Accepted Manuscript

Title: Preconditioning, Postconditioning: Underlying Mechanisms and Clinical Application

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PII: S0021-9150(08)00748-X
DOI: doi:10.1016/j.atherosclerosis.2008.10.029
Reference: ATH 10635

To appear in: *Atherosclerosis*

Received date: 3-9-2008
Revised date: 10-10-2008
Accepted date: 14-10-2008

Please cite this article as: Hausenloy DJ, Yellon DM, Preconditioning, Postconditioning: Underlying Mechanisms and Clinical Application, *Atherosclerosis* (2008), doi:10.1016/j.atherosclerosis.2008.10.029

Preconditioning and Postconditioning:

Underlying Mechanisms and Clinical Application

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Word count: 3,628

Figures: 1

Tables: 3

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Abstract

Coronary heart disease (CHD) is the leading cause of death world-wide. Its major pathophysiological manifestation is acute myocardial ischaemia-reperfusion injury. Innovative treatment strategies for protecting the myocardium against the detrimental effects of this form of injury are required in order to improve clinical outcomes in patients with CHD. In this regard, harnessing the endogenous protection elicited by the heart's ability to 'condition' itself, has recently emerged as a powerful new strategy for limiting myocardial injury, preserving left ventricular systolic function and potentially improving morbidity and mortality in patients with CHD.

'Conditioning' the heart to tolerate the effects of acute ischaemia-reperfusion injury can be initiated through the application of several different mechanical and pharmacological strategies. Inducing brief non-lethal episodes of ischaemia and reperfusion to the heart either prior to, during, or even after an episode of sustained lethal myocardial ischaemia has the capacity to dramatically reduce myocardial injury- a phenomenon termed ischaemic preconditioning, perconditioning or postconditioning, respectively. Intriguingly, similar levels of cardioprotection can be achieved by applying the brief episodes of non-lethal ischaemia and reperfusion to an organ or tissue remote from the heart, thereby obviating the need to 'condition' the heart directly. This phenomenon has been termed remote ischaemic 'conditioning', and it can offer widespread systemic protection to other organs which are susceptible to acute ischaemia-reperfusion injury such as the brain, liver, intestine or kidney. Furthermore, the identification of the signalling pathways which underlie the effects of 'conditioning', has provided novel targets for pharmacological agents allowing one to recapitulate the benefits of these cardioprotective phenomena- so-termed pharmacological preconditioning and postconditioning.

Initial clinical studies, reporting beneficial effects of 'conditioning' the heart to

tolerate acute ischaemia-reperfusion injury, have been encouraging. Larger multi-centred randomised studies are now required to determine whether these 'conditioning' strategies are able to impact on clinical outcomes. In this article, we provide an overview of 'conditioning' in all its various forms, describe the underlying mechanisms and review the recent clinical application of this emerging cardioprotective strategy.

Keywords: ischaemia, reperfusion injury, preconditioning, postconditioning, remote preconditioning.

Contents

1. Introduction

Coronary heart disease (CHD) is the leading cause of death and disability world-wide. Its major manifestation is as an acute myocardial infarction, an event which is heralded by the rupture of an unstable atherosclerotic plaque, leading either to a thrombotic coronary artery occlusion requiring emergency revascularisation using fibrinolytic therapy, primary percutaneous coronary intervention (PPCI) or emergency coronary artery bypass graft (CABG) surgery. Alternatively, CHD can present as stable coronary artery occlusive disease requiring elective PCI or CABG surgery. In all these cases, the heart is subjected to acute myocardial ischaemia-reperfusion injury and despite optimal therapy the morbidity and mortality in these patient groups remain significant. Innovative treatment strategies for protecting the myocardium against the detrimental effects of this form of injury are therefore required to improve clinical outcomes in patients with CHD.

In this regard, the endogenous protection elicited by the heart's ability to 'condition' itself, has emerged as a powerful new strategy for limiting myocardial injury, preserving left ventricular systolic function and potentially improving morbidity and mortality in patients with CHD. The ability to 'condition' the heart to tolerate the effects of acute ischaemia-reperfusion injury was first discovered by Murry and colleagues in 1986 and published in a seminal study in which the term ischaemic preconditioning was first introduced.[1] This landmark study has generated a huge research effort to elucidate the underlying protective mechanisms of this endogenous cardioprotective phenomenon and has now evolved into a form of 'conditioning' that is more amenable to clinical application- so-called ischaemic postconditioning. The purpose of this article is to provide an overview of the different forms of 'conditioning', their evolution and underlying mechanisms, and their emergence as clinical therapy. For a more detailed description of these endogenous cardioprotective phenomena the

reader is directed to the following comprehensive reviews [2-6].

