

Original Article

Remote ischemic postconditioning promotes collateral circulation and down-regulates TLR4/NF- κ B signaling pathway in patients with acute ischemic stroke

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Abstract: *Background:* This study aimed to examine the effect of remote ischemic postconditioning on collateral circulation and TLR4/NF- κ B signaling pathway in Chinese patients with acute ischemic stroke (AIS) due to middle cerebral artery (MCA) stenosis. *Methods:* A total of 96 patients with AIS due to MCA were randomly assigned to two groups (experimental group A and control group B). Patients in both groups underwent clinical treatment and physical training. The experiment group also received remote ischemic postconditioning training, where each patient was trained 5 days a week for 8 weeks. Computed tomography angiography (CTA) of intracranial and cervical arteries was used for evaluating leptomeningeal collaterals. Regional leptomeningeal collateral (rLMC) score was applied for all patients' collateral circulation evaluation. The National Institutes of Health Stroke Scale (NIHSS) score and the Fugl-Meyer Assessment (FMA) were applied for the evaluation of quality of life at baseline and endpoint. Blood samples were collected for analysis of plasma concentrations of TLR4 and NF- κ B. *Results:* Demographic data were similar between groups. At endpoint, compared with group B, the NIHSS score and serum levels of TLR4 and NF- κ B in group A were significantly lower ($P < 0.05$), while the scores of FMA and rLMC in group A were significantly higher ($P < 0.05$). Positive correlations were observed between levels of TLR4 and NF- κ B ($r = 0.689$, $P < 0.05$). TLR4 levels were inversely correlated with rLMC score ($r = -0.645$, $P < 0.05$). *Conclusions:* The current results indicated that remote ischemic postconditioning therapy can down-regulate the overexpression of TLR4 and NF- κ B after cerebral infarction, reduce inflammatory response, promote the formation of cerebral collateral circulation, improve motor function and improve quality of life in AIS patients, which might serve as a routine method for novel treatment of AIS.

Keywords: Remote ischemic postconditioning, acute ischemic stroke, TLR4, collateral circulation, rehabilitation

Introduction

Acute ischemic stroke (AIS) is one of the leading causes of disability with high morbidity and mortality.

The high incidence of stroke causes great harm and burden to families as well as society [3]. Ischemic stroke occurs due to insufficient blood and oxygen supply to the brain, which results in death of neurons, and ischemic stroke accounts for 77% of all strokes [4]. Following AIS, the cerebral collateral circulation can improve blood flow, and maintain good cerebral perfusion. Good collateral circulation can save the ischemic penumbra, which is of great predictive value for the prognosis of patients with intravenous thrombolysis [5]. Numerous stud-

ies have shown that inflammation is closely related to nerve cell death and leads to neurological deficits. Toll-like receptors (TLRs), a kind of transmembrane receptor distributed on the surface of the immune cells, participate in specific identification of different pathogens, which contributes to the systemic inflammatory response [6].

The transcription factor NF- κ B is one of the key factors leading to inflammation [7]. In clinical studies, rehabilitation exercise therapy increases brain volume in areas implicated in executive processing [8]. Remote ischemic postconditioning (RIPostC) is a kind of rehabilitation exercise therapy and an endogenous protective approach, in which several transient cycles of noninvasive ischemia and reperfusion are

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implemented to a remote organ or tissue in order to improve ischemic tolerance [9]. In the present study, patients with AIS due to MCA were studied to examine the effects of RIPostC treatment on collateral circulation and the TLR4/NF- κ B signaling pathway.

Methods

Subjects

Ninety-six inpatients (18 years or older) with AIS due to MCA from the Neurology Department were enrolled from Sept 2016 to Aug 2018. Inclusion criteria were (1) meeting the diagnostic criteria of "Chinese Guidelines for the Diagnosis and Treatment of Acute Cerebral Ischemic Stroke 2014"; (2) Fugl-Meyer Assessment (FMA) score no more than 75; and (3) having steady vital indexes. Exclusion criteria were: (1) a history of cerebral hemorrhage, brain trauma, tumor stroke; (2) cardiogenic embolization, endovascular treatment, or intravenous thrombolysis; (3) cardiogenic embolization and intravascular treatment; and (4) severe cognitive impairment or aphasia. All of our enrolled patients did not take nonsteroidal anti-inflammatory drugs, steroids, immunosuppressants or opioids for at least 2 months. Patients did not experience any events that could affect TLR4 expression, including surgery, blood transfusion, inflammation or tumor, in the last 3 months. This study was approved by the Ethics Committee of the Six Affiliated Hospital of Yangzhou Medical University. All subjects gave written informed consent.

