Stroke Net
Grand Round Webinar

Preconditioning the Brain for Stroke Prevention

April 4, 2019

Sebastian Koch
University of Miami
Department of Neurology
Disclosures

None
Objectives

- Unique challenges in brain conditioning
- Review clinical studies of brain conditioning
- Translational issues for interventional studies
- Discuss our efforts
What about the brain?

- Is it possible to precondition the brain?
- Least accessible organ.
- Blood brain barrier?
- Patients with cerebrovascular disease tend to be older.
  - Problems with conditioning the aged brain?
Pre-myocardial angina may improve cardiac outcomes. (Lorgis 2012)

- Reduced troponin elevation
- Arrhythmia
- Fewer ST segment changes
- Mortality

Does TIA prior to stroke have a preconditioning effect?
Brain Conditioning with TIA

- TIA prior to ischemic stroke lessens stroke severity and improves functional outcome:
  - Even if TIA occurred several years prior to index stroke. (Weih 1999)
  - Moncayo 2000
    - Lausanne Stroke Registry data in over 2000 patients.
    - Looked at duration and timing of TIAs.
    - TIAs lasting 10-20min improved outcome when compared to TIAs lasting <10min, or 20-40min.
    - TIAs <1 week from stroke more protective than TIAs between 1 week- 1 month, or >1 month before index stroke.
Benefit on imaging outcomes as well:

- Assessed the effects of TIA within 72h of index stroke.
- Reduced infarct volume at 4-7 days by brain CT.
- Better functional outcome at 90 days.
- Correlated protection from TIA with a higher TNF-\(\alpha\)/IL 6.

(Castillo 2003)
But...not a consistent finding:

- Northern California TIA study
- No effect of prior TIA on stroke outcome and disability.
- Even when assessing different durations of TIA and interval to index stroke
- Unable to confirm the protective effects of TIA on stroke severity

(Johnston 2004)
Clinical Brain Conditioning

Translational Challenges for Interventional Studies
Preclinical studies:
  › young animals.
  › healthy.
  › free of medications.

Clinical medicine:
  › older patients.
  › with comorbidities.
  › on medications.
No preconditioning effect of TIA was demonstrated in elderly (>65 years) patients with stroke. (Della Morte 2008)

Preclinical models of aged hearts have shown a reduction of the preconditioning effect. (Abete 1996)
Medication Effect on Conditioning

- Acute dosing of lovastatin aborted a preconditioning effect in rat myocardial ischemia model but did not affect postconditioning.

- Chronic lovastatin use did not affect preconditioning but affected postconditioning. (Kocsis 2008)
What Conditioning Method?

- What method of conditioning?
  - Direct conditioning impractical.
  - Limb conditioning
    - Which Limb?
  - Pharmacological conditioning?
Clinical Conditioning Methods

- Hauseloy 2007:
- 3 x 5min arm conditioning cycles prior to CABG in 57 patients.
- 30% reduction in post-operative troponin elevation.
# Preclinical Limb Preconditioning

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulus</th>
<th>Animal</th>
<th>Model</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vlasov 2005</td>
<td>30-min leg ischemia</td>
<td>Rat</td>
<td>Global ischemia</td>
<td>↓ endothelial function, ↓ cerebral edema</td>
</tr>
<tr>
<td>Jin 2006</td>
<td>3 x 10-min leg ischemia</td>
<td>Rat</td>
<td>Global ischemia</td>
<td>↑ pERK1/2, ↓ neuronal loss</td>
</tr>
<tr>
<td>Dave 2006</td>
<td>15 and 30-min leg ischemia</td>
<td>Rat</td>
<td>Global ischemia</td>
<td>↓ neuronal loss</td>
</tr>
<tr>
<td>Gurcon 2006</td>
<td>5-min renal ischemia</td>
<td>Rabbit</td>
<td>Spinal ischemia</td>
<td>↑ function</td>
</tr>
<tr>
<td>Sun 2006</td>
<td>3 x 10-min leg ischemia</td>
<td>Rat</td>
<td>Global ischemia</td>
<td>↓ neuronal loss, ↑ p38 MAPK expression</td>
</tr>
<tr>
<td>Rehni 2007</td>
<td>15-min mesenteric artery occlusion</td>
<td>Mouse</td>
<td>Focal ischemia</td>
<td>↑ function, ↓ infarct size</td>
</tr>
<tr>
<td>Zhao 2007</td>
<td>3 x 10-min leg ischemia</td>
<td>Rat</td>
<td>No cerebral ischemia</td>
<td>↑ serum and hippocampal NO and NOS expression</td>
</tr>
<tr>
<td>Ren 2008</td>
<td>5 and 16-min cycles of leg ischemia</td>
<td>Rat</td>
<td>Focal ischemia</td>
<td>↓ infarct size</td>
</tr>
<tr>
<td>Malhotra 2011</td>
<td>3x 10-min infra-renal aortic occlusion</td>
<td>Rat</td>
<td>Focal ischemia</td>
<td>↑ function, ↓ infarct size</td>
</tr>
<tr>
<td>Hahn 2011</td>
<td>4 x 10-min leg ischemia (tourniquet)</td>
<td>Rat</td>
<td>Focal ischemia</td>
<td>↑ function, ↓ infarct size</td>
</tr>
</tbody>
</table>

