Heliyon 9 (2023) e18181

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Remote ischemic conditioning in the treatment of acute cerebral infarction: A case control study

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ARTICLE INFO

Keywords:
Remote ischemic conditioning
Cerebral infarction
Modified Rankin scale scores
Hypoxia inducible factor-1α

ABSTRACT

Objective: This paired case-control study aimed to evaluate the efficacy and safety of remote ischemic conditioning (RIC) in patients with acute cerebral infarction (CI) and explore potential serological markers of RIC.

Methods: Patients with acute CI (<72 h) were matched 1:1 according to age, sex, and CI conditions and were divided into the RIC group and the control group. The RIC group received RIC intervention for 7 days on top of routine treatment, while the control group received a sham RIC. The curative effects and adverse reactions were observed.

Result: A total of 66 patients (mean age 60.00 ± 11.37 years; mean time of acute CI onset 32.91 ± 17.94 h) completed the study. The National Institute of Health stroke scale score on day 7, modified Rankin Scale scores on day 7 and day 90 were significantly lower than the baseline in the RIC group ($P < 0.001$, $P = 0.003$, $P = 0.004$, respectively) but not in the control group ($P = 0.056$, $P = 0.169$, $P = 0.058$, respectively). RIC was well-tolerated, and no adverse events were reported. Both plasma hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor increased in the RIC group from day 0 to day 7, while they decreased in the control group. The changes in plasma HIF-1α in the RIC group were statistically different from those in the control group ($P = 0.006$).

Conclusion: Early and short-term RIC treatment was well-tolerated and effective in improving the prognosis in acute CI. HIF-1α can be recognized as a biomarker for evaluating the efficacy of RIC treatment.

1. Introduction

Cerebrovascular disease has emerged as the primary cause of death and disability among the Chinese population. With a prevalence of 1114.8/100000 stroke cases in adults aged 20 and over, China has the highest incidence of stroke in the world [1]. Despite medical advancements, effective interventions for the protection and repair of neural function after cerebral infarction remain scarce [2]. Vascular recanalization treatment, while beneficial, can still result in 50%–70% disability and mortality rates in acute ischemic stroke patients [3]. Additionally, dual antiplatelet therapy in patients with mild stroke or transient ischemic attack (TIA) presents a high risk

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https://doi.org/10.1016/j.heliyon.2023.e18181
Received 20 February 2023; Received in revised form 1 June 2023; Accepted 10 July 2023
Available online 11 July 2023

of recent stroke recurrence (6%–8%) and potential complications such as bleeding [4,5]. Consequently, there is an urgent need to explore new avenues for the prevention and treatment of ischemic cerebrovascular disease in clinical practice.

Remote ischemic conditioning (RIC) is a feasible noninvasive and non-pharmacological intervention in clinical practice. RIC can stimulate the adaptation and tolerance of the brain to ischemic injury by repeatedly blocking and restoring the blood flow of the limbs. Animal experiments have demonstrated that RIC treatment can reduce the area of cerebral infarction, decrease brain edema and ischemia-reperfusion injury, maintain the stability of the blood-cerebrospinal fluid barrier, and promote the recovery of neurological function [6–9].

Transient ischemic attack (TIA) has similarities to cerebral ischemic conditioning. It has been observed that stroke patients with a previous history of TIA exhibited milder clinical symptoms and better prognoses than stroke patients without a TIA history [10]. As cerebral ischemia can cause irreversible damage to the nervous system, it is not suitable for cerebral ischemic conditioning training in clinical practice, and is replaced by RIC. Although limited clinical studies have suggested that RIC can improve cerebral blood perfusion in the ischemic area, enhance disease prognosis, and reduce the recurrence rate of cardiovascular and cerebrovascular diseases [11–14], some studies have not supported the benefit of RIC on cardiovascular and cerebrovascular diseases [15,16]. Moreover, it is still unclear whether remote ischemic adaptation can improve cognitive function in patients with cerebral infarction.

