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Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Review Article

Cardioprotective Effect of Remote Ischemic Preconditioning: From Bench to Bedside

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ARTICLE INFO

Keyword :
Cardioprotection;
Ischemic Preconditioning;
Remote Ischemic Preconditioning.

ABSTRACT

Remote ischemic preconditioning (rIPC) refers to a cardioprotective phenomenon in which short episodes of ischemia, followed by reperfusion, in one organ or tissue might provide future protection against ischemia/reperfusion damage in other organs, namely the heart. The process involves the activation of humoral, neural, or systemic communication channels, which in turn induce various intracellular signals inside the heart. The primary objective of this review is to provide a concise overview of the potential processes implicated in rIPC cardioprotection, as well as to elucidate current clinical studies aimed at establishing the effectiveness of these techniques in safeguarding the heart from detrimental ischemia/reperfusion injury. In this context, many variables contribute to the attenuation of subcellular processes of rIPC in patients, including advanced age, presence of comorbidities, medication use, and variations in anaesthetic protocols. These factors may account for the observed variability in outcomes across different clinical studies. Additional research, meticulously planned, is needed in order to enhance our comprehension of the pathways and mechanisms associated with both early and late rIPC. A comprehensive understanding of the various routes is crucial in facilitating the translation of medical advancements to the benefit of patients.

1. Introduction

Remote ischemic preconditioning (rIPC) refers to the occurrence in which short periods of ischemia and reperfusion, administered to a particular organ or tissue, provide protection to a distinct organ or cardiovascular region against subsequent bouts of ischemia and reperfusion.[1] The approach was elucidated by Przyklenk in the year 1993. The researchers administered anaesthesia to canines and conducted four instances of five-minute ischemia in the left circumflex coronary area. This was followed by a persistent ischemic insult lasting one hour in the left anterior descending coronary artery bed. In contrast to the control group of dogs who just had left anterior descending occlusion, the experimental group of animals that experienced short periods of circumflex occlusion prior to continuous left anterior descending occlusion exhibited a significant decrease in the extent of the myocardial infarction. Therefore, Przyklenk et al. expanded upon the notion of "Classic" ischemia preconditioning by demonstrating that several, short-term occlusions of a coronary artery provide protection not just to the specific region supplied by that artery, as proposed by Murry et al., but also to adjacent regions of the myocardium.[2] The term "regional ischemic preconditioning" was assigned to this intracardiac protection technique. This occurrence has presented the potential for the induction of protective mechanisms in distal tissue/organs via ischemia, a notion that has been corroborated by other researchers. A significant breakthrough in cardiac rIPC was achieved by the use of skeletal muscle as the ischemic stimulus. The application of a tourniquet to a limb has the potential to induce rIPC without the need for intrusive procedures. This procedure enables the extrapolation of rIPC to the clinical context of acute ischemia/reperfusion damage.[3]

This article aims to give a concise overview of the pathophysiological principles behind cardiac rIPC and to provide illustrative instances of potential therapeutic applications, while also providing a quick overview of the principal clinical studies conducted in this field.

2. Discussion

Mechanisms Implicated in Remote Ischemic Preonditioning

The cardioprotection provided by rIPC follows a similar pattern to that of "classic" preconditioning, occurring in two distinct periods. The first stage, also known as the "first window," has a duration of roughly four hours. On the other hand, the subsequent stage, referred to as the "second window" of protection, begins around 24 hours following the onset of ischemia and remains effective for a minimum of 48 hours. During the first stage, there are prompt chemical alterations occurring in the cardiomyocytes that result in a reduction in infarct size and mitigate the likelihood of reperfusion arrhythmias. The protein synthesis-dependent mechanism behind the second window of cardioprotection aligns with the alterations seen in cardiomyocyte gene expression and leukocyte activity during the post-myocardial ischemia interval.[4]

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https://doi.org/10.21776/ub/hsj.2024.005.02.6
Received 15 November 2023; Received in revised form 4 December 2023; Accepted 10 December 2023.
Available online 28 April 2024

