Review Article

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Website: http://www.braincirculation.org

DOI: 10.4103/2394-8108.186260

Rationale for ischemic conditioning to prevent stroke in patients with intracranial arterial stenosis

Sami Al Kasab, David C Hess[1], Marc I Chimowitz

Abstract:

Intracranial atherosclerotic arterial stenosis (ICAS) is one of the most common causes of stroke worldwide and is associated with particularly a high risk of recurrent stroke. Although aggressive medical management, consisting of dual antiplatelet therapy and intensive control of vascular risk factors, has improved the prognosis of patients with ICAS, subgroups of patients remain at very high risk of stroke. More effective therapies for these high-risk patients are urgently needed. One promising treatment is remote limb ischemic conditioning, which involves producing repetitive, transient ischemia of a limb by inflating a blood pressure cuff with the intention of protecting the brain from subsequent ischemia. In this study, we review the limitations of currently available treatments, discuss the potential mechanisms of action of ischemic conditioning, describe the preclinical and clinical data suggesting a possible role of ischemic conditioning in treating patients with ICAS, and outline the questions that still need to be answered in future studies of ischemic conditioning in subjects with ICAS.

Key words:

Intracranial atherosclerosis, ischemic conditioning, stroke

Introduction

Intracranial atherosclerotic arterial stenosis (ICAS) is responsible for 6–10% of ischemic strokes in whites, 6–29% in blacks, 11% in Hispanics, and 20–50% in Asians.[1-14] In the US, ICAS causes ~50,000 strokes per year (i.e., 8–10% of the 675,000 ischemic strokes per year)[15] at a cost of $7,50,000,000 in year 1 and $4.5 billion over the lifetime of these patients.[16] The worldwide burden of ICAS is enormous as it is especially prevalent in Asian, Hispanic, African, and Arabic countries, as well as in India and Pakistan.[7-12] In addition to being a common cause of stroke, ICAS also is associated with a higher risk of recurrent stroke compared with most other cerebrovascular diseases.[17-22]

Review of Previous ICAS Trials and Limitations of Current Treatments

The Warfarin Aspirin Symptomatic Intracranial Disease (WASID) stenosis trial showed that aspirin was safer and as effective as warfarin for preventing stroke in subjects with 50–99% ICAS who had a transient ischemic attack or stroke within 90 days before enrollment and that good control of blood pressure (BP) and low-density lipoprotein cholesterol (LDL) were associated with a lower risk of stroke.[23,24] Subjects with 70–99% stenosis whose qualifying event occurred within 30 days before enrollment were at highest risk of stroke.[25]

In the subsequent stenting and aggressive medical management for preventing recurrent ischemic stroke (SAMMPRIS) trial, subjects with 70–99% stenosis and a qualifying TIA or stroke within 30 days before enrollment were randomized to aggressive medical management (AMM) alone versus AMM plus stenting with the Wingspan stent system. AMM consisted of dual antiplatelet therapy (aspirin and clopidogrel) for 90 days after enrollment followed by aspirin alone in combination with intensive risk factor management (primarily targeting systolic BP (SBP) <140 mmHg and LDL cholesterol <70 mg/dL) and a lifestyle program.[26] Enrollment in SAMMPRIS was stopped early because of higher than expected rate of periprocedural stroke in the stenting group (14.7% at 30 days [10.2%, ischemic stroke and 4.5%, hemorrhagic stroke]) and much lower than projected rate of stroke in the medical group. The absolute risk reduction

Department of Neurology, Medical University of South Carolina, Charleston, SC 29425, [1]Department of Neurology, Medical College of Georgia, Augusta University, Augusta, GA, USA

Address for correspondence:
Dr. Sami Al Kasab, Department of Neurology, 96 Jonathan Lucas St., CSB 301.MSC 606, Charleston, SC 29425-6160, USA.
E-mail: alkasab@musc.edu

Submission: 04-05-2016
Revised: 12-05-2016
Accepted: 19-05-2016

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How to cite this article: Al Kasab S, Hess DC, Chimowitz MI. Rationale for ischemic conditioning to prevent stroke in patients with intracranial arterial stenosis. Brain Circ 2016;2:67-71.

