Since its original description in 1986 by Murry et al, the ability to condition, or protect, the heart from a lethal episode of prolonged ischemia (followed by reperfusion) has represented both an opportunity and a challenge to the many experimentalists, clinicians, and translationalists engaged in the struggle to reduce the risk of death and disability resulting from spontaneous (acute coronary syndromes) and procedurally associated (coronary artery bypass surgery, catheter-based coronary revascularization) myocardial ischemia. The potential to mitigate myocardial injury or death resulting from an ischemic insult is the opportunity. The inability to fully, consistently, and effectively translate experimentally established reductions in myocardial injury or death to the bedside is the challenge.2

Ischemic Preconditioning as an Adjunct to Percutaneous Coronary Intervention

Throughout the 1970s and well into the 1980s, cardiovascular physiologists were intensively studying the sequence of events culminating in frank necrosis of heart muscle as the result of coronary arterial occlusion3 and the benefits and hazards of reperfusion of ischemic myocardium.4 Around this same time, developments in catheter-based coronary revascularization clearly established that brief periods of controlled occlusion of an obstructed coronary artery, followed by reperfusion (release of the occlusion), could safely relieve the obstruction without overt myocardial injury.5 Key aspects of this emerging treatment modality were (1) the sequential nature of the controlled occlusions; (2) the importance of a period of reperfusion between the occlusive episodes; and (3) the almost universal attenuated clinical and electrocardiographic response to the second (or subsequent) occlusion compared with the initial occlusion.

In short order, this clinical model was widely studied and reproduced.6–11 In the first detailed coronary hemodynamic study of this model of controlled coronary occlusion in man, Deutsch et al8 showed that the second of two 90-second balloon occlusions separated by a 5-minute period of reperfusion was met with statistically significant reductions in objectively assessed angina score, ST-segment–elevation, left ventricle filling pressure increase, regional coronary blood flow, and lactate release from the coronary circulation. The correspondence between these findings and those of Murry et al8 in the animal model of ischemia and reperfusion was notable; the singular exception being the purposeful induction of myocardial infarction in the latter. Although not all clinical studies agreed with these early observations in humans during percutaneous coronary intervention (PCI), the majority of studies were able to duplicate the observations of Deutsch et al8 and supported the extension of these initial results to a broader spectrum of patients. Of equal, if not greater, importance was the message that PCI-induced ischemic injury was modifiable in a predictable manner using a standardized protocol.

There were, however, limitations and caveats to these mostly-in-agreement clinical studies, and the magnitude of clinical benefit associated with this model of ischemic preconditioning remained unclear. Although the mechanism(s) underlying this cardoprotective paradigm were increasingly understood in animal models, practical extension of this understanding (translation) to the clinical arena was met with limited success, despite numerous concordant observations and conclusions concerning the biology of preconditioning in laboratory animals and humans.12 From a clinical standpoint, the benefit derived from ischemic preconditioning was, for the most part, limited to a reduction in enzymatically defined myocardial necrosis in an elective PCI setting11 and in the cardiac surgery setting.11 The ongoing controversy surrounding the clinical relevance of biomarker-defined periprocedural myocardial injury,15,16 and the large scale of most contemporary PCI trials represent missed opportunities for rigorous testing of the hypothesis that ischemic preconditioning confers meaningful clinical benefit. In the 1 study with longer term follow-up of patients undergoing PCI with adjunctive ischemic preconditioning, a clinical benefit was observed.17 Equally important in the latter study was the observation that the failure to elicit the classic preconditioning response during PCI was associated with adverse late-term clinical outcomes.17 The classic ischemic preconditioning response was less frequently observed in the elderly, patients with diabetes mellitus, and women and suggested that the failure to precondition may be a functional biomarker for an abnormal myocardial metabolic response to ischemic stress. The latter hypothesis is consistent with the well-known higher rates of adverse clinical outcomes in these specific subgroups.

