

Postconditioning

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Abstract

Early and successful reperfusion is mandatory to limit infarct size, and reduce morbidity and mortality from acute coronary syndrome. However, reperfusion is a double edge sword, with the potential to induce additional damage to the ischemic myocardium (reperfusion injury). The reperfusion injury may account for up to 50% of final infarct size. By stimulating cardioprotective pathway, postconditioning (ischemic, remote and pharmacological postconditioning) can reduce the negative impact of ischemia and reperfusion on the heart. In the present article, we briefly elucidate the mechanisms involved in cardiac protection and discuss the available supporting data for the use of postconditioning in the clinical scenario.

Keywords: ischemia reperfusion injury; cardioprotection; post-conditioning; remote conditioning

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Introduction

In the clinical setting, the application of coronary thrombolysis or percutaneous coronary intervention (PCI) for faster recanalization has been shown to improve the outcomes of patients with acute myocardial ischemia. However, even if the ischemic period is short or limited, the functional recovery of a reperfused heart is often less successful than expected due to “reperfusion injury” [1]. Therefore, it is important to fully understand the mechanisms of ischemia-reperfusion injuries and to consider the naturally cardioprotective strategies that the heart uses to attenuates the damage induced by ischemia and subsequent reperfusion (Fig. 1). This concept is supported by the clinical observation that patients experiencing pre-infarctional angina (preconditioning) have better prognosis, and by animal and clinical studies in which a short periods of ischemia, preceding the index ischemia, induce less myocardial damage [2].

Despite increasing data supporting the importance of ischemia-reperfusion injury and therefore cardioprotection, little is known about these phenomena and even less about how to prevent and protect the heart from them.

Preconditioning

Before the concept of ischemic preconditioning (IPreC) arose, cardiologists observed that patients with acute myocardial infarction who had experienced episodes of prodromal angina often exhibited less chest pain, less variation in the ST segment of ECGs, less cardiac dysfunction, and smaller myocardial infarct size. This occurred despite a paradoxical increase in the total ischemic time. This phenomenon was called the “cardiac warm-up phenomenon” [3]. In 1986, Murry et al. [4] confirmed the existence of “preconditioning with ischemia” in a canine

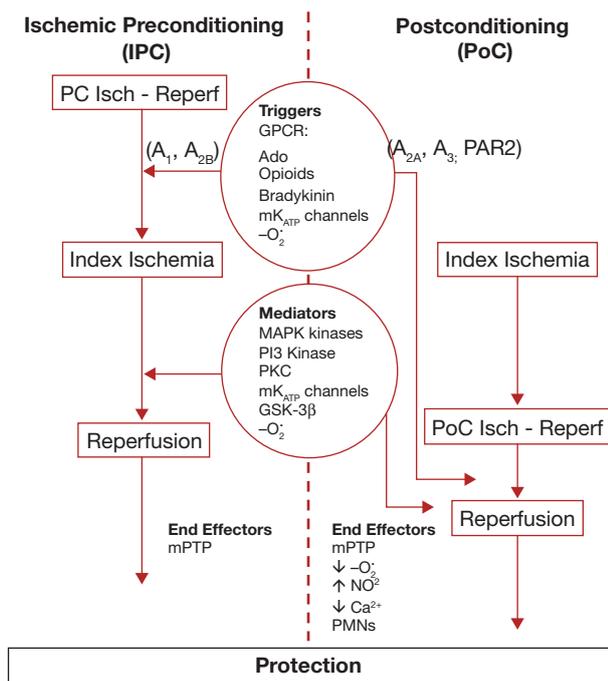


Fig. 1 Common mechanisms thought to be involved in cardioprotection. Differences and similarities between preconditioning and postconditioning pathways. See text for more details. Modified from [19].

model and defined it as a phenomenon where brief periods of ischemia followed by reperfusion just before sustained ischemia exerted 1) a delay in ATP depletion, 2) a reduction in oxygen consumption, 3) a retention of intracellular structure, and 4) a delay or reduction of cellular necrosis due to ATP expiration, finally resulting in delayed progression or reduction of infarct size, despite an increase in the total ischemic period. This is now recognized as a narrow definition of ischemic preconditioning.

