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MINI REVIEW

Pathophysiology of Ischemia/Reperfusion-induced Myocardial Injury: What We Have Learned from Preconditioning and Postconditioning?

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ABSTRACT

Organ damage after reperfusion of previously viable ischemic tissues is defined as ischemia/reperfusion injury. The pathophysiology of ischemia/reperfusion injury involves cellular effect of ischemia, reactive oxygen species and inflammatory cascade. Protection against ischemia/reperfusion injury may be achieved by preconditioning or postconditioning. In this review, we discuss basic mechanisms involved in the pathophysiology of ischemia/reperfusion injury. Moreover, the pharmacology of preconditioning and postconditioning is delineated.

Keywords: *Ischemia/reperfusion injury, Preconditioning, Postconditioning*

Ischemia is the condition in which the organ is deprived from blood flow followed by inadequate oxygen and nutrient supply. Although restoration of blood flow to an ischemic organ is essential to prevent irreversible cellular injury, reperfusion per se may augment tissue injury in excess of that produced by ischemia alone. Reperfusion of the previously-ischemic myocardium is often followed by the detrimental changes in coronary arteries and myocardial tissues, which ultimately results in cardiac dysfunction, known as ischemia/reperfusion (I/R) injury. The I/R injury has been implicated in the pathology of peripheral vascular insufficiency [1], angina [2], myocardial infarction [3] and stroke [4]. Brief intermittent periods of ischemia followed by reperfusion at a time prior to prolonged ischemia, known as ischemic preconditioning, or immediately after a period of ischemia before the onset of reperfusion, known as ischemic postconditioning, have been shown to reduce I/R-induced myocardial injury [5,6]. The present review has discussed basic mechanisms involved in the pathophysiology of I/R injury and the pharmacology of preconditioning and postconditioning.

Pathophysiology of Ischemia/Reperfusion Injury

The important consequences of ischemic reperfusion are reversible contractile dysfunction known as myocardial stunning and impairment of blood flow at microvascular level known as no-reflow with neutrophil plugging and vasoconstriction. Myocardial stunning is the contractile dysfunction of heart that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or nearly normal coronary flow [7]. The impairment in re-synthesis of high energy phosphates, alteration in sympathetic responsiveness, damage to collagen matrix, leukocyte activation, transient calcium overload, decreased sensitivity of myofilaments to calcium and generation of oxygen free radicals have been implicated in the pathogenesis of prolonged contractile dysfunction in myocardial stunning [8]. The ischemic myocardium reduces its metabolic needs and tends to adopt itself to survive with minimal requirements by reducing its own contractility. Such state is referred to as hibernating myocardium in which unlike myocardial stunning, the contractility is restored immediately once the blood flow is restored. The mechanisms responsible for the development of myocardial hibernation in which the heart reduces the contractile function in proportion to reduced blood flow are yet to be identified. The calcium responsiveness in experimental myocardial hibernation has been noted to be reduced and this reduction has not been related to decreased calcium sensitivity. Another important event of prolonged postischemic reperfusion is no-reflow phenomenon in which no blood flow occurs through coronary blood vessels due to increased leukocyte-endothelial cell adhesion, platelet-leukocyte aggregation, interstitial fluid accumulation and loss of endothe-

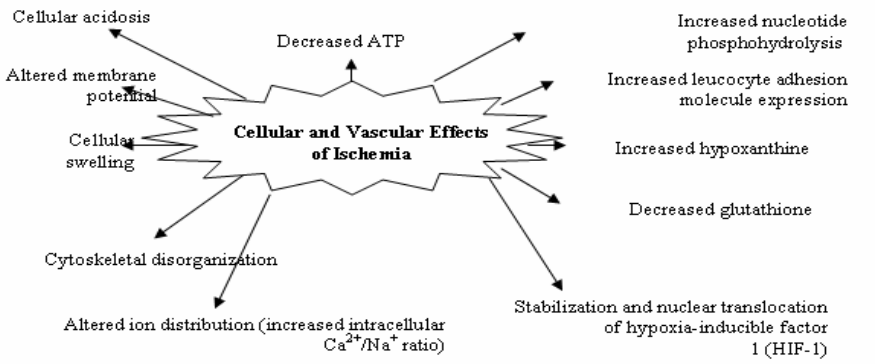

Fig. 1: Cellular and vascular effects of ischemia

lium-dependent vasorelaxation, which all together result in mechanical blood flow obstruction [9].

