

Ischemic Conditioning: *The Comorbidity Conundrum*

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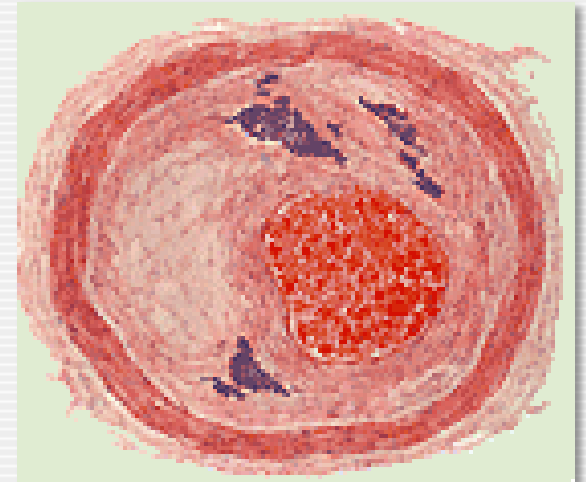
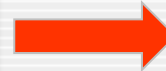
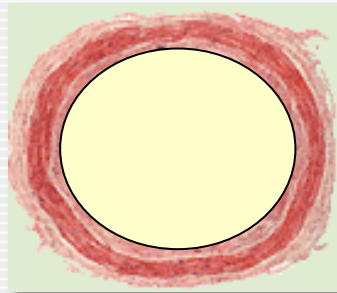
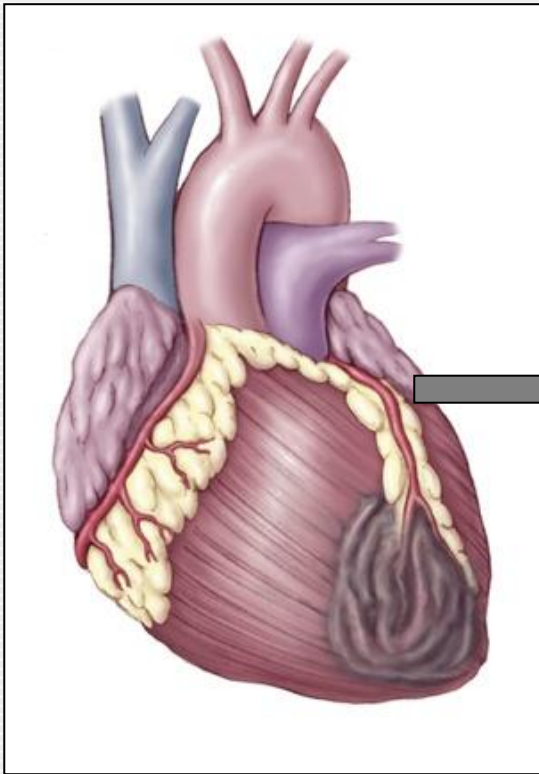
**14th Annual Dose Response Conference:
Preconditioning in Biology and Medicine
University of Massachusetts, Amherst MA
22nd April, 2015**



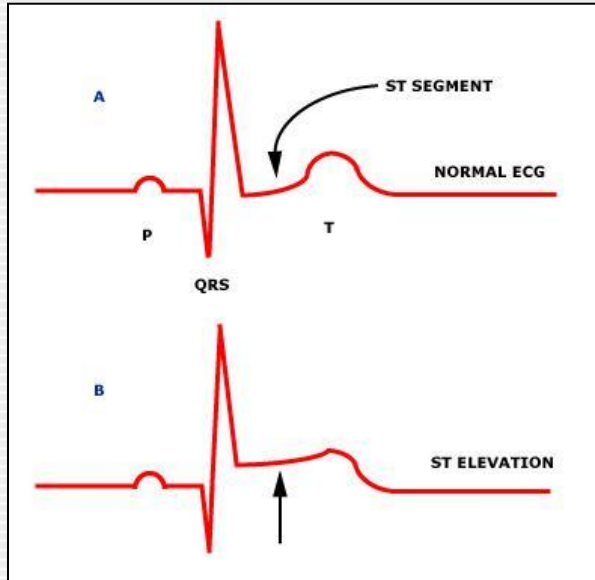
- cardiomyocytes need oxygen, nutrients to survive and function

- blood supply to myocytes provided via the coronary arteries

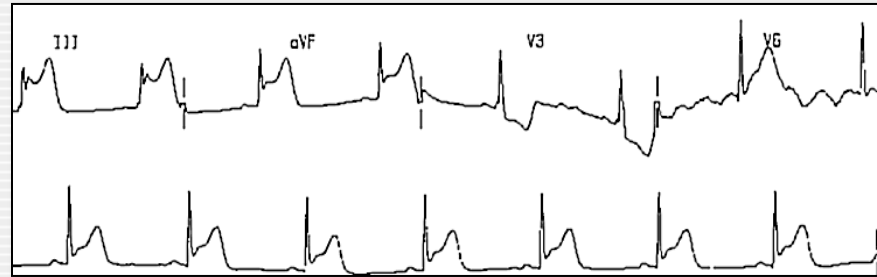
- if coronary arteries become occluded, myocytes become *ischemic*



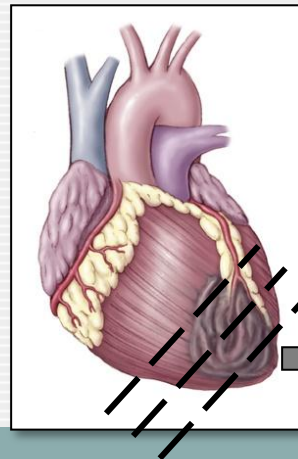
Occlusion → ischemia → myocardial infarction



Clinical Example



In 2015, >1 million Americans will have a 'heart attack'



Experimental Model



Occlusion → ischemia → myocardial infarction

- **goal: reduce myocardial infarct size**
- **current treatment: timely reperfusion**
 - 'price' of reoxygenation: *lethal reperfusion injury*
- ***can we do better?***



Occlusion → ischemia → myocardial infarction

- goal: reduce myocardial infarct size
- current treatment: timely reperfusion
- *can we do better?*
 - heart can be 'conditioned'; rendered resistant to ischemia-reperfusion injury
 - chemical, pharmacological, exercise conditioning
 - ischemic conditioning

Ischemic Conditioning

- definitions: 'what' and 'how'
- the goal: preclinical promise to clinical translation
 - *the comorbidity conundrum*

Ischemic Conditioning

- preconditioning
- postconditioning
- *remote* conditioning

initiate the up-regulation of endogenous protective mechanisms that **render the heart resistant to ischemia-reperfusion injury**; reduce infarct size

Control



'Conditioned'



Preconditioning

“ . . . brief, intermittent episodes of ischemia have a *protective effect* on myocardium that is later subjected to a sustained bout of ischemia.”

