Remote Ischemic Preconditioning for Coronary Artery Bypass Graft Operations

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Ischemia-reperfusion injury occurs during coronary artery bypass graft operations. Strategies are needed to lower the extent of damage. Attempts to find these strategies have been occurring for more than 40 years, with remote ischemic preconditioning being one method. This review provides a look at potential mechanisms involved in remote ischemic preconditioning, experimental evidence supporting it, clinical studies that support and negate it, and potential reasons for differences between clinical studies. With remote ischemic preconditioning having the potential to better clinical outcomes in patients undergoing coronary artery bypass graft operations, a large clinical trial needs to be undertaken to better assess its practical clinical application.

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D ecreased coronary artery flow causes an ischemic event that can lead to decreased contractile function and, if severe, myocardial infarction due to apoptosis and necrosis, the two forms of cell death. Restoration of blood flow after an ischemic event is the best way to restore contractile function, reduce infarct size, and improve clinical outcome. However, restoring myocardial perfusion, such as through a coronary artery bypass graft (CABG) procedure, can cause more damage through the process termed ischemia and reperfusion (I/R) injury, which can lead to increased postoperative morbidity due to increased infarct size. In addition, myocytes may not be totally protected during cardiopulmonary bypass, even with the use of an additional cardioprotective mechanism, such as cardioplegia, which may not provide 100% protection and could use another supportive mechanism.

Strategies are needed to lower the risk of myocardial damage due to I/R injury, especially in patients undergoing cardiac operations in which the injury from I/R is predicted [1, 2]. For nearly 40 years, attempts to find these strategies have been taking place, and although many have been successful in animal models, few have shown promise in clinical trials.

Ischemic Preconditioning

The natural cytoprotective phenomenon known as myocardial ischemic conditioning, in which the heart is subjected to brief episode(s) of I/R to decrease damage during acute I/R injury, seems like a logical place to explore a strategy for lowering the risk of infarction. First described by Murry and colleagues [3] in 1986, ischemic preconditioning (IPC) uses this phenomenon against a prolonged period of ischemia that follows. In an experimental dog model, brief episodes of I/R to the circumflex artery reduced the infarct size induced by a subsequent prolonged occlusion of the same artery. Other studies in a number of experimental models followed, consistently showing that IPC protects the heart by reducing infarct size, the extent of stunned myocardium, and also ventricular arrhythmias [4]; however, this protection only lasted a few hours. Further studies determined that a second window of protection returns about 24 hours later and lasts approximately 72 hours [5].

Remote IPC

With remote IPC (rIPC), an area of the heart, or the entire heart, is protected by applying the ischemic conditioning stimulus to another area of the heart, or to another organ or tissue, respectively, before the prolonged ischemic event to the heart. Therefore, the scope of rIPC extends beyond various regions of the heart, so this strategy surely consists of systemic protection mechanisms.

Przyklenk and colleagues [6] showed that preconditioning of one region of the myocardium protects other areas of the heart. Anesthetized dogs received four cycles of 5-minute circumflex artery branch occlusion and reperfusion, followed by 1 hour of left anterior descending coronary artery occlusion and 4.5 hours reperfusion. Infarct size in the preconditioned group was significantly less, averaging 4% of the area at risk (AAR) compared with 13% in the controls. They also reported that the protection was not related to the degree of collateral circulation, AAR, or hemodynamic variables.
In 1997, Birnbaum and colleagues [7] randomized anesthetized rabbits into groups: (1) controls, (2) 60% reduction of femoral artery blood flow, (3) electrical stimulation of the gastrocnemius muscle, and (4) femoral artery stenosis and electrical stimulation. The rabbits then received 30 minutes of coronary artery occlusion, followed by 4 hours of reperfusion. All risk zones were similar; however, the ratio of infarct size-to-risk zone was smaller in group 4 (stenosis plus stimulation) than in the other groups.

Inter-organ protection was further confirmed by observations that preconditioning stimuli applied to the small bowel or kidney reduced infarct size in the hearts of rats [8, 9]. Other studies used brief intermittent ischemia of a limb that protected the heart during a prolonged ischemia that followed [10, 11].