The cellular and vascular effects due to prolonged ischemia have been shown in Fig. 1. Ischemia reduces cellular oxidative phosphorylation and thus the synthesis of energy-rich phosphates is decreased, which alter the membrane ATP-dependent ionic pump function. This alteration favors the entry of calcium, sodium and water into cell, which ultimately leads to cellular swelling. The reduced mitochondrial oxidative phosphorylation results in loss of major source of ATP production for energy metabolism. A compensatory increase in anaerobic glycolysis for ATP production leads to accumulation of hydrogen ions and lactate, resulting in intracellular acidosis [10]. Moreover, ischemia promotes the expression of proinflammatory genes, leukocyte adhesion molecules, endothelins and thromboxane A2 [9,11], which all together may affect the integrity of coronary vascular endothelium. Polymorphonuclear leucocytes (PMNs) are mobilized from intravascular space to the interstitium during hypoxia, and such responses may contribute significantly to tissue damage during subsequent reperfusion [12,13]. The migration of PMNs through the endothelial barrier may disrupt such tissue barriers and create the potential for extravascular fluid leakage and oedema formation [14].

The adenine nucleotide catabolism during ischemia leads to intracellular accumulation of hypoxanthine, which subsequently generates reactive oxygen species (ROS) upon reperfusion (Fig. 2). During ischemia, cellular ATP is degraded to form hypoxanthine. Under normal condition, hypoxanthine is oxidized by xanthine dehydrogenase to xanthine, but during ischemia, xanthine dehydrogenase is converted to xanthine oxidase. Unlike xanthine dehydrogenase, which uses nicotinamide adenine dinucleotide as its substrate, xanthine oxidase uses oxygen and therefore, during ischemia, is unable to catalyze the conversion of hypoxanthine to xanthine, resulting in a buildup of excess tissue levels of hypoxanthine. When oxygen is reintroduced during reperfusion, conversion of the excess hypoxanthine by xanthine oxidase results in the formation of ROS [15], including superoxide anions (O_2^-) hydroxyl radicals (OH^-), hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), and peroxynitrite. ROS directly damage cellular membranes through lipid peroxidation [11]. Further, ROS stimulate leukocyte activation and chemotaxis by activating plasma membrane phospholipase A2 to form arachidonic acid, an important precursor for synthesis of eicosanoids such as thromboxane A2 and leukotriene B4. Moreover, ROS stimulate leukocyte adhesion molecule and cytokine gene expression *via* activation of transcription factors such as nuclear factor-kB (NF-kB) [11].

Multiple mechanisms have been postulated for the leukocyte-mediated tissue injury that occurs after ischemia/reperfusion. Microvascular occlusion [16], increased vascular permeability [17] and release of oxygen free radicals [18], cytotoxic enzyme [19] and inflammatory cytokines [20] have been demonstrated to contribute to leukocyte-induced tissue injury. I/R-induced leukocyte activation has been noted to release ROS, proteases and elastases, which result in increased microvascular permeability, edema, thrombosis, and cell death [11,21,22]. Various signaling systems such as tumor necrosis factor- α (TNF-α) [23-25], Rho-kinase [26,27], NF-κB [28], janus kinase (JAK/STAT) [29,30], poly (ADP-ribose) polymerase (PARP) [31,32], p38 mitogen activated protein kinase (MAPK) [33], Caspases [34-35], interleukin-1 (IL-1) [36] and IL-6 [37] have been implicated in the pathophysiology of I/R injury. Further, polymorphonuclear leukocyte (PMN) [38,39] and factor associated with neutral sphingomyelinase activation (FAN) [40] have been noted to play a pivotal role in affected myocardium. Moreover, resident cardiac mast cells play a key role in I/R injury. Mast cells originate from pluripotent progenitor cells in bone marrow and are major players in the inflammation process [41,42]. Degranulation of mast cells releases various cytotoxic mediators, which have been noted to be involved in the pathophysiology of ischaemia/reperfusion injury [43,44].