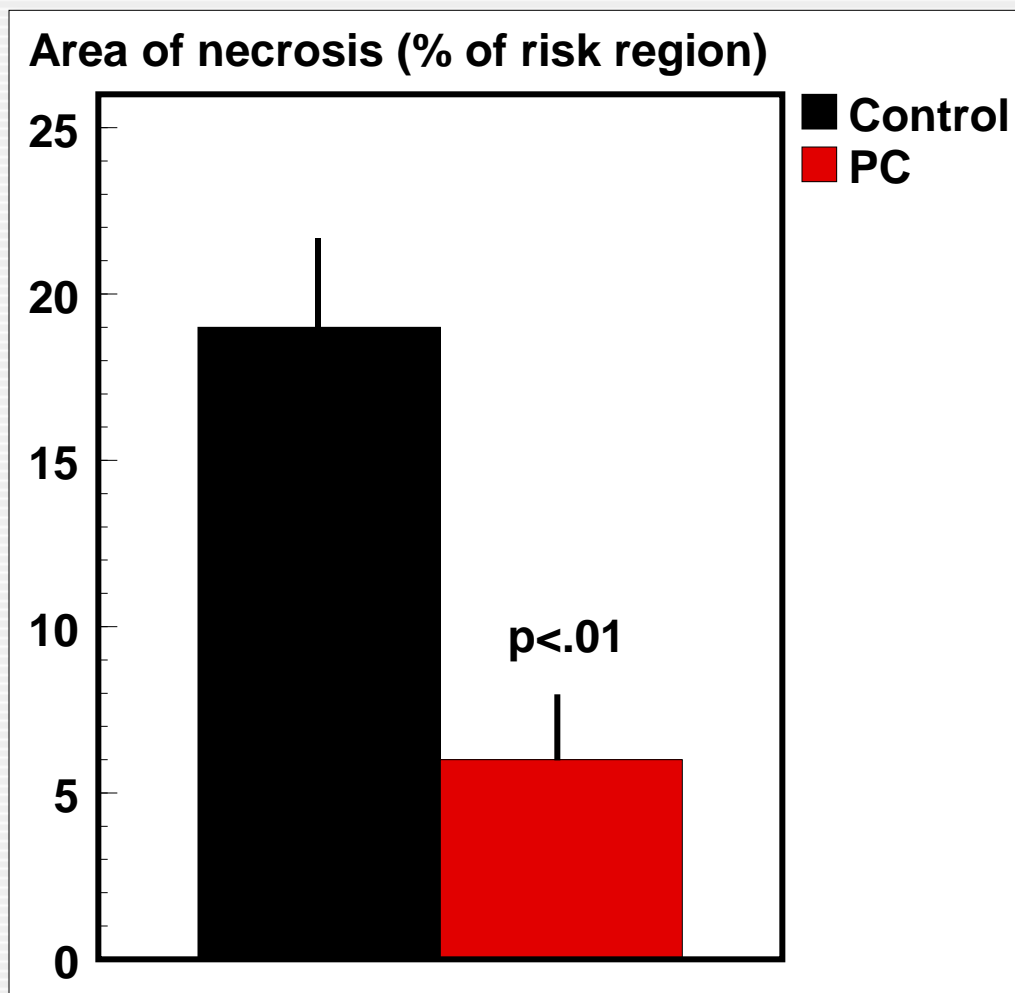
Murry et al, *Circulation* 1986;74:1124-1136.

i.e., that which does not destroy us makes us stronger

Control:



Preconditioned:

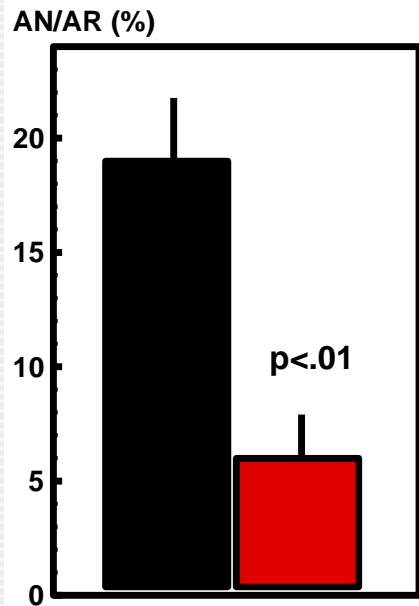


↑
area of necrosis
(% of risk region)

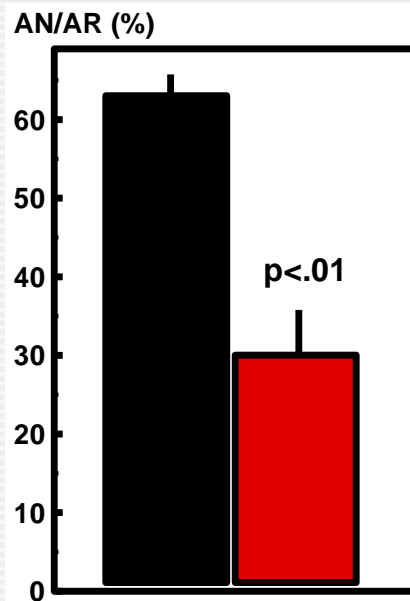
Reduction of Infarct Size with Preconditioning

