Preconditioning and postconditioning: from bench to bedside

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ABSTRACT

Coronary heart disease (CHD) is the leading cause of death world-wide. Since 1990, more people in the world have died from CHD than from any other disease (World Health Organisation, WHO). "Conditioning" the heart to render it more resistant to the detrimental effects of acute ischaemia-reperfusion injury harnesses the endogenous ability of the heart to protect itself. This can be achieved using various mechanical strategies including the application of brief episodes of ischaemia and reperfusion to either the heart itself (ischaemic preconditioning) or an organ/tissue remote from the heart (remote ischaemic preconditioning) prior to the sustained ischaemic insult. Importantly, this form of protection can be mimicked by pharmacological agents capable of recapitulating the protective effect of IPC (pharmacological preconditioning). Preconditioning-induced cardioprotection is clearly restricted to patients undergoing an anticipated ischaemic insult such as in patients undergoing cardiac surgery. In contrast, the other major form of "conditioning" termed postconditioning can be implemented in patients presenting with an acute myocardial infarction after the onset of the sustained ischaemic insult. In this setting, myocardial reperfusion is interrupted with intermittent short-lived episodes of myocardial ischaemia applied to the heart itself (ischaemic postconditioning) or an organ or tissue remote from the heart (remote ischaemic postconditioning) – an effect which can again be mimicked by pharmacological agents (pharmacological postconditioning). This article will briefly review these various forms of "conditioning" examining the underlying mechanistic pathways and their clinical application. SAHeart 2009; 6:24-29

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death world-wide. Since 1990 more people in the world have died from CHD than from any other disease (World Health Organisation, WHO). In South Africa alone, CHD is the third leading cause of death behind HIV and cerebrovascular disease, being responsible for 27 000 deaths in 2002 (WHO). New effective treatment strategies capable of improving clinical outcomes in CHD patients need to be developed to impact on this devastating affliction.

In this regard, the endogenous protection elicited by the heart's ability to "condition" itself, has emerged as a powerful new treatment strategy for limiting myocardial injury, preserving left ventricular systolic function and potentially improving morbidity and mortality in patients with CHD. The concept of harnessing the ability of the heart to protect itself originated from a seminal experimental study by Murry and colleagues,[1] in which it was first demonstrated that the heart could be rendered resistant to acute ischaemia-reperfusion injury by brief episodes of myocardial ischaemia and reperfusion – a phenomenon termed ischaemic preconditioning (IPC). The evolution of "conditioning" as a cardio-protective strategy will be briefly reviewed in this article. For a more comprehensive description of these endogenous cardio-protective phenomena the reader is directed to the following comprehensive reviews.[2-6]

ISCHAEMIC PRECONDITIONING: LABORATORY PHENOMENON TO CLINICAL APPLICATION

In 1986, Murry and colleagues[1] first made the intriguing observa-

tion that subjecting the heart to four 5 minute occlusions of the circumflex coronary artery, interspersed with 5 minute periods of reperfusion, was able to reduce the size of a subsequent myocardial infarct by 75% – a phenomenon termed ischaemic preconditioning (IPC). This endogenous cardioprotective effect, is an ubiquitous endogenous response to a brief episode of acute ischaemia-reperfusion injury having been reproduced in all species tested including humans and a variety of organs other than the heart including the kidney, liver, and brain.[2] IPC elicits two distinct windows of cardioprotection: the first window (classical IPC) manifests immediately and wanes after 2-3 hours and is replaced by a Second Window of Protection (SWOP) which appears 12-24 hours later and lasts 2-3 days.[7] This article will focus on classical IPC. For a comprehensive review of SWOP the reader is directed to the following reviews.[3,8]

