

Introduction to Ischemic Conditioning
Focus Group Meeting on Ischemic Conditioning
Sponsored by IC Therapeutics
Hyatt Regency McCormick Place
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Disclosure

Dr. Kloner is a consultant to IC Therapeutics



The Preconditioning Phenomenon

The heart's own self-preserving mechanism

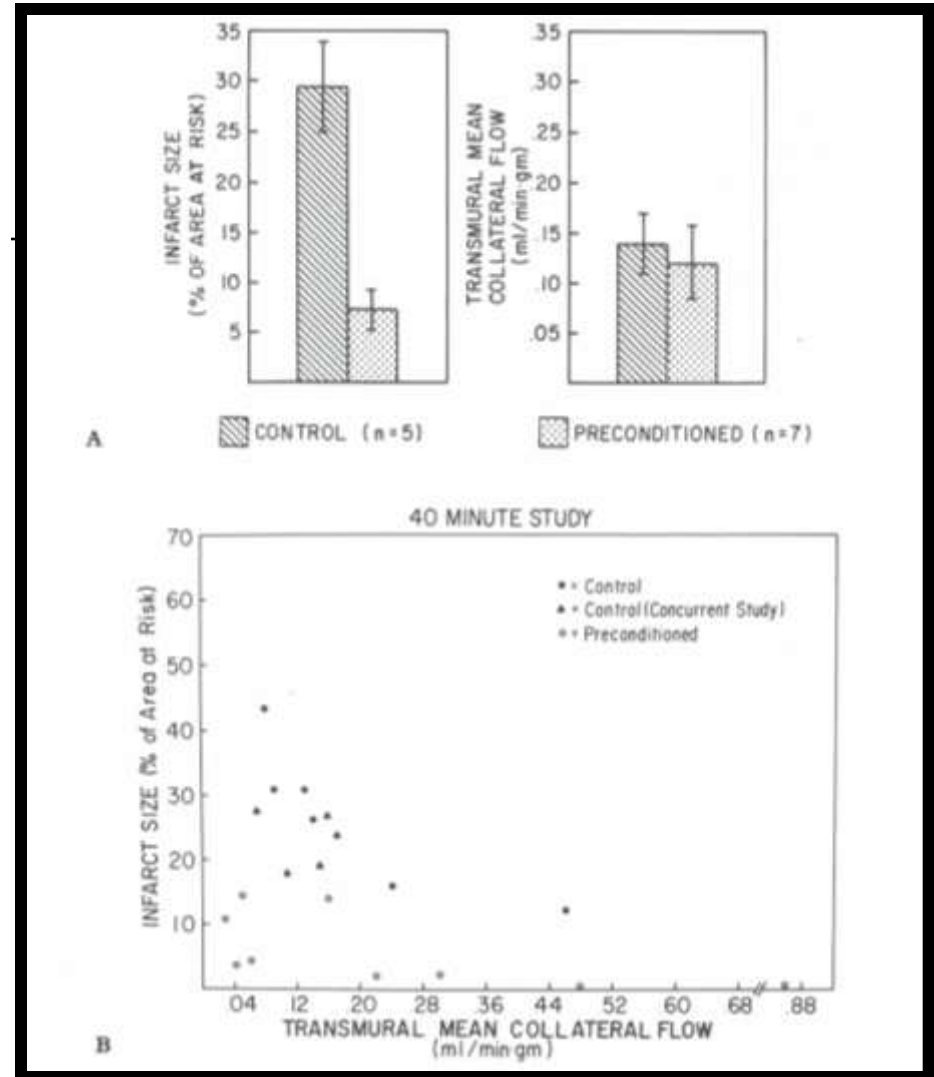
Brief periods of ischemia (2-5 minutes) prior to a longer duration of ischemia:

- Reduce infarct size in most models

- Reduce ventricular arrhythmias

If we can learn the mechanism of preconditioning, it may lead to potentially important therapies.

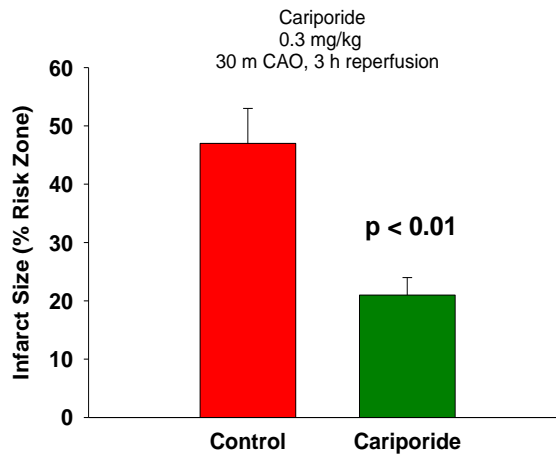
Effects of preconditioning on myocardial infarct size in dogs



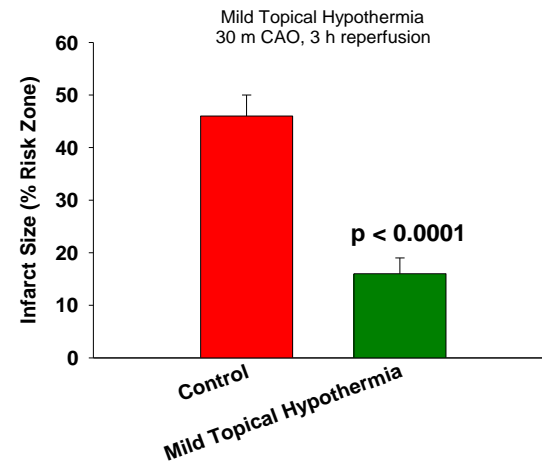
Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986 Nov;74(5):1124-36



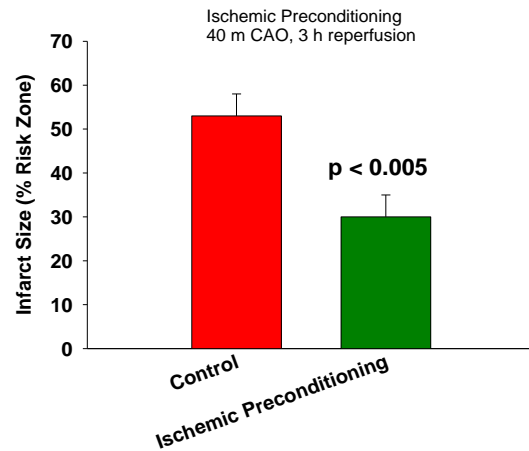
Some Interventions that Reduced Infarct Size in an Experimental Model of Ischemia/Reperfusion



