Stroke Net
Grand Round Webinar

Preconditioning the Brain for Stroke Prevention

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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?

Clinical Observations of Human Brain Conditioning

- **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.

Conditioning with TIA

- **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-α/IL 6.**

(Castillo 2003)

Conditioning with TIA

- **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

Translational Challenges

- **Preclinical studies:**
  - young animals.
  - healthy.
  - free of medications.
- **Clinical medicine:**
  - older patients.
  - with comorbidities.
  - on medications.

Effect of Age on Conditioning

- 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 preconditioing 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

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

pERK= extracellular signal-regulated kinases; NO=nitrous oxide; NOS=NO synthase; MAPK= mitogen-activated protein kinase

Clinical Cardiac Conditioning

Trial	Clinical Setting	Intervention
Cardiac		
Cheung 2006	Pediatric cardiac surgery	2 cycles of 5 min leg ischemia
Hausenloy 2007	Coronary bypass	3 cycles of 5 min arm ischemia
Ali 2007	Abdominal aneurysm repair	2 cycles of 10 min iliac artery occlusion
Hoole 2009	Coronary angioplasty	3 cycles of 5 min arm ischemia
Rahman 2010	Coronary bypass	3 cycles of 5 min arm ischemia
Thielman 2010	CABG Surgery	3 cycles of 5 min arm ischemia
Wagner 2010	CABG Surgery	3 cycles of 5 min arm ischemia
Ali 2010	CABG Surgery	3 cycles of 5 min arm ischemia
Hong 2012	Off pump CABG Surgery	4 cycles of 5 min arm ischemia

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)

Completed Studies in Brain Conditioning

- **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 10minutes
  - 2 DVTs in leg preconditioning group
  - Safe, feasible and tolerated

Completed Studies in Brain Conditioning

- 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.

Completed Studies in Brain Conditioning

- **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.

Completed Studies in Brain Conditioning

- **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 TIAs 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

	Preconditioning	Post-and Perconditioning
Extent of preclinical evidence	+++	+
Shown in multiple organ systems	+++	+
Innovation of approach to cytoprotection	+++	+
Clinical applicability	+	+++

Proving the Principle
Brain-Limb Conditioning

	Subarachnoid hemorrhage	Carotid artery stenting / endarterectomy	Cardiac bypass	Secondary stroke prevention
Favorable patient demographics	+++	+	+	+
Ischemic risk over time	+++ 20%	++ 3-6%	+ ~2%	+ 8%
Preconditioning length	++ 14 days	+++ One time	+++ One time	+ Months
Model for ischemia	+	+++	++	+++

Proving the Principle Brain-Limb Conditioning

	Subarachnoid Hemorrhage[1]	Coronary artery bypass surgery[2]	Carotid endarterecotmy[3]	Secondary Stroke Prevention[4]
Age (years)	53 ±12	67*	68*	60± 9
Hypertension (%)	42	61	62	29
Smoking (%)	48	65	21	30
Diabetes (%)	3	42	21	24
Ischemic heart disease (%)	1	100	23	Not available

[1] Koch 2012; [2] Hausenloy 2007; [3] Walsh 2010; [4] Meng 2012

Modified from Koch 2013

Proving the Principle
Brain-Limb Conditioning

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Preconditioning Duration	++ 14 days	+++ One time	+++ One time	+ Months
Model for ischemia	+	+++	++	+++

Comments and Opinions

Preconditioning the Human Brain

Proving the Principle in Subarachnoid Hemorrhage

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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

- Murry 1986 – direct 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.