

Review Article

Myocardial Protection through Pre- and Post-Conditioning: A Review of Mechanisms, Clinical Trials and Future Directions

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Abstract

Although the benefits of pre- and post-conditioning have been extensively documented in animal models, the translation from "bench to bedside" has been disappointing and slow. In this article we review the mechanisms of action and potential pharmacological targets of pre and post-conditioning, discuss key findings of clinical trials and provide a summary of ongoing clinical trials. Myocardial protection before planned myocardial ischemia and during reperfusion has the potential to significantly impact clinical outcomes. Industry and government support are critical to validate the findings of small-scale studies to the broader population with cardiovascular disease.

Keywords: Acute Myocardial Infarction; Clinical trials; Congestive Heart Failure; Percutaneous Coronary Intervention

Introduction

Morbidity and mortality from chronic coronary artery disease and Acute Myocardial Infarction (AMI) represents a significant public health burden in the United States and is the leading cause of death throughout the world [1]. Despite advances on multiple fronts to reduce ischemic injury from AMI such as thrombolytic therapy, primary Percutaneous Coronary Intervention (PCI) and establishment of regional networks for AMI transfer and care, many patients will develop post-AMI Left Ventricular (LV) dysfunction and Congestive Heart Failure (CHF), which is the leading hospital admission diagnosis in this country [2-6]. Additionally, many patients will also require placement of cardiac defibrillators and bi-ventricular pacemakers highlighting the critical need for identification and implementation of novel forms of cardioprotection in the setting of AMI [7-9].

Although the rapid restoration of coronary blood flow is the most effective means of reducing infarct size and preserving left-ventricular (LV) function, reperfusion may also be associated with further injury to the myocardium and vasculature [10]. Reperfusion injury may increase infarct size to a degree that is similar to the initial ischemic insult by increasing myocyte cell death, activation of apoptosis and promotion of endothelial dysfunction [11-13] (Figure 1). Unfortunately, reducing reperfusion injury replicating methods previously used in animal models has largely been unsuccessful in clinical trials [9]. To date, clinical trials to limit reperfusion injury have targeted many areas including Reactive Oxygen Species (ROS), reductions in calcium overload and Na⁺ - H⁺ exchange inhibitors and the inflammation. Reasons for disappointing results in the majority of trials may include the much longer duration of ischemia in humans with AMI compared to animals and failure to deliver the therapy at the immediate onset of reperfusion. This point is essential since even a delay of several minutes following reperfusion may render these therapies ineffective [14]. The objective of this review is to summarize current knowledge on myocardial protection through pre- and post-conditioning with emphasis on mechanisms of action and clinical trials.

Historical Notes on Myocardial Pre-conditioning

Murry and coauthors were the first to demonstrate the concept

of myocardial protection through pre-conditioning (PreC) [15]. The authors observed that repetitive episodes of ischemia, applied prior to a complete 40-minute duration circumflex artery occlusion, could beget protection (75% reduction in infarct size was reported in this first experiment) instead of the logically anticipated myocardial damage. These authors were also the first to notice the time-dependence of PreC.



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In a second set of animals exposed to more prolonged ischemic times (3 hours) PreC was not associated with a reduction in infarct size [15].

Postconditioning (PosC), on the other hand, refers to episodes of ischemia -reperfusion applied *after* a complete arterial occlusion. A critical early observation was that reperfusion injury could be modified by slowly initiating reflow [16]. This "gentle" reperfusion resulted in smaller infarcts, reduced edema in the area at risk, and was associated with less "no reflow". Zhao et al. showed in an animal model that the benefits of PreC and PosC are of the same magnitude [16]. This is important, as most ischemic insults in clinical practice are not planned and therefore not amenable to PreC.

