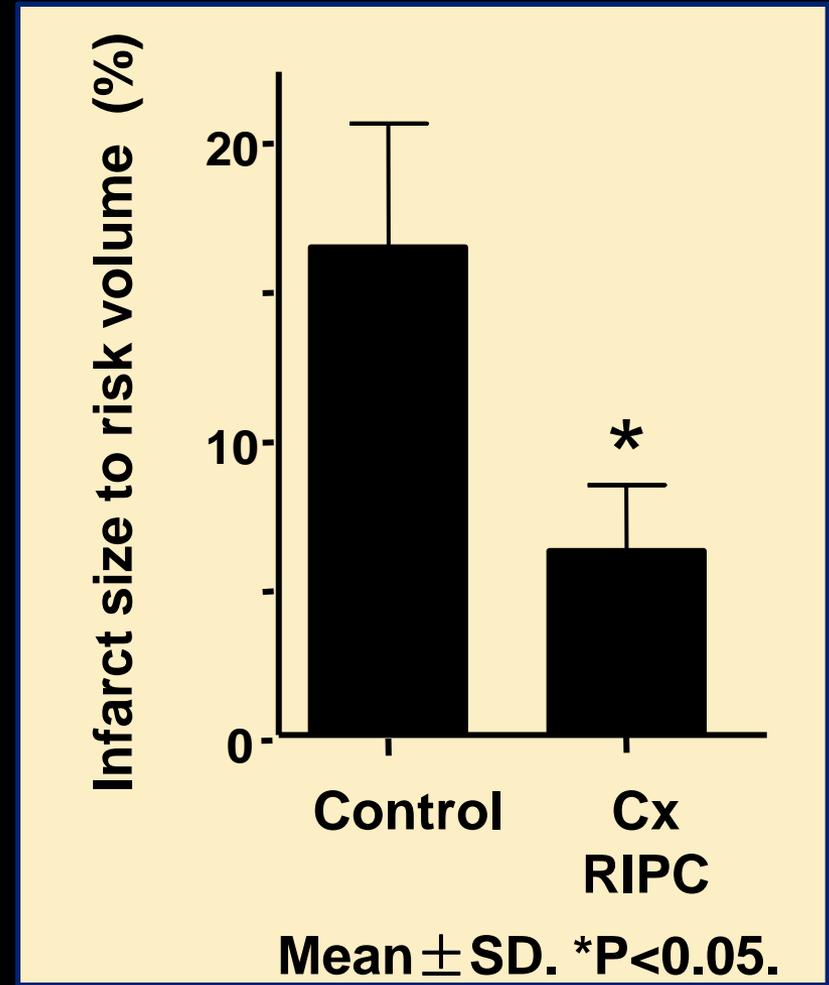
*Use brief episodes of ischemia/reperfusion to 'condition' the heart to protect it from IRI.*



# Remote Ischemic Conditioning

*Przyklenk et al Circ 1993;87;893.*

- 4x5 min cycles of Cx occlusion/reflow reduced MI size in LAD territory.
- Transferring protection from one coronary territory to another.
- Extended between organs.
- Non-invasively reproduced using cuff on arm or leg.



