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REVIEW ARTICLE

Clinical Applicability of Conditioning Techniques in Ischemia-Reperfusion Injury: A Review of the Literature

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Abstract: Ischemia refers to a reduced supply of oxygen and nutrient to the vital organ of the body. Reperfusion to the ischemic organ is the only way to salvage injury due to ischemia. Paradoxically, reperfusion itself induces the injury, which is more severe than the previous injury referred to as ischemia-reperfusion injury. Ischemia-reperfusion injury is the major cause of mortality in the case of ischemic diseases. The major hurdle for a clinician to treat ischemia is the reperfusion injury, which is encountered in different surgical as well as non-surgical situations. Several therapies, such as anti-platelets, anti-thrombolytic agents have been developed to contain ischemia-reperfusion injury, but with limited success. Over some time, some conditioning techniques such as preconditioning and postconditioning have been used by clinicians to overcome ischemia-reperfusion injury. The present review focuses on the clinical applications of different conditioning techniques in diverse pathological conditions of ischemia-reperfusion injury.

Keywords: Ischemia, ischemia-reperfusion, preconditioning, remote preconditioning, postconditioning, preconditioning.

1. INTRODUCTION

Cardiovascular Diseases (CVD's), including hypertension, heart failure, stroke, and coronary artery disease, are the major cause of mortality all over the world. WHO 2016 report says that around 17.4 million people died due to CVD's, and the number is projected to 23.3 million by the end of 2030 [1]. Besides this, about 12.7% of global mortality is due to Ischemic Heart Disease (IHD), mainly in developing countries [2, 3].

Ischemia is a condition of restricted blood supply to the tissue with a subsequent shortage of oxygen along with other nutrients vital for normal cellular metabolism and viability [4]. Ischemia can affect many organs such as the heart, brain, kidney, lungs, liver, intestine, *etc* [5]. IHD is the sudden interruption or insufficiency of blood supply to the heart, followed by sudden death. Restoration of blood supply is perhaps is an immediate intervention to salvage ischemic injury, however sudden restoration of blood supply after prolonged ischemia causes more severe and lethal injury, better known as reperfusion injury [6]. It is estimated that Ischemia-Reperfusion (IR) injury is responsible for around 30% of the deaths of ischemic patients in tertiary care.

A lot of research has been done to contain IR injury and its detrimental effects. Over time, some conditioning techniques like preconditioning and postconditioning are developed and have been applied clinically with variable success. This particular article aims to provide information on the available data of clinical studies related to different conditioning techniques applied in various pathological conditions of IR injury. The work also focuses on delineating the protective mechanism of conditioning techniques in IR injury. The review will also pinpoint the clinical applicability of pharmacological conditioning in IR injury of various organs.

2. ISCHEMIA-REPERFUSION (IR) INJURY

Restoration of blood flow to the ischemic organ is the only way to preserve the ischemic organ from irreversible tissue damage [6, 7]. Paradoxically, rapid reperfusion of the infarcted organ induces the death of cells of the organ and exacerbates the extent of injury of that particular organ, a phenomenon known as IR injury [4]. The concept of IR injury was first postulated in the 1960s and is now encountered in many surgical as well as non-surgical situations such as organ transplantation, cardiopulmonary bypass surgery, aneurysm repair, stroke, myocardial infarction, trauma, shock, hemorrhage [8-10], traumatic head injury, carotid endarterectomy and deep hypothermic circulatory arrest [11].

2.1. Pathological Mechanism of Ischemia and IR Injury (Fig. 1)

Ischemia is the main target of many pathological situations, as discussed above. Ischemia of longer duration leads to a variety of cellular, metabolic and ultra-structural changes such as altered membrane potential, increased intracellular calcium and sodium overload [12], cellular swelling, increase hypoxanthine, decrease Adenosine Triphosphate

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(ATP), phosphocreatine and glutathione level. When ischemia occurs in any particular organ, than aerobic metabolism switches to anaerobic metabolism. This further decreases oxidative phosphorylation that subsequently causes failure in the re-synthesis of energy-rich molecules such as ATP and phosphocreatine. In addition to this, it also increases the accumulation of hypoxanthine in that particular organ. Moreover, ATP-operated ion channels function is also impaired that further leads to increase in the entry of calcium, sodium, and water into the cell [13, 14]. During normal physiology, hypoxanthine gets oxidize to xanthine by xanthine dehydrogenase, but during the ischemic phase, xanthine dehydrogenase gets convert into xanthine oxidase. Xanthine dehydrogenase utilizes Nicotinamide Adenine Dinucleotide (NAD) as its substrate, while xanthine oxidase uses oxygen as its substrate. Therefore, during the ischemic phase, xanthine oxidase is unable to convert the hypoxanthine to xanthine, subsequently causing excess hypoxanthine in that particular organ. In addition to this, during the reperfusion phase, oxygen re-enters into that tissue, which causes the conversion of excess hypoxanthine (accumulated during the ischemic phase) to xanthine by xanthine oxidase [15]. This process further leads to the generation of large amounts of reactive oxygen species (ROS) such as superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-) [16]. This free radical activates the intracellular signaling pathway and causes membrane injury and finally leads to IR injury [17]. In addition to this, during reperfusion, oxygen will re-introduce into the cells and start damaging cellular proteins as well as Deoxyribonucleic Acid (DNA), which are also other main factors of IR injury [18]. Some studies showed that oxidative stress, neutrophil, leukocyte activation, and excessive intracellular osmotic load together are involved in the pathogenesis of IR injury [19, 20]. Beside these pathological mechanisms, several endogenous mediators such as caspase-3, caspase-8 [21, 22], calpains [23], interleukin-6 (IL-6) [24] and tumor necrosis factor-α (TNF-α) [25] also play an important role in the pathogenesis of IR injury (Fig. **1**).

