Neuropsychiatric Disease and Treatment

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REVIEW

Effects of Remote Ischemic Conditioning on Cerebral Hemodynamics in Ischemic Stroke

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

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Abstract: Ischemic stroke is one of the most common cerebrovascular diseases and is the leading cause of disability all over the world. It is well known that cerebral blood flow (CBF) is disturbed or even disrupted when ischemic stroke happens. The imbalance between demand and shortage of blood supply makes ischemic stroke take place or worsen. The search for treatments that can preserve CBF, especially during the acute phase of ischemic stroke, has become a research hotspot. Animal and clinical experiments have proven that remote ischemic conditioning (RIC) is a beneficial therapeutic strategy for the treatment of ischemic stroke. However, the mechanism by which RIC affects CBF has not been fully understood. This review aims to discuss several possible mechanisms of RIC on the cerebral hemodynamics in ischemic stroke, such as the improvement of cardiac function and collateral circulation of cerebral vessels, the protection of neurovascular units, the formation of gas molecules, the effect on the function of vascular endothelial cells and the nervous system. RIC has the potential to become a therapeutic treatment to improve CBF in ischemic stroke. Future studies are needed to highlight our understanding of RIC as well as accelerate its clinical translation.

Keywords: remote ischemic conditioning, cerebral hemodynamics, ischemic stroke, cerebral blood flow

Introduction

Ischemic stroke is a common kind of cerebrovascular disease with high morbidity, mortality, and disability rates. More than 10 million people worldwide suffer from ischemic stroke each year.[1] It becomes a socio-economic problem when it is more prevalent among a younger age group, with resultant permanent disability, cognitive and motor disorders, and dementia. This brings ischemic stroke to the attention of scientists who are endeavoring to search for advanced clinical treatments to improve the prognosis of patients with ischemic stroke. Remote ischemic conditioning (RIC) offers practical value: it is effective, noninvasive, economical, and convenient. It has thus been researched intensively by cardiovascular disease specialists for many years; it has also begun to be an object of study in cerebrovascular disease.

The normal function of the brain is based on the stable CBF and cerebral autoregulation. Several studies reveal the fact that RIC can affect cerebral hemodynamics in ischemic stroke.[2,3] The mechanism by which RIC influences cerebral hemodynamics is beyond full comprehension and needs our further exploration. Table 1 shows experimental and clinical studies available at present of RIC in ischemic stroke. In September 2019, a literature search in PubMed was performed based on the combination of the following terms: "remote ischemic conditioning",

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Table 1 Experimental and Clinical Studies Available at Present of Remote Ischemic Conditioning in Ischemic Stroke

Type	Study	Stroke Model	RIC Organ	RIC Timing	RIC Protocol	Main Pathway Investigated	Improve CBF
Experimental studies	Chen et al (2018)[4]	2 h of middle cerebral artery occlusion followed by 24 h of reperfusion, male Sprague Dawley rats	Femoral arteries	Remote ischemic postconditioning	3 cycles of 15 min ischemia and 15 min reperfusion, once at the beginning of middle cerebral artery reperfusion	The mTOR/p70S6K signal pathway	Not mentioned
	Cheng et al (2018)[5]	Transient middle cerebral artery occlusion, adult male C57BL/6 mice	Bilateral femoral arteries	Remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, once immediately after reperfusion	Astrocytic plasticity	Not mentioned
	Kitagawa et al (2018)[6]	45 min of left middle cerebral artery occlusion, adult C57BL/6 mice	Upper thigh	Remote ischemic preconditioning, remote ischemic preconditioning and remote ischemic postconditioning	4 cycles of 5 min ischemia and 5 min reperfusion, 24 h or 5 min before, during, or 5 min after middle cerebral artery occlusion	Collateral circulation	Yes
	Ren et al (2018)[2]	90 min of middle cerebral artery occlusion, adult male Sprague Dawley rats	Hind limb	Remote ischemic preconditioning and remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, once immediately after MCAO surgery and once at 1 day after reperfusion, then repeated every day thereafter up to endpoint of study (7 or 14 days)	Notch signal pathway	Yes
	Gao et al (2017)[7]	Transient middle cerebral artery occlusion, male Sprague Dawley rats	Bilateral femoral artery	Remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, after 0, 10 or 30 min of brain reperfusion (R-0, R-10 and R-30 groups, respectively)	BID-mediated mitochondrial apoptotic pathway	Not mentioned
	Huang et al (2017)[8]	Middle cerebral artery occlusion, male Sprague Dawley rats	Bilateral hind limbs	Remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, once	No specific pathway mentioned	Not mentioned
	Khaksari et al (2017)[9]	Bilateral carotid artery occlusion for 20 min followed by reperfusion for 72 h, adult male BALB/C mice	Left renal artery	Remote ischemic preconditioning	3 cycles of 5 min ischemia and 5 min reperfusion, 24 h before global cerebral ischemia	Erythropoietin	Not mentioned
	Ma et al (2017)[10]	Middle cerebral artery occlusion, male Sprague Dawley rats	Bilateral femoral artery	Remote ischemic preconditioning	3 cycles of 15 min ischemia and 15 min reperfusion, once at 60 min after middle cerebral artery occlusion	Prevention of collateral collapse	Yes