At present, the exact mechanism of RIC remains unclear and there is a lack of specific biomarkers to evaluate its efficacy. However, previous animal studies have indicated that hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) play crucial roles in regulating mammalian oxygen balance and are involved in the protective effects of RIC on stroke [17,18]. In particular, injection of HIF inhibitors has been shown to eliminate the protective effect of RIC on neurological function [19–21]. Nevertheless, further clinical studies are necessary to confirm whether HIF-1α and VEGF can be used as reliable biomarkers for RIC treatment.

In this paired case-control trial, we aim to investigate:i) the efficacy and safety of RIC in the treatment of acute cerebral infarction; and ii) whether plasma HIF-1α and VEGF can serve as biomarkers for the therapeutic effects of RIC.

2. Materials and methods

2.1. Study design and subjects

This was a single-center, prospective, 1:1 matched case-control study. The study design is illustrated in Fig. 1. Patients were recruited from the Department of Neurology, the First Affiliated Hospital of Shantou University Medical College, between June 2021 and April 2022. Inclusion criteria were age between 18 and 85 years and a diagnosis of ischemic stroke within the past 72 h. Exclusion criteria included intracranial hemorrhage, cerebral aneurysm or cerebrovascular malformation, systolic blood pressure >200 mmHg and/or diastolic blood pressure >100 mmHg with medication, any injury, infection, swelling or erosion of upper limbs, severe heart, hepatic or renal dysfunction, hematological diseases, and receiving or preparing for vascular recanalization treatment, such as

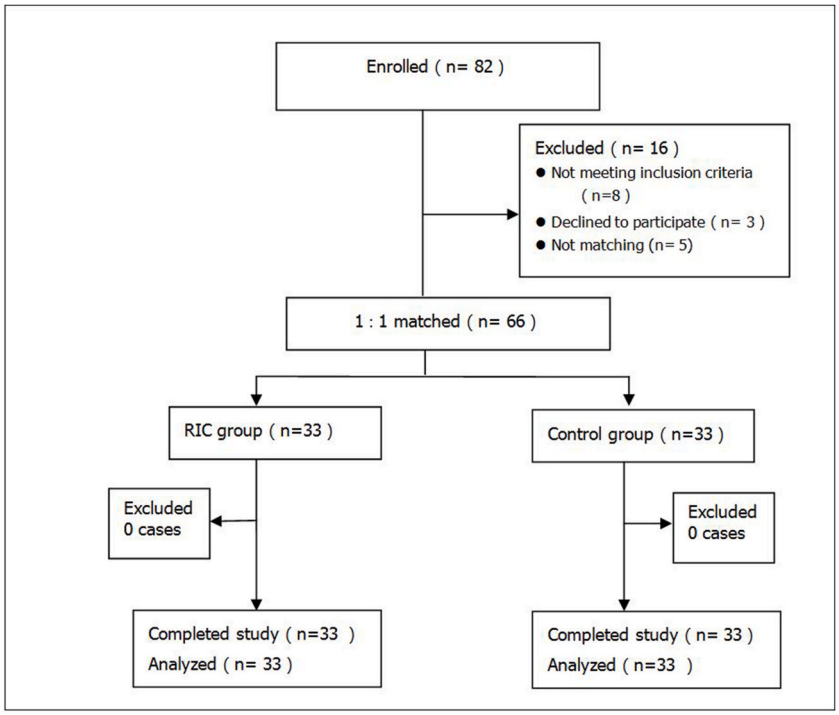

Fig. 1. Trial flow. RIC indicates remote ischemic conditioning.

intravenous thrombolysis therapy or mechanical thrombectomy.

