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# *Current Status of Research on the Protective Effects of Remote Ischemic Preconditioning on the Myocardium*

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***Abstract:*** After the blocked blood vessel regains blood supply, a more severe injury than the original injury will occur, called ischemia-reperfusion injury (IRI), and the current classical method to mitigate IRI is remote ischemic preconditioning (RIPC) is when severe ischemia/hypoxia occurs in essential organs of the body (heart, brain, kidneys), Intermittent blocking and re-communication of distal limbs are regulated, thereby inducing the endogenous protective mechanism in the body and exerting the ischemic protection effect of essential organs. RIPC can trigger a range of mechanisms in the body to mitigate IRI, particularly protective impacts on the heart, but the specific mechanisms are unclear. RIPC has gradually moved from basic research to clinical trials with continuous exploration. The primary purpose of this paper is to summarize the research progress of the endogenous protection mechanism of RIPC in recent years, including the study of humoral mechanism and neural mechanism; as well as to organize the clinical applications related to RIPC in recent years, suggesting the potential value of RIPC and providing ideas for future research and application of RIPC.

## 1. Introduction

As our population ages, the number of acute cardiovascular events increases yearly [1], The degree of ischemia-reperfusion injury (IRI) impacts the severity and prognosis of the patient's condition. The concept of ischemic preconditioning (IPC) was put forward early. However, intermittent clamping and release of aortic clamping forceps may result in peripheral vascular embolism caused by the detachment of thrombus. Meanwhile, many confounding factors such as smoking, diabetes, hypertension, or medications can affect the efficacy of IPC or even eliminate the protective effect of IPC [2], which has limited the clinical use of IPC. As Kerendi [3] et al. continue to refine and improve experiments to confirm the protective effect of ischemic preconditioning (RIPC), which refers to repeated ischemia or hypoxia to non-vital organs in the distal extremities other than the heart and brain, thereby improving the functional state of the blood vessels and increasing the tolerance of distal vital organs to severe ischemia or hypoxia, clinical studies have found that RIPC has an important impact on cardiac, cerebral and renal IRI [4-5]. However, the specific effective framework of RIPC

is not precise. It is believed that the cardioprotective effect of RIPC is through the transmission of cardioprotective signals from distal to the heart via humoral and(or) neurological factors act on cardiac cell membrane surface receptors to stimulate a series of conduction pathways to play a positive influence. Because of its safety, good applicability, and low price, RIPC has been widely used in clinical practice. This paper will summarize the mechanism research and clinical application of RIPC in recent years.

## 2. Possible Protective Mechanism of RIPC on Reperfused Myocardium

### 2.1. Humoral Mechanism of the Cardioprotective Effect of RIPC

RIPC, repeated ischemia-reperfusion in an organ or tissue, provides global protection against IRI in ischemic organs in vivo. A mathematical model developed by Whitaker [6] predicted that RIPC would trigger the release of internal protective factors. Subsequently, to test this hypothesis, Lieder [7] et al. administered RIPC to the limbs of recipient pigs and collected porcine plasma, which was isolated, diluted, and injected into isolated rat hearts with prior I/R, which reduced IRI in the subsequently injected isolated rat hearts. This confirms that the cardioprotective effect of RIPC may be achieved through humoral mechanisms and suggests that RIPC protection can be transferred between different species through plasma.

Subsequently, cardioprotective factors such as adenosine, microRNA, and prostaglandins were found in the blood of patients receiving RIPC, confirming the possibility that RIPC protection may be mediated by humoral mechanisms [8] and that the same protective effect can be achieved when blood from patients receiving RIPC is introduced into patients not receiving RIPC [9]. Subsequently, Böning [10] et al. performed RIPC on 14 patients undergoing cardiac surgery before surgery. They collected blood samples at thirteen-time points during and three-time points after operation to measure serum levels of RNase1, eRNA, and TNF-α and found that the impact of six cycles of RIPC was significantly higher than that of the currently customary four cycles of RIPC. This suggests that the positive effect of cardioprotection by RIPC may not be the most obvious in basic research experiments on RIPC or in clinical applications where four cycles of RIPC are customarily used to induce cardioprotection, and this may be the reason why a portion of RIPC does not reflect cardioprotective function. Although research scholars have successively found protective factors such as NO, adenosine, miRNA, and opioids from the plasma of people or animals receiving RIPC, the experimental results vary widely, and it is difficult to form a consistent conclusion at present. This paper elaborates on the common relevant humoral mediators.