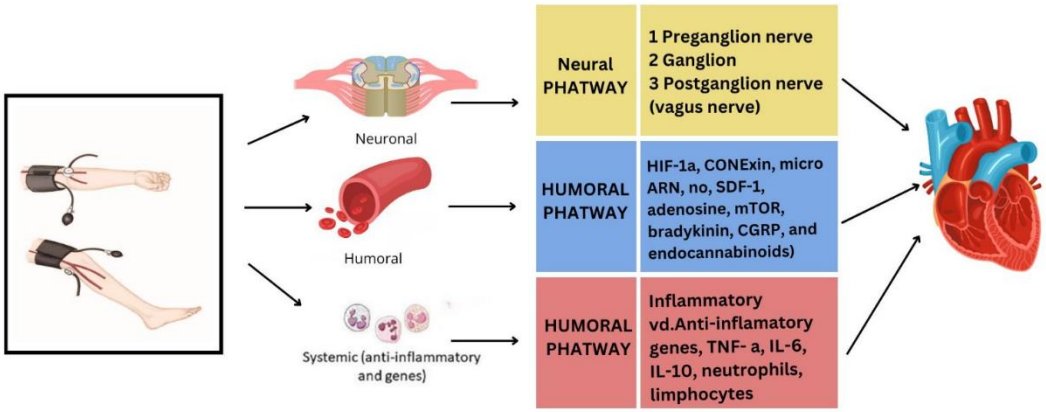

Figure 1. The signalling pathways behind rIPC cardioprotection. Intermittent limb ischemia and reperfusion have been shown to provide cardioprotection via many mechanisms, including neuronal, humoral, and systemic pathways. CGRP Calcitonin gene-related peptide, NO nitric oxide, ROS reactive oxygen species, ApoA1 apolipoprotein A-1, GLP-1 glucagon-like peptide-1, IL-10 Interleukin 10[8]

The precise pathophysiological mechanisms underlying remote ischemic preconditioning (rIPC) remain incompletely elucidated. However, these mechanisms can be categorised into three main components: (a) the liberation of the effector(s) within the distant ischemic tissue or organ; (b) the communication pathway connecting the remote territory to the myocardium; and (c) the initiation of a cardioprotective response, as depicted in Figure 1.[5]

The First Stage of Remote Ischemic Preconditioning

Episodes of transient ischemia followed by reperfusion induce the release of several chemical substances by the ischemic tissue or organ, as shown in Table 1. The presence and activity of different protective substances and processes may vary based on the anatomical site of the stimulus, such as the kidneys, mesentery, or skeletal muscles. Hence, the generalisation of results from one experimental approach to another is not feasible as a result of these variations. An exemplification of this phenomenon may be seen in the instance of hexamethonium, a pharmaceutical substance that functions as a ganglionic blocker. Previous studies have shown that hexamethonium has the ability to fully abolish the protective effects elicited by mesenteric ischemia, while leaving the protection generated by renal ischemia unaltered. The cardioprotection conferred by these mediators is attained by neuronal and/or humoral pathways, with substantiating data available for both mechanisms.[6]

The neural theory suggests that chemicals generated inside ischemic tissue or organs have a localised effect via sensory neural pathways, triggering various motor pathways that promote cardioprotection. Conversely, the humoral theory posits that the ischemia shock triggers the release of chemicals into the bloodstream, which subsequently reach the myocardium and provide a protective influence. Research has shown that in order to elicit the protective effect, reperfusion of the distant organ or tissue must occur prior to the initiation of coronary ischemia.[7]

The comprehensive understanding of the underlying processes of rIPC remains incomplete. Several investigations have shown that there are parallels in the underlying process between "classic" preconditioning and rIPC. As previously stated, the subject matter may be categorised into three distinct components: (a) the humoral pathway, (b) the neural pathway, and (c) the systemic pathway (refer to Figure 1). Nevertheless, the extent to which these pathways individually provide a protective impact on the target organ, as well as the potential involvement of crosstalk between them, remains little understood. It is plausible that these phenomena are not inherently incompatible and perhaps represent distinct aspects of the same pathophysiological sequence.[1]