Based on a review of previous references and preliminary experimental results, the significant efficacy rate of RIC therapy (mRS score $\leq$3) was estimated to be 70%, compared to a significant efficacy rate of 40% for the control group receiving standard treatment. The consistency rate between the two treatments was approximately 35%. A strict paired trial design was used with $\beta = 0.10$ and $\alpha = 0.05$, and the formula was applied: $N = \left(\frac{u_{\alpha/2}\sqrt{2\bar{p}}+u_{\beta}\sqrt{2(p_1-p)(p_2-p)/\bar{p}}}{p_1-p_2}\right)^2 = 33$. Therefore, at least 33 pairs of subjects needed to be observed in this study. A total of 82 patients were screened, and 66 patients were finally enrolled in the study. The enrolled patients were 1:1 matched and divided into an RIC group (n = 33) and a control group (n = 33) based on age, sex, conditions of cerebral infarction (infarct location, infarction area, onset time, National Institute of Health stroke scale (NIHSS) score). The study was approved by the ethics committee of the First Affiliated Hospital of Shantou University Medical College, and all participants provided written informed consent.

2.2. Intervention procedures

All patients received standard treatment, such as aspirin/clopidogrel, lipid regulation, plaque stabilization, blood pressure stabilization. In addition to standard treatment, patients in RIC group underwent RIC intervention, which consisted of 5 cycles of alternating bilateral upper arm ischemia for 5 min followed by reperfusion for another 5 min. The RIC procedure was performed using a sphygmomanometer that inflated to a pressure of 200 mmHg. The patients received RIC treatment once a day for 7 consecutive days. The control group was treated with sham RIC with the same procedure as above, but the inflation pressure of the brachial artery was 30 mmHg.

2.3. Clinical measures and safety

The NIHSS score were measured at day 0 (baseline) and day 7. The modified Rankin Scale (mRS) score, the Montreal Cognitive Assessment (MoCA) score and the Activity of Daily Living (ADL) score were measured at day 0 (baseline), day 7 and day 90. The frequency of stroke and TIA recurrent events in 2 groups was recorded at day 90.

Safety evaluation indicators include：hemorrhagic cerebrovascular disease, pain or subcutaneous hemorrhage during RIC procedure, seizure, pneumonia, deep vein thrombosis, pulmonary embolism, myocardial infarction.

Blood samples were collected at day 0 (baseline) and day 7 for laboratory tests of putative biomarkers surrogate markers of efficacy (HIF-1α、VEGF), inflammation (C-reactive protein，CRP) and other (blood routine and blood biochemical parameters). Plasma HIF-1α and VEGF were detected by Elisa (Takala, Japan).

Table 1
Baseline characteristics.

Characteristics	RIC group (n = 33)	Control group (n = 33)	P
Age (years)	63.10 ± 10.51	63.48 ± 8.36	0.867
Male	21 (63.63%)	21 (63.63%)	1.000
SBP (mmHg)	155.36 ± 24.61	162.76 ± 26.20	0.242
DBP (mmHg)	91.33 ± 14.68	97.48 ± 15.50	0.103
Heart rate (beat/min)	77.52 ± 8.89	81.21 ± 11.38	0.147
Diabetes mellitus	13 (39.39%)	15 (45.45%)	0.625
Coronary heart disease	3 (9.09%)	2 (6.06%)	0.648
Atrial fibrillation	2 (6.06%)	3 (9.09%)	0.648
Smoking	13 (39.39%)	17 (51.52%)	0.330
Drinking	4 (12.12%)	10 (30.30%)	0.073
HbA1c (%)	6.95 ± 1.47	6.90 ± 2.04	0.908
HDL-C (mmol/L)	1.08 ± 0.30	1.17 ± 0.30	0.230
LDL (mmol/L)	3.02 ± 0.77	3.26 ± 0.88	0.241
TC (mmol/L)	4.87 ± 1.14	5.30 ± 1.27	0.150
TG (mmol/L)	1.66 ± 0.94	1.66 ± 1.15	0.996
Time of onset of acute cerebral infarction (hour)	32.33 ± 16.06	33.48 ± 19.88	0.797
Location of infarction			
Anterior circulation	6	6	1.000
Posterior circulation	25	25	1.000
Both	2	2	1.000
D-dimer (mg/L)	769.26 ± 825.25	925.00 ± 1498.68	0.632
Fibrinogen (g/L)	3.25 ± 0.76	3.09 ± 0.78	0.412
CRP (mg/L)	9.65 ± 21.27	9.60 ± 21.06	0.970
NIHSS score	4.15 ± 3.01	4.06 ± 3.19	0.906
mRS score	3.15 ± 1.10	3.52 ± 1.35	0.246

