

RESEARCH PAPER

Remote ischemic conditioning for acute stroke patients treated with thrombectomy

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Introduction

Several clinical trials have found evidence for the superiority of endovascular treatment (ET) for the treatment of acute ischemic stroke (AIS) caused by an emergent large-vessel occlusion.^{1,2} However, only a small portion of AIS patients with an emergent large-vessel occlusion actually received ET under the current emergency medical services system (approximately 13% in the USA) because of the rigid therapeutic time window (less than 6 hours).³ Recently, two large-scale clinical trials have determined the superiority of ET for treating AIS patients with a mismatch between deficit or hypoperfusion and infarct if

Abstract

Objective: Remote ischemic conditioning (RIC) has been demonstrated to be safe and feasible for patients with acute ischemic stroke (AIS), as well as for those receiving intravenous thrombolysis. We assessed the safety and feasibility of RIC for AIS patients undergoing endovascular treatment (ET). **Methods:** We conducted a pilot study with patients with AIS who were suspected of having an emergent large-vessel occlusion in the anterior circulation and who were scheduled for ET within 6 hours of ictus. Four cycles of RIC were performed before recanalization, immediately following recanalization, and once daily for the subsequent 7 days. The primary outcome was any serious RIC-related adverse events. **Results:** Twenty subjects, aged 66.1 ± 12.1 years, were recruited. No subject experienced serious RIC-related adverse events. The intracranial pressure, cranial perfusion pressure, mean arterial pressure, heart rate, middle cerebral artery peak systolic flow velocity, and pulsatility index did not change significantly before, during, or after the limb ischemia ($P > 0.1$ for all). Of 80 cycles, 71 (89%) were completed before recanalization and 80 (100%) were completed immediately after recanalization; 444 of 560 cycles (78%) were completed within 7 days posttreatment. No patients had to stop RIC because it affected routine clinical managements. Six subjects (30%) experienced intracerebral hemorrhage, which was symptomatic in one case (5%). At the 3-month follow-up, 11 subjects (55%) had achieved functional independence, and two subjects (10%) died. **Interpretation:** RIC appears to be safe and feasible for patients with AIS undergoing ET. Investigations are urgently needed to determine the efficacy of RIC in this patient population.

selected by perfusion imaging within 6–24 h of ictus.^{4,5} The extended therapeutic time window would benefit more AIS patients. As the mismatch between the hypoperfusion and the infarct decay over time,⁶ there is an urgent need to explore strategies that could slow down – if not altogether prevent – the decay of the mismatch in clinical practice. Additionally, approximately 80% of occluded arteries can be recanalized by ET.^{1,7} However, less than 50% of patients achieved functional independence and over 15% died 90 days posttreatment.⁸ Although the mismatch of successful recanalization with poor prognosis can be attributed to many factors, the reperfusion injury may be among the most important.^{9,10}

Effective neuroprotective strategies to reduce reperfusion injury after ET are therefore urgently needed.

Remote ischemic conditioning (RIC) is a noninvasive strategy in which one or more cycles of brief and transient limb ischemia confers protection against prolonged and severe ischemia in distant organs.¹¹ In the embolic stroke model, a combination of RIC and intravenous thrombolysis was shown to reduce infarct size and improve neurological outcome more than either therapy did when used alone.¹² In addition, a clinical study has also found that the prehospital application of RIC reduces the risk of brain tissue infarction in AIS patients receiving intravenous thrombolysis.¹³ Furthermore, in the transient focal cerebral ischemia-reperfusion model, the application of RIC before reperfusion or both before and after reperfusion reduces reperfusion injuries and the final infarct size.^{14,15}

Because patients with AIS who are treated with ET can achieve high rate of recanalization after focal ischemia, this patient population is akin to the model of transient focal cerebral ischemia-reperfusion and embolic stroke treated with intravenous thrombolysis. Therefore, it may be reasonable to speculate that RIC could also benefit patients with AIS who were treated with ET. To date, RIC has been investigated in patients with AIS within 24 h of ictus, as well as in those receiving intravenous thrombolysis.^{13,16} However, no studies have yet recruited subjects treated with ET nor determined whether RIC is safe and feasible for such patients.

In this study, we aimed to investigate the safety and feasibility of RIC for patients with AIS undergoing ET and planned for a future phase II study that investigates the efficacy of RIC.

Methods

Study design and subjects

This study was a single-armed, open-label, safety, and feasibility trial registered on clinicaltrials.gov (REVISE-1, NCT03210051). The protocol was approved by the Ethic Committee of Xuanwu Hospital, Capital Medical University.

