ANNALS of Clinical and Translational Neurology
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REVIEW ARTICLE

Remote ischemic conditioning for stroke: clinical data, challenges, and future directions

Wenbo Zhao[1], Sijie Li[2], Changhong Ren[2], Ran Meng[1], Kunlin Jin[2,3] & Xunming Ji[2,4]

[1]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China
[2]Beijing Key Laboratory of Hypoxic Conditioning Translational Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China
[3]Center for Neuroscience Discovery, Institute for Healthy Aging, University of North Texas Health Science Center, Fort Worth, Texas
[4]Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China

Correspondence
Xunming Ji, Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, No. 45, Changchun Street, Xicheng District, Beijing, 100053, China. Tel: 011 86 10 8319 8952; Fax: 011 86 10 8315 4745; E-mail: jixm@ccmu.edu.cn

Funding Information
This study was supported by the National Key R&D Program of China (No. 2017YFC1308405), Chang Jiang Scholars Program (No. T2014251), and the Capital Health Research and Development of Special (No. 2016-4-1032).

Received: 27 August 2018; Revised: 11 October 2018; Accepted: 15 October 2018

Annals of Clinical and Translational Neurology **2019; 6(1): 186–196**

doi: 10.1002/acn3.691

Abstract

Despite great improvement during the past several decades, the management of stroke is still far from satisfactory, which warrants alternative or adjunctive strategies. Remote ischemic conditioning (RIC), an easy-to-use and noninvasive therapy, can be performed in various clinical scenarios (e.g., prehospital transportation, intrahospital, and at home), and it has been widely investigated for stroke management. RIC has been demonstrated to be well tolerated in patients with acute ischemic stroke and aneurysm subarachnoid hemorrhage, and it may benefit these patients by improving clinical outcomes; in patients with intracranial atherosclerosis, long-term repeated RIC could be safely performed and benefit patients by reducing recurrent ischemic stroke and transient ischemic attack, as well as improving cerebral perfusion status; long-term repeated RIC may also benefit patients with cerebral small vessel disease by slowing cognitive decline and reducing volume of white matter hyperintensities on brain MRI; in patients with severe carotid atherosclerotic stenosis undergoing stenting, preprocedural RIC could reduce the odds of new brain lesions on postprocedural MRI. Previous clinical studies suggest broad future prospects of RIC in the field of cerebrovascular diseases. However, the optimal RIC protocol and the mechanisms that RIC protects the brain is not fully clear, and there is lack of sensitive and specific biomarkers of RIC, all these dilemmas prevent RIC from entering clinical practice. This review focuses on recent advances in clinical studies of RIC in stroke management, its challenges, and the potential directions of future studies.

Introduction

Stroke has become the second leading cause of death and the third leading cause of disability worldwide, and its disease burden continues to increase.[1,2] Although most strokes are preventable by modifying its risk factors,[3] the preventive strategies never fully implemented despite advocating during the past three decades.[4,5] In addition, there are several therapeutic strategies for ischemic stroke, but only a small number of patients can receive these therapies. Significant costs and potential side effects associated with some of these strategies may be the most important reasons.[5] What is worse, few therapeutic strategies are available for hemorrhagic stroke. All these issues create a need for cost-effective alternative or adjunctive strategies for stroke management.

Remote ischemic conditioning (RIC), which evolves from ischemic preconditioning,[6] is a systemic protective strategy in which one or more cycles of brief focal ischemia followed by reperfusion confers protection against subsequent, more severe ischemia in distant organs.[7] After decades of development, RIC is now generally performed on limbs with blood pressure cuffs inflated to a pressure that blocks limbs blood perfusion.[8–10] The mechanisms by which RIC protects the brain are not fully clear, but it has been demonstrated to increase cerebral tolerance to ischemic injury,[11] reduce the risk of cerebral infarction,[12,13] improve cerebral perfusion status,[12] and promote the formation of cerebral collaterals.[14] RIC can be applied in various clinical scenarios that have been widely investigated in patients with both ischemic and hemorrhagic stroke,[8,15,16] and the results suggest broad future

prospects. In comparison to conventional treatments, RIC is noninvasive, easy-to-use, and cost effective; its safety and feasibility make it promising for clinical investigation and application.

