Ischemic Conditioning:

The Comorbidity Conundrum

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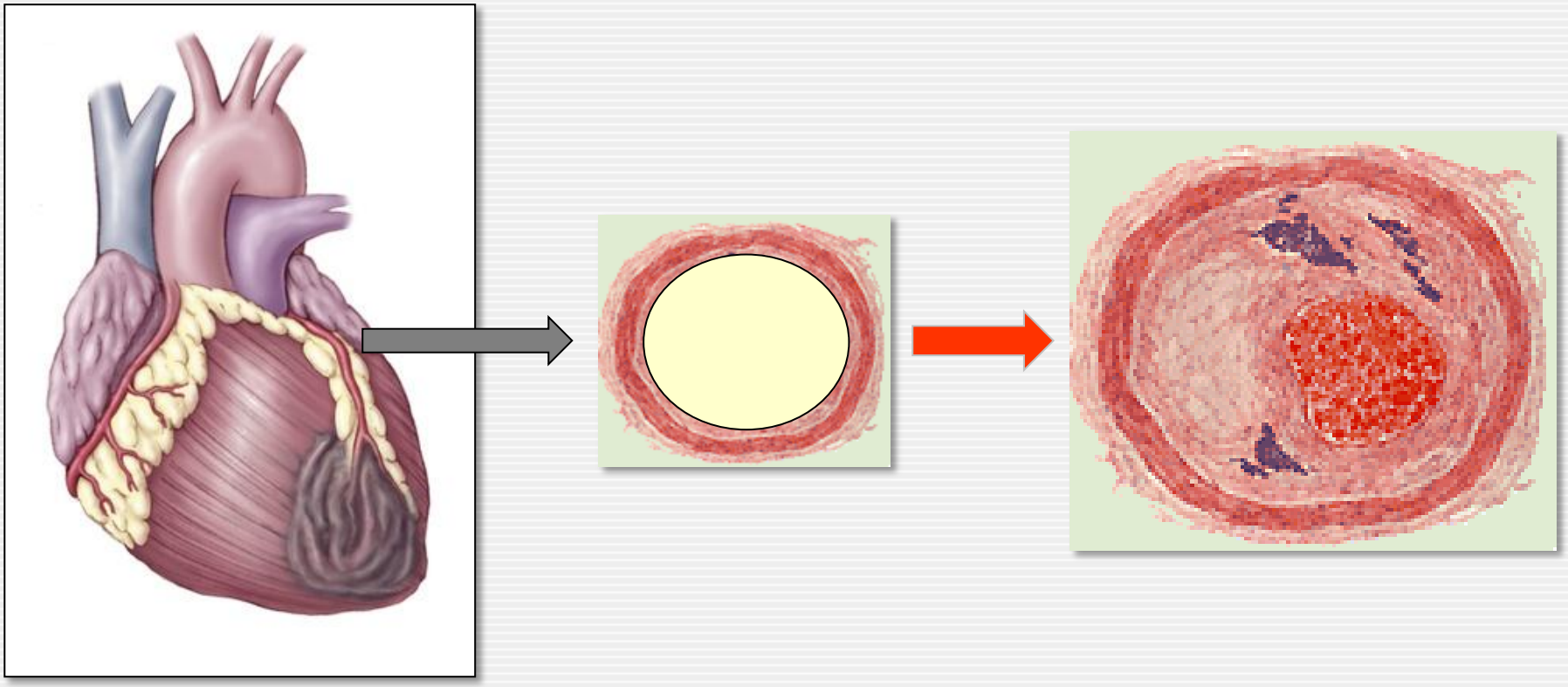
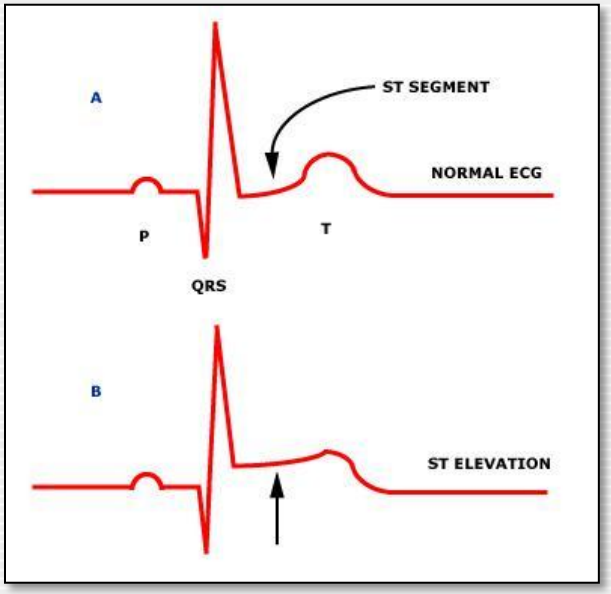
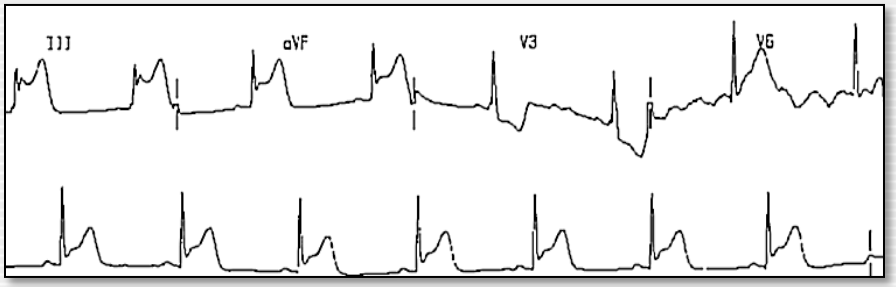
- cardiomyocytes need oxygen, nutrients to survive and function
- blood supply to myocytes provided via the coronary arteries
- if coronary arteries become occluded, myocytes become *ischemic*