#### 2.1.1. Nitric Oxide (NO)

Nitric oxide (NO) is an active gas in nature and has various biological effects in vivo, such as diastole of vascular endothelial cells, inhibition of platelet aggregation, and generation of free radicals. Endogenous NO is mainly produced by chemical synthesis, with levorotatory arginine being converted to NO catalyzed by nitric oxide synthase (NOS). Among them, either inhaled exogenous NO or endogenous NO produced by various interventions has critical protective effects on reperfused myocardium. Liu [11] et al. found that myocardial infarct size and leukocyte infiltration in a porcine reperfusion model can be reduced with inhaled NO. In contrast, Jacob et al. showed that this protective effect of NO on reperfused myocardium was achieved by activating the ATP-dependent potassium channel (KATP channel) and causing its opening. Several studies have shown that during RIPC, tissues can produce large amounts of NO and that increased NO levels in circulating blood have a protective effect on various organs in vivo [12]. A study by Kundumani-Sridharan [8] et al. found that RIPC induces Nrg-1β (transcription factor early growth response-1β) expression in

endothelial cells, which in turn interacts with Src to eNOS (endothelial nitric oxide synthase) function lost in IRI was restored, enhancing NO expression and preventing the damaging effects of IRI in the heart. Furthermore, Grau [13] et al. found in their experiment that RIPC prevented myocardial IRI injury by altering RBC variability and increasing RBC-NO synthase activity. In rats with middle cerebral artery occlusion (MCAO), RIPC induced enhanced collateralization, decreased infarct size, attenuated MMP-9 activity, and increased p-eNOS activity, restored blood flow in IRI rats after using RIPC [14]. RIPC may also modulate both NO and miRNA levels to reduce I/R injury [15]. However, in a human randomized controlled crossover trial, RIPC was found to not only fail to increase NO concentrations but may even decrease them [16]. This adds to the complexity of the relationship between RIPC regulation of NO content.

### 2.1.2. MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are a group of RNA molecules encoded by endogenous genes, which participate in gene regulation, the genes are stably present in plasma and have multiple modulatory effects. Numerous pieces of evidence show that miRNAs are significantly dysregulated in ischemic myocardial disease, suggesting that miRNAs are closely associated with the pathogenesis of myocardial IRI [17]. Among them, miR-144 is the most important in myocardial reperfusion protection. miR-144 was demonstrated by luciferase analysis by regulating the expression level of a vital forkhead transcription factor to work, FOXO 1. The role of FOXO 1 downstream has not been elucidated. RIPC can upregulate the expression level of various miRNAs, improve cardiac function, and reduce cardiomyocyte apoptosis through its many pathophysiological effects mediated [11]. Exosomes are cell-derived nano-vesicles containing a variety of biomolecules [18], where miRNAs secreted by exosomes have a crucial influence in myocardial IRI protection mechanisms[19]. Exosomes were isolated from rat plasma 48 hours after the RIPC regimen, and although plasma exosome levels did not change clearly in the RIPC group, miRNA arrays showed significant gather of miR-126a-3p in exosomes from the RIPC group. Under RIPC, the miR-126a-3p activates the RISK pathway and inhibits apoptosis to protect cardiomyocytes. Moreover, inhibited miR-126a-3p could attenuate the protective impact of RIPC exosomes in the heart of myocardial IRI rats, further demonstrating the critical impact of miRNA-126a-3p in RIPC [20]. Li [21] et al. found a specific function of circRNA and miRNA by qPCR in the brain tissue of RIPC group rats. This relationship was also found in PC12 cells. when the of circRNA was inhibited, the higher the level of miR-126a-3p, the lower the expression level of VLCAD. It point out that RIPC through the circRNA-miRNA-126a-3p-VLCAD pathway to compete I/R injury. Thus, miRNA-related families are expected to have a crucial impact in RIPC treating myocardial IRI.

### 2.1.3. Opioid Substances

Endogenous opioids are brain neuropeptides in vivo, which can prevent myocardial IRI by regulating pain in response to RIPC. Zatta [22] et al. found the application of opioid receptor antagonists could eliminate the protective effect of postprocessing, demonstrating the involvement of endogenous opioid peptides in the protective effect. Wang [23] et al. demonstrated that morphine enhances the protective ability of RIPC, which may be involved the regulation of the Bck-2-related apoptotic signaling pathway. Aggarwal [24] et al. used a Langendorff model for the induction of IRI after four cycles of inflation and deflation in their experiments and the expression level of LDH and CK was found to be decreased, and an improvement in post-ischemic left ventricular function, subsequent application of L-NAME would abrogate the cardioprotective effect of RIPC, and advance the application of morphine pretreatment did not attenuate this result, suggesting that morphine may be a downstream mediator of NO. Thus, RIPC may act by inducing NO release from the endothelium,

triggering endogenous opioid synthesis, which activates local KATP channels in the heart. Cheng [25] et al. found that in a RIPC model, β-endomorphin antiserum (AEP) given in the posterior ventricle attenuated the cardioprotective influence of RIPC. In contrast, intravenous administration before or after morphine injection AEP does not abrogate RIPC cardioprotection, suggesting that perhaps central rather than peripheral β-endomorphin assists morphine in RIPC, which provides new ideas for how the drug should be given clinically.