In this review, we focus on current clinical studies of RIC in stroke management (Table 1), analyze its challenges, as well as propose directions for future research studies.

Acute Ischemic Stroke

Acute ischemic stroke (AIS) is caused by occlusion of cerebral vessels, so early restoration of blood flow is the most effective therapy.[17] Currently, intravenous thrombolysis and endovascular therapy are the standard approaches for revascularization therapy. More recently, several large randomized controlled trials (RCTs) have demonstrated the superiority of endovascular therapy compared with intravenous thrombolysis for AIS, with a high rate of revascularization (60–90%) and improved functional outcome.[18–21] However, despite the significant improvement, there remains considerable room for further improvement, and novel modes of treatment are needed as well. Among other approaches, RIC has been investigated as an adjunctive therapy for patients with AIS.

A proof-of-concept RCT tested the effect of prehospital RIC as adjunctive therapy for AIS patients (≥18 years old) who were candidates to receive intravenous thrombolysis within 4.5 h of symptom onset.[11,22] Four cycles of RIC stimulus were performed by ambulance staff during transportation and, if not completed, the procedure was discontinued on arrival at the stroke unit. The final infarction lesions were measured on 1-month T2 fluid-attenuated inversion recovery scans, while penumbral salvage was quantified by identifying the tissue voxels in the volume difference between perfusion- and diffusion-weighted imaging at baseline. Among patients with confirmed AIS who received intravenous thrombolysis, there was no difference between the RIC (n = 91) and the control (n = 80) groups with respect to penumbral salvage, final infarct size, infarct growth over baseline, or clinical outcome at 3 months. However, subgroup analysis showed that RIC reduced the risk of infarction in brain tissue with elevated diffusion-weighted image intensity.

Another RCT (RECAST-1) investigated RIC in patients with AIS within 24 h of ictus, excluding those receiving intravenous thrombolysis, with severe disability (modified Rankins Scale score >3), and significant comorbidity.[23] Twenty-six patients with AIS were recruited and allocated to receive four cycles of RIC stimulus or sham RIC stimulus in the nonparetic arm; all patients completed the study. Results showed that RIC was safe and feasible in this patient population and 90-day National Institutes of Health Stroke Scale scores were significantly lower in those receiving RIC.

A phase I study (REVISE-1) investigated RIC in patients with anterior circulation stroke who were treated with endovascular thrombectomy within 6 h of ictus.[24] Twenty patients were recruited and underwent once RIC pre- and post-thrombectomy, respectively, and once daily for 7 consecutive days. Results showed that RIC was well tolerated and feasible in this patient population, it had no significantly influence on the vital signs (i.e., blood pressure and heart rate), intracranial pressure, cranial prefusion pressure, and the peak velocity of middle cerebral artery.

RIC may be endowed promising future for AIS patients, especially for those treated with reperfusion therapies (i.e., intravenous thrombolysis and endovascular therapy). However, the overall results of the study investigating RIC in patients treated with intravenous thrombolysis were neutral.[11] Some methodological limitations may be associated with the results, but the low rate of recanalization rate (20–30%) in this patient population may be another main reason. Although remote ischemic perconditioning during the transportation may be able to preserve the salvageable tissue for reperfusion therapy, if the occluded arteries are not recanalized, the salvaged cerebral tissue will infarct eventually. Therefore, AIS patients receiving endovascular therapy might be the optimal candidates to investigate the neuroprotective effects of RIC as endovascular therapy is capable of recanalizing the occluded artery at a much higher rate (60–90%).

Based on the studies described above, AIS may be a promising research field, and several clinical trials are now ongoing. A multicenter RCT is underway to further evaluate the efficacy of RIC for patients with AIS, within 6 h of ictus,[25] and another multicenter RCT (RESIST, NCT03481777) is ongoing to investigate the efficacy of RIC in patients with acute stroke (including both ischemic and hemorrhagic stroke within 4 h of ictus). Furthermore, RECAST-2 (NCT02779712) and REMOTE-CAT (NCT03375762) have also been registered to investigate the efficacy of RIC in AIS patients within 6 h and 8 h of ictus, respectively. All the above four studies include patients undergoing endovascular therapy. Additionally, REVISE-2 (NCT03045055) and RICE PAC (NCT 03152799) have been registered to specifically investigate RIC in AIS patients treated with endovascular therapy.