SBP = systolic blood pressure, DBP = diastolic blood pressure, HbA1c = glycosylated hemoglobin, TC = total cholesterol, TG = triglyceride, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, CRP═C-reactive protein.

2.4. Statistical analyses

All the statistical analyses were performed using SPSS 19.0. Means ± standard deviations and percentages were calculated for continuous variables and categorical variables respectively. The *t*-test and $\chi 2$ test were employed to assess differences in continuous and categorical variables at baseline between the RIC group and the control group, respectively. The paired *t*-test was used to determine differences in post-RIC data (day 7, day 90) between the RIC and control groups. Furthermore, the paired *t*-test was used to assess differences in measurement data between baseline and day 7/day 30. Finally, the Pearson Khi-Square test was employed to evaluate differences in the number of individuals with mRS scores ≤ 3 between the RIC and control groups on day 90.

3. Results

3.1. Baseline characteristics

The study included 66 individuals with acute cerebral infarction, aged 47–80 years, of which 63.63% were male (42/66). The mean age was 60.00 ± 11.37 years, and the mean time of onset of acute cerebral infarction was 32.91 ± 17.94 h. There were no significant differences between the RIC group and the control group in terms of age, sex, time of onset, location of infarction, presence of diabetes mellitus, presence of coronary heart disease, presence of atrial fibrillation, systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, blood lipids, D-dimer, fibrinogen, CRP, day 0 NIHSS score, and day 0 mRS score (all $P > 0.05$). (Table 1).

3.2. Clinical Outcomes

Clinical Outcomes are shown in Table 2. The NIHSS score on day 7 significantly decreased compared with baseline in the RIC group ($P < 0.001$). The mRS scores in the RIC group on day 7 and day 90 were significantly lower than baseline ($P = 0.003$ and $P = 0.004$, respectively), and both were also significantly different from the control group ($P = 0.045$ and $P = 0.043$, respectively). No significant differences were found in mRS score on baseline, day 7, and day 30 in the control group. Fig. 2 shows the number of individuals for different mRS scores on day 90. The number of individuals with mRS score ≤ 3 in the RIC group was 24/33, while in the control group, it was 14/33 on day 90 ($\chi 2 = 6.203$, $P = 0.013$). Furthermore, the ADL score on day 90 was significantly higher than that of the baseline in the RIC group ($P = 0.001$). No significant differences were found in MoCA score on baseline, day 7, and day 30 within either the RIC group or the control group. In this study, a TIA recurrent event was observed in the control group, whereas no stroke and TIA

Table 2
Clinical outcomes.

Variable	RIC group (n = 33)	Control group (n = 33)
NIHSS score		
Baseline	4.15 ± 3.01	4.06 ± 3.19
Day 7	2.52 ± 1.99*	3.12 ± 2.76
mRS score		
Baseline	3.15 ± 1.10	3.52 ± 1.35
Day 7	2.91 ± 1.21*△	3.33 ± 1.47
Day 90	2.73 ± 1.31*△	3.24 ± 1.48
ADL score		
Baseline	57.42 ± 24.53	48.55 ± 25.67
Day 7	63.87 ± 25.58	50.81 ± 28.49
Day 90	65.97 ± 25.61#	53.55 ± 27.69
MoCA score		
Baseline	24.18 ± 2.80	24.67 ± 4.35
Day 7	24.24 ± 2.73	24.85 ± 4.09
Day 90	25.15 ± 2.87	25.15 ± 3.97
D-dimer (mg/L)		
Baseline	769.26 ± 825.25	925.00 ± 1498.68
Day 7	883.89 ± 865.52	969.63 ± 1426.46
Fibrinogen (g/L)		
Baseline	3.25 ± 0.76	3.09 ± 0.78
Day 7	3.70 ± 1.01	4.20 ± 1.45
CRP (mg/L)		
Baseline	9.65 ± 21.27	9.60 ± 21.06
Day 7	11.18 ± 21.99	14.81 ± 22.32
The frequency of stroke, TIA and Miocardial infarction recurrent events on day 90		
TIA	0	1
Stroke	0	0
Miocardial infarction	0	0
SAE		
Baseline	0	0
Day 7	0	0