from medical therapy alone was 8.9% at 30 days and 9.0% at 3 years, indicating that there was no benefit from stenting beyond the periprocedural period.[26,27]

While the 1-year rate of the primary endpoint (any stroke or death within 30 days of enrollment or stroke in the territory beyond 30 days) in the AMM arm of SAMMPRIS was almost 50% lower than the projected rate, this reduction was driven by particularly a low event rate in subjects whose qualifying event for SAMMPRIS was a TIA (1-year primary endpoint rate of 5.6%).[28] In comparison, the 1-year rate of the primary endpoint in subjects in the AMM arm whose qualifying event for the trial was a stroke was 16.1%.[28] Additional WASID and SAMMPRIS analyses show that subjects with border zone infarcts on baseline imaging had a high frequency of impaired collaterals on cerebral angiography and were at highest risk of recurrent symptomatic infarct during follow-up.[29,30] Moreover, the recently completed VERITAS study of subjects with vertebrobasilar stenosis showed that impaired blood flow distal to the stenosis also was a strong predictor of recurrent stroke.[31] These findings indicate that hemodynamic factors (impaired distal blood flow and incomplete or absent collaterals) play an important role in the pathophysiology of stroke in ICAS patients and are important therapeutic targets for newer and more effective therapies for high-risk patients. One novel treatment that has emerged as a safe and potentially effective treatment for ICAS is remote limb ischemic conditioning (RLIC).

Possible Mechanisms of Action of Remote Limb Ischemic Conditioning

While the protective mechanisms of action of RLIC are uncertain, Rassaf *et al*. recently provided strong evidence that circulating plasma nitrite is a key mediator.[32] Studies using pharmacological blockade and genetic deletion techniques in rats showed that RLIC increased nitrite levels in plasma and confirmed that endothelial nitric oxide synthase-mediated upregulation of nitric oxide (NO) and conversion to nitrite are required for the protective effect.[32] Additional transfer experiments of plasma from healthy human subjects who underwent RLIC identified plasma nitrite as a cardioprotective agent in isolated Langendorff mouse heart preparations exposed to ischemia and reperfusion.[32] Nitrite provides a storage pool of NO that circulates in the blood associated with red blood cell/hemoglobin and is reduced to NO in areas of hypoxemia, mediating hypoxic vasodilatation, and increased blood flow.[33] Given that impaired collateral flow distal to ICAS was strongly associated with an increased risk of stroke in WASID and SAMMPRIS subjects, these preclinical findings suggest that if RLIC is effective in ICAS patients, the mechanisms may be related to increased plasma nitrite levels and improved cerebral blood flow (CBF). Nitrite also is involved in the nitrosylation of key mitochondria proteins, so increased nitrite levels may also be cytoprotective.[32]

Rationale for Evaluating Remote Limb Ischemic Conditioning in Subjects with ICAS

The scientific rationale for evaluating RLIC for stroke prevention in patients with ICAS rests on four lines of evidence: (1) Common mechanisms of action between RLIC and exercise, which was the most important predictor of a good outcome in the medical arm in SAMMPRIS; (2) preclinical data of the protective effect of RLIC in animal models of stroke and cardiac injury; (3) results of randomized trials evaluating RLIC in subjects with myocardial ischemia; and (4) two strikingly positive small pilot randomized clinical trials of RLIC in ICAS subjects performed in China.

Remote limb ischemic conditioning, exercise and stenting and aggressive medical management for preventing recurrent ischemic stroke

Exercise is a powerful cardio- and neuro-protectant that triggers an ischemia-resistant phenotype, similar to RLIC.[34-41] In a trial of healthy humans, dialysates prepared from plasma of subjects undergoing either vigorous exercise or RLIC were both protective in an isolated rabbit heart preparation and both were blocked by naloxone, suggesting that common humoral mediators of organ protection are shared by exercise and RLIC.[41] In SAMMPRIS, analyses of the impact of risk factor control on outcome showed that 3 factors were associated with significantly lower rates of stroke, myocardial infarction (MI), or vascular death in the AMM group: Achieving targets for (1) SBP (hazard ratio [HR]: 0.53, confidence interval [CI]: 0.31–0.93), (2) LDL (HR: 0.53, CI: 0.30–0.94), and (3) exercise (HR: 0.25, CI: 0.12–0.50).[42] In multivariable analyses, achieving SBP and LDL targets was significant only if exercise was not in the model ($P = 0.047$ and 0.040, respectively). With exercise in the model, only exercise was significant ($P < 0.0001$). Moreover, exercise was the only variable associated with a significantly lower risk of stroke (HR: 0.22, CI: 0.10–0.50).[42] Since RLIC and exercise may share common protective mechanisms, these *post hoc* data on the protective effect of exercise in SAMMPRIS provide indirect evidence of the potential of RLIC to prevent stroke in patients with ICAS.