● since 1986: has been the focus of >4,000 publications

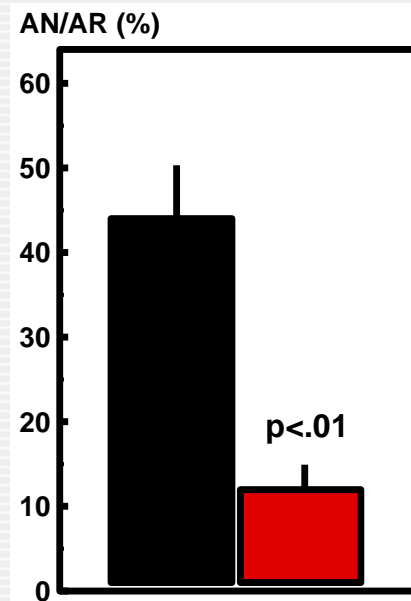
Dog



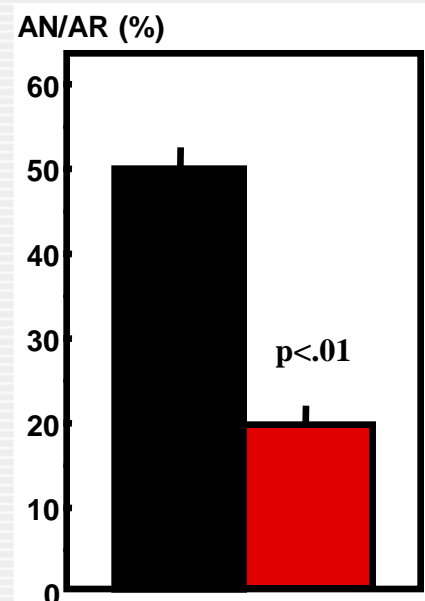
Rabbit



Rat

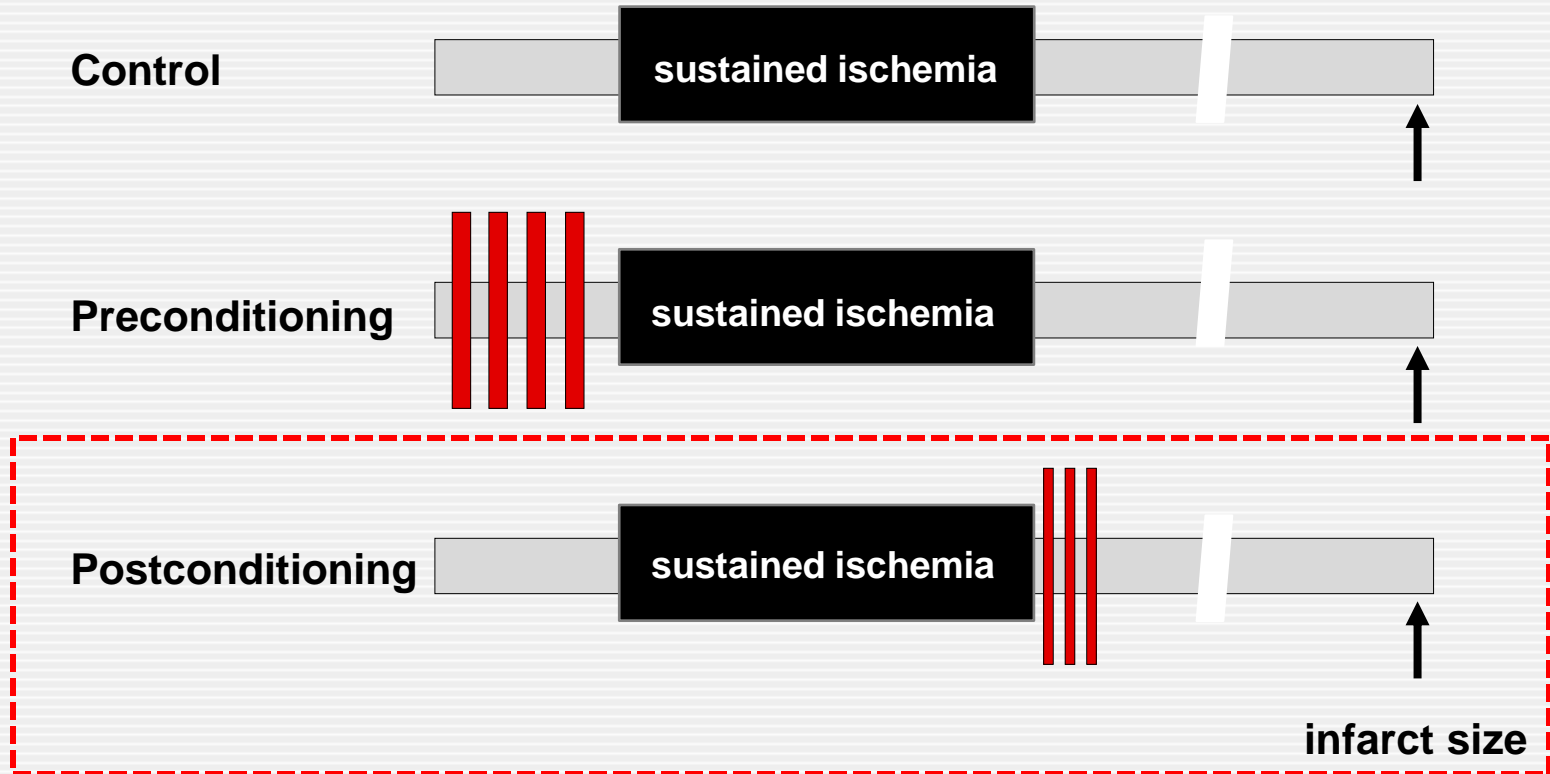


Mouse



Control **Preconditioned**

Expanding the paradigm



Postconditioning

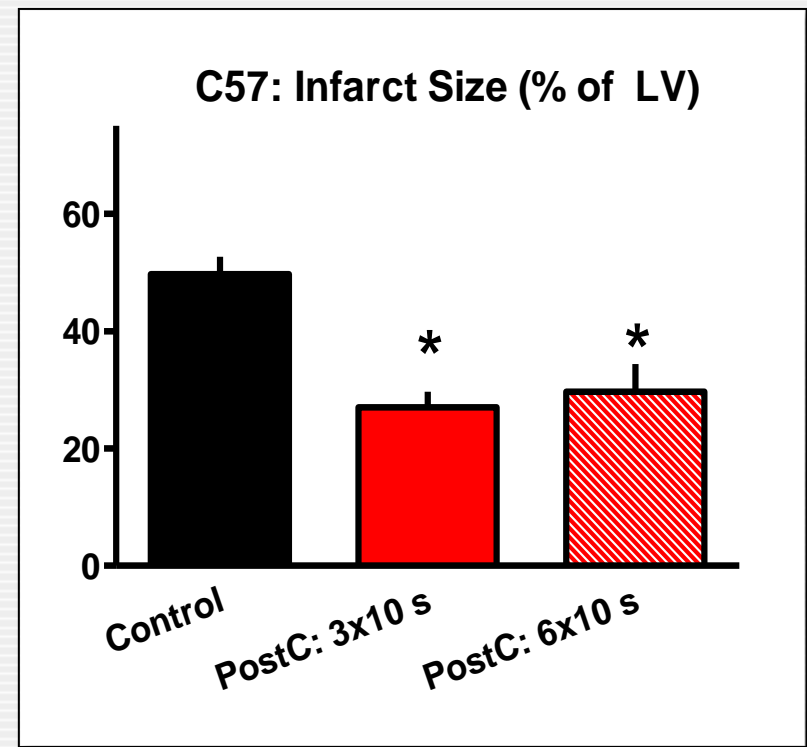
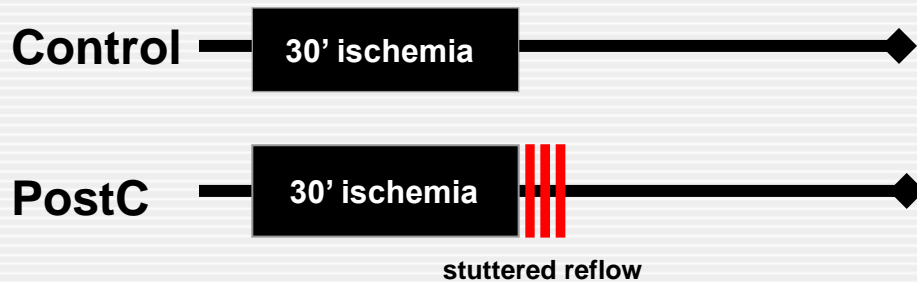
- mechanical strategy to **modify the early seconds of reperfusion**
- Initially described in the canine model; confirmed in multiple models and species
- definition: brief episodes of ‘stuttering’ reflow, followed by full and sustained reperfusion
- efficacy: **comparable to preconditioning**