2. Ischaemic preconditioning

In 1986, Murry and colleagues made the intriguing observation that the size of a myocardial infarct arising from a 40 minute occlusion of the circumflex artery, could be reduced by 75%, if the myocardium had been subjected to four-5 minute occlusions of the coronary artery, interspersed with 5 minute periods of reperfusion, immediately prior to the infarct [1]. This powerful cardioprotective effect, which has been named ischaemic preconditioning (IPC), appears to be a ubiquitous endogenous response to an 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]. The brief episodes of ischaemia and reperfusion which constitute the IPC stimulus elicit 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]

The mechanistic pathways underlying these endogenous cardioprotective phenomena are complex in nature and have conventionally been divided into trigger factors, mediators and effectors. One generally accepted signalling paradigm for classical IPC is depicted in figure 1- however, it must be appreciated that a number of other signalling pathways and effector mechanisms have been linked to IPC, but it is beyond the scope of this article to provide a comprehensive account. 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. 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. With respect to SWOP the transcription of protein mediators which link the IPC stimulus to the effectors mechanisms some 12-24 hours later at the time of the index ischaemic insult are fundamental to protection (reviewed in [3]).

Because both classical IPC and SWOP require an intervention which can be implemented before the onset of the index myocardial ischaemia, their clinical application has been largely restricted to specific scenarios such as cardiac surgery, in which the ischaemic insult can be anticipated. However, the recent discovery of ischaemic postconditioning has provided an intervention which can be applied after the onset of the index myocardial ischaemia and at the time of reperfusion, facilitating its application to patients presenting with an acute myocardial infarction (AMI).

3. Ischaemic postconditioning

Studies published in the mid-1980's first established that ischaemic myocardial injury could be reduced, if the myocardial reperfusion process was modified to a staged or gradual form of myocardial reperfusion [8, 9]. However, this concept did not capture the imagination in the same way that ischaemic postconditioning (IPost) has succeeded in doing so, in terms of regenerating interest in the myocardial reperfusion phase as a target for cardioprotection. Vinten-Johansen's laboratory [10] first noted that interrupting myocardial reperfusion with three cycles of 30 second coronary artery re-occlusions had several beneficial effects including a 44% reduction in infarct size, less myocardial oedema, less neutrophil accumulation, reduced apoptotic cell death and improved endothelial function. The ability of IPost, an intervention which can be applied at the onset of myocardial reperfusion to reduce

myocardial injury, also provided confirmatory evidence for the existence of lethal myocardial injury as an independent mediator of cardiomyocyte death. Crucially, IPost has been reported to target many of the proponents of lethal reperfusion injury such as oxidative stress, calcium accumulation, inflammation, and mitochondrial permeability transition pore opening [5, 11].

Since its initial description, the mechanism underlying IPost has been intensively investigated, and the data suggests that a signal transduction pathway, similar to that recruited by IPC, mediates the protection elicited by postconditioning (see figure 1). Crucially, the recent discovery that events occurring at the onset of myocardial reperfusion underpin IPC-induced cardioprotection, have revealed a common signalling pathway that is shared by both IPC and IPost. The implications of this finding being that the pharmacological manipulation of these signalling element may be able to recapitulate the powerful protective effects elicited by IPC and IPost [4, 12, 13]. In this respect a variety of diverse pharmacological postconditioning agents including inhalational anaesthetics, G-protein coupled receptor ligands such as opioids, adenosine and bradykinin, growth factors such as insulin and erythropoietin, natriuretic peptides, adipocytokines, and 'statins' have been linked to the activation of the Reperfusion Injury Salvage Kinase (RISK) pathway, a critical component of this signalling pathway [14]. Clearly, IPost as a clinical cardioprotective strategy can be applied to patients presenting with an acute myocardial infarction, yet as in the case of IPC, it requires an invasive intervention which can be applied to the heart itself. In this regard, the intriguing finding that cardioprotection can be elicited from applying the preconditioning or postconditioning stimulus to an organ or tissue remote from the heart offers an innovative treatment strategy for protecting the heart.