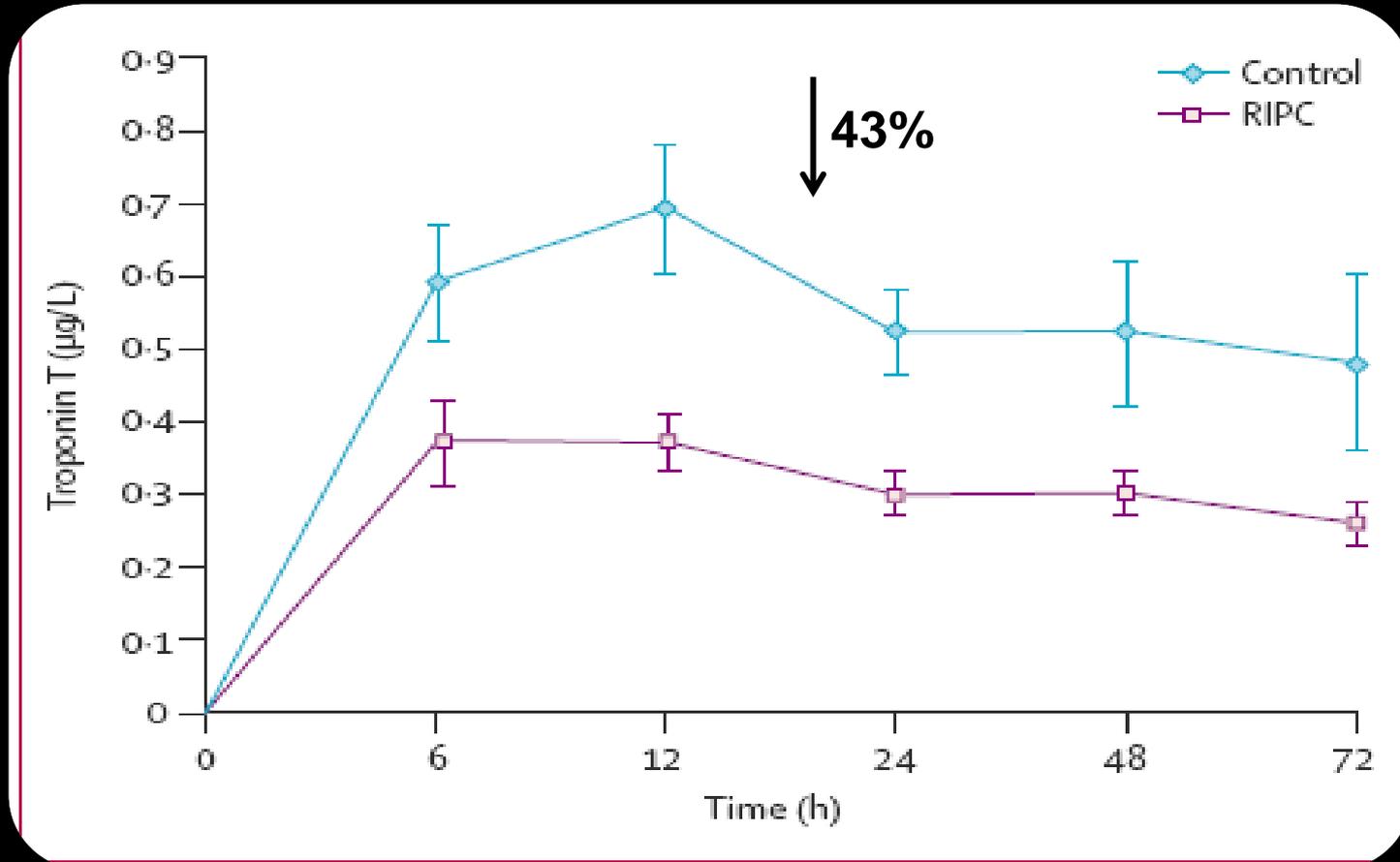


# RIC in CABG surgery

Hausenloy...Yellon Lancet 2007



- Higher risk patients undergoing CABG surgery.
- CK-MB/Trop linked to worse outcomes.
- 57 adult CABG patients RIPC- 3x5 min inflations.

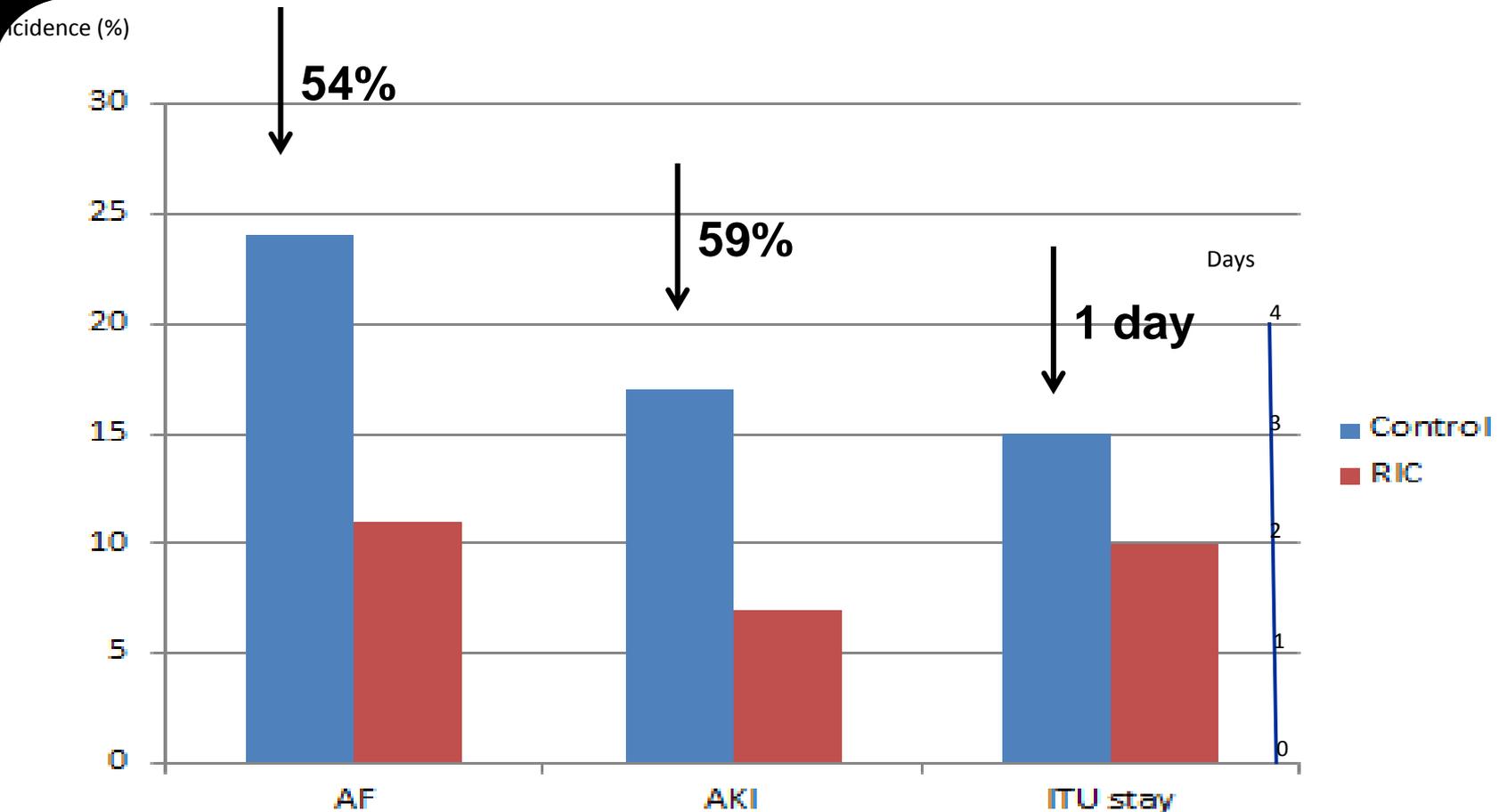


# RIC in CABG surgery



*Candilio, Hausenloy, Yellon Heart 2014*

190 patients RIC simultaneous arm/leg cuff (2x5 min cycles).