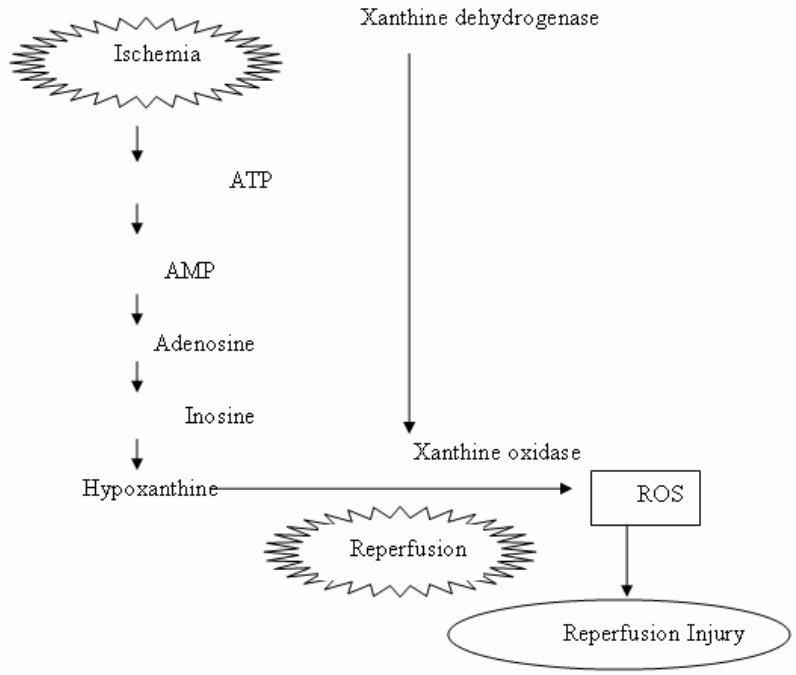

Fig. 2: Formation of ROS in ischemia–reperfusion injury. ATP indicates adenosine triphosphate, AMP indicates adenosine monophosphate, ROS indicates reactive oxygen species

Preconditioning

In 1986, Murry and colleagues described an endogenous protective strategy in which multiple brief ischemic episodes in canine hearts limited infarct size from a subsequent sustained ischemic insult termed as ischemic preconditioning (IPC). The IPC has two phases of protection in which an early phase is lasting from few minutes to hours known as early preconditioning, and a late phase starts after 12 hours and lasts up to 3 days is referred to as delayed preconditioning [5,45,46].

Following the finding of IPC by Murry and colleagues, several studies have investigated the mechanisms involved in its organ protective effects. Determining the mechanisms by which IPC confers myocardial preservation may eventually lead to the development of therapies to reduce cardiomyocyte injury following cardiopulmonary bypass. These studies led to the discovery that preconditioning could be induced by pharmacological means [47,48] in which drugs are administered before the ischemic event, with an intervening washout period before ischemia known as true pharmacological preconditioning or without a washout period known as pharmacological pretreatment. Preconditioning may be triggered by substances like adenosine, bradykinin, NO, diazoxide, a mitochondrial ATP sensitive K^+ channel (K_{ATP}) opener, PKC activators, opioids and prostaglandins [49]. In addition, anesthetics were investigated for their potential to precondition the heart before ischemia. All halogenated, volatile substances were found to be protective and their actions were comparable to that of ischemic preconditioning [50,51]. In consequence, this form of preconditioning was introduced into the clinical setting. Indeed, studies in cardiac surgery confirmed the efficacy of this anesthetic preconditioning that postoperative Troponin I in preconditioned hearts was noted to be significantly reduced [51].