Humoral Pathway

Multiple findings support the concept that the humoral factor transduces rIPC signals. Circulation carries protective chemicals throughout the body. They connect to receptors and start intracellular signalling pathways in the heart. Konstantinov et al. examined the humoral channel effects of remote limb preconditioning on denervated donor heart recipient pigs. Their investigation showed a significant reduction in infarct size, indicating humoral-mediated cardioprotection via rIPC. Dickson et al. showed that transferring blood from preconditioned rabbit hearts to a non-preconditioned isolated rabbit heart reduced infarct size. This research also showed that coronary effluent from a preconditioned ex vivo rabbit heart may boost a similar effect. Shimizu et al. found that plasma dialysate from a preconditioned rabbit and human blood applied remotely can protect the ex vivo rabbit heart from ischemia/reperfusion.[9]

Table 1. Different substances involved in the remote ischemic preconditioning mechanism[1]

Renal Ischemia	Adenosine Erythropoietin
Mesenteric Ischemia	Bradykinin Cannabinoids CGRP Opioids
Skeletal Muscle Ischemia	Adenisine Opioids NO Noradrenaline ROS ApoA-1 GLP-1 Stromal cell-derived factor-1a Prostanoitds IL-10 Glycine Exosomes and MicroRNAs

CGRP Calcitonin gene-related peptide, NO nitric oxide, ROS reactive oxygen species, ApoA1 apolipoprotein A-1, GLP-1 glucagon-like peptide-1, IL-10 Interleukin 10

The transfer of cardioprotection via plasma dialysate from one animal to another's heart shows humoral signalling. Several amino acids, cytokines, neuropeptides, and other chemicals, including as adenosine, Apo-A1, GLP-1, and nitrite, have been postulated as humoral components of rIPC.[1] In the heart, humoral factors activate intracellular signalling pathways that send cardioprotective signals to end-effectors. The intracellular routes are the nitric oxide synthase/protein kinase G route, the reperfusion injury salvage kinase pathway (RISK), and the survival activating factor enhancement (SAFE) pathway.[10]

The cardioprotective action of rIPC is likely mediated by humoral components that carry the protective signal from a distant tissue or organ to the target organ, namely the heart. These findings were reported in tests employing cardiac cross-perfusion with donor animal blood during rIPC. Peptides, endogenous opioids, endocannabinoids, endovanilloids, prostanoids, norepinephrine, adrenomedullin, leukotrienes, calcitonin gene-bound peptide, and exosome-bound miRNAs have been involved in this process.[11]

Weber et al. found that bilateral rIPC reduced kidney damage better than unilateral. This shows that conditioned tissue mass may affect protection. However, the best number of cycles, duration, and time of administration for ischemia/reperfusion remains unknown. In a mouse model of ischemia and reperfusion, Jhonsen et al. found that the number and length of cycles, not the number of limbs exposed, dictate the efficiency of rIPC. Additionally, their data imply that rIPC's protective effects fade 1.5 to 2 hours after stimulus removal.[12]

Therefore, the signalling pathway of rIPC is characterised by a high degree of complexity, including several components and the intricate interaction between distinct humoral factors and their respective targets. Understanding the minimum effective dosage required to produce positive outcomes of an intervention has significant therapeutic significance. This particular set of information has potential use in the optimisation of rIPC protocols.[1]