Start slow . . .



Reduction of infarct size with postconditioning: mouse model



Expanding the paradigm

Control



Preconditioning



Postconditioning



Remote preconditioning



remote

infarct size

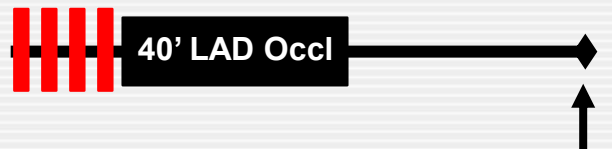
Reduction of infarct size with remote conditioning: swine model

- model: anesthetized pig
- **remote stimulus: skeletal muscle ischemia**
- endpoint: infarct size

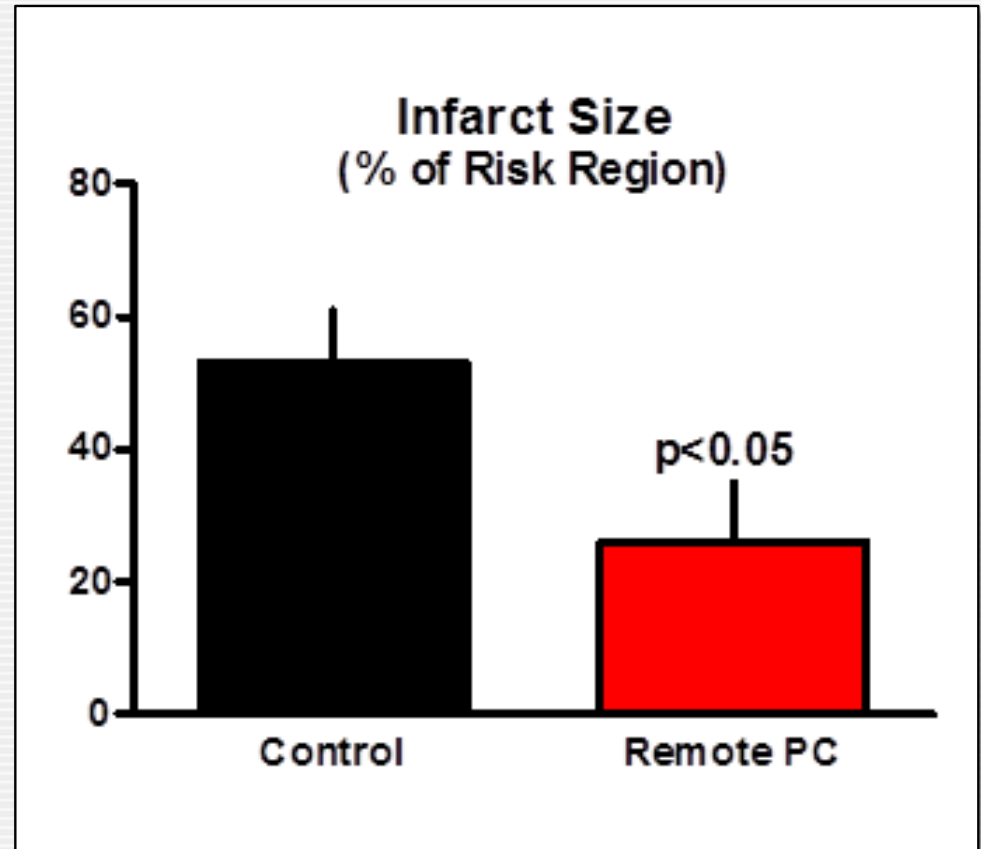
Control



Hindlimb ischemia



infarct size
(% of risk region)