	Ramagiri et al (2017)[11]	Bilateral common carotid occlusion, male Wistar rats	Bilateral femoral artery	Remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, once after cerebral ischemia	Heme oxygenase-1/BDNF pathway	Not mentioned
	Xu et al (2017)[12]	30 min of bilateral common carotid arteries occlusion combined with permanent occlusion of the left distal middle cerebral artery, adult male Sprague Dawley rats	Left femoral artery	Remote ischemic postconditioning	3 cycles of 15 min ischemia and 15 min reperfusion, once at 1.5 h before distal middle cerebral artery occlusion	Extrinsic apoptotic pathway and TRAIL-receptors expression	Not mentioned
	Zhang et al (2017)[13]	Middle cerebral artery occlusion, male Sprague Dawley rats	Bilateral femoral artery	Remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, once at the beginning of the reperfusion	AKT pathway	Not mentioned
	Chen et al (2016)[14]	Middle cerebral artery occlusion, male Sprague Dawley rats	Left femoral artery	Remote ischemic postconditioning	3 cycles of 5 min ischemia and 5 min reperfusion, once at 0, 1 or 3 h after reperfusion	MyD88-TRAF6-P38 MAP-kinase pathway of neutrophils	Not mentioned
	Liu et al (2016)[15]	90 min occlusion of the right middle cerebral artery, male Sprague Dawley rats	Bilateral hind limb	Remote ischemic preconditioning	4 cycles of 5 min reperfusion and 5 min ischemia, once at 1 h before middle cerebral artery occlusion	Significant alterations in peripheral immune responses	Not mentioned
	Wang et al (2016)[16]	120 min middle cerebral artery occlusion, adult male Sprague Dawley rats	The expression and location of HMGB1	Remote ischemic preconditioning	4 cycles of 5 min ischemia and 5 min reperfusion, once at 40 min prior to reperfusion	The expression and location of HMGB1	Not mentioned
	Li et al (2015a)[17]	Transient middle cerebral artery occlusion, male CD1 mice	Bilateral femoral artery	Remote ischemic postconditioning	3 cycles of 5 min reperfusion and 5 min ischemia, once immediately after stroke onset	Nrf2 ARE (antioxidant response element) pathway	Not mentioned
	Li et al (2015b)[18]	Transient middle cerebral artery occlusion, adult female Sprague Dawley rats	Bilateral femoral arteries	Remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, once at the same time as reperfusion	AQP4 downregulation in astrocytes	Not mentioned
	Li et al (2015c)[19]	Transient middle cerebral artery occlusion, male Sprague Dawley rats	Bilateral femoral arteries	Remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, once at the same time as reperfusion	p38MAPK signal pathway	Not mentioned

(*Continued*)

Table 1 (Continued).

Type	Study	Stroke Model	RIC Organ	RIC Timing	RIC Protocol	Main Pathway Investigated	Improve CBF
	Qi et al (2015)[20]	Middle cerebral artery occlusion, male Sprague Dawley rats	Bilateral femoral arteries	Remote ischemic preconditioning and remote ischemic postconditioning	3 cycles of 10 min occlusion/10 min reperfusion, once at 30 min of ischemia or at the onset of reperfusion	AKT pathway	Not mentioned
	Xiao et al (2015)[21]	Distal middle cerebral artery occlusion, adult male Sprague Dawley rats	Bilateral femoral arteries	Remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, once at the same time as the bilateral common carotid arteries reperfusion	Peripheral nerves	Not mentioned
	Zong et al (2015)[22]	Middle cerebral artery occlusion, male Sprague Dawley rats	Proximal hind limbs	Remote ischemic postconditioning	3 cycles of 10 min ischemia and 10 min reperfusion, once at the beginning of reperfusion	HIF-1α	Not mentioned
	Chen et al (2014)[23]	2 h of middle cerebral artery occlusion, Sprague Dawley rats	Left femoral artery	Remote ischemic postconditioning	3 cycles of 15 min reperfusion and 15 min ischemia, once at the same time as reperfusion	By reversing endothelial nitric oxide synthase uncoupling	Not mentioned
	Cheng et al (2014)[24]	90 min of middle cerebral artery occlusion, male Sprague Dawley rats	Right hind limb	Remote ischemic postconditioning	3 cycles of 5 min reperfusion and 5 min ischemia, once at the beginning of reperfusion	Upregulating STAT3 and reducing apoptosis	Not mentioned
	Hoda et al (2014)[25]	Embolic middle cerebral artery occlusion, C57BL/6J wild type ovariectomized mice	Limb	Remote ischemic preconditioning	4 cycles of 10 min ischemia and 10 min reperfusion, once at 2 h poststroke	No specific pathway mentioned	Yes
	Hoda et al (2012)[26]	Embolic middle cerebral artery occlusion, C57BL/6J wild-type male mice	Left limb	Remote ischemic preconditioning	5 cycles of 5 min ischemia and 5 min reperfusion, once at 2 h after embolic middle cerebral artery occlusion	No specific pathway mentioned	Yes
	Hu et al (2012)[27]	2 h right middle cerebral artery occlusion, male Sprague Dawley rats	Right hind limb	Remote ischemic preconditioning	3 cycles of 5 min ischemia and 5 min reperfusion, once at 1 h before brain ischemia	Depend on the activation of adenosine A1 receptors and by reduction in oxidative stress, inflammation and endogenous antioxidant preservation	Not mentioned