Occlusion → ischemia → myocardial infarction

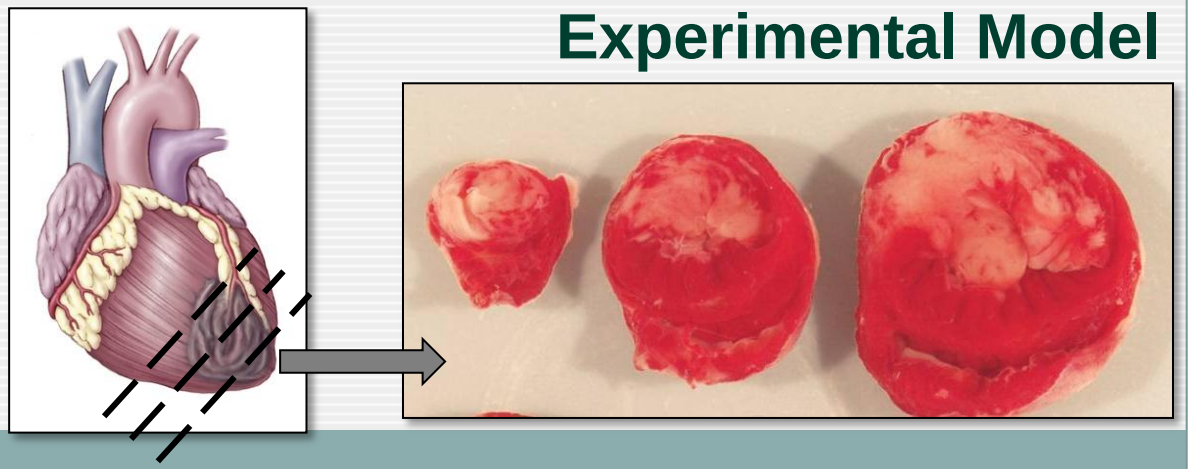


Clinical Example



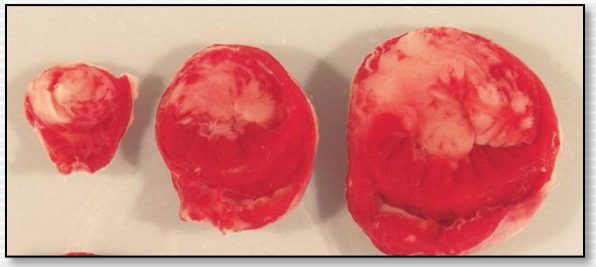
In 2015, >1 million Americans will have a 'heart attack'

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

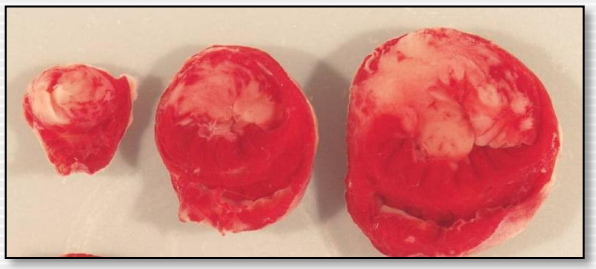
- **definitions: ‘what’ and ‘how’**
- **the goal: preclinical promise to clinical translation**
  - ***the comorbidity conundrum***

Ischemic Conditioning

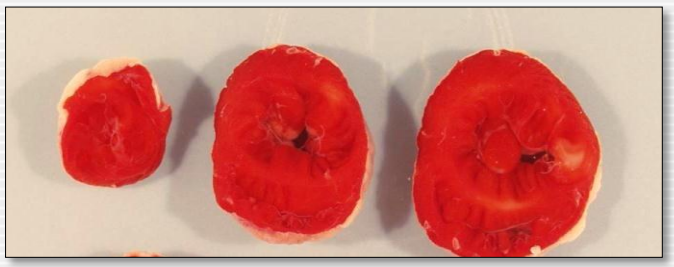
- preconditioning
- postconditioning
- *remote* conditioning

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

Control



‘Conditioned’

