

Remote Ischemic ‘Conditioning’: *From Inspiration . . . to Clinical Translation*

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School of Medicine

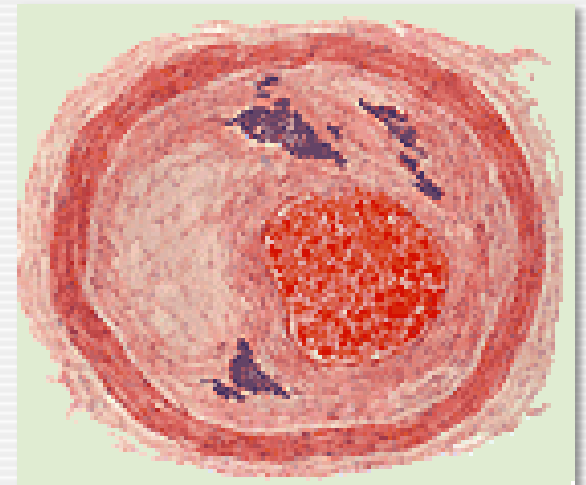
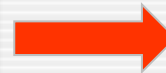
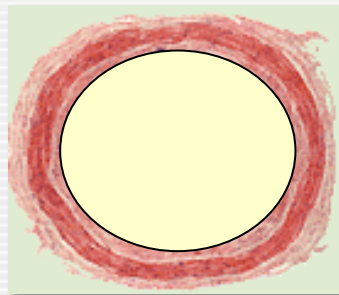
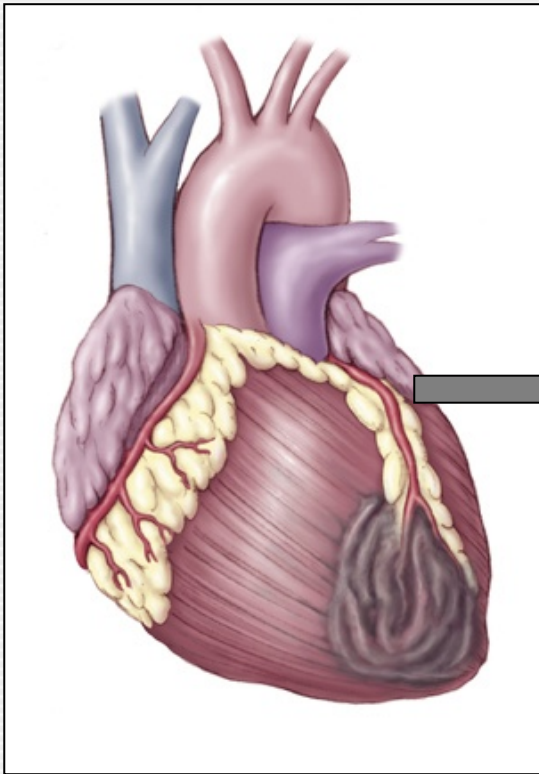
**2014 Dose Response Conference:
Adaptive Responses in Biology and Medicine
University of Massachusetts, Amherst MA
22nd April, 2014**



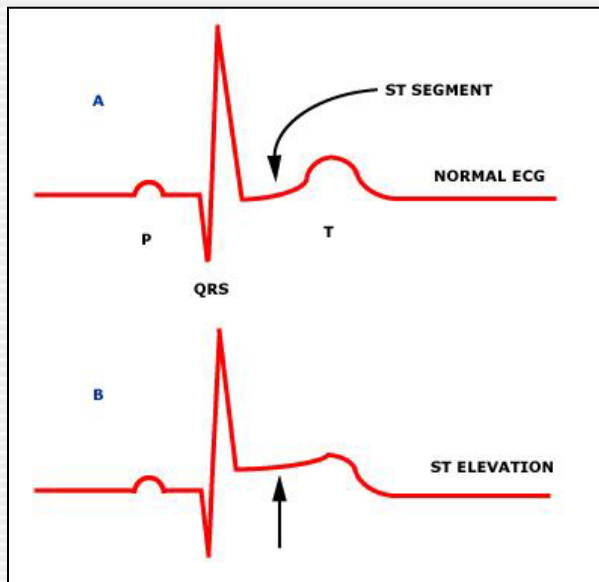
- cardiomyocytes need oxygen, nutrients to survive and function

- blood supply to myocytes provided via the coronary arteries

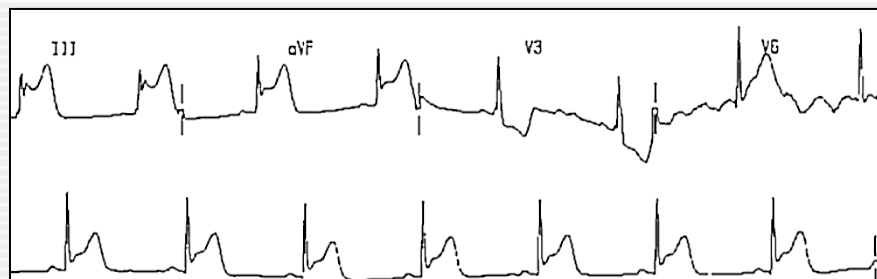
- if coronary arteries become occluded, myocytes become *ischemic*



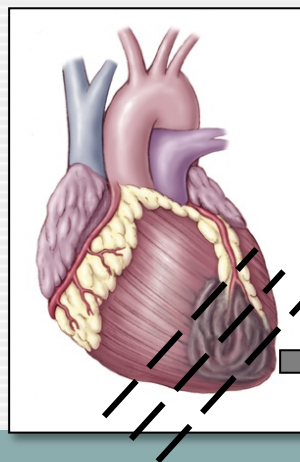
Occlusion → **ischemia** → **myocardial infarction**



Clinical Example



In 2014, >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: preconditioning, postconditioning, remote ischemic conditioning

Control



'Conditioned'



Remote Ischemic 'Conditioning'

- **Inspiration**
 - genesis of the concept
- **Current knowledge**
 - physiology, mechanisms?
- **Clinical translation?**

Remote Ischemic 'Conditioning'

- **Inspiration**

- developed a hypothesis based on **analysis, extrapolation of data from conventional ischemic preconditioning**

- **Current knowledge**

- physiology, mechanisms?