	Peng et al (2012)[28]	8 min of four-vessel occlusion in rats, adult male Sprague Dawley rats	Bilateral hind limbs	Remote ischemic postconditioning	3 cycles of 15 min ischemia and 15 min reperfusion, once immediately after 8 min of four-vessel	PI3K/Akt pathway	Not mentioned
	Qi et al (2012)[29]	Transient middle cerebral artery occlusion, Sprague Dawley rats	Bilateral femoral artery	Remote ischemic postconditioning	3 cycles of 10 min occlusion/10 min release, at 0, 10, or 30 min of reperfusion	AKT/GSK3β-dependent autophagy	Not mentioned
	Sun et al (2012)[30]	90 min of middle cerebral artery occlusion followed by 72 hrs of reperfusion, male Sprague Dawley rats	Bilateral femoral artery	Delayed remote limb ischemic postconditioning	3 cycles of occlusion 15 seconds/5 mins/8 mins ischemia/15 seconds/5 mins/8 mins reperfusion, once at 3 or 6 h after reperfusion	Mitochondrial K(ATP) channels	Not mentioned
	Wei et al (2012)[31]	Left distal middle cerebral artery occlusion, male Sprague Dawley rats	Left hind limb	Remote ischemic preconditioning	3 cycles of 5 min ischemia and 5 min reperfusion, once immediately before stroke	No specific pathway mentioned	Not mentioned
	Yuan et al (2012)[32]	Occlusion of the left common carotid arteries for 30 min combined with permanent occlusion of the left distal middle cerebral artery, male Wistar rats	Left thigh	Remote ischemic preconditioning	3 cycles of 5 min ischemia and 5 min reperfusion, 3 times per day for 3 days	No specific pathway mentioned	Not mentioned
	Hahn et al (2011)[33]	120 min middle cerebral artery occlusion, and 24 h reperfusion, P60 rats	Left hind limb	Remote ischemic preconditioning and perconditioning	4 cycles of 5 min ischemia and 5 min reperfusion, at 40 min prior to middle cerebral artery occlusion	No specific pathway mentioned	Not mentioned
	Ren et al (2009)[34]	30 min bilateral common carotid arteries occlusion combined with permanent occlusion of the left distal middle cerebral artery, male Sprague Dawley rats	Femoral artery occlusion in the left limb	Remote ischemic postconditioning	3 cycles of 15 min ischemia and 15 min reperfusion, once at the beginning of reperfusion or 3 or 6 h after reperfusion	Protein synthesis inhibitor and nerve blocker eliminate the protective effect of rapid limb remote ischemic postconditioning	Not mentioned
	Ren et al (2008)[35]	Permanent occlusion of the left distal middle cerebral artery combined with a 30 min occlusion of the bilateral common carotid arteries, male Sprague Dawley rats	Left femoral artery	Remote ischemic preconditioning	2 or 3 cycles of 5- or 15-min occlusion followed with the same period of reperfusion, immediately or 12 h, 2 d before brain ischemia	No specific pathway mentioned	Not mentioned

(*Continued*)

Table 1 (Continued).

Type	Study	Stroke Model	RIC Organ	RIC Timing	RIC Protocol	Main Pathway Investigated	Improve CBF
Clinical studies	(Che et al, 2019)[36]	Acute ischemic stroke patients with intravenous recombinant tissue plasminogen activator thrombolysis	Bilateral upper limbs	Remote ischemic postconditioning	5 cycles of alternating 5 mins inflation (200 mmHg) and 5 mins deflation, once on the first day after IVT, and twice a day for 6 consecutive days	No specific pathway mentioned	Not mentioned
	Zhao et al (2018)[37]	Patients with acute ischemic stroke having large-vessel occlusion in the anterior circulation and scheduled for endovascular treatment (ET) within 6 hrs of ictus	Unilateral arm	Remote ischemic preconditioning and remote ischemic postconditioning	4 cycles of alternating 5 mins inflation (200 mmHg) and 5 mins deflation, once pre-ET, once post-ET, and once daily for 7 consecutive days	No specific pathway mentioned	No
	(Li et al, 2018)[38]	Nonthrombolysis patients with acute ischemic stroke within 72 hrs of ictus	The nonparetic arm	Remote ischemic postconditioning	4 cycles of alternating 5 mins inflation (20 mmHg above systolic blood pressure) and 5 mins deflation, from the time of enrollment to Day 14	No specific pathway mentioned	Not mentioned
	England et al (2017)[39]	Patients with acute ischemic stroke of 24 h of ictus	The nonparetic arm	Remote ischemic preconditioning	4 cycles of alternating 5 mins inflation (20 mmHg above systolic blood pressure) and 5 mins deflation, the control group received a sham procedure (cuff inflation to 30 mmHg), once within 24 h of ictus	No specific pathway mentioned	Not mentioned
	Hougaard et al (2014)[40]	Patients with acute ischemic stroke	One arm	Remote ischemic preconditioning	4 cycles of alternating 5 mins inflation (either 200 or 25 mmHg above systolic blood pressure) and 5 mins deflation, once before rt-PA treatment	No specific pathway mentioned	Not mentioned

"ischemic stroke", "ischemic preconditioning", "ischemic perconditioning", "ischemic postconditioning", "cerebral hemodynamics" and "cerebral blood flow". The reference list of relevant papers was also screened. The search was limited to publications in English, and the final references included were chosen based on the relevance to the scope of this review.

Findings of Animal Experiments and Clinical Studies

RIC mainly exerts endogenous protective effects on important organs of the body through nerve, humoral, and immune-inflammatory pathways. Its safety and efficacy in ischemic stroke have been reported.[40,41] Recent studies have shown that RIC can alleviate ischemia-reperfusion (I/R) injury.[42–44] Cerebral ischemia leads to cerebral hypoperfusion. After reperfusion, hyperperfusion is the first to be observed in almost all experimental animals, followed by hypoperfusion.[45] Neither hyperperfusion nor hypoperfusion is harmless to the recovery from cerebral ischemia. Wang et al found that after ischemia reperfusion, the hyperperfusion time in the control group lasted for 30 mins, followed by several hours of hypoperfusion. In the RIC group, in contrast, the hyperperfusion time was shortened to 20 mins, and the decreasing of hyperperfusion values was observed while the hypoperfusion values increased. These findings suggest that RIC can reduce I/R injury and improve disturbed CBF by reducing the duration and degree of hyperperfusion.[42] Zhao et al demonstrated for the first time that RIC had remarkable effects on CBF in focal cerebral ischemic rat models. They found that bilateral common carotid artery occlusion reduced CBF to approximately 30% of the baseline, and additional middle cerebral artery occlusion further decreased CBF to 20% approximately. After the common carotid artery was released, a transient hyperemic response was observed, which could be broken off by three cycles of reperfusion and occlusion of the bilateral common carotid artery. The results indicated that RIC could protect against I/R injury and be conducive to CBF.[43] Clinical trials also show this positive result. Meng et al evaluated the protective effects of RIC in patients with symptomatic atherosclerotic intracranial arterial stenosis. They found RIC could prevent recurrent stroke and shorten the average time to recovery. The degree of the abnormally elevated peak systolic velocities decline was more pronounced in the RIC group vs the control group.[44] In addition, the middle cerebral artery peak systolic blood flow velocity and pulsatility index did not change significantly before, during, or after RIC in AIS patients treated with thrombectomy.[37] And it has been demonstrated that RIC may reduce infarction tissue risk as an adjunct therapy to thrombolysis in patients with acute ischemic stroke.[40]