Intracranial Atherosclerosis

Intracranial atherosclerosis (ICAS) is one of the leading causes of ischemic stroke worldwide, especially in Asian countries, where it accounts for 33–67% of strokes and

Table 1. Clinical studies of remote ischemic conditioning in stroke.

Study	*n*	Type of patients	RIC protocol	Main results	Type	Status
AIS						
Hougaard et al. (2014)[11]	274/196	Patients with suspected AIS	1 4 × 5 min inflations/deflations of cuff on one arm 2 Cuff pressure: 200 mmHg or 25 mmHg above systolic pressure 3 Times: Once during transportation to hospital	RIC was safe, feasible, and may reduce tissue risk of infarction in AIS patients receiving intravenous thrombolysis	Phase 3	Completed
England et al. (2017)[23]	13/13	Patients with AIS of 24 h of ictus	1 4 × 5 min inflation/deflation of cuff on one arm 2 Cuff pressure: 20 mmHg above systolic pressure 3 Times: Once within 24 h of ictus	RIC was safe, feasible, and may improve neurological outcome in AIS patients	Not applicable	Completed
Zhao et al. (2018)[24]	20	Anterior circulation stroke patients treated with ET	1 4 × 5 min inflation/deflation of cuff on one arm 2 Cuff pressure: 200 mmHg 3 Times: Once pre-ET and post-ET, respectively, and once daily for 7 consecutive days	RIC was safe and feasible in AIS patients undergoing thrombectomy	Phase 1	Completed
RESCUE-BRAIN	100/100	AIS patients within 6 h of ictus	1 4 × 5 min inflation/deflation of cuff on one arm 2 Cuff pressure: 110 mmHg above systolic pressure 3 Times: Once prehospital	No available	Not applicable	Ongoing
RESIST	2500	Patients with acute stroke (including both ischemic and hemorrhagic stroke) within 4 h of ictus	1 5 × 5 min inflations/deflations of cuff on one arm 2 Cuff pressure: 200 mmHg or 35 mmHg above systolic pressure if the systolic pressure is above 175 mmHg 3 Times: Once prehospital, 6 h later in-hospital, and twice daily for 7 days	No available	Not applicable	Ongoing
REMOTE-CAT	286/286	AIS patients within 8 h of ictus	1 5 × 5 min inflation/deflation of cuff on one arm 2 Cuff pressure: unclear 3 Times: Once prehospital	No available	Not applicable	Ongoing
RECAST-2	30/30	AIS patients within 6 h of ictus	1 4 × 5 min inflation/deflation of cuff on one arm 2 Cuff pressure: 20 mmHg above systolic blood pressure 3 Times: Once, again one hour after first treatment, or twice daily until day 4	No available	Phase 2	Ongoing
RICE PAC	30/30	Anterior circulation stroke patients treated with ET	1 Unclear 2 Times: Once at time of revascularization and then daily for 7 days	No available	Phase 1	Ongoing
REVISE-2	90/90	Anterior circulation stroke patients treated with ET	1 4 × 5 min inflation/deflation of cuff on one arm 2 Cuff pressure: 200 mmHg 3 Times: Once pre-ET and post-ET, respectively, and once daily for 3 consecutive days	No available	Phase 2	Ongoing

(*Continued*)

Table 1. Continued.