Development of several therapeutic strategies like primary percutaneous coronary intervention (PPCI) and thrombolytic approaches such as new generations of antiplatelet drugs and antithrombotic agents have been major steps forward to clinically handle ischemic injury [26, 27]. However, until today, neither pharmacological therapies nor non-pharmacological interventions have been ultimately successful in protecting the organ against IR injury [28, 29]. Over time some conditioning techniques have been developed involving brief episodes of ischemia followed by reperfusion either before (preconditioning) or after (postconditioning) restoration of blood supply in the affected region to mitigate IR injury [30, 31].

3. ISCHEMIC PRECONDITIONING (IPC)

The concept of IPC was first introduced in 1986 by Murry *et al*. IPC is a protective strategy in which brief episodes of ischemia and reperfusion protects the organ from subsequent prolonged ischemia [32, 33]. It is hypothesized that the brief episodes of non-lethal ischemia decrease the rate of ATP depletion during subsequent ischemic episodes and that intermittent reperfusion may be beneficial to the ischemic organ by washing out catabolites that have accumulated during ischemia [34]. Several preclinical and clinical studies have been done to demonstrate the decrease in infarct size using a protocol of repetitive occlusion and reperfusion before a prolonged ischemic insult [35, 36]. It has been suggested that preconditioning results in the generation and release of various endogenous ligands such as adenosine [37], bradykinin [38, 39], opioids [40], norepinephrine [41] and acetylcholine [42] with subsequent activation of their corresponding receptors [43]. Activation of these receptors further initiates several signaling cascade such as Phosphatidylinositol-3-Kinase (PI3K) [44], Akt [45], Protein Kinase-C (PKC), endothelial Nitric Oxide Synthase (eNOS) [46], glycogen synthase kinase-3β (GSK-3β) phosphorylation, extracellular receptor kinase (ERK1/2), p38 mitogen-activated protein kinase (MAPKs) [47] and Janus kinase-signal transducer activated transaminase (JAK–STAT3), which eventually provide protection in IPC [48, 49]. IPC is documented to have two windows of protection:

3.1. First Window of Protection (FWOP)

This is an acute phase of protection and it may start within 5 min of reperfusion and last up to 4-6 hours [32]. In this phase, signaling is believed to occur through the activation of ERK [50] and Akt [45].

3.2. Second Window of Protection (SWOP)

This is also referred to as a delayed phase of protection, and it begins within 12 hours of reperfusion and lasts up to 72 hours [51]. In this phase, signaling is believed to occur through the activation of some transcription factors, including Activation Protein (AP-1), hypoxic-inducible factor-1α (HIF-1α), and STAT.

3.3. Remote Ischemic Preconditioning (RIPC)

RIPC is potentially the most attractive and safest ischemic conditioning technique because it avoids the target lesion and non-culprit vessels that may cause further injury [52]. RIPC may also be a non-invasive technique in which transient, repeated episodes of ischemia and reperfusion applied to remote organ, renders the tissue resistant against sustained ischemic insult [53, 54]. Such protection-at-distance was subsequently extended from cardiac to non-cardiac tissue, and reduction of infarct size has been elicited from several organs, including the brain, kidney, intestine, skin, and skeletal muscle [53, 55].