4. Remote ischaemic preconditioning and postconditioning

Intriguingly, it transpires that similar levels of cardioprotection can be achieved by applying the brief episodes of non-lethal ischaemia and reperfusion to an organ or tissue remote from the heart, thereby obviating the need to 'condition' the heart directly. This phenomenon has been termed remote ischaemic 'conditioning', a treatment strategy which can offer widespread systemic protection to other organs which are susceptible to acute ischaemia-reperfusion injury such as the brain, liver, intestine or kidney.[6]

In 1993, Przyklenk and colleagues [15] made the intriguing observation that short episodes of myocardial ischaemia and reperfusion applied to the left anterior descending coronary territory were able to subsequently reduce the size of a myocardial infarct generated in the circumflex coronary artery territory- a phenomenon which they termed 'regional ischaemic preconditioning'. This concept of intramyocardial preconditioning was later extended to 'remote ischaemic preconditioning', with the exciting finding that the preconditioning protocol could be applied to organs and tissue distant or remote from the heart such as the kidney or small intestine [16-18]. However, it was the subsequent discovery that transient ischaemia and reperfusion of the limb could also elicit RIPC that has facilitated the translation of this endogenous cardioprotective phenomenon into the clinical arena.

The underlying mechanism remains unclear. Many of the signalling pathways underlying myocardial preconditioning and postconditioning have been implicated in RIPC, but the conundrum has been the mechanistic pathway through which the preconditioning stimulus in an organ or tissue remote from the heart, manages to exert such profound cardioprotection [6]. A popular theory has proposed that substances released from the preconditioned organ or tissue such as adenosine, bradykinin or opioids stimulate local afferent nerves pathways which then activate efferent nerve pathways which terminate on the myocardium. An alternative suggestion has been that a substance or humoral factor is carried in the blood stream from the preconditioning organ or tissue to the heart where it manifests its

protective effect. Clearly, further studies are required to dissect the underlying mechanism.

More recently experimental studies suggest that remote ischaemic conditioning can be effective even if applied after the onset of myocardial ischaemia- a phenomenon which has been termed remote ischaemic postconditioning [19], although the term 'perconditioning' may have been more suitable given that the conditioning ischaemia to the remote organ or tissue is applied during the myocardial ischaemia [20] and not necessarily at the point of reperfusion [21]. These findings open up the possibility of applying remote ischaemic conditioning to patients presenting with an acute myocardial infarction (see section 5.5).

5. Clinical application of conditioning

The ability to translate and implement the various 'conditioning' strategies into clinical therapy is dependent on the clinical situation to which it is applied. For example, where the episode of acute myocardial ischaemia-reperfusion injury can be reliably anticipated, a preconditioning strategy such as IPC (both acute and the SWOP), or RIPC may be applied. This would include patients undergoing a planned surgical procedure such as cardiac surgery, cardiac transplantation or even percutaneous coronary intervention (PCI). In contrast, in those patients presenting with an acute myocardial infarction (AMI) or a cardiac arrest, the conditioning strategy has to be proven to be effective after the onset of myocardial ischaemia or at the time of reperfusion- in this respect either IPost or RIPost can be used.

The setting of cardiac bypass surgery provides for a controlled setting of acute myocardial ischaemia-reperfusion injury in which both mechanical and pharmacological interventions can be examined for their potential for cardioprotection, and in which documented myocardial necrosis has been reported using gadolinium late-enhancement cardiac MRI [22]. Importantly, it must be appreciated that the myocardial injury encountered

during cardiac bypass surgery is multi-factorial and in addition to global ischaemia-reperfusion injury arising from aortic clamping and de-clamping, myocardial injury can be due to coronary micro-embolisation, direct myocardial handling and so forth. Clearly, well-established techniques such as cross-clamp ventricular fibrillation and cardioplegia are already in clinical use for protecting the heart against the period of cardiac stand-still required for surgery. Therefore, any new cardioprotective strategy has to be capable of reducing myocardial injury in patients undergoing cardiac bypass surgery using the latest technique for myocardial protection, which today is cold-blood cardioplegia.