Study	*n*	Type of patients	RIC protocol	Main results	Type	Status
ICAS						
Li et al. (2015)[30]	34	10 patients with ICAS24 healthy volunteers	1 5 × 5 min inflation/deflation of cuff on both arms 2 Cuff pressure: 200 mmHg 3 Times: Once	RIC was safe and feasible in ICAS patients.	Not applicable	Completed
Meng et al. (2012)[12]	51/52	Symptomatic ICAS (age <80 years)	1 5 × 5 min inflations/deflations of cuff on both arms 2 Cuff pressure: 200 mmHg 3 Times: Twice daily for 300 days	RIC improved cerebral perfusion and reduced stroke recurrence	Phase 2	Completed
Meng et al. (2015)[13]	40/39	Symptomatic ICAS (age 80–95 years)	1 5 × 5 min inflations/deflations of cuff on both arms 2 Cuff pressure: 200 mmHg 3 Times: Twice daily for 180 days	RIC safe and effective in inhibiting stroke recurrence	Phase 2	Completed
Hou et al. (2016)[31]	1500/1500	Symptomatic ICAS (age <80 years)	1 5 × 5 min inflation/deflation of cuff on both arms 2 Cuff pressure: 200 mmHg 3 Times: Twice daily for 360 days	No available	Phase 3	Ongoing
EPIC-sICAS	50/50	Symptomatic ICAS (age 18–45 years)	1 Five cycles of 3 min inflation and 5 min deflation of cuff on both arms 2 Cuff pressure: 180 mmHg 3 Times: Twice daily for 180 days	No available	Not applicable	Ongoing
PICASSO	5/5	Symptomatic ICAS (age 30–90 years)	1 4 × 5 min inflation/deflation of cuff on both arms 2 Cuff pressure: 200 mmHg 3 Times: Once daily for 30 days	No available	Not applicable	Ongoing
CAS and CEA						
Zhao et al. (2017)[39]	63/63/63	Carotid artery stenosis patients undergoing CAS	1 5 × 5 min inflation/deflation of cuff on both arms 2 Cuff pressure: 200 mmHg 3 Times: Twice daily for 2 weeks	RIC reduced incidence of new brain lesion on MRI after CAS	Phase 2	Completed
Walsh et al. (2010)[40]	34/36	Patients undergoing CEA	1 10 min ischemia of each leg 2 Cuff pressure: Doppler-confirmed occlusion of posterior tibial or dorsalis pedis artery 3 Times: Once	RIC safe in patients undergoing CEA	Not applicable	Completed
Garcia et al. (2016)[41]	30/19	Patients undergoing CEA	1 3 × 5 min inflation/deflation of cuff on one arm 2 Cuff pressure: 200 mmHg (sham RIC:40–50 mmHg) 3 Times: Once, initiated 12–24 h before surgery	Unknown	Phase 2	Completed
Healy et al. (2015)[42]	24/21	Patients undergoing CEA	1 4 × 5 min inflation/deflation of cuff on one arm 2 Cuff pressure: 200 mmHg or ≥15 mmHg above systolic pressure	No reduction in stroke with RIC	Not applicable	Completed

(*Continued*)

Table 1. Continued.

Study	*n*	Type of patients	RIC protocol	Main results	Type	Status
			3 Times: Once, initiated 50–60 min before surgery			
CSVD						
Mi et al. (2016)[47]	9/8	Patients with CSVD	1 5 × 5 min inflation/deflation of cuff on both arms 2 Cuff pressure: 200 mmHg 3 Times: Twice daily for 1 year	RIC may benefit patients with CSVD	Phase 2	Completed
Wang et al. (2017)[48]	18/18	Patients with CSVD-related mild cognitive impairment	1 5 × 5 min inflation/deflation of cuff on both arms 2 Cuff pressure: 200 mmHg 3 Times: Twice daily for 1 year	RIC slowed cognition decline and reduced white matter hyperintensities	Phase 2	Completed
REM-PROTECT	40/20	Patients with clinical lacunar stroke syndrome	1 4 × 5 min inflation/deflation of cuff on one arm 2 Cuff pressure: 200 mmHg 3 Times: Once daily for 1 year	No available	Not applicable	Ongoing
ASAH						
Koch et al. (2011)[51]	26/7	Patients with aSAH	1 Lead-in phase: 3 × 5 min inflation/deflation of cuff on one arm or leg 2 Dose escalation phase: 3 × 7.5 min or 3×10 min ischemia of one leg 3 Cuff pressure: 200 mmHg or 20 mmHg above systolic pressure 4 Times: Cuff pressure: Once	RIC safe and well tolerated	Phase 1b	Completed
Gonzalez et al. (2014)[52]	20	Patients with aSAH	1 4 × 5 min inflation/deflation of cuff on one leg 2 Cuff pressure: 20 mmHg above systolic pressure 3 Times: four sessions on nonconsecutive days	RIC safe and well tolerated	Phase 1	Completed
Laiwalla et al. (2016)[53]	21/61	Patients with aSAH	1 4 × 5 min inflation/deflation of cuff on one leg 2 Cuff pressure: 20 mmHg above systolic pressure, increased until dorsalis pedis pulse abolished 3 Times: four sessions on nonconsecutive days	RIC improved functional outcome	Not applicable	Completed
RIPC-SAH	50/50	Patients with SAH	1 4 × 5 min inflation/deflation of cuff on one leg 2 Cuff pressure: 20 mmHg above systolic pressure 3 Times: Once	No available	Not applicable	Ongoing

(*Continued*)

transient ischemic attacks (TIA).[26,27] Current management of ICAS is based on a combination of antiplatelet drugs and control of cardiovascular risk factors through lifestyle modification and drug treatment (e.g., antihypertensives, statins).[28] However, the annual risk of recurrent ischemic stroke and TIA remains very high, occurring at

Table 1. Continued.