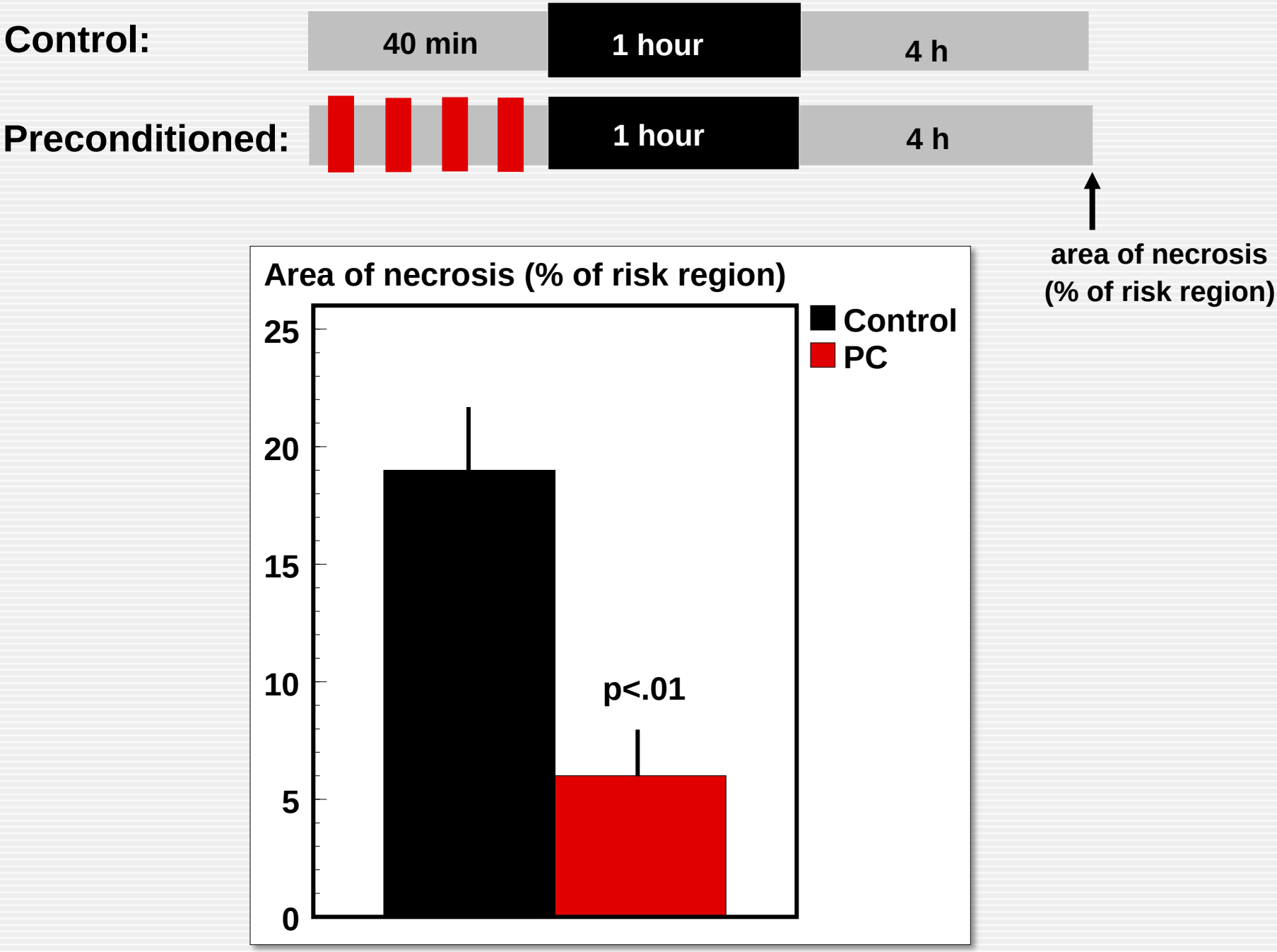


Preconditioning

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

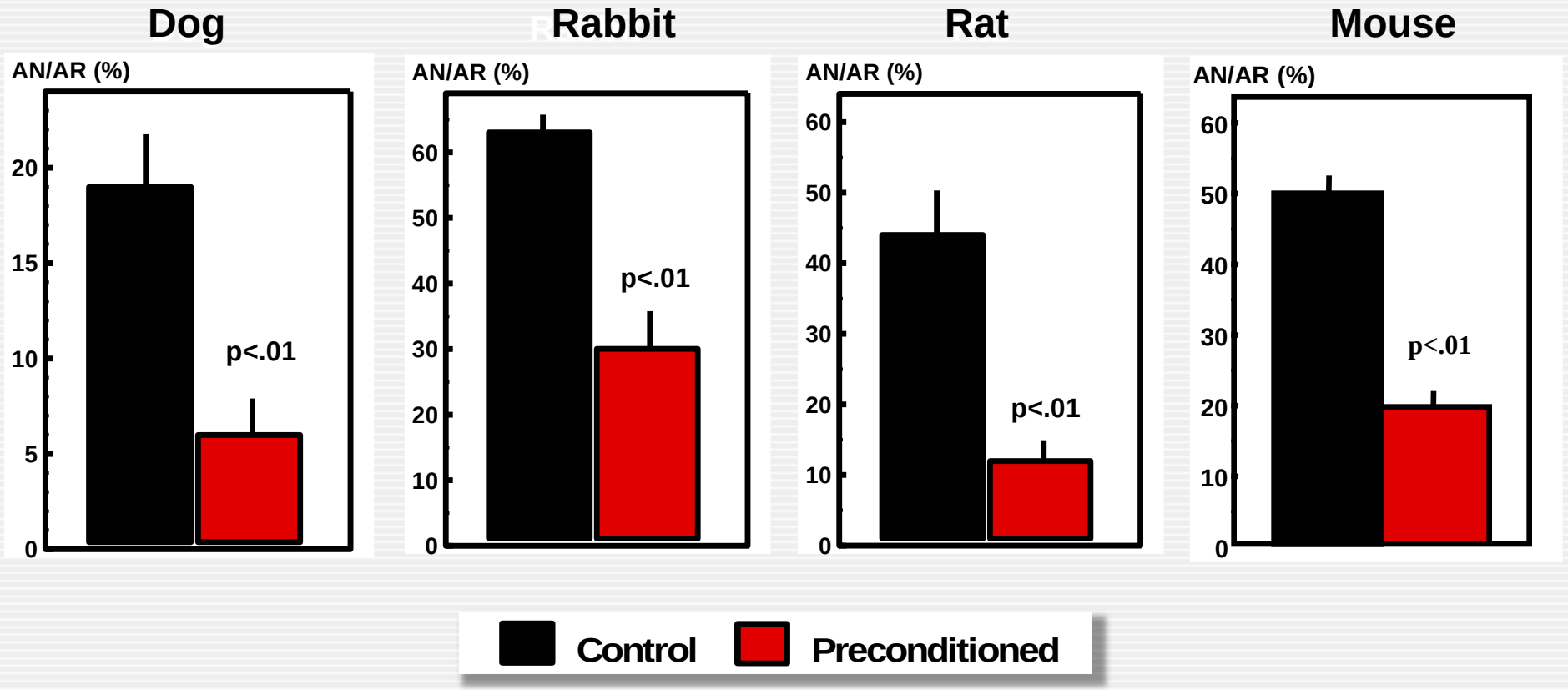
Murry et al, *Circulation* 1986;74:1124-1136.

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

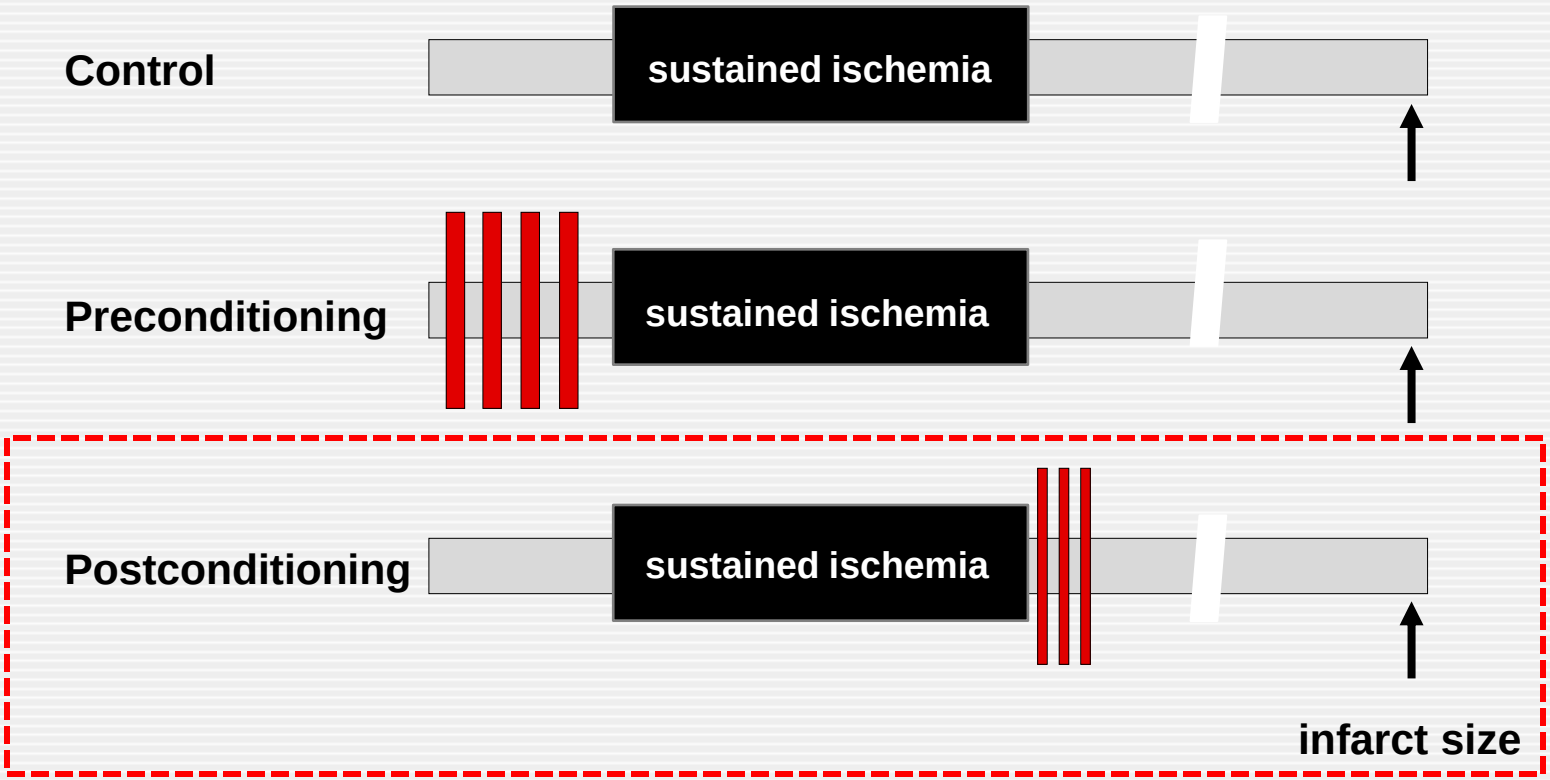

Control:
40 min
1 hour
4 h
Preconditioned:
1 hour
4 h
area of necrosis
(% of risk region)
Area of necrosis (% of risk region)
25
20
15
10
5
0
Control
PC
p<.01