Although the detailed mechanism is not fully understood, these experimental findings opened the door for studies to determine whether this phenomenon could become a practical clinical application. Because it can be produced nonpharmacologically with a blood pressure cuff on an arm or leg, the approach is noninvasive and effective, yet technically easy, virtually cost-free, and safe when performed by trained health care providers; therefore, rIPC can offer many interesting possibilities for surgeons and their patients [1].

Is rIPC able to protect the heart during elective CABG without the need for cardiac or aortic manipulation? This review will focus on rIPC applied before CABG for reducing myocardial injury and the potential for incorporating it into standard surgical practice.

Mechanisms of rIPC
rIPC allows the preservation of adenosine triphosphate (ATP), normalization of tissue pH, reduction in reactive oxygen species, stimulation of antioxidant defenses, reduction of cell necrosis, and avoidance of excessive contraction [1, 12–15], thereby reducing the adverse effects of I/R injury. The exact mechanisms have not been completely determined but are probably multifactorial. There are probably interrelationships among all of these components [12], and all cell types of the myocardium are likely acted upon in direct and indirect ways [16].

Triggers and Mediators of rIPC
Triggers involved in the mechanism(s) of rIPC turn on mediators that then activate transcription factors. The mediator p38 mitogen-activated protein kinase (MAPK) has been shown to be involved in a model of brain ischemic tolerance through its increased expression after limb IPC that protects against delayed neuronal death [13]. On the basis of this information, the p38 MAPK pathway was hypothesized to play a role in myocardial rIPC, and studies showed that cardioprotection is eliminated if p38 MAPK is inhibited [13].

The second window of protection involves some or all of the initial phase mediators and factors in addition to the synthesis of inducible nitric oxide synthase (iNOS), manganese superoxide dismutase, heat shock proteins, and cyclooxygenase-2 [15, 17]. Evidence of the importance of iNOS is provided by a study showing that knocking out iNOS abolishes the effect of preconditioning [18]. It may also require genomic and proteomic responses, including downregulation of proapoptotic gene expression and suppression of proinflammatory gene expression in leukocytes [15]. A few studies have observed a delayed protection of the heart after rIPC, from 24 hours after intestinal IPC to 4 weeks after chronic skeletal muscle ischemia [19].

Humoral Factors in rIPC
Blood-borne humoral factor involvement in mediating the systemic spread of the rIPC stimulus is supported by studies which observed that remotely generated protective factors can be transferred to the myocardium to activate their respective receptors without any neuronal involvement. Plasma collected from rabbits that had undergone rIPC significantly reduced infarct size when used to perfuse naïve donor hearts mounted on a Langendorff apparatus and subjected to 30 minutes ischemia and 120 minutes reperfusion [20]. Cross-species protection may also be offered, because perfusing Langendorff rabbit hearts subjected to I/R with human rIPC dialysate resulted in significantly reduced infarct sizes [20]. Attempts to characterize this protective factor(s) suggest it is dialyzable, less than 15 kDa, hydrophobic, not easily denatured, and heat-stable [15, 20].

Many rIPC endogenous humoral protective factors have been identified, including adenosine, bradykinin, calcitonin gene-related peptide, and endocannabinoids [13, 17]. rIPC probably also works through the activation of opioid receptors, because antagonists (eg, naloxone) block the cardioprotective effect, while a specific k-opioid receptor agonist (U-50,488H) decreases infarct size similar to rIPC [20, 21].
Another factor may be angiotensin I. A blocker of its receptor can abolish the reduction of myocardial infarct size produced by renal rIPC in rats [13]. Also, the release of vasodilatory factors from the remotely preconditioned organ or tissue may have effects on the heart or other distant organs and tissues [22]. Other factors, such as nitric oxide, heme oxidase 1, and reactive oxygen species, are involved in the complex cascades necessary for transferring the rIPC humoral factor from the organ or tissue it was generated in to the myocardium, and may also be involved in neuronal pathways [13].

