Remote Ischemic Preconditioning for Reduction of Peri-Procedural Myocardial Injury During Percutaneous Coronary Intervention

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Coronary artery disease (CAD) is the single most common cause of death in the developed world.1 In the US during 2009 it was estimated that stable CAD affected 16.8 million people.2 In Europe it is estimated that 20,000–40,000 per million of the population suffer from stable CAD.3 Coronary revascularisation with lifestyle alteration and medical therapy constitute the modern management of patients with significant CAD.4,5 Elective percutaneous coronary intervention (PCI) is the primary intervention for coronary revascularisation in patients with single- or two-vessel stable CAD.4 PCI offers greater relief from symptoms arising from stable CAD than standard medical approaches.6 PCI may also prevent vulnerable plaques from precipitating an acute coronary syndrome (ACS), and confer a prognostic benefit, especially in patients with a significant mass of ischaemic myocardium.7,8

In the absence of significant ischemic burden or an ACS, PCI has not been shown to improve clinical outcomes of stable CAD as compared to medical therapy alone.9 Even with an antecedent recent myocardial infarction (MI), late PCI to establish recanalisation of the artery and myocardial reperfusion, in stabilised patients, does not appear to confer benefit in terms of clinical outcome, especially in patients with little residual ischaemia.10

Even though technical advances in PCI over the past two decades have resulted in a safe procedure with minimal complications, in several patients the procedure is complicated by peri-procedural injury, detected by elevated values of biomarkers of myocardial necrosis. According to the biomarker used, the incidence of peri-procedural myocardial injury in elective procedures ranges between 20% and 45%, with the widespread adoption of troponin tests allowing the detection of smaller amounts of necrosis.11,12 Peri-procedural cardiac troponin elevation has been associated with new irreversible myocardial injury, detected by delayed-enhancement magnetic resonance imaging (MRI),13 and even though the prognostic significance of peri-procedural CK-MB and cardiac troponin elevation has been highly debated, several studies have reported that peri-procedural injury is associated with a worse prognosis.14,15

Peri-procedural myocardial injury may be categorised according to its pathogenesis into two types (Figure 1). Type 1, or proximal type of peri-procedural myocardial injury, is mainly attributed to side-branch occlusion during balloon inflation or stent deployment. Side-branch occlusion, occurring in 12.5–19% of cases, is mainly caused by plaque shift, thrombus formation, or dissection at the takeoff of...
Type 1 peri-procedural myocardial injury
- Microemboli
- Platelet activation
- Thrombosis
- Microvascular plugging
- Neurohormonal activation
- Endothelial inflammation

Type 2 peri-procedural myocardial injury
- Balloon Inflation
- Plaque Shift

Atherosclerotic plaque

Intracoronary stent

Distal Emboli

Mechanisms of type 2 injury

Figure 1. Mechanisms of peri-procedural myocardial injury. Type 1, or proximal type of peri-procedural injury may be attributed to side-branch occlusion. Type 2, or distal type of peri-procedural injury may be attributed to microvascular obstruction, precipitated by several mechanisms. Modified from reference 12.

If peri-procedural injury incidence could be attenuated, then the clinical outcomes of stable CAD following PCI might be expected to improve. One approach to reducing myocardial injury is through cardioprotective intervention.\textsuperscript{12} Conditioning the myocardium to protect against procedural ischaemia/reperfusion (I/R) injury is such an intervention, used in both the experimental and the clinical setting.\textsuperscript{16} Conditioning refers to an intrinsic myocardial mechanism of cardioprotection triggered by inducing brief, sub-lethal episodes of ischaemia and reperfusion.\textsuperscript{17} Conditioning can be defined according to the temporal relationship between the conditioning intervention and the onset of the ischemic insult: conditioning before the sustained insult is preconditioning, conditioning during the sustained insult is perconditioning, whilst conditioning after the sustained insult is postconditioning.\textsuperscript{17} Furthermore, preconditioning of the myocardium can be achieved from a remote organ, via a non-invasive approach.\textsuperscript{17} Here, the focus is on remote ischaemic preconditioning (RIPC) and its potential effect in reducing myocardial I/R injury.
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induced during PCI, thus improving the clinical outcomes of elective PCI for stable CAD.