Short periods of ischemia in remote vessels or even distant organs protected the myocardium from injury induced by coronary artery ischemia/reperfusion. Thus, substances must have been released from the remote ischemic-reperfused tissue that protected the jeopardized myocardium [52]. The occlusion of circumflex artery has produced protection of myocardium supplied by left anterior descending coronary artery and this phenomenon is termed as intracardiac preconditioning [53]. Short occlusion of renal artery [54,55] abdominal aorta [56,57] and mesenteric artery [58-60] have been documented to protect myocardium against I/R-induced injury. This phenomenon is termed as remote preconditioning [61-62] or intra organ preconditioning [62] or preconditioning at a distant site [63].

Postconditioning

Brief intermittent episodes of ischemia and reperfusion, at the onset of reperfusion after a prolonged period of ischemia confer cardioprotection, a phenomenon is termed as ischemic postconditioning. This concept was first introduced by Zhao and colleagues [6].In a canine left anterior descending coronary artery ligation (LAD) model, they compared the protective effects of IPC to that of postconditioning. The brief ischemia and reperfusion of 30 seconds each after prolonged ischemia significantly reduced infarct size and endothelial dysfunction [6]. The word postconditioning was given since the stimulus (10-30 seconds for 3-6 times) is applied after a period of ischemia.

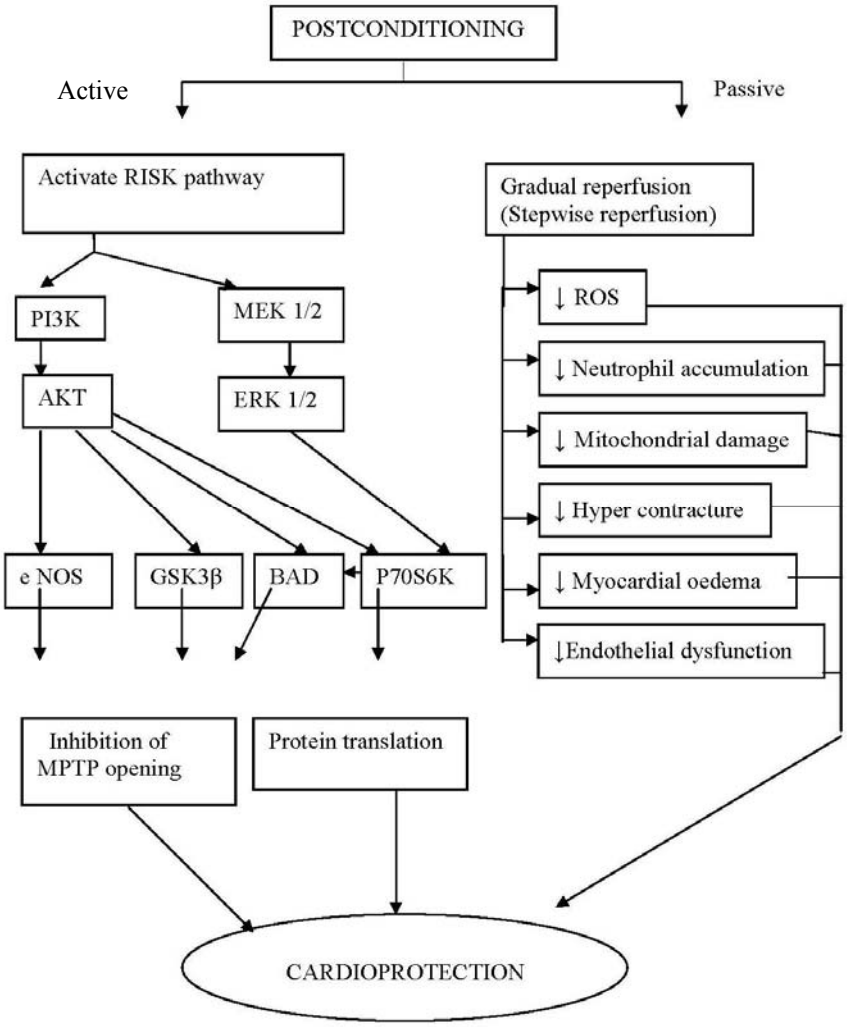

Fig. 3: Schematic representation of active and passive mechanisms of postconditioning