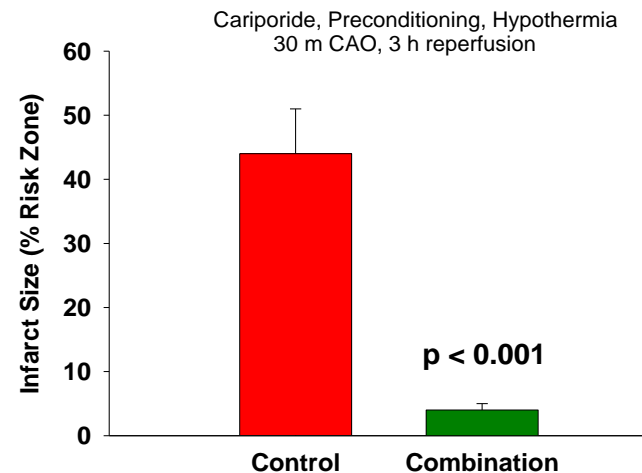
Hale & Kloner, Am J Physiol, 2000



Hale & Kloner, Am J Physiol, 1997

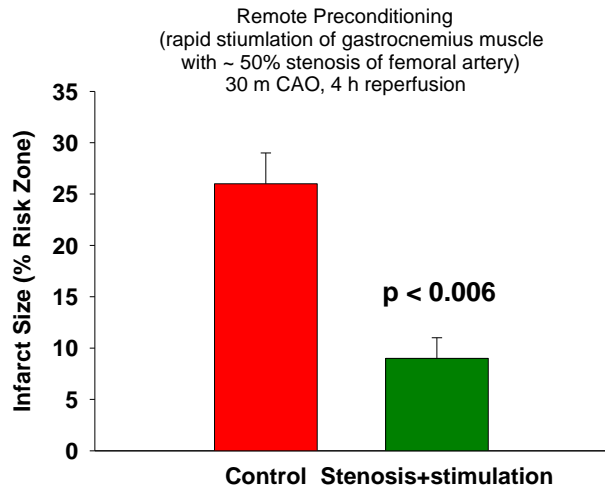


Hale & Kloner, Coronary Artery Dis, 1992

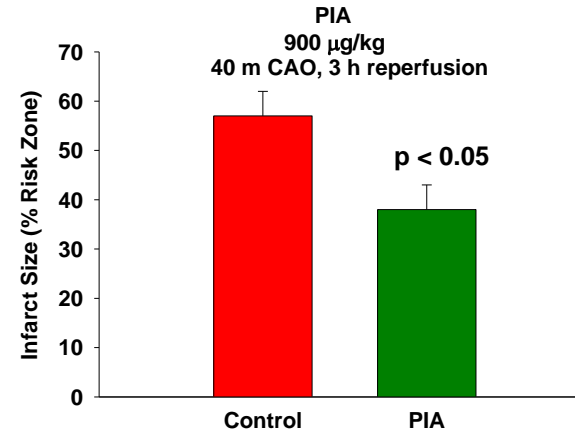


Hale & Kloner, Heart Disease, 2001

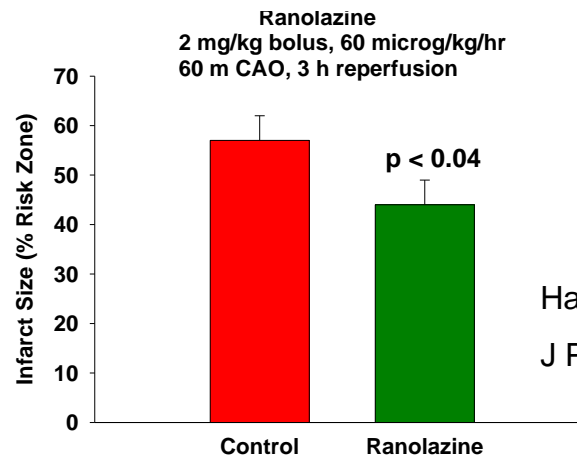
Interventions that Reduced Infarct Size in an Experimental Model of Ischemia/Reperfusion Continued