Reduction of Infarct Size with Preconditioning

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



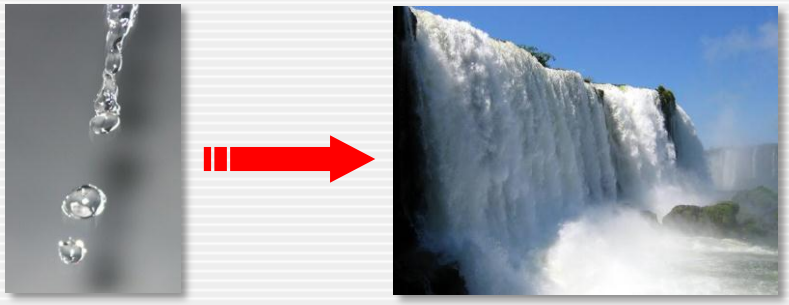
Expanding the paradigm



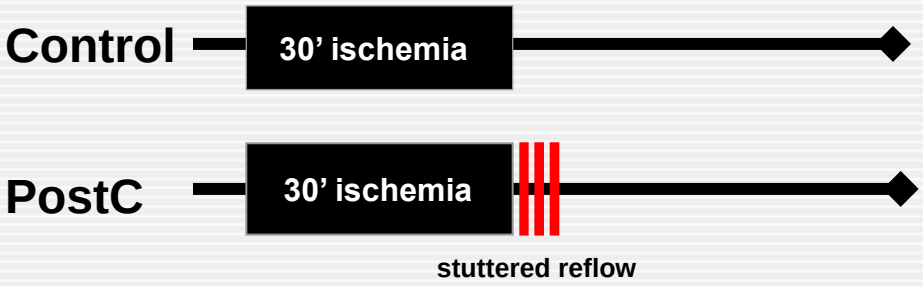
Postconditioning

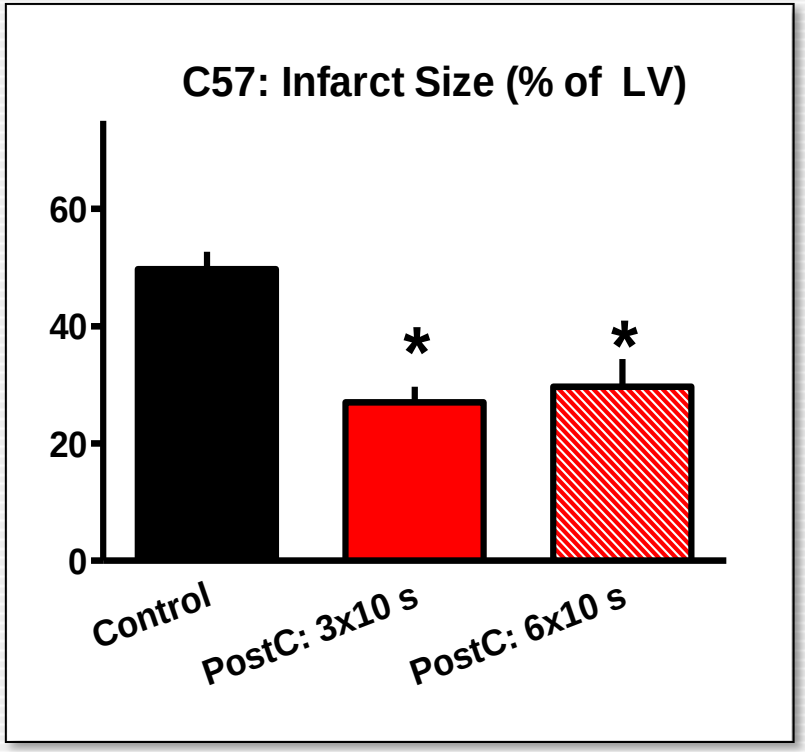
- mechanical strategy to modify the early seconds of reperfusion
- Initially described in the canine model; confirmed in multiple models and species
- definition: brief episodes of ‘stuttering’ reflow, followed by full and sustained reperfusion
- efficacy: comparable to preconditioning

Start slow . . .

