Remote ischemic conditioning: the brain's endogenous defense against stroke

Introduction to ischemic conditioning: In 1986, Murray built upon a series of accumulated works to demonstrate that brief ischemic "training" episodes fortisied cardiac tissue against impending prolonged infarction (Murray et al., 1986). This discovery overturned the dogmatic understanding that time-dependent tissue compromise during infarction was bimodal, not linear, in nature. Instead of being invariably deleterious, an organ's response to ischemia is dependent upon both the duration of the infarction as well as adaptations from previous, transient ischemic episodes.

During prolonged ischemia, ATPase-dependent ion transport is impaired, disrupting cellular homeostasis to incite calcium overload and volume dysregulation. Tissue reperfusion in turn has paradoxically pathological effects, such as the generation of reactive oxygen species and sequestration of proinflammatory immunocytes in ischemic tissue. Any combination of these accumulative insults following ischemic/reperfusion injury results in wide-spread mitochondrial permeability, cell lysis and death (Kalogeris et al., 2016). Transient ischemia, in contrast, confers a conditioning stimulus protecting against subsequent infarction.

Conditioning agents: Ischemic conditioning has been successfully tested in animal models, initially via direct vascular occlusion. The high risk of permanent vascular and tissue damage prompted further research into alternative conditioning agents. Numerous other cellular insults aside from ischemia were discovered to produce conditioning responses, indicating a lack of specificity between ischemic tolerance and ischemia. Likely, these related responses are due to integration into cellular degeneration or defense pathways. The "cross-tolerance" of conditioning to various insults provoked the study of ischemic mimetics. For example, successful cerebral conditioning techniques altered metabolic states (e.g., hypoxia, hypothermia, hypoglycemia) and included some existing pharmaceuticals (e.g., fluranes) (Thushara Vijayakumar et al., 2016). Despite improvements over direct conditioning, ischemic mimetics still require an underlying neuronal insult, drastically limiting their clinical application.

Remote ischemic conditioning (RIC): RIC is a novel conditioning method involving application of ischemia in one organ to stimulate ischemic tolerance in another. In clinical settings, this is most frequently accomplished by using a blood pressure cuff to intermittently induce transient ischemia in a peripheral limb, such as an arm or leg. RIC avoids direct insult to cerebral tissue and has been studied in critically ill patients, where no adverse effects were observed following its use (Koch et al., 2011). Following RIC, a systemic messenger transverses to the target organ.

RIC: systemic pathways: Several systemic pathways have been described for RIC: 1) blood-borne factor release, 2) neuronal pathway activation, 3) systemic modification of immune cells, and 4) activation of hypoxia inducible genes (Tapuria et al., 2008; Le Page and Prunier, 2015; Anttila et al., 2016) (Figure 1A). While the literature centers around cardioprotective pathways, consistencies between organs systems are apparent. For example, following RIC for cerebral conditioning, a reduction in circulating cerebrocortical leukocytes is observed (Anttila et al., 2016). The numerous pathways converge on the target organ to trigger a protective intracellular signaling response that reduces mitochondrial permeability, conserves ATP levels, and prevents apoptosis (Tapuria et al., 2008).

Clinical models: Remote ischemic preconditioning (RIPC): To study RIPC, Meng et al. (2012) identified a population at high risk for recurrent stroke: patients with intracranial stenosis. Following their first episode of infarction, Meng et al. (2012) applied twice-daily bilateral-limb ischemia for 300 days. They found increased cerebral perfusion, decreased incidence of recurrent stroke, and faster recovery time after primary and recurrent stroke. The success of preconditioning in Meng's study stems from using

Clinical models: introduction: Integrating RIC into clinical practice remains challenging due to the erratic nature of cerebral infarction. Following a conditioning stimulus, there are two windows of ischemic tolerance. Acute tolerance is developed within minutes and confers short-term benefits lasting a few hours. This effect is thought to be related to post-translational modifications. Delayed tolerance emerges following genetic alterations and de novo protein synthesis. Its effects last several days to 1 week (Thushara Vijayakumar et al., 2016). The conditioning response may be delivered prior, during or before the event via ischemic pre/postconditioning, respectively. The limited window of neuroprotection provided and mantra of "time is brain" highlight the essentialness of selecting an appropriate conditioning model. Clinical models to be discussed are summarized in Additional Table 1.