- **Clinical translation?**

Preconditioning

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

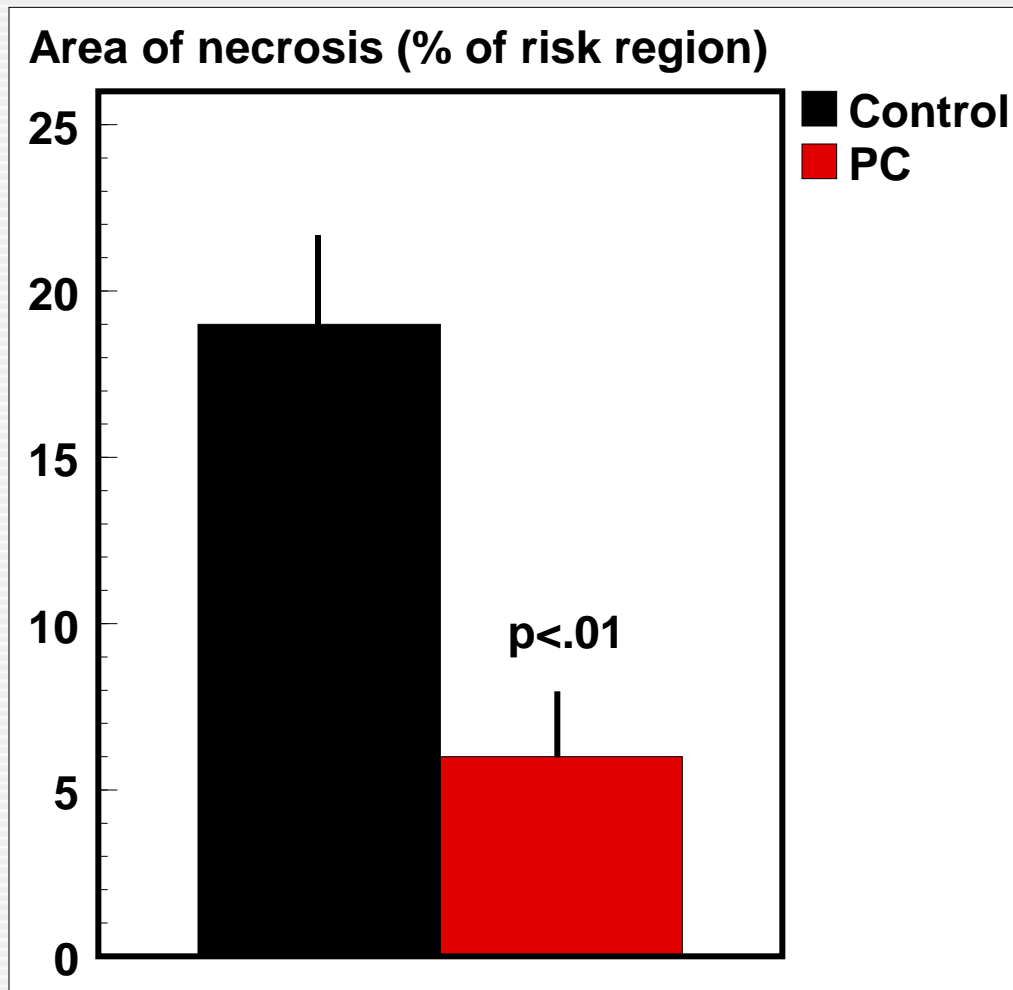
Murry et al, *Circulation* 1986;74:1124-1136.

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

Control:



Preconditioned:

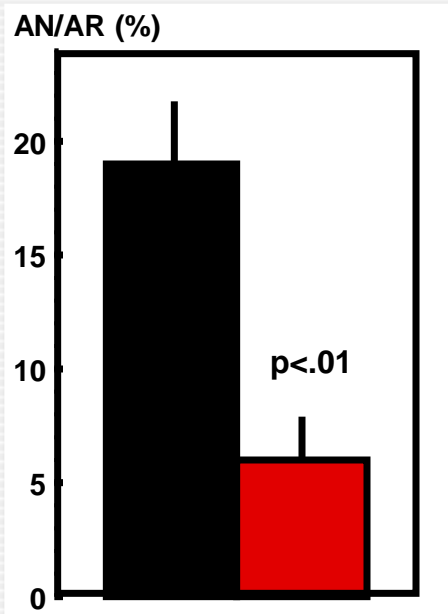


↑
area of necrosis
(% of risk region)

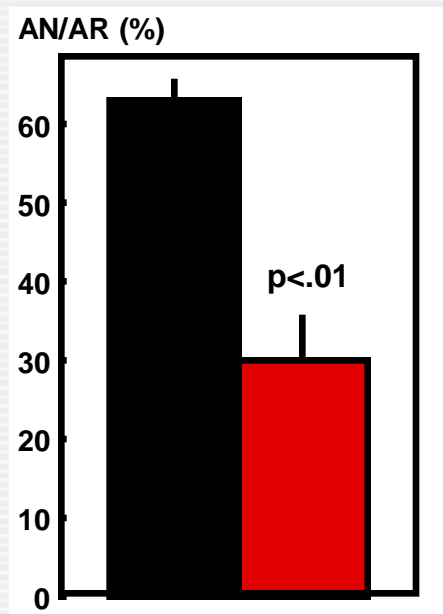
Reduction of Infarct Size with Preconditioning

- since 1986: has been the focus of >5,000 publications (PubMed)

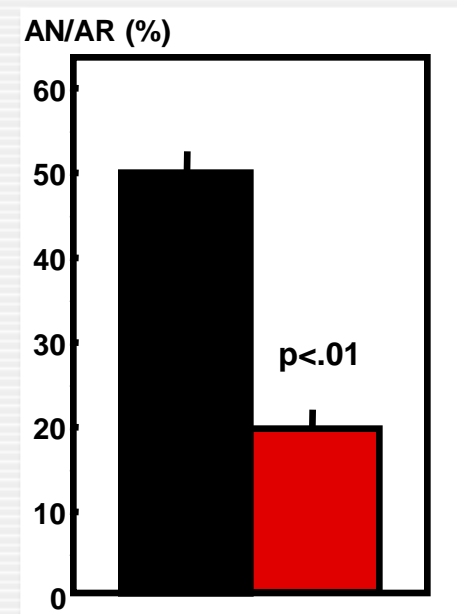
Dog



Rabbit

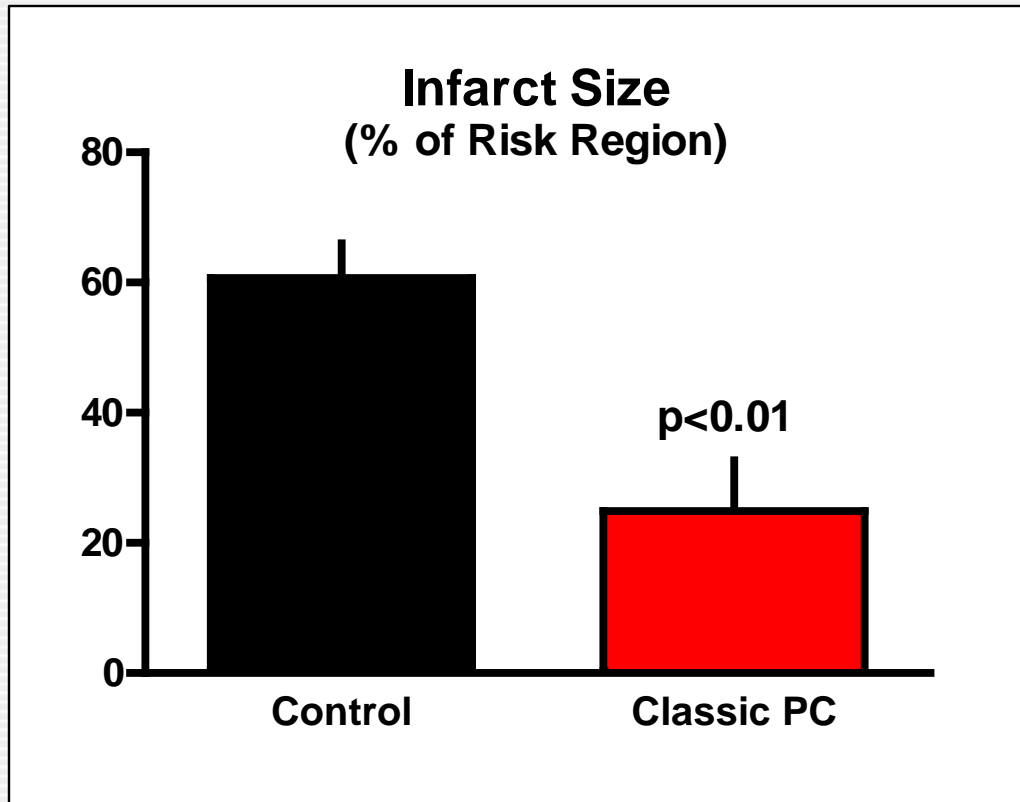


Mouse



■ Control ■ Preconditioned

Preconditioning: Rat Model



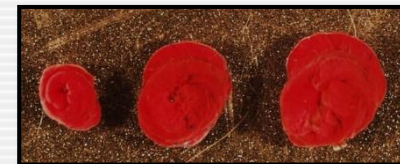
In the rat model:

- mean infarct size (expressed as % of risk region) was reduced in preconditioned hearts vs controls

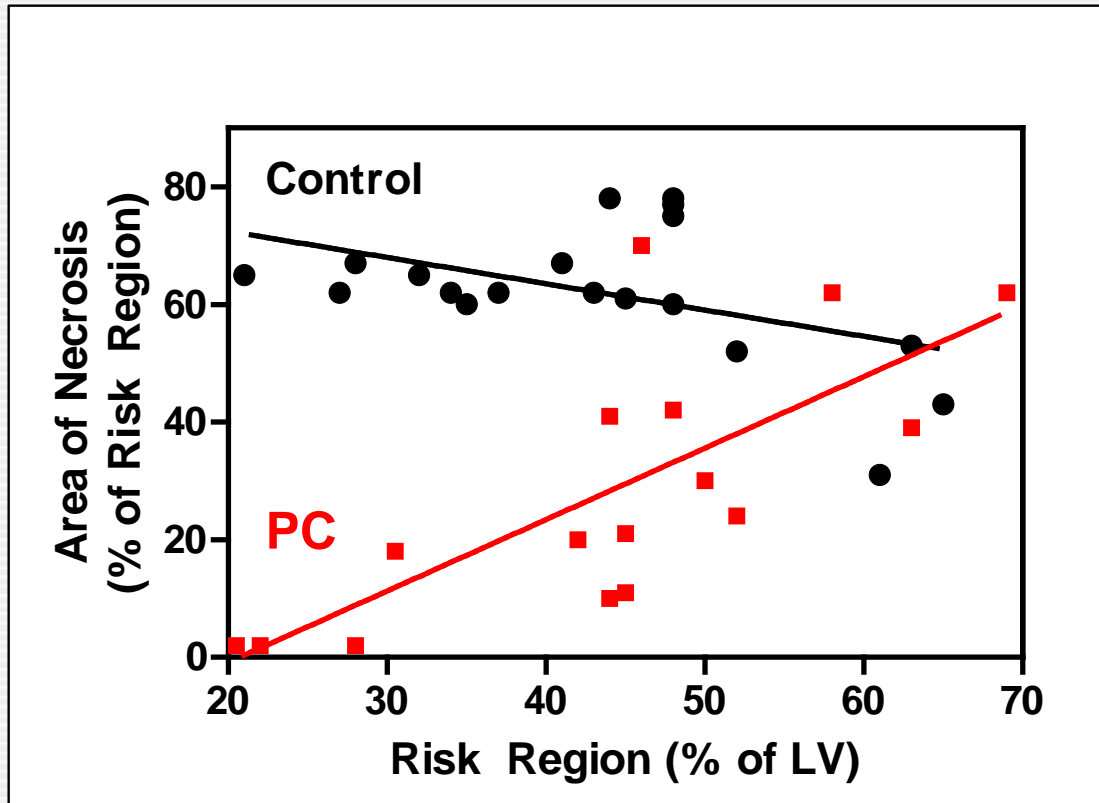
Control



PC

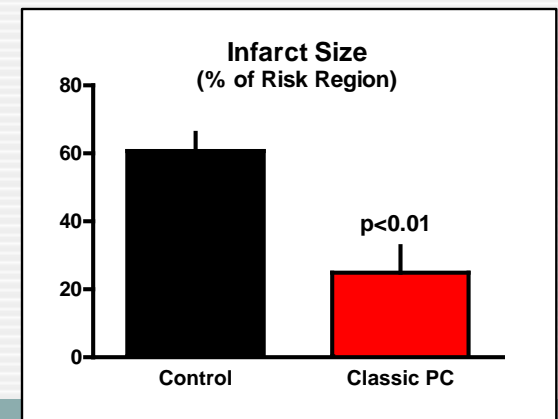


Genesis of the Concept



- in control hearts: infarct size (% of risk region) was ~constant, irrespective of risk region
- in the PC group: large risk regions → greater proportion of risk region becoming necrotic

Whittaker & Przyklenk, *Basic Res Cardiol* 1994;89:6-15.
Przyklenk & Whittaker, *J Cardiovasc Med* 2013;14:180-6.



RR/LV = 20%

RR/LV = 50%

RR/LV = 70%

Control

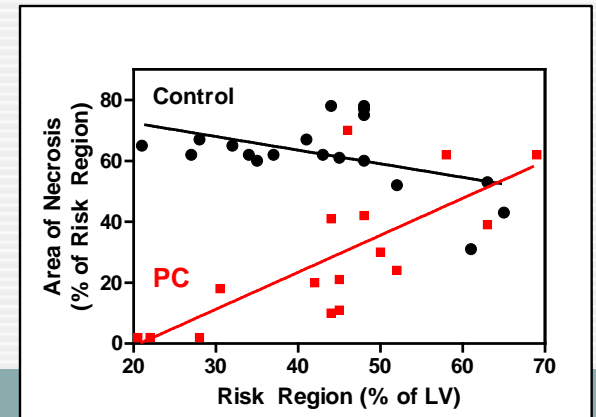


Classic PC



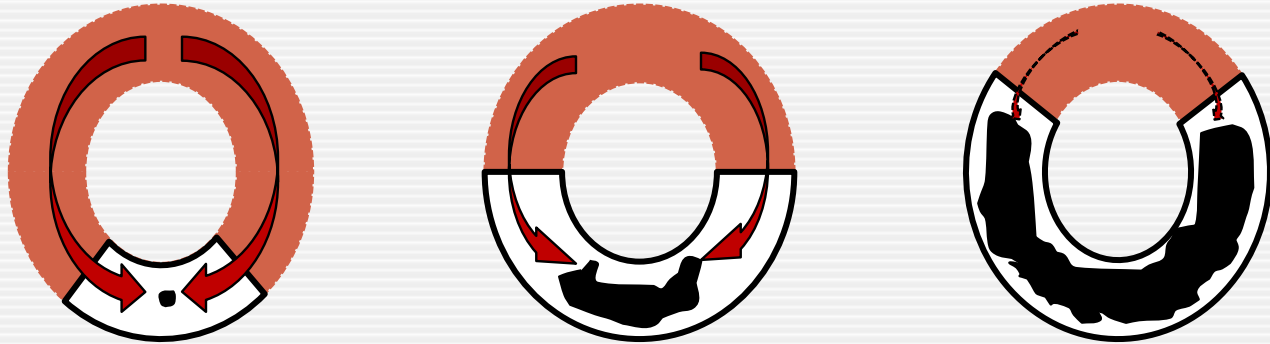
□ Risk Region (RR)
■ Area of Necrosis (AN)

Whittaker & Przyklenk, *Basic Res Cardiol* 1994;89:6-15.
Przyklenk & Whittaker, *J Cardiovasc Med* 2013;14:180-6.