Neuronal Communication in rIPC

Neuronal communication involving the autonomic nervous system has been studied as part of the rIPC phenomenon, and a few of the factors linked to humoral signaling (ie, adenosine, bradykinin, and calcitonin gene-related peptide) also play a role here due to their stimulation of nerve fibers terminating in the myocardium [15, 17]. When rIPC is induced using renal ischemia in a rabbit model, sympathetic nerve activity increases, indicating an adrenergic component of the autonomic system is involved [15]. In a rat model of myocardial infarction, rIPC achieved by mesenteric artery occlusion (MAO) was only effective if reperfusion of the small intestine was allowed. Hexamethonium, a ganglionic blocker, abolished the cardioprotection achieved by MAO but had no effect on protection by direct myocardial IPC [23], and another ganglion blocker inhibited rIPC cardioprotection in a human model [15].

Adenosine may play a role in this complex mechanism, because its administration into the mesenteric artery of animal models established cardioprotection similar to MAO/reperfusion; however, adenosine delivered into the portal or inferior caval veins did not produce cardioprotection. The adenosine must be acting in the small intestine or released from there, or both, stimulating local afferent nerves leading to the activation of myocardial adenosine receptors [23]. Also, the cardioprotective effect is eliminated by hexamethonium and several adenosine receptor inhibitors [23, 24].

Bradykinin, shown to stimulate local sensory nerves of the autonomic nervous system in animal models, might also play a role in MAO rIPC, because hexamethonium abolishes cardioprotection when administered before bradykinin [15]. Also, calcitonin gene-related peptide, a neurotransmitter in capsaicin-sensitive sensory nerves, increases systemically after rIPC, and pretreatment with capsaicin blocks this. Further, release of these or other dialyzable humoral factors is prevented by hind limb denervation [15].

Systemic Inflammatory/Apoptosis Modification in rIPC

Aiding in the reduction of infarct size, rIPC stimulates systemic antiinflammatory response(s). It increases interleukin-10, decreases tumor necrosis factor-α and monocyte-platelet aggregates, and suppresses the expression of CD41 and platelet endothelial cell adhesion molecule in response to ischemia [13, 25–27]. Proinflammatory genes are downregulated, antiinflammatory genes are upregulated, and functional responses of leukocytes and neutrophils are also altered [13, 25].

Inhibition of apoptosis occurs through the reduction of CASP8AP2 gene expression, increasing levels of phosphor-Akt, activation of nuclear factor-κB and the Wnt pathway, and upregulation of tissue inhibitor of metalloproteinase [25, 28]. Although these systemic modifications have been documented during rIPC, their relevance to the cardioprotection has not been clarified and need to be further investigated [29].

Signaling Pathways and Mitochondria in rIPC

Once the cardioprotective signal(s) from the remotely preconditioned organ or tissue has been received by the heart, pathways in the cardiomyocytes, such as the reperfusion injury salvage kinase pathway made up of antiapoptotic prosurvival kinase-signaling cascades, are activated [15] and influence the functioning of many cellular components. One of those cellular components triggered by many mediators are the mitochondria. The mitochondrial, as well as sarcolemmal, ATP-sensitive potassium (K<sub>ATP</sub>) channel plays an important role in all models of ischemic conditioning. Its activation reduces ATP depletion and maintains intracellular pH during ischemia, allows ATP levels to be restored during reperfusion, and closes the mitochondrial permeability transition pore [13]. Opening of the mitochondrial permeability transition pore during the first few minutes of reperfusion would allow mitochondrial swelling and the uncoupling of oxidative phosphorylation to occur, leading to cell death [13, 17].