Materials and methods

Subjects were randomly assigned to two groups, experimental group A (n=48) and control group B (n=48). There were no significant differences between the two groups in general information (gender ratio, age, body mass index [BMI], hypertension, diabetes, blood lipids). All patients received routine therapies. Neurological routine treatment included maintaining the stability of vital signs, controlling blood pressure and blood glucose, providing anti-platelet aggregation and nutrition to brain cells. Routine rehabilitation training programs included physical therapy, bed activities, balance training and transfer. In addition to routine therapies, patients in the experimental group also received RIPostC. The sphygmomanometer sleeve was

fixed to the upper limb of the patient's healthy side, pressurized to 200 mmHg for 5 min and rested for 5 min. This cycle was repeated 5 times, for 5 days a week, and lasting for 8 weeks. During hospitalization, it was performed by trained nurses, and the family members who take care the patients were trained before the patients were discharged from the hospital. Weekly telephone visits and training supervision were conducted. All the rating scales were conducted by one attending physician in the Department of Neurology and one rehabilitation therapist. The unified scale was used for the test in order to minimize environmental interference on the test.

Data collection and laboratory measurements

Computed tomography angiography (CTA) of intracranial and cervical arteries was used to evaluate leptomeningeal collaterals. Regional leptomeningeal collateral (rLMC) score [10] was applied for all patients' collateral circulation evaluation, with the following main contents of the valuation: M1-M6 areas of Alberta Stroke Program Early CT Score (ASPECTS), lateral fissure in basal ganglia region, and anterior cerebral artery (ACA). The National Institutes of Health Stroke Scale (NIHSS) score and the FMA score for motor impairment were used before treatment and 8 weeks after treatment to assess therapeutic efficacy. TLR4/NF- κ B levels in serum were measured with ELISA (Kanlang Biological Technology Co., LTD. Shanghai KL-H1539c) before and after treatment.

Statistical analysis

General clinical data including mean age, BMI, TC, TG, HDL-C, LDL-C between groups were compared with independent sample t-test, while dichotomous variables such as gender, hypertension, hyperlipidemia, diabetes, and history of smoking and drinking between groups were compared with chi-square analysis. Data of NIHSS, FMA, TLR4, NF- κ B, and rLMC at baseline, at endpoint, and their corresponding changes between groups were compared with independent sample t-test. The potential relationships between rLMC score and serum levels of TLR4 and NF- κ B were analyzed with Spearman's correlation analysis. All statistical analyses were performed using SPSS v24.0 software (SPSS, Chicago, IL). A P value of <0.05 was considered as statistical significance.

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Table 1. Baseline characteristics of patients

	Experimental Group A (n=48)	Control Group B (n=48)	t/ χ^2	P
Demographics	-	-	-	-
Mean age (y)	55.7±9.0	55.6±10.7	1.46	0.98
Men, No. (%)	25 (52.1%)	23 (47.9%)	0.167	0.683
Smoking	13 (27.1%)	15 (31.3%)	0.202	0.653
Drinking history	19 (39.6%)	17 (35.4%)	0.178	0.673
BMI (kg/m ²)	24.6±2.2	25.1±3.2	2.145	0.49
Hypertension	33 (68.8%)	30 (62.5%)	0.416	0.519
Diabetes	20 (41.7%)	24 (50.0%)	0.617	0.413
Hyperlipidemia	31 (64.6%)	35 (72.9%)	0.776	0.378
TC (mmol/L)	4.76±0.91	4.73±1.15	2.738	0.614
TG (mmol/L)	1.88±0.09	1.86±1.01	3.127	0.811
HDL-C (mmol/L)	1.26±0.27	1.25±0.29	-4.302	0.076
LDL-C (mmol/L)	2.55±0.65	2.59±0.61	-1.321	0.431