### 2.1.4. Adenosine (Adenosine)

Adenosine, an endogenous and widely distributed adenosine triphosphate (ATP) catabolic product in humans, has a crucial influence in RIPC-mediated cardioprotection [26]. Leung [27] et al. collected perfused rabbit heart effluent in an experiment where mixing exogenous adenosine to act as RIPC in another animal would reduce the production of reactive oxygen species and maintain outer membrane integrity, exerting a cardioprotective effect. Administration of adenosine receptor blockers maintained the mitochondrial integrity and function, suggesting that adenosine would be a humoral factor in cardioprotection by RIPC. Using Langendorff's isolated rat heart model, pharmacological pretreatment with adenosine produces similar results to RIPC-induced cardioprotection [28], administration of exogenous adenosine enhances the beneficial impacts of RIPC in the heart [29]. Both point out adenosine has a crucial influence in RIPC. Adenosine can exert different physiological effects by activating different adenosine receptors. The central adenosine receptors are A1, A2, and A3 subtypes. Paez [30] et al. found in their experiments that RIPC can not attenuate myocardial infarct size after the use of A1 receptor blockers before reperfusion in rats performing three hind limb I/R cycle protocols and RIPC lost the ability to protect myocardium after the use of NO synthesis inhibitors even after the reapplication of adenosine agonists, demonstrating not only did it prove that adenosine is an important humoral factor for RIPC to function, but it was also clear that RIPC exerted its cardioprotective effect by activating A1 receptors to induce nitric oxide synthase (NOS) phosphorylation. Subsequently, Zhao [31] et al. similarly demonstrated that adenosine binds to A1 receptors, generates NOS, and then mediates the KATP channel for myocardial protection. Adenosine also cooperates with opioid receptors to alleviate IRI. With the progressive understanding of adenosine, the protective effect in heart of adenosine relies mainly on the activation of A1 and A3 receptors mediating related pathways.

## 2.2. Neural Mechanisms Underlying the Cardioprotective Effect of RIPC

Gourine [32] et al. proposed a "remote preconditioning reflex" consisting of "afferent nerve-central efferent nerve," which gave some theoretical support to the neuromodulation mechanism in RIPC. A wealth of data showing that using RIPC during coronary occlusion releases new protective signals transmitted through neurons and attenuates ischemia-induced ST-segment elevation on the ECG, which means the neural factors are important [33]. In a myocardial IRI model, pre-excision of the model lower limb nerve and subsequent application of the RIPC protocol reveals RIPC lost the ability to protect the cardiac; similarly, the organ protective effect of RIPC on I/R injury is lost after pretreatment of afferent fibers with the afferent nerve blocker capsaicin [34], demonstrating the vital impact of afferent nerves in implementing RIPC.

Sympathetic nerves are a large class of afferent nerves in the body, and studies have shown that when myocardial IRI occurs in the body, the sympathetic response is enhanced, leading to intracellular calcium overload, which in turn causes myocardial injury [35]. However, RIPC played a positive impact on the myocardium of rats with sympathetic nerve removal but did not significantly improve myocardial metabolism [36]. Elisabeth [37] et al. demonstrated that RIPC delayed sympathetic activation and ameliorated endothelial cell function in ischemic tissues in a human I/R

model, moreover, the myocardial protective function of RIPC failed after systemic administration of hexapotassium ammonium to block sympathetic and parasympathetic transmission [38]. This suggests that the sympathetic nervous system has an essential influence in RIPC.

