Clinical Implications of Myocardial Pre-And Postconditioning: Who is the Better Player?

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Abstract
Brief cycles of ischemia followed by reperfusion before prolonged ischemia is referred to as ischemic preconditioning (IPC), while brief periods of ischemia and reperfusion applied after prolonged ischemia denote ischemic postconditioning (IPOS). IPC and IPOS have been designated as two cardioprotective phenomenon against myocardial ischemia-reperfusion (I/R) injury by certain mechanisms like activation of prosurvival kinases, activation of eNOS (endothelial nitric oxide synthase) and release of NO. Recently, IPC and IPOS have been widely used in the clinical practice affording variable degrees of protection. The present review article deals with the mechanisms involved in IPC and IPOS mediated cardioprotection. Additionally, the clinical applications of myocardial pre-and postconditioning in patients with high prevalence of ischemic heart disease have been critically discussed.

Introduction
Ischemic heart disease (IHD) represents one of the major burdens on healthcare systems today [1]. Ischemia/reperfusion (I/R) injury is a major contributory factor to cardiac dysfunction that can be defined as the damage to cardiac tissue when blood supply is restored after a prolonged period of ischemia [2-3]. Ischemic preconditioning (IPC) and postconditioning (IPOS) represent two such interventions that are noted to afford cardioprotection. Brief episodes of ischemia and reperfusion applied before prolonged ischemia and reperfusion represents IPC [4], whereas brief episodes of ischemia and reperfusion applied after prolonged ischemia and just at the onset of reperfusion represents IPOS [5]. These two anti-jeopardized phenomenons are the most potent and reproducible methods of rescuing cardiac tissue from undergoing irreversible

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ischemic damage. IPC and IPOS have been shown to protect the heart against I/R injury by certain mechanisms involving activation of pro-survival kinases like phosphatidylinositol-3-kinase (PI-3K) and Akt/protein kinase B, activation of eNOS (endothelial nitric oxide synthase), release of NO and opening of mitochondrial potassium (Mito K$_{ATP}$) channels [6-8]. The efficacies of myocardial pre-and postconditioning in cardiac surgery and percutaneous coronary interventions in humans have confirmed their potential in the clinical practice [9-10]. In the present review, the mechanisms involved in the cardioprotective effects of pre-and postconditioning are discussed. Moreover, the article provides a better understanding about the clinical applications of myocardial pre-and postconditioning in patients with high prevalence of IHD.

**IPC and IPOS: Mechanisms of Cardioprotection**

Murry et al (1983) firstly described IPC as a well-characterized phenomenon in which brief periods of ischemia could protect the heart against subsequent ischemic insult [11], whereas Zhao et al (2003) has reported that brief episodes of coronary occlusion and reperfusion at the onset of reperfusion after prolonged ischemia conferred cardioprotection against I/R-injury known as IPOS [12]. Numerous studies have shown that various triggering substances like NO, adenosine (A$_1$/A$_3$ receptors), bradykinin (B$_2$ receptors), heat shock proteins (HSPs), calcitonin gene-related peptide (CGRP), oxygen free radicals and Mito K$_{ATP}$ channels induce the cardioprotection afforded by IPC [4,7,13]. These triggering substances amplify their signals to activate numerous mediators like protein kinase C (PKC), tyrosine kinase (TK), PI-3K and MAPK (mitogen-activated protein kinases) [11,13]. These mediators finally induce cardioprotection by opening Mito K$_{ATP}$ channels, blocking mitochondrial permeability pore transition (MPTP), activating antioxidant defense system, improving myocardial energy balance and inhibiting the release of pro-apoptotic substances [13-15].

In addition, several mechanisms have been proposed in IPOS-induced cardioprotection that include attenuating the generation of reactive oxygen species, mitochondrial calcium overload and inflammation and improvement of endothelial function. Moreover, IPOS activates pro-survival kinases such as PI3K and Akt/protein kinase B in conjunction with RISK pathway that includes various signaling systems like PI3K/Akt, glycogen synthase-3 beta (GSK-3β) and MEK1/2-Erk1/2, which are activated at the time of myocardial reperfusion in both IPC and IPOS-mediated cardioprotection [12,16]. PKC and PKG has been suggested to be an important mediator involved in IPOS-mediated myocardial protection. Further, IPOS has been noted to afford cardioprotection by opening Mito K$_{ATP}$ channels, activating eNOS and enhancing NO bioavailability [17-18].