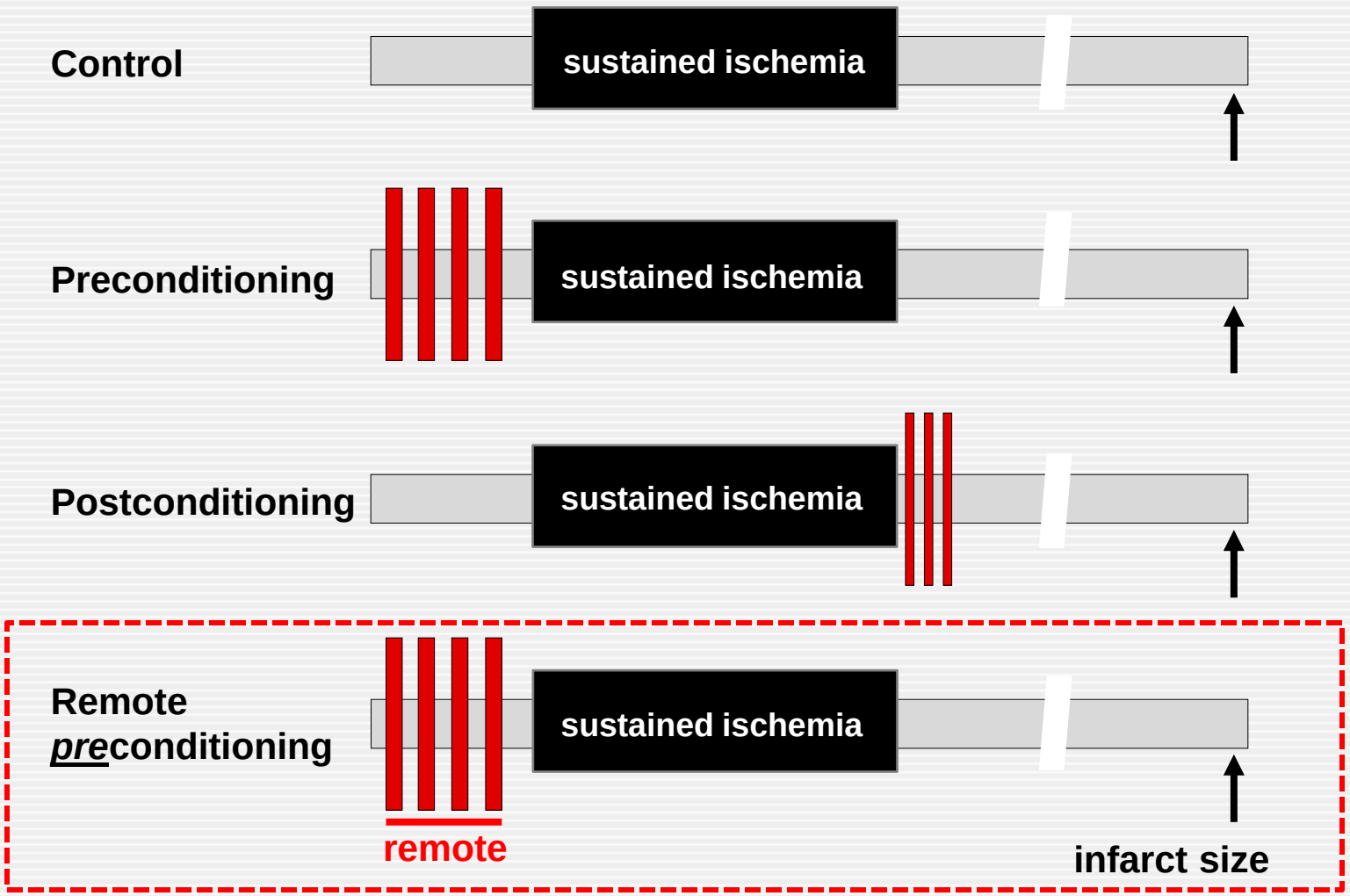


Reduction of infarct size with postconditioning: mouse model



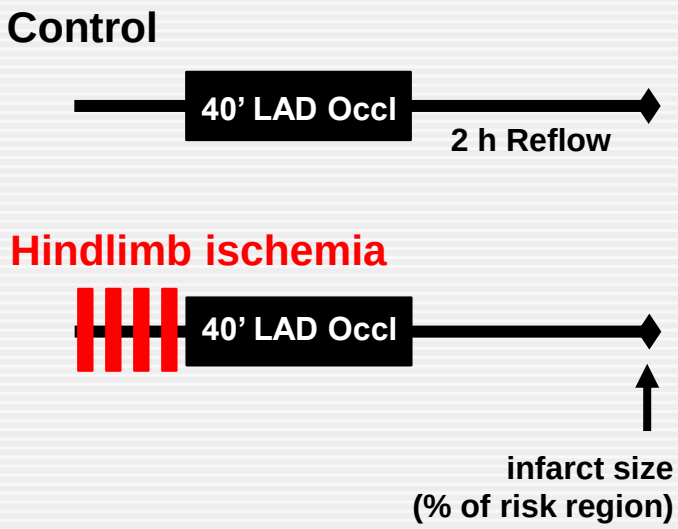


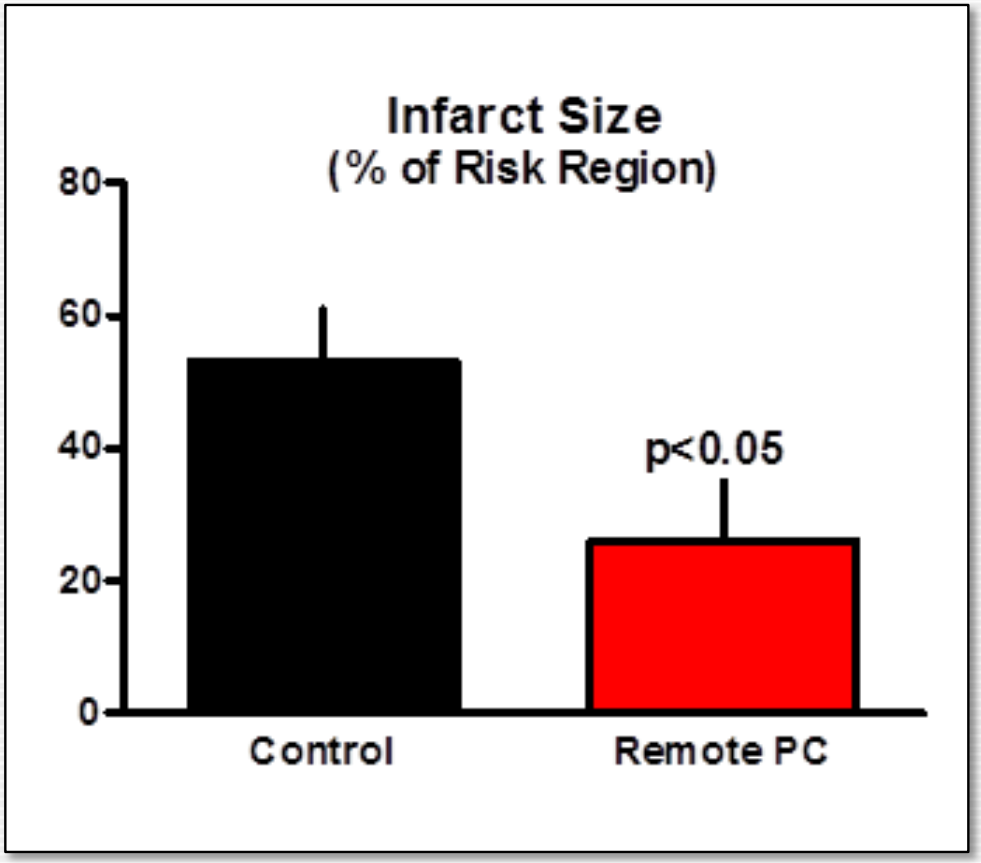
Expanding the paradigm



Reduction of infarct size with remote conditioning: swine model

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





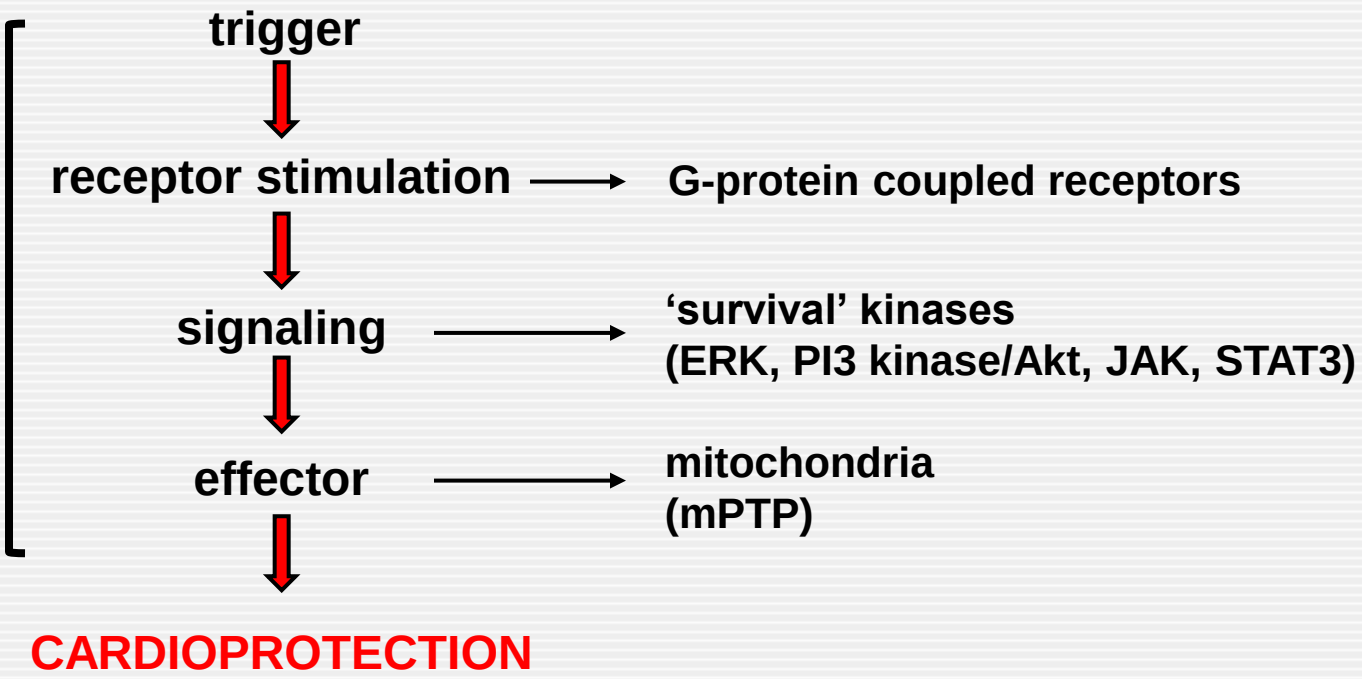
Kharbanda et al, *Circulation* 1997;106:2881-83.