Genesis of the Concept

Classic PC

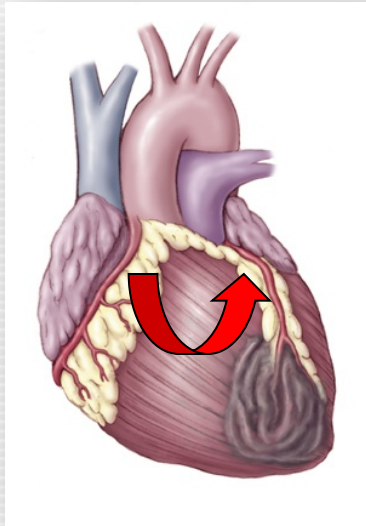


Interpretation: a stimulus or trigger, *generated in nonischemic tissue*, may contribute to the cardioprotection achieved with classic PC

Prediction: brief PC ischemia applied in one coronary vascular bed may protect remote, naïve myocardium from sustained ischemia – i.e., remote ischemic preconditioning

Whittaker & Przyklenk, *Basic Res Cardiol* 1994;89:6-15.
Przyklenk & Whittaker, *J Cardiovasc Med* 2013;14:180-6.

Remote Ischemic Conditioning (RIC): First Evidence



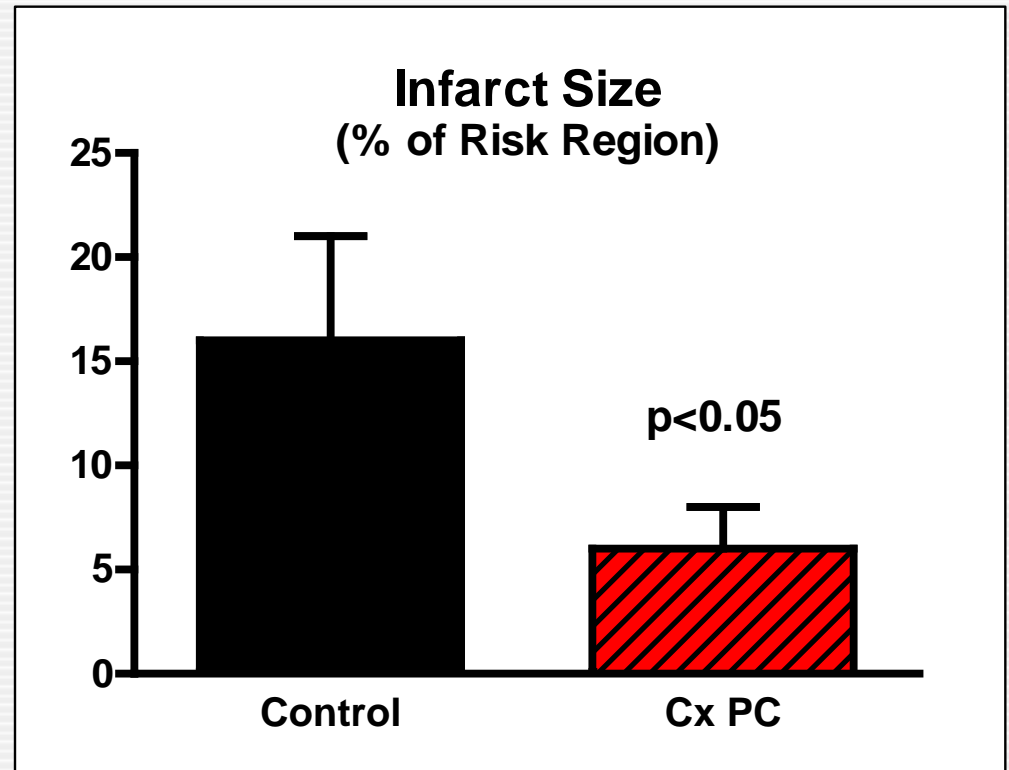
Control



Circumflex (Cx) PC



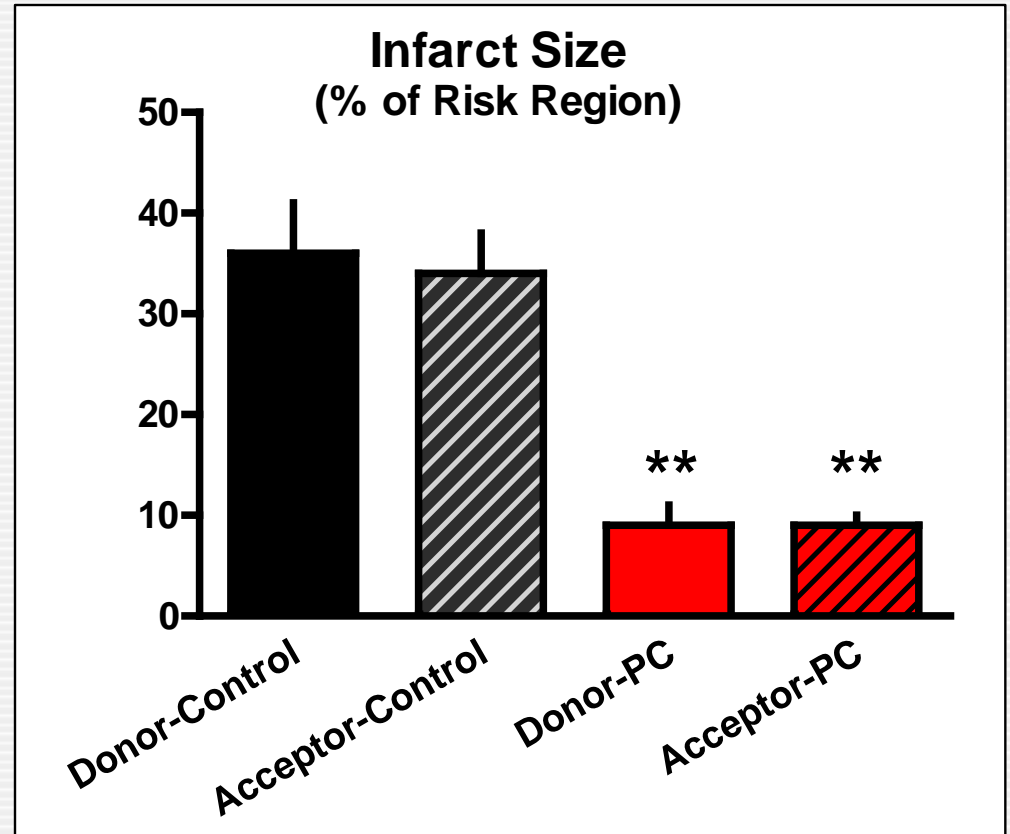
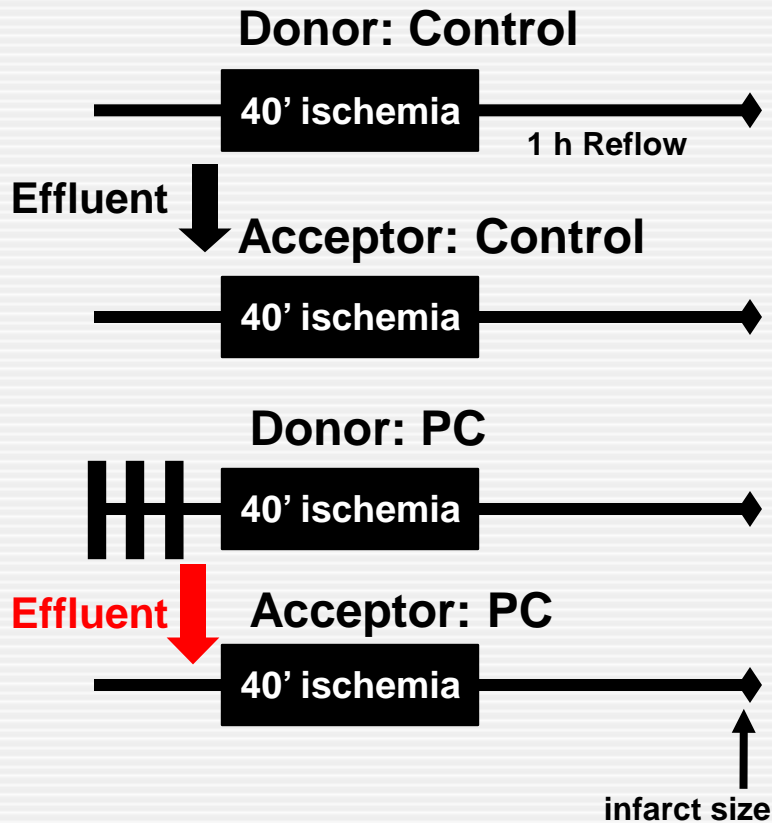
↑
infarct size
(% of risk region)