Birnbaum, Hale & Kloner, Circulation, 1997



Hale, Bellows, Hammerman & Kloner, Cardiovasc Res, 1993

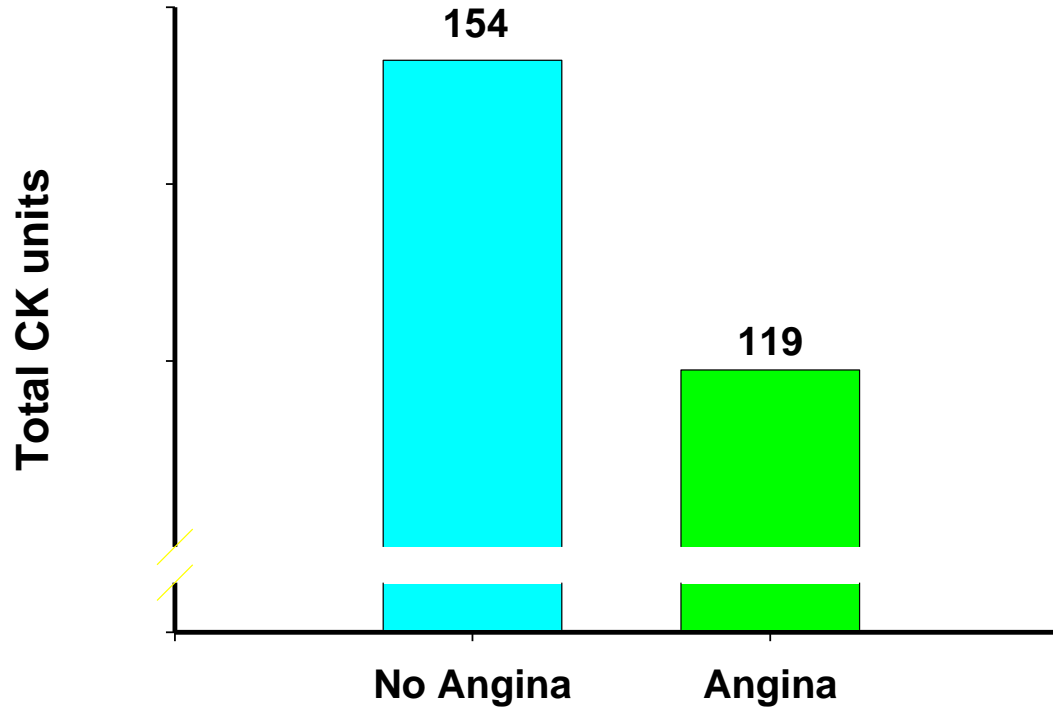


Hale, Leeka & Kloner,
J Pharmacol Exp Therap, 2006

Clinical Evidence For Preconditioning

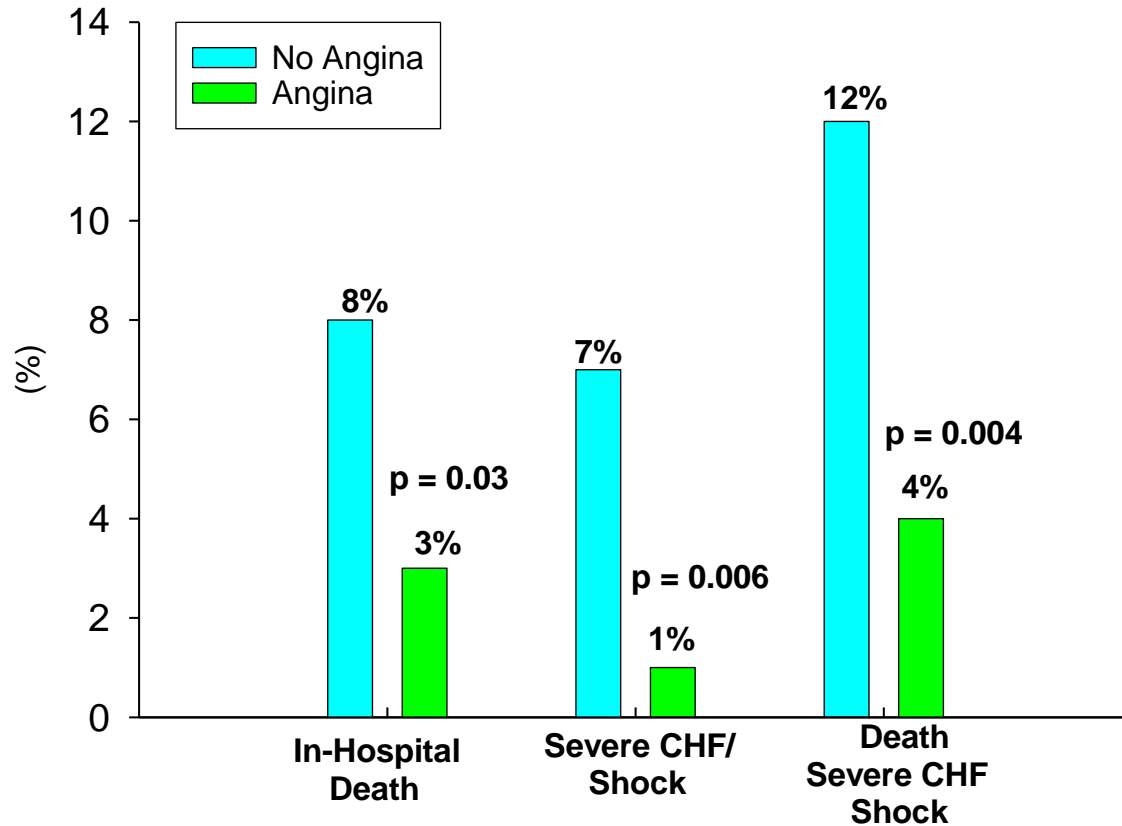
- Less chest pain, ST-segment elevation, lactate production with subsequent compared to first angioplasty balloon inflation
- Reduction in infarct size, mortality and CHF in patients with history of angina before acute MI
- Acute tolerance to angina (warm up phenomenon)
- Studies performed on human cardiac tissue:
 - ATP levels during CABG
 - In vitro studies on isolated human muscle
 - In vitro studies on human myocytes

History of Any Angina - TIMI 4



Kloner RA, Shook T, Przyklenk K, Davis VG, Junio L, Matthews RV, Burstein S, Gibson M, Poole WK, Cannon CP, McCabe C, Braunwald E, for the TIMI 4 Investigators. Previous angina alters in-hospital outcome in TIMI 4. A clinical correlate to preconditioning? *Circulation* 1995; 91:37-45.

History of Any Angina - TIMI 4

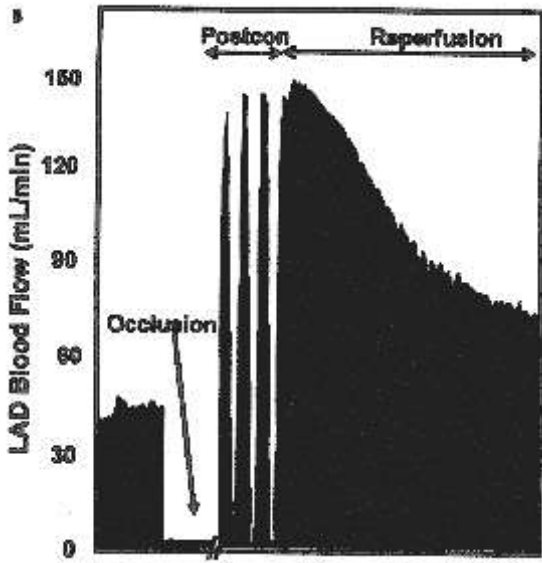
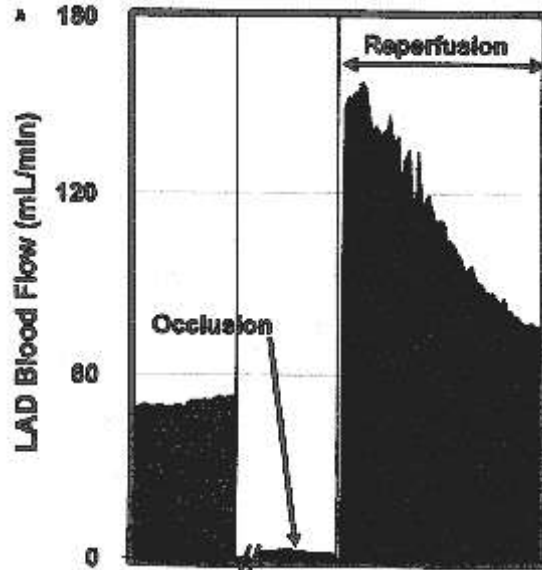