The concept of "Remote" Ischemic Preconditioning (RIPC) was first described by Przylenk et al. in 1993 [17]. The notion that repetitive episodes of ischemic-reperfusion in one circulatory bed would result in protection of other circulatory beds when exposed to an acute ischemic insult was first tested in the coronary circulation. Using anesthetized dogs, the authors found that 4 episodes of 5 minutes of circumflex coronary artery occlusion interspersed with 5 minutes of reperfusion before a 1-hour sustained Left Anterior Descending (LAD) coronary artery occlusion plus 4.5 hours of reperfusion reduced infarct size in the LAD bed to 6% of the area at risk (AAR) compared to 16% in controls. The magnitude of the benefit with RIPC applied to the Circumflex artery (35%) was similar to that observed when PreC was applied directly to the LAD. The finding that PreC "at a distance" is as effective as Pre C allowed testing the concept of RIPC in several human clinical trials.

Evaluation of Pre-Conditioning in Humans

Several trials have assessed the benefits of PreC and RIPC in patients undergoing procedures involving "planned" myocardial ischemia such as coronary angioplasty or Coronary Artery Bypass Surgery (CABG) [18-21]. The most common circulatory bed for applying remote PreC has been the forearm by externally compressing the brachial artery with a blood pressure cuff. This is typically performed with a standard blood pressure cuff inflated over the patient's systolic blood pressure (usually to 200 mmHg) for five minutes and then deflated for 5 minutes to allow for reperfusion. This cycle is then repeated 3-5 times. The approach of inducing PreC by inflating a blood pressure cuff is noninvasive, safe, and technically feasible [18,19].

Hoole et al. showed in 242 patients undergoing PCI that transient limb ischemia applied before arrival in the catheterization laboratory resulted in decreased median troponin I concentrations at 24 hours (0.06 ng/ml vs. 0.16 ng/ml, P=0.04) and numerically lower number of major adverse cardiac events at 6 months (4 vs. 13, p=0.018) [18].

Hausenloy et al. randomized 57 patients undergoing Coronary Artery Bypass Surgery (CABG) to RIPC or control. RIPC consisted of three 5-minutes cycles of right upper limb ischemia (cuff inflated to 200 mmHg) and 5 minutes of reperfusion (cuff deflation) after induction of anesthesia. The total area under the curve for RIPC patients decreased by 43% (21 μ g/L vs. 36 μ g/L, p=0.005) [19].

Ali et al. randomized 82 patients undergoing open Abdominal Aortic Aneurysm (AAA) repair to RIPC, induced by intermittent (10minutes cycles) cross clamping of the common iliac artery, or conventional surgery. RIPC was associated with a 27% reduction in the incidence of myocardial injury, assessed by troponin I level >0.4 ng/ml, a 22% reduction in the incidence of myocardial infarction, and a 23% reduction in the incidence of renal failure [20].

The beneficial effects of PreC are not restricted to patients with atherosclerosis-related ischemia. Cheung et al. randomized 37 pediatric patients undergoing corrective cardiac repair surgery for congenital heart disease with a mean age of 1-2 years to RIPC or conventional surgery. Troponin I levels and postoperative inotropic requirements were lower in the RIPC group as compared to the control group [21]. Several larger trials using RIPC in various clinical situations are ongoing (Table 1).

Evaluation of Post-Conditioning in Humans

Zhao et al. were the first to demonstrate that after 45 minutes of myocardial ischemia, coronary reperfusion coupled with three interspersed 30-second cycles of myocardial ischemia reduced infarct size in dogs from 47% to 11%. They named this form of cardioprotection "ischemic postconditioning" [16]. Since the first animal study was published in 2003 several human studies have been conducted with positive results.

Our group showed in a pilot, non-randomized study that PosC was associated with significant reductions in infarct size and better cardiac function [22] (Table 2).

Staat et al. randomized 30 patients with acute ST-segment myocardial infarction (STEMI) to undergo primary angioplasty vs. primary angioplasty plus ischemic PosC. The authors found that PosC was associated with smaller infarct sizes (Figure 2), as determined by the area under the curve of CK release, better myocardial blush grades and more complete ST-segment resolution when compared to primary angioplasty alone [23]. The early benefits of PosC persisted over time, as evident by improved Ejection Fraction (EF) in patients treated with PosC (56%) relative to controls (49%) (p=0.04) [24].