3.4. Clinical Applications of Preconditioning

3.4.1. Evidence

Several clinical studies have given the evidence of the cardioprotective effect of preconditioning in patients undergoing mitral valve surgery, vascular surgery, and pediatric surgery. A clinical trial study of 30 patients suffering from

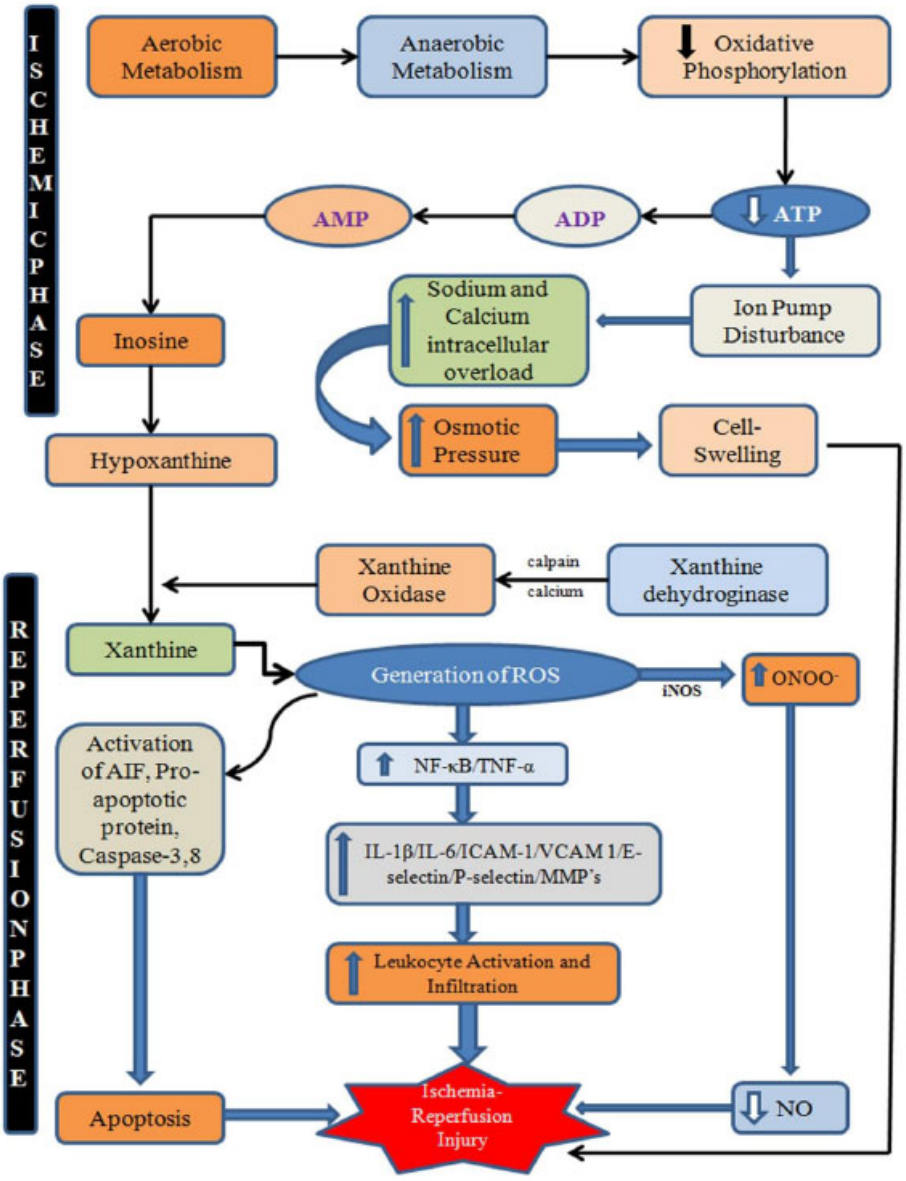

Fig. (1). Pathological mechanism of ischemia and the ischemia-reperfusion injury; ATP: adenosine triphosphate; ADP: adenosine diphosphate; AMP: adenosine monophosphate; ROS: reactive oxygen species; ONOO: peroxynitrite; AIF: apoptotic inducing factor; iNOS: inducible nitric oxide synthase; NF-κB: nuclear factor kappa-B; TNF-α; tumour necrosis factor-α; IL: interleukin; ICAM: intracellular adhesion molecule; VCAM: vascular cell adhesion molecule; MMP: matrix metalloproteinase; NO: nitric oxide. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

rheumatic heart disease undergoing mitral and aortic valve replacement was included. Patients were subjected to preconditioning by giving two cycles of 2 minutes ischemia of vena cava and aorta followed by 3 minutes reperfusion. There was a significant improvement in myocardial contractility, decrease in the release of creatinine kinase-MB (CK-MB) along with the decreased incidence of ventricular fibrillation [56].

Another study was conducted in which 40 patients suffering from rheumatic heart disease undergone double valve replacement therapy by using cold blood cardioplegic techniques. Among these, 20 patients were subjected to preconditioning with two cycles of 3 min aortic cross-clamping and followed by 2 min of reperfusion before the cardioplegic arrest. Significant reduction in the release of CK-MB, production of ROS was noticed and improvement in cardiac function [57].

Another study, carried out by Lin *et al.* described the protective effect of IPC in IR injury of the lower limb. Thirty patients were included undergoing lower extremity surgery

and divided into two groups. Lower limb IR injury was induced by application of a tourniquet on unilateral thigh followed by reperfusion. Preconditioning was provided by giving three cycles of 5 min of ischemia and 5 min of reperfusion. The Protective effect was assessed in terms of significant reduction of malondialdehyde (MDA), IL-6, and IL-8 levels from 2 hours to 24 hours after the release of the tourniquet in comparison to the control group [58].