5.1. Ischaemic preconditioning in cardiac surgery patients

The first clinical application of IPC in the clinical setting was a study by our group in 1993, in which we reported that aortic clamping of the aorta could preserve levels of myocardial ATP in hearts of patients undergoing elective CABG surgery [23]. In a subsequent study we demonstrated that the same IPC protocol was capable of reducing myocardial injury in patients undergoing cardiac bypass surgery [24]. A number of studies have since investigated cardioprotection with IPC, using aortic clamping, in the setting of cardiac bypass surgery (summarised in see table 1), although there has been some controversy surrounding the efficacy of IPC in patients receiving hypothermia and/or cardioplegia during cardiac bypass surgery. However, the invasive nature of the surgical IPC protocol and the attendant risks accompanying repeated clamping and declamping of the aorta have limited its clinical application. In this regard, the use of pharmacological preconditioning agents such as adenosine, bradykinin, opioids, inhalational anaesthetics and others have been investigated in this clinical setting [25]. In addition, another conditioning strategy which has been reported to be beneficial in the setting of surgery is remote ischaemic preconditioning, an intervention

which does not require an invasive myocardial preconditioning protocol (see section 5.3).

5.2. Ischaemic postconditioning in cardiac surgery

Three recent clinical studies from the same research group have investigated the potential of IPost in patients undergoing elective cardiac surgery [26-28]. However, like IPC, this particular cardioprotective strategy requires an invasive protocol of aortic clamping and declamping, but in this setting it is applied at the time of aortic declamping following coronary artery bypass. In 24 children undergoing repair for Tetralogy of Fallot, Luo and colleagues [26] examined the beneficial effects of a surgical postconditioning protocol applied at the time of aortic declamping, comprising re-clamping the aorta for 30 seconds and declamping it for 30 seconds, a process which was repeated twice. This invasive treatment protocol was found to reduce myocardial injury as evidenced by less peri-operative troponin-T and CK-MB release and smaller inotrope requirements post-surgery. A similar protocol has been demonstrate to reduce myocardial injury in adult patients undergoing valve surgery and in children undergoing corrective surgery [27] for congenital heart disease using cardioplegia [28]. However, the invasive nature of this interventional treatment strategy and the inherent risks of thromboembolism associated with aortic clamping and declamping will surely limit its clinical application.

5.3. Remote ischaemic preconditioning in cardiac surgery

The finding that remote ischaemic preconditioning could be elicited by applying brief episodes of ischaemia and reperfusion to the lower limb skeletal muscle [29] was pivotal in terms of the clinical application of this cardioprotective phenomenon. Subsequently, in a small under-powered clinical study comprising only 8 patients undergoing CABG surgery, RIPC using lower limb ischaemia was found not to be cardioprotective [30]. Pioneering work

by MacAllister and colleagues characterised a non-invasive RIPC protocol in human volunteers comprising an automated cuff placed on the upper arm to induce brief episodes of forearm ischaemia and reperfusion, and using endothelial function as the measured end-point [31]. Subsequent clinical studies by our laboratory and others have now demonstrated reduced myocardial injury in terms of cardiac enzyme release in the settings of both cardiac surgery [32, 33] and surgery for repair of an abdominal aortic aneurysm [34] (see table 2).

It must be appreciated that RIPC is capable of eliciting widespread systemic protection against ischaemia-reperfusion injury in other organs and tissues such as the brain, kidney, liver and intestine. As a case in point, the RIPC protocol used by Ali and colleagues not only reduced myocardial injury but also limited the injury sustained by the kidneys [34]. So far, RIPC has been examined in elective relatively low-risk surgical settings- it would be interesting to investigate whether RIPC is capable of reducing myocardial injury in the setting of high-risk urgent surgery, where the magnitude of myocardial injury and therefore the potential for benefit are amplified.

The role of RIPC in patients undergoing low-risk elective PCI was recently examined in a small clinical study and paradoxically, myocardial injury was reported to be increased [35]. However, a larger more robust clinical study comprising 242 patients undergoing elective PCI, managed to show a reduction in troponin I in patients receiving the RIPC protocol [36]. This finding suggests that even peri-procedural injury sustained during an elective PCI procedure, a setting in which there is no clear-cut acute ischaemia-reperfusion injury, except perhaps for side-branch occlusion, is a potential target for cardioprotection. It would be interesting to determine whether RIPC is beneficial in patients with unstable angina or a non-ST-elevation MI undergoing urgent PCI.

