Remote ischemic conditioning in the STEMI and stroke: are we ready for clinical implementation?

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The following relationships exist related to this presentation:

- **Shareholder in CellAegis**
  a start-up company developing automated preconditioning devices
MI size prognostic determinant

- "Traditional" determinants of MI size
  - Area-at-risk (AAR)
  - Ischemia duration
  - Residual perfusion of AAR (collaterals)
  - (Systemic hemodynamics)
Reperfusion injury

Normoxic heart + 90 min ischemia + 1 min of reperfusion
Reperfusion injury

"It is interesting to look back 100 years ... and observe the great advances that have been made," said Braunwald. However, he noted that despite these advances AMI continues to be a major cause of mortality. Braunwald went on to highlight three therapeutic approaches — prevention of lethal myocardial reperfusion injury, post-AMI inhibition of thrombin generation, and post-AMI cell therapy — as examples of future opportunities to improve cardiovascular care.
The chain of infarct size reduction

- Myocardial infarction without reperfusion
  - Infarct size (IS) 70%

- Myocardial infarction with reperfusion
  - IS 30%

- Myocardial infarction with reperfusion and cardioprotection
  - IS 5%

- Reducing referral delay

- Microcirculation

- Cardioprotection

References:
- 2010;375:727-34
- 2011; 32: 430-6
- 2006;114:40-7
Cardioprotection by ischemic preconditioning

Ischemia | Reperfusion | Tissue death

Ischemia | Modified reperfusion | Less tissue death

Experimental evidence

Adaptation to Ischemia During Percutaneous Transluminal Coronary Angioplasty
Clinical, Hemodynamic, and Metabolic Features
Ezra Deutsch, MD, Mark Berger, MD, William G. Kussmaul, MD, John W. Hirshfeld Jr., MD, Howard C. Herrmann, MD, and Warren K. Laskey, MD

Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium
CE Murry, RB Jennings and KA Reimer
Circulation 1986; 74: 1124-36

Preconditioning the human myocardium
D M Yellon, A M Alkulaifi, W B Pugsley
THE LANCET 1993;342:276-7
Concept of remote preconditioning

<table>
<thead>
<tr>
<th>Ischemia</th>
<th>Reperfusion</th>
<th>Tissue death</th>
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</thead>
<tbody>
<tr>
<td>Ischemia</td>
<td>Modified reperfusion</td>
<td>Less tissue death</td>
</tr>
</tbody>
</table>

**Local remote**

Occlusion of CX
Infarct size in LAD

Przyklenk K et al. *Circulation* 1993;87:893-9

**Distant remote**

Three of four cycles of 5 minutes of limb ischemia induced by blood pressure cuff inflation (200 mm Hg)

Birnbaum Y et al. *Circulation* 1997;96:1641-6
Kharbanda R et al. *Circulation* 2002;106:2881-3
## Translational studies – predictable ischemia