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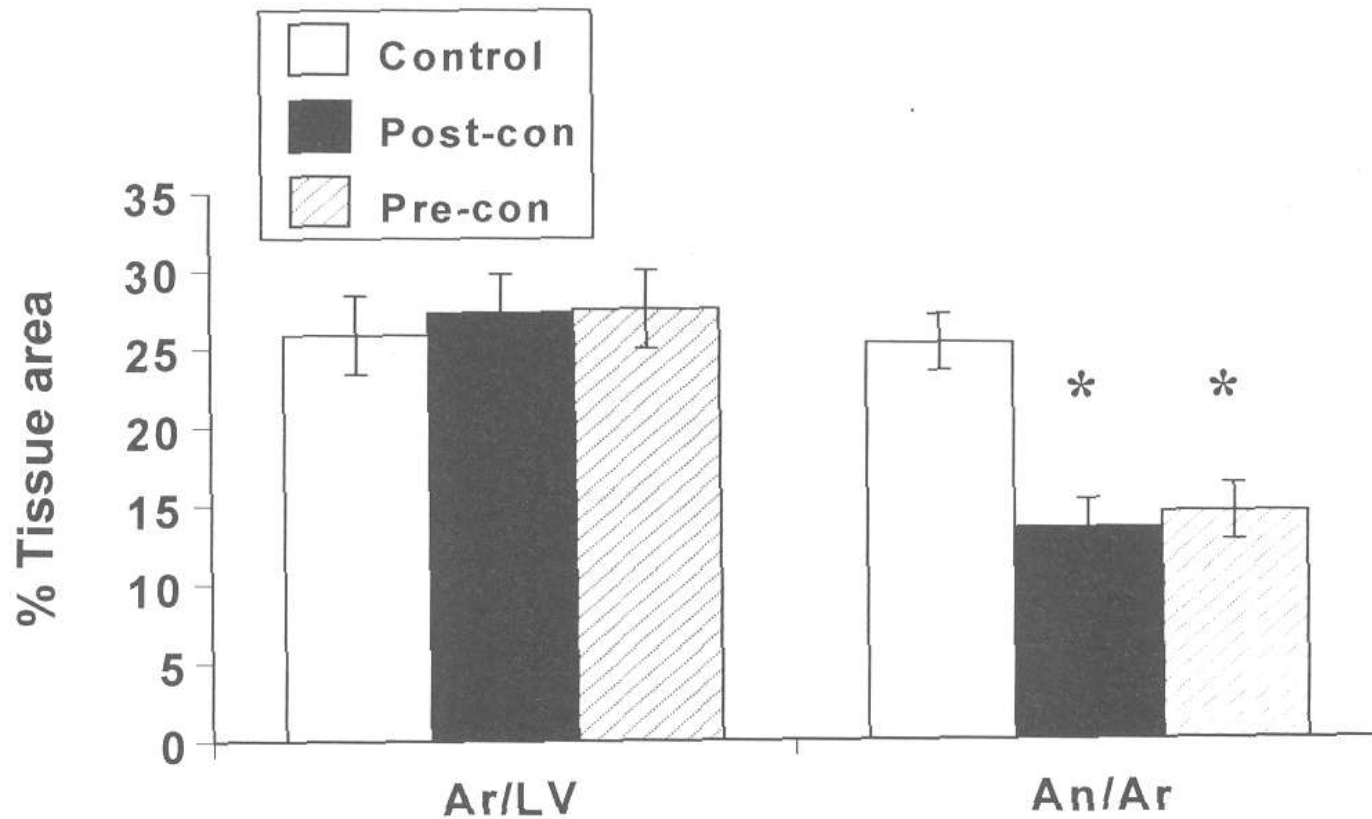
Postconditioning

Postconditioning is the phenomenon whereby several brief coronary artery reperfusion/reocclusion cycles at the end of a long coronary artery occlusion (stuttering reperfusion) reduces infarct size

- Zhao, Z-Q et al. *Am J Physiol* 2003;285:1574
- Yang, X-M et al. *JACC* 2004;44:1103

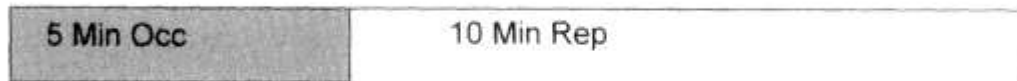


Vinten-Johansen J, Zhao ZQ, Zatta AJ, Kin H, Halkos ME, Kerendi F. Postconditioning--A new link in nature's armor against myocardial ischemia-reperfusion injury. *Basic Res Cardiol.* 2005 Jul;100(4):295-310.

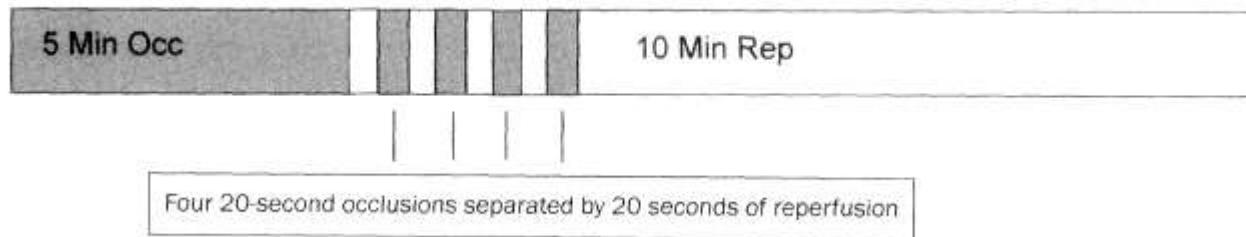


Vinten-Johansen J, Zhao ZQ, Zatta AJ, Kin H, Halkos ME, Kerendi F. Postconditioning--A new link in nature's armor against myocardial ischemia-reperfusion injury. *Basic Res Cardiol.* 2005 Jul;100(4):295-310.