Researches found that the vagus nerve also has import impact in RIPC and that vagus nerve stimulation before ischemia-reperfusion can counteract reperfusion-induced myocardial injury and reduce myocardial infarct size [39-40]. Buchholz [41] et al. found that the mechanisms mediated by vagal excitation at different times differed. Before ischemia activating, the Akt/GSK-3β pathway fulfils a role. In contrast, vagal excitation at the onset of reperfusion activated the α7nAChR and JAK-2 pathways. In their experiments, Pickard [42] et al. found that RIPC-derived rat plasma dialysate reduced infarction and had a positive effect on hemodynamic recovery in isolated hearts of rats with myocardial IRI injury; subsequently, Pickard obtained plasma dialysate from rats with vagus nerve severed, or applied the ganglion blocker hexamethyl bisammonium or muscarinic to ex vivo hearts, and found that RIPC-treated rat plasma dialysate did not work. These findings suggest that the release of humoral factors depends on vagal nerve integrity. Similarly, Svetlana [43] et al. found that the protective impact of RIPC is strongly dependent on DVMN, suggesting experimentally that humoral mechanisms of myocardial protection require the functional integrity of DVMN neurons. Moreover, Verouhis [44] et al. found a significant increase in GLP-1 release by vagal innervation in subjects who implemented RIPC in the forearm of 12 healthy subjects, which was abolished by the application of the GLP-1 antagonist toxic lizard exocytosis (9-39), demonstrating that RIPC has the ability to protect the myocardium from IRI. This suggests that the combined factor of the "humoral" and "neural" hypotheses of RIPC may be GLR-1, providing a new idea for clinical research. In addition, peripheral nerves are also involved in myocardial protection. Redington [45]et al. demonstrated that the corresponding protective factor could be produced in rabbits after stimulation of sensory nerves, which disappeared after the application of sensory neuroleptics. It was shown that transcutaneous electrical nerve stimulation could also produce a corresponding protective effect.

Although a large amount of data support that RIPC protection of the heart may act through neural mechanisms, it is still unknown about the neuroprotective mechanisms of RIC in the brain, kidney, and liver. Studying the neuroprotective framwork of RIPC will not only better reveal the protective mechanisms of RIPC in the ischemia-reperfused heart but also more effectively utilize RIPC to protect multiple organs in vivo.

## 3. Clinical Application of RIPC in Surgical Procedures

### 3.1. Application of RIPC in Patients with Angina Pectoris and Percutaneous Coronary Intervention (PCI)

Angina is a clinical syndrome caused by insufficient coronary artery blood supply, and RIPC is often used in clinical practice in cooperation with PCI to treat patients with angina pectoris. RIPC improves prognosis at the cellular level in both patients with stable angina pectoris (SAP) and patients with unstable angina (UA) undergoing PCI [46-47]. In addition, clinical trials have shown that RIPC improves the success rate of angina pectoris patients undergoing PCI by improving intraoperative chest discomfort and the incidence of postoperative myocardial infarction [48-49]. RIPC reduces myocardial injury from elective PCI and protects the kidneys, providing both cardiac and renal protection [50]. However, Prasad [51] et al. found preprocedural RIPC had no beneficial effect in low- and intermediate-risk patients, which may be related to the experimental population, treatment modality, and risk factors. For post-PCI-induced angina, RIPC combined with external counterpulsation may provide symptomatic relief for patients [52]. The timing and intensity of RIPC also had an impact on its protective effect, with UA treated with PCI, the protective effect of RIPC was stronger in late RIPC (24-72 hours post-ischemia) than in early RIPC (3h post-ischemia) [53],

and the best protection was achieved with six cycles of RIPC [54], which echoes the previous findings of Böning [10] and represents a transition from basic research to clinical trials. With the gradual promotion of PCI technology and the affordable and easy-to-use RIPC simple training device, which enables angina patients to improve their quality of life, RIPC technology will receive more attention.