Study	*n*	Type of patients	RIC protocol	Main results	Type	Status
PreLIMBS	30/30	Patients with SAH within 2 weeks of initial bleeding	1 Three cycles of 10 min inflation and 5 min deflation of cuff on arm or leg 2 Cuff pressure: 200 mmHg 3 Times: 3 cycles every 24–48 h during the first 14 days after SAH	No available	Not applicable	Ongoing

RIC, remote ischemic conditioning; AIS, acute ischemic stroke; ICAS, intracranial atherosclerosis; CAS, carotid stenting; CEA, carotid endarterectomy; CSVD, cerebral small vessel disease; ET, endovascular thrombectomy; aSAH, aneurysmal subarachnoid hemorrhage.

a rate of up to 25% in the first year after an initial stroke.[29] Against this background, strategies to improve the therapeutic effects for ICAS, including RIC, have been investigated in several clinical studies.

To investigate the safety and feasibility of RIC in ICAS, a small pilot study recruited 10 patients 40–65 years old with unilateral middle cerebral artery stenosis, and 24 healthy volunteers 40–70 years old (males:females:1:1 in both groups), all of whom underwent RIC.[30] The results showed that RIC was safe and well tolerated in both healthy control subjects and patients with ICAS, and it had no significant influence on heart rate, oxygenation index, or mean flow velocity of intracranial arteries.

Based on this pilot clinical trial, two RCTs evaluated the efficacy of RIC in patients with ICAS.[12,13] The first trial recruited 103 patients who had experienced a stroke or TIA caused by ICAS within 30 days of the index event.[12] All patients received standard medical management, and patients in the intervention group underwent additional RIC treatment twice daily for 300 consecutive days. Sixty-eight patients completed the study. The incidence of recurrent stroke at 90 and 300 days was 5% and 7.9% in the intervention group, and 23.3% and 26.7% in the control group. Additionally, RIC increased the rate of recovery and shortened the time until the modified Rankins Scale score improved to 0–1, which occurred in 65.8% in the intervention group versus 13.3% in the control group by 90 days. Moreover, cerebral perfusion, measured by single photon emission computed tomography, was significantly improved at 300 days in patients treated with RIC.

Using the same RIC treatment protocol, another RCT was conducted in 79 patients (aged 80–95 years) who had ischemic stroke or a TIA caused by severe intracranial arterial stenosis within the previous 7 days.[13] All patients received standard medical management. Patients in the intervention group received RIC for 180 consecutive days, while those in the sham group received sham RIC. Fifty-eight patients completed the study, and RIC appeared to be safe and well tolerated. The incidence of recurrent ischemic cerebrovascular events at 180 days was significantly reduced in the RIC group (22.5% vs. 48.7%), and plasma hypersensitive C-reactive protein, interleukin-6, leukocyte count, and platelet aggregation rates were significantly decreased at day 30 in the intervention group as compared with the sham group.

Although both RCTs demonstrated the efficacy of RIC in preventing recurrent ischemic events in patients with ICAS, there were large percentages of patients lost to follow-up in the two studies (34% and 27%, respectively), which could have caused considerable biases. Therefore, a large multicenter phase III clinical trial (RICA, NCT02534545), which will enroll 3000 patients with symptomatic ICAS, is ongoing in China to confirm the safety and efficacy of repeated RIC in patients with ICAS.[31] Furthermore, a phase II trial is ongoing to investigate the effects of RIC in young patients with ICAS (NCT02323425). In addition, in the United States, a pilot study of RIC for ICAS is ongoing to further investigate effects of RIC on cerebral blood flow in patients with ICAS (NCT03208166). These studies may provide evidence for the benefits and harms of RIC in patients with ICAS.