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

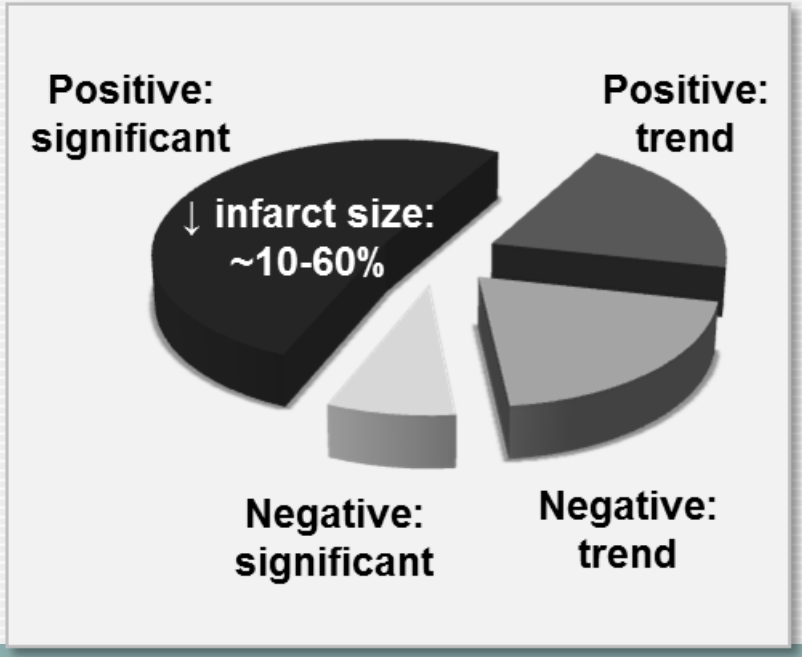


Ischemic Conditioning

- 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



Ovize, Thibault & Przyklenk, *Circulation Research* 2013;113:439-50.

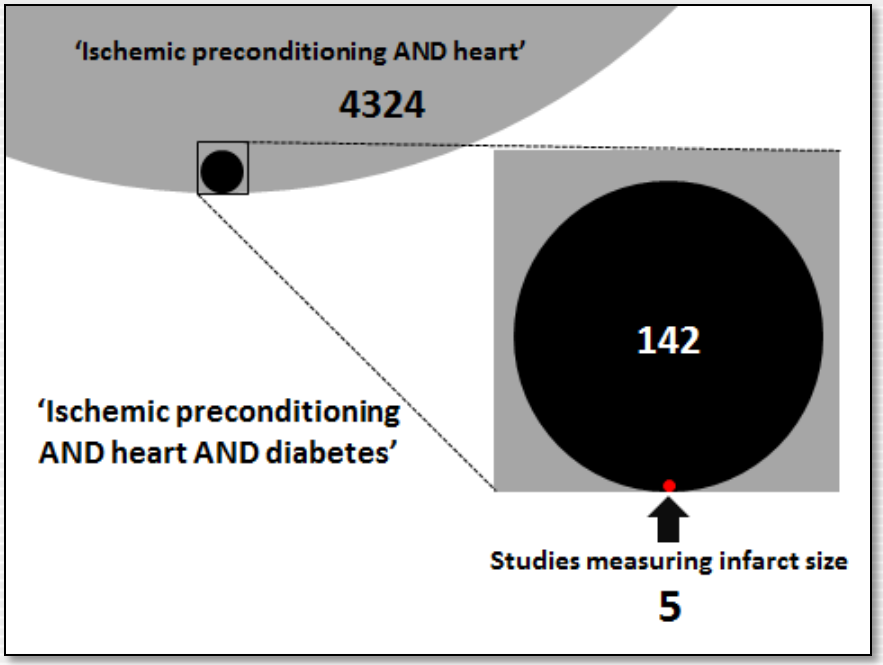
Ischemic Conditioning

- **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 . . .**

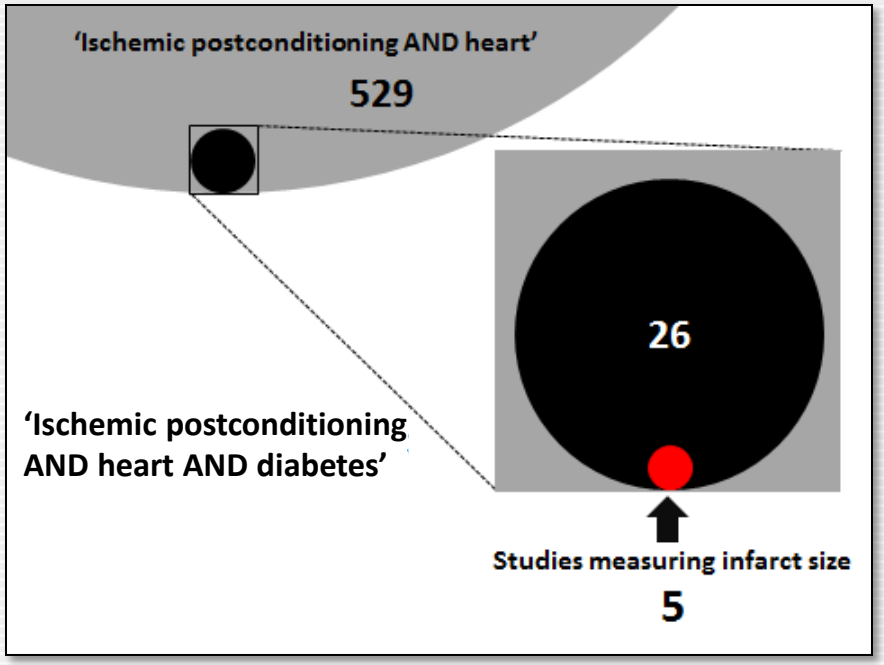
The problem . . .