The mechanistic pathways underlying ischaemic preconditioning have been the subject of intensive investigation since the endoge-nous cardioprotective phenomenon was first described in 1986. The current paradigm proposes that the IPC stimulus generates several substances including adenosine, bradykinin and opioids among others, which stimulate their respective receptors, recruiting a variety of signal transduction pathways the majority of which converge on the mitochondrion, which is widely believed to be the end-effector of cardioprotection. Clearly, it is beyond the scope of this article to mention all the different signalling pathways which have been implicated in IPC, but the major signalling path-ways include phosphoinositide 3-kinase (PI3K)-Akt, mitogen-activated protein kinase kinase 1/2-extracellular regulated kinase 1/2 (MEK1/2-Erk1/2), p38 mitogen-activated protein kinase (p38 MAPK),[9-12] Janus kinases (JAKs) and Signal Transducers and Activators of Transcription (STATs),[13,14] cyclic guanosine mono-phosphate (cGMP)-protein kinase G (PKG) and protein kinase C (reviewed in).[2]

Interestingly, it transpires that the IPC stimulus has the ability to modify events occurring in the first few minutes of myocardial reperfusion, thereby protecting the heart from myocardial reperfusion injury.[15,16] The identification of the signalling pathways underlying IPC, has facilitated the use of pharmacological agents which are able to recapitulate the cardioprotection elicited by

IPC (termed pharmacological preconditioning), thereby obviating the need for an invasive IPC protocol. Because IPC requires an intervention which can be implemented before the onset of the index myocardial ischaemia, their clinical application has been largely restricted to specific settings such as cardiac surgery, in which the ischaemic insult can be anticipated.

In 1993, our research group[17] were the first to apply the concept of IPC to the clinical setting of cardiac surgery. Prior to going on cardiopulmonary bypass, the aorta is clamped, thereby rendering the heart globally ischaemic. Following cardiopulmonary bypass, the clamp on the aorta is released allowing reperfusion of the heart. Despite optimal myocardial preservation techniques using intermittent cross-clamp fibrillation or cold-blood cardioplegia, a significant amount of myocardial injury still occurs, resulting in the peri-operative release of cardiac enzymes, the release of which has been associated with worse short-term and long-term clinical outcomes.[18] Therefore, the setting of cardiac surgery provides for a controlled model of acute myocardial ischaemia-reperfusion injury for assessing the clinical efficacy of various treatment strategies. However, it must be appreciated that other factors such as coronary micro-embolisation and direct handling of the heart may also contribute to the myocardial injury sustained during cardiac surgery.

In the initial clinical study conducted by our research group, the IPC protocol, which was instituted prior to putting the heart on bypass, comprised clamping the aorta for 3 minutes to induce global myocardial ischaemia followed by unclamping of the aorta for 2 minutes to allow myocardial reperfusion, a cycle which was repeated.[17] Compared to control, IPC was reported to preserve myocardial adenosine triphosphate (ATP) levels[17] and result in less peri-operative troponin-T release.[19] A number of clinical studies have confirmed the cardioprotective benefits of IPC in terms of fewer ventricular arrhythmias, lower inotrope scores, less myocardial necrosis, and improved LV systolic function,[20-25] although not all the studies have been positive.[26,27] Even for patients undergoing off-pump coronary artery bypass (OPCAB) surgery, IPC has been reported to exert beneficial effects.[28,29] A recent meta-analysis of 933 patients in 22 trials found that IPC resulted in less ventricular arrhythmias, lower inotrope score and shorter

intensive care unit stays.[30] However, the application of this IPC protocol is limited by its invasive nature and inherent risk for thromboembolism. As such, pharmacological agents such as adenosine, inhalational anaesthetics and bradykinin have been used to mimic IPC protection in patients undergoing cardiac surgery, but with mixed results (reviewed in).[31]

The benefits of IPC are limited to clinical scenarios in which the index ischaemic event can be anticipated. For patients presenting with an acute myocardial infarction (AMI), an interventional strategy capable of eliciting cardioprotection after the onset of myocardial ischaemia and at the time of reperfusion is required. In this regard ischaemic postconditioning represents a treatment strategy capable of benefiting AMI patients.

