Remote Ischemic Conditioning: toward kidney perspectives?

Fabrice Prunier

EA 3860 « Cardioprotection, Remodelage et Thrombose »

& Service de Cardiologie, CHU d’ Angers, France

Réseau INSERM RIRE : Réseau Infarctus de REperfusion
Lethal reperfusion injury

Myocardial ischemia in absence of reperfusion
Infarct size, 70%

Myocardial ischemia with reperfusion
Reperfusion reduces infarct size by 40%
Part of the remaining 30% infarct is due to lethal reperfusion injury and is therefore preventable

Myocardial ischemia with reperfusion and cardioprotection
Preventing lethal reperfusion injury reduces infarct size by a further 25%, realizing the full benefits of reperfusion
Local Ischemic Preconditioning

From G Heusch ESC 2012

Murry et al., Circulation 74:1124-1136 (1986)
Local ischemic Postconditioning


Infarct size (%)

Control PreC PostC

* *
Postconditioning algorithm

- Occluded coronary artery
- Reperfusion
- Control
- Direct stenting
- Postcond
- Balloon inflations - deflations

Staat et al. Circulation. 2005;112:2143-2148
CK release during reperfusion

Staat et al. Circulation. 2005;112:2143-2148
Survival signaling pathways

Heusch et al., Circulation 118:1915-1919 (2008)
Cardioprotective ligands

Remote Postconditioning

Local Postconditioning

Activation of RISK pathway

Reperfusion

Inhibition of mPTP opening

mPTP inhibitor (CsA)

Reduced myocardial infarct size

Improved clinical outcomes

STEMI patients
NSTEMI patients
CABG patients
Cardiac arrest patients
Remote Preconditioning

- Anesthetized dogs
- Remote intraorgan preconditioning
- 4 episodes of 5min LCX occlusion interspersed with 5min reperfusion before 1h LAD occlusion
- 35% reduction of infarct size (similar range than direct LAD preconditioning)

Przyklenk et al. Circulation 1993;87:893-99
**Remote Perconditioning**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>Ischemia (30 min)</th>
<th>Reperfusion (180 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote PostC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent RA Occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**

- **Infarct Size (%):**
  - Control
  - Remote PostC
  - Permanent RA Occlusion

*Kerendi et al. Basic Res Cardiol 2005;100:404-12*
7612 articles:
- 7353 on Medline
- 257 on Cochrane
- 2 from other sources

1189 duplicates

6423 articles screened

6342 articles excluded:
- 6178 « on title »
- 161 « on abstract »
- 2 studies in Chinese
- 1 full-text not available

81 full-text articles screened

53 full-text articles = 44 studies
- 2 referred to Botker 2010
- 1 referred to Hoole 2009
- 6 referred to Thielmann

53 articles / 44 studies included in QUALITATIVE analysis

28 full-text articles excluded:
- 4 ongoing studies
- 24 not meeting inclusion

1 study completely excluded from final analysis (Hoole 2009b)