5.3. Ischaemic postconditioning

For patients presenting with an acute myocardial infarction (AMI), any cardioprotective strategy requires an intervention which can be applied after the onset of myocardial ischaemia or at the onset of myocardial reperfusion. In this regard, Ischaemic Postconditioning (IPost) provides for a cardioprotective intervention which can be applied at the time of myocardial reperfusion in those receiving percutaneous coronary intervention (PCI). In fact, the first studies reporting the clinical application of IPost in patients presenting with an AMI were published within two years of the study first describing the phenomenon [37, 38]. In these clinical studies, it has been reported that following stent deployment in the infarct-related coronary artery, interrupting myocardial reperfusion with four-1 minute low-pressure inflations and deflations of the coronary angioplasty balloon improved myocardial reperfusion, reduced myocardial infarct size both acutely and at 6 months, and improved left ventricular ejection fraction at one year [37-39] (see table 2). Further, multi-centred clinical studies are required to determine whether IPost has the ability to impact on clinical outcomes in this patient group. The clinical application of IPost is limited by the fact that it requires an invasive treatment protocol and that it is restricted to those AMI patients undergoing primary PCI. The use of pharmacological agents capable of recapitulating the cardioprotection elicited by IPost- so-called pharmacological postconditioning, would obviate the need for an invasive treatment protocol and could also be applied to AMI patients undergoing myocardial reperfusion with fibrinolytic therapy.

5.4. Pharmacological postconditioning

Intensive investigation of the signalling pathway underlying IPost has identified key targets for pharmacological manipulation. The term pharmacological postconditioning has been used to describe a diverse array of pharmacological agents which have been demonstrated in experimental studies to reduce myocardial infarct size when administered at

the point of myocardial reperfusion. Many of these cardioprotective agents target the Reperfusion Injury Salvage Kinase (RISK) pathway, a group of pro-survival kinases whose activation at the onset of myocardial reperfusion exerts powerful cardioprotection [14]. Another critical downstream target for protecting the heart at the time of myocardial reperfusion, is the mitochondrial permeability transition pore (mPTP) [40]. Interestingly, the RISK-mPTP pathway appears to underlie the cardioprotection elicited by the endogenous phenomena of both ischaemic preconditioning and postconditioning [4]. Several clinical studies have reported beneficial effects using drugs such as adenosine[41], GLP-1[42], and atrial natriuretic peptide [43] which are known to activate the RISK pathway or cyclosporine-A[44, 45] which is known to inhibit mPTP opening, when used as adjunctive therapy to primary PCI, although not all the studies have been so encouraging (see table 4).

It is important to appreciate that the majority of the aforementioned clinical studies are small proof-of-concept investigations not capable in themselves of changing clinical practice and forming the basis of practice guidelines. To achieve this, one requires large prospective randomised placebo-controlled multicentre clinical studies capable of demonstrating clinical efficacy with respect to short-term and long-term clinical endpoints such as death and major adverse cardiac events. A recent meta-analysis comprising 22 clinical trials and 933 patients has been undertaken to assess ischaemic preconditioning as a cardioprotective intervention in cardiac surgery [46]. These authors reported fewer ventricular arrhythmias, smaller inotrope requirements and shorter stays on the intensive care unit in patients treated with IPC [46]. Two recent meta-analyses have investigated the potential benefits of inhalation anaesthetics in the setting of cardiac surgery and have reported better LV function, less troponin release, less inotrope use, shorter ventilation time and shorter hospital stay, although there was no effect on peri-operative myocardial infarction or death [47, 48].

5.5. Future applications of 'conditioning'

Clinical studies are underway to determine whether remote ischaemic conditioning using brief limb ischaemia is capable of reducing myocardial injury in patients presenting with an AMI and undergoing primary PCI. In this regard, the pre-hospital implementation of the RIPC protocol by paramedics is being examined in those patients in which the time to transfer to the PCI centre is anticipated to exceed >20-30 minutes. RIPC using brief limb ischaemia and reperfusion has, because of its non-invasive nature, the potential to provide widespread organ protection during any form of surgery in which acute ischaemia-reperfusion injury of an organ or tissue is anticipated.