The delivery of drugs that open the K<sub>ATP</sub> channel can create a cardioprotective state similar to that induced by IPC, whereas K<sub>ATP</sub> channel-blockers attenuate IPC cardioprotection [30, 31]. In a study by Konstantinov and colleagues [32], hearts transplanted from pigs with brain death caused by severe brain ischemia, had a reduction in the infarct size/AAR ratio after I/R compared with hearts transplanted from pigs without brain ischemia. Also, rIPC immediately before I/R preserved brachial artery endothelial function, possibly through the preservation of blood flow and dilator function, but had no direct effect on its smooth muscle function, regardless of the extent of atherosclerosis [33]. However, rIPC protection in both studies was abolished by a K<sub>ATP</sub> channel-blocker.

Mechanisms Summary

Many different mediators and pathways are likely involved in rIPC (Fig 1). However, something to keep in mind is that a number of these mediators and pathways may differ between animal models and humans. Therefore, more research is needed to delineate which mediators and pathways are associated with rIPC in humans to move closer to routine use in cardiac surgeries.

Clinical Trials Using rIPC

Multiple studies have shown the beneficial effect of rIPC in various body organs, leading to many potential uses
Numerous clinical trials have been conducted during the past 12 years to determine the potential of rIPC in reducing myocardial injury after operations using levels of cardiac injury markers (e.g., troponin T or I, creatine kinase-MB) and clinical outcome. We examined six randomized controlled studies that reported encouraging results with rIPC before CABG (Table 1), and compared them with seven others that were not favorable, observing little to no significant difference in enzyme leak and clinical outcome (Table 2).

The supportive studies were more cohesive in their patient populations, rIPC protocols, operations performed, and end points analyzed, reflected in the significant reductions in troponin release after the operations. Troponin release can be used as a marker of myocardial cell necrosis [2], and thus, the extent of infarction. Therefore, minute troponin release can equate to permanently damaged tissue. However, there is currently no excepted consensus on the meaning of released troponin values.

There was more variability in the nonsupportive studies that used different CABG procedures, rIPC protocols, and surgical populations. This may be the reason(s) no differences were observed in the cardiac injury markers measured between the control and rIPC groups.

**Potential Reasons for Discrepancies Between Trials**

Several differences between the studies that showed a positive outcome and the nonsupportive studies may be observed, including the use of different anesthetics and rIPC protocols.

**ANESTHETICS**

Many studies have shown that inhaled anesthetics produce whole-body preconditioning, based on decreased release of cell death biomarkers and protective effects seen in multiple organs [54, 56–58]. This preconditioning likely involves many factors, including the activation of the mitochondrial K_{ATP} channel and attenuation of oxidative damage.

The use of isoflurane alone or followed by propofol has shown cardioprotection [48, 59]; however, propofol alone did not provide protection [48]. This may be because propofol does not react with K_{ATP} channels, at least in vitro. It has a structure similar to free radical scavengers, so it
Table 1. Trials Supporting Remote Ischemic Preconditioning in Coronary Artery Bypass Grafting