It has become clear that the strength of protection by ischemic preconditioning critically depends on the interval between preconditioning ischemia and the onset of index ischemia. Two windows of cardioprotection have been identified, termed “early and late phase” preconditioning. The first period is limited to the initial 3 hours and the second one, associated with the increased expression of cardioprotective heat shock proteins (HSPs), is in the following 24–72 h. These two phases appear to involve different pathways; the former involving reactions that are completed in a short period of time, such as activation of ion channels, phosphorylation/activation of existing enzymes, or rapid turnover/translocation of sub-

stances, the latter involving more time-consuming reactions, such as genomic modulation and expression of channel proteins, receptor proteins, enzymes, molecular chaperone proteins, or immunotransmitters. Multiple, parallel mechanisms seem to induce cardioprotection by preconditioning ischemia, among these adenosine, the activation of alpha and/or beta receptor, G protein-coupled receptor (GPCR) members, opioid receptors, and bradykinin-B2 receptors. However, controversies still exist about the multiple and complicated mechanisms involved in cardiac protection before the onset of prolonged ischemia.

Postconditioning

Because the clinical application of cardioprotection induced by preconditioning is limited by the unpredictable occurrence of acute coronary syndromes, most of the recent translational therapeutic strategies aimed at reducing the damage related to ischemia-reperfusion injury, are applied at the time of reperfusion, after the onset of ischemic insult. Indeed, postconditioning has recently been shown to have potential as a novel cardioprotective intervention against ischemia-reperfusion injury, when applied at the onset of reperfusion following sustained ischemia [5]. This protocol is followed because the “final effectors of preconditioning” share some common pathways with the “contributors of postconditioning” at reperfusion [6]. Three forms of postconditioning: ischemic (IPoSC), remote (RPostC), and pharmacological conditioning (discussed in another section of this journal issue) have been explored both in the bench and the bedside.

Ischemic postconditioning

IPoSC is defined as brief periods of ischemia alternating with brief periods of re-flow applied at the onset of reperfusion following sustained ischemia. Recently, IPoSC has been introduced as mechanical intervention to attenuate reperfusion injury specifically [7]. Similarly to ischemic preconditioning, where brief episode of ischemia preceding prolonged ischemia induce resistance to IRI, ischemic postconditioning effectively reduces myocardial infarct size in all species tested so far, including humans (Fig. 2). IPoSC is a simple and safe maneuver, but because reperfusion injury is initiated within minutes of reflow,

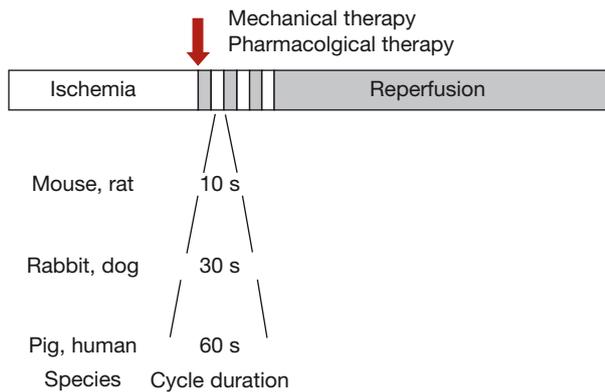


Fig. 2 Ischemic postconditioning protocols used in animal and human studies. Modified from [20].

postconditioning must be applied at the onset of reperfusion. The mechanisms through which postconditioning induces protection include: formation and release of several autacoids and cytokines; maintained acidosis during early reperfusion; activation of protein kinases; preservation of mitochondrial function, most strikingly the attenuation of opening of the mitochondrial permeability transition pore. It has also been documented that IPosC reduces neutrophil accumulation and attenuate endothelial injury. Exogenous recruitment of some of the identified signaling steps can induce cardioprotection when applied at the time of reperfusion in animal experiments, but more recently also cardioprotection was observed in a proof-of-concept clinical trial [8].

Although postconditioning is in its relative infancy as clinical strategy, several studies have shown it to be cardioprotective in both the catheterization laboratory in conjunction with PCI and in cardiac surgery. Studies in patients with an acute myocardial infarction showed a reduction of infarct size and improved left ventricular function when undergoing ischemic postconditioning. In the catheterization laboratory setting, repeated balloon inflations attenuated electrocardiographic changes (ST-segment elevation), lactate release, and left ventricular segmental dysfunction relative to the first balloon inflation suggestive of a preconditioning-like effect. Laskey [9] reported that repetitive 90-s balloon occlusions during angioplasty reduced ST-segment elevations, increased the rate of ST-segment elevation resolution (a marker of improved viability and perfusion) and increased flow velocity reserve in the infarct-related artery.