*: $P < 0.05$, compare with Baseline; #: $P < 0.05$, compare with 7 days; △: $P < 0.05$, compare with control.

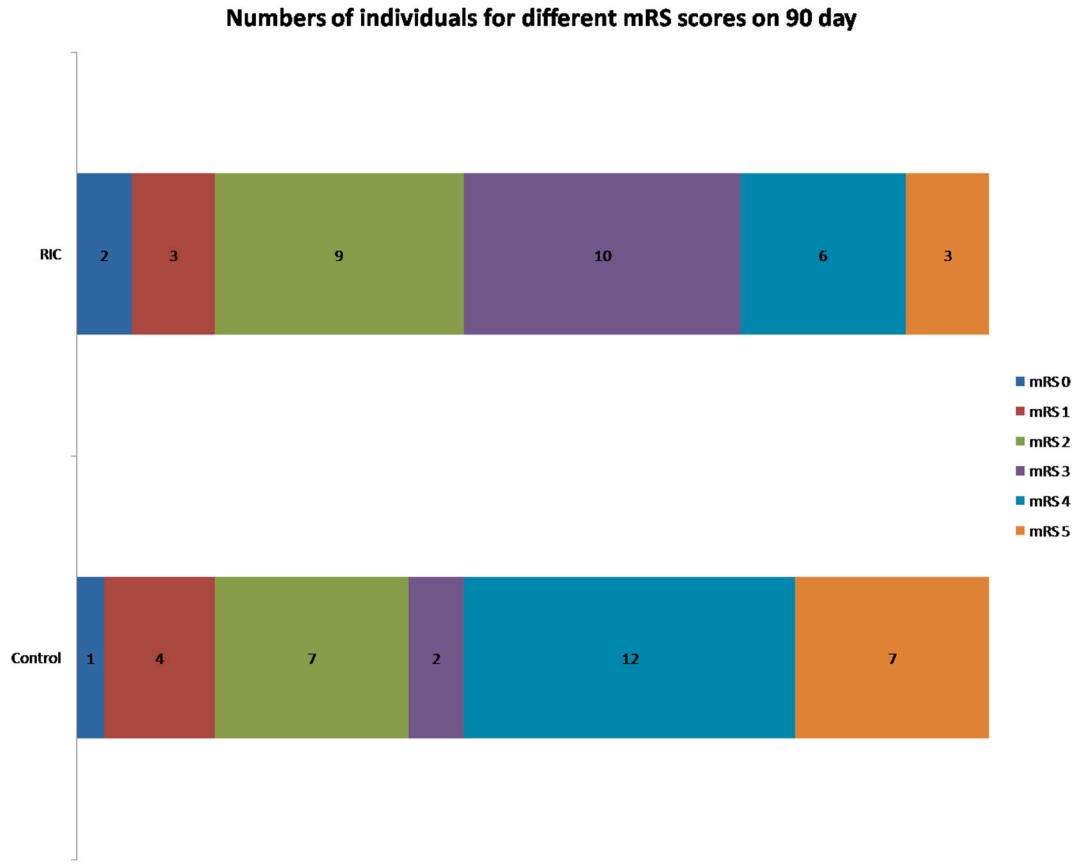

Fig. 2. mRS score between the RIC group and the control group on day 90. The number of individuals with mRS score ≤3 in the RIC group (24/33) was significantly different with that in the control group (14/33) ($\chi 2 = 6.203$, $P = 0.013$).