It has been proposed that passive and active phases are involved in cardioprotective mechanisms of postconditioning. The passive phase is initiated via stepwise reperfusion that reduces the delivery of oxygen radicals and mitochondrial Ca^{2+} overload. In active phase, the reperfusion injury salvage kinases (RISK) pathways which include PI3K, Akt and ERK-1/2 are activated by endogenous stimulators such as adenosine, opioids and some unidentified endogenous substances [64-66]. Postconditioning mediated activation of PI3 kinase, Akt and subsequently eNOS inhibit the opening of mitochondrial permeability transition pore (mPTP) to afford cardioprotection (Fig. 3) [67,68]. Further, postconditioning activates p70s6K through MEK ½ and ERK ½ signaling systems that initiates protein translation to mediate cardioprotection. It has been suggested that postconditioning mediated cardioprotection is likely produced via the ERK1/2 pathway rather than PI3 kinase/Akt pathways [69]. On the other hand, it has been noted that Akt and ERK activated during postconditioning do not protect myocardium from reperfusion injury [70]. These contradictory reports need future investigations.

Pharmacological agents like adenosine administered initially at reperfusion have been shown to be cardioprotective is known as pharmacological postconditioning [71-73]. The pharmacological postconditioning may reduce the effective dose of a cardioprotective drug. Inhalational anaesthetics such as isoflurane [74,75] and sevoflurane [76] given just before the onset of reperfusion reduce infarct size, termed as anaesthetic postconditioning. The administration of isoflurane and sevoflurane at the onset of reperfusion has decreased infarct size through activation of K_{ATP} channels and opening of mPTP [76,77].

Following to an established remote preconditioning, remote postconditioning has been demonstrated. The concept of remote postconditioning is not merely laboratory inquisitiveness, but it may have clinical application [78]. The occlusion of the renal artery immediately before the onset of reperfusion of a coronary artery significantly reduced myocardial infarct size [79]. One may have significant nervousness in applying cyclical angioplasty balloon inflations in the target coronary artery. An alternative approach is to stimulate postcon-

ditioning via another part of body like leg, which is much more accessible than kidney [79]. A tourniquet could be applied to the leg during transport to the emergency room to set up a strong postconditioning strategy. The tourniquet could then be removed just before completion of the angioplasty procedure and in advance of the onset of reperfusion to afford cardioprotection in first minutes of reperfusion [80].

Preconditioning and Postconditioning: A Fleeting Look

Preconditioning and postconditioning have many features in common, but they have important differences too. The immediate difference between preconditioning and postconditioning is the impact of the timing of application. While preconditioning can stimulate adaptive changes in risk areas that increase the tissue tolerance to ischemia, postconditioning can have no such biochemical or molecular effect. In postconditioning, the trigger, mediator and effector released would be active during early reperfusion, but in preconditioning, the adaptive changes take place before or during ischemia. It has been reported that the degree of infarct size reduction was similar in postconditioning as well as preconditioning; however, these two interventions have not been additive [81]. In contrast, an additive effect of these two cardioprotective strategies in the in vivo rabbit model has been demonstrated [82]. It is unclear whether such additive effects are sensitive to duration of ischemia since Yang et al has employed 45 min ischemia and 3 hrs reperfusion. The existing data suggest that preconditioning and postconditioning express the same physiological and cellular aspects of protection. Both provide infarct size reduction, attenuation of endothelial dysfunction, reduction in neutrophil adherence to coronary vascular endothelium and tissue accumulation, reduction in superoxide anion generation in postischemic myocardium, reduction of reperfusion arrhythmias, similar engagement of survival kinases, inhibition of the permeability transition pore and reduction in apoptosis [83-85]. Adenosine, PI3 kinase and Akt pathways are commonly involved in the cardioprotecive effects of preconditioning and postconditioning. However, these protective strategies may differ since ERK1/2 has not been noted to be involved in preconditioning, but may be involved in postconditioning [82]. The involvement of effectors such as K_{ATP} channels and mPTP in both preconditioning and postconditioning would also suggest common pathways, but the time at which these pathways exert cardioprotection may differ. However, the classical differences between preconditioning and postconditioning are yet to be well clarified and distinguished.