Preclinical evidence

Although there are no animal models for ICAS, RLIC has been studied in a bilateral carotid artery stenosis (BCAS) model in the mouse. Khan *et al*. placed microcoils around the internal carotid arteries to produce stenosis and on day 7, began daily RLIC using a conditioning device applied to one of the mouse's hind limbs until day 21.[43] RLIC increased CBF at 21 days, as measured by laser speckle contrast imaging, and CBF remained elevated at 28 days, 1 week after cessation of conditioning. In addition, the mice randomized to RLIC had improved cognition at 28 days as well as less inflammation and reduced damage of the white and gray matter when sacrificed at 28 days compared with mice randomized to sham RLIC.[43] Other preclinical work using RLIC with acute ischemic stroke models shows that CBF increases within 6–24 h of treatment.[44-46] Hess *et al*. tested the hypothesis that upregulation of nitrite might explain the increase in CBF seen after RLIC in the BCAS model.[47] They compared plasma nitrite levels (measured by ozone-chemiluminesence [GE Sievers NOA 280]) at 28 days postcoiling in three groups of mice: Bilateral carotid sham coiling, coiling and sham RLIC, and coiling with RLIC. Coiling alone (sham RLIC) reduced plasma nitrite but coiling with RLIC applied for 2 weeks significantly increased plasma nitrite [Figure 3], which remained elevated 1 week after RLIC was stopped indicating a sustained effect.[47]

Trials of remote limb ischemic conditioning for myocardial ischemia

A meta-analysis of several small randomized cardiac clinical trials of RLIC showed that RLIC reduced the incidence of MI and troponin release.[48] In addition, RLIC effectively reduced myocardial injury when used just once (inflation of the BP cuff to 200 mm Hg for 5 min followed by reperfusion for 5 min, repeated for 4 cycles) in the prehospital setting in ST elevation MI patients before percutaneous coronary interventions (PCIs).[49] In a meta-analysis of 11 small PCI trials, RLIC reduced perioperative MI and acute kidney injury.[50] Moreover, some of these studies showed that just one RLIC treatment before PCI reduced long-term mortality and major cardiac and cerebrovascular events.[48,51-53] In one of these studies, 333 patients with a suspected acute ST-elevation MI were randomized to PCI with (n = 166) or without (n = 167) RLIC. RLIC was initiated in the ambulance during transport to the interventional center and was achieved by performing 4 cycles of 5 min inflation followed by 5 min deflation of BP cuff. In the per-protocol analysis of 251 patients fulfilling trial criteria, a major adverse cardiac or cerebrovascular event occurred in 17 (13.5%) of patients in the intervention group compared with 32 (25.6%) patients in the control group (HR: 0.49, 95% CI: 0.27–0.89, P = 0.018) during a median follow-up of 3.8 years.[51]

On the other hand, two recent trials that evaluated RLIC treatment just once before cardiac bypass surgery did not show a benefit of RLIC for preventing major vascular events at 90 days or 1 year.[54,55] However, one possible reason for the lack of benefit of RLIC in these two trials is that propofol, which was used for general anesthesia in most of these subjects (but not in the earlier small cardiac studies), is known to counteract the effects of RLIC.[56,57]