6. Conclusion

'Conditioning' the heart to protect itself from acute ischaemia-reperfusion injury has evolved from its initial description as a pre-ischaemic cardioprotective intervention (ischaemic preconditioning) to one that can be applied after the onset of myocardial ischaemia (ischaemic postconditioning) and to one that can be applied to an organ or tissue remote from the heart (remote ischaemic conditioning). Exploiting the cardioprotective potential of 'conditioning' has been limited although emerging clinical studies investigating RIPC and IPost have been encouraging. The elucidation of the mechanistic pathways underlying 'conditioning' has identified several promising targets for cardioprotection which are amenable to pharmacological manipulation, providing potentially new cardioprotective treatment therapies that are capable of improving clinical outcomes in patients with coronary heart disease.

Disclosures

None.

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Figure legends

Figure 1

Overview of the signalling pathways underlying the endogenous cardioprotective phenomenon of 'conditioning'. Ischaemic preconditioning (IPC) and possibly remote ischaemic preconditioning (RIPC) recruit signalling pathways comprising cell surface receptors to numerous autocoids (such as adenosine, bradykinin, opioids), signalling kinases (PI3K-Akt-eNOS, Erk1/2, p38, JNK MAPK, JAK-STAT3, PKC, and PKG) and mitochondrial components (the ATP-dependent mitochondrial potassium channel [mK_{ATP}] the mitochondrial permeability transition pore [mPTP], PKC, signalling reactive oxygen species, [ROS]) prior to the index myocardial ischaemic episode. Ischaemic postconditioning and possibly remote ischaemic post/perconditioning recruit similar signalling pathways comprising cell surface receptors, signalling kinases and mitochondrial components at the onset of myocardial reperfusion. In addition, IPC and probably RIPC are able to recruit signalling pathways at the onset of reperfusion. Neural and/or hormonal pathways are believed to connect the remote organ or tissue to the heart. Pharmacological agents may be used which target components of the signalling pathways either prior to the index myocardial ischaemic episodes (pharmacological preconditioning) or at the onset of reperfusion (pharmacological postconditioning) to recapitulate endogenous cardioprotection.