Neural Communication Pathway

Different experiments have revealed that an intact neural route is essential for transmitting protective signals from a distant organ or tissue to the target organ during rIPC. The limb utilised for preconditioning must have innervation since the protective benefits of transient ischemia of a lower limb are lost when the femoral nerve or spinal cord is cut. Bilateral cervical vagal section eliminated the protective advantage of rIPC, whereas subdiaphragmatic vagal section did not. This supports the idea that a parasympathetic vagal pathway is involved in action. Mastitskaya et al. found that rIPC's cardioprotective effects are influenced by vagus nerve dorsal motor nucleus neurons. As said, the vagus nerve's efferent route sends the cardioprotective signal to the heart. Acetylcholine activates muscarinic receptors to cause preconditioning (IPC). By inhibiting synaptic vesicle neurotransmitter absorption, nicotinic receptor antagonists and reserpine may eliminate rIPC.[13]

In contrast, Gho et al. have shown evidence that the temporary blockage of the anterior mesenteric artery results in cardioprotective effects, which may be negated by the administration of ganglionic blockers. This conclusion was substantiated by the hypothesis that rIPC triggers the secretion of many chemicals, including adenosine, bradykinin, and CGRP, in the distant organ or tissue, therefore activating sensory neurons. According to Liem et al., adenosine has been proposed to be involved in a neuronal circuit associated with cardioprotection. The researchers documented that the release of adenosine by the mesenteric artery during the preconditioning stimulus resulted in a significant reduction in the extent of the infarct. Furthermore, they observed that this effect was nullified when hexamethonium was administered.[14]

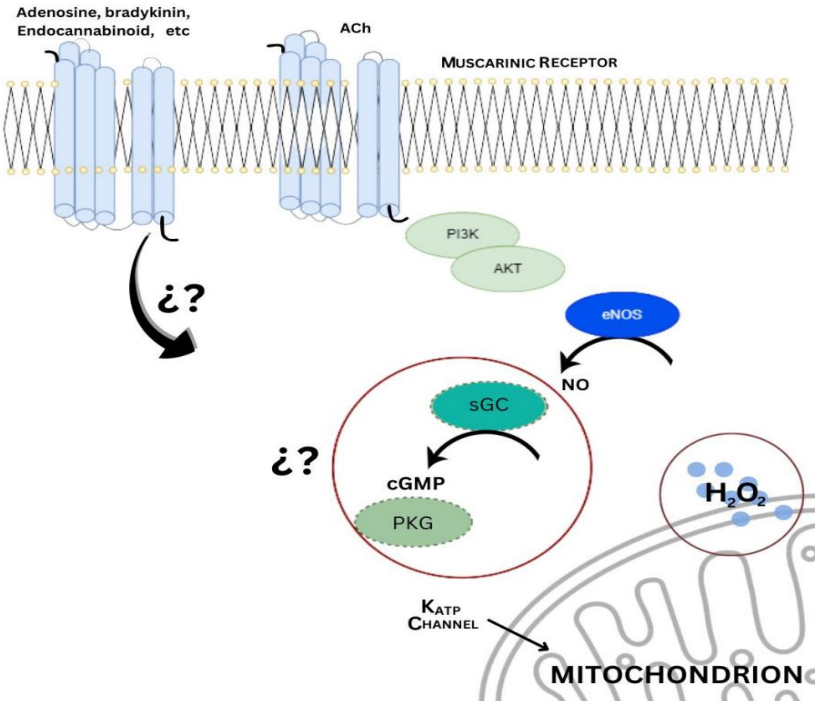

Figure 2. This study presents a schematic depiction of the intracellular pathways that are engaged by distant ischemic preconditioning prior to the onset of myocardial ischemia. Acetylcholine and other autacoids elicit the activation of distinct receptors that are situated inside the plasma membrane of cardiomyocytes. Specifically, the stimulation of muscarinic receptors resulted in the phosphorylation of Akt and eNOS enzymes. Following this, the activation of soluble guanylate cyclase and protein kinase G may result in the opening of mKATP channels and an elevation in the generation of mitochondrial H2O2. Thus, it is plausible that hydrogen peroxide (H2O2) may function as a secondary messenger for the protective signal of rIPC. eNOS endothelial nitric oxide synthase, mKATP mitochondrial KATP channels, NO nitric oxide, P13K Phosphatidylinositol 3-kinase, PKG protein kinase G, and sGC soluble guanylate cyclase.[1]