Patients with AIS who were suspected of having an emergent large-vessel occlusion in the anterior circulation and who were eligible for ET within 6 h of ictus were recruited. The inclusion criteria for this study included the following: (1) age between 18 and 80 years; (2) initial National Institute of Health Stroke Scale (NIHSS) score ≥ 6 ; (3) baseline Cincinnati Prehospital Stroke Severity Scale (CPSSS) score ≥ 2 ; (4) could complete groin puncture within 6 h after symptom onset; (5) no remarkable prestroke functional disability (modified Rankin scale

[mRS] score ≤ 1); (6) informed consent obtained from subjects or their legally authorized representative. The exclusion criteria included the following: (1) hypodensity on pretreatment noncontrast CT scans amounting to an Alberta Stroke Program Early CT score (ASPECTS) of less than 6; (2) significant mass effect with midline shift on CT or MRI scans; (3) subjects participating in other ongoing study; (4) unlikely to be available for 90-day follow-up; (5) woman of childbearing potential who is known to be pregnant or lactating; (6) contraindicating for remote ischemic conditioning: severe soft tissue injury, fracture, dysmelia, and other known peripheral vascular disease in the upper limbs.

RIC intervention

After recruiting participants for this study, RIC was performed before recanalization of the occluded artery, immediately following successful recanalization, and once daily for the subsequent 7 days. The RIC procedure consisted of four cycles of unilateral arm ischemia for 5 minutes, which was followed by reperfusion for another 5 minutes. The procedure was performed with an electric, autocontrol device with a cuff that inflated to a pressure of 200 mmHg during the ischemia period. If four cycles were not completed after arriving to the catheter laboratory, the procedure was discontinued if it affected the preparations for ET. RIC was also discontinued if the subject died or was discharged in under 7 days.

Assessment of intracranial pressure and cerebral perfusion pressure

The intracranial pressure and cerebral perfusion pressure were measured on the first day post-ET, when RIC was performed. Intracranial pressure was measured using a noninvasive intracranial pressure monitoring system (Chongqing Hiwelcom Iatrical Apparatus Co. Ltd, Chongqing, China) that was based on flash visual evoked potentials¹⁷ at the following three time points in each cycle: before the initiation of limb ischemia, during limb ischemia, and after limb ischemia. Cerebral perfusion pressure was calculated from the intracranial pressure and corresponding blood pressure with the following formula: cerebral perfusion pressure = (Systolic blood pressure + 2 * Diastolic blood pressure) / 3 - intracranial pressure.

Assessment of cerebral hemodynamics

Cerebral hemodynamics were measured on the first day post-ET, when RIC was performed. Transcranial Doppler, which was performed by an experienced technician, was used to continuously monitor the middle cerebral artery

peak systolic blood flow velocity and pulsatility index. The values were documented at the following three time points in each cycle: before the initiation of limb ischemia, during limb ischemia, and after limb ischemia.

Assessment of vital signs

Systolic blood pressure, diastolic blood pressure, and heart rate were continuously monitored with a multiparameter electrocardiac monitor. Blood pressure (with cuff placed on the contralateral arm) and heart rate were documented at the following three time points in each cycle: before the initiation of limb ischemia, during limb ischemia, and after limb ischemia. Mean arterial pressure was calculated with the formula: mean arterial pressure = (Systolic blood pressure + 2 * Diastolic blood pressure) / 3.

Assessment of imaging

Pretreatment head CT was performed for all patients immediately after their admission to our institution. Post-treatment head CT was generally performed 12–24 h post-ET, and reperformed seven to nine days post-ET or before discharge (whichever came earlier), and whenever an intracranial hemorrhage was indicated by clinical evidence. The ASPECTS was evaluated using the pretreatment CT. All images (including the angiograms, the pre-ET CT, and the post-ET CT) were analyzed separately by a neurologist and a neuroradiologist. Disagreements were resolved by a consensus reached between the two reviewers, or, if no consensus could be reached, a third reader had the final decision.

Assessment of clinical outcomes and adverse events

All clinical outcomes (including NIHSS score, mRS score, and symptomatic intracranial hemorrhage) and adverse events were evaluated separately by two investigators. Any disagreements were resolved by a consensus reached between them. If the disagreement persisted, a third investigator made the final decision.

Endpoints assessment

Safety assessment

The primary safety outcome was any serious RIC-related adverse events. Other safety outcomes included any other RIC-related adverse events as well as any significant changes in intracranial pressure, cerebral perfusion pressure, cerebral hemodynamics, mean arterial pressure, and heart rate before, during, or after limb ischemia.