Carotid Stenting and Endarterectomy

Carotid artery stenting (CAS) and carotid endarterectomy (CEA) are standard revascularization therapies for carotid atherosclerotic stenosis.[32] The combined rate of stroke and death at 30 days ranges from 2 to 9%.[33,34] However, new cerebral ischemic lesions are commonly detected by postprocedural MRI, with frequencies ranging from 20 to 70% for CAS and 4 to 17% for CEA.[35,36] Although most of the new brain lesions on postprocedural MRI cause no acute neurological deficits, studies indicate that they might have adverse long-term effects on cognitive function.[37,38] Beneficial research results for RIC in patients undergoing percutaneous coronary intervention and

coronary artery bypass grafting[9] may provide a strong scientific premise for clinical studies of RIC in patients undergoing CAS and CEA.

Aiming to evaluate the protective value of RIC for patients treated with CAS, a RCT recruited 189 patients (>18 years old) with severe symptomatic or asymptomatic carotid artery atherosclerotic stenosis and allocated them to three groups (RIC, sham, and control).[39] Head MRI scans were performed before CAS and within 48 h posttreatment. All patients received standard medical treatment, and those in the RIC and sham groups received additional RIC or sham RIC, respectively, twice daily for 2 weeks before CAS; 162 patients completed CAS and MRI follow-up. The incidence of new cerebral ischemic lesions on posttreatment MRI was significantly lower in the RIC (15.87%) than the sham (36.51%) or control (41.27%) group. Furthermore, the volume of new infarcts was also significantly smaller in the RIC group than in the other two groups.

Three clinical trials investigated the effects of RIC in patients undergoing CEA. A pilot trial evaluating RIC for cerebral and cardiac protection in patients undergoing CEA recruited 70 patients, 55 of whom completed the primary endpoints.[40] However, no patient developed postoperative stroke or TIA during the study period. Two other RCTs evaluated the effects of RIC in patients undergoing vascular surgery, including CEA. In one trial, 49 of 201 patients underwent CEA, but no subgroup analysis was performed.[41] In the other, 45 of 189 patients underwent CEA, but subgroup analysis of those undergoing CEA showed no significant difference in composite clinical outcome (12.5% vs. 9.5%).[42]

The low incidence of stroke and TIA after CEA and CAS may help to explain the failure to demonstrate a significant neuroprotective effect of RIC in reducing these clinical endpoints. However, the tendency for reduced incidence of stroke and TIA after CAS in patients treated with RIC argues for further studies with larger sample sizes, or in those with a high risk of postoperative stroke or TIA. Additionally, more specific studies on CEA should be conducted to determine the neuroprotective effects of RIC, with plasma biomarkers and incidence of new posttreatment brain lesions better incorporated into clinical outcome assessment.

Cerebral Small Vessel Disease

Cerebral small vessel disease (CSVD) is responsible for approximately 15–25% of all ischemic strokes.[43] Generally, strokes caused by CSVD are less severe during the acute phase and have a better short-term prognosis,[44] but its long-term effects on functional impairment, cognitive decline, and mortality are not benign.[45,46] Unfortunately, there is currently no effective treatment for CSVD. As a result, two RCTs have been done to investigate the effect of RIC in patients with CSVD.

One trial recruited 17 patients with CSVD (aged 40–80 years) documented by lacunar infarction or generalized white matter lesions on MRI.[47] Patients received medical management plus RIC ($n = 9$) or sham RIC ($n = 8$) twice daily for 1 year, after which ultrasound and MRI were used to assess cerebral hemodynamics and brain lesions. Mean flow velocity in the middle cerebral artery was increased and the volume with white matter hyperintensities was reduced after RIC, but there were no significant differences between groups. Using the same treatment protocol, another trial was conducted in 36 patients (aged 45–80 years) with CSVD-related mild cognitive impairment.[48] Thirty patients completed the 1-year follow-up, with the volume of white matter hyperintensities on MRI significantly reduced, and visuospatial and executive ability significantly improved, in those receiving RIC. Perfusion status, measured by pulsation indices of the middle cerebral arteries, was also significantly improved by RIC.