Rakic and co-workers carried out a single-center randomized control trial to check the hepatoprotective effect of IPC on the patients of colorectal cancer who underwent liver resections. Patients were subjected to preconditioning of liver through three cycles of 15 min ischemia by portal triad clamping and 10 min reperfusion followed by subsequent reperfusion. The hepatoprotective effect of preconditioning was observed by a significant reduction of serum transaminase, bilirubin, and albumin levels of patients in comparison to the control group [59].

In addition to this, several other studies confirmed the implication of different preconditioning protocols using upper and lower limb ischemia in the protection of myocardial necrosis as well as in improvement in cardiac function [60-62].

3.5. Clinical Applications of RIPC

RIPC is a non-invasive, simple, safe, and cheap intervention clinically. Therefore, RIPC is more applicable in clinical settings as compare to preconditioning and provides a similar protective effect.

3.5.1. Evidence

A number of clinical trials have been carried out on the patients undergoing ventricular septal defect repair [63], PPCI [64], coronary angioplasty, elective abdominal aortic aneurysm repair [65], acute myocardial infarction and coronary artery bypass surgery [66, 67] to investigate the role of RIPC.

A randomized control trial carried out by Candilio and co-workers investigated the protective effect of RIPC on the patients undergoing cardiac surgery. A total of 180 patients undergoing cardiac bypass surgery or valve replacement were selected and divided into two groups. RIPC was provided through tying blood pressure cuff on the upper arm and upper thigh by giving two cycles of inflation of 5 min and deflation of 5 min, followed by subsequent reperfusion. The cardioprotective effect of RIPC was assessed by a significant reduction of incidence of perioperative myocardial injury and postoperative arterial fibrillation in comparison to patients who did not receive RIPC [68].

In another study, Wu and co-workers observed the cardioprotective effect of limb IPC on the patients undergoing mitral valve replacement. Patients were subjected to RIPC through three cycles of 5 min of inflation and 5 min of deflation by tying a pressure cuff on the right upper arm. Cardioprotection through RIPC was assessed by a significant reduction of cardiac troponin-1 level in comparison to control group patients [61].

In addition to this, Sales *et al.* examined the protective effect of RIPC in brain tumor patients undergoing elective surgical resection. They employed 60 patients in their study, divided into two groups based on tumors type (glioma or metastasis). Three cycles (each consist of 5 min of inflation and 5 min of deflation) of RIPC was applied by inflating a blood pressure cuff at 200 mmHg placed on the upper arm after induction of anesthesia. The protective effect of RIPC was assessed by the reduction of incidence of postoperative ischemic lesions in comparison to the control group [69]. Besides this, RIPC is also found to be applicable in brain injuries such as elective decompression surgery [70] and kidney transplantation [71].

Li *et al.* evaluated the protective effect of RIPC on intestinal and pulmonary injury in the patients undergoing open infrarenal abdominal aortic aneurysm repair. They selected 62 patients undergoing infrarenal abdominal aortic aneurysm repair and were divided into 2 groups. Patients were subjected to RIPC by giving three cycles of 5 min of ischemia and 5 min of reperfusion through blood pressure cuff tied on the left upper arm, followed by reperfusion of 24 hours. The protective effect of RIPC on the lung was observed as a significant increase in arterial-alveolar oxygen tension ratio in RIPC patients as compared to control group patients. The intestinal protection by RIPC was assessed by a significant reduction in serum TNF-α, IL-1 (inflammatory mediators), and MDA (oxidative stress) levels as compared to the control group [72].

In another study, Wu *et al.* checked the protective effect of RIPC on IR injury occurring after kidney transplantation. For this, 48 patients undergoing kidney transplantation were included and divided into 2 groups. RIPC was provided through three cycles of 5 min ischemia and 5 min reperfusion by clamping of the external iliac artery. Renal protection by RIPC was assessed through reduction of serum level of creatinine and improved glomerular filtration rate at different time intervals of 2 hours, 12 hours, 7 days, 14 days and 30 days after kidney transplantation in comparison to control group patients [73].

Robertson and co-workers, carried out a pilot randomized controlled study to investigate the protective effect of RIPC on liver IR injury in the patients undergoing liver transplantation. Forty patients were selected and subjected to RIPC through three cycles of 5 min ischemia and 5 min reperfusion by tying a pneumatic tourniquet on the left thigh before liver transplantation. The protective effect was indicated by a significant reduction of IL-2, IL-6, IL-10, and TNF-α level after liver transplantation [74].