Significant reduction of infarct size with 'intra-cardiac' remote ischemic conditioning (RIC)

Expanding the Paradigm

'Transferred' RIC



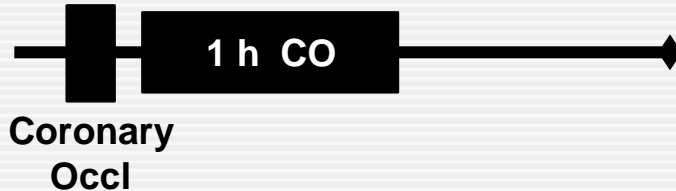
Expanding the Paradigm

'Inter-organ' RIC

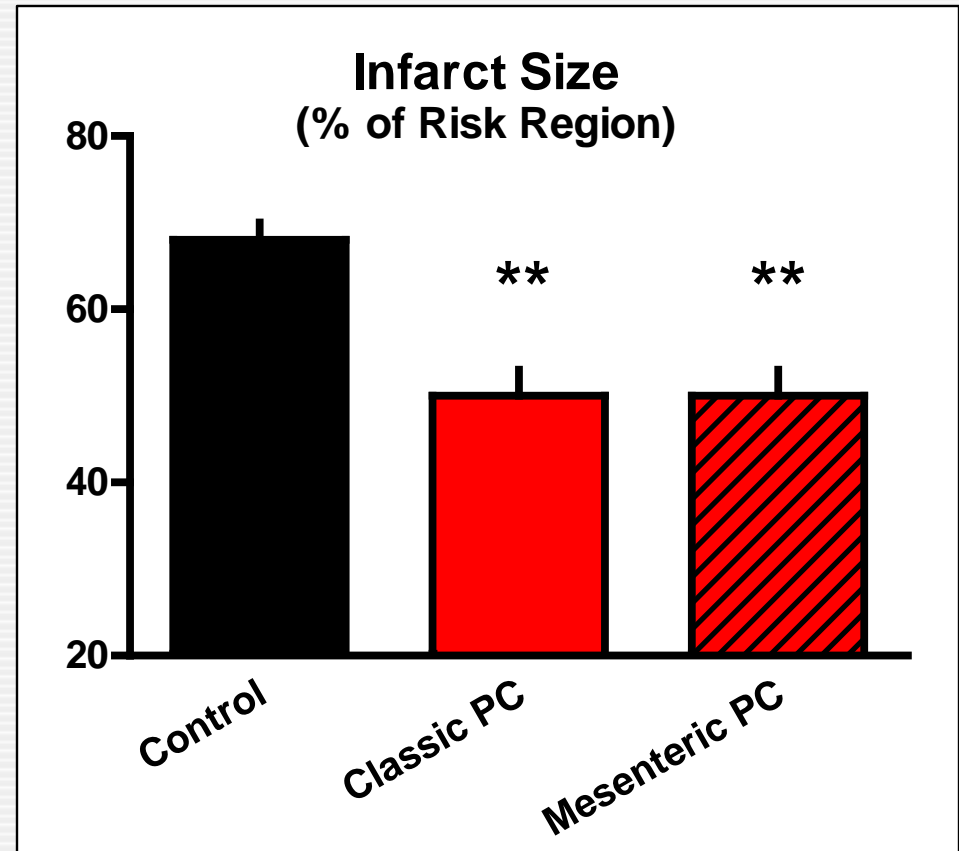
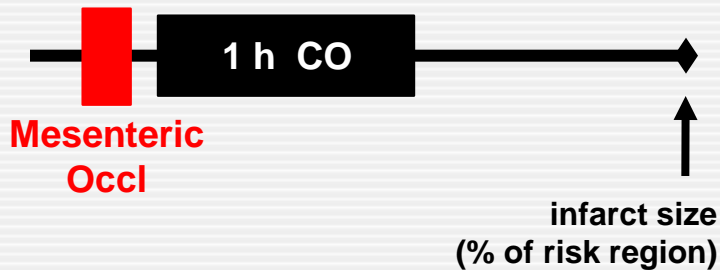
Control



Classic PC

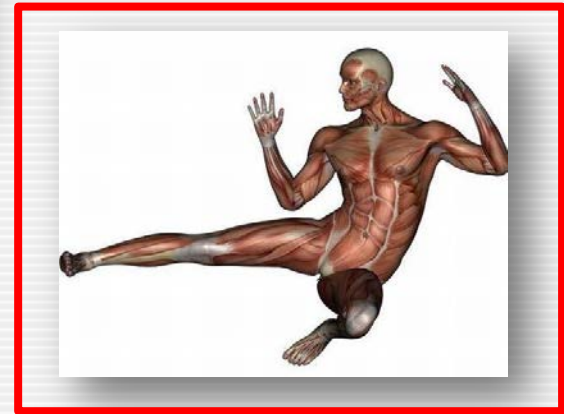
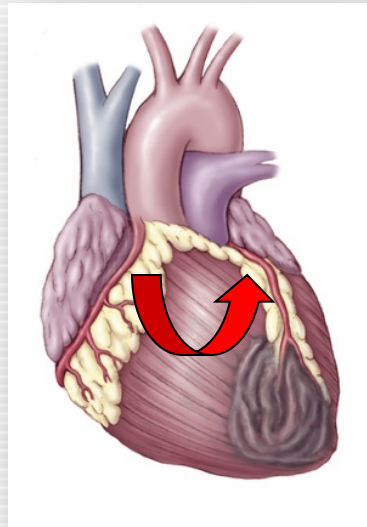
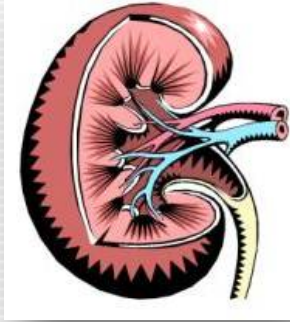