Clinical evidence for ischaemic preconditioning

Several lines of evidence suggest that brief episodes of non-lethal ischaemia can be cardioprotective. After a brief period of exercise-induced ischaemia in patients with CAD, a well-known phenomenon occurs (termed warm-up or first-effort angina), which renders the myocardium resistant to subsequent exercise and minimises further anginal symptoms. Studies during consecutive exercise testing have reported a reduction in angina severity and the degree of ST-segment depression with a reduction in myocardial oxygen consumption.\(^{18,19}\)

Studies investigating the temporal profile of warm-up angina have demonstrated a time course that parallels classic ischaemic preconditioning.\(^{20,21}\) Other studies have evaluated the effect of preinfarction angina on infarct size and clinical outcome. In a retrospective analysis of the TIMI-4 trial by Kloner et al, pre-infarction angina was associated with a smaller infarct size, a lower incidence of heart failure and lower mortality.\(^{22}\) These results were further corroborated by several subsequent reports.\(^{23-26}\) Furthermore, preinfarction angina is associated with a greater degree of ST-resolution after primary PCI and a lower risk of no-reflow phenomenon.\(^{27,28}\)

Experimental evidence for ischaemic preconditioning

The discovery of a functioning preconditioning protocol can be attributed to Murry et al.\(^{29}\) Their protocol involved short bursts of sub-lethal ischaemia and reperfusion in the circumflex coronary artery of dog hearts, before ligating the artery. Ligation was followed by reperfusion. Preconditioning before brief occlusion reduced the rate of infarct development and restricted ultimate infarct size by nearly 75%\(^{29}\). It was thus hypothesised that multiple anginal episodes, which often precede MI in humans, may be of cardioprotective nature. Since this seminal work, the cardioprotective effect of preconditioning has been reproduced by many studies.\(^{16}\)

To directly precondition the myocardium for cardioprotective purposes, one must be able to predict the long duration of ischaemia.\(^{30}\) Therefore, preconditioning has been restricted to situations where myocardial ischaemia can be readily predicted, as in open-heart surgery or elective PCI.\(^{30}\) Intermittent aortic cross-clamping, for example, before coronary artery bypass surgery has been observed to preserve cardiac high-energy phosphate levels.\(^{31}\) Interestingly, it was observed by Przyklenk et al that subjecting the circumflex coronary artery to sub-lethal, brief episodes of ischaemia and reperfusion had the capacity to limit the size of a subsequent infarct arising from occlusion of the left anterior descending coronary artery.\(^{32}\) Additionally, the authors showed that the effects of remote preconditioning were comparable to the effects of preconditioning the coronary bed that was to be occluded. Thus, the concept that preconditioning the myocardium can be achieved from a remote origin was developed.\(^{32}\) Currently, it is known that remote conditioning can achieve inter-organ protection.\(^{33}\) It was observed that sub-lethal intestinal ischaemia in rats protected the rat heart following coronary artery occlusion.\(^{34}\) It was subsequently shown that low-flow ischaemia combined with pacing of the gastrocnemius muscle in rats reduced infarct size and improved myocardial function.\(^{35}\) Soon after, it was demonstrated in humans that non-invasive preconditioning of one limb protects the contralateral limb from endothelial I/R injury.\(^{36}\) The same study demonstrated that the non-invasive limb RIPC protocol may reduce infarct size in porcine hearts and improve myocardial function post-occlusion, as assessed by real-time left ventricular function.\(^{36}\) Studies of RIPC in a surgical context have also revealed a benefit in terms of restraining myocardial I/R injury.\(^{33}\)

The mechanism of preconditioning

Mechanistically, preconditioning is best considered in terms of triggers, mediators, and effectors.\(^{16,37}\)

Triggers

The activators of the preconditioning cascade are termed “triggers” and are broadly extracellular receptor/ligand interactions with autacoid, endocrine or paracrine signaling molecules. The ischaemic conditioning signal is a summation of signals derived from multiple disparate receptor/ligand interactions, which reaches a threshold once sufficient combined signals are generated.