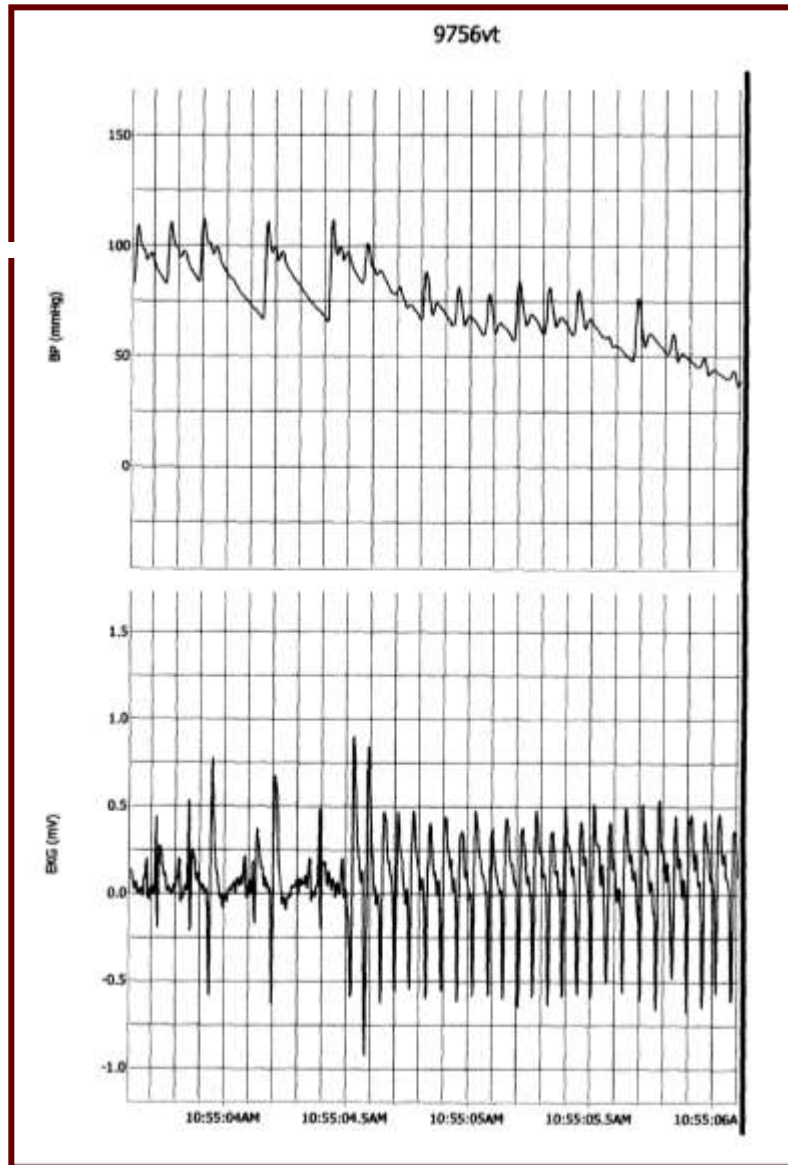
NON-POSTCONDITIONING CONTROL



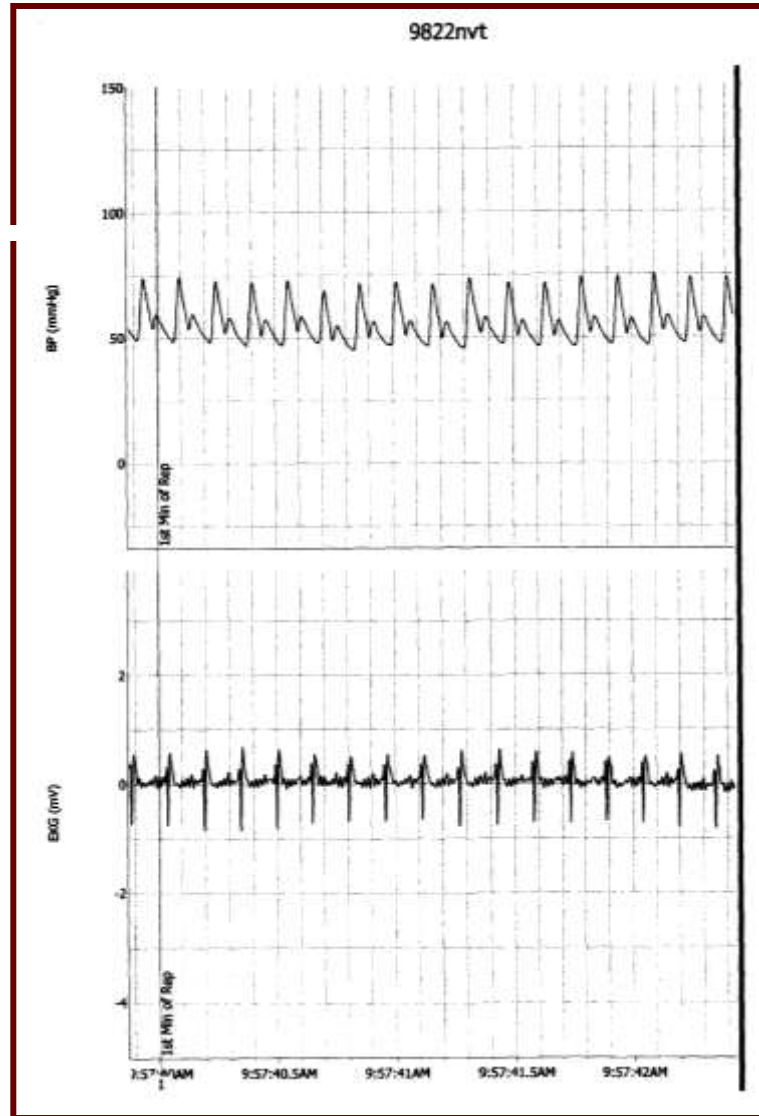
POSTCONDITIONING



Kloner RA, Dow J, Bhandari A. Postconditioning markedly attenuates ventricular arrhythmias after ischemia-reperfusion. *J Cardiovasc Pharmacol Ther.* 2006 Mar;11(1):55-63.

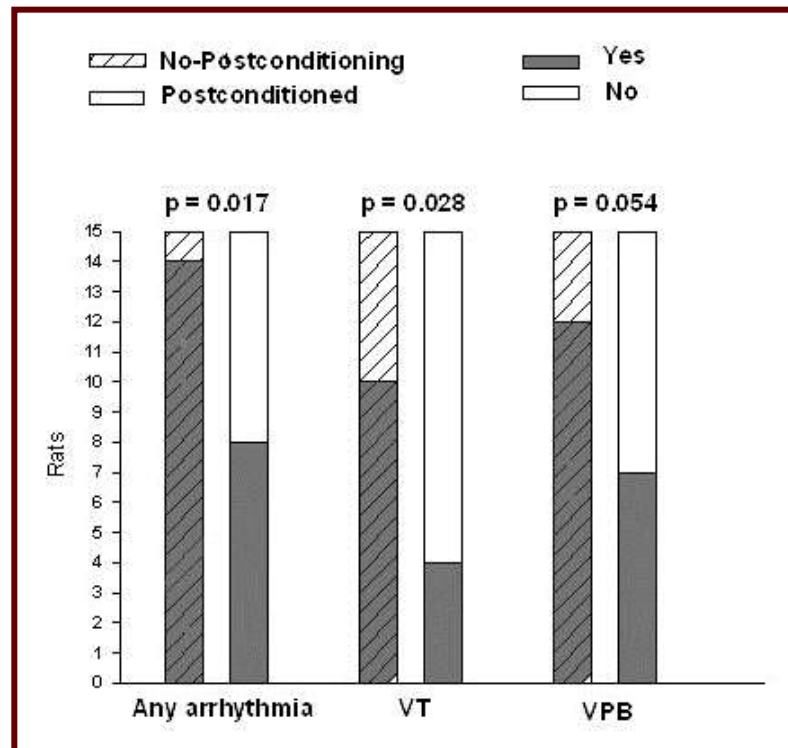


Kloner RA, Dow J, Bhandari A. Postconditioning markedly attenuates ventricular arrhythmias after ischemia-reperfusion. *J Cardiovasc Pharmacol Ther.* 2006 Mar;11(1):55-63.