**Myocardial Pre-and Postconditioning: Clinical Point of View**
Various clinical studies have demonstrated the cardioprotective potential of pre-and postconditioning in patients with IHD. However, several studies have proven to bring forth cardioprotection in animal models and failed to do so in humans but IPC has been reported to afford cardioprotection in both animals and humans [19]. The percutaneous transluminal coronary angioplasty (PTCA) procedure involves repeated intracoronary balloon inflations with intervening periods of perfusion which offers the opportunity to electively and selectively apply ischemia to a well-defined myocardial region [20]. PTCA has been noted to improve ischemia-induced myocardial dysfunction providing the evidence for clinical potential of IPC to protect ischemic myocardium. Interestingly, the first coronary occlusion in a series of occlusions has been noted to offer increased resistance to subsequent occlusions. Further, the ST-segment shift on electrocardiography and subjective anginal pain were decreased during the second coronary occlusion that further evidenced the clinical benefits of IPC [19, 21]. However, the aortic valve might get damaged during these clinical procedures and thus the application of pharmacological preconditioning was suggested. Pretreatment with bradykinin has been reported to improve the myocardial performance associated with preconditioning in patients undergoing PTCA procedure [22]. Nicorandil, a Mito K\textsuperscript{ATP} channel opener has been noted to precondition the myocardium by preventing the incidence of ventricular arrhythmias and myocardial dysfunction after coronary reperfusion [23]. Moreover, adenosine preconditioning decreased the severity of ischemia during the first balloon inflation that was significantly improved on subsequent balloon inflations during PTCA [21]. The second maneuver in which cardiac ischemia can be planned is coronary artery bypass grafting (CABG) in which IPC can be studied while avoiding the possible complications of collateral vessels by applying global cardiac ischemia instead of local ischemia. [9] In CABG, two cycles each consisting of three-minutes of cross-clamping ischemia and reperfusion before the period of ten minutes ischemia resulted in improved preservation myocardial ATP content and reduced postoperative troponin t release followed by improved myocardial performance, which support the myocardial protective potential of IPC [24]. It was demonstrated that the pretreatment with nicorandil afforded cardioprotection in patients undergoing CABG by attenuating ischemic damage [25]. Moreover, it was reported that exogenously infused bradykinin showed cardioprotective effect in the low-risk patients undergoing CABG as evidenced by reduction in CK-MB level [26]. Other promising agents such as adenosine and inhibitor of Na\textsuperscript{+}/H\textsuperscript{+} exchanger have been shown clinically to confer cardioprotection when given as an adjunct to reperfusion. It has been demonstrated that pretreatment with adenosine before CABG is associated with better postoperative
ventricular performance and reduced CK-MB release [19, 27].

The clinical data obtained to date are remarkably consistent regarding the potential of recently demonstrated cardioprotective phenomenon of postconditioning. IPOS is a simple and feasible method when compared to preconditioning in patients with acute myocardial infarction (AMI) since IPC is not extensively feasible in such a clinical practice in which the coronary artery of patient is already blocked at the time of hospitalization. The postconditioning stimulus applied in such a patient with AMI using PTCA procedure of inflation and deflation of angioplasty balloon after reopening of coronary artery reduced the infarct size evidencing its potential in clinical practice [17, 28]. Moreover, IPOS offers sole viewpoint to be applied in clinical practice since brief episodes of ischemia and reperfusion can be performed at the time of reperfusion during PTCA procedure. It has been demonstrated that postconditioning during PTCA significantly protects the human heart against I/R-induced myocardial injury as evidenced by marked reduction in infarct size [29]. The patients undergoing percutaneous coronary intervention were subjected to repeated balloon inflation of 90 sec each after angioplasty, markedly reduced the magnitude of ST-segment elevation compared to controls [30]. 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 that further evidenced its clinical potential [9]. Moreover, IPOS can be effectively used prior to removal of aortic cross-clamping after CABG [9-10]. IPOS has been potentially shown to assemble the cardioprotection of endogenous autacoids and other mechanisms to reduce the multiple manifestations of reperfusion injury after removal of the cross-clamping during CABG [19]. Postconditioning can be applied by temporarily removing and reapplying the cross-clamp in a cyclical manner to induce reperfusion and ischemia that mimic the cyclical perfusion pattern of myocardial postconditioning. IPOS with two cycles of 30 sec each of aortic declamping and reclamping before complete reperfusion was restored, afforded cardioprotection during CABG as evidenced by reduction of plasma troponin I and CK levels at 4 h post-reperfusion [31]. In another study of adult patients undergoing valve replacement using cardiopulmonary bypass and a crystalloid cardioplegia solution, the postconditioned hearts showed lower levels of CK-MB compared to control group with standard cardioplegia and resuscitation protocols at 4 and 8 h after aortic declamping [32]. Furthermore, it has been suggested that IPOS involves alternating cross-clamping of aorta in order to protect the myocardium which might be associated with increased
Complications of the operative procedure. Hence, pharmacological postconditioning would be the most beneficial approach as it would avoid the unfavorable consequences linked with intermittent cross-clamping and provide a simple method of myocardial protection subsequent to all cardiac procedures \[9, 33\]. Taken together, IPOS can be considered to be a safe and simple cardioprotective intervention to reduce reperfusion injury in patients with IHD \[34-35\].

Conclusions
IPC and IPOS are the two cardioprotective phenomenons that have the potential to reduce myocardial injury and improve the clinical outcomes in patients presenting with an AMI. Myocardial pre-and postconditioning have been reported to modify reperfusion injury and reduce infarct size sufficiently to improve outcomes in the treatment of acute coronary syndromes. Unfortunately, IPC has to be applied before the onset of ischemia which has restricted its clinical application to elective procedures like cardiac surgery in which the ischemic episode can be predictable whereas IPOS is being applied at the time of myocardial reperfusion that enhanced the interest of clinical investigators. The reports have shown that the ultimate myocardial protective strategy involves a combination of both IPC and IPOS. Although there has been tremendous progress in the understanding of IPC and IPOS but a more comprehensive understanding of these cardioprotective interventions might result in a significant decrease in the morbidity and mortality associated with IHD. Hence, further human studies are needed that use the traditional end points in the evaluation of the clinical potentials of IPC and IPOS in the ischemic heart.

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References
of Diabetes Mellitus Type II. Exp Diabetes Res 2011; in press.


16. Hausenloy DJ, Tsang A, Yellon DM. The reperfusion injury salvage kinase pathway: a common target for both ischemic preconditioning and


27. Wei M, Kuukasjarvi P, Laurikka J, et al. Cardioprotective effect of


