The effects of ischemic conditioning on arterial function in the context of AMI. Is there a clinical benefit?

Dimitrios Vlastos, MD
2nd Cardiology Department, Attikon
Remote Ischemic Conditioning

Gerd Heusch, MD,* Hans Erik Bøtker, MD, PhD,‡ Karin Przyklenk, PhD,§ Andrew Redington, MD,** Derek Yellon, PhD, DSc||

- Ischemic conditioning utilises **brief, reversible episodes of ischemia and reperfusion** to invoke a **protective phenotype against ischemia-reperfusion injury (IRI)**
- This concept has evolved in space (**intracardiac to remote**), trigger nature (**ischemic to non-ischemic**), and time (**pre-, per-, and post-conditioning**), utilising **similar pathophysiological pathways**; remote ischemic conditioning appears as the **most clinically attractive application**
- The aim of this presentation is to shed light on some implicated underlying mechanisms related to arterial function
<table>
<thead>
<tr>
<th>SOURCE ORGAN OF RIC SIGNAL</th>
<th>NATURE OF STIMULUS</th>
<th>PROTECTIVE SIGNAL TRANSFER</th>
<th>ORGANS PROTECTED</th>
<th>SIGNAL TRANSDUCTION RESPONSE (HEART)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Ischemia/Reperfusion</td>
<td>Neuronal: Activation of peripheral sensory fibers with involvement of PKC gamma</td>
<td>Heart</td>
<td>Extracellular signaling molecules acting on specific receptors: Adenosine, Bradykinin, Interleukin 10, Opioids, Stromal derived factor-1α</td>
</tr>
<tr>
<td>Brain</td>
<td>Surgical trauma</td>
<td></td>
<td>Brain</td>
<td>Membrane protein: Connexin 43</td>
</tr>
<tr>
<td>Skin</td>
<td>Autacoids (i.e. adenosine, bradykinin)</td>
<td></td>
<td>Skin</td>
<td>Intracellular signal transduction: RISK pathway (Phosphatidylinositol-4, 5-bisphosphate 3-kinase, protein kinase B, extracellular regulated kinase, glycogen synthase kinase 3β)</td>
</tr>
<tr>
<td>Mesentery</td>
<td></td>
<td></td>
<td>Skin</td>
<td>Protein kinase C, Endothelial nitric oxide synthase</td>
</tr>
<tr>
<td>Kidney</td>
<td>Peripheral nerve stimulation: Electrical or chemical (capsaicin)</td>
<td>Humoral: Nitric oxide, MicroRNA-144, Stromal derived factor-1α (Humoral transfer includes lung passage)</td>
<td>Liver</td>
<td>Signal transducer and activator of transcription 5, Nitric oxide</td>
</tr>
<tr>
<td>Muscle</td>
<td></td>
<td></td>
<td>Kidney</td>
<td>Mitochondrion: (ATP-dependent potassium channel, mitochondrial permeability transition pore, nitrosation)</td>
</tr>
</tbody>
</table>

Heusch, G. et al. J Am Coll Cardiol. 2015; 65(2):177-95
Remote Ischemic Conditioning

Ischemic conditioning utilises brief, reversible episodes of ischemia and reperfusion to invoke a protective phenotype against ischemia-reperfusion injury (IRI).

This concept has evolved in space (intracardiac to remote), trigger nature (ischemic to non-ischemic), and time (pre-, per-, and post-conditioning), utilising similar pathophysiological pathways; remote ischemic conditioning appears as the most clinically attractive application.

The aim of this presentation is to shed light on some implicated underlying mechanisms related to arterial function.
A. Endothelial function
Prospective study that investigated the effects of experimental IRI on endothelial function in 31 healthy volunteers

IRI induced by brachial blood pressure cuff inflation to 200 mm Hg for 20 min; IPC by 3x5 min ischemic stimuli

a) Radial artery flow in response to ACh and b) FMD were measured at baseline and 15 min after IRI, with or without IPC

IRI attenuated the blood flow response to ACh and FMD caused by IRI, but NOT when preceded by IPC
• Prospective study that investigated the time course of endothelial protection induced by RIPC in 16 healthy volunteers; IPC is known to confer a second window of protection, 24 hours after its activation
• IRI induced by 20 min brachial cuff inflation at 200 mm Hg; RIPC by 3x5 min ischemic stimuli immediately, 4 hours, 24 hours, and 48 hours before IRI
• Brachial artery FMD measured at baseline and after IRI, with or without RIPC
• FMD preserved by RIPC except for its application 4 hours before the IRI; thus, two separate windows of protection are activated
Seven-Day Remote Ischemic Preconditioning Improves Local and Systemic Endothelial Function and Microcirculation in Healthy Humans

Helen Jones, Nicola Hopkins, Tom G. Bailey, Daniel J. Green, N. Timothy Cable, and Dick H.J. Thijssen