In contrast, our study revealed that rIPC elicits the activation of a parasympathetic pathway that leads to the activation of the Akt enzyme and phosphorylation of endothelial nitric oxide synthase (eNOS), opening of mitochondrial ATP-sensitive potassium (mKATP) channels, and formation of hydrogen peroxide (H2O2) in the cardiac tissue prior to the onset of myocardial ischemia. Hence, it is plausible to classify them as rIPC triggers (Figure 2).[1]

At now, there is a prevailing belief that the transmission of the rIPC signal to the designated organ involves many factors, including humoral, neuronal, and systemic systems. It is worth noting that the specific mechanisms involved in this transmission may vary depending on the model being studied. The dependence of humoral factor release in response to rIPC on sensory innervation to the preconditioned limb has been shown. Nevertheless, the specific outcome of activating sensory nerves, which subsequently triggers the release of a humoral factor, remains uncertain.[15]

On the other hand, it is well recognised that there is a cardiac intrinsic neuronal network responsible for the processing of sensory input and the regulation of efferent autonomic outputs originating from intrinsic cardiac ganglia. The neuronal network is also susceptible to ischemia/reperfusion injury and the subsequent remodelling that occurs after a myocardial infarction, leading to a deterioration in ventricular function. Hence, it is essential to investigate the function of these intracardiac neurons in the process of rIPC.[16]

The Delayed Phase of Remote Ischemic Preconditioning

The second window of protection, also known as the delayed phase of rIPC, is initiated by alterations in the gene expression associated with the myocardium's reaction to oxidative and inflammatory damage.[1]

The occurrence of cardiac tissue necrosis leads to the initiation of an inflammatory reaction that is distinguished by the infiltration of cells and the release of inflammatory signals. Neutrophils exhibit infiltration into the infarcted region during the first hours subsequent to the initiation of ischemic conditions. These cells play a crucial role in the innate immune response. These cells generate elevated amounts of ROS and release enzymes such as myeloperoxidase and proteases, therefore increasing the extent of vascular and tissue damage in the immediate vicinity.[17]

Konstantinov et al. found that rIPC reduces leukocyte inflammation in humans. In the acute phase of rIPC stimulation, genes involved in chemotaxis, adhesion and migration, exocytosis, apoptosis, and innate immunity were downregulated. The anti-inflammatory effects were substantially greater 24 hours after rIPC. The researchers found that postponed rIPC increases Hsp73 protein expression and protects Hadhsc, Prdx4, and Fabp4 from oxidative stress. However, numerous pro-inflammatory genes were downregulated.[9]

Previous studies have provided evidence indicating the involvement of nuclear factor kappa-B (NF-kB), a transcription factor that is sensitive to redox changes, in the regulation of many inflammatory genes (iNOS and inducible cyclooxygenase). These findings support the notion that NF-kB plays a role in rIPC cardioprotection. While the activation of NF-kB during ischemia/reperfusion is known to have negative consequences, such as the production of leukocyte adhesion molecules, cytokines, and chemokines, its activation during rIPC has been shown to have an adaptive effect during the delayed phase. This adaptive effect may be attributed to the upregulation of its inhibitor.[10]

Therefore, rIPC has the potential to mitigate the inflammatory response that occurs after reperfusion by activating NF-kB, which then upregulates the synthesis of its endogenous inhibitor, resulting in an elevation in NO production. The precise function of NO in the delayed phase remains uncertain; nonetheless, it is likely to have antiapoptotic and anti-inflammatory properties.[18]

In contrast, Singh et al. found that the neurogenic pathway is heavily engaged during late rIPC and adenosine preconditioning. The humoral and neurogenic pathways may act cooperatively to protect the heart, according to the scientists. Adenosine, a humoral molecule, may activate the neurogenic pathway and induce cardioprotection during rIPC.[1]