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Stimulus</th>
<th>Outcome</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac surgery</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cheung (2006)</td>
<td>Pediatric</td>
<td>‡ TnT, inotropic score, airway resist</td>
<td>37</td>
</tr>
<tr>
<td>Hausenloy (2007)</td>
<td>CABG ± valve</td>
<td>‡ TnT</td>
<td>57</td>
</tr>
<tr>
<td>Venugopal (2009)</td>
<td>CABG (cold-blood cardiopl)</td>
<td>‡ TnT</td>
<td>45</td>
</tr>
<tr>
<td>Thielman (2010)</td>
<td>CABG (crystaloid cardiopl)</td>
<td>‡ TnT</td>
<td>53</td>
</tr>
<tr>
<td>Li (2010)</td>
<td>Valve replacement</td>
<td>‡ TnI, ‡ defibrillation</td>
<td>81</td>
</tr>
<tr>
<td>Hong (2010)</td>
<td>CABG (off-pump)</td>
<td><strong>No statistically significant</strong> ‡ Tnl</td>
<td>130</td>
</tr>
<tr>
<td>Wagner (2010)</td>
<td>CABG (crystaloid-tramadol)</td>
<td>‡ Tnl; ‡ iNOS; ‡ eNOS</td>
<td>101</td>
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<tr>
<td>Zhou (2010)</td>
<td>Pediatric</td>
<td>‡ inotropic score</td>
<td>60</td>
</tr>
<tr>
<td>Zimmerman (2011)</td>
<td>Pediatric</td>
<td>‡ kidney injury</td>
<td>120</td>
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<tr>
<td>Rahman (2011)</td>
<td>Cardiac with CP by-pass</td>
<td><strong>No effect</strong> on TnT, inotropic, kidney, ECG</td>
<td>162</td>
</tr>
<tr>
<td>Young (2012)</td>
<td>CABG electiv + urgent</td>
<td><strong>No effect</strong> on TnT, inotropic, kidney</td>
<td>96</td>
</tr>
<tr>
<td>Kottenberg (2012)</td>
<td>High risk CABG and valve</td>
<td>‡AUC TnI by isoflurane, <strong>No effect</strong> by propofol</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>CABG</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non cardiac</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ali (2007)</td>
<td>Open AAA</td>
<td>‡ Tnl, ‡ periopratative MI, kidney</td>
<td>82</td>
</tr>
<tr>
<td>Walsh (2009)</td>
<td>EVAR</td>
<td><strong>No effect</strong> on renal funct and cardiac events</td>
<td>40</td>
</tr>
<tr>
<td>Walsh (2010)</td>
<td>Open infrarenal AAA</td>
<td><strong>No effect</strong> on renal function</td>
<td>40</td>
</tr>
<tr>
<td>Walsh (2010)</td>
<td>Carotid endarterectomy</td>
<td><strong>No effect</strong> on neurological + cardiac outcome</td>
<td>70</td>
</tr>
<tr>
<td><strong>Elective PCI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iliodromitis (2009)</td>
<td>Stent implantation</td>
<td>‡ TnI, ‡ CKMB, ‡ CRP</td>
<td>41</td>
</tr>
<tr>
<td>Hoole (2009)</td>
<td>Elective PCI</td>
<td>Reduced TnI; reduced MACCE</td>
<td>242</td>
</tr>
</tbody>
</table>
Predictable ischemia: PCI

Distribution of 24-hour cTnI in patients after PCI

Kaplan-Meier graph of the MACCE rate up to 6 years after elective PCI in 215 patients

Hoole et al. Circulation 2009;119:820-827

Hoole et al. AHA Scientific Sessions 2012
Challenges in unpredictable ischemia

Predictable:

- Local and remote pre-

Unpredictable:

- Pharmacological-
- Post-
- Remote-

Perconditioning

Ischemia Reperfusion Tissue death

Modified reperfusion

Less tissue death

Drug

Ischemia
INTERMITTENT PERIPHERAL TISSUE ISCHEMIA DURING CORONARY ISCHEMIA REDUCES MYOCARDIAL INFARCTION THROUGH A $K_{ATP}$ DEPENDENT MECHANISM: FIRST DEMONSTRATION OF REMOTE ISCHEMIC PERCONDITIONING

Remote conditioning in the ambulance

ECG

Randomization

Patient

Ambulance
Translation into clinical practice:
rlPerC during transportation to pPCI

Salvage Index (median [IQR])

PCI only  rlPerC

Bøtker et al. Lancet 2010;373: 727-34

p=0.033

Salvage Index (median [IQR])

PCI only  rlPerC

0.55

0.75
Influence of infarct location and vessel patency

Infarct Location

- LAD
  - PCI only: 16
  - rlPerC: 7
  - p = 0.011
- Non-LAD
  - PCI only: 4
  - rlPerC: 3
  - p = 0.94