Lønborg et al. evaluated the role of PosC in 118 patients undergoing primary angioplasty for the treatment of ST-elevation myocardial infarction. The primary end-point of the study was salvage index as assessed by cardiac Magnetic Resonance Imaging (MRI). The authors found a significant 31% increase in myocardial salvage index and a 19% reduction in infarct size among patients treated with PosC. Clinically, this benefit translated into less patients developing heart failure (27% vs. 46%, p=0.04) at follow-up [25].

Piot et al. used cyclosporine, an inhibitor of the mitochondrial transitional pore considered a postconditioning mimetic, to limit infarct size in patients undergoing primary PCI for STEMI. Opening of the mitochondrial transitional pore is believed to play a crucial role in reperfusion injury and PosC, as well as PreC, appear to block the opening of this pore (see next section). Cyclosporine, given at a dose of 2.5 mg per kilogram of body weight, was associated with a significant reduction in infarct size assessed by CK release and cardiac MRI (Figure 3) [26].

Potential Mechanisms of Pre-Conditioning and Postconditioning

Although reperfusion salvages myocardium that would ultimately die in its absence, restoring blood flow to the myocardium carries the potential to exacerbate reperfusion injury [10,11]. Reperfusion injury then offsets the optimal salvage of myocardium achieved during coronary angioplasty. Early strategies to attenuate reperfusion injury applied concepts derived from cardiac surgery, in which protecting the myocardium from ischemia-reperfusion injury was a mainstay of the operative strategy. Pre- and post-conditioning marshal a variety of endogenous mechanisms that operate at numerous levels and target a Citation: Iqbal Q, Garcia S (2013) Myocardial Protection through Pre- and Post-Conditioning: A Review of Mechanisms, Clinical Trials and Future Directions. J Cardiovasc Dis Diagn 1: 115. doi:10.4172/2329-9517.1000115