Among the most well-established preconditioning triggers are adenosine, bradykinin and opioids. Adenosine is thought to be crucial in initiating the preconditioning cascade.\(^{38}\) Activation of the G-coupled adenosine A1 receptor triggers IPC protection, whereas adenosine receptor antagonists can block
IPC protection. In a similar manner, bradykinin infusion induces cardioprotection, which can be abolished by bradykinin receptor blockers.

Several lines of evidence suggest that opioid receptors are also important triggers of IPC. Selective pharmacological antagonists of the delta- or kappa-opioid receptor have been shown to block IPC, and agonists of the same receptors have been shown to mimic the IPC stimulus in intact animals, isolated hearts or isolated cardiomyocytes.

A common characteristic of these triggers is that they bind to G-protein-coupled receptors, with protein kinase C (PKC) as a common downstream target, and PKC inhibition can abolish their protective effects. Several other ligands to G-coupled receptors in the heart were also found to have the ability to mimic preconditioning through PKC activation, including ligands to angiotensin AT1, endothelin ET1 and muscarinic receptor. Other triggers include direct activation of the preconditioning pathway by reactive oxygen species (ROS) and transient elevations in intracellular Ca2+ concentration. The effect of ROS may be deleterious at the time of reperfusion; however, their increase during the ischaemic stimulus triggers a cardioprotective signal that prevents their detrimental action on mitochondrial permeability transition pore (mPTP) opening during reperfusion.

**Mediators**

Mediators of the triggering events include the intracellular effects of pro-survival kinases, most notably PKC. PKC is believed to hold a central role in mediating the effects of IPC, possibly through multiple targets, by modulating components associated with mitochondrial membranes, such as mPTP, mitochondrial KATP, BAX/BAD and Bcl-2. Mitochondrial KATP channels may trigger, mediate and maintain the preconditioned state in myocardial cells. Administering a KATP channel blocker prior to preconditioning blocks protective effects on vascular endothelium, while administering the antagonist after preconditioning but before ischaemia also blocks the protective effects. One popular hypothesis states that PKC and other kinases interact with the KATP channel to prevent the mPTP from opening and producing ROS. This confers resistance against a high mitochondrial Ca2+ load, a major cause of cell death from I/R injury. Other mediating (ROS for example) signals may directly interact with the mPTP to the same effect. The ability of preconditioning to increase myocardial cell tolerance to osmotic imbalance, decrease cytoskeletal fragility, decrease apoptosis and prevent infarct spread through abolishing gap junctions are other possibilities that may mediate cardioprotection.

The way by which tissues may communicate protection to distant sites, as in RIPC, is just as elusive as the mechanism of myocardial signaling in preconditioning. (For an in-depth review of the signaling pathways in preconditioning the interested reader is referred elsewhere.)

**End-effectors**

Potential mechanisms to explain how remote preconditioning may confer cardioprotective signals to the myocardium include a neuronal pathway, a humoral pathway, or a systemic response. Evidence for a neuronal pathway is derived from studies using autonomc ganglion blockers or nerve resection to attenuate the protective effect of RIPC. According to the prevailing concept of the neuronal pathway, the release of endogenous autacoids, including calcitonin gene-related peptide, adenosine, and bradykinin from the remotely conditioned organ activates local afferent nerves that terminate at the remote organ and mediate protection. Evidence for a humoral pathway includes the observation that coronary effluent from an ischaemic conditioned heart may confer protection from I/R injury on a naïve heart, and the observation that a period of reperfusion of the remote conditioned organ is required in order to achieve protection at the target organ. Activation of several receptors has been implicated in the humoral pathway, including adenosine, bradykinin-2, opioids, erythropoietin, CB2 endocannabinoid, angiotensin-1, and prostaglandin receptors; however, the specific humoral factors that are generated in the conditioned organ and are transported through blood circulation to the target organ remain elusive. Converging data from several studies suggest that these humoral factors are likely to be hydrophobic, with a molecular mass between 3.5 and 8 kDa.