Research on cerebral hemodynamics has shifted from purely vascular concepts to a complex interaction of biochemical and molecular mechanisms. Factors that can affect the cardiac function, the coupling of nerves and blood vessels, the content of blood gas, the blood viscosity, the body temperature, and the automatic regulation of cerebral blood vessels may affect cerebral hemodynamics.[46] The influence of RIC on the cerebral hemodynamics of ischemic stroke may occur through the following means: it may improve cardiac function, improve collateral circulation of cerebral vessels, protect neurovascular units (NVU), induce the formation of gas molecules, affect the function of vascular endothelial cells, and affect the nervous system [Figure 1].

Mechanisms

RIC Can Improve Cardiac Function

The cerebrovascular system and the cardiovascular system are highly correlated in anatomy and physiological functions. Left ventricular ejection enters the cerebrovascular system through the aortic arch to supply blood and oxygen to the brain tissue. The brain receives one fifth of the cardiac output. It has been reported that moderate and regular physical exercise can improve cardiac function, increase CBF, and improve microcirculation.[47–49] Lieshout et al found that there was a linear correlation between CBF and cardiac output in healthy subjects, that is, when the muscles of the lower limbs were tense, cardiac output increased and the mean blood flow velocity of the middle cerebral artery (MCA) increased simultaneously.[50] Evidence also showed that left ventricle ejection fraction was one of the strongest predictors of the poststroke improvement. Preserved ejection fraction is associated with early favorable outcome in ischemic stroke.[51] All the evidence supports that improving cardiac function could be a nice way to affect cerebral hemodynamics.

Recently, several studies have shown that RIC may have an exercise equivalent.[2,52] For example, a prospective study showed that dialysates prepared from plasma of human subjects undergoing high-intensity exercise or RIC were both protective in reducing the infarct size of an isolated rabbit heart after I/R injury.[52] Kono et al studied 10 heart failure patients with left ventricular ejection fraction reduced and 10 healthy subjects. All subjects received RIC treatment for 1 week. The results showed that RIC increased coronary

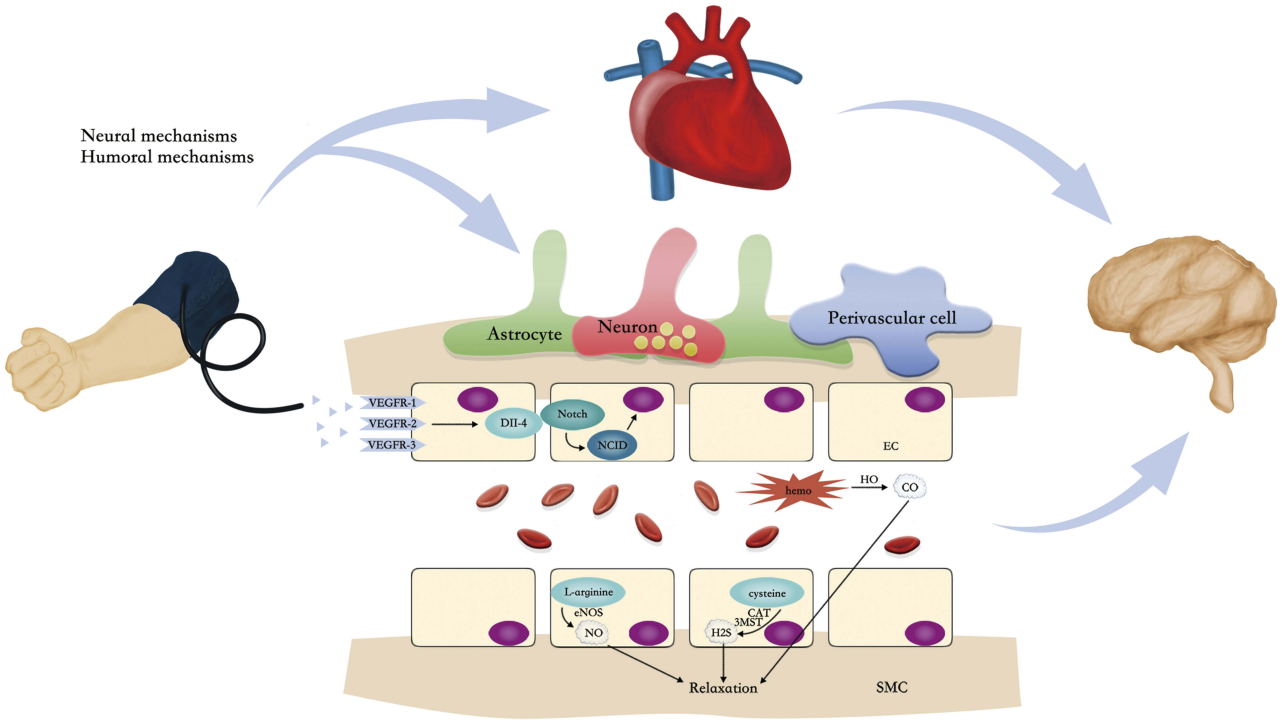

Figure 1 The simplified schema graph of potential mechanisms through which RIC influences CBF. The hypoxia induced by RIC upregulates the VEGF production, which activates VEGFR. Then, Dll-4 expression is induced and NCID is proteolytically cleaved to liberate an adjacent endothelial cell. NICD enters the nucleus and activates the transcription of Notch-responsive genes. The interaction between VEGF and the Notch signaling pathway plays a crucial role in angiogenesis. RIC can also induce the formation of three main gas molecules: NO, CO, and H_2S. They can improve CBF by relaxing smooth muscle cells. RIC can also improve CBF by protecting cardiac function and NVU.