The two single-center RCTs described above each recruited a very small number of patients with CSVD, and 16.7% of patients were lost to follow-up in one study. In addition, many key variables that can impact the results were not well studied. All these could have biased the studies' results. Accordingly, the efficacy of RIC in patients with CSVD will need to be confirmed by further investigations. Another study (NCT02169739), to further evaluate the safety and feasibility of RIC in 60 patients with CSVD, is ongoing.

Aneurysm Subarachnoid Hemorrhage

Rupture of intracranial aneurysms accounts for about 80% of all subarachnoid hemorrhage (SAH). The average mortality is 51%, and 46% of SAH survivors have long-term cognitive impairment, which leads to approximately one third of survivors requiring lifelong support.[49] In addition, delayed cerebral ischemia remains an important cause of disability and death after SAH.[50] Coil embolization and open surgery have been the standard approaches to prevent re-rupture of aneurysms, but there is need for improving acute treatment of SAH. RIC therefore has been investigated as an adjunctive therapy for patients with aneurysmal subarachnoid hemorrhage (aSAH).

To evaluate the safety and feasibility of increasing the duration of limb ischemia in patients with aSAH, a phase Ib study recruited 33 patients with aSAH after coiling or surgical clipping of the aneurysm within 96 h of ictus. All patients received RIC every 24–48 h for 14 days.[51] This study found that RIC was safe and well tolerated, even

for ischemia times of 10 min in critically ill patients with aSAH. In another trial, 20 patients with aSAH were recruited after endovascular coiling or surgical clipping within 14 days posthemorrhage, and each received up to four RIC sessions on nonconsecutive days.[52] RIC was also safe in these patients, and none developed delayed ischemic neurological deficits. In addition, a matched cohort study of 21 patients with aSAH who were treated with RIC and 61 matched controls found that RIC was independently associated with good clinical outcomes, and there was a tendency toward a lower incidence of stroke and death in patients receiving RIC.[53]

Thus, previous studies demonstrate that RIC is well tolerated in patients with aSAH and may benefit these patients. Much larger studies are needed to confirm these results and investigate the underlying mechanisms. Based on previous promising studies, two RCTs, RIPC-SAH (NCT02381522) and PreLIMBS (NCT02411266), are ongoing to further investigate the safety, feasibility, and efficacy of RIC in patients with SAH.

Challenges of RIC

While RIC has been widely investigated, its underlying mechanisms are still not entirely clear. Researches indicate that protective signals may be transmitted from stimulus organs to remote organs through three routes: humoral, neuronal, and immune pathways.[54] However, the triggers of these pathways remain unknown, which could limit the application of RIC.

To date, the optimal RIC protocol is also undefined. The most popular protocol in clinical studies is four cycles of unilateral arm ischemia for 5 min, followed by 5 min of reperfusion, which is derived from the first experiment on ischemic preconditioning conducted over 30 years ago.[6] Another commonly used protocol is five cycles of bilateral arm ischemia for 5 min , followed by 5 min of reperfusion. Furthermore, thigh is also commonly used as the stimulus site. Efforts have been made to explore RIC algorithms,[55,56] but the optimal "dose" and other parameters for RIC are still unknown. In addition, the appropriate duration of RIC treatment remains unclear. Some studies have tested a single RIC treatment, and others repeated treatment over 2 weeks, 180 days, 300 days, or 1 year. Accordingly, an ongoing clinical study aims to optimize RIC treatment in patients with ICAS (NCT03105141).

The aforementioned challenges may make it difficult for investigators or patients to accept RIC; this may be one of the reasons why such a noninvasive and easy-to-use strategy is still not entering clinical practice. Furthermore, the lack of sensitive and specific biomarkers that can objectively evaluate the efficacy of RIC also prevents RIC from entering clinical practice. Therefore, efforts should be paid to explore the mechanisms, biomarkers, and the optimal protocol, which are of great importance to the conduction of further investigations and for RIC entering clinical practice.

Future Directions

Although the exact mechanisms underlying its efficacy are still unclear, RIC has been found to confer protection to a wide range of organs. Based on current clinical evidence for RIC in stroke management, future studies deserve to be conducted in the following directions.