The beneficial effect of postconditioning have been demonstrated to be persistent, with improved functional recovery and reduced infarct size at 1 year [10]. However, the salvage impact varies among the studies, probably depending on critical requirements in postconditioning maneuvers, and it seems that protocol with fewer cycles or longer intermission [11], or applied after long ischemic time are less protective [11–13]. In cardiac surgery, postconditioning was induced by two 30-s cycles of aortic clamping and declamping at the time of reperfusion (release of the aortic cross-clamp) in children undergoing surgery for congenital malformations. Plasma troponin I levels were significantly less in the postconditioning group compared with no postconditioning. An alternative way to subject the heart to postcondition is to deliver a reperfusate via the cardioplegia line in a cyclical manner, i.e., 30–60 s pulses that mimic the cyclical perfusion pattern of the IPosC. Yellon et al. [14] and Alhulaifi et al. [15] reported that preconditioning the heart by short periods of aortic cross-clamping preceding elective ventricular fibrillation conserved high energy phosphate (i.e., ATP) levels in myocardial biopsy samples, suggestive of a cardioprotective effect. The impact of these observations is limited by the declining use of induced ventricular fibrillation during aorto-coronary artery bypass in favor of some form of chemical cardioplegia and by the hesitation of surgeons to repeatedly cross-clamp aorta that may have some degree of atheromatous plaque and/or adherent thrombi that may dislodge and embolize, particularly in the brain, causing stroke. Alternatively, the heart may be preconditioned remotely, for example by inducing transient limb ischemia before ventricular fibrillation or ischemia. Less CK release, greater myocardial ATP levels, and greater dP/dt values (a soft surrogate measure of function in vivo) suggestive of better contractility upon reperfusion were reported after ischemically preconditioning of patients undergoing chemical cardioplegia and aortic and mitral valve replacement surgery [16]. However, in a study using chemical cardioplegia during surgery, preconditioning was reported to be associated with increased release of CK-MB compared with non-preconditioned patients. All these data need to be verified in largemulticenter-studies that may explore the role of postconditioning in other surgical procedures such as correction of the ascending aortic aneurism, which are associated with high rates of cardiac dysfunction and mortality.

Remote postconditioning

Another step forward, cardioprotection is the discovery that ischemia at a distant site can elicit the same protective effects of ischemic preconditioning. Przyklenk et al. [17] first demonstrated that brief ischemic episodes of the left circumflex coronary artery significantly reduced myocardial infarct size following sustained occlusion of the left anterior descending coronary artery. Following the initial discovery of RPostC in the heart, it was reported that brief, intermittent ischemia of distant organs such as the skeletal muscle, kidney and intestine could also induce protection of the heart against prolonged myocardial ischemia and reperfusion. From a mechanistic standpoint, RPostC very closely resembles traditional IPreC and depends on the very same trigger mechanisms and second messenger signaling pathways to promote cardioprotection. At present, there are three main hypotheses regarding the mechanism responsible for RPostC [18]. The first theory is the neural hypothesis, which proposes that the ischemic remote organ releases endogenous substances (i.e., adenosine, bradykinin) that activate local afferent neural pathways that, in turn, activate efferent neural pathways to trigger target organ protection. A second theory is the humoral hypothesis, which suggests that the target organ releases humoral mediators such as adenosine and bradykinin into the blood stream, which are then transported to the remote organ where the humoral factor directly triggers the intracellular survival pathways. A third theory is termed as the “inflammatory suppression theory,” which proposes that the transient, remote organ ischemia produces a systemic anti-inflammatory phenotype that protects the distant target organ against subsequent ischemia-reperfusion injury. It is not clear which of the three proposed hypotheses accounts for the majority of cardioprotective effects mediated by RPostC. However, it is possible that all three of these hypotheses are correct, and there are interactions between endogenous substances such as adenosine, and local afferent neural pathways that synergize to promote cardioprotection and subsequently produce systemic suppression of inflammation.

Pitfalls of postconditioning

Currently, the most important issue is how to transfer the results of basic research into the clinical scenario

and how to incorporate them in therapeutic strategies. It is unfortunately true that there is an inevitable gap in the scientific approaches used in basic science and in clinical medicine. Clinical science largely relies on statistics because of heterogeneity of disease conditions and individuals, such as age, sex, background diseases, and their comorbidities. It has been suggested that cardioprotection by ischemic and pharmacological postconditioning is attenuated in animal models of left ventricle hypertrophy and it seems to be the same in humans, although few studies have been published on this point. Discrepancy regarding the efficacy of postconditioning has also been reported in animal models of hypercholesterolemia, diabetes and obesity.

Future directions and conclusion remarks

Postconditioning has shown to be an effective and easy strategy to be applied in the clinical setting, and is able to exert protective effects on the heart and reduce the ischemia reperfusion injury. Therefore, we strongly support the use of this approach to protect the heart in addition to other pharmacological agents to further optimize the beneficial effect of reperfusion and revascularization. However, it must be admitted that no definitive results are available regarding the beneficial effect of this strategy in special subset population such as diabetic, obese and hypercholesterolemic patients. More animal and clinical studies are warranted in order to elucidate and encourage the widespread use of this cost-effective technique. •

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