Remote Ischemic ‘Conditioning’:

*From Inspiration . . . to Clinical Translation*

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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
Clinical Example

In 2014, >1 million Americans will have a ‘heart attack’
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.”


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)

- Control
- PC

p < .01

Area of necrosis (% of risk region)
Reduction of Infarct Size with Preconditioning

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

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

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.

Risk Region (RR) vs. Area of Necrosis (AN)

Control

Classical PC

RR/LV = 20%  RR/LV = 50%  RR/LV = 70%

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.

Remote Ischemic Conditioning (RIC): First Evidence

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

‘Transferred’ RIC


**p<0.01 vs Donor-Control
Expanding the Paradigm

‘Inter-organ’ RIC

Control

Classic PC

Mesenteric PC

Expanding the Paradigm
Expanding the Paradigm

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

![Graph showing infarct size comparison between control and remote PC treatment](image)
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?
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
For pre-, postconditioning:

- **trigger**
- **receptor stimulation**
- **signaling**
- **effector**

**CARDIOPROTECTION**
Mechanisms

For pre-, postconditioning:

- trigger
- receptor stimulation
- signaling
- effector

CARDIOPROTECTION

For remote ischemic conditioning:

- trigger
- receptor stimulation
- signaling
- effector

COMMUNICATION

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 . . .
Paradigms: neuronal and/or humoral

Candidates include:

- adenosine, bradykinin, opioids
- by HPLC: ‘small (<15 kDa) hydrophobic molecule’
- from proteomic screens: Apo-A1

- 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

In all likelihood . . . model-dependent
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

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‘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