**30 UK centres, 1610 patients, £1.5 m NIHR/EME/BHF study**

**CABG±valve surgery/ Euroscore≥5/ blood cardioplegia**

*Randomisation/allocation*

**RIC: 4 x 5 min cuff**

**Sham RIC: 4 x 5 min simulated**

**Inflation 200mmHg/deflation**

**Inflations/deflations**



**Primary outcome at one year**

**CV death, Non-fatal MI, Revascularisation, Stroke**

**1612 patients recruited - Results Mar 2015 at ACC**

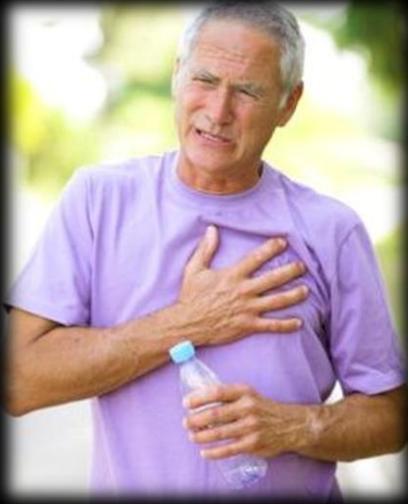


# ERIC-STEMI trial

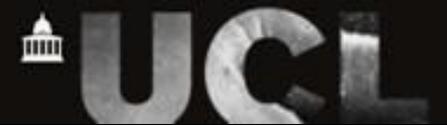


*White.....Hausenloy JACC Intervention 2014*

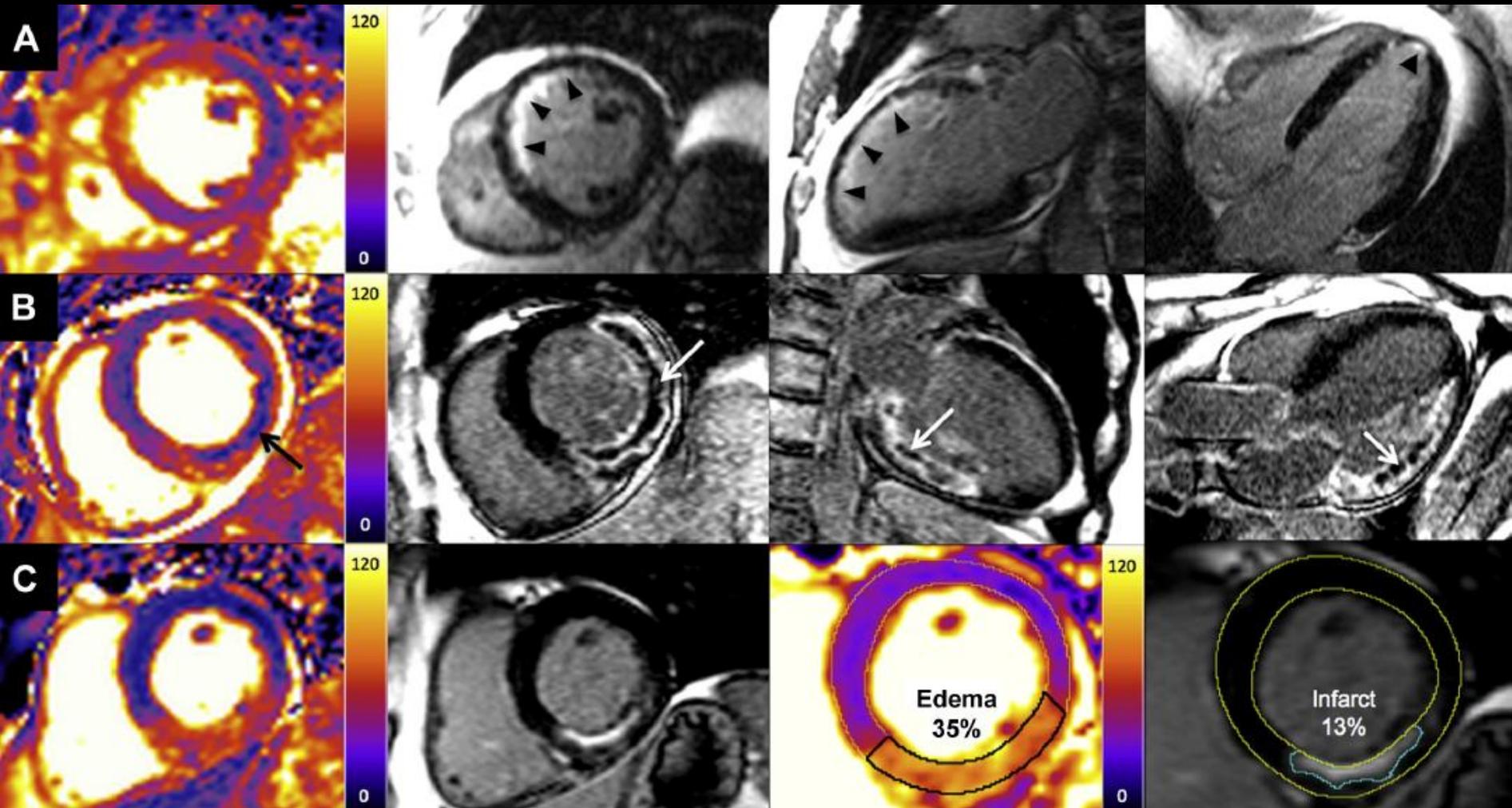
- RIC on MI size (assessed by CMR) in STEMI patients.
- 83 STEMI patients: RIC (4x5 min cycles).