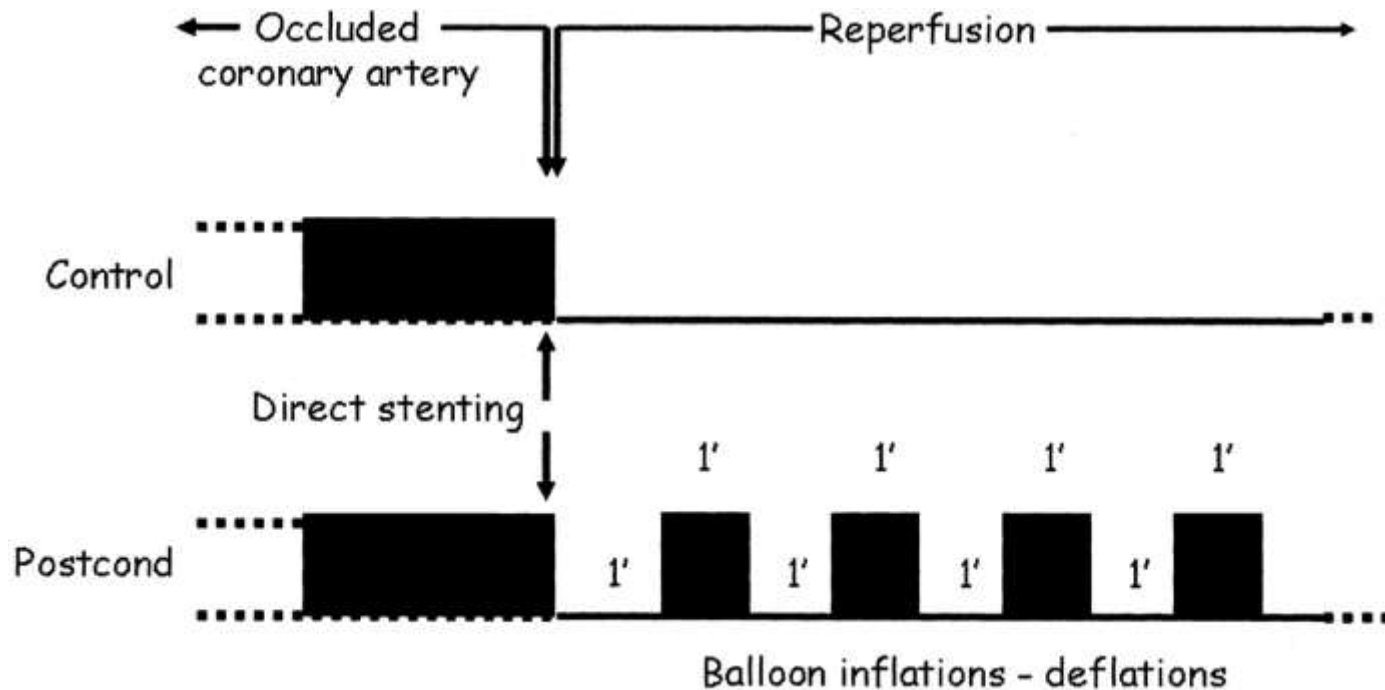
Kloner RA, Dow J, Bhandari A. Postconditioning markedly attenuates ventricular arrhythmias after ischemia-reperfusion. *J Cardiovasc Pharmacol Ther.* 2006 Mar;11(1):55-63.

Ventricular arrhythmias with and without postconditioning



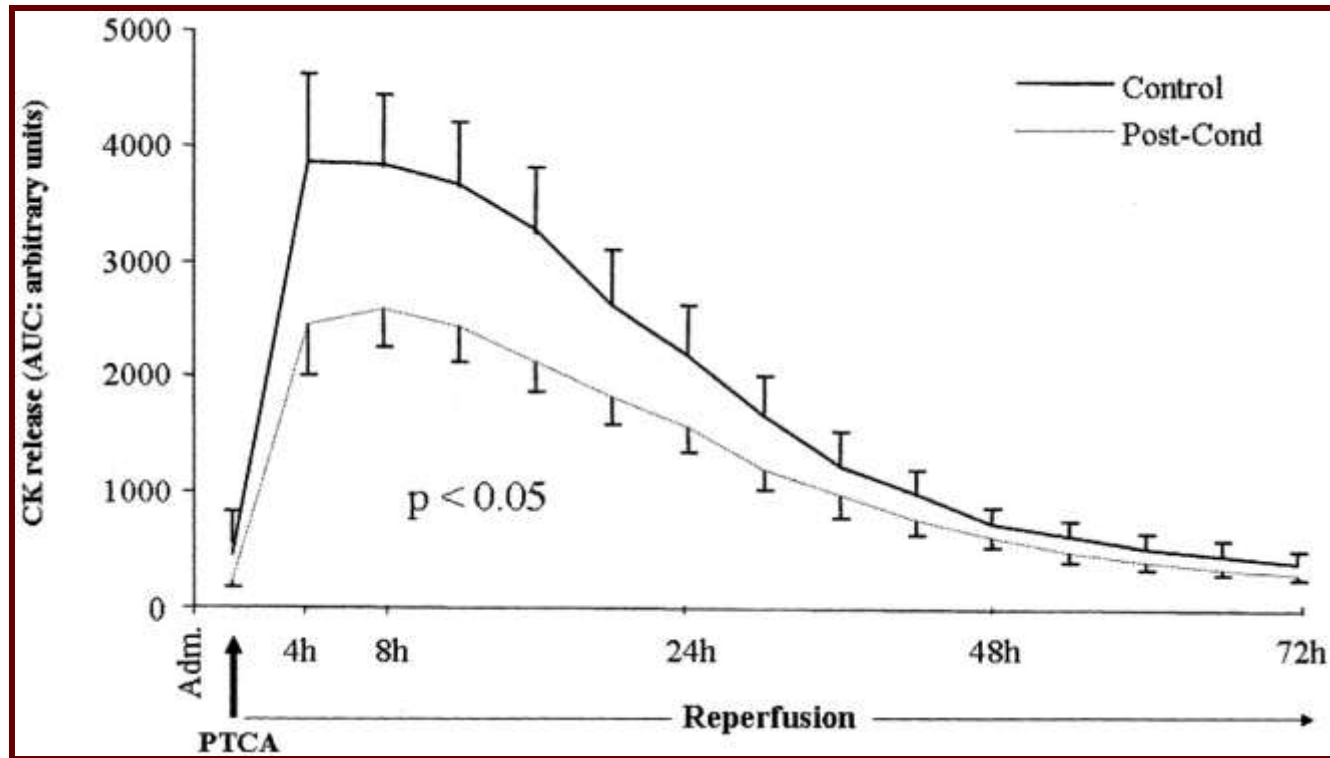
Kloner RA, Dow J, Bhandari A. Postconditioning markedly attenuates ventricular arrhythmias after ischemia-reperfusion. *J Cardiovasc Pharmacol Ther.* 2006 Mar;11(1):55-63.