ISCHAEMIC POSTCONDITIONING: EFFECTIVE CLINICAL CARDIOPROTECTION

In 2003, Zhao and colleagues[32] first introduced ischaemic postconditioning (IPost) as a mechanical interventional strategy comprising interrupting myocardial reperfusion with intermittent episodes of myocardial ischaemia, capable of preventing lethal reperfusion injury and reducing myocardial infarct size in the canine heart. In this landmark experimental study, following a sustained episode of left anterior descending coronary artery occlusion, IPost comprised interrupting myocardial reperfusion with three-30 second episodes of myocardial ischaemia and reperfusion, a manoeuvre which resulted in a dramatic reduction in myocardial infarct size to a level comparable to that elicited by ischaemic preconditioning.[32] Interestingly, modifying myocardial reperfusion by gradually reperfusing the heart had been previously reported to limit myocardial infarct size.[33,34] In fact, the term postconditioning had been previously used to refer to the anti-arrhythmic effect of intermittent reperfusion in the feline heart.[35] Providing the IPost protocol is modified appropriately, most animal hearts appear amenable to IPost, including human myocardium.[36,37] Other organs in which IPost has reported to be beneficial include, the brain,[38] kidney[39] and liver.[40] As well as reducing myocardial infarct size, IPost has been demonstrated to exert a broad range of beneficial effects including reducing oxidative stress, reducing cellular calcium accumulation, maintaining endothelial function, reducing neutrophil accumulation, attenuating apoptotic cell death and inhibiting mitochondrial permeability transition pore (mPTP) opening (reviewed in).[5,41]

The introduction of IPost as a mechanical treatment intervention which can be applied at the onset of myocardial reperfusion, has not only regenerated interest in the myocardial reperfusion phase as a target for cardioprotection, but has also demonstrated the existence of lethal reperfusion injury in man. In several small clinical studies comprising patients presenting with an ST-elevation myocardial infarction (STEMI), IPost has been demonstrated to be clinically effective in terms of reducing myocardial infarct size acutely (assessed by cardiac enzymes). At one week and at 6 weeks by Single Photon Emission Computed Tomography (SPECT) analysis, and improving left ventricular (LV) systolic function (by echocardiography) at one year.[37,42,43] In these proof-of-concept clinical studies, in the STEMI patients randomised to receive IPost, following stent-deployment in the infarct-related coronary artery, the angioplasty balloon was withdrawn upstream of the stent and inflated for 1 minute to a low-pressure and then deflated for 1 minute, a cycle which was repeated 4 times. This invasive protocol interrupted normal myocardial reperfusion with intermittent episodes of coronary artery re-occlusion.[37,42,43]

Emerging clinical studies suggest that the concept of IPost may be beneficial in patients undergoing cardiopulmonary bypass surgery. Releasing the aortic clamp following cardiopulmonary bypass subjects the heart to global ischaemia-reperfusion injury, which can be measured by the release of cardiac enzymes. Several small proof-of-concept clinical studies have reported that applying brief episodes of aortic clamping and declamping at this time can reduce myocardial injury in patients undergoing cardiac surgery.[44-47] Clearly, one can envisage this invasive treatment strategy potentially benefiting children undergoing cardiac surgery, but for adult patients with atherosclerotic aortas, such an invasive post-conditioning protocol being applied to the aorta may result in thromboembolic complications.

The mechanism underlying IPost is under intensive investigation with experimental studies suggesting a three-tiered signalling cascade, initiated by ligand-binding at particular specific receptors

which include the adenosine, bradykinin, natriuretic peptide, opioid and platelet-activating factor receptors, followed by the activation of signalling pathways which include the Reperfusion Injury Salvage Kinase (RISK) pathway, and finally the mitochondria as end-effectors of cardioprotection.[5,48] It is clear that many of the signalling components implicated in IPost protection are recruited by IPC. The important implication of this being that it is possible to mimic protection elicited by either IPC or IPost by administering pharmacological agents at reperfusion which target specific components of this cardioprotective signalling pathway-so-termed pharmacological postconditioning. In this regard, pharma-cological targeting of the RISK pathway by a diverse variety of pharmacological agents has the ability to reduce myocardial infarct size in experimental animal models[49,50] and inhibiting mPTP opening has been recently demonstrated to be beneficial in AMI patients undergoing primary PCI.[51] Both IPC and IPost require invasive cardioprotective strategies applied to the myo-cardium itself, thereby limiting their clinical applicability. The important finding that myocardial protection can be elicited at a distance, away from the heart, has given rise to the concept of remote ischaemic conditioning of the heart.