# ERIC-STEMI trial



White.....Hausenloy JACC Intervention 2014





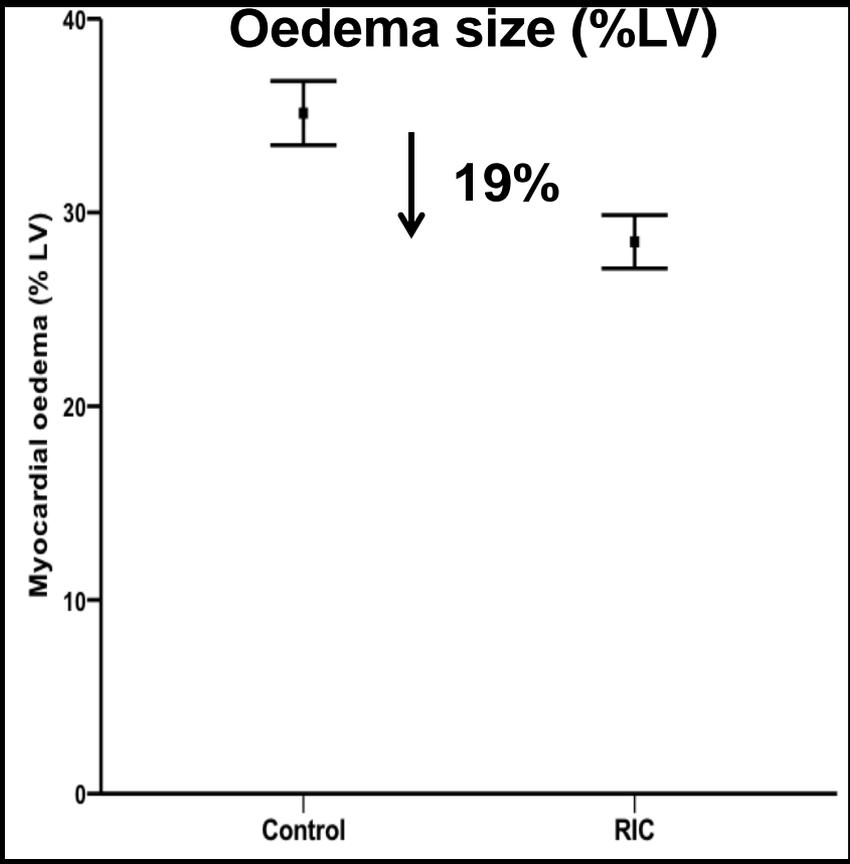
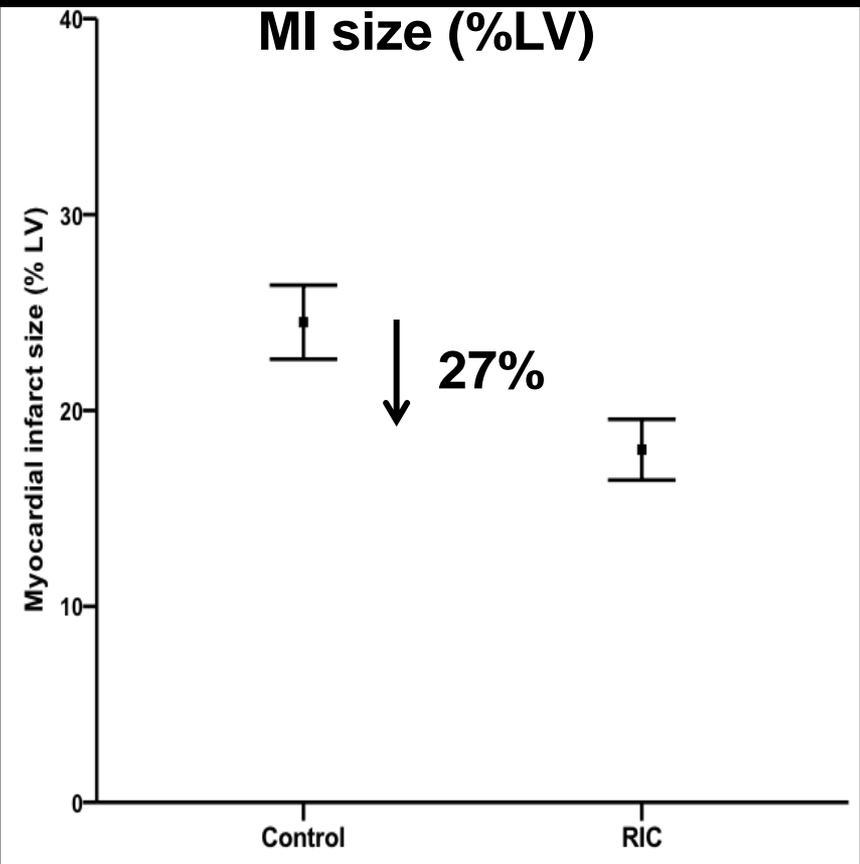
# ERIC-STEMI trial