Feasibility assessment

Feasibility was assessed by the percentage of patients who completed the RIC procedures before and after reperfusion, and the percentage of those whom the doctors or nurses requested to cease the RIC procedure on account of the influence of other treatments.

Other endpoints assessment

Other endpoints included any post-ET intracranial hemorrhage, symptomatic intracranial hemorrhage according to the European Cooperative Acute Stroke Study III definition¹⁸ during the study period, and functional outcomes assessed by mRS at the 3-month follow-up.

Statistical analysis

For continuous data, either means \pm standard deviation or medians (interquartile range, IQR) were used to summarize data. For binary data, frequencies and percentages were used. The values for intracranial pressure, cerebral perfusion pressure, cerebral hemodynamics, mean arterial pressure, and heart rates measured before, during, and after limb ischemia were self-compared using repeated-measures ANOVA. All data were analyzed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA) with p values less than 0.05 (two sides) indicating significance.

Results

In total, 87 patients who were suspected to have AIS were screened in Xuanwu Hospital between July 2017 and September 2017. Twenty of them who were suspected of having an emergent large-vessel occlusion in the anterior circulation were enrolled in this study.

Baseline characteristics

The demographic characteristics of the subjects are summarized in Table 1. The average age at onset was 66.1 ± 12.1 years. Thirteen subjects (65%) were male and seven subjects (35%) had received intravenous thrombolysis. The median baseline NIHSS score was 16 (IQR: 12–18), the median baseline ASPECTS was 10 (IQR: 8–10), and the median times from onset to groin puncture and recanalization were 325 min (IQR: 296–371) and 408 min (IQR: 367–471), respectively. Seventeen subjects (85%) achieved good or excellent reperfusion (Thrombolysis in Cerebral infarction $\geq 2b$), while one subject (5%) failed to achieve any recanalization (Thrombolysis in Cerebral infarction = 0). The vascular risk

factors, etiology of stroke, and operational details are shown in Table 1.

Safety

No serious RIC-related adverse events occurred. One subject experienced arm skin petechiae without discomfort, and RIC was performed continually.

Values of intracranial pressure, cerebral perfusion pressure, mean arterial pressure, and heart rate measured before, during, and after limb ischemia did not change significantly ($P > 0.1$ for all) (Figure 1 and Table 2). The peak systolic blood flow velocity and pulsatility index of the affected side and nonaffected side of the middle cerebral artery did not significantly change either ($P > 0.1$ for all) (Figure 1 and Table 2).

Feasibility

In total, 71 of 80 cycles (89%) were completed before recanalization and 80 cycles (100%) were completed

immediately after recanalization; 444 of 560 cycles (78%) were completed within 7 days posttreatment. Six subjects did not complete the four cycles of RIC prerecanalization because the time from their admission to the catheter laboratory was too short. Ten subjects did not complete the 7-day post-ET RIC. Eight subjects were discharged early because of their good recovery, while two subjects died before completing the RIC procedure. No patients were asked to cease RIC because of it influencing routine clinical management (e.g., intravenous fluids through arms and rehabilitation).

Clinical outcomes

Six subjects (30%) experienced intracranial hemorrhage, with one case (5%) being symptomatic. At the 3-month follow-up, 11 subjects (55%) achieved functional independence (mRS ≤ 2), while two subjects (10%) died (mRS = 6).

Discussion

In this study, we found that RIC was well-tolerated and had no significant influence on the intracranial pressure, cerebral perfusion pressure, mean arterial pressure, heart rate, or cerebral hemodynamics of AIS patients treated with ET – even of those after receiving intravenous thrombolysis – and it did not influence routine clinical managements. In addition, over half of the subjects achieved functional independence, and 10% of the subjects died by the 3-month follow-up.

RIC could be performed before (i.e., preconditioning) and after reperfusion (i.e., postconditioning). Preconditioning has been demonstrated to reduce the risk of brain tissue infarction,^{12,13} and strong evidence shows that postconditioning attenuates reperfusion injury in transient focal ischemia-reperfusion model.^{11,19} These observations informed our study, in which we combined preconditioning with postconditioning in these patients whose afflictions resembled the transient focal ischemia-reperfusion model.

This phase I study was designed to obtain safety and feasibility data for RIC in patients with AIS undergoing ET. Although the safety and feasibility of RIC have been investigated in humans and in patients with acute stroke,^{11,20–22} patients with AIS who were treated with ET have its own specific characteristics. Generally, patients with AIS and emergent large-vessel occlusion are much more severely affected than the previously studied patients with AIS, and the rates of recanalization and sufficient reperfusion are much higher in patients treated with ET.^{8,13,16} Furthermore, this patient population is vulnerable, and slight hemodynamic changes may lead to

Table 1. Demographic and clinical characteristics.