pERK = extracellular signal-regulated kinases; NO = nitrous oxide; NOS = NO synthase; MAPK = mitogen-activated protein kinase
<table>
<thead>
<tr>
<th>Trial</th>
<th>Clinical Setting</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheung 2006</td>
<td>Pediatric cardiac surgery</td>
<td>2 cycles of 5 min leg ischemia</td>
</tr>
<tr>
<td>Hausenloy 2007</td>
<td>Coronary bypass</td>
<td>3 cycles of 5 min arm ischemia</td>
</tr>
<tr>
<td>Ali 2007</td>
<td>Abdominal aneurysm repair</td>
<td>2 cycles of 10 min iliac artery occlusion</td>
</tr>
<tr>
<td>Hoole 2009</td>
<td>Coronary angioplasty</td>
<td>3 cycles of 5 min arm ischemia</td>
</tr>
<tr>
<td>Rahman 2010</td>
<td>Coronary bypass</td>
<td>3 cycles of 5 min arm ischemia</td>
</tr>
<tr>
<td>Thielman 2010</td>
<td>CABG Surgery</td>
<td>3 cycles of 5 min arm ischemia</td>
</tr>
<tr>
<td>Wagner 2010</td>
<td>CABG Surgery</td>
<td>3 cycles of 5 min arm ischemia</td>
</tr>
<tr>
<td>Ali 2010</td>
<td>CABG Surgery</td>
<td>3 cycles of 5 min arm ischemia</td>
</tr>
<tr>
<td>Hong 2012</td>
<td>Off pump CABG Surgery</td>
<td>4 cycles of 5 min arm ischemia</td>
</tr>
</tbody>
</table>
Preconditioning the Brain

What Setting?

- Carotid endarterectomy or stenting.
- Subarachnoid hemorrhage.
- Coronary artery bypass.
- Secondary prevention in high risk patients with TIA/stroke.
Per and Post-conditioning the Brain

- Acute cerebral infarction.
- Cardiac arrest?
Completed Studies in Brain Conditioning

- Walsh 2010 & Zhao 2017
  - Carotid intervention

- Koch 2011, Gonzalez 2013
  - Subarachnoid hemorrhage.

- Meng 2012 & 2015
  - Symptomatic Intracranial disease.

- Hougard 2013
  - Ischemic stroke and tPA.
Completed Studies in Brain Preconditioning

Zhao 2017:
- 139 participants with high grade carotid stenosis
- Preconditioned for 2 weeks prior to carotid stenting
- 5x 5min cycles of arm conditioning, twice daily
- MRI after showed reduction in lesion volume and number of new lesions (RR~40%)
- No difference in clinical outcomes (but very low event rates)
Koch 2012:
- Subjects with aneurysmal SAH
- Leg preconditioning every other day from day 4-14
- To ameliorate delayed cerebral ischemia
- Safety and feasibility study
- Escalating durations of limb ischemia
  - 5, 7.5 and 10 minutes
- 2 DVTs in leg preconditioning group
- Safe, feasible and tolerated
Gonzalez 2013:

- Subjects with aneurysmal SAH.
- Leg preconditioning 4x 5min every other day from day 2-12.
- Assessed metabolic and hemodynamic effects.
  - TCD, microdialysis.
- Transient vasodilation with decrease in MCA TCD velocities.
- Reduction of lactate/pyruvate ratio and glycerol for up to 2 days.
Meng 2012