Pilot trials of remote limb ischemic conditioning in China

The most compelling rationale for further evaluating RLIC in patients with ICAS emerges from two small completed Chinese randomized trials.[58,59] In the first Chinese trial, subjects aged 18-80 years with TIA or stroke attributed to 50–99% ICAS were randomized to bilateral upper extremity (BUE) conditioning twice daily for 300 days (n = 38) or standard medical management alone (n = 30). The RLIC group had a significant reduction in the incidence of recurrent strokes at both 90 days (5% vs. 23.3%) and 300 days (7.9% vs. 26.7%, a 70% relative risk reduction, P < 0.01), and increased CBF as measured by single photon emission computed tomography and transcranial Doppler compared with the control group.[58]

In the second trial, 58 subjects aged 80–95 with symptomatic 70–99% ICAS were randomized to BUE RLIC twice daily (n = 30) or sham BUE RLIC twice daily (n = 28) for 180 days. All subjects also received standard medical management. Compared with sham RLIC, active RLIC elevated plasma tissue plasminogen activator and reduced plasma high sensitive C-reactive protein, interleukin-6, plasminogen activator inhibitor-1, leukocyte count, and platelet aggregation rate (all P < 0.01) at 30 days. By 180 days, 2 infarctions and 7 TIAs were observed in the active RLIC group compared with 8 infarctions and 11 TIAs in the sham group (P < 0.05).[59] These data provide the best available direct evidence on the potential efficacy of RLIC in subjects with ICAS. In addition, the results of these Chinese trials also suggest that the protective mechanism of RLIC may be related to multiple mechanisms, including increasing CBF as well as anti-inflammatory and antithrombotic effects.

The Chinese group also recently reported the results of a randomized trial in 189 subjects that evaluated the role of RLIC twice daily for 2 weeks before extracranial carotid stenting for limiting the number and size of new cerebral ischemic lesions detected by magnetic resonance imaging (MRI) 48 h after the procedure. All MRI studies were evaluated by readers who were blinded to the subjects' treatment assignments. Subjects who underwent RLIC before carotid stenting had a significantly lower incidence of new lesions (19.2% in the RLIC group vs. 46.4% in the control group; relative risk 0.41; 95% CI: 0.22–0.77; P = 0.003) and significantly smaller median volume of lesions (P < 0.01) than subjects in the control arm who did not undergo RLIC.[60]

Unresolved Research Questions Regarding Remote Limb Ischemic Conditioning

While the results of these preclinical studies, some of the cardiac clinical trials, and the Chinese RLIC clinical trials in subjects with ICAS are encouraging, several key research questions regarding RLIC remain unresolved: (1) What is the optimal duration (in days) and frequency of RLIC for preventing stroke? (2) Is there evidence of potential efficacy of RLIC compared with AMM for preventing stroke? This is an important issue because the medical management in the Chinese trials used standard medical treatment and not the aggressive medical regimen used in SAMMPRIS, which is the new standard of care for patients with ICAS. (3) Are CBF and select biomarkers (vasodilatory, inflammatory, fibrinolytic, and microRNA) valid indicators of the conditioning response? (4) Is RLIC durable, i.e., will any changes in CBF and biomarkers be maintained after RLIC treatment ends? Future studies are needed to address these key questions before a definitive Phase III trial comparing AMM alone versus AMM plus RLIC can be undertaken.

Conclusion

Subgroups of patients with ICAS remain at high risk of recurrent stroke despite AMM. Therefore, more effective therapies for these high-risk patients remain an urgent need. RLIC has promise as a noninvasive treatment option for patients with ICAS; however, further studies are needed before a definitive Phase III trial can be undertaken in the United States comparing AMM alone versus AMM plus RLIC. Since the risk of recurrent stroke in ICAS patients is highest in the first few months after a stroke, a Phase III trial that established the efficacy of RLIC would likely be widely accepted by patients and physicians because RLIC would not have to be used indefinitely (unlike many medications), which is very attractive to patients. In addition, this device could be applied while a subject is performing sedentary activities (e.g., reading, watching television, or listening to music). RLIC devices can record correct use, providing reliable data on treatment adherence in practice, which is difficult to obtain with medications. A positive Phase III trial for RLIC would not only improve the outcome of high-risk patients with

ICAS but also lead to paradigm-shifting treatment of other cerebrovascular diseases (e.g., extracranial carotid stenosis, small vessel disease, vascular cognitive impairment, and subarachnoid hemorrhage).[61]

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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