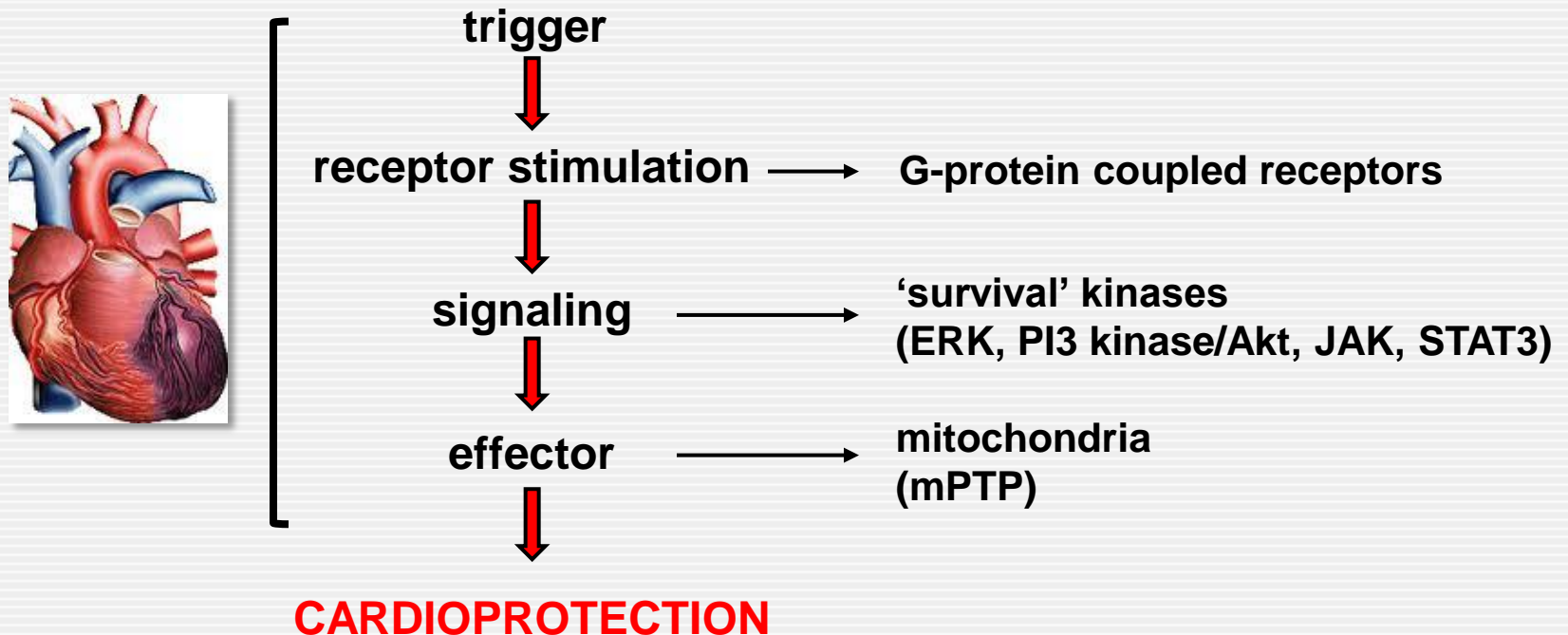


Ischemic Conditioning

- **unprecedented agreement** among ~5,000 preclinical studies: pre- post- and remote conditioning reduce infarct size
- **molecular mechanisms**

Ischemic Conditioning

- unprecedented preclinical agreement: pre- post- and remote conditioning reduce infarct size
- molecular mechanisms

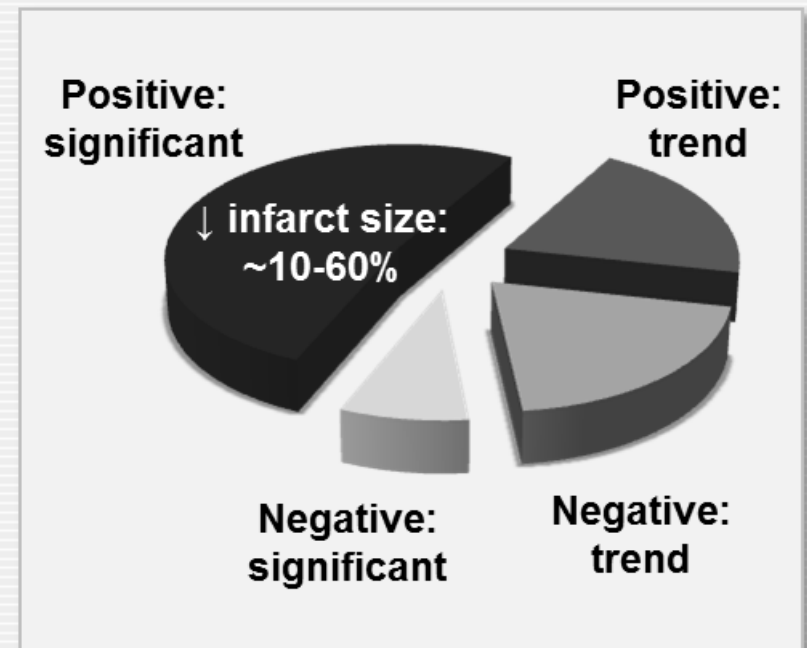


Ischemic Conditioning

- **unprecedented preclinical agreement: pre- post- and remote conditioning reduce infarct size**
- **postconditioning, remote conditioning: poised for clinical translation . . .**
 - **focus of Phase II, Phase III clinical trials**

Ischemic Conditioning

- unprecedented preclinical agreement: pre- post- and remote conditioning reduce infarct size
- in contrast:
 - **results of Phase II trials have been mixed**
 - i.e., remote conditioning: outcomes have ranged from positive to neutral to deleterious



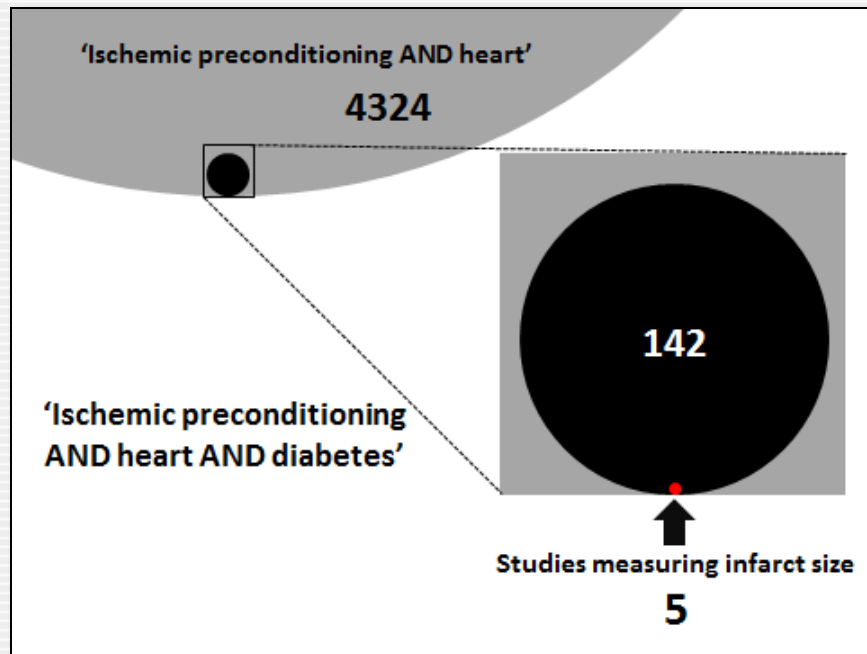
Ischemic Conditioning

- **unprecedented preclinical agreement: pre- post- and remote conditioning reduce infarct size**
- **in contrast:**
 - **results of Phase II trials have been mixed**
 - **recent meta-analyses have not confirmed significant benefit**
 - **outcome of a highly anticipated Phase III trial: negative**
- **progress toward clinical translation: ‘*somewhere between frustrating and disappointing*’ (Shevchuck & Laskey, *Circulation Cardiovasc Interv* 2013;6:484-492)**
- **many potential explanations . . .**