Mesenteric PC



**p<0.001 vs Control

Expanding the Paradigm



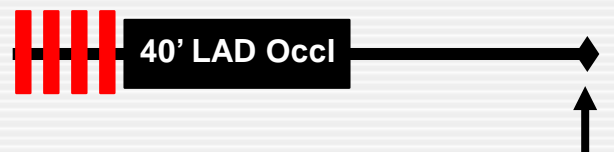
Expanding the Paradigm

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

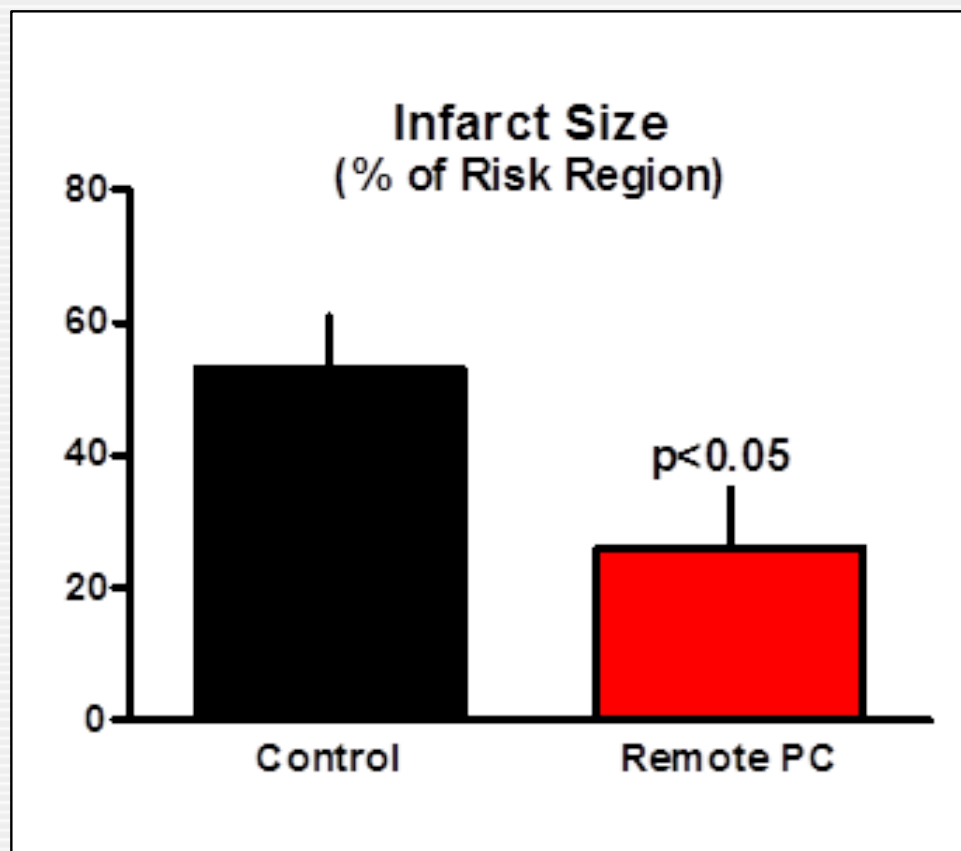
Control



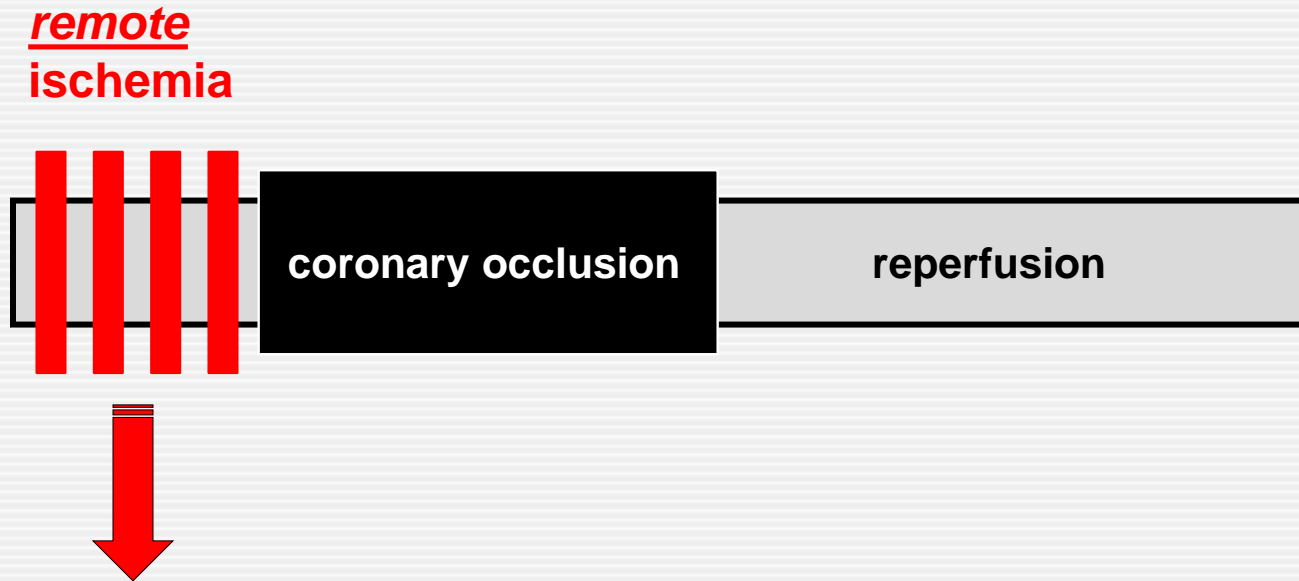
Hindlimb ischemia



infarct size
(% of risk region)



Remote Ischemic Conditioning



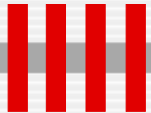
Reversible ischemia *applied at a remote site* is cardioprotective; renders the heart resistant to a sustained period of ischemia

Remote Ischemic 'Conditioning'

- **Inspiration**
 - genesis of the concept
- **Current knowledge**
 - physiology, mechanisms?
- **Clinical translation?**

Physiology

remote



sustained ischemia

Remote stimulus (skeletal muscle):

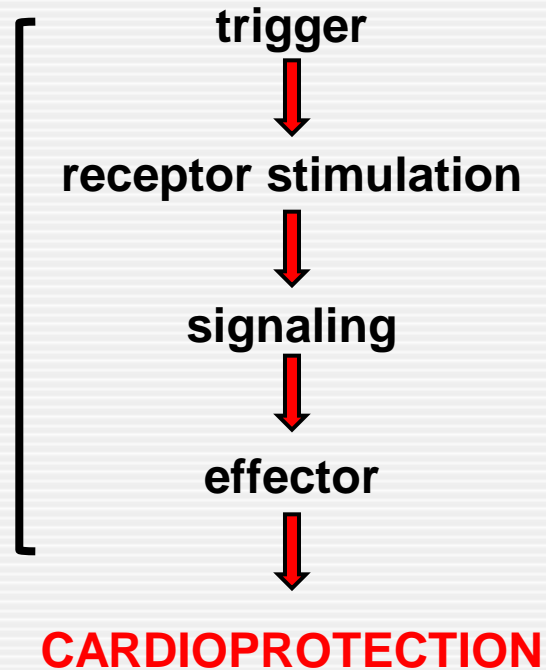
- duration of brief, remote ischemic episodes? 5 min
- how many cycles? ~3-4
- arm(s)? leg(s)?
- complete occlusion?