Characteristics	Value, $n = 20$
Age	66.1 \pm 12.1
Male	13 (65)
NIHSS	16 (12–18)
ASPECTS	10 (8–10)
Treatment with intravenous alteplase	7 (35)
Onset to groin puncture time	325 (296–371)
Onset to recanalization time	408 (367–471)
Vascular risk factors	
Hypertension	14 (70)
Diabetes mellitus	9 (45)
Atrial fibrillation	5 (25)
Smoking	11 (55)
Etiology of stroke	
Large artery atherosclerosis	12 (60)
Cardioembolism	6 (30)
Other	2 (10)
Occluded vessel	
Internal carotid artery	7 (35)
Middle cerebral artery	13 (65)
Operational details	
General anesthesia	10 (50)
Permanent stenting	5 (25)
Intracranial stenting	3 (15)
Extracranial stenting	2 (10)
Balloon angioplasty	1 (5)
TICI=2b/3	17 (85)
TICI=0	1 (5)

Data are mean \pm standard deviation, n (%) or median (interquartile range). NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT score; TICI, Thrombolysis in Cerebral Infarction.

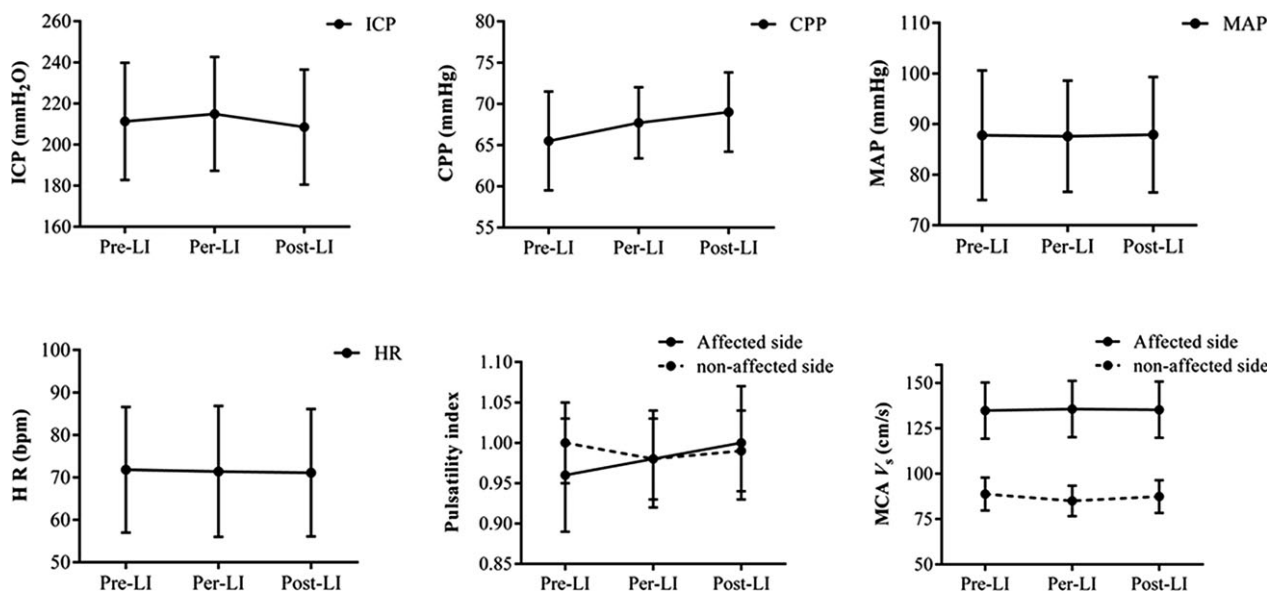


Figure 1. The distribution of ICP, CPP, MAP, HR, and cerebral hemodynamics before, during, and after limb ischemia. Data presented are mean and standard deviation. LI: limb ischemia; ICP, intracranial pressure; CPP, cranial perfusion pressure; MAP, mean arterial pressure; HR, hear rate; MCA V_s, middle cerebral artery peak systolic blood flow velocity. Repeated-measures ANOVA was used for statistical test, no significant difference was found ($P > 0.1$ each).

Table 2. Changes of ICP, CPP, MAP, heart rate, and cerebral hemodynamics.