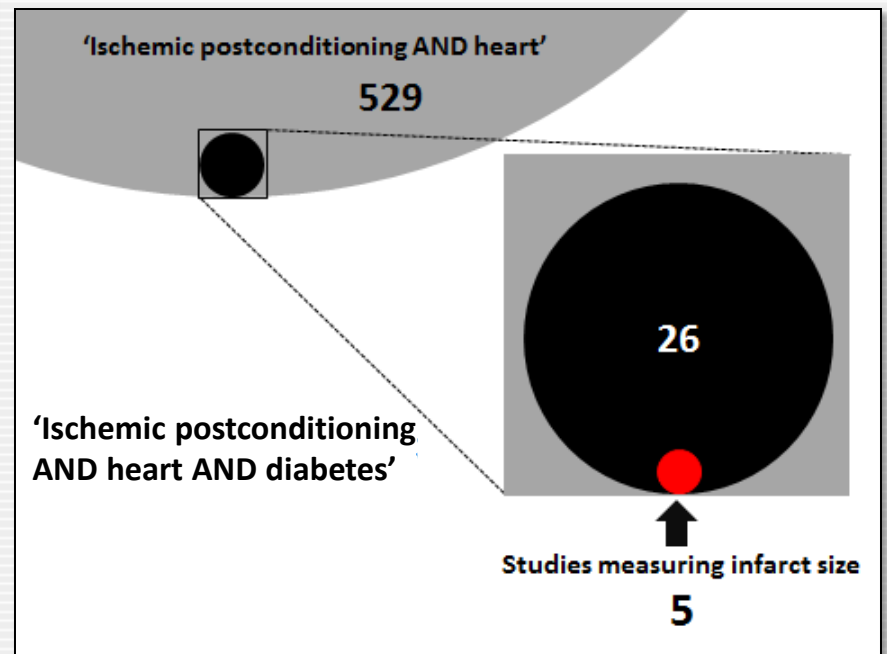
The problem . . .

- overwhelming majority of preclinical studies showing infarct size reduction with ischemic conditioning have been conducted using healthy, adult cohorts
 - does not reflect the risk factors and comorbidities associated with cardiovascular disease; acute myocardial infarction (**diabetes, aging**, hypertension, hyperlipidemia, etc.)

