The Protective Effects of Remote Ischemic Conditioning in a Septic Mouse Model


The University of Arizona
BACKGROUND

Hospital Admission with Sepsis
BACKGROUND

- SEPSIS
- COMPLEX MECHANISM
- INTERPLAY OF MEDIATORS
BACKGROUND

LPS - LPS binding protein complex

Activation of coagulation cascade.

Activation of complement cascade.

Endothelial damage

Multiple Organ System Failure and Death

Cytokine Storm

IL-1β

TNF-α

IFN-γ

IL-10

Antibiotic Therapy

CD14, CD11/CD18, TLR-2/TLR-4 LPS-Receptors
Monocyte deactivation in septic patients: Restoration by IFN-γ treatment

- Steroids
- Anti-oxidants
- Prostaglandins
- Mono-clonal Antibodies
- IL-1 receptor Antibodies
- Leukotriene Inhibitors
Remote Ischemic Conditioning

**BACKGROUND**

- Occlude upper arm intermittently with cuff
- 4 cycles: 5 min ON, 5 min OFF - 40 min total

**Cell Signaling**
- (RISK) Reperfusion Injury Salvage Kinases
- Mitochondria - close permeability transition pore

**Systemic Protection**
- Reduced infarct size
- Reduced inflammation
Postconditioning the human heart

Cardiac stress protein elevation 24 hours after brief ischemia or heat stress is associated with resistance to myocardial infarction
Marber MS, Latchman DS, Walker JM, Yellon DM.

Preconditioning with ischemia:
A delay of lethal cell injury in ischemic myocardium
C E Murray, R B Jennings and K A Reimer
BACKGROUND
BACKGROUND

Promising effects of ischemic preconditioning in renal transplantation

JOAN TORRAS, IMMACULADA HERRERO-FRESNEDA, NURIA LLOBERAS, MARTA RIERA, JOSEP Mª CRUZADO, and JOSEP Mª GRINYÓ

Limb Remote Ischemic Preconditioning for Intestinal and Pulmonary Protection during Elective Open Infrarenal Abdominal Aortic Aneurysm Repair

A Randomized Controlled Trial

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Remote Ischemic Preconditioning: Making the Brain More Tolerant, Safely and Inexpensively

Michael A. Moskowitz and Christian Waeber

Remote Preconditioning Reduces Microcirculatory Disorders in Pancreatic Ischemia/Reperfusion Injury

Christina Oehmann, MD, Stefan Benz, MD, Oliver Drognitz, MD, Przemyslaw Pisarski, MD, Ulrich T. Hoit, MD, and Robert Obermaier, MD
Remote Ischemic Conditioning

**BACKGROUND**

- **Neural**
  - Nitric oxide
  - CGRP

- **Systemic**
  - Anti-apoptotic
  - Anti-inflammatory

- **Humoral**
  - Opioids
  - Angiotensin
Remote Ischemic Conditioning (RIC) improves survival in septic mouse model
AIM

• **PRIMARY AIM:**
  - Survival advantage to RIC
  - Optimal timing for survival

• **SECONDARY AIM:**
  - Inflammatory profile
8-12 week C57BL/6 mice

LPS Injection (44 mice)

RIC group (30 mice)

Control group (14 mice)

0-hour (10mice)
2-hour (10mice)
6-hour (10mice)

12.5mg/kg

METHODS – PRIMARY AIM

Outcome = Survival

• Euthanized on 5th day

Kaplan Meier Analysis
METHODS – PRIMARY AIM

• **RIC Group**

  • Femoral artery clamp
  
  • 6 cycles x 4 min cycles ischemia and reperfusion.
RESULTS - PRIMARY AIM

Control

Survival 21% (3/14)

RIC

Survival 57% (17/30)

p 0.02
RESULTS - PRIMARY AIM

Control

RIC

Survival

p

Survival

21%
(3/14)

0-hour

50%
(5/10)

0.14

2-hour

70%
(7/10)

0.04

6-hour

50%
(5/10)

0.39
RESULTS - PRIMARY AIM

SURVIVAL

\[
p = 0.04
\]

\[
HR = 0.3 \ (0.09-0.98)
\]
SECONDARY AIM

Inflammatory profile
BACKGROUND – SECONDARY AIM

TNF-α

IL 1-β

INF-γ

IL - 10
METHODS – SECONDARY AIM

ELISA Assay (15 mice) → Baseline (3 mice)

LPS (12 mice)

- 0 hrs (3 mice)
- 2 hrs (3 mice)
- 4 hrs (3 mice)
- 24 hrs (3 mice)

RIC at 2 hours post LPS
RESULTS – SECONDARY AIM

TNF - α

IL 1- β
RESULTS – SECONDARY AIM

INF - γ

IL - 10
SUMMARY

• RIC provides survival benefit in septic mouse model

• 2 hours is the optimal timing for RIC

• RIC lowers inflammatory cytokines
CONCLUSIONS

• Early RIC is an effective therapy in a septic mouse model.

• RIC can have immunomodulatory role in sepsis.
THANKS