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	Control Group	RIC Group	Difference (95% CI)	p Value
CMR findings	40	43		
Infarct size, %LV	24.5 ± 12	18.0 ± 10	6.5 (1.7-11.3)	0.009
Absolute infarct mass, g	26.0 ± 17	18.8 ± 12	7.2 (0.7-13.7)	0.029
Indexed infarct mass, g/m <sup>2</sup>	12.9 ± 8	9.4 ± 6	3.5 (0.4-6.6)	0.026
T <sub>2</sub> extent of edema, %LV	35.1 ± 10	28.5 ± 9	6.6 (2.4-10.9)	0.003
Mean T <sub>2</sub> value, ms				
Remote myocardium	50.1 ± 2.0	49.9 ± 2.5	0.2 (-0.8 to 1.2)	0.633
Infarct zone	73.1 ± 6.1	68.7 ± 5.8	4.32 (1.7-6.9)	0.001
Myocardial salvage index				
Using CMR to estimate AAR	0.26 (0.15, 0.42)	0.35 (0.16, 0.57)	-0.07 (-0.17, to 0.03)	0.171
Using BARI to estimate AAR	0.27 ± 0.30	0.41 ± 0.28	-0.14 (-0.27 to -0.02)	0.028
Using APPROACH to estimate AAR	0.28 ± 0.29	0.42 ± 0.29	-0.14 (-0.27 to -0.01)	0.031
MVO	22 (55)	20 (47)		0.440

# ERIC-STEMI trial

White.....Hausenloy JACC Intervention 2014





**25 UK centres, 2000 patients, £1.3 m BHF study**

**STEMI patients undergoing PPCI**



**RIC: 4 x 5 min cuff**

**Inflation 200mmHg/deflation**

**Sham RIC: 4 x 5 min simulated**

**Inflations/deflations**



**Primary outcome at one year**

Cardiac death and Hospitalisation for Heart Failure

*Begin recruitment March 2015*

*Collaboration with Hans Botker, Denmark (CONDI-2 trial)*

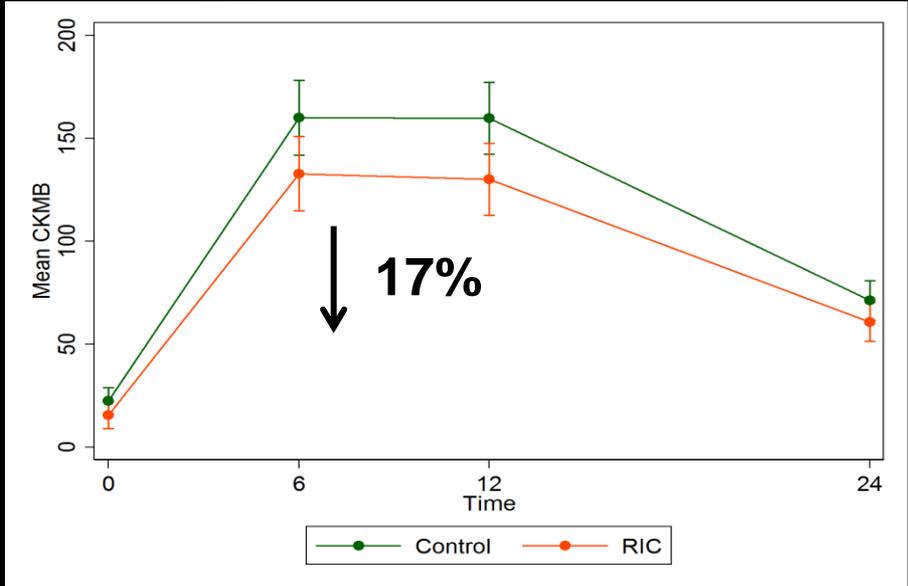
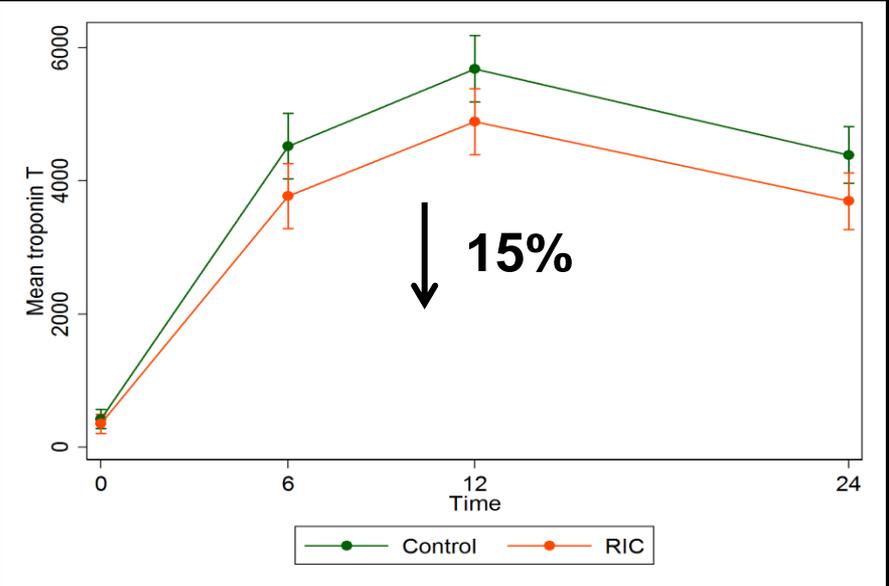


# ERIC-LYSIS

Yellon & Hausenloy et al (unpublished)



- Mauritius (multi-ethnic developing country)
- Multi-centre (5 hospitals) 520 patients.
- RIC (4x5min) in STEMI thrombolysis.
- 40% diabetic, 40% hypertensive, <12% Rx
- Potential for SE Asia.