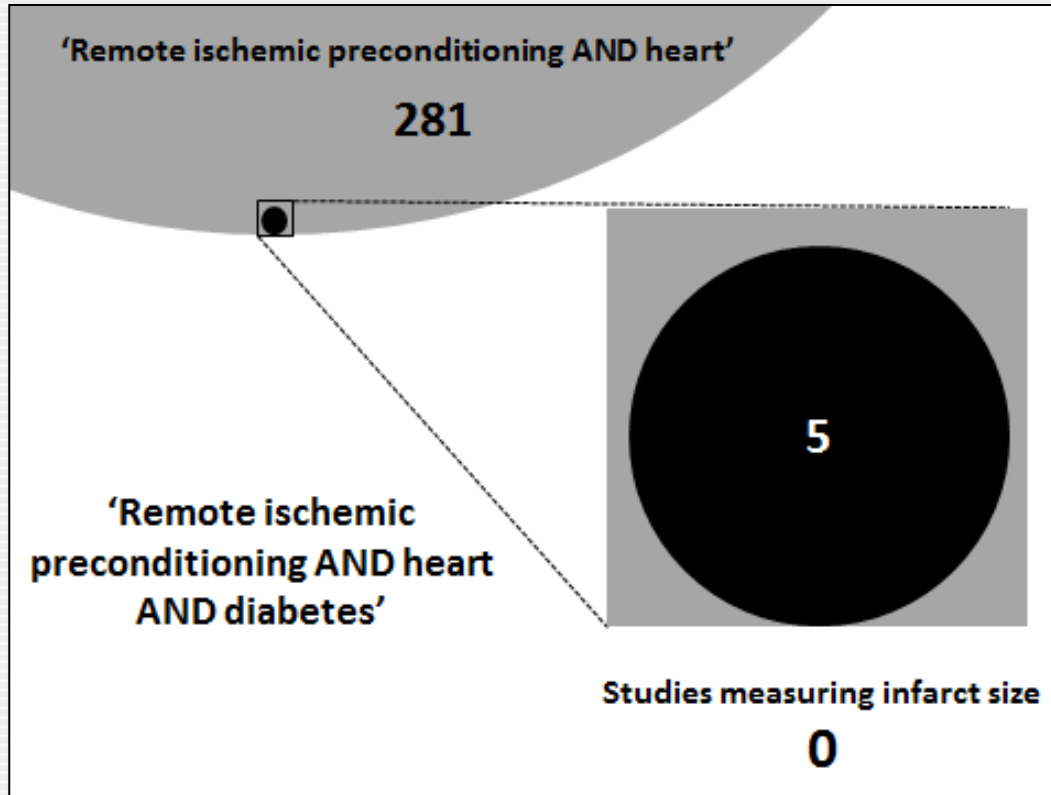
Preconditioning



Postconditioning



Remote Preconditioning

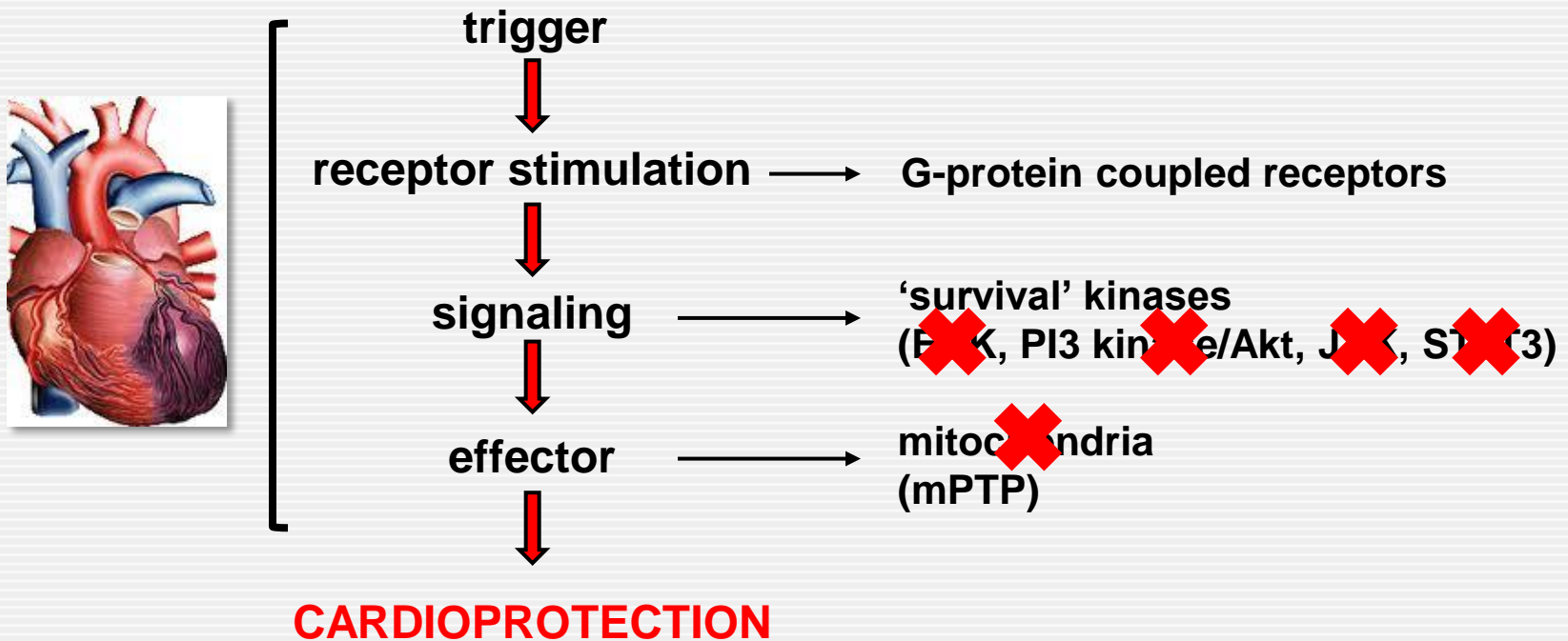


The problem . . .

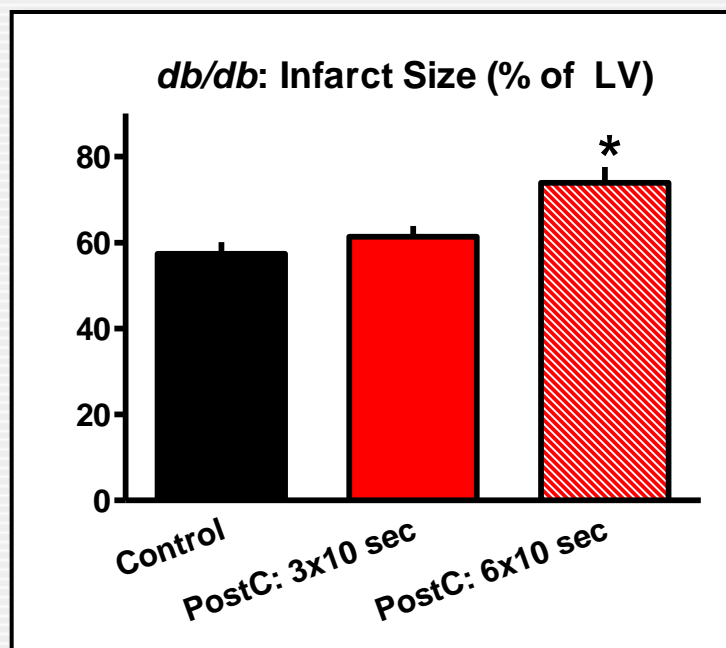
- overwhelming majority of preclinical studies showing infarct size reduction with ischemic conditioning have been conducted using healthy, adult cohorts
 - does not reflect the risk factors and co-morbidities associated with cardiovascular disease; acute myocardial infarction (**diabetes, aging**, hypertension, hyperlipidemia, etc.)
 - growing evidence that aging, diabetes are associated with differences in expression of key cardioprotective mediators; **dysregulation of cardioprotective signaling** ('survival' kinases)

Ischemic Conditioning

- in models of diabetes, aging . . .

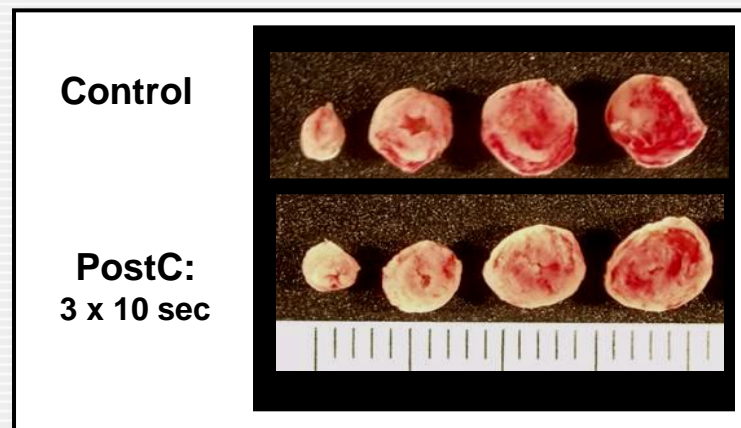


Postconditioning: model of type-2 diabetes

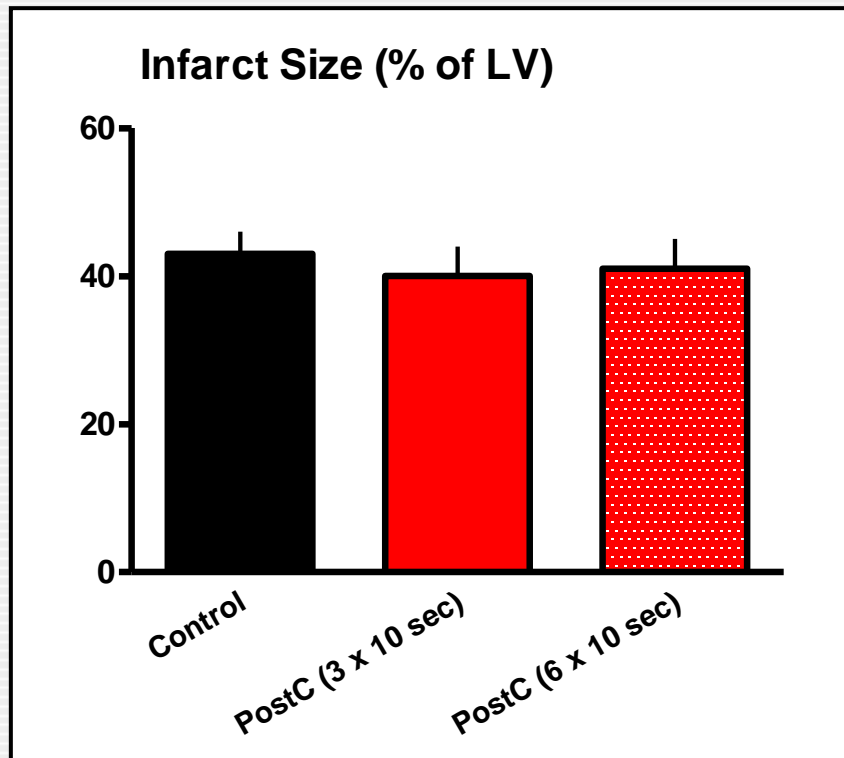


- postconditioning was not cardioprotective in *db/db* mice
- rather, infarct size was *exacerbated* in mice that received the amplified, 6-cycle postconditioning stimulus