BMI, body mass index; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

Table 2. Comparisons of rLMC and TLR4/NF- κ B between groups

		Experimental Group A	Control Group B	F	P
NIHSS score	Baseline	12.43±4.11	13.40±2.86	4.503	0.189
	Endpoint	5.31±1.01	8.46±1.11	0.780	0.000*
FMA score	Baseline	31.0±14.39	32.85±12.07	2.10	0.496
	Endpoint	66.30±11.08	61.09±10.78	2.875	0.013*
TLR4 (ng/mL)	Baseline	3.70±0.58	3.90±0.41	1.461	0.497
	Endpoint	2.10±0.13	2.90±0.17	0.145	0.019*
NF- κ B (ng/mL)	Baseline	115.63±24.45	120.41±18.97	4.473	0.071
	Endpoint	73.13±14.15	85.67±9.57	6.669	0.010*
rLMC score	Baseline	6.75±1.76	7.15±1.56	0.067	0.796
	Endpoint	14.53±2.01	11.77±1.98	2.768	0.014*

NIHSS, National Institutes of Health Stroke Scale; FMA, Fugl-Meyer Assessment; TLR4, Toll-like receptors 4; NF- κ B, Nuclear factor kappa-B; rLMC, Regional leptomeningeal collateral. *Compared with control group B, P<0.05.

Results

Demographic and clinical data

As shown in **Table 1**, there were no significant differences between groups in gender and age distribution, BMI, blood lipid levels, and history of smoking or alcohol consumption.

Comparisons of rLMC and TLR4/NF- κ B between groups

There were no significant differences in NIHSS score, FMA score, rLMC score, and TLR4 and NF- κ B levels between the two groups before

treatment (P>0.05). At the endpoint, compared with group B, the NIHSS score and serum levels of TLR4 and NF- κ B in group A were significantly lower (P<0.05), while the scores of FMA and rLMC in group A were significantly higher (P<0.05). Detailed data were shown in **Table 2**.

Correlation of serum TLR4 levels with the rLMC score

In addition, positive correlations were found between serum levels of TLR4 and NF- κ B (r=0.689, P<0.05, **Figure 1**), while serum TLR4 levels were inversely correlated with the rLMC Score (r=-0.645, P<0.05, **Figure 2**).

Discussion

Remote ischemic post-conditioning (RIPostC) involves repeated cessation of blood flow to healthy sites distant from ischemic foci to create ischemia in the tissue. Clinical trials involving RIPostC have mainly focused on cardiac surgeries such as coronary artery bypass grafting and stent implantation, yet there are very few studies on the effectiveness of RIPostC

in cerebral ischemic diseases. Our study aimed to explore the correlation between RIPostC and collateral circulation, and to examine whether RIPostC could down-regulate TLR4/NF- κ B signaling pathway in patients undergoing acute cerebral infarction so as to alleviate inflammatory responses and promote neurological functional recovery.

Effect of RIPostC on collateral circulation in patients undergoing acute cerebral infarction

Good cerebrovascular collateral circulation can increase blood flow to cerebral foci so as to lengthen the survival duration of ischemic pen-

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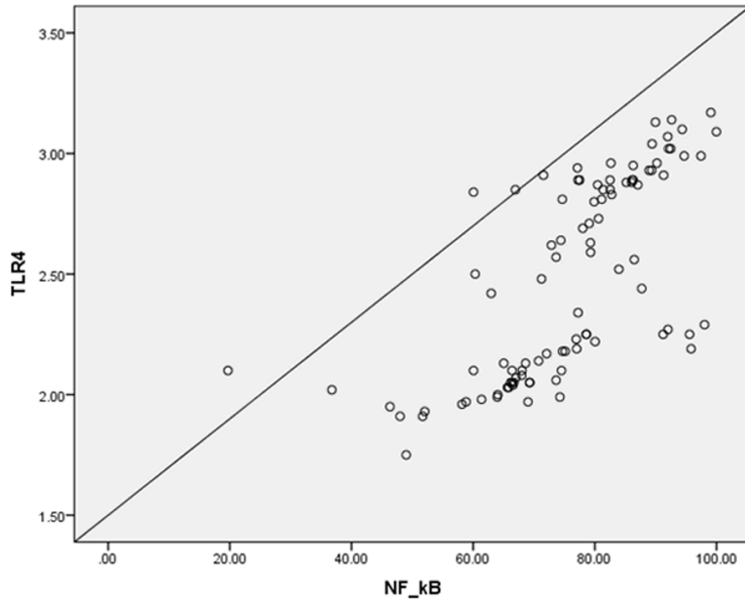


Figure 1. Positive correlations were found between serum levels of TLR4 and NF- κ B ($r=0.689$, $P<0.05$).