Abbreviations: CAT, cysteine aminotransferase; CBF, cerebral blood flow; CO, carbon monoxide; Dll-4, Delta-like 4; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; H_2S, hydrogen sulfide; HO, heme oxygenase; I/R, ischemia/reperfusion; 3MST, 3-mercaptopyruvate sulfurtransferase; NCID, Notch intracellular domain; NO, nitric oxide; NVU, neurovascular unit; RIC, remote ischemic conditioning; SMC, smooth muscle cell; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

microcirculation in both patients and healthy subjects.[53] Previous experimental studies showed that although RIC failed to improve the left ventricular ejection fraction, RIC could reduce the level of plasma N-terminal pro brain-type natriuretic peptide, improve the myocardial systolic function of most patients with severe compensatory heart failure, reduce systolic blood pressure, and reduce the cardiac afterload, so as to have a positive impact on hemodynamics.[54] In a randomized controlled study involving 50 subjects with mild ischemic heart failure, RIC treatment of the upper limb twice a day for 6 weeks could improve the cardiac function of patients, improve the left ventricular ejection fraction, extent the 6 mins walk distance, and reduce the level of B-type natriuretic peptide, thereby affecting the New York Heart Function Assessment score.[55] RIC may play the role of myocardial protection through the survival activating factor enhancement (SAFE) pathway and the reperfusion injury salvage kinases (RISK) pathway:

The SAFE Pathway

The SAFE pathway is a novel protective pathway against reperfusion injuries, which consists of the Janus kinase 2 (JAK2) signal transducer and activator of transcription 3 (STAT-3) signaling cascade.[56] Previous research has indicated the cardioprotection by RIC was associated with activation of the SAFE signaling pathway.[57] Tamareille et al reported that local ischemic postconditioning +RIC increased phospho-STAT-3 levels when compared to local ischemic postconditioning alone, which highlighted the key role of the SAFE pathway.[58] Additional study has revealed that remote ischemic postconditioning protects myocardial cells by the recruitment of the RISK and SAFE pathways. However, remote ischemic preconditioning may not.[59] The activation of SAFE pathway may be different in different RIC protocols.

The RISK Pathway

The RISK pathway is another universal signaling cascade composed of two parallel cascades, the phosphoinositide-3 kinase/Akt and MEK1-ERK1/2. Activation of the RISK pathway by RIC has been confirmed to be associated with cardioprotection in many experimental models.[60] Recent studies also observe that interaction exists between the RISK and SAFE signaling pathways in mediating RIC.[58]

Further studies are required to determine the relationship between the SAFE and RISK pathway and their function of myocardial protection.

Based on the researches cited above, RIC may exert their myocardial protection through the SAFE pathway and RISK pathway, thereby improving cerebral hemodynamics. Long-term RIC treatment may be beneficial to patients either with heart failure or with ischemic stroke. The protective effects of exercise and RIC on cardiac function and cerebral hemodynamics deserve further study.

RIC Can Improve Cerebral Collateral Circulation

The primary collaterals consist of circulatory anastomoses that constitute the circle of Willis, and the secondary collaterals consist of the pial or leptomeningeal collaterals. The collateral circulation plays an important role in maintaining tissue viability in the first hours of ischemic stroke. It has been reported that collateral circulation is a key factor in predicting the prognosis of ischemic stroke.[61] Thus, promoting collateral circulation formation and strengthening collateral circulation function are important strategies for the treatment or prevention of ischemic diseases.[62] Evidence showed that the higher the ischemic edge microvascular density, the better the clinical outcome in stroke patients.[63] RIC has been proven that it could significantly develop leptomeningeal anastomoses and enhance the vessel diameter of anterior cerebral artery-middle cerebral artery anastomoses. RIC may play a neuroprotective role by enhancing the leptomeningeal collateral circulation.[64] In addition, it has been reported that RIC significantly induced angiogenesis and collaterals formation, which was manifested as an increase in the number and volume of blood vessels. And these changes had an effect on improving CBF.[3] RIC may improve the collateral circulation of cerebral vessels through the following ways:

Notch Signaling Pathway

The Notch signaling pathway is a biologically ancient intercellular signaling pathway. The Notch receptor is a highly conserved membrane-bound receptor, which directly transfers signals from the cell surface to the nucleus by regulating intramembrane proteolysis. Notch1 and Notch4 are the only two kinds of Notch receptors expressed in vascular endothelial cells, which have an important effect on the vascular development and physiological process of vertebrates. These effects include the regulation of the arterial/venous differentiation of endothelial cells and vascular smooth muscle cells, the regulation of the germination and branching of blood vessels during normal development and tumor angiogenesis, and the differentiation and physiological responses of vascular smooth muscle cells.[65] Lawson et al first confirmed the effect of the Notch signaling pathway on arteriovenous differentiation in zebrafish experiments. They found that loss of the Notch signaling pathway lead to defective arteriovenous differentiation. Activation of the Notch signaling pathway, by contrast, resulted in repression of venous cell development, and promoted the differentiation of cells into arteries. The Notch signaling pathway is essential for the normal development of arteries and veins.[66] It has been demonstrated that the promoting of the Notch signaling pathway contributed to the proliferation of endothelial progenitor cells and angiogenesis of the brain in cerebral ischemic stroke mice.[67] And blockade of Notch signaling decreased vascular smooth muscle cells' investment of developing arteries.[68] In the mouse model of hind limb ischemia, the arteriogenesis of the ischemic hindlimb of mice with Notch1 heterozygous deletion was also impaired.[69] In conclusion, the Notch signaling pathway plays an important role in the normal function of angiogenesis.