3.6. Pharmacological Preconditioning

Several pharmacological agents such as adenosine [75], bradykinin, acetylcholine [76], angiotensin-II [77], opioids [40], norepinephrine [78], platelet-activating factor (PAF) [79], alcohol and volatile anesthetics [80] are reported to reduce the severity of IR injury. Some studies indicated that pharmacological conditioning is a safer way of protection against IR injury [81-83]. During pharmacological precondi-

tioning, a therapeutic agent is administered before the major ischemic event. Although, this therapeutic agent itself eliminates from the body it further activates several initiators, mediators, and triggers which confer the protection to the organ from IR injury [84].

3.6.1. Clinical Applications of Pharmacological Preconditioning

3.6.1.1. Evidence

A study done by Beck-Schimmer and co-workers, demonstrated the protective effect of sevoflurane preconditioning in the patients undergoing liver surgery. In this randomized trial, they included 64 patients undergoing liver surgery and among these, 30 patients were subjected to sevoflurane preconditioning before inflow occlusion. Liver protection was assessed by a significant decrease in postoperative serum transaminase, alanine transaminase, and aspartate transaminase levels [85].

Barros *et al.* conducted a randomized double-blind study to investigate the protective effect of L-alanyl-glutamine preconditioning in the IR injury of the liver during liver transplantation. Thirty- three patients undergoing liver transplantation were selected and divided into two groups. Among these, half of the patients received 50 gm L-alanyl-glutamine and normal saline was administered to the rest of the patients through a portal vein before liver transplantation. The protective effect of L-alanyl-glutamine preconditioning was indicated in terms of significant reduction of MDA level in L-alanyl-glutamine treated patients in comparison to normal saline-treated patients [86].

Yu and co-workers demonstrated the protective effects of dexmedetomidine preconditioning in the IR injury of the lung. Sixty patients were selected and divided into two groups. Patients were subjected to intravenous infusion of dexmedetomidine at a dose of 0.125 ml/kg for 10 min and control group patients received an equal volume of normal saline. After 10 min, patients of both groups were subjected to ischemia by occluding sciatic nerve with tourniquet followed by reperfusion. The protective effect of pharmacological preconditioning was indicated by a significant reduction of serum IL-6, IL-8, and TNF-α level as compared to control group patients [87].

Another study carried out by Xu *et al.* investigated the protective effect of remifentanil preconditioning in patients undergoing coronary artery bypass surgery. A total of 24 patients undergoing coronary bypass surgery were selected and divided into two groups. Remifentanil was administered by infusion at the dose 5 μg/kg in 50 ml after anesthesia induction in preconditioning group patients and normal saline was administered in control group patients. Cardioprotection was determined by a significant reduction of serum cardiac troponin-1 level after an operation in comparison to control group patients [88].

In addition to this, another study investigated the protection of sevoflurane preconditioning to improve endothelial dysfunction induced by the IR injury of the forearm. For conducting this study, 5 male healthy volunteers were selected and subjected to forearm ischemia of 15 min followed by reperfusion of 30 min to induce IR injury. Sevoflurane was given through inhalation from 15 min before ischemia until 5 min after the onset of reperfusion. The protective effect was measured in terms of decreased activation of leukocytes after sevoflurane preconditioning in comparison to the control group [89].

3.7. Disadvantages of IPC

The major drawback of this therapeutic strategy is that it needs to be applied before the index ischemic event, which, in the case of clinical practices, is impossible to predict. IPC is an invasive intervention because it is applied directly to the ischemic organ or tissue, which may not be feasible in all clinical settings [90].

4. ISCHEMIC POSTCONDITIONING (IPOSTC)

IPostC was first described by Zhao *et al.* in a dog model of myocardial IR injury [91]. IPostC is a relatively newer approach involving brief episodes of ischemia/reperfusion after prolonged ischemia immediately at the onset of reperfusion to reduce infarct size [92-94]. It is also found that IPostC decreases the generation of ROS, mitochondrial calcium overload, inflammation, and improve endothelial function [95]. Moreover, IPostC is also demonstrated to activate pro-survival kinases such as PI3K [96, 97], eNOS [98], ERK1/2 [99], GSK-3β, beta-catenin and reperfusion injury salvage kinase (RISK) pathway like Akt/protein kinase B [100, 101]. At the molecular level, several initiators; mediators and triggers have been suggested to mediate the protective effect of IPostC. PostC like preconditioning is believed to have two phenomena of protection, *i.e.*, an early phase, which starts immediately after the major ischemic events and a delayed phase, which appears after 24 hours of ischemic events.