52 articles / 43 studies included in QUANTITATIVE analysis
AUC troponin

Le Page et al. Bas Res Cardiol 2015
### MACCE < 1 year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RIC Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh 2009</td>
<td>3</td>
<td>18</td>
<td>2</td>
<td>22</td>
<td>2.7%</td>
<td>2.00 [0.30, 13.51]</td>
<td>2009</td>
</tr>
<tr>
<td>Hoole 2009</td>
<td>4</td>
<td>104</td>
<td>13</td>
<td>97</td>
<td>23.1%</td>
<td>0.26 [0.08, 0.82]</td>
<td>2009</td>
</tr>
<tr>
<td>Walsh 2010</td>
<td>0</td>
<td>34</td>
<td>0</td>
<td>36</td>
<td>Not estimable</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Botker 2010</td>
<td>7</td>
<td>166</td>
<td>7</td>
<td>167</td>
<td>12.0%</td>
<td>1.01 [0.35, 2.93]</td>
<td>2010</td>
</tr>
<tr>
<td>Ghaemian 2012</td>
<td>4</td>
<td>40</td>
<td>2</td>
<td>40</td>
<td>3.2%</td>
<td>2.11 [0.36, 12.24]</td>
<td>2012</td>
</tr>
<tr>
<td>Thielmann 2013</td>
<td>3</td>
<td>162</td>
<td>14</td>
<td>167</td>
<td>24.2%</td>
<td>0.21 [0.06, 0.73]</td>
<td>2013</td>
</tr>
<tr>
<td>Hong 2013</td>
<td>15</td>
<td>644</td>
<td>16</td>
<td>636</td>
<td>28.1%</td>
<td>0.92 [0.45, 1.89]</td>
<td>2013</td>
</tr>
<tr>
<td>Crimi 2013</td>
<td>4</td>
<td>48</td>
<td>3</td>
<td>48</td>
<td>4.9%</td>
<td>1.36 [0.29, 6.45]</td>
<td>2013</td>
</tr>
<tr>
<td>Carasco-Chinchilla 2013</td>
<td>4</td>
<td>127</td>
<td>1</td>
<td>123</td>
<td>1.8%</td>
<td>3.97 [0.44, 36.01]</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1343</td>
<td>1336</td>
<td>100.0%</td>
<td>0.75 [0.50, 1.12]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>44</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 12.97, df = 7 (P = 0.07); I² = 46%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 1.42 (P = 0.16)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### MACCE > 1 year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RIC Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoole 2009</td>
<td>23</td>
<td>95</td>
<td>36</td>
<td>97</td>
<td>37.0%</td>
<td>0.54 [0.29, 1.01]</td>
<td>2009</td>
</tr>
<tr>
<td>Botker 2010</td>
<td>17</td>
<td>126</td>
<td>32</td>
<td>125</td>
<td>38.1%</td>
<td>0.45 [0.24, 0.87]</td>
<td>2010</td>
</tr>
<tr>
<td>Thielmann 2013</td>
<td>4</td>
<td>162</td>
<td>19</td>
<td>167</td>
<td>25.0%</td>
<td>0.20 [0.07, 0.59]</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>383</td>
<td>389</td>
<td>100.0%</td>
<td>0.42 [0.28, 0.64]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>44</td>
<td>87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 2.49, df = 2 (P = 0.29); I² = 20%</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 4.12 (P &lt; 0.0001)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Le Page et al. Bas Res Cardiol 2015
### Mortality < 1 year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RIC Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali 2007</td>
<td>2</td>
<td>41</td>
<td>3</td>
<td>41</td>
<td>7.3%</td>
<td>0.65 [0.10, 4.11]</td>
<td>2007</td>
</tr>
<tr>
<td>Hoole 2009</td>
<td>0</td>
<td>104</td>
<td>1</td>
<td>97</td>
<td>4.0%</td>
<td>0.31 [0.01, 7.65]</td>
<td>2009</td>
</tr>
<tr>
<td>Walsh 2009</td>
<td>1</td>
<td>18</td>
<td>0</td>
<td>22</td>
<td>1.1%</td>
<td>3.86 [0.15, 100.58]</td>
<td>2009</td>
</tr>
<tr>
<td>Botker 2010</td>
<td>3</td>
<td>126</td>
<td>3</td>
<td>125</td>
<td>7.5%</td>
<td>0.99 [0.20, 5.01]</td>
<td>2010</td>
</tr>
<tr>
<td>Luo 2011</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Xie 2012 (1)</td>
<td>0</td>
<td>38</td>
<td>1</td>
<td>35</td>
<td>3.9%</td>
<td>0.30 [0.01, 7.58]</td>
<td>2012</td>
</tr>
<tr>
<td>Ghaemian 2012</td>
<td>0</td>
<td>40</td>
<td>1</td>
<td>40</td>
<td>3.8%</td>
<td>0.33 [0.01, 8.22]</td>
<td>2012</td>
</tr>
<tr>
<td>Lucchinetti 2012</td>
<td>0</td>
<td>27</td>
<td>1</td>
<td>28</td>
<td>3.7%</td>
<td>0.33 [0.01, 8.55]</td>
<td>2012</td>
</tr>
<tr>
<td>Zhong 2013</td>
<td>0</td>
<td>34</td>
<td>0</td>
<td>35</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Carasco-Chinchilla 2013</td>
<td>9</td>
<td>127</td>
<td>5</td>
<td>123</td>
<td>12.1%</td>
<td>1.80 [0.59, 5.53]</td>
<td>2013</td>
</tr>
<tr>
<td>Crimi 2013</td>
<td>0</td>
<td>47</td>
<td>1</td>
<td>48</td>
<td>3.8%</td>
<td>0.33 [0.01, 8.39]</td>
<td>2013</td>
</tr>
<tr>
<td>Hong 2013</td>
<td>10</td>
<td>644</td>
<td>14</td>
<td>636</td>
<td>35.5%</td>
<td>0.70 [0.31, 1.59]</td>
<td>2013</td>
</tr>
<tr>
<td>Jones 2013</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>19</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Prasad 2013</td>
<td>1</td>
<td>47</td>
<td>1</td>
<td>48</td>
<td>2.5%</td>
<td>1.02 [0.06, 16.83]</td>
<td>2013</td>
</tr>
<tr>
<td>Thielmann 2013</td>
<td>3</td>
<td>162</td>
<td>6</td>
<td>167</td>
<td>14.9%</td>
<td>0.51 [0.12, 2.06]</td>
<td>2013</td>
</tr>
<tr>
<td>Slagsvold 2014</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>30</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>RIC Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Overall Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1525</td>
<td>1514</td>
<td>100.0%</td>
<td>0.79</td>
<td>0.49, 1.27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Total events: 29
- Heterogeneity: Chi² = 5.11, df = 11 (P = 0.93); I² = 0%
- Test for overall effect: Z = 0.97 (P = 0.33)