Ren et al utilized the middle cerebral artery occlusion (MCAO) model in rats and divided the rats into a sham operation group, an MCAO control group, and an MCAO + RIC group. The study showed that compared with the MCAO control group, Notch1 and the intracellular domain expression of Notch1 in the MCAO +RIC group was increased, the artery diameter was enlarged, the leptomeningeal anastomoses branch was significantly increased, and local CBF was also significantly elevated.[2] Therefore, RIC may stimulate the Notch1 signaling pathway to promote collateral circulation generation and improve CBF in ischemic regions, thereby affecting cerebral hemodynamics. The Notch signaling pathway may be a new therapeutic target for ischemic stroke.

eNOS/NO Pathway

The production of nitric oxide (NO) in vivo is catalyzed by three different enzymes, neuronal nitric oxide synthase (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS). NO production by vascular endothelial cells is mainly dependent on eNOS.[70] The eNOS catalyzes the conversion of L-arginine to L-citrulline to generate NO. Nitrite is the storage pool of NO generated by endogenous eNOS, which is reduced to NO in the hypoxic area,

mediating vascular dilatation and increasing CBF. Murohara et al research showed that vascular remodeling was impaired in an eNOS knockout murine model of operatively induced hindlimb ischemia.[71] Thus, the eNOS/NO pathway is considered one of the major regulators of angiogenesis after ischemia.

An experiment divided 30 adult rats into a sham operation group, a bilateral carotid artery occlusion group (2VO), and a 2VO+RIC group. The experiment found that compared with 2VO group, in the 2VO+RIC group, the expression of phosphorylated endothelial nitric oxide synthase (p-eNOS) increased, microvascular density and collateral vessels increased, and the cerebral perfusion significantly increased as well. Intraperitoneal injection of NOS inhibitors can reverse this phenomenon.[72] Moreover, RIC treatment could up-regulate the content of nitrite in the plasma of mice, and the up-regulation of nitrite was related to the increase of CBF.[73] Hoda et al reported that RIC up-regulated the expression of eNOS mRNA in blood vessels of the regulatory site by about 10 times, and increased the plasma concentration of NO.[74] These results suggest that RIC can improve cerebral perfusion in ischemic regions by promoting angiogenesis, and this effect is mediated by eNOS/NO pathway. Nitrite levels are easily measured in the blood and can therefore be used as a promising circulating biomarker for ischemic treatment.

VEGF Pathway

Vascular endothelial growth factor (VEGF) is now considered one of the most effective highly specific cell factors promoting vascular endothelial growth, participating directly in the angiogenesis of ischemic or hypoxic tissues or organs. In the human genome, VEGF A, B, C, D, E and placental growth factor are included. They need to bind to the corresponding receptors and activate different downstream signaling pathways to play their respective roles. VEGF-A was the first discovered among them, with the richest content and the strongest function in tissues and cells. Therefore, VEGF refers to VEGF-A in most literature. Accumulating evidence supports the protective role of VEGF in inducing angiogenesis and increasing vascular permeability, thus affecting hemodynamics.[75–77] Zhang et al used male Wistar rats to construct the MCAO model, and they discovered that VEGF expression began to increase 2 hrs after cerebral infarction, and lasted for at least 28 days. The increase in the number of new capillaries in the ischemic area was correlated with the up-regulation of VEGF, indicating that VEGF mediated the angiogenesis in the ischemic area and increased cerebral blood perfusion.[78] In addition, VEGF-A is also a potent vasodilator and has been reported to not only induce neuroprotection directly in ischemic disorders, but also to improve cerebral autoregulation through hypoxia-inducible transcription factor-1-regulated pathways.[79]

Evidence suggests that RIC is able to elevate the circulating VEGF significantly, even at the mRNA and protein levels,[80] which is considered to be a key mediator of protective RIC effects.[81] Ueno et al investigated the relationship between RIC and VEGF by clamping abdominal aortas in mice. The results also showed that RIC could increase the level of VEGF in plasma, thus producing a neuroprotective effect.[82] All the studies above have confirmed that RIC can effectively promote the up-regulation of VEGF expression, so as to play its physiological role in promoting the neovascularization in the ischemic area and affecting cerebral hemodynamics. This is probably a main molecular biological mechanism through which RIC mediates brain protection.

RIC Can Prevent the Collapse of Pial Collaterals

The cerebral collaterals are pivotal auxiliary vascular pathways. They can maintain blood flow to ischemic tissue up to a point when the primary vascular routes to the brain are obstructed.[83]

An experiment showed constriction of pial collaterals and distal MCA segments at all time points after MCAO was apparent in controls, but this did not happen in RIC-treated animals. This result demonstrated that RIC could prevent the collapse or constriction of cerebral collaterals after ischemia took place. And it could also improve CBF through its influence on cerebral collaterals. But no significant effect or interaction was observed in blood flow velocity.[10]

Above all, it is proved that RIC has a positive influence on cerebral collateral circulation. On the one hand, RIC can promote the establishment of collateral circulation in several ways. On the other hand, RIC can prevent the collapse of pial collaterals after ischemia. That is, RIC is beneficial to the status of collateral circulation and collateral blood flow. Therefore, RIC is a potential therapeutic method for ischemic stroke.