Experimental protocol



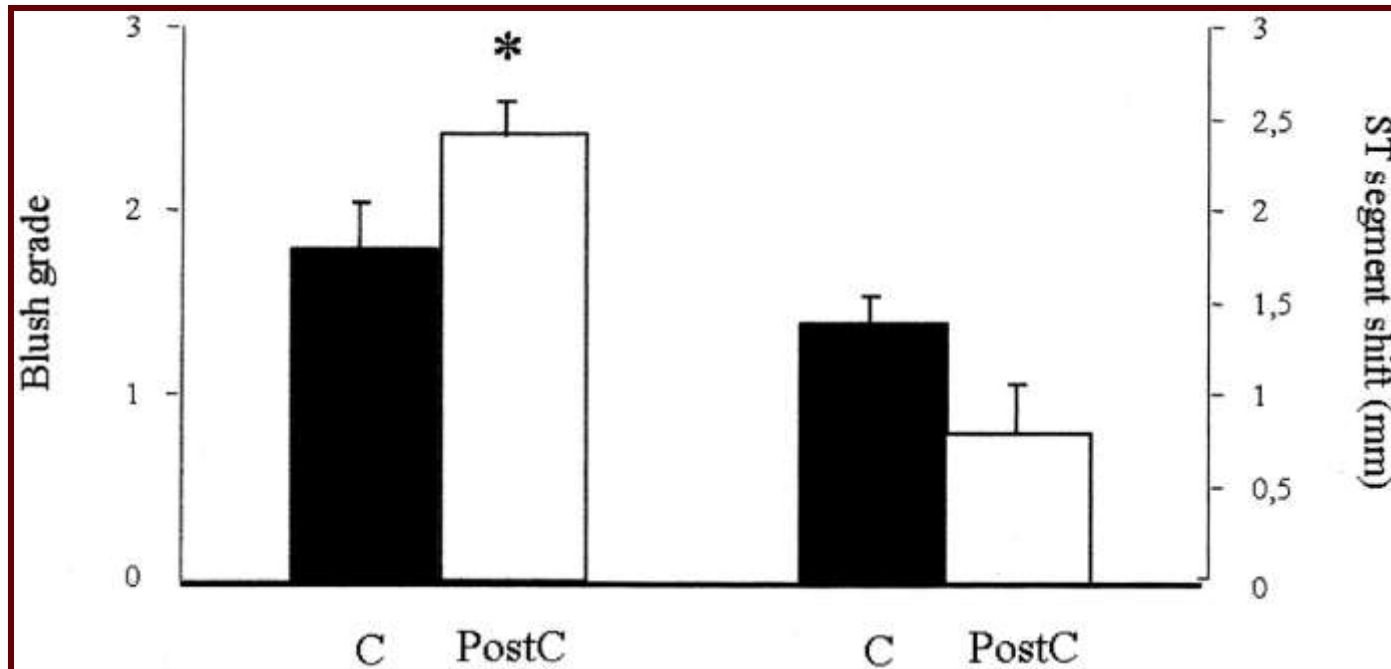
Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L'Huillier I, Aupetit JF, Bonnefoy E, Finet G, André-Fouët X, Ovize M. Postconditioning the human heart. *Circulation*. 2005 Oct 4;112(14):2143-8.

Serum CK release over the first 72 hours of reperfusion



Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L'Huillier I, Aupetit JF, Bonnefoy E, Finet G, André-Fouët X, Ovize M. Postconditioning the human heart. *Circulation*. 2005 Oct 4;112(14):2143-8.

Blush grade and ST-segment shift during reperfusion



Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L'Huillier I, Aupetit JF, Bonnefoy E, Finet G, André-Fouët X, Ovize M. Postconditioning the human heart. *Circulation*. 2005 Oct 4;112(14):2143-8.

Potential Mechanisms of Postconditioning

A. Triggers including:

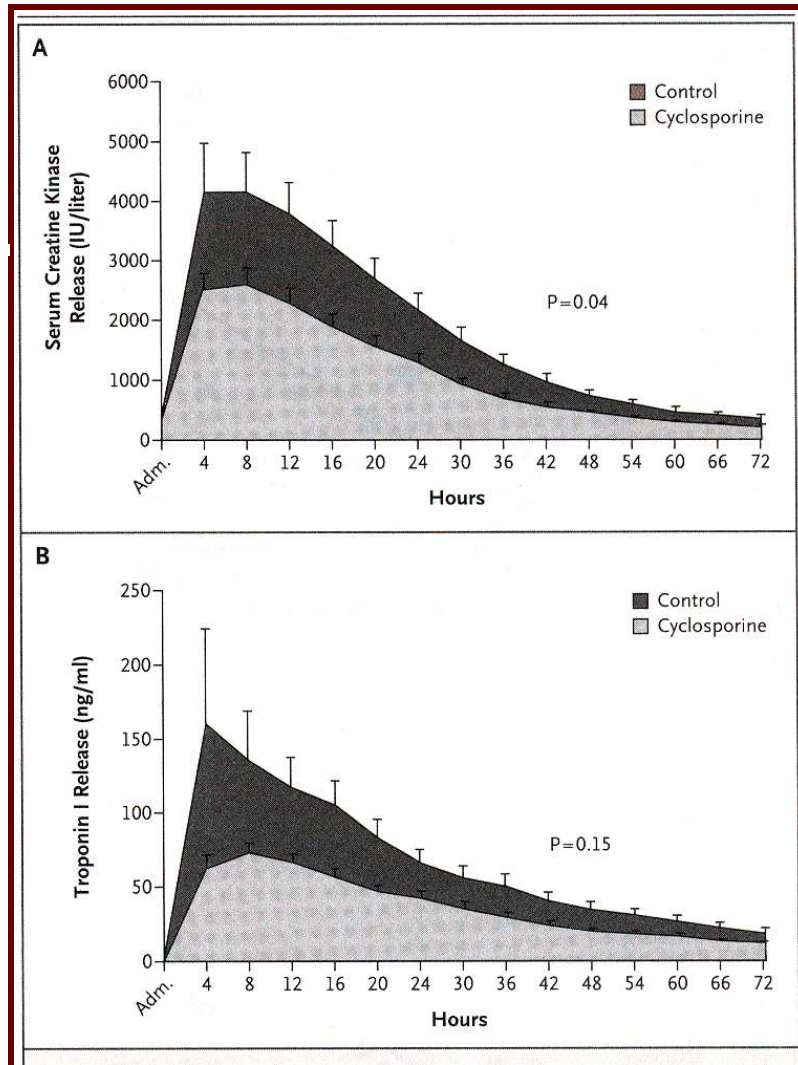
1. Adenosine
2. Opioids
3. Erythropoietin
4. Endogenous nitric oxide
5. Reactive oxygen species
6. Acetylcholine
7. Tissue factors
8. Pro-inflammatory cytokines and bradykinin
9. Hydrogen sulfide

B. Mediators –Reperfusion injury salvage kinase pathways including:

1. Phosphoinositide-3-kinase
2. Extra-cellular signal regulated kinase (1/2) pathways
3. Protein kinases G and C

C. End-effectors such as:

1. Mitochondrial permeability transition pore
2. Mitochondrial potassium ATP channel



Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D, Macia C, Raczka F, Sportouch C, Gahide G, Finet G, André-Fouët X, Revel D, Kirkorian G, Monassier JP, Derumeaux G, Ovize M. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med.* 2008 Jul 31;359(5):473-81.


Concordant improvements in coronary flow reserve and ST-segment resolution during percutaneous coronary intervention for acute myocardial infarction: a benefit of postconditioning

- ❑ 24 patients with evolving anterior STEMI were randomized to ischemic postconditioning or usual care during PCI
- ❑ Postconditioned pts had a greater and more rapid resolution of ST segment elevation (70% vs. 48%, $p = 0.0002$) by the end of the procedure
- ❑ Postconditioned pts had greater hyperemic coronary vasodilator reserve (2.2 vs. 1.5, $p < 0.001$)
- ❑ Peak serum creatine kinase was lower in postconditioned pts (1,524 vs. 1,862 IU/L in controls, $p = 0.03$)
- ❑ Conclusion: Postconditioning performed during PCI for STEMI improved ST-segment resolution and coronary flow reserve, measures of microcirculatory function, as well as reducing tissue necrosis.