AIS undergoing thrombectomy

Although the prognosis for AIS patients treated with endovascular therapy is far from satisfactory, endovascular therapy does show a high rate of recanalization and provide an unprecedented opportunity to investigate neuroprotection in humans. Because RIC could be applied in prehospital and intrahospital scenarios even by nondoctors, future studies should emphasize investigations of the effects of RIC before and after reperfusion. Currently, several trials are underway to investigate RIC in this patient population, but more works will need to be done.

Silent cerebral embolism

Postprocedural silent cerebral ischemic lesions are not an uncommon complication in many endovascular or vascular surgeries, including CAS, CEA, cerebrovascular angiogram, and endovascular embolization of cerebral aneurysms. RIC may be able to reduce silent cerebral embolisms after CAS,[39] and the effects of RIC in preventing silent cerebral embolism during other procedures deserved to be tested. Because silent infarcts caused by microemboli have potential adverse effects on long-term cognitive function,[37, 38] future studies should include long-term cognitive and psychological function in their outcome assessments.

Vascular cognitive impairment

Vascular cognitive impairment might be the most common form of cognitive impairment.[57] Although vascular cognitive impairment can potentially be prevented and cognitive decline may be reversible, current diagnosis and treatment of vascular cognitive impairment are far from satisfactory.[58] White matter damage, the pathological hallmark of vascular cognitive impairment, can be detected on MRI as white matter hyperintensities. Previous studies found that RIC may be able to reduce the volume of

white matter hyperintensities and improve cognitive function in patients with CSVD, so RIC might benefit vascular cognitive impairment due to other forms of cerebrovascular disease. The RIPSVD (NCT03022149) study has been registered to determine whether RIC is effective in the treatment of mild-to-moderate vascular dementia.

Intracerebral hemorrhage

Besides SAH, intracerebral hemorrhage is another more common type of cerebral hemorrhage. To date, clinical trials failed to demonstrate the superiority of surgical hematoma evacuation and stereotactic or endoscopic clot aspiration over medical management.[59,60] As such, medical management is still the standard care for most patients with intracerebral hemorrhage, leading to it as the least treatable form of stroke. More recently, preclinical study found that repeated RIC accelerated hematoma resolution and improved neurological outcome after intracerebral hemorrhage.[61] Previous clinical study had demonstrated RIC to be safe and well tolerated in patients with SAH, and it might benefit these patients by improving clinical outcomes.[51,52] As SAH and intracerebral hemorrhage share many common pathophysiological mechanisms, the safety, feasibility, and efficacy of RIC in patients with intracerebral hemorrhage urgently deserve to be investigated.

Chronic RIC

Recently, repeated RIC has been proposed to mimic the effects of regular exercise in healthy individuals.[62] Due to its cost effectiveness, ease of use, and good safety profile, it would be worthwhile to explore the effects of RIC in preventing initial strokes, as well as the potential benefits of long-term repeated RIC treatment for stroke management. Additionally, investigating chronic RIC in all-comers patients with cerebrovascular diseases might be new research interests.

Summary

RIC has been investigated as an adjunctive therapy for stroke management. Pilot clinical studies with small sample sizes indicate that RIC is well tolerated, and may benefit patients with intracranial atherosclerosis, cerebral small vessel disease, acute ischemic stroke, aneurysmal subarachnoid hemorrhage, and those undergoing carotid artery stenting. The effectiveness of RIC in stroke management needs to be confirmed in future studies with large sample sizes. Identifying its mechanisms of action, sensitive and specific biomarkers, and optimal conditions for application may also encourage its clinical use. As RIC is relatively easy to use and unlikely to be harmful, based on current clinical evidence, its effects in AIS patients treated with endovascular therapy, silent cerebral embolism, vascular cognitive impairment, intracerebral hemorrhage, and all-comers patients with cerebrovascular disease merit further investigations.

Acknowledgments

This study was supported by the National Key R&D Program of China (No. 2017YFC1308405), Chang Jiang Scholars Program (No. T2014251), and the Capital Health Research and Development of Special (No. 2016-4-1032).

Author Contributions

Wenbo Zhao and Sijie Li researched data for the review, wrote and revised the manuscript, contributed substantially to discussions of its content, and undertook review and editing of the manuscript before submission. Changhong Ren, Ran Meng, Kunlin Jin, and Xunming Ji contributed substantially to discussions of the article content. Xunming Ji supervised the preparation of the manuscript.

Conflict of Interest

All authors declare that they have no conflict of interest.

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