Variable	Pre-LI	Per- LI	Post- LI	P value
ICP, mmH ₂ O	211.3 ± 28.5	214.9 ± 27.7	208.5 ± 28.0	0.429
CPP, mmHg	65.5 ± 6.0	67.7 ± 4.3	69.0 ± 4.8	0.291
MAP, mmHg	87.8 ± 12.8	87.6 ± 11.0	87.9 ± 11.4	0.824
Heart rate, bpm	71.8 ± 14.8	71.4 ± 15.4	71.1 ± 15.0	0.784
Affected MCA peak V _s (cm/sec)	134.8 ± 15.5	135.7 ± 15.5	135.3 ± 15.5	0.961
Healthy MCA peak V _s (cm/sec)	88.8 ± 9.1	85.0 ± 8.4	87.4 ± 9.0	0.161
Affected MCA pulsatility index	0.96 ± 0.07	0.98 ± 0.06	1.00 ± 0.07	0.441
Healthy MCA pulsatility index	1.00 ± 0.05	0.98 ± 0.05	0.99 ± 0.05	0.807

Data are mean ± standard deviation. RIC, remote ischemic conditioning; ICP, intracranial pressure; CPP, cranial perfusion pressure; MAP, mean arterial pressure; MCA, middle cerebral artery; V_s: systolic blood flow velocity; LI, limb ischemia.

disastrous consequences (e.g., ischemic or hemorrhagic stroke).²³ Additionally, these patients often need complicated intensive care, and several peripheral venous accesses might be used.^{2,24} Therefore, the application of RIC may be more difficult. Consistent with previous studies that investigating the safety and feasibility of RIC in human,^{11,20–22,25} we found that RIC could also be safely used in AIS patients treated with ET.

The main concern of the use of RIC in this patient population was repeated limb ischemia induced by occlusion of upper limb vessels, as it might potentially elevate blood pressure and cerebral perfusion pressure, as well as impact cerebral hydrodynamics, which may cause cerebral hyperperfusion. Fortunately, self-comparisons of blood

pressure, intracranial pressure, cerebral perfusion pressure, bilateral middle cerebral artery peak systolic blood flow velocity, and pulsatility index before, during, and after limb ischemia were sufficient to determine the influence of RIC on the aforementioned parameters. Therefore, only one group of participants was recruited in this study, and a separate control group may not be needed. Furthermore, this analysis method could avoid any known or unknown biases between the treatment and control groups.

Several subjects completed only two to three cycles of preconditioning because of the time from their admission to the catheter laboratory was too short to perform the four cycles that the investigation required. Therefore,

much earlier (e.g., in prehospital scenarios) initiation of RIC may be a better choice for future studies; it would not only give enough time for four cycles of RIC but also preserve more brain tissue at risk of infarction.²⁶ In addition, the preconditioning protocol has yet to be defined: two or three cycles of stimuli might have similar protective effects as four cycles. Therefore, patients who did not complete four cycles of stimuli might also have benefited from RIC. Compared with previous studies of endovascular treatment for AIS,^{7,8,27} this study found a slightly higher proportion of patients who had achieved functional independence (mRS \leq 2) at 3-month follow-up.

This study has several limitations. First, this is a single-armed study, and data were not compared with control group. Instead, the data of before, during, and after the limb ischemia were self-compared, and the clinical outcomes were compared with those of previous studies. Second, the RIC protocol used in this study was rather pragmatic, and the optimal protocol for this patient population needs further investigations. Finally, the trend of improvement in clinical outcome was not powered to determine the efficacy of RIC in patients with AIS who were treated with ET, and this requires further urgent investigation, which is planned in the REVISE-2, a phase 2 parallel-group study (<https://clinicaltrials.gov/ct2/show/NCT03045055>).

In conclusion, these results suggest that RIC is safe and feasible for patients with AIS who were treated with ET, but the preliminary clinical benefit was not supported by current data. Further studies are needed to confirm these results and determine the efficacy of RIC in this patient population.

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Author Contributions

Wenbo Zhao, Changhong Ren, Ran Meng, and Xunming Ji contributed to the conception and design of study. Wenbo Zhao, Ruiwen Che, Sijie Li, Chuanjie Wu, Chuanhui Li, Hui Lu, Jian Chen, and Jiangang Duan contributed to the acquisition and analysis of data. Wenbo Zhao and Xunming Ji contributed to the drafting and revising of the manuscript.

Conflict of Interest

Dr Xunming Ji is one of the inventors of the electric autocontrol device that has been patented in China (ZL 200820123637.X). The other authors declare that they have no conflict of interest.

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