Vessel patency

- Occluded TIMI 0-1
  - PCI only: 13
  - rlPerC: 9
  - p = 0.056
- Non-occluded TIMI 2-3
  - PCI only: 1
  - rlPerC: 1
  - p = 0.62

Bøtker et al. Lancet 2010; 373: 727-34
Relation between AAR and FIS

Difference in slope: 0.16 (0.05; 0.26), p = 0.003

- PCI only
- rIPerC

Final infarct size (% of LV) vs. Area at risk (% of LV)

Bøtker et al. Lancet 2010;373:727-34
Translation into improvement of LV-function in most severely affected patients

Patients with LAD STEMI: 30-day EF by echo and gated SPECT

Munk K et al. Circ Cardiovasc Imaging 2010;3:656-662
Further clinical evidence

Effect of rIPerC enhanced by morphine (n=96)

Translation into long term benefit
Cumulative incidence of MACE

Sloth et al. TCT 2012
Long term effect of rIPerC

<table>
<thead>
<tr>
<th>Event</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.61 (0.38-0.96)</td>
<td>0.034</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.46 (0.22-0.96)</td>
<td>0.040</td>
</tr>
<tr>
<td>Myocardial reinfarction</td>
<td>0.47 (0.21-1.06)</td>
<td>0.070</td>
</tr>
<tr>
<td>Readmission for heart failure</td>
<td>0.78 (0.32-1.89)</td>
<td>0.585</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.68 (0.21-2.16)</td>
<td>0.510</td>
</tr>
</tbody>
</table>

Sloth et al. TCT 2012
Long term follow-up after RIPC in CABG

Hazard ratio, 0.317 (95% CI, 0.141-0.710)
P = 0.005 (Cox regression)
P = 0.003 (Log rank)

Thielman et al.
AHA Annual meeting 2012
Challenges in translation

From healthy experimental animals to patients with risk factors and comorbidity

Age
Loss of cardioprotective signalling

Comorbidity
DM, hypertension, cholesterol

Clinical heterogeneity
Reperfusion through residual stenosis
Microembolization
Area-at-risk
Timing of reperfusion

Medication
anti-DM (metformin, SU)
opioids,

Medication
β-blockers, statins,
ACEI, AT1-blockers, NTG,
adenosine a.o.
rIPC in thrombolytically treated STEMI
Experimental results (rats):
Remote ischemic perconditioning in evolving stroke

Focal cerebral ischemia:
Transiet middle cerebral artery occlusion 120 min
Reperfusion: 24 hours

**Pre-conditioning:**
40 min before ischemia

**Remote Per-conditioning:**
40 min before reperfusion

Protection by both IPC and rIPerC ($p<0.001$) – rIPerC > local IPC

*Hahn CD et al. Stroke 2011;42:2960-2962*
Clinical results

Patients with TIA or ischemic stroke (N=295)

Penumbral salvage

N=149

\( \div \) rPerC: 14.10 ml (1.60;79.82)
\( + \) rPerC: 11.89 ml (0.53;63.39)

NIHSS on admission

Median (IQR)

NIHSS = National Institutes of Health Stroke Scale

Clinical perspectives: combination of stimuli

Perspectives: efficacy of combination

Repeated rIPostC improves survival in a rat model of myocardial infarction despite absence of further reduction of infarct size compared to rIPerC alone

Underlying mechanisms

Stimulus → Effector → Cell-signalling → Protection

Four cycles of 5 min limb ischemia and 5 min reperfusion → Systemic release of circulating conditioning substances → Opening of mK$_{ATP}$ → Closure of MTPT → Intracellular pathways → Reduced IS – improved function → Antiinflammatory effect → Prevents endothelial dysfunction and platelet activation
Conclusion

- Reperfusion injury is a true treatment target
- rIPerC activates endogenous cardioprotection
- rIPerC can be translated into a clinical context, but true clinical benefit awaits larger multicenter trials
- Challenges in the translation of rIPerC in thrombolytically treated stroke
Thank you!