Chronic Effect of Remote Ischemic Preconditioning

Acute myocardial infarction (AMI) causes an abrupt increase in ventricular loading, which remodels the infarcted border zone and the non-infarcted myocardium elsewhere. After a myocardial infarction, ventricular remodelling comprises two phases: early in the first week and late thereafter. The initial stage involves infarcted region enlargement, which may cause early ventricular rupture or aneurysm. The next step of remodelling involves ventricular dilation, shape change, and hypertrophy.[5]

As previously stated, the first phase of remodelling is distinguished by the enlargement of the infarct due to the inflammatory response and the breakdown of the extracellular matrix (ECM) by serine proteases and the activation of matrix metalloproteinases (MMPs). The process of early remodelling is characterised by the occurrence of wall thinning and ventricular dilatation, which subsequently leads to an increase in diastolic and systolic wall stresses. The occurrence of ventricular dilatation in the early stages of infarct expansion has been conclusively seen in human subjects, and it serves as a significant factor in predicting the outcome of the condition. The process of late remodelling encompasses the enlargement of myocytes and alterations in the structure of the ventricles. These modifications aim to distribute the heightened pressures on the walls more uniformly. Additionally, the ECM develops a collagen scar to stabilise the forces causing expansion and to impede further deformation.[19]

Few studies have examined how rIPC affects ventricular remodelling. After reperfusion, rIPC was linked to lower levels of pro-inflammatory cytokines, IL-1β and TNF-α. IL-10 concentrations increase with rIPC given 24 hours before ischemia/reperfusion. STAT5, a transcription factor involved in the survival activating factor enhancement pathway, increases IL-10. In human heart injury, this route is downstream of JAK. In another study, rIPC increased IL-6 levels, which have reparative capabilities in myocardial infarction-affected myocardium, via early growth response protein 1.[13,20,21]

In stroke models, rIPC impacts circulating leukocytes and spleen immunological precursors. After rIPC, rats with middle cerebral artery closure infarction had enhanced splenic capacity and cerebral lymphocyte infiltration on day 3. Rat splenectomy reversed the aforementioned alterations, indicating splenic conditioning. Previous study has shown that rIPC activates the splenic-vagal nerve axis to protect the heart. Splenectomy and vagotomy diminish rIPC's cardioprotective effects, corroborating this. In SAFE, splenectomy lowers STAT3. Finally, IL-10 may aid splenic axis rIPC cardioprotection. Given the research, including ours, on the parasympathetic nervous system and rIPC, it would be fascinating to study how rIPC influences remodelling via modulating the inflammatory response.[1]

As previously said, the aforementioned data indicate that rIPC may serve as a viable approach for individuals experiencing left ventricular remodelling. Further investigations using larger patient cohorts and animal models are necessary to ascertain the specific contributions of rIPC in the process of left ventricular remodelling.[1]

Inter-Organ Preconditioning

Acute ischemia/reperfusion stress causes cell death in the heart, kidneys, liver, gut, lungs, brain, and skeletal muscle. Many organs and tissues share ischemia/reperfusion damage pathophysiology. Thus, emerging acute ischemia/reperfusion damage treatments seem to work similarly across numerous organs and tissues.

Thus, rIPC has been extended to several organs, establishing itself as a real inter-organ protection against acute ischemia/reperfusion harm.[22]

Due to its high energy needs and complicated microvascular network, the kidney is prone to ischemia/reperfusion injury. Various studies reveal rIPC's renoprotective benefits. These studies found that rIPC lowers serum creatinine, blood urea nitrogen, and histological damage relative to untreated controls. Interestingly, these studies found no difference between local and rIPC.[10]