- 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

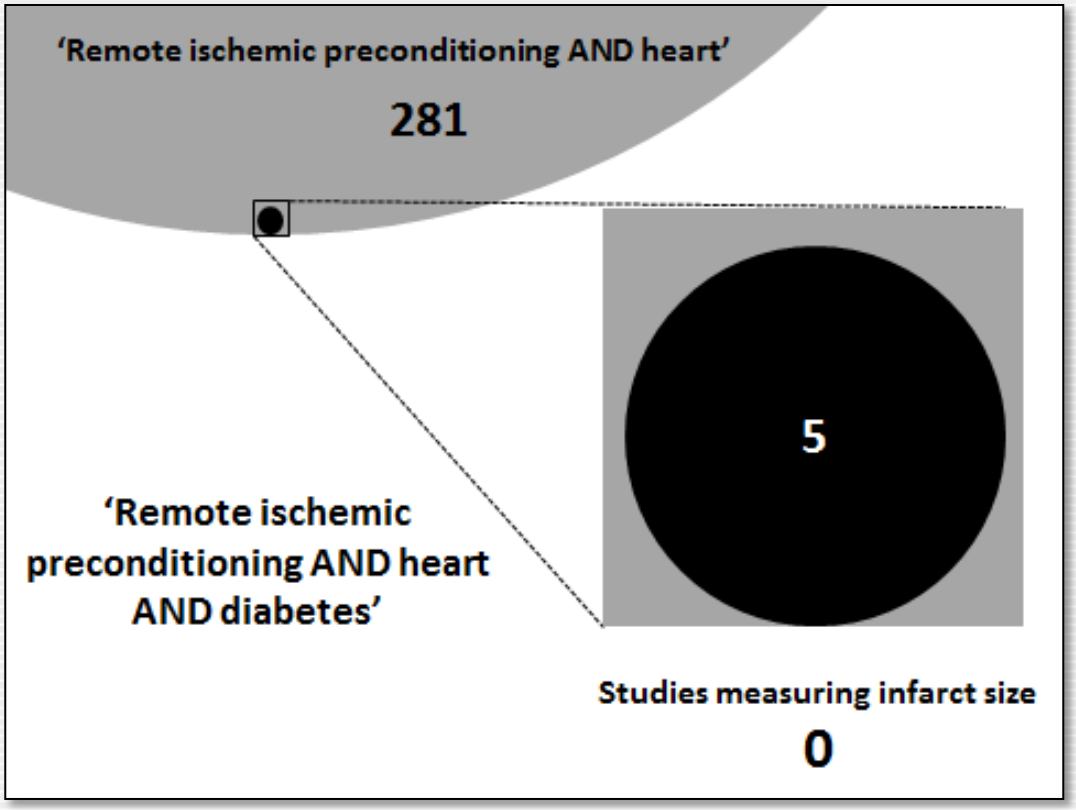


Postconditioning



Wider & Przyklenk, *Cardiovascular Diagnosis & Therapy* 2014;4:383-396.

Remote Preconditioning



Wider & Przyklenk, *Cardiovascular Diagnosis & Therapy* 2014;4:383-396.

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 . . .

trigger

↓

receptor stimulation → G-protein coupled receptors

↓

signaling → 'survival' kinases (~~ERK~~, PI3 kinase/Akt, ~~JAK~~, ~~STAT~~3)

↓

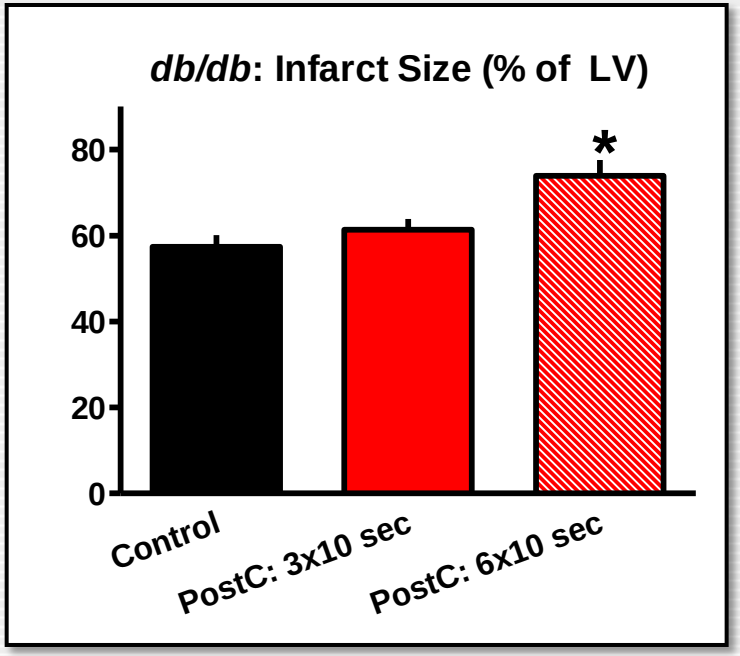
effector → ~~mitochondria~~ (mPTP)

↓

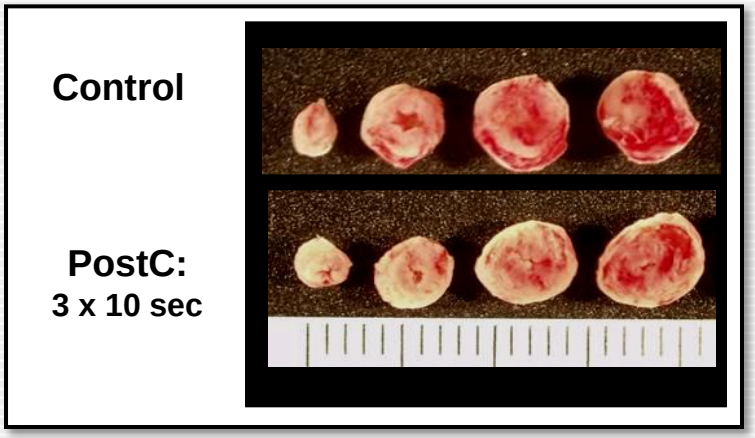
CARDIOPROTECTION

Przyklenk, *British J Pharmacol* 2015;172:1961-73.

Postconditioning: model of type-2 diabetes



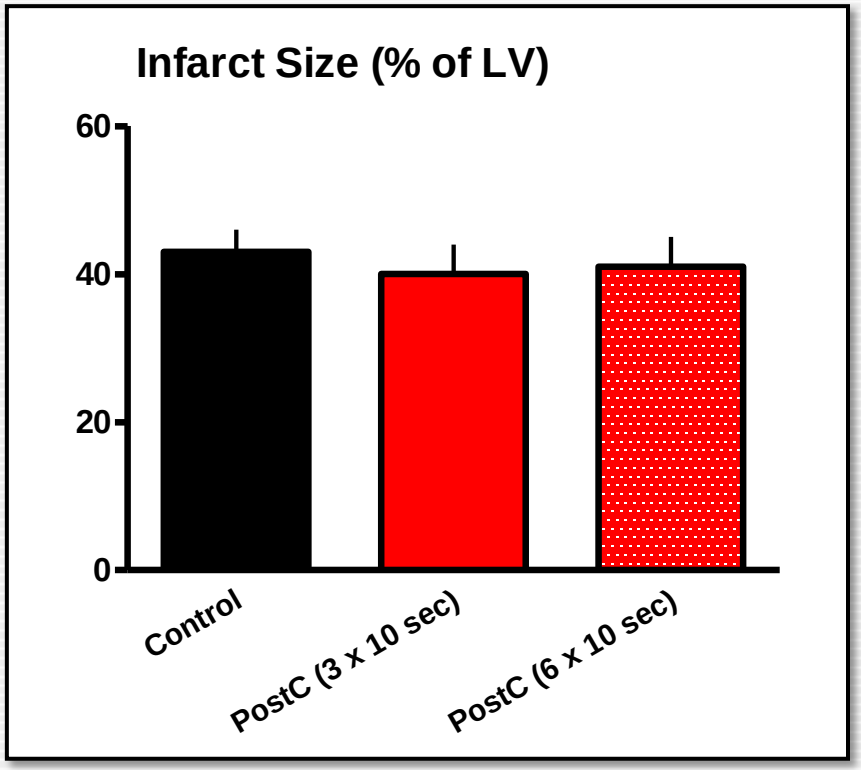
- postconditioning was not cardioprotective in *db/db* mice
- rather, infarct size was *exacerbated* in mice that received the amplified, 6-cycle postconditioning stimulus



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

Przyklenk et al, *Antiox Redox Signal* 2011;14:781-90.