4.1. Remote Ischemic Postconditioning (Ripostc)

RIPostC is the phenomenon in which conditioning stimulus (brief ischemia-reperfusion episodes) is given through the distant organ at the onset of reperfusion of the main ischemic organ [102]. RIPostC appears to be more applicable in clinical settings because it is applied at the onset of reperfusion; can be performed on non-vital organs; can avoid the risk of ischemic postconditioning on vital organs and is suitable for long term rehabilitation [103, 104]. Basic protective mechanism of RIPostC is the activation of eNOS, PI3K [105], Akt, GSK-3β, T-LAK-cell-originated protein kinase (TOPK) [106, 107] pathways and improvement in endogenous antioxidant enzyme activity [108] and inhibition of δ-protein kinase-C (δ-PKC) [109] in IR injury model of different organs in animals.

4.2. Clinical Applications of Postconditioning

4.2.1. Evidence

Several clinical studies evaluated postconditioning in patients undergoing cardiac surgery for the treatment of Con-

gestive Heart Disease (CHD) [110-112]. Luo *et al.* demonstrated the effect of postconditioning on the patients suffering from rheumatic heart disease and undergoing valve replacement. Fifty adult patients were randomly selected and subjected to three cycles of 30 sec. ischemia and 30 sec. reperfusion by using aortic re-clamping and de-clamping started 30 sec. after cardioplegic arrest. After this, they were found to have a significant reduction of CK-MB and lactate levels in comparison to the control group as a sign of myocardial protection [111].

In another study, Li *et al.* carried out a randomized trial to check the protective effect of postconditioning in cardioprotection in patients undergoing treatment of tetralogy of fallot. They employed 99 patients with tetralogy of fallot and subjected to postconditioning performed by aortic clamping after reperfusion and found a significant reduction in troponin-1 and lactate levels [112]. Cardioprotective effect of postconditioning was subsequently confirmed by other studies on the patients suffering from myocardial infarction, tetralogy of fallot, and other cardiac diseases [113-116].

In another study, Ricca and co-workers demonstrated the protective effect of IPostC in liver IR injury that occurs during liver transplantation. For conducting this study, 100 patients undergoing liver transplantation were selected and divided into two groups. IPostC was provided by three cycles of 1 min ischemia (by occluding hepatic artery) and 1 min reperfusion. Hepatoprotection was assessed by improved histology of liver and better tolerance to IR injury of postconditioning treated patients as compared to control group patients [117].

In another study, the protective effect of IPostC was investigated in endothelial dysfunction induced by ischemia-reperfusion of the forearm. IR injury was induced by inflation of a blood pressure cuff around the upper arm (brachial artery) to a pressure of 200 mm/Hg for 20 min followed by reperfusion. At the onset of reperfusion after global ischemia, postconditioning was provided by giving three cycles of 30-sec ischemia and 30-sec reperfusion by inflating and deflating a pressure cuff on the upper arm. The protective effect of postconditioning was indicated by reduced endothelial dysfunction induced by IR injury in comparison to the control group [118].

4.3. Clinical Applications of RIPostC

4.3.1. Evidence

Zhong and co-workers investigated the cardioprotective potential of RIPostC on the children undergoing open-heart surgery for repair of congenital heart defects. Total of 69 children undergoing open-heart surgery were selected and randomized into two groups. RIPostC was provided through three cycles of 5 min ischemia and 5 min reperfusion by using a blood pressure cuff on the lower limb at the onset of aortic de-clamping. Cardioprotection through RIPostC was assessed by a significant reduction of serum cardiac troponin-1 and CK-MB levels in comparison to the control group [119].

In another study, the protective effect of RIPostC was checked in the improvement of graft function in kidney transplantation. For this study, 60 patients undergoing kidney transplantation were selected and divided into the patients received RIPostC and patients did not receive RIPostC. At the onset of reperfusion, RIPostC was given through three cycles of 5 min ischemia and 5 min reperfusion on the upper limb. The protection of graft function through RIPostC was indicated by a significant reduction of serum creatinine level and improvement of Glomerular Filtration Rate (GFR) after 24 hr of kidney transplantation [120].

In addition to this, Kim and co-workers conducted another study to evaluate the protective effect of RIPostC on graft function and Acute Kidney Injury (AKI) after liver transplantation. Total of 78 patients undergoing liver transplantation were included and randomized into RIPostC treated patients and non-treated patients. RIPostC was provided by four cycles of 5 min ischemia and 5 min reperfusion through upper limb at the onset of reperfusion after liver transplantation. After 28 days of surgery, graft function was assessed by determining serum bilirubin, and liver enzyme level and AKI was also investigated. The protective effect of RIPostC was evidenced by improved AKI but there was no significant improvement in bilirubin and liver enzyme level [121].

Cao *et al.* demonstrated the cardioprotective effect of RIPostC on the IR injury of the patients undergoing PPCI for acute ST-segment Elevation Myocardial Infarction (STEMI). For this, 80 patients undergoing PPCI were selected and divided into two groups. Patients were subjected to RIPostC by giving four cycles of 5 min ischemia and 5 min reperfusion by inflation and deflation of cuff through upper arm just after PPCI. Cardioprotection through RIPostC was indicated by a significant reduction of serum CK-MB, creatinine, nitric oxide (NO), and stromal cell-derived factor-1a (SDF-1a) level at the different time interval of 0.5, 8, 24, 48 and 72 hours after PPCI as compare to control group patients [122].