### 3.2. Application of RIPC in Coronary Artery Bypass Grafting (GABG)

Patients who have clinical cardiovascular disease but not intolerant to PCI and in the elderly, the opening of coronary collateral branches is significant for the surgical management of the cardiovascular disease; thus, the status of GABG surgery is self-evident. Findings show patients who underwent RIPC earlier performed well in subsequent CABG procedures and improved patient prognostic outcomes. Similarly, Gorjipour [55] et al. randomized 43 CABG patients from the Imam Hossein Educational Hospital into a RIPC group versus a control group and statistically showed that RIPC modulates inflammatory cytokines that translate into cardioprotective effects during CABG surgery. However, the role of RIPC in CABG should be further studied with larger sample size, and the use of anesthetic drugs should be carefully considered. Therefore, reports of the clinical role of RIPC for cardiovascular surgery are often divergent. Data from two prospective studies that subjected patients undergoing cardiovascular surgery to RIPC and evaluated the clinical outcomes in those had CABG surgery found no difference in troponin release or outcomes at one year between patients undergoing RIPC and controls. It did not support an improved prognosis for CABG surgery with RIPC [56]. Furthermore, in a prognostic investigation of a homogeneous group of 124 patients undergoing aortic valve replacement (transcatheter aortic implantation (TAVI) or CABG surgery, by serially measuring myocardial damage markers such as cardiac troponin 1, interleukin 6 and 8, it was found that in patients undergoing TAVI or CABG surgery, a reduction in levels of inflammatory markers and preservation of right and left ventricular energy metabolites, RIPC did not provide an influential impact [57]. However, Tuter [58] et al. reported in 2019 a randomized controlled study of 87 patients with ischemic heart disease, which showed no effect of RIPC on the outcome of CABG surgery under propofol anesthesia, but subsequently found that propofol may interfere the ability of RIPC to protect myocardium, thus explaining to some extent why the role of RIPC in clinical surgery is two-sided. The reason for the bidirectional effect of RIPC in CABG surgery may be due to potential factors such as study protocol, age of the sample population, presence or absence of underlying disease, and use of anesthetic drugs, so further evaluation of a broader sample population is needed to clarify the role of RIPC in CABG surgery.

### 3.3. RIPC in Patients with Acute Myocardial Infarction (AMI) Undergoing PCI

In a prospective design study, RIPC prior to PCI could improve clinical recovery after surgery and reduce the incidence of postoperative heart failure in STEMI patients. To further verify whether RIPC improves prognosis in STEMI patients is clinically valid, Cao [59] et al. randomized 80 STEMI patients into two groups and collected post-procedure patient blood for analysis, which showed that myocardial injury marker levels were lower in patients who received pre-RIPC than in the control group, suggesting that pre-RIPC before PCI in STEMI patients would significantly improve patient prognosis and suggests that RIPC may improve the prognosis of STEMI patients through the effects of SDF-1α and NO. However, in a large trial of STEMI patients undergoing RIPC-assisted PCI at 33 international centers followed for 12 months, no improvement in patient prognosis was observed with RIPC-assisted PCI [60]. The reasons why RIPC ease IRI and improve clinical outcomes are unclear, probably due to incomplete research scheme or the short duration of the investigation. Although there is disagreement about whether RIPC has a positive effect in AMI patients undergoing PCI, RIPC is still implemented before PCI in clinical, and it is essential to explore more deeply the potential

mechanisms by which RIPC improves the prognosis of AMI patients.

## 4. Conclusion

The concept of RIPC has been proposed by scholars as early as the 20th century, but RIPC has only been applied and developed clinically in large numbers in the last 5-10 years, which may be related to the unclear mechanism with RIPC or the limitations in the technical development of clinical tools. As an emerging technique, RIPC protects vital organs by stimulating endogenous neurological and humoral mechanisms to counteract the damage caused by ischemia and reperfusion in the distal limbs through brief and repeated ischemia-reperfusion stimulation and also protects vital organs such as the brain, kidneys, and lungs. The RIPC also protects the brain, kidneys, lungs, and other vital organs. In today's aging population, the incidence of cardiovascular diseases is also increasing, and using the RIPC principle to create the corresponding physical therapy equipment is essential to improve patients' quality of life. However, the time window for RIPC to work is unclear, the pathways activated by RIPC before and after ischemia implementation are not the same, and the clinical use of RIPC is still very controversial. The use of anesthetic drugs may also hinder the effect of RIPC, which indicates the complexity and uncertainty in the practical application of RIPC. These issues deserve further discussion in the future.

Regarding the RIPC mechanism, two essential ideas are reviewed in this paper: (1) humoral mechanisms. (2) Neural mechanisms. However, it is not excluded that RIPC can act through other derived mechanisms. Regarding the humoral mechanism, this paper mainly introduces the relevant roles of NO, miRNA, opioids, and adenosine, which may act singly or assist each other to exert protective effects. Other humoral factors that may be induced by RIPC, such as bradykinin, CGRP, and cytokines, are not described. In the neural mechanism, RIPC passes through the "afferent nerve-central efferent nerve" to form the "remote preprocessing reflex" loop and cutting off either loop often results in the loss of RIPC protection. The RIPC loses its protective effect.

In practical clinical applications, the use of RIPC has received a lot of support, however, there are confounding factors such as disease classification and underlying disease that interfere in the clinical setting, making it challenging to clarify the detailed mechanisms of RIPC completely. Therefore, in-depth studies exploring the specific cellular mechanisms of RIPC may open up new avenues for future patient protection and injury mitigation clinical aspects.

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