In cardiac, orthopaedic, lung resection, and transplantation, acute lung damage causes morbidity and death. In CABG surgery, cytokine-mediated systemic inflammation impairs lungs. This response decreases alveolar oxygenation and increases pulmonary vascular resistance, necessitating artificial breathing. Peralta et al. discovered that liver rIPC decreased lung and other organ neutrophil concentration and systemic inflammation after prolonged hepatic ischemia/reperfusion. Researchers have explored how rIPC prevents acute lung ischemia/reperfusion damage in animals. These studies consistently lower systemic inflammatory markers, pulmonary edoema, and respiratory failure. Pulmonary vascular resistance, pressure, PaO2, and lung compliance decreased. Peak inspiratory pressure and pulmonary resistance decreased.[12]

In the first study on liver ischemia/reperfusion injury, hind-limb rIPC reduced ALT levels. It has been established that rIPC protects against acute hepatic ischemia/reperfusion injury in rats, rabbits, and mice by many authors using different procedures.[23] Stroke and carotid endarterectomy cause acute ischemia/reperfusion damage to the brain. Several studies suggest that rIPC may build brain resistance to ischemia/reperfusion injury. This mechanism improves cerebral perfusion, reduces cerebral infarction, and promotes cerebral collaterals. Previous investigations have indicated that rIPC reduces leukocyte migration and provides brain protection.[24]

Comprehensive experiments with several stimuli, focusing on cross-preconditioning, are advised. Using rIPC with pharmacological pretreatment may be a future therapeutic technique since it seems to mitigate the negative effects of ischemia/reperfusion injury across organs and tissues more effectively.[1]

Clinical Evidence and Potential Challenges of Remote Ischemic Preconditioning

The suitability of preconditioning procedures in the clinical environment is contingent upon the characteristics of the ischemia/reperfusion event, which may be either predictable, such as in the case of CABG surgery and elective percutaneous coronary intervention (PCI), or unanticipated, as shown in STEMI.[1]

A preliminary investigation conducted on paediatric patients following surgical repair of congenital heart diseases was among the first studies to use rIPC protocol. The findings of this study indicated that rIPC intervention resulted in a reduction in postoperative troponin I levels and a decreased need for inotropic support. A following experiment was conducted using a similar rIPC methodology, with a sample size of 57 patients having CABG. The findings of this trial demonstrated outcomes that were consistent with the aforementioned study. Subsequent to these first investigations, a series of modest nevertheless affirmative research have emerged, substantiating the advantageous impact of rIPC within the context of cardiac surgery. However, it is worth noting that a few studies have shown neutral or worse outcomes as well.[25]

Three big multi-center clinical trials on rIPC with cardiac surgery revealed modest cardioprotection. The first South Korean clinical study randomised 1280 heart surgery patients. Surgery includes CABG, valve replacement, congenital heart disease treatment, and aortic surgery. Mortality, myocardial infarction, arrhythmia, stroke, coma, renal failure or dysfunction, respiratory failure, cardiogenic shock, gastrointestinal problems, and multi-organ failure were not improved by rIPC before or after cardiopulmonary bypass. For reconciliation, ERICCA and RIPHEART examined different trial findings. ERICCA was a multicenter phase III study of 1612 CABG patients with or without valve surgery. Note that the study did not use conventional anaesthetic. Neutral except for the 6-minute walk test, which favoured rIPC. The phase III RIPHeart study comprised 1403 propofol-anesthetized heart surgery patients from several locations. The main endpoint and troponin release were neutral. Over 90% of ERICCA study participants and all RIPHeart trial participants used propofol anaesthesia without precautions as previously reported. Another potential complicating factor was the random assignment of all participants to rIPC, an upper arm blood pressure cuff.[26,2,5]