<table>
<thead>
<tr>
<th>Study</th>
<th>rIPC I/R Protocol and Location</th>
<th>Anesthetics</th>
<th>Timing of rIPC to Anesthesia</th>
<th>Timing of rIPC to Skin Incision</th>
<th>Other Cardioprotective Agents</th>
<th>End Point(s)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hausenloy et al [44]</td>
<td>57 3 x 5 min; right arm</td>
<td>I: midazolam, etomidate, propofol, fentanyl, pancuronium. M: oxygen, propofol infusion.</td>
<td>After induction</td>
<td>Before incision</td>
<td>Cross-clamp fibrillation or cardioplegia</td>
<td>TnT AUC at 48 h</td>
<td>43% reduction</td>
</tr>
<tr>
<td>Venugopal et al [45]</td>
<td>45 3 x 5 min; right arm</td>
<td>I: midazolam, etomidate, propofol, fentanyl, pancuronium. M: halogenated anesthetics, propofol.</td>
<td>After induction</td>
<td>Before incision</td>
<td>Cold-blood cardioplegia</td>
<td>TnT AUC at 72 h</td>
<td>42% reduction</td>
</tr>
<tr>
<td>Ali et al [46]</td>
<td>100 3 x 5 min; left arm</td>
<td>General anesthesia</td>
<td>After induction</td>
<td>Before incision</td>
<td>Warm-blood hyperkalemic cardioplegia</td>
<td>CK-MB at 8–48 h</td>
<td>Significant reduction</td>
</tr>
<tr>
<td>Thielmann et al [37]</td>
<td>53 3 x 5 min; left arm</td>
<td>I: sufentanil, etomidate, rocuronium. M: isoflurane, propofol.</td>
<td>After induction</td>
<td>Before incision</td>
<td>Cold crystalloid Bretschneider cardioplegia</td>
<td>TnI AUC at 72 h</td>
<td>45% reduction</td>
</tr>
<tr>
<td>Wagner et al [47]</td>
<td>66 3 x 5 min; arm</td>
<td>I and M: diazepam, sufentanil, pancuronium.</td>
<td>Before induction</td>
<td>Before incision</td>
<td>Cold crystalloid cardioplegia</td>
<td>TnI at 8–24 h</td>
<td>Significant reduction at 8 h</td>
</tr>
<tr>
<td>Kottenberg et al [48]</td>
<td>72 3 x 5 min; left arm</td>
<td>I: sufentanil, etomidate, rocuronium. M: isoflurane, propofol.</td>
<td>After induction</td>
<td>Before incision</td>
<td>Bretschneider cardioplegia</td>
<td>TnI AUC at 72 h</td>
<td>50% reduction with isoflurane, not with propofol</td>
</tr>
</tbody>
</table>

AUC = area under the curve; CK-MB = creatine kinase-MB; I = induction; I/R = ischemic-reperfusion; M = maintenance; rIPC = remote ischemic preconditioning; TnI = troponin I; TnT = troponin T.
### Table 2. Trials Not Supportive of Remote Ischemic Preconditioning in Coronary Artery Bypass Grafting

<table>
<thead>
<tr>
<th>Study</th>
<th>rIPC I/R Protocol and Location</th>
<th>Anesthetics</th>
<th>Timing of rIPC to Anesthesia</th>
<th>Timing of rIPC to Skin Incision</th>
<th>Other Cardioprotective Agents</th>
<th>End Point(s)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Günaydin et al [49]</td>
<td>8</td>
<td>I: diazepam, fentanyl. M: fentanyl.</td>
<td>After induction</td>
<td>After incision</td>
<td>Moderate systemic hypothermia (28°–30° C), blood cardioplegia</td>
<td>CK-MB at 5 min</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Hong et al [50]</td>
<td>130</td>
<td>I: midazolam, sufentanil. M: sevoflurane, remifentanil, vecuronium.</td>
<td>After induction</td>
<td>After incision</td>
<td>NA; off-pump CABG</td>
<td>TnI AUC at 72 h</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Rahman et al [51]</td>
<td>162</td>
<td>I: etomidate, fentanyl, pancuronium. M: propofol, alfentanil, supplemented by enflurane, sevoflurane.</td>
<td>After induction</td>
<td>Before incision</td>
<td>Cold-blood cardioplegia</td>
<td>TnT AUC at 48 h</td>
<td>No significant reduction</td>
</tr>
<tr>
<td>Karuppasamy et al [52]</td>
<td>54</td>
<td>I: remifentanil, propofol, atracurium. M: isoflurane, followed by propofol.</td>
<td>After induction</td>
<td>Before incision</td>
<td>Cross-clamp fibrillation or cold-blood cardioplegia</td>
<td>TnI, CK-MB, BNP at 6–48 h</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Lomivorotov et al [53]</td>
<td>80</td>
<td>I: fentanyl, pipercuronium bromide. M: isoflurane.</td>
<td>After induction</td>
<td>Before incision</td>
<td>Cold crystalloid cardioplegia</td>
<td>TnI, CK-MB at 6–48 h</td>
<td>Improved cardiac index; no improvement in cardiac markers</td>
</tr>
<tr>
<td>Lucchinetti et al [54]</td>
<td>55</td>
<td>I: opioids, propofol. M: isoflurane.</td>
<td>After induction</td>
<td>Before incision</td>
<td>Cold-blood cardioplegia</td>
<td>TnT at 1–72 h</td>
<td>No protection</td>
</tr>
<tr>
<td>Young et al [55]</td>
<td>96</td>
<td>I: midazolam, fentanyl. M: propofol, isoflurane.</td>
<td>After induction</td>
<td>Began with 1st incision</td>
<td>Tepid-blood cardioplegia</td>
<td>TnT at 6 and 12 h</td>
<td>No significant reduction</td>
</tr>
</tbody>
</table>