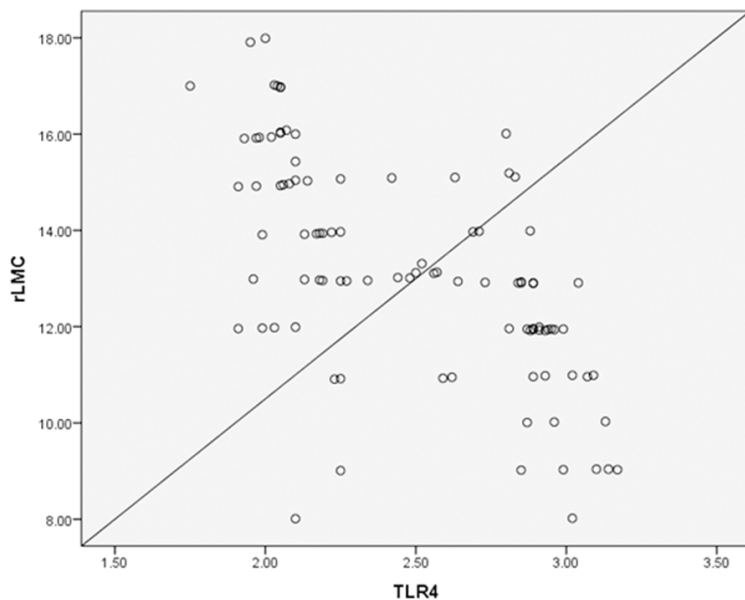


Figure 2. Serum TLR4 levels were negatively correlated with the rLMC Score ($r=-0.645$, $P<0.05$).

umbra and improve clinical neurological function. Previous research showed that RPostC increased myocardial blood perfusion and accelerated revascularization to facilitate neovascularization [11]. Results of our study showed that there was no difference in terms of rLMC score between these two groups at baseline, and that the cerebrovascular collateral cir-

ulation at endpoint was significantly better in group A with RPostC as compared with group B. This finding indicated that RPostC could facilitate the establishment of cerebrovascular collateral circulation in patients with AIS due to MCA. This might be because RPostC stimulates the release and recruitment of vascular endothelial growth factor, playing a positive role in angiogenesis [12]. The relationship between serum indexes and cerebrovascular collateral circulation as well as the underlying mechanism remain to be examined in further research.

Roles of TLR4/NF- κ B signaling pathway in ischemia-reperfusion injuries induced by cerebral infarction

Upon occurrence of cerebral infarction, blood supply to part of the brain is blocked and disordered energy metabolism occurs, resulting in ion imbalance, generation of oxygen free radicals and acute inflammatory reactions [13, 14]. Toll-like receptors (TLRs) are a family of pattern recognition receptors on the immune cell surface with a variety of ligands, of which TLR4 are widely distributed in the central nervous system and participate in the genesis and development of cerebral ischemia. Previous research demonstrated that TLR4 could recognize endogenous ligands released by cerebral ischemia-reperfusion injuries to activate the TLR4/NF- κ B sig-

nalizing pathway, which may further result in overexpression of adhesion molecules and corresponding receptors and induce a series of inflammatory reactions, thereby influencing the neurological function [14].

Acute cerebral infarction may involve the blood-CSF barrier to infiltrating peripheral leukocytes