Evidence that remote ischaemic preconditioning elicits a systemic protective response has been provided by Konstantinov et al, who demonstrated that brief forearm ischaemia suppresses pro-inflammatory genes encoding key proteins involved in leukocyte
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Delayed ischaemic preconditioning

Apart from the benefits of the standard form of ischaemic preconditioning, in 1993 two research laboratories discovered independently that the cardioprotective effect of preconditioning reappears 24 hours after the preconditioning stimulus, a phenomenon characterised as a second window of protection (SWOP), or delayed or late IPC. A reduction in infarct size was observed by Marber et al 24 hours following a standard IPC stimulus in a rabbit model.57 Similarly, Kuzuya et al observed infarct size reduction 24 hours after an IPC stimulus in a canine model; however, an infarct-limiting effect was not observed at 3 or 12 hours after the IPC stimulus.58 These data confirmed experimental findings of a weaning cardioprotective effect one hour past the IPC stimulus, which reappears at 24-48 hours but not at 72 hours.59

Even though several similarities between the standard and the delayed form of IPC exist, two significant differences are that the cardioprotection conferred by delayed IPC is not as powerful as early IPC, and that delayed IPC requires de novo protein synthesis of distal mediators.60 Delayed IPC may be elicited by the same ischaemic stimuli as classical IPC, and it has been shown that as little as one cycle of 5-minute ischaemia is sufficient for cardioprotection.61 In accordance with standard IPC, the underlying mechanism of delayed IPC requires triggers such as adenosine, bradykinin, opioids, cytokines, nitric oxide and ROS, which recruit early mediators (such as PKC, tyrosine kinase, PI3K-Akt, MEK 1/2-Erk1/2, and JAK). Early mediators in turn activate transcription factors (such as STAT1/3, NFκB, AP-1, Nrf2 and HIF-a), resulting in the synthesis 12-24 h later of de novo transcribed proteins, termed distal mediators, such as MnSOD, heat stress proteins, iNOS, and COX-2. These mediators protect the heart against infarction by acting on end-effectors such as the mPTP and the mitochondrial K<sub>ATP</sub> channel.60
Evidence for a benefit of remote ischaemic preconditioning in percutaneous coronary intervention

In the clinical setting, non-invasive RIPC can be induced pharmacologically or manually prior to PCI. Manually inducing RIPC usually involves inflating a blood pressure cuff, normally placed around the upper limb, to 200 mmHg or more; a period of inflation-induced ischaemia is followed by a period of reperfusion. However, there is no consensus in the available literature regarding the optimum cycle length and frequency that would confer most cardioprotection by RIPC. In fact, laboratory-based protocols for RIPC application differ significantly from clinically-based ones.

The clinical benefit of RIPC has been investigated in a recent meta-analysis of 23 studies, including 1878 patients undergoing cardiac surgery (15 studies), percutaneous coronary intervention (4 studies), or vascular surgery (4 studies). In this meta-analysis, RIPC was associated with a significant reduction in MI incidence (odds ratio: 0.50 [0.31-0.82]) and peak troponin release (mean difference: -0.28 ng/mL). Nevertheless, the incidence of mortality or major adverse cardiovascular events was not affected by RIPC.