- Studied the effects of **daily RIPC** on endothelial function and microcirculation in 13 healthy individuals, and thus, the potential benefits of **chronic RIPC**

  - **RIPC daily by 4x5min** brachial cuff inflations for **7 days**; bilateral a) **brachial FMD** and b) **CVC** measured **at baseline, on day 8, and on day 15**

  - **FMD and CVC increased in both arms** and remained elevated **at least 8 days** after the last RIPC application

*CVC: cutaneous vascular conductance (laser Doppler flow/MAP)*
RCT that investigated the effects of an 8-week RIPC program on endothelial function in 18 healthy males

- RIPC by 4x5 min ischemic stimuli, 3 qw, for 8 weeks (utilising the second RIPC window); control: normal routine
- Brachial FMD measured before, and following 2 and 8 weeks of RIPC
- FMD significantly improved in the intervention group
• RCT that studied the effects of RIPC on endothelial function in 48 patients with AMI (45 with STEMI, 3 with NSTEMI) who underwent primary PCI

• **Group I: RIPC prior to PCI** (during preparation), n=23

• **Group II: PCI without RIPC**, n=25

• Brachial **FMD** measured **on admission, 1-3 hours post-PCI, and on days 2 and 7 after PCI**

• Post-PCI TIMI III flow grade frequency and CTFC similar between groups

• **FMD significantly higher in group I**, in all measurements
B. Coronary microcirculatory function
Studied the effects of RIPC on coronary microcirculation in 18 healthy males

- LAD flow was recorded by TTDE at baseline and within 1, 3, 6, and 9 min of 3 RIPC cycles

- Mean coronary flow velocity, peak diastolic velocity, and mean diastolic velocity significantly increased within 3 min of reperfusion
• RCT that studied the effects of RIPC on 60 patients with **stable CAD undergoing elective invasive coronary angiography**

• RIPC by 4x5 min inflations (n=30); sham procedure by cuff placement without inflation (n=30)

• **Endothelial-dependent vasoreactivity** (mean coronary diameter at max ACh dose) by QCA

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>RIPC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cor. diam.</td>
<td>2.08 (0.72)</td>
<td>2.5 (0.66)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

• No difference in comorbidities, cardiovascular risk factors, or baseline Rx between the two groups

• **Significantly lower mean percentage change in coronary luminal diameter in the RIPC group**
RCT that studied the effects of per-conditioning (staccato reperfusion) on coronary microcirculatory function and LV remodeling, in 39 patients with ACS (STEMI/ NSTEMI) undergoing semi-elective PCI and revascularisation

- Coronary microcirculation was assessed by MCE immediately before and 48h, 1 month, and 12 months after PCI
- No differences in CV risk factors, culprit arteries, or TIMI flow before or after PCI between SR and AR groups
- Myocardial contrast time-intensity curve plateau ($A_n$), slope of myocardial contrast time-intensity curve ($\beta$), and myocardial perfusion index ($A \times \beta$) were significantly higher after SR, at all times
Staccato reperfusion improves myocardial microcirculatory function and long-term left ventricular remodelling: a randomised contrast echocardiography study
SR also resulted in greater LVEDV and LVESV reduction, and a greater probability of reverse remodeling.
Prospective study that investigated the effects of 1 week of RIPC on 10 healthy subjects and 10 patients with HFrEF

- RIPC by 4x5 min inflations bqd for 1 week
- CFR was measured by TTDE at baseline and after 1 week of RIPC
- CFR significantly increased in both healthy participants and patients with HFrEF
Double-blind RCT that studied the effects of RIPC on coronary microcirculation in 30 patients referred for cardiac catheterisation and FFR measurement

- **RIPC by 3x5 inflations** (n=15); **sham** by cuff inflation to 10 mm Hg (n=15)

- **Coronary physiology study** before and after intervention
- Groups similar regarding comorbidities, cardiovascular risk factors, and baseline Rx

- IMR and IMR$_{calc}$ significantly reduced, CFR significantly increased by RIPC
Remote Ischemic Preconditioning Acutely Improves Coronary Microcirculatory Function

Jerrett K. Lau MBBS; Probal Roy, MBBS; Ashkan Javadzadegan, PhD; Abouzar Moshfegh, PhD; William F. Fearon, MD; Martin Ng, PhD; Harry Lowe, PhD; David Brieger, PhD; Leonard Kritharides, PhD; Andy S. Yong, PhD

A $\text{IMR}_{\text{calc}}$

B $\text{IMR}$

C CFR

D $T_{mnH}$

Coronary flow reserve

Pre RIPC Post RIPC

P=0.001

$T_{mnH}$ (seconds)