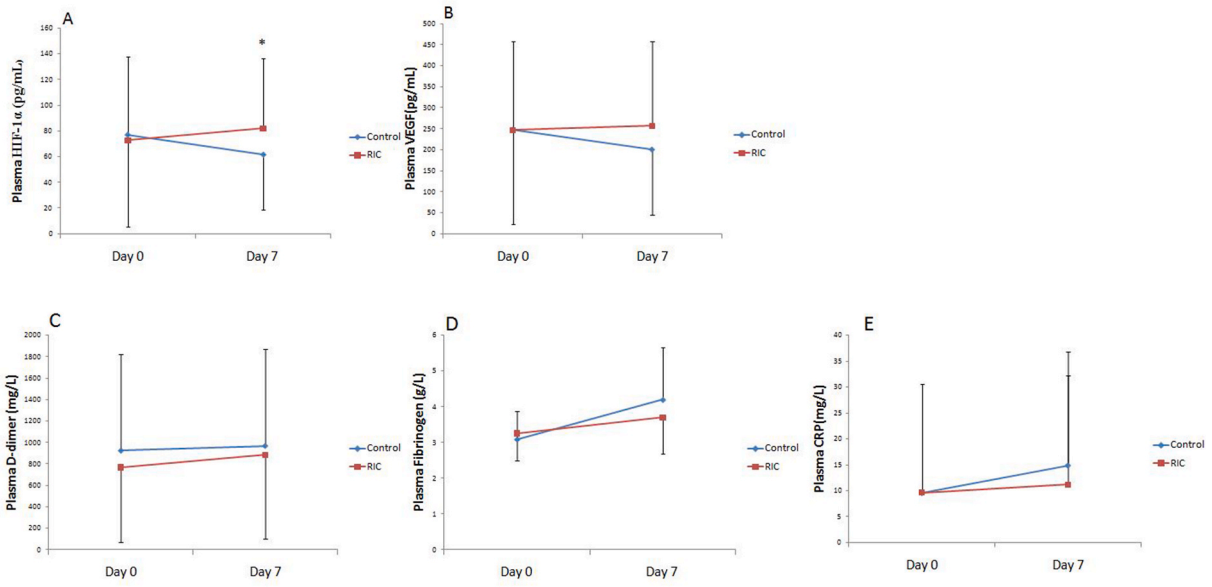

Fig. 3. Effects of RIC vs sham on plasma levels of (A) HIF-1α, (B) VEGF, (C) D-dimer, (D) Fibrinogen and (E) CRP. *P < 0.05.

recurrent events were reported in the RIC group. No adverse events were reported in either group.

3.3. Laboratory measures

Both plasma HIF-1α and VEGF increased in the RIC group from day 0 to day 7, while they decreased in the control group. The changes in plasma HIF-1α in the RIC group were statistically different from those in the control group ($P = 0.006$). However, the changes in plasma VEGF in the RIC group were not statistically different from those in the control group ($P = 0.067$). Further analysis showed that HIF-1α on day 7 was correlated with mRS score on day 90 in the RIC group ($r = -0.55$, $P = 0.045$). Furthermore, no significant differences were found in D-dimer, fibrinogen, and CRP between baseline and day 7 in either the RIC group or the control group (all $P > 0.05$). Please refer to Fig. 3 for details.

4. Discussion

In our case-control study, we assessed the effectiveness and safety of RIC in patients with acute cerebral infarction. Our results indicated that : i) Early short-term RIC treatment (7 d) can effectively improve the prognosis of neurological function in patients with acute cerebral infarction (<72 h); ii) The RIC treatment was well tolerated with good adherence; iii) The RIC treatment significantly elevated the serum HIF-1a levels, which can serve as a biomarker for the effectiveness of RIC therapy; iv) There was no evidence to support that the RIC treatment can improve cognitive function.