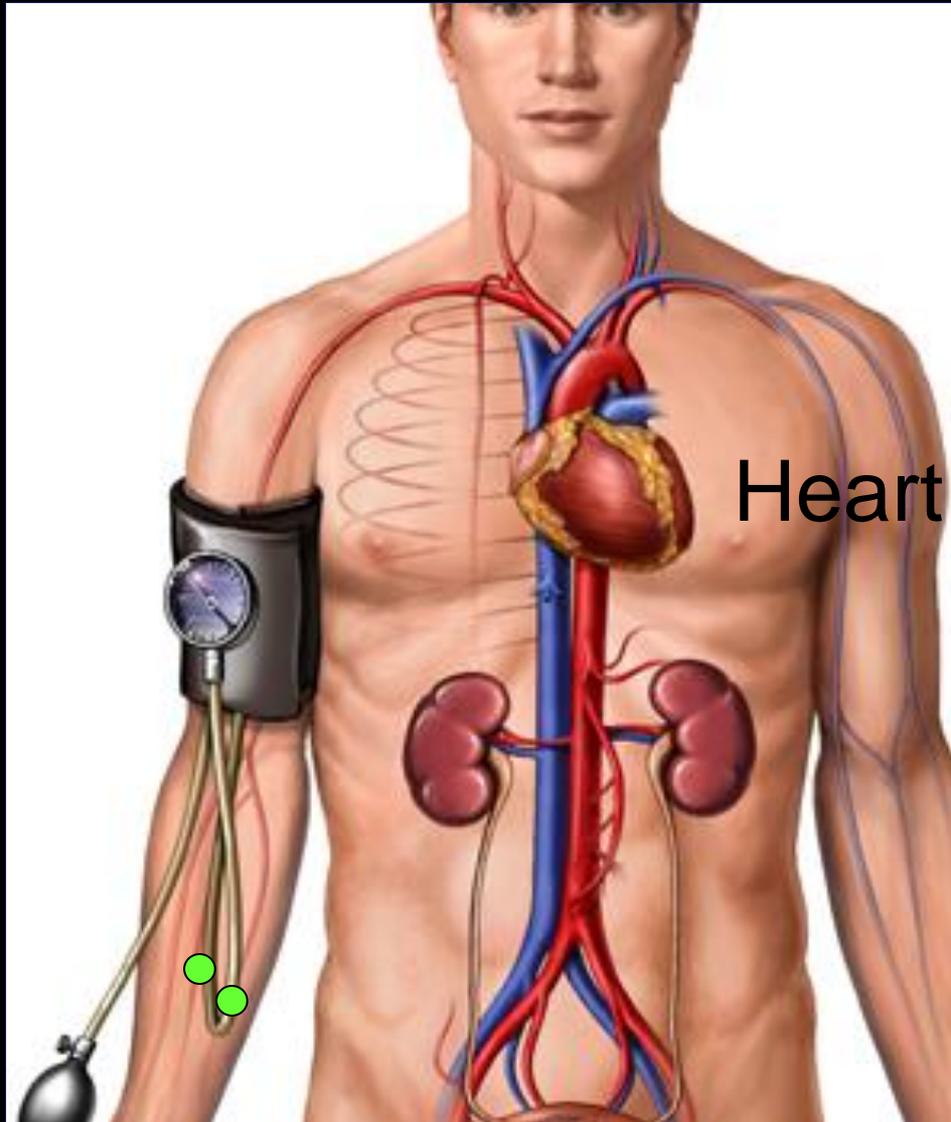


# How does it work?

Neural Pathway  
(activated by autocoids)

Remote organ  
or tissue

Humoral factor  
(Peptide 3-15kDa)



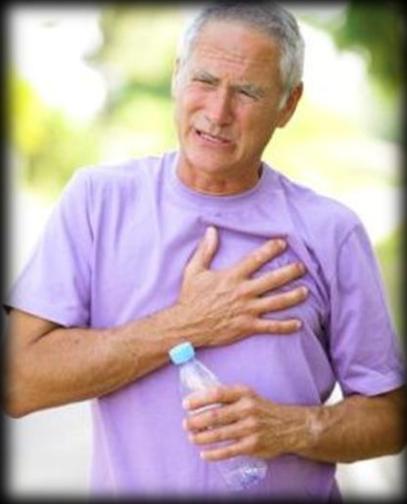
Myocardium  
Established intracellular  
Protective pathways