Clinical Relevance of Preconditioning and Postconditioning

Numerous *in vitro* findings suggest that the human myocardium can be protected by ischemic preconditioning. In addition, the existence of this phenomenon *in vivo* has also been well demonstrated. Intermittent aortic cross-clamping before the sustained period of global ischemia required for the insertion of coronary artery bypass grafts during cardiac surgery has been shown to provide cardioprotection [86]. The findings from many preclinical studies in which cardioprotection has been seen in healthy animal hearts might not be reproducible in the human myocardium since human ischemic heart disease is frequently associated with various disorders such as diabetes mellitus and its complications and left ventricular hypertrophy etc or with other contributing factors like older age. The presence of these conditions might interrupt with the protection induced by ischemic preconditioning [87,88]. The use of pharmacologic agents to target different components of the signaling pathway that mimic the protection induced by ischemic preconditioning, known as pharmacologic preconditioning, might enable this approach to be recognized as a clinical therapy [89,90]. Nicorandil has cardioprotective effects when given as an adjunctive therapy at the time of reperfusion in cardiac patients during surgery [91,92]. Other promising agents such as adenosine and inhibitor of Na^+/H^+ exchanger have been shown clinically to afford cardioprotection when given as an adjunct to reperfusion. Preclinical studies demonstrated that pharmacologic inhibition of Na^+/H^+ exchanger before myocardial ischemia could reduce infarct size through a reduction in myocardial calcium accumulation, to a level comparable to ischemic preconditioning [93,94]. Adenosine has been shown to be a great promising cardioprotective agent in different clinical settings of myocardial I/R [95].

The postconditioning has been shown to be effective in patients with coronary artery disease. The patients undergoing percutaneous coronary intervention were subjected to repeated balloon inflation (n =10, 90 sec each) after angioplasty markedly reduced the magnitude of ST-segment elevation compared to controls [96,97]. The postconditioning with 4 cycles of 1 min reinflation followed by 1 min deflation of the angioplasty balloon in patients with total coronary artery occlusion showed reduced infarct size. Marked improvement in coronary blood flow has been noted in postconditioned patients [98]. Taken together, postconditioning would be a safe cardioprotective intervention to reduce reperfusion injury in patients with ischemic heart diseases.

CONCLUSION

The postconditioning and preconditioning strategies have the drawback of intermittent cross clamping of artery, which may be harmful in patients with severe artery disorders. A significant limitation of IPC has been the inability to apply this maneuver clinically except in situations where the ischemic event can be predicted. The advantages of postconditioning over preconditioning are that it can be initiated after an ischemic insult. Unlike preconditioning, postconditioning does not require initiation prior to the ischemic event. This aspect offers several interesting opportunities to cardiac surgeons. Postconditioning may be a safe and efficient cardioprotective strategy to reduce reperfusion injury in patients with ischemic heart diseases. However, further

studies are warranted to investigate the cardioprotective role of postconditioning in broader patients of coronary artery disease with hypertension, hypercholesterolemia, obesity and diabetes. In addition, studies are obligatory to recognize the major signaling mechanisms involved in the cardioprotective effects of postconditioning, which may open a novel vista to use pharmacological interventions in the name of pharmacological preconditioning to limit lethal reperfusion injury during cardiac surgery.

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