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REVIEW

Cardiac Remote Ischaemic Preconditioning: Mechanistic and Clinical Considerations

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Brief, non-harmful ischaemic insults to an organ remote from the heart, remote ischaemic preconditioning (RIPC), has been proposed to confer protection to the heart against ischaemia-reperfusion injury. While most clinical trials of RIPC during coronary interventions (PCI) suggest benefit, recent large, multicentre trials in coronary artery bypass surgery suggest a lack of efficacy. Mechanistically, RIPC most likely promotes the release of circulating factors which modulate multiple cellular pathways in the heart, promoting cell survival. This review explores potential mechanisms underlying RIPC and includes a contemporary evaluation of clinical studies in PCI and cardiac surgery, highlighting methodological differences which may explain discrepant findings between these two clinical groups.

Keywords Remote ischaemic preconditioning • Ischaemia reperfusion injury • Percutaneous coronary intervention • Coronary artery bypass grafting surgery

Introduction

First described in 1993 [1], remote ischaemic preconditioning (RIPC) describes the phenomenon whereby brief, non-harmful insults to remote tissues can protect against ischaemia-reperfusion (IR) injury in a tissue or organ of interest such as the heart. The observation that RIPC can confer cardiac protection through an ischaemic stimulus to the limbs has facilitated its clinical application in humans including its use prior to percutaneous coronary intervention (PCI) and coronary artery bypass grafting surgery (CABG).

Recent negative studies in CABG necessitate a reappraisal of the clinical benefits. Consideration of the mechanisms implicated in RIPC may help explain discrepant results and outline future studies. A clinical reappraisal and mechanistic considerations are therefore the focus of the present review.

What is RIPC and How is it Delivered?

Remote ischaemic preconditioning involves the delivery of repeated non-harmful ischaemia to a tissue remote from the heart. In contemporary clinical studies, RIPC is most commonly delivered with a sphygmomanometer inflated on the upper limb to 200 mmHg for five minutes, followed by deflation for five minutes with the cycle performed three to four times [2–12]. Ischaemia to upper and lower limbs may differ

Abbreviations: ALDH-2, aldehyde dehydrogenase-2; CABG, coronary artery bypass grafting; ERK, extracellular signal regulated kinases; IPC, ischaemic preconditioning; IR, ischaemia-reperfusion; HIF-1, hypoxia inducible factor-1; HSP-70, heat shock protein-70; MACCE, major adverse cardiac and cerebrovascular events; miRNA, micro ribonucleic acid; PCI, percutaneous coronary intervention; PKC, protein kinase C; RIPC, remote ischaemic preconditioning; RIPerC, remote ischaemic perconditioning; RISK, reperfusion injury salvage kinase; SAFE, survival activating factor enhancement; SDF-1α, stromal cell derived factor-1α; STAT, signal transducer and activator of transcription; STEMI, ST elevation myocardial infarction

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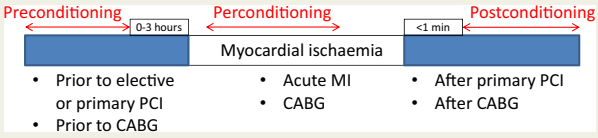

Figure 1 Cardiac ischaemic conditioning
Temporal differences between preconditioning, perconditioning and postconditioning with examples of clinical scenarios where the conditioning stimulus may be used. CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention. Adapted from Hausenloy D, 2016 [15].

in relation to RIPC [13], and variations in the interval between RIPC and subsequent myocardial IR may also influence the effectiveness of RIPC [14].

While RIPC is delivered prior to the onset of myocardial ischaemia, remote ischaemic perconditioning (RIPerC) refers to intermittent limb ischaemia occurring after onset of myocardial ischaemia such as is the case during efforts to condition the myocardium during acute myocardial infarction, prior to primary PCI. Remote ischaemic postconditioning refers to intermittent limb ischaemia occurring after myocardial reperfusion (Figure 1).