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Title	Trial Number	Primary Outcome Measure	
Effects of Remote Ischemic PreConditioning in Off-pump Versus On-pump			
Coronary Artery Bypass Grafting (RIPCON)	NCI 01608984	Perioperative extent of myocardial injury	
Protective Effects of Long-term Remote Limb Ischemic Preconditioning For Carotid Artery Stenting	NCT 01654666	The Incidence of Brain or Cardiac Ischemic Events and Death	
Clinical Trial on Remote Ischemic Preconditioning and Cerebral Small Vessel Disease (RIPC-SVD)	NCT 01658306	Changes in brain lesions of small vessel disease	
Remote Ischemic Preconditioning in Subarachnoid Hemorrhage (RIPC-SAH)	NCT 01158508	Occurrence of neurological events, or vasospasm at day 3, 7, 15 and 30	
Reduction of Myocardial Infarction by Preconditioning in Patients With Ruptured Abdominal Aortic Aneurysm (PreconRAAA)	NCT 00883363	Reduction in myocardial infarction	
Remote Ischemic Preconditioning in Neurological Death Organ Donors (RIPNOD)	NCT 01515072	Improvement in donor stability, organ quality, organ yield, and early post transplant clinical outcomes after preconditioning	
Pilot Study of Remote Ischemic Preconditioning in Heart Failure	NCT 01128790	Exercise performance - VO2, exercise time, exercise workload, anaerobic threshold	
Remote Ischemic Preconditioning and Risk of Contrast-Induced Acute Kidney Injury in Patients Undergoing Coronary Stent Implantation (REPAIR)	NCT 01827891	Acute kidney injury within 72 hr after PCI	
Remote Ischemic Preconditioning Mechanism Study	NCT 01541436	Effect of RIPC on Areas of hyperalgesia and allodynia to mechanical stimuli.	
Remote Ischaemic Preconditioning for Heart Surgery (RIPHeart-Study)	NCT 01067703	Composite of all-cause mortality, non-fatal myocardial infarction, any new stroke, and/or acute renal failure	
Limb Remote Ischemic Preconditioning for Heart and Intestinal Protection During Laparoscopic Colorectal Surgery	NCT 01832337	Protection of RIPC on heart and intestinal injury in patients undergoing elective laparoscopic colorectal surgery	
The Neuroprotection of Remote Ischemic Preconditioning (RIPC) on Cardiac Surgery in Multicenter	NCT 01231789	Neurological injury markers	
Remote Ischemic Preconditioning Prior to Vascular Surgery (CRIPES)	NCT 01558596	Troponin I elevation	
Remote Ischemic PreConditioning Effect on Postsurgical Pain (RIPCEPP)	NCT 01383317	Comparison of pain intensity and unpleasantness postoperatively	
Effect of Ketorolac and Remote Ischemic Preconditioning on Renal Ischemia- reperfusion Injury in Patients Undergoing Partial Nephrectomy	NCT 01836406	Serum creatinine at baseline, 2 hr, 12hr, 24 hr, 48 hr, 72 hr after clamping release	
Limb Ischemic Preconditioning for Prevention of Contrast Media Induced Nephropathy in Diabetic Kidney Patient	NCT 01763034	Kidney injury before and after coronary angiogram	
Remote Ischemic Preconditioning Combined to Local Ischemic Postconditioning in Acute MI (RIRE-1)	NCT 01390142	Infarct size as assessed by 72 hrs area under curve serum CK-MB & cardiac magnetic resonance imaging at 3-month.	
Seattle Cardiorenal Remote Ischemic Preconditioning Trial (SCRIPT)	NCT 01260259	Incidence of acute kidney injury (AKI)	
Effect of Remote Ischemic Preconditioning on Incidence of Atrial Fibrillation in Patients Undergoing Coronary Artery Bypass Graft Surgery	NCT 01500369	Post op atrial fibrillation	
Evaluation of a Local Preconditioning Effect in Patients Undergoing Cardiac Surgery	NCT 01482780	Enzyme leakage (Troponin T, CK-MB) will be measured preoperatively, at the beginning of the operation, the beginning of ECC at the time of reperfusion the arrival on the ICU and 6,12,24,48 and 72 hours postop and the area under the curve will be calculated	
The Effect of Remote Ischemic Postconditioning on Liver Graft and Renal Function in Patients Undergoing Living-related Liver Transplantation	NCT 01637038	Total bilirubin before surgery and at 6, 12, 24, 36, 48, 60, 72, 84, 96 hours after the end of surgery	
Study of Remote Ischemic Postconditioning	NCT 01450475	The primary outcome is assessing whether cTnI or CK-MB concentration reduce at 24 hours after remote ischemic postconditioning.	
The Effect of Remote Postconditioning on Graft Function in Patients Undergoing Living-related Kidney Transplantation	NCT 01363687	Renal function of recipient after living-related kidney transplantation	
Postconditioning in ST-elevation Myocardial Infarction (POSTEMI)	NCT 00922675	Infarct size, assessed by MRI	
Phase II Clinical Trial to Evaluate the Benefits of Postconditioning in ST- Elevation Myocardial Infarction (STEMI)	NCT 01324453	Myocardial Salvage Index	
Ischemic Postconditioning in Cardiac Surgery (IPICS)	NCT 01813968	Change in cardiac index between the groups during the first postoperative day	
Delayed Postconditioning (PRIME)	NCT 01483755	Size of the infarct estimated by magnetic resonance imaging at day 5 post-reperfusion $% \left({{\left[{{{\rm{S}}_{\rm{T}}} \right]}_{\rm{T}}} \right)$	
Remote Ischemic Postconditioning During Percutaneous Coronary Interventions (RIP-PCI)	NCT 00970827	To study the effects of different degrees of remote ischemic postconditioning on myocardial necrosis and inflammation following PCI.	
DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction (DANAMI-3)	NCT 01435408	Cardiac death, re-infarction, heart failure	
Remote Ischemic Preconditioning Combined to Local Ischemic Postconditioning in Acute Myocardial Infarction (RIRE-1)	NCT 01390142	Infarct size	
Effect of Remote Ischemic Preconditioning on Acute Kidney Injury in Adult Valve Replace	NCT 01476969	Renal function	
Effect of Remote Ischemic Preconditioning in Patient Undergoing Cardiac Bypass Surgery	NCT 00397163	Troponin-T release over the perioperative 72-hour period	
Chronic Remote Ischemic Conditioning to Modify Post-MI Remodeling (CRIC- RCT)	NCT 01817114	Change in LVEDV from baseline	