4.4. Pharmacological Postconditioning

Unlike pharmacological preconditioning, pharmacological postconditioning is the therapeutic strategy in which therapeutic agent is administered after the major ischemic event or at the onset of reperfusion. Several studies have been given evidence of the protective effect of pharmacological postconditioning in different clinical settings [123, 124].

4.5. Clinical Applications of Pharmacological Postconditioning

4.5.1. Evidence

Zhang and co-workers demonstrated the cardioprotective effect of morphine postconditioning in IR injury of the patients undergoing Tetralogy Of Fallot (TOF). For this study, 89 children undergoing correction of TOF were involved and randomized into two groups. Patients were subjected to administration of morphine (0.1 mg/kg) *via* a cardioplegia needle into the aortic root for direct delivery to the heart

within 3 min before removal of aorta cross-clamp. Cardioprotection provided *via* morphine postconditioning was evidenced by a significant reduction of cardiac troponin-I level and improved cardiac function at the different time intervals of 4, 8, 12, 24, and 48 hours after reperfusion in comparison of control group patients [123].

In another study, the hepatoprotective effect of propofol postconditioning was investigated on IR injury in the patients undergoing liver transplantation. Total of 37 patients undergoing liver transplantation were involved and randomized into two groups. Propofol postconditioning (2mg/kg) was provided by infusion within 10 min of reperfusion after liver transplantation. The protection through propofol postconditioning was evidenced by a significant increase in heme oxygenase-1 (HO-1) and NADPH: quinone oxidoreductase-1 (NQO1) expression and decreased in oxidative stress 24 hours after surgery in comparison of control group patients [124].

Zuo *et al.* conducted a randomized clinical study to evaluate the protective effect of sufentanil postconditioning on IR injury in the patients undergoing mitral valve replacement (MVR). Total of 53 patients undergoing MVR were selected and divided into two groups. To the 24 patients, bolus infusion of sufentanil (0.2 μg/kg) was given through aortic root cardioplegia perfusion catheter and to the rest 29 patients; normal saline was administered 5 min before aortic declamping after surgery. The protective effect was determined by a significant reduction of serum CK-MB and cardiac troponin-1 levels and improved other parameters of heart functioning including heart rate, mean arterial pressure, central venous pressure, cardiac output, stroke volume and duration of mechanical ventilation 24 hours after surgery in comparison to control group patients [125].

5. PRECONDITIONING AND POSTCONDITIONING: *VIS-À-VIS*

The basic difference between preconditioning and postconditioning is that preconditioning has to be applied before the major ischemic event while postconditioning is applied after the main ischemia or at the onset of reperfusion. Both preconditioning and postconditioning have two phases of protection. In the case of preconditioning, both the 1st and 2nd phases are active and involve the release/activation of some endogenous mediators to confer the protection. However, in postconditioning, 1st phase is passive but the 2nd phase is active. From a clinical point of view, preconditioning is not much feasible clinically because it has to be applied before the major ischemic event and which is very difficult to predict in clinical conditions. However, postconditioning theoretically appears to be more feasible at clinical level because it is applied after the major ischemic event and this is indeed dually supported by some recent clinical usefulness success of postconditioning.

6. ISCHEMIC PERCONDITIONING (IPERC)

Schmidt *et al*. first reported the concept of IPerC in experimental studies [126] and later, Botker *et al*. reported IPerC in clinical studies [127]. IPerC is the phenomenon in which conditioning stimulus is applied during the main ischemic event and normally it is applied in a remote organ. The basic protective mechanism of IPerC is the inhibition of oxidative stress and activation of ATP sensitive potassium (K_{ATP}) channels [126], Akt, ERK1/2, PI3K, and eNOS [128] pathways.

6.1. Clinical Applications of IPerC

6.1.1. Evidence

In a randomized clinical trial, the salvaging effect of IPerC was assessed before hospital admission of 333 adult patients suffering from acute myocardial infarction. They were randomly selected and divided into patients receiving PPCI with remote perconditioning and without remote perconditioning. Remote perconditioning was provided (during ambulance transport to the hospital) by giving four cycles of 5 min inflation and 5 min deflation by using a blood pressure cuff. Beneficial effects of perconditioning were noted as increased myocardial salvage index 30 days after PPCI in comparison to the patients did not receive perconditioning [127].

Li and co-workers demonstrated the protective effect of IPerC on IR injury in patients undergoing valve replacement therapy. Total of 81 patients subjected to valve replacement were involved in the study and randomized into three groups. IPerC was done in the lower limb through four cycles of 4 min ischemia and 4 min reperfusion during the surgery by inflating to 600 mm/Hg and deflating using a tourniquet. The cardioprotection was assessed through a significant reduction of serum cardiac troponin-1 level at different time intervals of 30 min, 4, 12, and 72 hours after unclamping in comparison to control group patients [129].