Previous studies have demonstrated that RIC intervention in patients with cerebral infarction within 24 h [11] (RECAST-1 study) or 72 h [13] of onset can significantly improve cerebral blood flow perfusion in the ischemic area, and improve MRS and NHISS scores at 90 days of onset. Moreover, Hougaard KD's study found that RIC treatment for patients with suspected acute ischemic stroke within 4.5 h after onset could reduce the risk of ischemic brain tissue infarction in the ischemic penumbra ($P = 0.0003$) [22]. However, the RESCUE-BRAIN study found no significant effect of RIC treatment in hospital on cerebral infarction volume in 24 h ($P = 0.57$) and neurological function at 90 days of onset ($P = 0.12$) in patients with acute ischemic stroke who plan to undergo intravenous thrombolysis or mechanical thrombectomy, compared with routine treatment [11]. Our study results suggest that short-term RIC treatment (once a day for 7 consecutive days) can effectively improve the prognosis of neurological function (day 7 NIHSS score, day 30 mRS score, day 90 mRS score, day 90 ADL score, and the number of individuals with mRS score ≤3 on day 90) in patients with acute cerebral infarction (<72 h).

Recently, the RECAST-2 study, building on the RECAST-1 study, confirmed that RIC treatment administered within 6 h of acute ischemic stroke onset was safe and well-tolerated and did not worsen neurological function and brain injury [23]. Moreover, the RICAMIS trial published in JAMA confirmed that RIC therapy for adults with acute moderate ischemic stroke (≤48 h) compared to standard care significantly increased the probability of excellent neurologic function at 90 days [24]. We recommend the prompt application of RIC treatment to suitable patients with acute ischemic stroke based on the proven efficacy and safety of RIC. Even short-term RIC therapy may be beneficial to the recovery of neurological function.

One of the major objectives and achievements of this study was to identify the serological markers of RIC treatment. Despite the therapeutic effect of remote ischemia adaptation, there remained a lack of specific biomarkers of RIC treatment that reflected this effect. Hypoxia-inducible factor 1 (HIF1), which was closely related to ischemic stroke, was identified as a key regulator of mammalian oxygen balance. The active subunit of HIF1, HIF-1α, played a major role in the pathophysiology of hypoxic-ischemic brain injury after acute cerebral infarction [17,19]. HIF-1α was the core transcriptional regulator of the hypoxic-ischemic response. Vascular endothelial growth factor (VEGF), which was regulated by HIF1, was an important factor that stimulated the formation of vascular endothelial cells in the human body. VEGF could stimulate the proliferation of vascular endothelial cells and promote the formation of collateral circulation [25]. During tissue ischemia, humoral molecules with anti-ischemic injury effects, such as HIF1 and VEGF, could be produced. These molecules could circulate throughout the body after blood flow reperfusion and play an essential role in the endogenous protection of RIC [26]. There was a significant correlation between VEGF and HIF. Previous studies have shown that HIF-1α played a key role in the protective effect of RIC on stroke. RIC could regulate the expression of HIF, such as HIF-1α, and played a key role in ischemic tissues, including in the brain and heart of experimental animals. RIC could reverse the regulation of HIF-1α in the middle cerebral artery occlusion (MCAO) model and reduce the levels of pro-inflammatory cytokines IL-1β, IL-6, and IFN-γ in the blood of aged stroke rats. Furthermore, the administration of HIF inhibitors to rats eliminated these changes and also eliminated the protective effects of RIC on infarct size, neurological function, and behavioral function. RIC activated the Akt signaling pathway rather than the ERK signaling pathway to regulate HIF level. To our knowledge, this was the first clinical study to evaluate the changes of HIF-1α and VEGF in peripheral blood of patients with acute cerebral infarction during RIC treatment. The study showed a significant increase in plasma HIF and an insignificant increase in plasma VEGF in the RIC group. Plasma HIF and VEGF decreased significantly in patients receiving RIC sham intervention. This was consistent with the results of animal experiments and previous basic studies: RIC played a protective role in cerebral infarction by regulating HIF-1a and VEGF. Interestingly, plasma HIF-1α on day 7 was significantly correlated with mRS score on day 90 in the RIC group in this study, suggesting that the level of HIF-1α after RIC intervention could partly predict the prognosis of patients. HIF-1α could be recognized as a biomarker of efficacy of RIC treatment.