REMOTE ISCHAEMIC PRECONDITIONING: GIVING YOUR RIGHT ARM TO PROTECT YOUR HEART

In 1993, Pryzklenk and colleagues[52] made the intriguing observa-tion that the preconditioning effect elicited by brief ischaemia in the circumflex artery territory could actually be manifested in myocardium supplied by the left anterior descending artery territory, indicating for the first time that protection could be conveyed from one region of the heart to another. This concept has been further evolved and developed to extend to organs and tissue distant from the heart such as the kidney, small intestine, liver, and the limbs, such that brief episodes of ischaemia and reperfusion applied to these organs or tissue have been reported to protect against myocardial infarction – a phenomenon termed remote ischaemic preconditioning (RIPC) (reviewed in).[6] Indeed, remote ischaemic preconditioning appears to confer multi-organ protection against acute ischaemia-reperfusion injury.

The mechanisms underlying this intriguing protective phenomenon are unclear but it has been postulated that many of the protective mechanisms implicated in conventional myocardial preconditioning are recruited in RIPC. The mystery surrounds the mechanistic pathway linking the remote preconditioning organ or tissue to the heart. Two mechanisms which has been proposed to link the preconditioning organ or tissue with the myocardial protection include a neural pathway and a hormonal pathway, but the two are not mutually exclusive given that the most popular paradigm proposes that substances generated locally such as adenosine or bradykinin within the preconditioned organ or tissue stimulate local neural pathways, which then activate neural pathways that terminate at the heart capable of activating endogenous myocardial protective pathways either directly or through the release of other substances such as bradykinin or noradrenaline.[6]

The discovery that myocardial infarct size could be limited by applying brief episodes of ischaemia and reperfusion to the lower limb[53] resulted in the development of a non-invasive strategy for eliciting RIPC in the clinical arena.[54,55] We and others have demonstrated that brief episodes of ischaemia and reperfusion applied to either the upper limb (non-invasively using a blood pressure cuff) or the lower limb (by invasive clamping of the iliac arteries) is capable of reducing myocardial injury in patients undergoing cardiac surgery[56,57] or surgical repair of an abdominal aortic aneurysm.[58] Interestingly, Ali and colleagues[58] were able to demonstrated renal protection using RIPC of the lower-limb in addition to myocardial protection. Clearly, further multi-centred clinical studies are required to determine whether RIPC is able to impact on clinical outcomes in these patient groups.

The infarct-limiting effects of RIPC can also be achieved even if the preconditioning protocol is applied after the onset of myo-cardial ischaemia, a phenomenon which has been labelled remote ischaemic postconditioning (RIPost). Although it is not truly a postconditioning phenomenon in so much as the intervention is usually applied after the onset of myocardial ischaemia and prior to myocardial reperfusion, IPost refers to a specific strategy for modifying the myocardial reperfusion phase itself. Irrespective of the terminology, one may expect RIPost to be beneficial to patients presenting with an acute myocardial infarction

undergoing primary PCI. Clinical studies are currently underway examining this exciting novel treatment strategy.

CONCLUSIONS

"Conditioning" the heart represents a treatment strategy for reducing myocardial injury by harnessing the endogenous ability of the heart to protect itself. It can be readily elicited using several different approaches: (1) brief episodes of ischaemia and reperfusion applied to the heart itself either prior to the index ischaemic insult (ischaemic preconditioning, IPC) or at the time of myocardial reperfusion (ischaemic postconditioning IPost); (2) pharmacological agents which target the signalling pathways underlying conditioning (pharmacological preconditioning and postconditioning); and finally (3) brief episodes of ischaemia and reperfusion applied to an organ or tissue distant from the heart itself, applied either prior to the index ischaemic insult (remote ischaemic preconditioning, RIPC) or after the onset of myocardial ischaemia (remote ischaemic postconditioning, RIPost). Depending on the clinical situation, "conditioning" the heart has made the transition from being a laboratory phenomenon to being a potentially beneficial treatment strategy for patients with coronary heart disease.

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