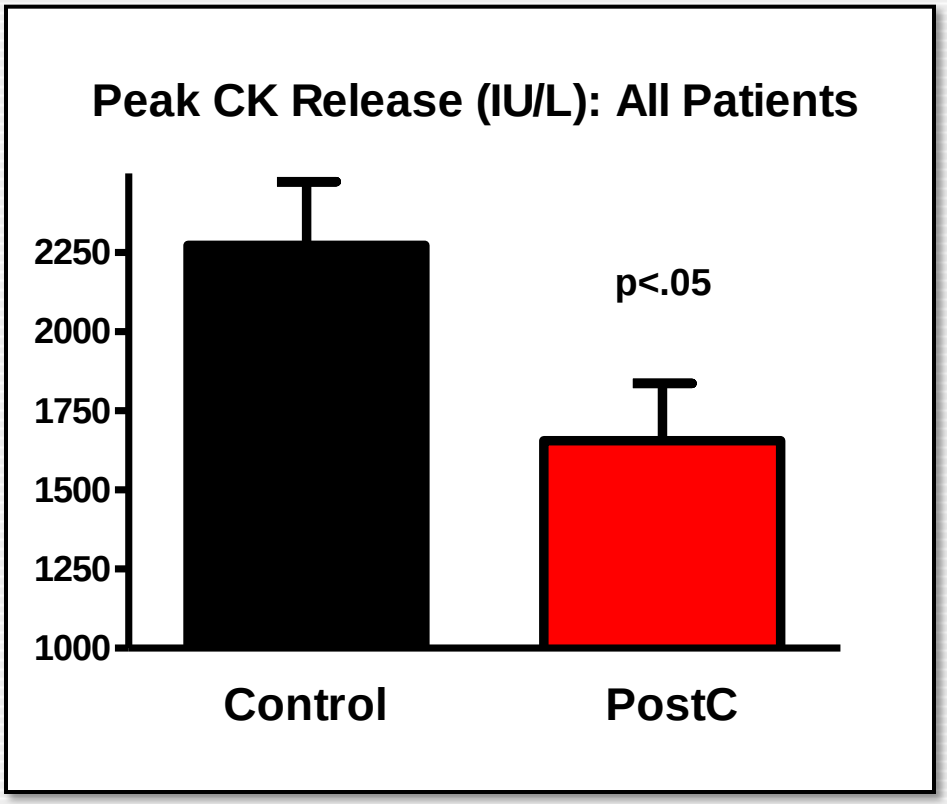
Postconditioning: model of aging



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

Przyklenk et al, *JACC* 2008;51:1393-98.

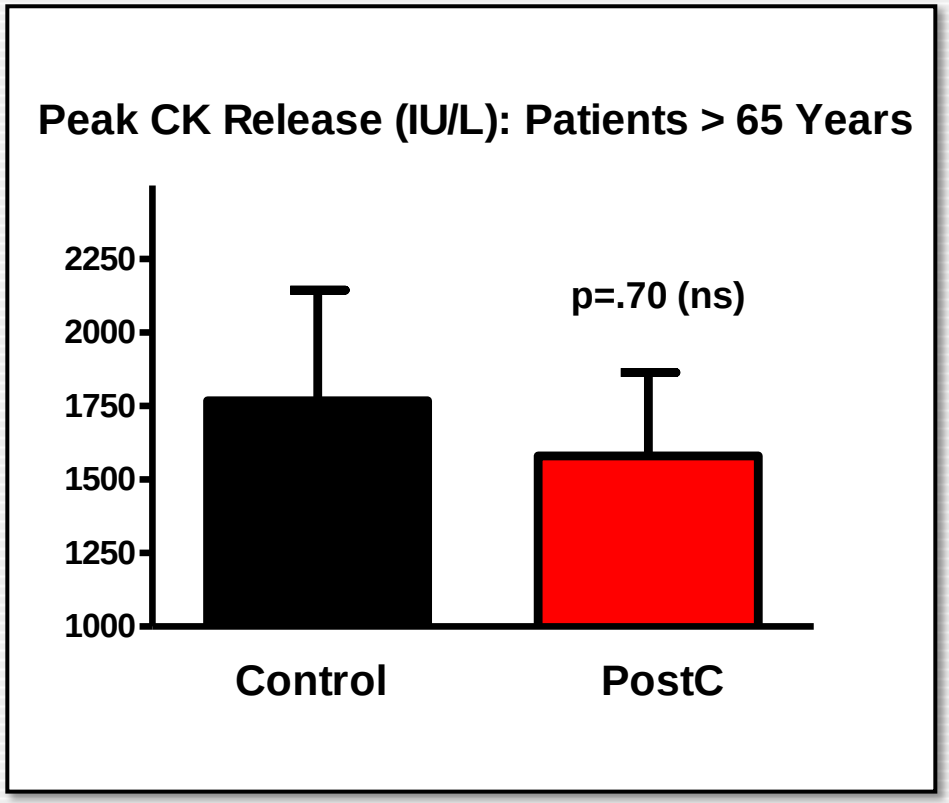
Postconditioning: all patients (n=115)



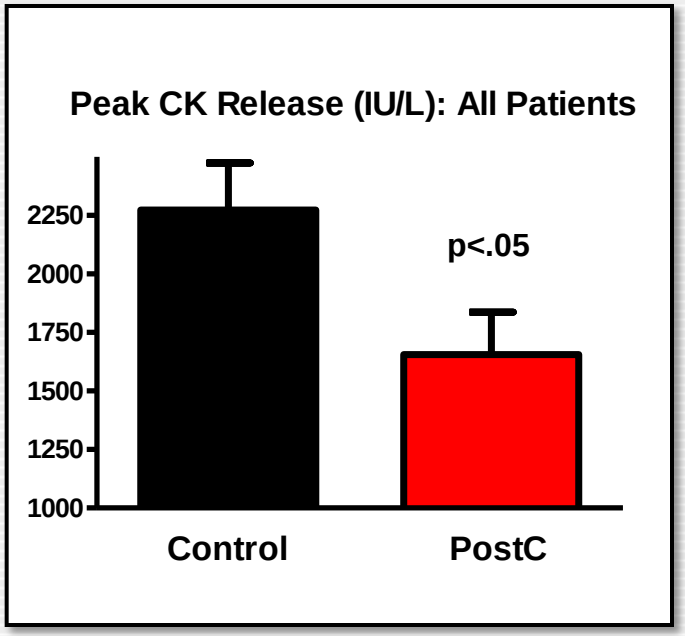
- CK release (surrogate for infarct size) was attenuated in the postconditioned group receiving stuttered reflow (multiple balloon inflations) *vs* controls

Darling, Przyklenk et al, *Basic Res Cardiol* 2007;102:274-278.

Postconditioning: subset >65 years (n=37)



- favorable reduction in CK release with postconditioning was diminished



Vinten-Johansen, Przyklenk et al, *Antiox Redox Signal* 2011;14:791-80.

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**