Figure 1

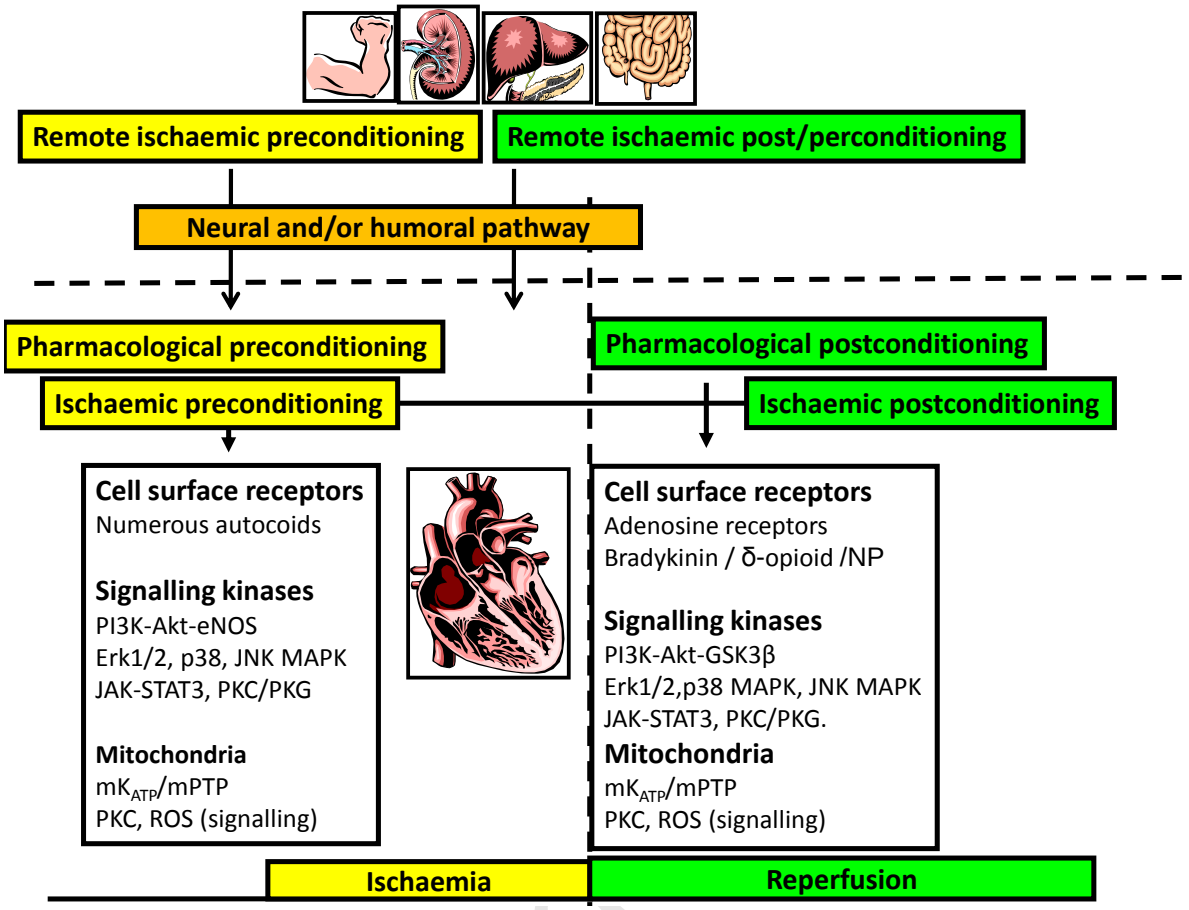

Table 1

Study	Surgical details	Cardiac protection	N	Protocol I/R	Effect
Yellon 1993[23]	Elective CABG	ICCF	14	3'2' (x2) aortic clamping	Improved myocardial ATP levels.
Perrault 1996[49]	Elective CABG	Warm cardioplegia	20	3'2' (x1) aortic clamping	Higher CK-MB at operation
Jenkins 1997[24]	Elective CABG	ICCF	33	3'2' (x2) aortic clamping	Less troponin-T at 72hr.
Lu 1997[50]	AVR/ MVR	Cold crystalloid cardioplegia	30	2'3' (x2) aortic clamping	Improved myocardial ATP levels. Less CK-MB released. Improve myocardial contractility.
Cremer 1997 [51]	Elective CABG	Cold blood cardioplegia	14	5'10' (x2) aortic clamping	No difference in CKMB/troponin-T.
Kaukoranta 1997[52]	Elective CABG	Normothermic retrograde cardioplegia	41	5' (x1) aortic clamping	No difference in CKMB/troponin-T.
Szmagala 1998[53]	Elective CABG	ICCF	56	4'6' (x1) aortic clamping	Less troponin-T at 1 hour.
Wu 2000[54]	Elective CABG	Cold blood cardioplegia	40	2'3' (x2) aortic clamping	Improved LV function but no difference in trop-I or CKMB.
Wu 2001[55]	Elective CABG	Cold blood cardioplegia	40	2'3' (x2) aortic clamping	Improved LV function
Laurikka 2002[56]	Elective CABG	Off-pump	32	2'3' (x2) aortic clamping	Improved LV function Less trop-I but no difference in CK-MB
Teoh 2002[25]	Elective CABG	ICCF	30	3'2' (x2) aortic clamping	Less troponin-T at 72 hours.
Wu 2002 [57]	Elective CABG	Cold blood cardioplegia	86	2'3' (x2) aortic clamping	Less VF/VT and lower inotrope score

Ghosh 2003 [58]	Elective CABG	ICCF vs cold blood cardioplegia vs Off-pump	120	5'5' (x1) aortic clamping	Less trop-T only in patients undergoing Off-pump surgery.
Wu 2005[59]	Elective CABG	Cold blood cardioplegia	86	2'3' (x2) aortic clamping	Less heart rate variability.
Codispoti 2006[60]	Elective CABG	ICCF± hypothermia	104	3'2' (x2) aortic clamping	Less trop-T only in patients undergoing Off-pump surgery
Ji 2007[61]	Elective CABG	Cold blood cardioplegia	40	2'3' (x2) aortic clamping	Less trop-I at 6 and 12 hours post surgery.