CABG surgery may not be ideal for rIPC evaluation. Due to advancements in surgery, anaesthesia, and cardioplegia, CABG surgery produces minimal myocardial damage. Myocardial damage in cardiac surgery may result from inflammation, direct heart manipulation, and coronary micro-embolization. Preconditioning methods, age demographics, comorbidities, pharmacological therapies, and anaesthetic procedures may affect rIPC surgical trial outcomes. Due to rIPC technique variations, clinical studies are not comparable, making cardioprotective strategy development challenging. The arm's rIPC efficacy is unknown because to considerable vascularization and innervation discrepancies between the upper and lower extremities. Dezfulian et al. discovered no significant variations in reactive hyperemia physiological response and plasma nitrite concentration when rIPC was delivered to the arm or thigh in healthy participants. The anatomical location for rIPC stimulus delivery should be considered in future investigations.[9]

rIPC may be more effective in AMI, when cardioprotection is greater. In STEMI patients, rIPC before thrombolysis or primary PCI reduces infarct size in many clinical studies. In their meta-analysis, Wang et al. evaluated rIPC in 16 randomised trials. The research found that recurrent, brief limb ischemia/reperfusion may preserve elective PCI patients' hearts and kidneys. However, rIPC does not reduce cTnI during PCI. In addition, Manchurov et al. found that rIPC before primary PCI improves endothelial function in acute myocardial infarction patients. Importantly, this benefit lasts at least one week. CONDI-2/ERIC-PPCI, a prospective, single-blind, randomised controlled study of 5401 STEMI patients after primary PCI, examined the impact of rIPC on clinical outcomes. The experiment divided patients into control and rIPC groups. The study found that rIPC did not enhance clinical outcomes in this patient group after one year. Thus, rIPC application in clinical settings remains problematic despite intensive study. Confounding factors may diminish rIPC's effect.[1]

Ageing reduces cardiomyocyte contractile function and cardioprotective systems. Certain interventions for elderly people may be limited by these changes. Comorbidities may also affect rIPC. Jensen et al. showed that type 2 diabetes causes ischemia/reperfusion damage resistance. High glycosylated protein levels modify mitochondrial function and inhibit mitochondrial permeability transition pore activity, causing this resistance. This is due to rIPC. The researchers found that dialysate from patients with and without diabetes, who do not have peripheral neuropathy, undergoing rIPC reduced infarct size compared to control dialysate. The cardioprotective effect of rIPC was reduced in diabetics with neuropathy. The studies indicate that brain circuits mediate release.[1]

Patient medication also affects rIPC. Sulphonylureas, used to treat type 2 diabetes, reduce preconditioning in experimental and clinical settings. Glibenclamide blocks ATP-sensitive potassium ion channels, preventing ischemia preconditioning benefits. However, medications such as insulin, metformin, GLP-1 analogues, gliptins (DPP-4 inhibitors that limit GLP-1 breakdown), and SGLT-2 inhibitors may protect the heart and enhance further benefits. Pharmacological therapies, such as β-blockers, ACE inhibitors, opioids, and anti-platelet drugs, may change the effect of rIPC by lowering the cardioprotection threshold. Further research is needed to determine whether pharmaceutical interactions affect rIPC cardioprotection.[1]

3. Conclusion

Remote ischemic preconditioning is a multifaceted approach aimed at enhancing the heart's ability to withstand ischemic conditions by inducing cytoprotective stimuli. There is an optimistic outlook for the potential implementation of this approach in many therapeutic situations, with the expectation that it will contribute to the mitigation of ischemia/reperfusion harm. Additional research endeavours should be meticulously planned in order to cultivate a more comprehensive comprehension of the pathways and mechanisms behind both early and late rIPC. Comprehending the routes is crucial for the successful translation of medical interventions to patients.

4. Declaration

4.1 Ethics Approval and Consent to participate
Not applicable.

4.2. Consent for publication
Not applicable.

4.3 Availibility of data and materials
Data used in our study were presented in the main text.

4.4 Competing interests
Not applicable.

4.5 Funding Source
Not applicable.

4.6 Authors contributions
Idea/concept: IMS. Design: IMS. Control/supervision: SA. Data collection/processing: IMS. Analysis/interpretation: IMS. Literature review: SA. Writing the article: IMS. Critical review: SA. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

4.7 Acknowledgements
We thank to Brawijaya Cardiovascular Research Center

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