Interval between remote stimulus and sustained ischemia:

- for remote ischemic preconditioning . . . ?
- concepts of remote per- and postconditioning

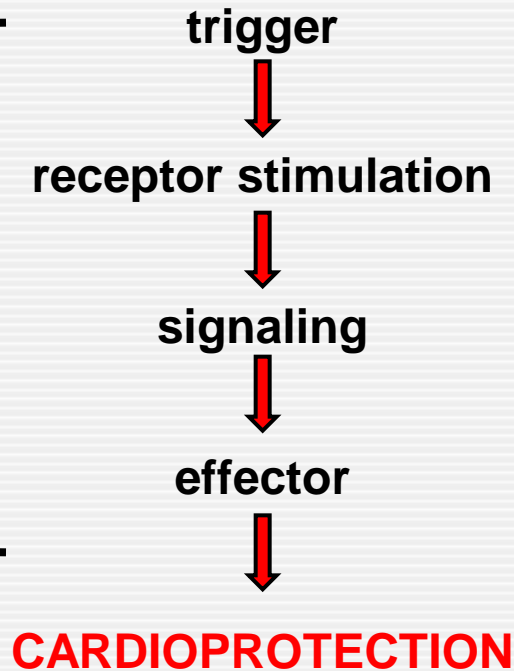
Mechanisms

For pre-, postconditioning:

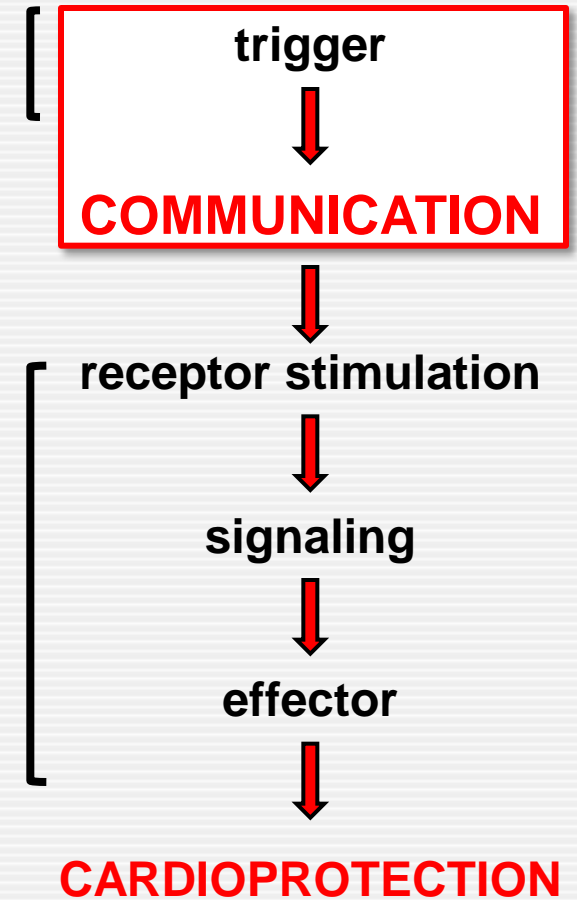


Mechanisms

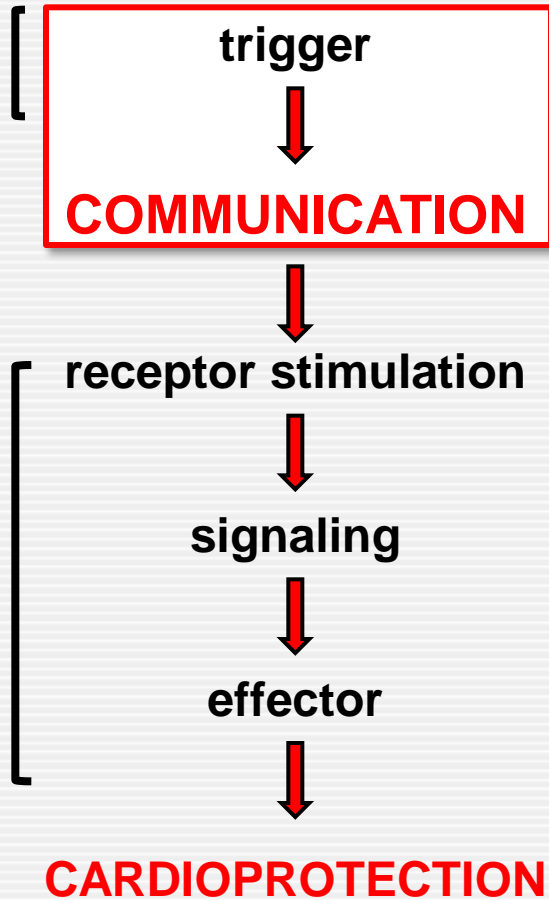
For pre-, postconditioning:



For remote ischemic conditioning:



Mechanisms



In 1993:

the infarct-sparing effect of remote conditioning '*... may be mediated by factor(s) activated, produced, or transported throughout the heart during brief ischemia-reperfusion.*'

In 2014 . . .

Mechanisms: Communication

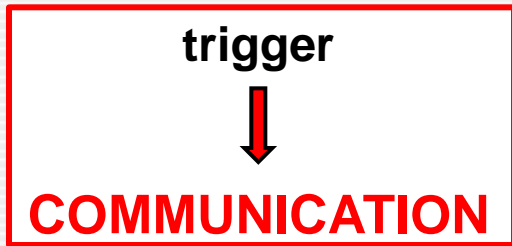
Paradigms: neuronal *and/or* humoral

Candidates include:

- adenosine, bradykinin, opioids
- by HPLC: ‘small (<15 kDa) hydrophobic molecule’
- from proteomic screens: Apo-A1
 - Hilbert et al, *PLoS* 2013;8:e77211
 - Hepponstall et al, *PLoS* 2012;7:e48284
- targeted hypotheses: SDF (stromal cell derived factor)1- α /CXCR4; change in expression of miRNAs
 - Davidson et al, *Basic Res Cardiol* 2013;108:377
 - Duan et al, *Cardiology* 2012;122:36-43
 - Slagsvold et al, *Circ Res* 2014;114:851-9

In all likelihood . . . *model-dependent*

Mechanisms



receptor stimulation

↓
signaling

↓
effector

↓
CARDIOPROTECTION



In 1993:

the infarct-sparing effect of remote conditioning '*... may be mediated by factor(s) activated, produced, or transported throughout the heart during brief ischemia-reperfusion.*'

In 2014 . . .

- multiple candidates
- . . . no integrated, unifying hypothesis

Remote Ischemic 'Conditioning'

- **Inspiration**

- genesis of the concept; first evidence

- **Current knowledge**

- physiology, mechanisms?