*(1) 30 days mortality only because lost to follow-up*

### Mortality > 1 year

<table>
<thead>
<tr>
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<th>Total</th>
<th>Control Events</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Hoole 2009</td>
<td>1</td>
<td>95</td>
<td>5</td>
<td>97</td>
<td>16.3%</td>
<td>0.20 [0.02, 1.71]</td>
<td>2009</td>
</tr>
<tr>
<td>Botker 2010</td>
<td>5</td>
<td>126</td>
<td>15</td>
<td>125</td>
<td>48.2%</td>
<td>0.30 [0.11, 0.86]</td>
<td>2010</td>
</tr>
<tr>
<td>Thielmann 2013</td>
<td>3</td>
<td>162</td>
<td>11</td>
<td>167</td>
<td>35.5%</td>
<td>0.27 [0.07, 0.98]</td>
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</tbody>
</table>

**Total (95% CI)**

<table>
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<th>RIC Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Overall Weight</th>
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<tbody>
<tr>
<td>383</td>
<td>389</td>
<td>100.0%</td>
<td>0.27</td>
<td>0.13, 0.58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Total events: 9
- Heterogeneity: Chi² = 0.13, df = 2 (P = 0.94); I² = 0%
- Test for overall effect: Z = 3.35 (P = 0.0008)
Circulating factors?

- <30 kD
- hydrophobe

Figure: Biological effects of remote ischaemic preconditioning
Transient ischaemia of the arm liberates a circulating effector that induces remote cellular adaptation to a subsequent, extended, and potentially lethal period of ischaemia in remote tissues.

Kharbanda et al. Lancet 2009
Microparticle release in remote ischemic conditioning mechanism

Julien Jeanneteau, Pierre Hibert, Maria Carmen Martinez, Simon Tual-Chalot, Sophie Tamareille, Alain Furber, Ramaroson Andrianitsitohaina, and Fabrice Prunier

1Université d'Angers, laboratoire Cardioprotection, Remodelage et Thrombose, Angers, France; 2Centre Hospitalier Universitaire Angers, Service de Cardiologie, Angers, France; 3Université d'Angers, laboratoire Stress oxydant et pathologies

Cell activation

Apoptosis

Vesiculation

Disruption of the membrane skeleton

Membrane skeleton

Activation of kinases

Inhibition of phosphatases

Activation of calpain

Talin breakdown

Cytosolcalcium↑

Receptor

Agonists

Actin-myosin force → Cell contraction
generation

Active ROCK I

ROCK I

Activation of caspases

Apoptosis inducers

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Apolipoproteine A-I: A potential mediator of RIC

Hibert et al. PlosOne 2013
Stromal derived factor 1α: A chemokine that delivers a two-pronged defence of the myocardium

Daniel I. Bromage, Sean M. Davidson, Derek M. Yellon

The Hatter Cardiovascular Institute, 67 Cheylesmore, London WC1E 6HX, United Kingdom
MicroRNA-144 is a circulating effector of remote ischemic preconditioning

Jing Li · Sagar Rohaila · Nitai Gelber · James Rutka · Nesrin Sabah · Rachel A. Gladstone · Can Wei · Pingzhao Hu · Rajesh K. Kharbanda · Andrew N. Redington
Remote Ischemic Conditioning in kidney injury?
Elective coronary angiography
- Creat>1.4 mg/dL or GFR<60mL/min
- Sham (n=50) vs. remote preconditioning (n=50)
- remote preconditioning : 4x5/5min upper-arm blood pressure cuff (SBP+50mmHg)
- Sham: 4x5/5min upper-arm blood pressure cuff (diatolic BP)

- **Primary end-point:** increase in serum creat >25% or >0.5mg/dL at 48h
- PCI in NSTEMI within 72h
- Sham (n=112) vs. remote postconditioning (n=113)
- remote postconditioning: 4x30/30 s, stent balloon at nominal pressure
- Sham: 4x30/30 s, stent balloon at 3 atm max

- **Primary end-point:** increase in serum creat >25% or >0.5mg/dL within 96h
Remote ischaemic preconditioning by brief hind limb ischaemia protects against renal ischaemia-reperfusion injury: the role of adenosine