In addition to this, another study was carried out to check the protective effect of IPerC on multi -organ injury, including heart, liver, kidney, and lung in the patients with rheumatic heart disease undergoing valve replacement therapy. Patients were subjected to IPerC by giving three cycles of 5 min ischemia and 5 min reperfusion through the right thigh during the surgery. The clinical parameters for heart, liver, kidney, and lung were evaluated after 48 hours of surgery. The level of cardiac troponin-1 in serum was significantly reduced in comparison to the control group patients. The incidence of acute lung and liver injury was also reduced by perconditioning but there was no improvement in renal injury [130].

7. DISCUSSION

A large number of studies indicated above have been carried out over the last decade to establish conditioning techniques as one of the main interventions to prevent deleterious effects of IR injury in various pathological conditions. The clinical studies involving different experimental protocols of conditioning techniques under different experimental conditions have been observed to provide substantial protection in multi-organs *viz*, heart, liver, kidney, brain, intestine,

etc. IR injury [68, 111, 119, 127]. Preconditioning, the oldest technique in the category has seen limited clinical success; on the contrary, techniques like RIPC, postconditioning have been fairly successful in clinical set up [85, 123, 124]. However, a substantial clinical success with all these techniques is still warranted. Further, a critical review of the published studies hints towards an important role of various downstream pathways such as PI3K, ERK, Akt, MAPK, eNOS, GSK-3β, *etc*. at the molecular level in the protective mechanism of these techniques [44-46, 97, 98]. Although, a lot of insight has been given into the role of the above pathways, still in-depth research is needed to delineate the appropriate molecular mechanism of various conditioning techniques so that these techniques are applied clinically in the best possible manner.

CONCLUSION

Studies over the last decade have documented that conditioning techniques can be of great value in containing IR injury. Both preconditioning and postconditioning have been successfully applied to some extent in clinical settings to prevent injury due to ischemia and reperfusion. However, the clinical feasibility of preconditioning is limited as it has to be applied before an ischemic event which is difficult to predict in clinical practice. In contrast, postconditioning looks practically more feasible and applicable in clinical settings since it can be applied after the ischemic event. Currently, the focus of future research is to investigate molecular mechanisms of postconditioning so that it can be translated into clinical practice.

AUTHOR CONTRIBUTIONS

Kuldeep Kumar carried out the literature research and prepared the primary draft; Dr. Nirmal Singh conceived the idea and prepared the final draft of the manuscript; Dr. Amteshwar S. Jaggi and Dr. Leonid N. Maslov co-conceptualized and provided valuable inputs in finalizing the manuscript.

LIST OF ABBREVIATIONS

ATP	=	Adenosine Triphosphate
NAD	=	Nicotinamide Adenine Dinucleotide
ROS	=	Reactive Oxygen Species
O^{2-}	=	Superoxide Anion
H_2O_2	=	Hydrogen Peroxide
OH^-	=	Hydroxyl Radical
I/R	=	Ischemia-Reperfusion
DNA	=	Deoxyribonucleic Acid
IL-6	=	Interleukin-6
TNF-α	=	Tumor Necrosis Factor-alpha
MAPK	=	Mitogen-Activated Protein Kinase
PARP	=	Poly (ADP-Ribose) Polymerase
JAK/STAT	=	Janus Kinase/Signal Transducer and Activator of Transcription
IPC	=	Ischemic Preconditioning
PI3K	=	Phosphatidylinositol-3-Kinase
PKC	=	Protein Kinase-C
eNOS	=	endothelial Nitric Oxide Synthase
GSK-3β	=	Glycogen Synthase Kinase-3β
Erk1/2	=	Extracellular receptor kinase
AP-1	=	Activation Protein
HIF-1α	=	Hypoxic-Inducible Factor 1
CK-MB	=	Creatinine Kinase-MB
RIPC	=	Remote Ischemic Preconditioning
MDA	=	Malondialdehyde
IPostC	=	Ischemic Postconditioning
RISK	=	Reperfusion Injury Salvage Kinase
RIPostC	=	Remote Ischemic Postconditioning
TOPK	=	T-LAK-cell-Originated Protein Kinase
cTnI	=	Cardiac Troponin-1
GFR	=	Glomerular Filtration Rate
AKI	=	Acute Kidney Injury
PCI	=	Percutaneous Coronary Intervention
NO	=	Nitric Oxide
SDF-1a	=	Stromal cell-Derived Factor-1a
PAF	=	Platelet-Activating Factor
TOF	=	Tetralogy of Fallot
HO-1	=	Heme Oxygenase-1
NQO1	=	NADPHQuinone Oxidoreductase-1

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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