Remote Ischemic Conditioning: Increasing the Pressure for Rigorous Efficacy Trials

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Remote ischemic conditioning (RIC) is a treatment strategy aiming to protect distant organs, such as the brain, from ischemic injury.[1] It consists of delivering repetitive, transient, noninjurious ischemia to a limb through a blood pressure cuff.[1] RIC is based on the concept that distant transient episodes of limb ischemia will initiate signals that will translate at the brain level as an increase in blood flow and mitochondrial protection.[1] The way such signals are transmitted, however, is poorly understood. The involvement of humoral mediators, including chemokines and nitric oxide (NO) and immune, anti-inflammatory, and neural mechanisms have all been proposed.[1–4] We are in need for additional stroke treatments, in particularly interventions that could synergize with intravenous thrombolysis and mechanical thrombectomy to improve patient outcomes.[5] RIC, perconditioning to be exact because the treatment has to be initiated while the patient is undergoing brain ischemia, is an appealing treatment strategy for acute ischemic stroke. The use in stroke is supported by strong preclinical evidence of its effectiveness,[6] including using animal models with comorbidities and accounting for sex differences and the interaction with intravenous thrombolysis,[7] all of which aligns with the recommendations to advance neuroprotective therapies.[8] RIC is simple to deliver and deemed safe in clinical trials in patients with acute ischemic stroke.[9] It was well tolerated in a variety of acute stroke settings, and there were no signs of neurologic injury, deep venous thrombosis, or coagulopathy associated with the intervention.[9–11] Although those preliminary results are promising, more data are needed before RIC could be adequately tested for efficacy in large trials.

In this issue of the *Journal of the American Heart Association* (*JAHA*), England et al address some of the issues needed to further advance stroke clinical trials of RIC.[12] They report the results of a phase 2b 2-center, randomized, placebo-controlled trial in which they specifically address feasibility and maximum tolerated dose of RIC.[12] They randomized 60 patients with acute ischemic stroke <6 hours from symptom onset to receive RIC or sham/control. All subjects were placed on a pressure cuff, which was manually operated by trained staff aware of their group assignment. Each treatment session consisted of 4 cycles of 5 minutes of cuff inflation, alternating with 5 minutes of cuff deflation. In the active RIC group, the cuff was inflated to 20 mm Hg above systolic blood pressure, whereas in the sham/control group, it was inflated to <30 mm Hg. The first 20 participants received only 1 treatment session. The next set of 20 patients received 2 treatment sessions 1 hour apart. The last 20 patients received 2 sessions a day, up to a total of 8. The primary outcome measures chosen were those of trial efficiency, whereas tolerability and safety of RIC, laboratory measures, and functional outcome measures were secondary outcomes in this trial. In an attempt to establish biomarkers for RIC, the authors measured S100-ß protein, matrix metalloproteinase-9, and neuron-specific enolase at day 1 and day 4.[12]

This trial showed reasonable efficiency by enrolling an average rate of 1.5 subjects per month/center. Previous trials that studied RIC in acute ischemic stroke were single-center trials that recruited at a rate that ranged from 1 to 29 patients per month.[9,11,13] These findings are supportive of the feasibility of conducting a large multicenter trial. The blinding of the RIC intervention appeared to work for the subjects, as shown by their responses in exit interviews. This is encouraging and suggests that a strategy that uses automated cuff devices could keep both researchers and subjects blinded. Using automated devices of delivering RIC is important not only to preserve the blinding of the experiment, but to reduce operator variability and standardize the intervention. RIC appeared to be well tolerated, as shown by the lack of difference in cuff inflation duration or adherence between the active treatment and sham groups. Adherence decreased after day 2 for both groups,

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perhaps suggesting logistical barriers rather than a RIC-specific intolerability. The trial design, however, could not inform whether patients could tolerate higher doses than 2 sessions per day because that was the maximum daily dose received. Most trials that studied RIC in the setting of stroke used 5-minute cycles of cuff inflation, alternating with 5 minutes of deflation.[14] The number of cycles per session varied between 4 and 5.[14] The number of sessions ranged between 1 and 2 per day, while the number of treatment days varied widely, with more treatment days applied in trials on nonacute strokes.[14,15] The uncertainty about the maximal dose of RIC that can be tolerated per day in acute stroke is a potential concern for future trial design. It may raise concerns of undertreating patients with an intervention that is deemed safe.

In fact, this trial endorsed the safety of RIC in the acute stroke setting. There were no major adverse events, including no episodes of limb ischemia, venous thromboembolism, neurovascular limb damage, or tissue injury. The safety of the intervention in the acute stroke setting is reassuring, but not surprising. After all, RIC is being used as a long-term exposure in patients with intracranial atherosclerosis, with safety and effectiveness in this group of patients.[14,15] Another contribution of this trial is the pursuit of adequate biomarkers for RIC. This is a limitation of RIC, and the identification of valid biomarkers would facilitate the development of rigorous clinical trials while informing about the mechanism of action. One of the surrogates of brain injury collected, protein S100-ß, increased between day 1 and 4 in the placebo group but not in the RIC-treated group. This finding is promising, but perhaps limited by the lack of a dose-response with RIC, as well as the lack of comparative neuroimaging.

Functional measures and stroke recurrence rates were considered as secondary outcomes. The trial did not show any benefit on the modified Rankin Scale at 3 months, recurrent ischemic events, or hemorrhagic transformation. These exploratory variables were likely underpowered in a pilot trial. Other small trials failed to show improvements in functional outcome as well. Still, the modified Rankin Scale scores at 3 months show a nonsignificant mild shift in favor of RIC, which could be used to inform a sample size determination in future trials. Similarly, the trial showed a nonsignificant trend toward fewer recurrent events. This is consistent with observations in the setting of intracranial atherosclerosis, where RIC has been shown to lower incidence of recurrent strokes and has led to shorter time to recovery.[14,15]

In conclusion, the trial of England and colleagues[12] is an important contribution to the emerging field of RIC. It proves it is feasible to conduct such a trial in an acute ischemic stroke setting with safety. It shows that the tolerability of this intervention is good but limited to the first 2 days. This suggests that future clinical trials should focus on delivering the intervention in that early time period. Still, the study has limitations, and the jump from feasibility pilot studies into large efficacy trials is a large one. Given the proven safety of RIC, one approach is to proceed with efficacy trials with the hope that a large sample could compensate for the remaining uncertainties and variability. In fact, several trials are currently underway.[16,17] Such a pragmatic approach, however, has risks. The magnitude of effect of this intervention would need to be better defined to avoid underpowered trials. We must ensure that the maximal tolerated dose is used to dissipate any future concerns of undertreatment. We also need adequate humoral and imaging biomarkers, not only to guide future trial design, but also our mechanistic understanding of this therapy. That includes identifying a subgroup of patients with acute stroke who is more likely to benefit from this therapy. This could be based on their clinical presentation, presumed stroke mechanism, size of ischemic core, presence of ischemic penumbra and arterial status, or successful reperfusion. Otherwise, we risk unfairly dismissing a simple, promising, and unusually low-risk intervention that could help patients with ischemic stroke in a variety of clinical settings.

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