RIC Can Protect the Neurovascular Unit

The concept of "neurovascular unit (NVU)" was first introduced by Lo et al in 2003.[84] The NVU is a special structural and functional unit of the mammalian nervous system. It includes vascular cells (endothelium, pericytes, and vascular

smooth muscle cells), glial cells (astrocytes, microglia, and oligodendroglia), and neurons, which are tightly connected to modulate regional blood flow in response to local metabolic demand.[85,86] This modulation enables rapid increase in CBF in response to neuronal activation, despite the relatively stable global blood flow.[86] Many physiological studies have confirmed that there is communication between cerebral blood vessels and adjacent nerve cells in NVU. The NVU plays a crucial role in modifying cerebrovascular function, controlling CBF and permeability in health and in specific diseases.[87] Therefore, the regulation of regional and local cerebral hemodynamics depends on the structural and functional integrity of the NVU.[88]

Several diseases can lead to impaired cellular communication between neurovascular unit components, and thus result in brain dysfunction. Microvessel responses, astrocyte injury, and neuron injury occur almost simultaneously when the ischemia/reperfusion (I/R) happens.[89] Damage to any part of the NVU could lead to dysfunction in cerebral hemodynamics. Thus, we should make efforts to protect the functional and structural integrity of the NVU in patients with ischemic stroke. Han et al first demonstrated that ischemic treatment could reduce the I/R injury to the cellular structures of neurons, astrocytes, and microvessels.[90] Researches then advanced to RIC. Astrocytes are important part of NVU, they undergo rapid hypertrophy and hyperplasia in response to injury of brain tissue. Cheng et al reported that RIC could protect NVU by adjusting the proportion of astrocyte subtypes and weakening the activation of astrocytes in the brains of ischemic mice, thereby improving neurological function as well as reducing mortality, infarct area, and hemispheric swelling after ischemic stroke.[5]

The evidences above give us reason to think that RIC can be effective in improving CBF by protecting NVU during ischemic stroke. The understanding of NVU highlights that attention should be shifted from neurons or blood vessels, respectively, to the whole NVU. It also provides a platform for potential therapies for ischemic stroke. RIC may be an effective and promising treatment for ischemic stroke due to its convenience of operation and positive impact on NVU. However, there is still much to learn about the mechanism and function of the neurovascular unit and RIC.

RIC Can Induce the Formation of Gas Molecules

Numerous studies have demonstrated that hypoxia can induce vascular endothelial cells to produce gaseous messenger molecules, such as nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S).[91–93] These gasotransmitters share several common properties among their physiological and pathological functions.

NO

As mentioned above, NO is considered one of the main endothelium-derived vasodilation factors. NO plays a potential role in cerebral autoregulation, the expansion of cerebral blood vessels, and the improvement of CBF. A study discovered that a decrease in transmural pressure from 60 mmHg resulted in the increasing release of vascular NO by intraparenchymal arterioles isolated from rats. The result supports that NO contributes to the autoregulatory vasodilation intrinsic to the vessel during hypotension.[94] White et al compared the effect of the NOS inhibitor N(G)-monomethyl-L-arginine on dynamic autoregulation with that of noradrenaline in healthy humans. They found reduced NO secretion was associated with impaired cerebral autoregulation, suggesting that nitric oxide mediates cerebral autoregulation in humans.[95] Recently, a number of studies have focused on the function of NO on cerebral autoregulation.[96–98] It is demonstrated that inhaled nitric oxide had the function of preventing impairment of cerebral autoregulation, reducing hippocampal necrosis and blocking the reductions in CBF.[96–98] Thus, NO is an important medium of the regulating of cerebral hemodynamics and contributes to the adequate blood supply to the brain. However, there are still dissenting voices.[99,100] The effect of NO on cerebral hemodynamics needs further study, including the effective dose and its possible toxic effect.

CO

CO is a gaseous second messenger endogenously generated from heme by heme oxygenase (HO). Three isoforms of HO (e.g., HO-1, HO-2, and HO-3) have been discovered.[101] Endogenous CO production occurring at low concentrations is thought to be protective.[101] In animal models, 250 ppm CO in the central nervous system have been demonstrated to have protective effects.[102,103] CO can generate cyclic guanosine phosphate by activating guanosine cyclase. The increase of intracellular cyclic guanosine phosphate can expand blood vessels and inhibit platelet aggregation. An increasing number of studies have shown that endogenous CO may be one of the factors involved in regulating vascular tension during hypoxia.[104] The vascular tone of the resisting arteries and arterioles determines the resistance of the surrounding vessels, which helps to regulate blood pressure and blood flow, thus affecting the hemodynamics

inside tissues and organs.[105] Several experiments confirm that CO also can influence NVU by its impact on neurogenesis, angiogenesis, and synaptic plasticity.[102,106,107] HO-1 knockout mice (HO-1(-/-)) had fewer positive cells for axon migrating markers after MCAO.[108] Mice exposed to 250 ppm CO for 2 hrs each day have significant endothelial progenitor cells mobilization.[106] And, relatively low concentration of endogenous CO production is thought to play an important role at the synapse leading to long-term potentiation.[109] Therefore, the potential efficacy of CO therapy in ischemic stroke may be its influence on neurogenesis, angiogenesis, and synaptic plasticity, which can improve the CBF by affecting NVU.