- consensus among 5 published studies: protection lost or attenuated in type-2 diabetic models (*Br J Pharmacol* 2015;172:1961-73)

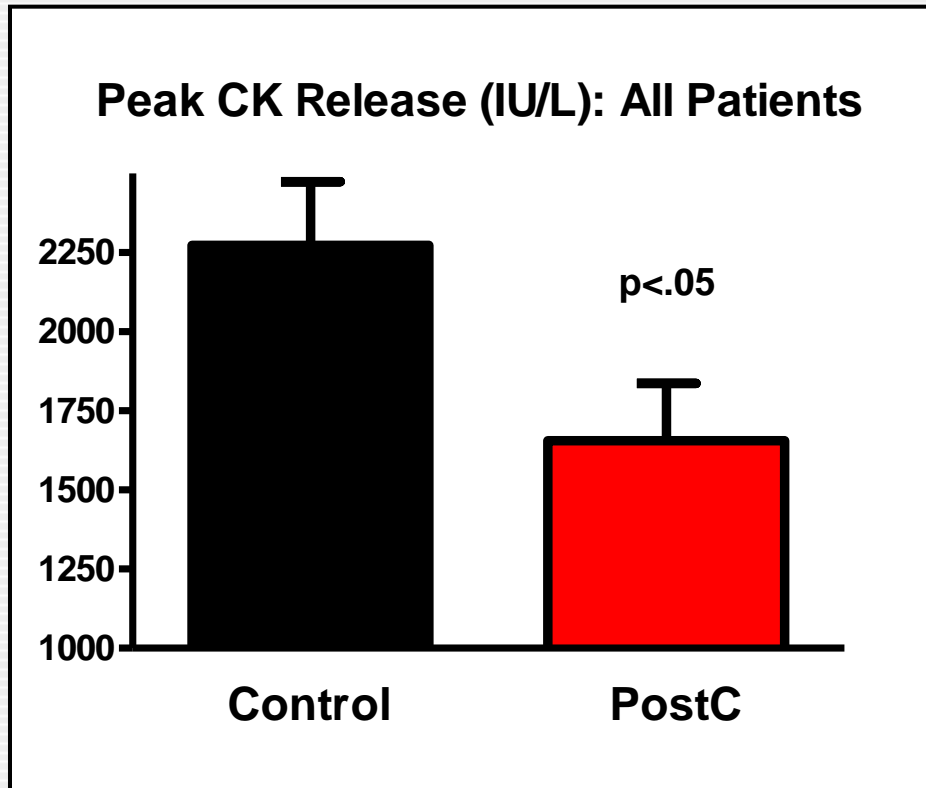


Postconditioning: model of aging



- 2 year old mice: characterized by physiologic, molecular hallmarks of cardiovascular aging
- postconditioning failed to reduce infarct size

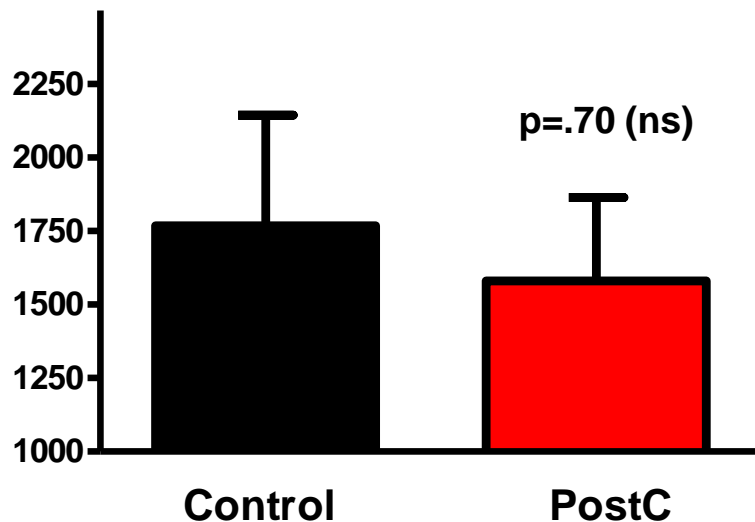
Postconditioning: all patients (n=115)



- CK release (surrogate for infarct size) was attenuated in the postconditioned group receiving stuttered reflow (multiple balloon inflations) vs controls

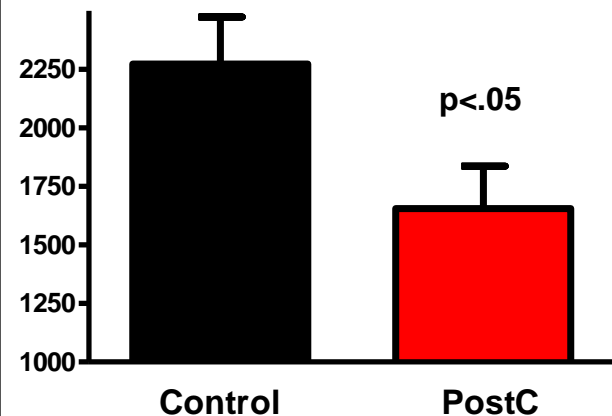
Postconditioning: subset >65 years (n=37)

Peak CK Release (IU/L): Patients > 65 Years



- favorable reduction in CK release with postconditioning was diminished

Peak CK Release (IU/L): All Patients



Ischemic Conditioning

- **compelling preclinical evidence: preconditioning, postconditioning and remote conditioning reduce infarct size**
- **postconditioning, remote conditioning: poised for clinical translation . . .**
- **however, success will depend on improving our understanding of the effects of comorbidities on the ‘conditioned’ phenotype**