Remote Ischemic Preconditioning or Ischemic Conditioning at a Distance

Ischemic conditioning of one vascular bed may protect a remote vascular bed. This could occur within the same organ or between different organs.



Regional ischemic preconditioning protects remote virgin myocardium from subsequent sustained coronary occlusion

Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation*. 1993 Mar;87(3):893-9

Showed that “Brief episodes of ischemia in one vascular bed protect remote, virgin myocardium from subsequent sustained coronary artery occlusion in canine model.”

First Evidence: 'Intracardiac' RIPC

- rationale: RIPC predicted by mathematical modeling [Whittaker & Przyklenk, *Basic Res Cardiol* 1994;89:6-15]
- model: anesthetized dog
- PC stimulus: Cx bed
- LAD occlusion
- endpoint: infarct size

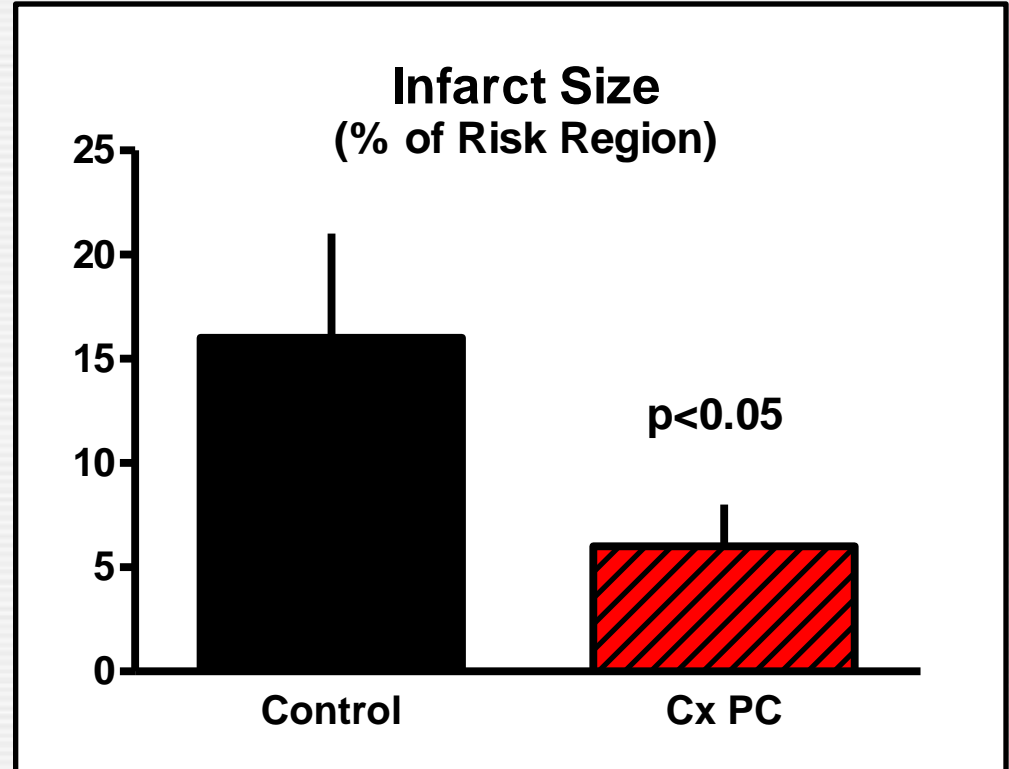
Control



Circumflex (Cx) PC



↑
infarct size
(% of risk region)



Expanding the Paradigm

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

Control



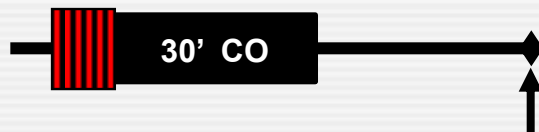
Femoral artery stenosis



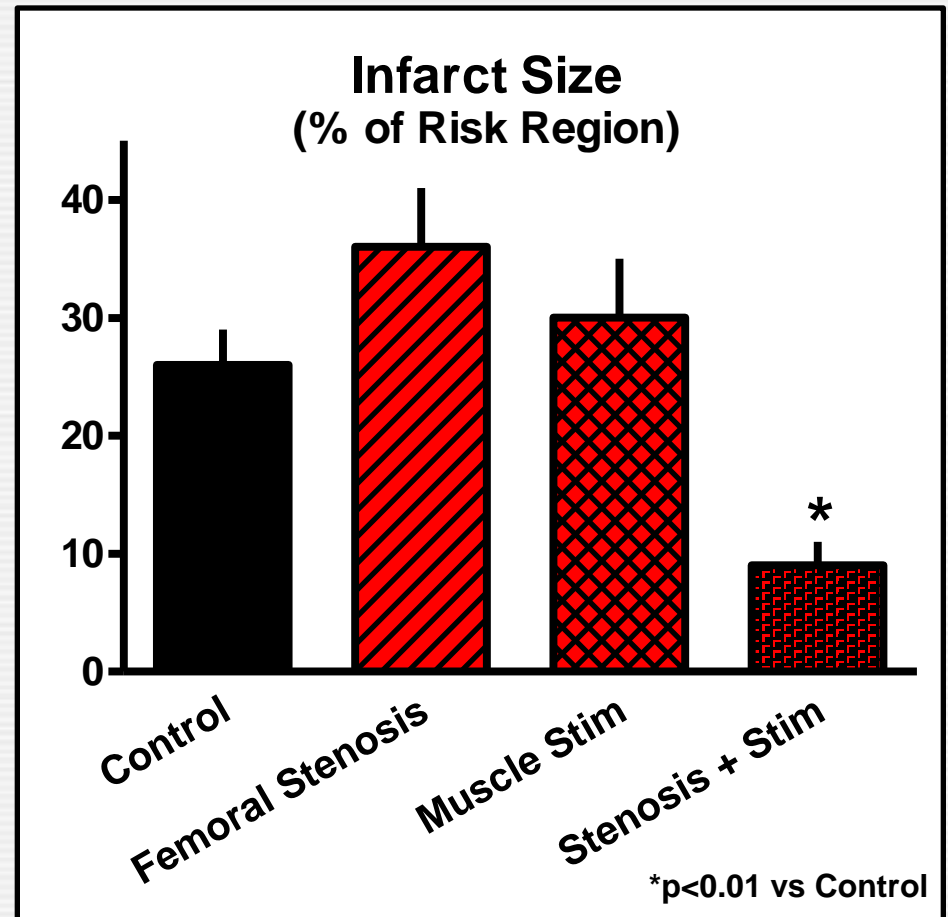
Stimulation of gastrocnemius



Stenosis + stim



↑
infarct size
(% of risk region)





Summary

Conditioning: Pre-, post-, remote and now per-, appear to be promising, low-cost therapies that can further protect the ischemic myocardium as adjunctive therapy.