Pre RIPC Post RIPC

P=0.010
• C. Arterial stiffness
- Studied the effects of IRI, with or without RIPC, on hyperemia induced PWV decline in 25 healthy males (vasodilatory reserve)
- Hyperemia (cuff inflation 50 mm Hg above SBP for 5 min) induced before and after IRI (cuff inflation 50 mm Hg above SBP for 7.5 min), with and without pre- or post-conditioning
- PWV measured by Sphygmocor immediately before and after hyperemia
The effects of ischemia with and without remote conditioning on hyperemia induced decline in carotid-radial pulse wave velocity

Nwamaka Onegbu, Haroon Kamran, Bhawna Sharma, Manasi Bapat, Stephen Littman, Nikhil Warrier, Rinkesh Patel, Muhammad Tanweer Khalid, Louis Salciccioli, Jason M. Lazar*
Cross-over RCT that studied the effects of RIPC on arterial stiffness in 30 CAD (stable angina) patients and 20 healthy controls.

RIPC by 3x5 min inflations; sham by inflation to DBP.

Arterial stiffness was evaluated by Sphygmocor, before and after the RIPC/sham intervention.

Participants crossed-over to the alternative intervention.
Table: Effects of RIPC on arterial stiffness of CAD patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base</th>
<th>After RIPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>134.7 ± 5.3</td>
<td>119.4 ± 4.0 *</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79.2 ± 2.7</td>
<td>75.2 ± 2.3</td>
</tr>
<tr>
<td>Central SBP, mm Hg</td>
<td>132.9 ± 5.8</td>
<td>118.5 ± 4.0 *</td>
</tr>
<tr>
<td>Central DBP, mm Hg</td>
<td>78.7 ± 2.8</td>
<td>76.1 ± 2.3</td>
</tr>
<tr>
<td>Pp, mm Hg</td>
<td>54.3 ± 4.2</td>
<td>42.25 ± 2.3 *</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>97.2 ± 0.4</td>
<td>97.3 ± 0.3</td>
</tr>
<tr>
<td>AP (augmentation pressure), %</td>
<td>131.4 ± 2.6</td>
<td>127.2 ± 1.8 *</td>
</tr>
<tr>
<td>Pp amplification, %</td>
<td>12.3 ± 1.0</td>
<td>11.7 ± 1.2</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>5.37 ± 0.8</td>
<td>4.95 ± 0.49</td>
</tr>
</tbody>
</table>
• D. Blood pressure
• Studied the effects of **daily RIPC for 30 days** on BP in 15 newly diagnosed, never treated, office SDB/DBP > 130/80 mm Hg primary **hypertensives**

• RIPC by 3x5 min inflations

• **BP measured by clinic and 24-h ABPM** the day before and after the long-term RIPC protocol

• **Endothelial function** assessed by **finger RHI** measurement using **Endo-PAT 2000**
Chronic remote ischemic preconditioning-induced increase of circulating hSDF-1α level and its relation with reduction of blood pressure and protection endothelial function in hypertension

Xin-zhu Tong¹ · Wan-fu Cui¹ · Yan Li¹ · Chen Su¹ · Yi-jia Shao¹ · Jia-wen Liang¹ · Zi-ting Zhou¹ · Chan-juan Zhang¹ · Jian-ning Zhang¹ · Xiao-yu Zhang¹ · Wen-hao Xia¹ · Jun Tao¹

<table>
<thead>
<tr>
<th></th>
<th>Clinic systolic blood pressure (mmHg)</th>
<th>Clinic diastolic blood pressure (mmHg)</th>
<th>24-h systolic blood pressure (mmHg)</th>
<th>24-h diastolic blood pressure (mmHg)</th>
<th>Daytime systolic blood pressure (mmHg)</th>
<th>Daytime diastolic blood pressure (mmHg)</th>
<th>Nighttime systolic blood pressure (mmHg)</th>
<th>Nighttime diastolic blood pressure (mmHg)</th>
<th>RHI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>139.13 ± 6.68</td>
<td>131.45 ± 7.45</td>
<td>89.67 ± 4.98</td>
<td>83.83 ± 6.65</td>
<td>136.33 ± 9.10</td>
<td>131.33 ± 7.12</td>
<td>138.33 ± 9.40</td>
<td>132.33 ± 7.98</td>
<td>1.95 ± 0.34</td>
</tr>
<tr>
<td>p</td>
<td>0.002*</td>
<td>0.004*</td>
<td>0.019*</td>
<td>0.002*</td>
<td>0.012*</td>
<td>0.002*</td>
<td>0.096</td>
<td>0.632</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

b) Clinic blood pressure

d) 24-hour blood pressure

f) Reactive hyperemia index

p-values: p=0.002, p=0.019, p=0.004, p=0.002, p=0.006
• Prognostic significance
Remote Ischemic Perconditioning to Reduce Reperfusion Injury During Acute ST-Segment–Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis

Shelley L. McLeod, PhD(c), MSc; Alla Iansavichene, BS, MLIS; Sheldon Cheskes, MD, CCFP(EM), FCFP

**MYOCARDIAL SALVAGE INDEX**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Within 7 days</td>
<td></td>
</tr>
<tr>
<td>White 2015</td>
<td></td>
</tr>
<tr>
<td>Verouhis 2016</td>
<td></td>
</tr>
<tr>
<td>Eitel 2015</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
</tr>
<tr>
<td>1.1.2 30 days</td>
<td></td>
</tr>
<tr>
<td>Botker 2010</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
</tr>
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INFARCT SIZE
MAJOR ADVERSE CARDIAC EVENTS
(DEATH, REINFARCTION, HEART FAILURE, STROKE)
Brachial FMD impairment is significantly associated with future cardiovascular events. A 1% decrease and 1-SD decrease in FMD have been associated with an 8% and 22% increase in the risk of future cardiovascular events, respectively.
• Neunteufl et al.: 0.77 relative risk of death, MI, or revascularization per 1% increase in FMD (patients with chest pain- CAG) ; 5-year follow-up
• Patti et al.: 0.76 relative risk of CV death, MI, angina, or in-stent restenosis (patients with CAD undergoing stenting); 6-month follow-up
Global Coronary Flow Reserve Is Associated With Adverse Cardiovascular Events Independently of Luminal Angiographic Severity and Modifies the Effect of Early Revascularization

Viviany R. Taqueti, MD, MPH; Rory Hachamovitch, MD, MS; Venkatesh L. Murthy, MD, PhD; Masanao Naya, MD, PhD; Courtney R. Foster, MS; Jon Hainer, BS; Sharmila Dorbala, MD, MPH; Ron Blankstein, MD; Marcelo F. Di Carli, MD

• Studied the association between CFR and cardiovascular outcomes in 329 patients referred for invasive coronary angiography after stress testing with myocardial perfusion PET

• 3.1 (median) year follow-up for MACE (death, CV death, and MI or CHF hospitalisation)

• CFR was significantly associated with freedom from MACE (hazard ratio per CFR unit decrease= 2.02) independently of pretest clinical score, LVEF, global LV ischemia, angiographic score, and revascularization strategy
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## Arterial stiffness and coronary artery disease

**Ignatios Ikonomidis, George Makavos, and John Lekakis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Shlomo et al. [2**]</td>
<td>PWV</td>
<td>With factors for atherosclerosis</td>
</tr>
<tr>
<td>Weber et al. [43]</td>
<td>Ax</td>
<td>Documented CAD Composite of all-cause mortality, MI, stroke, and cardiac, cerebrovascular, and peripheral revascularization</td>
</tr>
<tr>
<td>Weber et al. [44]</td>
<td>Ax</td>
<td>Documented CAD Death, MI and restenosis</td>
</tr>
<tr>
<td>Chirinos et al. [45]</td>
<td>Augmentation pressure, Ax</td>
<td>Documented CAD Death and MACE (unstable angina, acute MI, coronary revascularization, stroke, or death)</td>
</tr>
</tbody>
</table>

**Pulse waveform characteristics predict cardiovascular events and mortality in patients undergoing coronary angiography**

Thomas Weber<sup>a,b</sup>, Michael F. O'Rourke<sup>c,d</sup>, Elisabeth Lassnig<sup>a</sup>, Michael Porodko<sup>a</sup>, Marcus Ammer<sup>a</sup>, Martin Rammer<sup>a</sup> and Bernd Eber<sup>a</sup>

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![Graph showing event-free survival probability over time](image)

- **Alx@75 tertiles**
  - **Alx 75 T1**
  - **Alx 75 T2**
  - **Alx 75 T3**

**Event-free survival probability (%)**

- **Time (months)**
  - 0
  - 20
  - 40
  - 60
  - 80
Conclusions

• Diseased vasculature is both a culprit and a victim of IRI
• RIPC attenuates IRI, increasing the proportion of salvaged myocardium and conferring protection from MACE
• In this context, RIPC results in improvement of markers of vascular and microcirculatory function of prognostic significance
• The direct relationship this improvement in vascular function and clinical outcomes remains to be elucidated
THANK YOU !!!
Οργάνωση: ΕΛΛΗΝΙΚΟ ΚΟΛΛΕΓΙΟ ΚΑΡΔΙΟΛΟΓΙΑΣ

Οργανωτική Επιτροπή:
Βαΐα Λαμπαδιάρη,
Ιγνάτιος Οικονομίδης,
Ιωάννης Παρίσης
Λάμπρος Κ. Μιχάλης

Σύγχρονες Μέθοδοι Πρόληψης,
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Χωκαρδιογραφία
& Αντίθεσης (Contrast Echo)
Εφαρμογές στην κλινική πράξη

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