and excite endogenous microglial cells, leading to the release of heat shock protein, S100 protein and other damage-associated molecular patterns (DAMP) that specifically bind to and activate TLRs [2]. TLR4 may be expressed to activate NF- κ B signaling pathway and NF- κ B may in turn be converted into p60 heterodimer of transcriptional activity from p50 homodimer. Activated NF- κ B may move from cytoplasm to the nucleus to perform transcription. Consequently, a series of inflammatory factors may be produced, and inflammatory reactions may be induced to increase apoptosis of cerebral tissue and cells, resulting in brain tissue damage. At the same time, endogenous substances generated from brain damage may further develop into TLR4 ligands, which may aggravate inflammatory reactions and induce neurological functional lesions [15]. According to the result of our study, the TLR4/NF- κ B level was lower in the group that received RPostC compared with the control. TLR4 expressed by peripheral inflammatory cells plays a critical role in ischemic stroke-induced inflammatory damage [1, 2]. Therefore, our results of lower serum TLR4/NF- κ B suggest alleviation of inflammation with RPostC intervention. Both NIHSS Score and Fugl-Meyer Assessment are internationally recognized tools for assessing limb motor function in cerebral stroke patients. These assessments with detailed content, high sensitivity and specificity include consciousness, muscular force, coordination movement and other aspects. For both groups, the NIHSS and FMA scores before RPostC did not differ from each other. After receiving eight-week RPostC, however, the NIHSS score was significantly lower in group A than in the control group, and the FMA score was significantly higher in group A than in the control group. In addition, serum TLR4 level was negatively correlated with rLMC score and was positively correlated with serum NF- κ B level. These results suggested that RPostC could down-regulate inflammatory reactions, promote neurological functional recovery and help patients improve their motor ability and activities of daily living. It was found in a recent animal study using rat models of cerebral infarction that ischemia-reperfusion injuries may increase the expression of TLR4 and NF- κ B; chrysanthemum ester, an NF- κ B inhibitor, might reduce the expression of TLR4 and NF- κ B to improve the neurological function [16]. Animal studies also have shown that curcumin might suppress inflammatory

reactions through inhibiting TLR4/NF- κ B signaling pathway, thereby protecting ischemic brain injuries [17]. In an experiment using rat models of middle cerebral arterial infarction, RPostC administration to left lower extremities reduced the volume of cerebral infarction and improved the result of behavioral testing compared to the control group [18]. This is the first clinical trial to report that treatment with RPostC inhibits the overexpression of TLR4 and NF- κ B in patients with ischemic stroke. In rats with middle cerebral artery infarction, RPostC treatment significantly inhibited the overexpression of TLR4 and NF- κ B, thereby effectively improving neurological defects and reducing the infarction volume [19]. The results in this clinical trial are consistent with animal studies.

Summary on the protective effect of RPostC and possible mechanisms

The neuroprotective effect of RPostC on acute cerebral infarction patients may involve complex mechanisms. Rat experiments suggest that possible mechanisms may be as follows: caspase3 activity and cytochrome C transfer from mitochondria to cytoplasm are inhibited, which reduces the generation of endogenous inflammatory substances, thereby inhibiting apoptosis. Furthermore, RPostC can improve cerebral blood flow and decrease the generation of oxygen free radicals, which may help improve ischemia-reperfusion injuries. RPostC can also activate such endogenous active substances as adenosine, opioids and bradykinin to protect vessels [20]. Clinical trials have also confirmed that early RPostC therapy is safe and effective in patients with intravenous thrombolysis and intravascular therapy and can improve clinical prognosis and NIHSS score of patients [21, 22].

In summary, for patients undergoing cerebral infarction, RPostC can down-regulate the overexpression of TLR4/NF- κ B, reduce inflammatory reactions, facilitate the formation of collateral circulation, and improve motor function to enhance the quality of life of stroke patients. With advantages such as simplicity, low cost and high safety, RPostC is expected to gain popularity as a secondary preventive measure for cerebral infarction. Timing of RPostC and whether it can be applied jointly with neurovascular intervention or intravenous thrombolysis are topics of further research.

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So far, research on the effect of RPostC on prognosis of cerebral infarction has mainly focused on its stimulatory effect on neovascularization, while research on its effect on the control of post-cerebral infarction inflammation are rare. Our study found that RPostC was able to alleviate ischemia-reperfusion injuries induced by cerebral infarction, down-regulate inflammatory reactions and increase the body's tolerance to ischemia and anoxia so as to achieve a better prognosis. Although RPostC can lower the risk of cerebrovascular events in ischemic stroke patients [23], research on RPostC intensity has been scanty at present, and whether the therapeutic effect varies depending on RPostC intensity still remains to be established. Our study also had some limitations, namely the short follow-up duration and failure to track the relapse rate of cerebral stroke.

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Disclosure of conflict of interest

None.

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