Potential Mechanisms

Given the mixed results in recent clinical studies, it is important that the candidate mechanisms underlying RIPC are understood. Mechanistic considerations may allow the differences between study results to be evaluated and guide the design of future studies better defining optimal administration and the clinical populations that might benefit. Finally, novel therapies which recapitulate the favourable effects of RIPC could be developed in their own right once mechanisms are elucidated.

Neural Pathways

There are two predominant theories explaining the cardioprotective effects of RIPC. The humoral hypothesis proposes that a substance is released from the remote organ or tissue after RIPC and this is transferred to the heart in the circulation. Conversely, advocates of the less widely studied neural hypothesis suggest that RIPC protection is transduced from the remote organ or tissue via somatosensory nerves to the spinal cord and then to the heart via autonomic nerves [16] (Figure 2).

The contribution of neural pathways in conveying a protective stimulus to the heart after RIPC is suggested by several animal studies. For example, transection of the femoral nerve prior to RIPC delivered to the hind limb of a rabbit abolished the protection RIPC conferred against cardiac IR injury [17]. In rats, the administration of hexamethonium, a nicotinic acetyl choline ganglion blocker, attenuated RIPC-mediated reduction in infarct size after

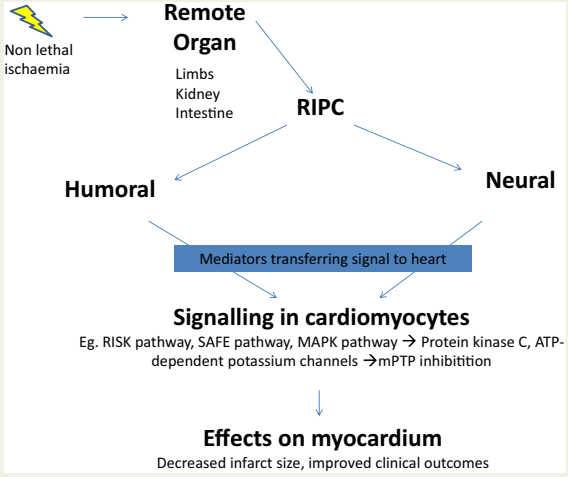

Figure 2 Mechanisms involved in remote ischaemic preconditioning
Proposed mechanisms by which remote ischaemic preconditioning may confer protection to the heart.
ATP, adenosine triphosphate; MAPK, mitogen activated protein kinases; mPTP, mitochondrial permeability transition pore; RIPC; remote ischaemic preconditioning; RISK, reperfusion injury salvage kinase; SAFE, survival activating factor enhancement.

cardiac IR injury [18]. It has also been suggested that opioid receptors may be involved in RIPC related neural pathways [19–21].

Circulating Mediators

Plasma from animals subjected to RIPC may be used to transfer cardioprotection to other animals and between species suggesting a protective factor in the circulation [19,20,22,23]. In some studies the mediator(s) appears to be hydrophobic, resistant to freezing and thawing with a molecular weight between 15 and 30 kDa [19,24]. A number of molecules have been implicated in RIPC-mediated cardioprotection. Most studies have used specific inhibitors to elucidate the cellular pathways involved in RIPC. Most, if not all of these pathways relate to myocyte biology, but some relate to vascular tone.

A study of the human plasma proteomic profile found 51 proteins found to be differentially expressed in response to RIPC, including upregulation of albumin, α1-antitrypsin, apolipoprotein A1, haptoglobin, lipoprotein B100 and transferrin [25]. In the same study, antithrombin III complex, complement C1r and immunoglobulin M, amongst other proteins, were found to be downregulated after RIPC. The change in proteomic profile after RIPC was apparent immediately after the protocol and increased further by 24 h. Similarly, a study of RIPC in children undergoing cardiac surgery found that RIPC was associated with upregulation of 48 peptides corresponding to six proteins compared to control [26]. In contrast to the previously described study, the difference in the plasma proteome between the RIPC and

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