Full Steam Ahead with Remote Ischemic Conditioning for Stroke

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The finding that brief periods of ischemia can protect tissues from later ischemic damage (ischemic preconditioning, IPC; [1, 2]) has not only engendered much research into underlying mechanisms [3–5] but also debate as to how to translate these findings to the clinic [6–11]. This was a focus of the 2nd Translational Preconditioning meeting held in Miami in 2012 [12] and likely to be a major focus of the 3rd meeting to be hosted by Dr. John Zhang in Los Angeles in 2014.

Although preconditioning can be induced by many stimuli other than ischemia [13, 14], the finding that brief periods of tissue ischemia can induce protection in other tissues (so-called remote ischemic preconditioning, RIPC) has generated the most clinical interest. Thus, for example, brief periods of limb ischemia may protect the brain and heart from later ischemic damage [15–18]. Because of relative simplicity (repeated inflation of a cuff around arm or leg) and perceived safety, this has become the stimulus of choice for examining whether preconditioning has clinical utility. This has led to a plethora of clinical trials, with ClinicalTrials.gov currently listing 55 and 12 trials focused on cardio- and neuroprotection, respectively. It really is full steam ahead with RIPC, and there also trials of remote ischemic per- and

postconditioning (where the cuff is inflated during [19, 20] or after the ischemic event; [21]).

In the brain, there has been discussion over the best neurological conditions in which to test RIPC [6–11], and clinical trials have focused on a range of conditions. Thus, there are those focusing on the effects of RIPC on neurological complications following cardiac surgery (NCT01835392; NCT00877305), neurosurgery (NCT00866489, NCT01654666, NCT01175876), subarachnoid hemorrhage (NCT01158508, NCT01110239), and ischemic stroke (NCT00975962, remote ischemic preconditioning; NCT01672515, remote ischemic postconditioning). While these trials have focused on relative short-term neuroprotection by RIPC, others have focused on the effects of RIPC in patients with underlying cerebrovascular disease, examining stroke occurrence and hemodynamic parameters (NCT01658306, NCT01321749, and NCT01570231). Data on a number of these trials have now been published. Meng et al. [22] examined the effects of twice daily RIPC for 300 days (a herculean effort) on the recurrence of stroke in patients with symptomatic atherosclerotic intracranial arterial stenosis. They found that RIPC (bilateral arm) reduced recurrent stroke from 7.9 to 5 %. Hougaard et al. [20] examined the effect of remote ischemic preconditioning in ischemic stroke patients undergoing thrombolysis. They found no overall benefit on the clinical outcome at 3 months, but did find a reduced tissue risk of infarction. Koch and colleagues have been examining the effects of RIPC in relation to subarachnoid hemorrhage and have shown general safety and some biochemical evidence of efficacy [23, 24].

While the clinical effects of RIPC in the brain in relation to stroke are only now being investigated, there has been a much greater history of clinical trials of RIPC in the heart (for recent reviews, see [25, 26]). The results of those trials have been inconsistent with no definitive proof of benefit. These inconsistent outcomes suggest that there may be icebergs that brain RIPC may need to avoid.

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A major concern in the cardiac field has been the potential effects of anesthesia on RIPC efficacy in relation to surgery [25–27]. Volatile anesthetics (e.g., isoflurane) can induce preconditioning, and therefore, patients treated with this anesthetic may not be further preconditioned with RIPC [25]. There has been a particular concern over the use of propofol for cardiac surgery and whether that anesthetic blocks RIPC [28]. Beta-blockers are also used in cardiac surgery, and there is evidence that they may block the effects of RIPC [26]. Such effects may complicate the assessment of RIPC in patients that will undergo anesthesia.

In the cardiac field, there are concerns over the potential interaction of RIPC with currently approved therapies, such as cardioplegia, hypothermia, and potassium chloride, which may reduce efficacy [25]. With the dearth of clinically approved treatments for stroke, this is not a concern for acute neuroprotection. Hougaard et al. [20] have examined the effect of remote preconditioning as an adjunct therapy for thrombolysis in ischemic stroke patients and found some limited evidence of protection (see above). Whether there is any interaction between RIPC and treatments designed to prevent stroke occurrence is largely unstudied.

A concern in both the heart and brain field is that some patients may be already preconditioned, limiting the effect of applied RIPC. Examples of such potential preconditioning include the effects of surgical incisions [25] and underlying vascular disease. Recently, Connolly et al. [29] found that patients with pre-existing arterial peripheral vascular disease may be protected from acute ischemic stroke. This might be a result of limb hypoperfusion having similar effects to RIPC.

There are still concerns about the impact of comorbid conditions on the efficacy of ischemic preconditioning and possibly RIPC. In particular, studies suggesting that aging reduces the efficacy of preconditioning [30] are a concern considering that stroke occurrence increases in the elderly. One reason for studying RIPC in subarachnoid hemorrhage is that it generally occurs in younger individuals than ischemic stroke [31].

Another concern has recently been raised in the heart at the opposite end of the age spectrum. Schmidt et al. [32] found that prior RIPC increased rather than reduced myocardial injury in the isolated neonatal rabbit. This finding merits further investigation in relation to the use of RIPC for neonatal heart surgery and if ever RIPC were considered for babies at risk for cerebral hypoxia/ischemia at birth.

While clinical trials on RIPC are full steam ahead, there continues to be a relative dearth of preclinical studies (~25 studies since 2006). This may be a case of waiting to see how clinical trials fare, but such preclinical studies could help to inform such trials. Greater elucidation of the mechanisms underlying RIPC may help in understanding how comorbidities and clinical practice (e.g., anesthetics) could impact the effectiveness of RIPC.

In short, this is an exciting time for research in remote ischemic preconditioning. However, definitive clinical evidence of the efficacy of this approach is still in the future and there may be a number of icebergs to avoid in pursuing that goal.

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