Clinical models: Remote ischemic preconditioning (RIPC): Figure 1B. Pathways for remote ischemic conditioning. (A) Remote ischemia (e.g., blood pressure cuff occlusion of femoral artery) induces a systemic pathway, possibly through humoral, neuronal, systemic, or HIF pathways, that triggers an ischemic conditioning response at the target organ (e.g., brain). (B) PVD causes prolonged hypoperfusion that acts as remote ischemic mimetic, triggering a systemic response and cerebral conditioning. CGRP: Calcitonin gene-related peptide; EPO: erythropoietin; HIF: hypoxia inducible factor; PVD: peripheral vascular disease; VEGF: vascular endothelial growth factor.
Concluding thoughts: In the nearly three decades since the term ischemic preconditioning was coined, great strides have been made to translate its impressive potential to a clinical platform. Unfortunately, the envisioned paradigm shift predicted to accompany it has not yet come to fruition. Further, despite being the most susceptible organ to ischemic damage in the human body, evidence supporting ischemic conditioning in the brain lags behind other specialties. Preliminary results remain promising and developing trials will serve to elucidate a model of cerebral conditioning. The reasons for pursuing clinical models of cerebral conditioning are clear: over fifteen million people suffer stroke world-wide per year, incurring massive amounts of personal and economic cost. For these patients, ischemic conditioning holds potential to minimize stroke’s damage, improve its recovery, and even prevent its occurrence altogether.

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Additional file: Additional Table 1: Summary of clinical studies.

References

Anttila V, Haapanen H, Yannopoulos F, Herajarvi J, Anttila T, Juvenon T (2016) Review of remote ischemic preconditioning: from laboratory studies to clinical trials. Scand Cardiovasc J 50:355-361.

Anttila V, Haapanen H, Yannopoulos F, Herajarvi J, Anttila T, Juvenon T (2016) Review of remote ischemic preconditioning: from laboratory studies to clinical trials. Scand Cardiovasc J 50:355-361.

Connolly N, Collin B, Foot J, Hay J, Joyce M, Kaps A, Lesschen JP, Partington S, Proctor S, Quinton F, Rees AJ, Sandercock P, Serruys P, Smith H, Stott DJ, Tindal G, Zwingenberg J, Zuccarello S, Zimmerman D, Zucco R (2014) Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized clinical trial. Stroke 45:159-167.
### Additional Table 1 Summary of clinical studies

| Study                  | Design   | Conditioning | Outcomes                                                                                                                                 |
|------------------------|----------|--------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Meng et al., 2012      | RCT      | RIPC/RIPostC | Following AIS, the treatment group of intracranial stenosis patients had quicker recovery time (RIPostC related) and decreased recurrent stroke (RIPC related) |
|                        |          |              | (300 days, 2x Daily RIC after first stroke in intracranial stenosis patients followed through recurrent stroke)                           |
| Hougaard et al., 2014  | RCT      | RIPerC       | Although the overall results were neutral, a tissue survival analysis suggests that RIPerC may have immediate neuroprotective effects     |
|                        |          |              | (4 cycles RIC in route to the hospital, suspected AIS patients)                                                                          |
| Koch et al., 2011      | Prospective | RIPostC     | No adverse effects in critically ill-populations and evidence of improved cerebral perfusion with RIPostC                                 |
| Gonzalez et al., 2014  | Prospective | (14 days [Koch] or 4 sessions [Gonzalez] of RIC in hospitalized aSAH patients)                                                            |
| Connolly et al. 2013   | Retrospective | Prolonged hypoperfusion | PVD was correlated with lower NIHSS and stroke volume upon admission, improved mRS recovery, and lower mortality                       |
| Heilberger et al., 2019|          |              | (modeled by PVD in patients prior to AIS)                                                                                               |

AIS: Acute ischemic stroke; aSAH: aneurysmal subarachnoid hemorrhage; mRS: modified ranking scale; NIHSS: National Institute of Health Stroke Scale; PVD: peripheral vascular disease; RCT: randomized controlled trial; RIC: remote ischemic conditioning; RIPC: remote ischemic preconditioning; RIPerC: remote ischemic perconditioning; RIPostC: remote ischemic postconditioning.