AUC = area under the curve; BNP = brain natriuretic peptide; CABG = coronary artery bypass graft; CK-MB = creatine kinase-MB; I = induction; I/R = ischemic-reperfusion; M = maintenance; NA = not applicable; rIPC = remote ischemic preconditioning; TnI = troponin I; TnT = troponin T.
may quench reactive oxygen species, which are needed for some preconditioning mechanisms [48].

Which anesthetic used and when may, therefore, make a difference in the extent of protection achieved and whether rIPC at any point may be beneficial. It may be that the inhaled anesthetic, with or without the combined use of propofol, can reach the efficacious threshold of preconditioning cardioprotection alone, and the use of rIPC would not be able to add to the protection [60]. Many of the studies, both supportive and nonsupportive of rIPC, applied the stimulus after anesthetic induction and used propofol and inhaled anesthetics extensively.

**SURGICAL INCISION.** The skin incision made at the start of the operation induces a form of cardioprotection termed remote preconditioning of trauma. In animal models of I/R injury, this nonischemic stimulus decreased AAR and infarct size when performed 15 minutes before an I/R protocol [61–63]. The cardioprotection is initiated by sensory nerve fibers in the skin, followed by neurogenic signaling involving spinal nerves and the activation of cardiac sensory and sympathetic nerves by bradykinin-2 receptors. Roles for epoxyeicosatrienoic acids and the mitochondrial $K_{ATP}$ channel have also been shown [61, 62].

As with the anesthetic preconditioning effects discussed above, remote preconditioning of trauma may also mask the cardioprotective effect of rIPC, depending on when the stimulus is administered in relation to the skin incision. In two studies with negative results [49, 50], rIPC was applied after skin incision, and another [55] began the rIPC protocol at the start of the first incision, which may not have allowed sufficient time for the rIPC to fully take effect.

**MUSCLE MASS PRECONDITIONED.** Does the use of 1 arm or leg during rIPC allow enough muscle mass to be conditioned so that the affect is adequately transferred to the heart to establish cardioprotection? This is unknown, because the most adequate “dose” of rIPC has not yet been determined [54, 64]. In 2011 Wu and colleagues [65] compared a rIPC protocol to the right arm with another that preconditioned both the right arm and leg. Only the rIPC using both the arm and leg produced significant cardioprotection, suggesting that a certain threshold (amount of muscle mass preconditioned or signaling factors released, or both) may need to be reached. However, this is the only study to date that preconditioned 2 extremities at the same time, whereas other studies that showed rIPC cardioprotection only used 1 arm (predominantly) or leg.

Kottenberg and colleagues [48] tried to show which arm was best to use by determining that the cardiac sympathetic nerves of the left arm project to most of the left ventricle, whereas the nerves of the right arm project more to the atria and the anterior wall of the left ventricle. However, many more factors come into play, such as the overall health of the patient (ie, circulation in the arms and legs, extent of heart damage, etc.), number of rIPC cycles, and time of rIPC application. Hausenloy and Yellon [64] suggest applying the rIPC stimulus 2 to 3 hours before anesthesia induction, whereas most studies have applied it after anesthesia but before the skin incision.