- 68 patients with symptomatic intracranial stenosis.
- 5 cycles x 5 min arm conditioning twice daily for 300 days vs. control group.
- Outcomes: recurrent stroke, mRS, TCD and SPECT at 90 and 300 days.
- Recurrent stroke at 90 days: 5% vs. 23% (p<0.01)
- Improved functional recovery by mRS 0-1 (p<0.01)
- Improved cerebral perfusion by SPECT
- Improved TCD blood flow velocities.
Hougaard 2013:

- Randomized 453 stroke patients who received IV tPA.
- 3x 5 min arm conditioning cycles with start in ambulance.
- Primary endpoint: volume of tissue in PWI/DWI mismatch not progressing to infarction.
- No evidence of effect on penumbral salvage and final infarct volume.
- No difference in clinical outcomes at 3 months.
- But reduced the amount of tissue at risk of infarction.
- Reduced admission NIHSS in conditioned subjects (p=0.016).
- More TIA's in conditioned group (p=0.006).
Interventional Studies
Conclusion

- Proof on concept and exploratory

- Signal of efficacy

- Intervention is safe

- Currently ongoing larger studies in acute ischemic stroke (France, Denmark), and secondary stroke prevention in intracranial disease (China)
### Proving the Principle

**Brain -Limb Conditioning**

<table>
<thead>
<tr>
<th></th>
<th>Preconditioning</th>
<th>Post-and Perconditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of preclinical evidence</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Shown in multiple organ systems</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Innovation of approach to cytoprotection</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Clinical applicability</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Subarachnoid hemorrhage</td>
<td>Carotid artery stenting / endarterectomy</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Favorable patient demographics</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Ischemic risk over time</td>
<td>+++ 20%</td>
<td>++ 3-6%</td>
</tr>
<tr>
<td>Preconditioning length</td>
<td>++ 14 days</td>
<td>+++ One time</td>
</tr>
<tr>
<td>Model for ischemia</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>
## Proving the Principle
**Brain-Limb Conditioning**

<table>
<thead>
<tr>
<th></th>
<th>Subarachnoid Hemorrhage(^1)</th>
<th>Coronary artery bypass surgery(^2)</th>
<th>Carotid endarterectomy(^3)</th>
<th>Secondary Stroke Prevention(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ±12</td>
<td>67*</td>
<td>68*</td>
<td>60±9</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>42</td>
<td>61</td>
<td>62</td>
<td>29</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>48</td>
<td>65</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>3</td>
<td>42</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>1</td>
<td>100</td>
<td>23</td>
<td>Not available</td>
</tr>
</tbody>
</table>

\(^1\) Koch 2012; \(^2\) Hausenloy 2007; \(^3\) Walsh 2010; \(^4\) Meng 2012

Modified from Koch 2013
## Proving the Principle
### Brain-Limb Conditioning

<table>
<thead>
<tr>
<th></th>
<th>Subarachnoid hemorrhage</th>
<th>Carotid artery stenting / endarterectomy</th>
<th>Cardiac bypass</th>
<th>Secondary stroke prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable patient demographics</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ischemic risk over time</td>
<td>+++ 20%</td>
<td>++ 3-6%</td>
<td>+ ~2%</td>
<td>+ 8%</td>
</tr>
<tr>
<td>Preconditioning Duration</td>
<td>++ 14 days</td>
<td>+++ One time</td>
<td>+++ One time</td>
<td>+ Months</td>
</tr>
<tr>
<td>Model for ischemia</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Comments and Opinions

Preconditioning the Human Brain
Proving the Principle in Subarachnoid Hemorrhage

Sebastian Koch, MD; Nestor Gonzalez, MD

Stroke. 2013;44:1748-1753; originally published online April 18, 2013;
doi: 10.1161/STROKEAHA.111.000773

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628
PreLIMBS IIa
Preconditioning with Limb Ischemia for Subarachnoid Hemorrhages

- Safety and Feasibility in SAH
- Biomarker Exploratory Aim
  - Serum marker, MRI outcomes
- 4 x 5min cycles vs. 3x 10min vs. sham
- Sample size 150 participants, 10 sites
Preconditioning

- Przylenk 1993 – regional, remote preconditioning.
- 400 BC Hippocrates - prescribed small doses of mandrake root, which causes mania, to treat mania.
- 16th Paracelsus - what makes a man ill also cures him.
- 18th century - Samuel Hahneman.
  - Diseases should be treated by drugs that cause similar symptoms in humans.
- 19th Nietzsche - what does not kill me makes me stronger.