Several studies have investigated in detail the effects of remote ischaemic conditioning during PCI. In the setting of an acute coronary syndrome, two studies have provided evidence for a beneficial role of remote ischaemic conditioning as an adjunct to primary PCI. The introduction of an ischaemic stimulus after the onset of MI and before reperfusion, termed preconditioning, has been shown to reduce cardiac troponin I (cTnI) release and increase myocardial salvage.

In the setting of elective PCI, 3 cycles of 5 minutes of ischaemia followed by 5 minutes of reperfusion were used by Hoole et al to induce RIPC just before the procedure. The primary outcome measure used was cTnI, a surrogate marker of myocardial ischaemia. ST-segment deviation and chest pain/discomfort during angioplasty were also assessed as signs of peri-procedural myocardial injury. Secondary clinical outcomes were assessed according to major adverse cardiac and cerebrovascular event (MACCE) rates at 6-month follow up. Patients who received RIPC had significantly lower cTnI levels 24 hours after PCI and a better clinical outcome at 6 months, with less clinically significant adverse effects. Moreover, patients who were preconditioned complained of less discomfort, and had less notable ST deviation during PCI. There were also fewer PCI related MIs, whilst cardiac comorbidities (primarily diabetes mellitus, hypertension and previous MI) did not affect the benefit of RIPC. According to a recent paper by the same research group, the benefits from RIPC were sustained during long-term follow up of the majority of the patients included in the first study. The MACCE rate at 6 years remained lower in the RIPC group (hazard ratio 0.58, 95% confidence interval 0.35-0.97; p=0.039), and was associated with higher cTnI post-PCI.

The findings of Hoole et al have been confirmed by several other studies (Table 1). According to two recently published studies, RIPC using a protocol of 3 cycles of 5-minute upper arm ischaemia/5-minute reperfusion is effective in reducing post-procedural cTnI after elective PCI and can reduce the incidence of type 4a MI. However, these effects are attenuated in elderly patients with diabetes mellitus.

Given that the majority of PCI procedures nowadays are conducted ad hoc, the introduction of a 30-minute interval between coronary angiography and subsequent PCI is not feasible in a high-volume catheterisation laboratory: therefore, several approaches to reducing the required time have been tested. Significant reduction of peri-procedural myocardial injury has been achieved using a protocol of 2 cycles of lower-limb ischaemia and reperfusion, or a single 5-minute cycle of upper-arm ischaemia/reperfusion. In contrast, a recently tested method of 3 cycles of 3-minute ischaemia/reperfusion failed to induce cardioprotection in a cohort of low to moderate risk patients.

The majority of available data suggest that the protection offered by RIPC could temporally exceed the peri-procedural myocardial injury-induced damage, which could affect the clinical outcome of PCI. Nevertheless, the clinical application of RIPC in the setting of PCI does have limitations. Primarily, it is hard to ascertain if there is no added protection (in both control and study populations) from the preconditioning effect of successive balloon inflations, recruitment of collateral vessels, or the addition of intracoronary preconditioning agents (e.g. glyceryl trinitrate). Studies that control for confounding by collateralisation have been published, all of which reach the same intrinsic conclusion: that RIPC is in fact cardioprotective, attenuating peri-procedural myocardial injury-related I/R injury. For example, in studies where intracoronary pressure-derived collateral...
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Flow indices were used, the recruitment of collaterals during balloon inflation could not solely explain the benefit of preconditioning. Authors also argue that collateral recruitment is not significant for myocardial protection during peri-procedural myocardial injury, whilst inducing RIPC via the limb may confer greater protection, as it minimises the risk of precipitating peri-procedural myocardial injury resulting from successive balloon inflations.

Not all data support a cardioprotective effect of RIPC. In fact, Iliodromitis et al, in the first implementation of an RIPC protocol in patients undergoing elective PCI—aiming to investigate whether RIPC, apart from reducing myocardial injury, may attenuate the inflammatory response sometimes observed after PCI—found that C-reactive protein and cTnI were significantly increased in preconditioned patients.