**OTHER CARDIOPROTECTIVE AGENTS.** Cardioprotective agents, such as cardioplegia, hypothermia, and potassium chloride, are given to patients to protect the heart. Can the addition of rIPC enhance this cardioprotection? In 1996 Kolacakassis and colleagues [66] showed that IPC, followed by cardioplegia with 34°C St. Thomas solution in rats, provided no significant additional protection over the cardioprotection achieved by each procedure alone. A similar study performed by Valen and colleagues [67] using 7°C St. Thomas solution showed that IPC might offer only marginally more protection in addition to the cold cardioplegia. However, Li and colleagues [68] showed that IPC enhanced 4°C cold-blood cardioplegia protection in valve replacement patients. Could cardioplegia at colder temperatures allow more of the protective effects of rIPC to play a role in overall cardioprotection? Many of the CABG studies supporting rIPC, and most of those not supportive, used cold cardioplegia. What role does anesthesia play in this combined process? Zaugg and colleagues [60] suggest that rIPC may only be capable of providing protection under isoflurane anesthesia when the other cardioprotective mechanism used is not completely effective.

In a rat model of moderate hypothermia (20°C) and cardioplegia, IPC improved functional recovery and reduced creatinine kinase leakage during reperfusion [69]. Also, during and after mild hypothermia (27°C) in isolated guinea pig hearts, IPC offered additive protection through an increase in mitochondrial bioenergetics and redox balance [70]. Thus, mild to moderate hypothermia or cold cardioplegia, or both, may influence the mechanisms of preconditioning, whereas deep hypothermia may stop the biochemical reactions needed [67]. All this depends on many factors, including length of hypothermia, length of I/R, and timing of the preconditioning stimulus.

Endogenous calcium stimulates protein kinase C, a mediator of cardiac preconditioning. Therefore, calcium chloride, a safe, routinely administered agent, should induce protein kinase C-mediated cardiac preconditioning. Meldrum and colleagues [71] administered exogenous calcium chloride to isolated, perfused rat hearts 10 minutes before their I/R protocol and found improved myocardial function. However, overloading of intracellular free calcium did not have any protective effect; in fact, it plays a prominent role in cardiomyocyte damage [72], so cytosolic calcium homeostasis must be maintained to regulate cardiomyocyte function and potentially achieve cardioprotection.

The patient’s presenting heart condition, type of operation performed, and form(s) of cardioprotection used can affect the extent that stunned myocardium vs apoptotic/necrotic tissue is involved in the effectiveness of rIPC. Both occur as a result of I/R injury, with stunned myocardium referring to an area of prolonged postischemic cellular dysfunction without necrosis. This condition is reversible; the tissue remains viable,
eventually regaining normal contractile function with adequate reperfusion [73]. Apoptotic/necrotic tissue cannot regain function. Although the effect of rIPC on reducing apoptotic/necrotic tissue is well researched, its effect on stunned myocardium remains unknown.

PATIENT POPULATIONS AND STUDY SIZES. Some of the studies discussed included elective as well as urgent CABG, which may have made the results more difficult to interpret; although statistical analysis of each separately was similar. The use of study-specific patient populations and types of operations within a study will allow for better statistical interpretation of results. In addition, using larger sample sizes may help detect more subtle differences in study parameters.

In conclusion, more than 2 decades of research have been spent examining rIPC. From bench research to animal studies and clinical trials, more and more data support this protective phenomenon; yet, this simple and safe technique has not yet been used during CABG in humans, outside of the realm of research, because not all clinical studies showed a promising outcome.

In this current era of expensive medicine and procedures, along with major changes in medical care, rIPC has the potential to improve patient outcomes without major resource utilization and cost. Consequently, there is a need for a large clinical trial that is designed to mirror the mainstream published literature that supports rIPC in many aspects, such as a specific patient population, anesthetic(s) used and when delivered in regards to the skin incision, form of CABG procedure, and additional cardioprotective mechanisms used, among other variables. The study should have enough power to satisfy stringent statistical analyses, yet be simply designed so that it can be easily implemented in preanaesthesia units. The end points must be solid, clinically relevant measures with additional biochemical indices that support the clinical measures. With a supportive outcome, the trial’s analyses can be combined with other current positive results to be translated into a definitive recommendation that may benefit patients undergoing CABG operations.

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References