Kimberley E. Wever¹, Michiel C. Warlé², Frank ADTG. Wagener¹,³, José W. van der Hoorn⁵, Rosalinde Masereeuw¹, J. Adam van der Vliet² and Gerard A. Rongen¹,⁴

1. Sham (6)
2. No RIPC (10)
3. 12′/12′ unilat (9)
4. 12′/12′ bilat (11)
5. 3x 4′/4′ unilat (9)
6. 3x 4′/4′ bilat (11)
Protective effects of three remote ischemic conditioning procedures against renal ischemic/reperfusion injury in rat kidneys: a comparative study

Ischemia 5 min  Reperfusion 5 min

A  SCr levels among five groups at 24 h after reperfusion

B  BUN levels among five groups at 24 h after reperfusion
- Porcine kidney transplantation model
- 2 kidneys from Donors (65kg): 1 for rIPC group, 1 for Sham group
- Nephrectomized recipient pigs (15kg) randomized to rIPC or non-rIPC
- RiPC in recipient (n=8): 4x5 min clamping of abdominal aorta
- non-rIPC in recipient (n=8): sham procedure

**Endpoints:** GFR ($^{51}$Cr-EDTA), renal plasma perfusion (MRI), heme-oxygenase 1 in renal tissue
Table 1. Basic physiological parameters, cold ischaemia time and fluid replacement in the two groups.

<table>
<thead>
<tr>
<th></th>
<th>rIC pigs</th>
<th>Non-rIC pigs</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>108 (9)</td>
<td>114 (20)</td>
<td>0.44</td>
</tr>
<tr>
<td>At reperfusion</td>
<td>79 (15)</td>
<td>84 (21)</td>
<td>0.62</td>
</tr>
<tr>
<td>Arterial lactate (medians, mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.7 (range 1.1–2.8)</td>
<td>1.3 (range 0.7–4.1)</td>
<td>0.34</td>
</tr>
<tr>
<td>At reperfusion</td>
<td>3.1 (range 2.1–4.3)</td>
<td>2.3 (range 1.1–5.1)</td>
<td>0.37</td>
</tr>
<tr>
<td>Cold ischaemia time</td>
<td>21 h34 min (86 min)</td>
<td>21 h43 min (74 min)</td>
<td>0.83</td>
</tr>
<tr>
<td>Duration of brain death before explantation</td>
<td>4 h48 min (44 min)</td>
<td>4 h47 min (44 min)</td>
<td>0.96</td>
</tr>
<tr>
<td>Supplement fluid (median, ml)</td>
<td>589 (range 0–1800)</td>
<td>937 (range 0–1963)</td>
<td>0.32</td>
</tr>
<tr>
<td>Baseline weight (kg)</td>
<td>15 (1)</td>
<td>15 (1)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Baseline was defined as the beginning of anaesthesia. Data are presented as mean and standard deviation (SD), unless noted otherwise. No significant differences between the rIC and the non-rIC group were observed.
Renal protection against ischaemia-reperfusion in transplantation: a randomised double blind placebo-controlled trial of 400 living-donor renal transplant patients

406 patients randomised

Recruitment has now closed

Many thanks to everyone involved for helping to exceed our target
LIVING-DONOR RENAL TRANSPLANT PATIENTS

RANDOMISATION
1:1:1:1
(Control : Early RIPC : Late RIPC : Dual RIPC)

CONTROL
(Sham RIPC)

EARLY RIPC
(Sham RIPC)

LATE RIPC
(RIPC)

DUAL RIPC
(RIPC)

24 hours pre-op
Sham RIPC (Donor+Recipient)

Immediately pre-op
Sham RIPC (Donor+Recipient)

RIPC (Donor+Recipient)

Sham RIPC (Donor+Recipient)

RIPC (Donor+Recipient)

RIPC (Donor+Recipient)

TRANSPLANTATION
Renal biopsy/vascular tissue harvest for assessment RIPC-induced alteration of protein phosphorylation/expression, baseline tubulointerstitial fibrosis

7 days
Serum creatinine, time for serum creatinine to fall by 50%, inflammatory response

3 months
Estimated GFR (MDRD), tubulointerstitial fibrosis, acute rejection, graft survival

12 months
Primary end-point: GFR (iohexol clearance)
Acute rejection, graft/patient survival

Annual follow-up (2-5 years)
Serum creatinine, eGFR, graft/patient survival
Future potential of remote conditioning

- Easy to deliver, no known adverse risks, cheap
- Potential interest in MI, Stroke, cardiac surgery, organ transplantation, contrast nephropathy prevention…

But…
- Mechanism?
- So far only small-scale proof-of-principle human studies with surrogate endpoints
- Need for large-scale multicenter studies powered to hard clinical outcomes