# Hybrid PET/MR in STEMI patients

*Bulluck.... Hausenloy (unpublished)*

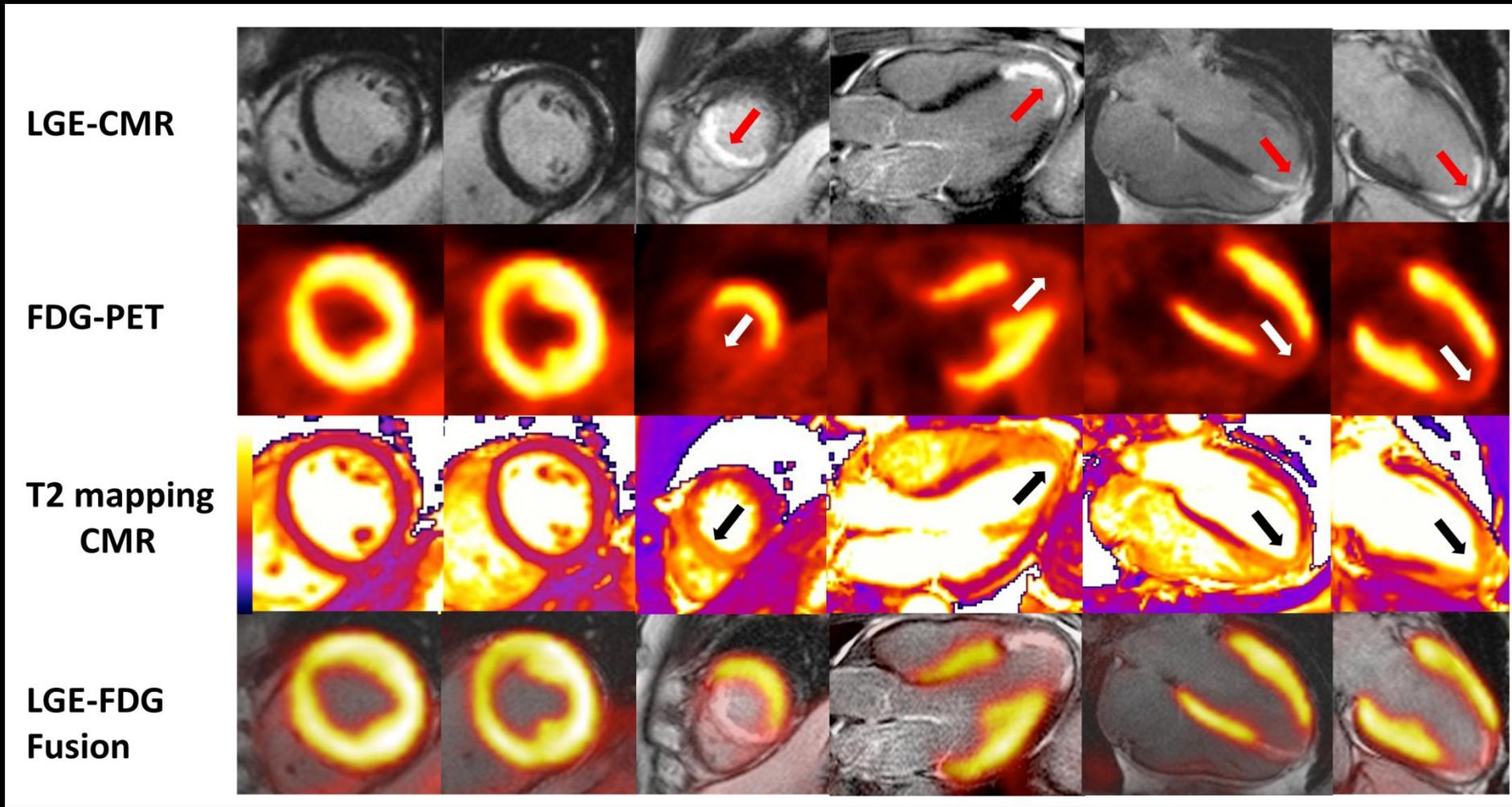
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- 21 STEMI patients imaged by PET/MR in first week.
- Co-localise changes in metabolism in patients with cardiac disease