Moreover, another clinical trial concluded that RIPC did not attenuate contractile dysfunction induced by ischaemic injury. Patients underwent left ventricular conductance catheter assessment during serial coronary artery balloon occlusions. In between occlusions, RIPC was delivered to a subgroup of the patient population. Another group of patients underwent dobutamine stress echocardiography with tissue Doppler analysis, once with and once without RIPC. In both protocols left ventricular function was not im-

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<th>Reference</th>
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<td>Iliodromitis et al</td>
<td>Patients with stable angina, positive exercise treadmill test and single-vessel disease, an undefined proportion of patients had increased TnI before PCI</td>
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<td>5/20*</td>
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<td>Hooke et al 2009</td>
<td>Patients undergoing elective PCI, 17% multivessel disease, negative TnI in all patients before PCI</td>
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<td>Ghaemian et al 2012</td>
<td>Patients undergoing elective PCI, 44% multivessel disease, 7.5% of patients had increased TnT before PCI</td>
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<td>5/40§</td>
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<td>Ahmed et al 2013</td>
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<td>9/47¶</td>
<td>0.014</td>
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* A TnI cut-off level > 1 ng/mL was reported by the authors; † A TnI cut-off level > 0.03 ng/mL was reported by the authors; § A TnT cut-off level ≥0.12 (3 times the upper reference limit) was reported by the authors; ¶ A TnI cut-off level of ≥0.20 (5 times the upper reference limit) was reported by the authors; ‡ A TnT cut-off level > 0.042 (3 times the upper reference limit) was reported by the authors; † Flisher's exact test based on published data. TnI – troponin I; PCI – percutaneous coronary intervention; TnT – troponin T; CAD – coronary artery disease; UA – unstable angina.
proved by RIPC. This dual protocol excluded the possibility that RIPC was of no benefit because of myocardial stunning produced by balloon inflation.\textsuperscript{78} Interestingly, the authors argued that the SWOP protects from post-ischaemic left ventricular dysfunction, whereas the initial phase acts to limit infarct development.

In terms of pharmacological preconditioning, many agents that induce cardioprotection have been used in laboratory studies. In the clinical setting, evidence for preconditioning effects of intracoronary adenosine administration during PCI is limited to trial phases;\textsuperscript{79} however, a beneficial effect in terms of peri-procedural ischaemic markers (ST deviation and chest pain) and post-procedure surrogate ischaemic markers (cTnI) has been reported.\textsuperscript{79}

**Concluding remarks and future directions**

Is it then possible to attenuate peri-procedural myocardial injury by RIPC? The few, small clinical trials that are available, on the whole, appear to support a beneficial role of RIPC. Nevertheless, it should be noted that most available studies have used peri-procedural troponin release as a surrogate endpoint: therefore, further studies are needed to directly assess the effect of RIPC on infarct size and its long-term benefit in MACE reduction. To this end, the results of the Saint Francis Remote Ischemic Preconditioning Trial (SaFR) are much anticipated. The SaFR trial is designed to assess the effect of RIPC on MRI-detected myonecrosis and on MACE at 6 months in an estimated sample size of 500 patients.\textsuperscript{80}

Additionally, basic research is needed to improve our understanding of the mechanisms underlying I/R injury and preconditioning, which would allow for more targeted therapies. For instance, our recognition of the role of mPTP has led to studies investigating the effect of mPTP inhibition by cyclosporine. Cyclosporine has been shown to reduce infarct size in the setting of acute ST-elevation MI, and a large multicentre trial is under way to further investigate cyclosporine as a cardioprotective agent.\textsuperscript{81} The findings of these studies could be potentially extrapolated to elective PCI, although verification in this setting is also needed.

In conclusion, converging clinical evidence suggests that, 20 years after its discovery, the phenomenon of RIPC could be incorporated in clinical practice to minimise post-PCI myocardial injury, through simple to apply, non-invasive, and virtually cost-free protocols.

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