H_2S

H_2S can also be produced by cells under ischemic conditions, and it has been considered the third important gaseous signaling molecule following NO and CO. It used to be regarded as a poisonous gas. However, as research progresses, an increasing number of experiments have revealed its role as a bioactive molecule in biological systems. There are conflicting results concerning the role of H_2S in ischemic stroke.[110–114] Chen et al showed that increased production of H_2S in the brain was significantly correlated with either poor clinical outcome or early deterioration in clinical stroke.[110] There is also strong information supporting the important role that H_2S plays in the induction of angiogenesis,[111] regulation of neuronal activity,[113] vascular relaxation,[114] and protection against I/R injury in important organs. It is confirmed that H_2S could protect neurons against hypoxic injury via the K (ATP)/PKC/ERK1/2/Hsp90 pathway.[115] Wang et al proved that H_2S protected blood-brain barrier (BBB) integrity following middle cerebral artery occlusion (MCAO).[116] Jang et al reported that treatment with H_2S augmented angiogenesis in the peri-infarct area, and it improved functional outcomes after 2 weeks significantly through PI3K/AKT signaling in a rat MCAO model.[117] Their findings manifest that H_2S has potential therapeutic value in regenerative and even hemodynamic recovery after stroke. Similar to NO, H_2S can relax smooth muscle cells and expand blood vessels. H_2S synthase has been found in mammals.[93] So H_2S may have the potential of becoming the mediator of RIC affecting cerebral hemodynamics.

It is reasonable to infer that RIC may induce the generation of endogenous gas molecules through the I/R of distant limbs.[93,118] Gas molecules enter the central nervous system through blood circulation, thereby regulating cerebral vascular tone and affecting cerebral hemodynamics. Natural products that are induced by RIC can provide an innovative tool for improving treatments for stroke recovery. More investigations should be done to gain a clearer understanding of these gas molecules. And considerable attention should be paid to RIC as a target for novel therapeutic treatment against for ischemic stroke.

RIC Can Affect the Function of Vascular Endothelial Cells

Blood vessels are composed of the tunica adventitia, tunica media and the tunica intima. The contractile force of blood vessels is mainly regulated by the contractile force of tunica media smooth muscle cells, while the latter are affected by vascular endothelial cells. Vascular endothelial cells can generate NO, prostacyclin, hydrogen peroxide, and hydrogen sulfide, and activate potassium ion channels. Vascular endothelial cells change vascular reactivity through the production and release of vasoactive factors, which can regulate local vascular perfusion and are important substances for regulating vascular tone.[119]

Nakamura et al studied 15 smokers and 15 non-smokers, who were given upper extremity RIC six times a day for 1 month. The results showed that the RIC stimulation could significantly increase the level of circulating progenitor cells in the non-smoking group, enhance the response of the forearm blood flow to acetylcholine, and enhance the endothelium-dependent vasodilatory function. No such changes were observed in the smoking group. RIC may be a simple and safe treatment for peripheral vascular endothelial protection.[120] A recent study also confirmed that RIC can improve the endothelium-dependent vasodilatory function of brachial arteries in the forearm.[121]

The effector of RIC may act on the whole body through blood circulation. Therefore, it is inferred that the effector produced by RIC may have the same effect on cerebrovascular endothelial cells, thereby affecting cerebrovascular reactivity and improving cerebral hemodynamics.

RIC Can Affect the Nervous System

The nervous system also plays an important part in the effects of RIC on cerebral hemodynamics. Primarily, the proper function of RIC is reliant on the presence of intact neuronal pathways. There is a trend toward attenuation of RIC protection when femoral and sciatic nerves are sectioned in a rabbit model.[122] Local muscle ischemia induced through RIC may lead to the release of adenosine

bradykinin or opioid, which may activate the nervous system. A recent study confirmed that RIC could reduce the I/R injury of endothelial cells and enhance the endothelium-dependent vasodilatory function by mediating the production of glucagon-like peptide-1, thus affecting the circulatory system. Glucagon-like peptide-1 is an endocrine hormone released by L cells of the small intestine under the regulation of the efferent activity of the vagus nerve.[121] It has been discovered that selective severing of the posterior gastric branch of the vagus nerve can eliminate the protective effect of RIC, and stimulation of this branch can induce the protective effect of RIC. Scientists thus believe that the circulating factors of RIC are generated and released into the systemic circulation by the internal organs innervated by the posterior gastric branch of the vagus nerve.[112] Activation of the vagus nerve by RIC may also inhibit inflammatory processes mediated by the liver and spleen via the cholinergic anti-inflammatory pathway.[123] A study from Azevedo et al showed that neurovascular coupling was impaired in individuals with autonomic dysfunction, and so was cerebrovascular regulation.[124] It also has been reported that activation of other parasympathetic nerves by RIC, such as the sphenopalatine ganglion, may increase CBF.[125]

Therefore, RIC can affect the nervous system, especially the vagus nerve, and exert an influence on cerebral hemodynamics. The vagus nerve may become a potential therapeutic target for ischemic stroke. However, the interaction between the sympathetic and parasympathetic nerves is extremely mazy. It is difficult to affect only one without affecting the other. Further studies are needed to confirm the interaction between the nervous system and its relationship with RIC.

Conclusions

In conclusion, during the initial stage of ischemic stroke, the CBF decreases and the autoregulation of the cerebral vascular system is damaged, leading to cerebral ischemia and hypoxia, and this may lead to a poor prognosis. Multiple mechanisms are involved in the process of regulation of CBF. Several animal experiments and clinical studies have shown that RIC can trigger the endogenous protection mechanisms through a variety of ways, thus having a positive impact on cerebral hemodynamics. RIC has the potential to become a therapeutic treatment to improve CBF during the initial phase of ischemic stroke with the advantages of being simple, safe, non-invasive, and inexpensive. Renewed efforts are needed to improve our understanding of RIC and to provide important insights into developing more effective therapies for ischemic stroke.

Acknowledgments

We thank Liyang Bao for assistance with figure preparation.

Funding

This project was supported by the National Key R&D Program of China (2016YFC1301600) and JLUSTIRT (2017TD-12) to Yi Yang.

Disclosure

The authors report no conflicts of interest in this work.

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