ICCF- intermittent cross-clamp fibrillation. I/R- ischaemia/reperfusion times referring to the preconditioning protocols. AVR- aortic valve replacement. MVR- mitral valve replacement.VF- ventricular fibrillation. VT- ventricular tachycardia.

Table 2

Study	Patient selection	N	Protocol I/R	Effect
Gunaydin 2000 [30]	Adults Elective CABG	8	Arm 3'2' (x2) 300mmHg	No effect on LDH
Cheung 2006 [32]	Children With CHD	37	Leg 5'5' (x4) 15mmHg>SBP	Reduced 30 hr Trop-T Improved airway, inotrope
Iliodromitis 2006 [35]	Adults Elective PCI	41	Both arms 5'5' (x3) 200mmHg	Increased CK/Trop-I
Hausenloy 2007 [33]	Adults Elective CABG	58	Arm 5'5' (x3) 200mmHg	43% reduced 72hr Trop-T
Ali 2007 [34]	Adults Elective AAA	82	Legs 10' 200mmHg	40% reduced 7d Trop-I Less renal dysfunction
Hoole 2008 [36]	Adults Elective PCI	242	Arm 5'5' (x3) 200mmHg	61% reduced median Trop-T. Less 6 mth MACCE.

I/R- ischaemia/reperfusion times referring to the preconditioning protocols. MACCE- major adverse cardiac and cerebral events.

Table 3

Study	Patient selection	Time (min)	N	Protocol	Effect
Laskey 2005 [37]	<12hr LAD, RCA, Cx	341	17	90s x2	Improved ST-segment resolution. Improved coronary flow velocity. No difference on peak CK.
Staat 2005 [38]	<6hr LAD or RCA	318	30	60s x4	Improved ST-segment resolution. Improved MBG 1.7-2.4. 36% reduced 72hr CK.
Ma 2006 [62]	<12hr LAD, RCA, Cx	396	94	30s x3	Improved WMSI, endothelial function. Less CK, MDA (P=NS)
Yang 2007 [63]	<12hr LAD, RCA, Cx	312	41	30s x3	27% reduced 72 hr CK. 27% reduced MI SPECT 1week LVEF 44 to 54% (P=NS)
Thibault 2008 [39]	<6hr LAD or RCA	283	38	60s x4	40%, 47% reduced CK, Trop I 39% reduced MI SPECT 6mths 7% increased LVEF 49-56%
Laskey 2008 [64]	<6hr LAD	228	24	90s x2	Improved ST-segment resolution. Improved coronary flow velocity.

Patient selection- time from onset of chest pain. ST-elevation myocardial infarction in LAD (left anterior descending) artery, RCA (right coronary artery) and Cx (circumflex) artery. Time denotes the average time from onset of chest pain to primary PCI.

Table 4

Study	Patient selection	Time (min)	N	Protocol	Effect
Nikolaidis 2004 [42]	<12 hr LAD,RCA,Cx	128	21	GLP-1 infusion for 72 hours	Improved LV ejection fraction.
Mehta 2005 [65]	<12hr LAD,RCA,Cx	240	20,201	Glucose-insulin-potassium (GIK therapy)	No beneficial effect.
Kloner 2006 [41]	<3.12 hr LAD	128	1066	50 or 70 mg/kg/min adenosine <15 min	Less 1mth mortality 9.4-4.2% Less 6mth mortality 11.2-7.3%
Kitakaze 2007 [43]	<12hr LAD,RCA,Cx	240	41	72hr(ANP) carperitide infusion Post-PCI	15% reduced total CK. No difference Trop-T. Improved reperfusion.
Bates 2008[66]	<6hr LAD	127	94	0.05-5.0 mg KAI-9803	Safe. Trend to reduced CK,Trop, SPECT MI
Piot 2008 [44]	<12hr LAD,RCA	292	58	2.5mg/kg CsA bolus Pre-PCI	40% reduced CK. 13% reduced Trop-I (P=NS) 20% reduced MI CMR (N=27)

Patient selection- time from onset of chest pain. ST-elevation myocardial infarction in LAD (left anterior descending) artery, RCA (right coronary artery) and Cx (circumflex) artery. Time denotes the average time from onset of chest pain to primary PCI.