- **Clinical translation?**

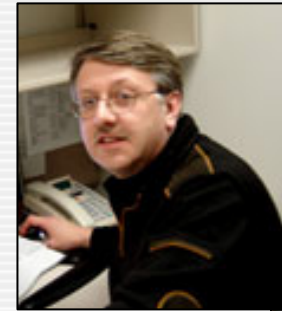
- ~25 published Phase II clinical trials
- Phase III trials: in progress

Remote Ischemic 'Conditioning'

- **Inspiration**
 - *discovery of RIC was data- and hypothesis-driven*
- **Current knowledge**
 - *understanding of the physiology, mechanisms of RIC (i.e., communication) remain incomplete*
- **Poised for clinical application?**

Collaborators

Peter Whittaker, PhD



Michelle Maynard

Eric W. Dickson, MD

Chad E. Darling, MD

Craig Smith, MD

Dale Greiner, PhD

Thomas Sanderson, PhD

Rita Kumar, PhD

Yi Dong, MBBS

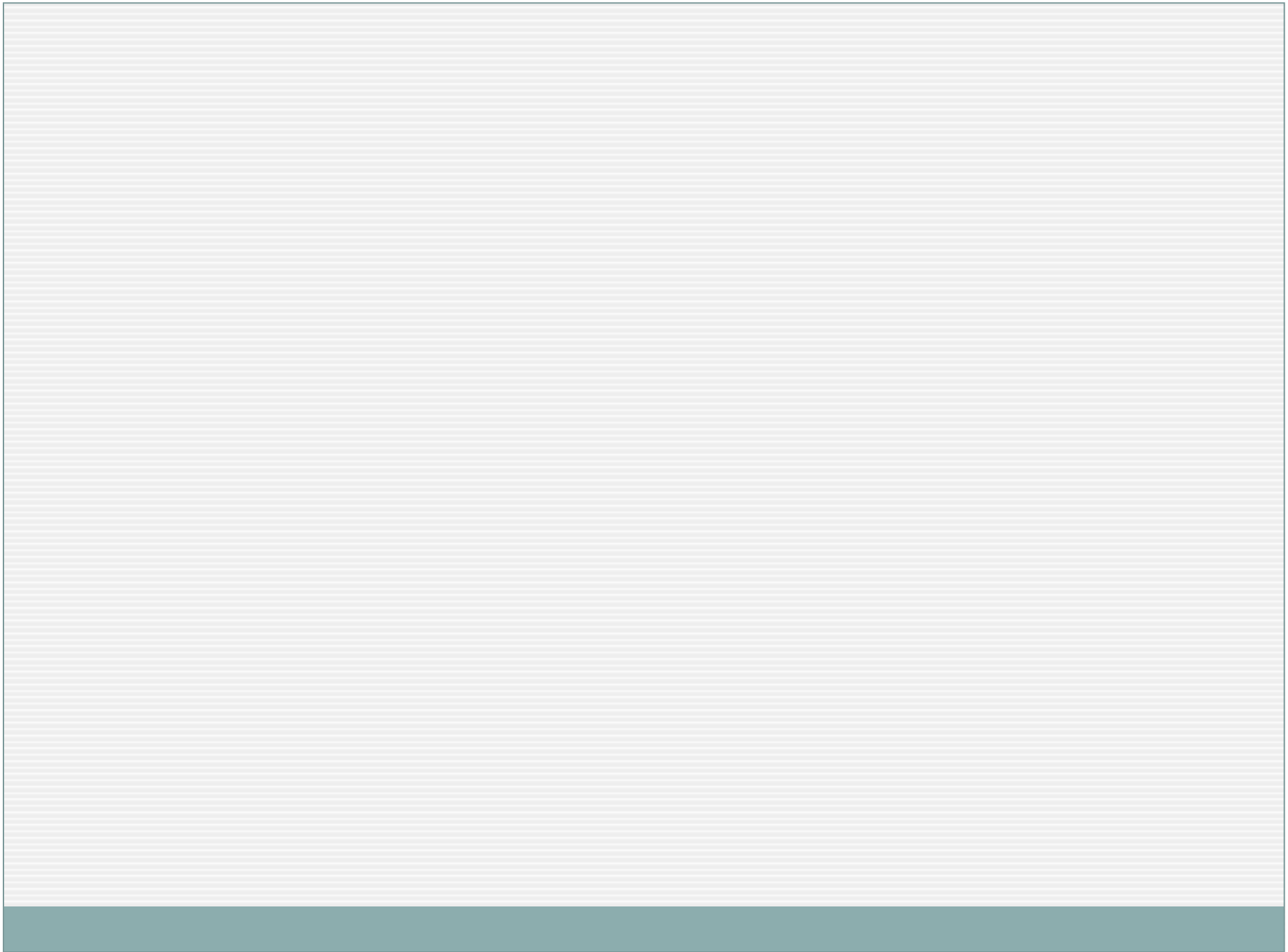
Christian Reynolds

Joe Wider

Lesley Calo

Vishnu Undyala, MS

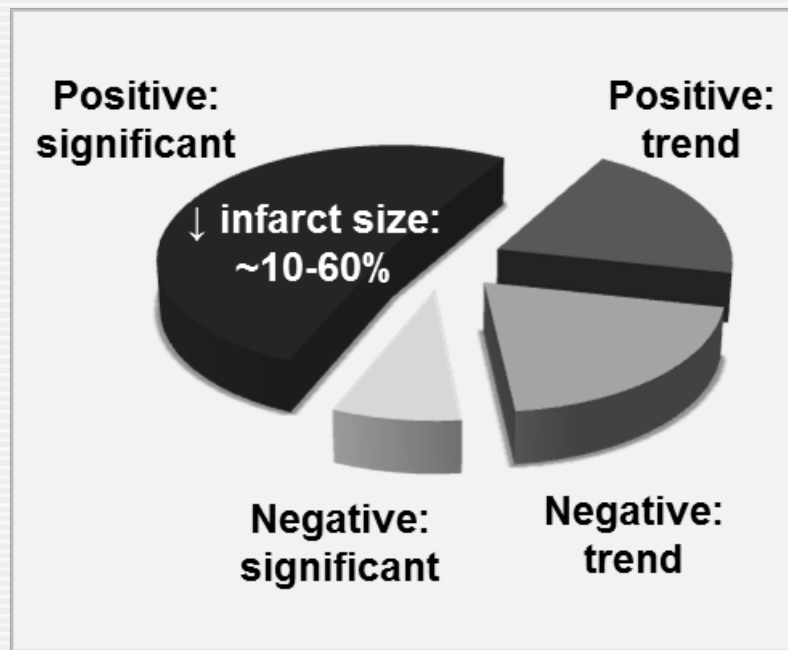




'Heart attack' . . . *scope of the problem*

- >1 in 3 Americans has some form of cardiovascular disease
- in 2014, **>1 million will have a heart attack**
- economic cost (hospitalization; lost productivity): >\$200 billion
- human cost: >15% of persons who have a heart attack will die
- **heart disease is the single largest killer of Americans**

- ~25 published Phase II clinical trials
- cardiac surgery; elective PCI; primary PCI in patients with STEMI
- stimulus: multiple (3-4) 5 min episodes of limb ischemia
- primary endpoint: infarct size or its surrogate
- outcomes have been mixed . . .



. . . possibly a consequence of gaps in our understanding of the mechanisms of RPC