 Table 1: Ongoing clinical trials of myocardial pre-conditioning listed on clinicaltrials.gov website as of June 2013.

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broad range of pathological mechanisms [27-34]. These mechanisms include ligands, such as adenosine and opioids that act as proximal triggers to stimulate molecular pathways involving mediators such as protein kinase C, mitochondrial ATP-sensitive potassium channels, and survival kinases [27-33]. Post-conditioning may also inhibit deleterious pathways such as p38 and JNK Mitogen-Activated Protein (MAP) kinases and attenuate the damage to endothelial cells and cardiomyocytes from oxidants, cytokines, proteases, and inflammatory cells [34-36]. Post-conditioning induces the expression of mRNA

	N	Ischemic time (hs)	Age	CK (IU)	LVEF (%)
PostC	22	4.5	61 ± 3	1987 ± 281	53 ± 2
Control	21	4.5	56 ± 3	2335 ± 434	45 ± 3

Table 2: Effect of PosC on infarct size and ventricular function in patients undergoing primary PCI for the treatment of acute myocardial infarction. Infarct size and ejection fraction were better among PosC treated patients. Adapted from Garcia S et al. [22]. PosC=Post-conditioning, Ck= Creatinine kinase, LVEF= Left Ventricular Ejection Fraction.



Figure 2: The area under the curve of CK release was significantly lower (36%) in STEMI patients treated with Post- conditioning reproduced from *Circulation* Oct 4 2005; 112(14): 2143-2148 with permission of Wolters Kluwer Health.







for iNOS; a key enzyme for the production of nitric oxide, which is a potent vasodilator [31-33]. At a cellular level, the effects of pre- and post-conditioning converge on the mitochondria, in particular the mitochondrial transition pore [37] (Figure 4). This pore opens during the first minutes of reperfusion in response to mitochondrial calcium overload and oxidative stress. Post-conditioning protects the heart through the inhibition of mitochondrial transition pore opening, which reduces calcium influx into the mitochondria [37]. Other salutary effects of PosC include less production of reactive oxygen species and inflammatory markers [34]. Post-conditioning is also thought to confer protection to the microcirculation [22,24,25]. Recent studies (including ours) have shown that PosC patients had increased TIMI frame counts and improved endothelium-dependent vasodilatation [22,38].

Future Directions

Although recent advances in medical therapy, procedural techniques and integration of systems of care, cardiovascular disease continues to impose a heavy toll on society; both in terms of morbidity as well as financial costs. More recently the concept of protecting the myocardium through myocardial pre- and post-conditioning has evolved "from bench to bedside" with several small trials reporting positive results. As the field moves forward the next wave of clinical trials should focus on clinically meaningful end-points such as heart failure incidence, cardiovascular hospitalizations, arrhythmias, and cardiovascular death. To have enough power and external validity these trials should involve multiple centers, which will not be easy without industry or government support. Mechanistic studies are also needed to better understand the underpinnings of cardiac protection and provide a framework in which new pharmacological agents can be developed.

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