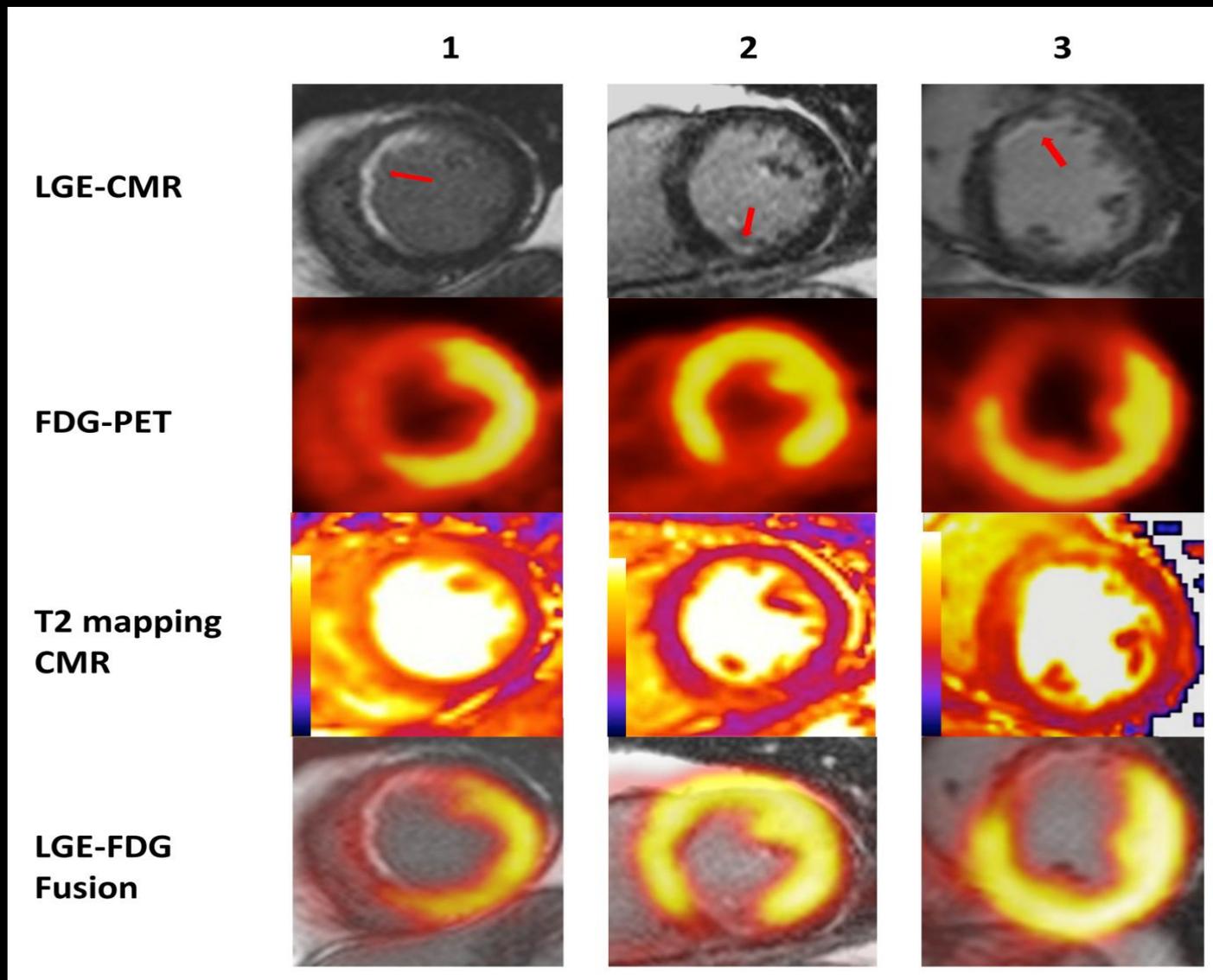
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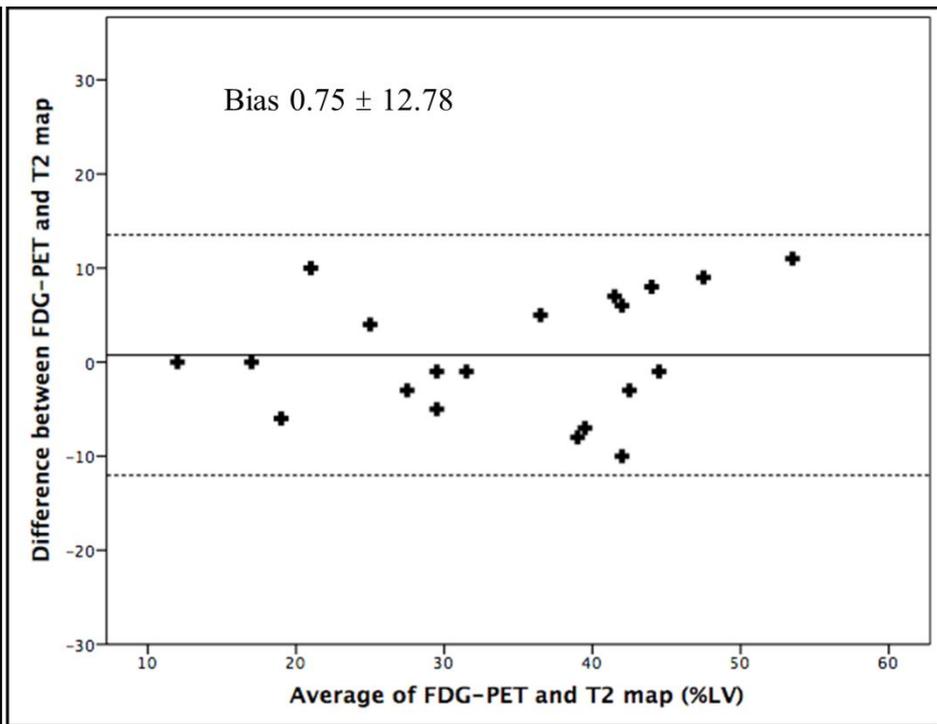
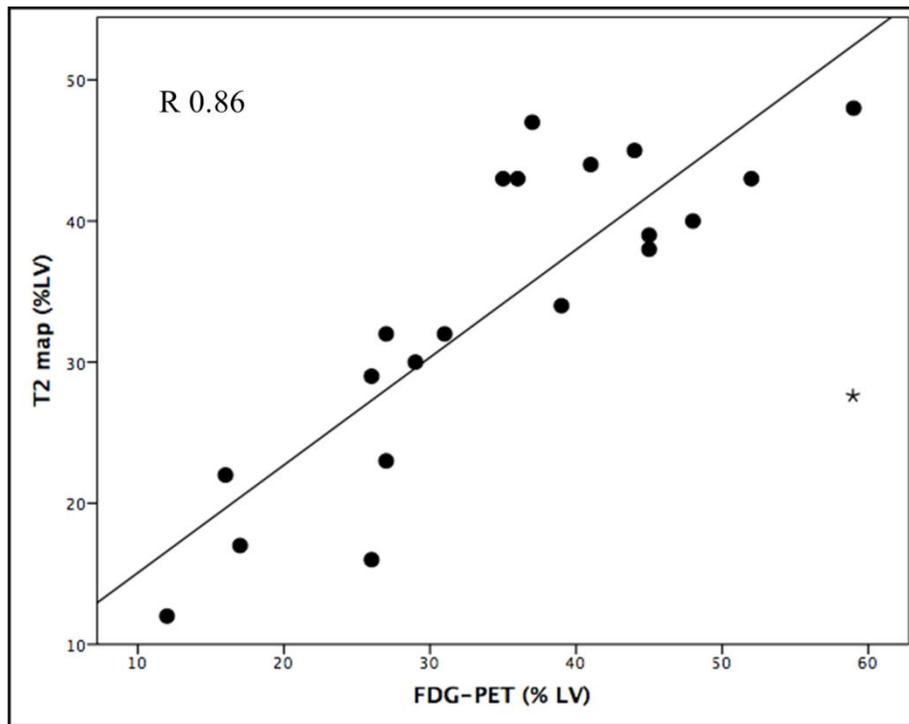
# Hybrid PET/MR and the AAR

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# Hybrid PET/MR and the AAR

*Bulluck.... Hausenloy (unpublished)*



*New tracers for fibrosis, inflammation, apoptosis and angiogenesis.*

- Novel therapeutic interventions are still required to protect the heart against acute IRI.
- Remote ischemic conditioning is a non-invasive, low cost-treatment strategy for cardioprotection- beneficial in proof-of-concept clinical studies.
- Large clinical studies will determine whether RIC can improve long-term clinical outcomes.

# Acknowledgements

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All patients and staff

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