It seems that the effectiveness of RIC treatment on cognitive function in patients with acute cerebral infarction is still inconclusive and requires further studies. Liang KK's Study demonstrated that continuous 14-day RIC treatment in patients with acute ischemic stroke led to improved MoCA scores [(25.26 ± 1.48) and (23.92 ± 1.75), $(P = 0.002)$] [27]. This suggests that RIC treatment may be beneficial in improving cognitive impairment after acute ischemic stroke. Similarly, Zhao W's study found that 12-month RIC treatment can improve cognitive impairment in patients with cerebrovascular disease, particularly in visuospatial and executive

ability in cognitive function tests [28]. The existing mechanisms suggest that RIC treatment may upregulate the target genes of hypoxia-inducible factors such as vascular endothelial growth factor, erythropoietin, and glucose transporter to protect nerve cells [29, 30]. It may also protect mitochondria, increase antioxidant mechanisms, and have anti-apoptotic and anti-inflammatory effects [31] to improve patients' cognitive impairment. However, the RECAST study [11] found no significant difference in Mini-Mental State Examination (MMSE) scores between the RIC treatment group and control group at 90 days. Similarly, Joung et al. found that RIC could not reduce the risk of cognitive impairment in patients undergoing off-pump coronary artery bypass graft surgery [32]. In this present study, no significant difference was found in MoCA scores between the groups (the RIC group and the control group) or within the group (baseline, day 7, and day 30). Given the sample size and follow-up time of this study, a larger clinical study is required to clarify the relationship between RIC treatment and cognitive function.

Previous studies have demonstrated that RIC treatment can be administered via unilateral or bilateral ischemia of the upper or lower limbs. For instance, in the RESCUE BRAIN study, patients with acute ischemic stroke were treated with RIC on one lower limb [15]. However, in the field of ischemic cerebrovascular disease treatment, most studies have employed RIC treatment on unilateral or bilateral upper limbs [33]. Currently, no clinical study has compared the advantages and disadvantages of RIC treatment between upper and lower limbs, or between unilateral and bilateral limbs. Nevertheless, based on the research findings of non-human primates, specifically rhesus monkeys, RIC treatment via bilateral limb ischemia was more effective than that via unilateral limb ischemia [34]. In this study, we applied RIC treatment through bilateral upper limb ischemia induction, which yielded a favorable therapeutic effect in clinical practice.

As a prospective case-control study, this research aimed to evaluate the effectiveness and safety of early short-term RIC therapy and identify HIF-1a as a serological marker of RIC treatment. However, there are several limitations to the study. Firstly, the sample size was relatively small. Secondly, RIC treatment was only administered for 7 days. Thirdly, all patients were inpatients. These limitations restrict our ability to conduct deeper hierarchical research on certain issues. For instance, it remains unclear whether longer RIC treatment would result in better benefits or whether there are differences in efficacy between upper or lower limb RIC and unilateral or bilateral limb RIC. Therefore, larger clinical studies are necessary to explore these issues in more depth.

5. Conclusions

In conclusion, this study suggests that RIC is a clinically feasible, noninvasive, effective, and well-tolerated intervention for patients with acute cerebral infarction. Early short-term RIC treatment, performed through bilateral upper limb induction ischemia, can effectively improve the prognosis of neurological function. HIF-1α can serve as a biomarker for assessing the effectiveness of RIC treatment. Ongoing further investigations are needed to develop this promising stroke therapy.

Author contribution statement

Qiong Zeng: Kun Lin: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Peiqi Huang: Ziteng Wang: Performed the experiments.
Liling Wei: Contributed reagents, materials, analysis tools or data.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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