During the past several years, there has been renewed interest in ischemic preconditioning during elective PCI using a remote ischemic stimulus.18,19 Although not as extensively...
In-depth reviews of this chronology are the subject of several excellent publications and are beyond the scope of the current clinically focused discussion. However, readers need to appreciate 2 fundamental transitions (paradigm shifts) in the evolution of our understanding of the underlying biology of preconditioning, both of which have important implications for ischemic conditioning in the PCI setting. The first transition was the departure from the concept of metabolic downregulation as a primary mechanism underlying the preconditioned phenotype and the realization that the adaptive biochemical response was considerably more active than passive. Signaling events at the cell surface led to a series of phosphorylation and oxidative events within the RISK pathways, culminating in the opening (in the case of the K⁺-ATP-dependent channel) or closing (in the case of the mitochondrial permeability transition pore (mPTP)) within the mitochondrion. The second transition was in the realization that the cardioprotective effect of ischemic preconditioning was conferred on reperfusion rather than during the antecedent ischemic period. Thus, notwithstanding the well-described downregulation of myocardial metabolic activity seen with preconditioning, the phenotypic protective effect of ischemic conditioning conferred on reperfusion supported hypotheses positing activation of survival pathways, themselves acting within multiple final common pathways on the necessary and sufficient effector—the mPTP. This critical role for the reperfusion of ischemically conditioned myocardium provides a natural segue to the subject of ischemic postconditioning.

**Ischemic Postconditioning as an Adjunct to PCI**

Despite continuous improvements in pharmacotherapy, reperfusion techniques, emergency activation, and healthcare delivery systems, ST-segment–elevation myocardial infarction (STEMI) remains a worldwide major cause of morbidity and mortality. The final infarct size (IS) has been identified as a

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**Table 1. Summary of Findings From Randomized Controlled Clinical Trials of Remote Ischemic Preconditioning in Patients Undergoing Elective PCI**

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Age, y</th>
<th>Remote-con Site</th>
<th>Inflation Time/Deflation Time, min</th>
<th>No. of Cycles</th>
<th>Major End Point(s)</th>
<th>Conditioning</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ilidromitis et al,24 2006</td>
<td>41</td>
<td>Both UE</td>
<td>5/5</td>
<td>3</td>
<td>IS, TnI AUC, ng/mL</td>
<td>24±7</td>
<td>8±1.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IS, CKMB AUC, ng/mL</td>
<td>83±24</td>
<td>21±8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hoole et al,21 2009</td>
<td>242</td>
<td>UE</td>
<td>5/5</td>
<td>3</td>
<td>IS, TnI, median (IQR), ng/mL</td>
<td>0.06</td>
<td>0.16</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MACCE* at 6 m, %</td>
<td>4</td>
<td>13</td>
<td>0.018</td>
</tr>
<tr>
<td>Ghaemian et al,22 2012</td>
<td>80</td>
<td>LE</td>
<td>5/5</td>
<td>2</td>
<td>IS, TnI at 24 h, ng/mL</td>
<td>0.063±0.11</td>
<td>0.016±0.02</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MACCE† at 1 y, %</td>
<td>10</td>
<td>5</td>
<td>0.68</td>
</tr>
<tr>
<td>Luo et al,23 2013</td>
<td>205</td>
<td>UE</td>
<td>5/5</td>
<td>3</td>
<td>IS, TnI at 16 h, ng/mL</td>
<td>0.11</td>
<td>0.21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prasad et al,24 2013</td>
<td>95</td>
<td>UE</td>
<td>3/3</td>
<td>3</td>
<td>Frequency of PCI-related biomarker-defined myonecrosis</td>
<td>47</td>
<td>40</td>
<td>0.42</td>
</tr>
<tr>
<td>Ahmed et al,25 2013</td>
<td>149</td>
<td>UE</td>
<td>5/5</td>
<td>3</td>
<td>IS, TnI at 16 h after PCI, ng/mL</td>
<td>0.020</td>
<td>0.047</td>
<td>0.047</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; CKMB, creatinine kinase myocardium-bound (MB) fraction; IQR, interquartile range; IS, infarct size; LE, lower extremity; MACCE, major cardiac and cerebral events; PCI, percutaneous coronary intervention; TnI, troponin I; TnT, troponin T; and UE, upper extremity.

*MACCE defined as hospital admissions with unstable angina/acute coronary syndrome, MI, heart failure, and stroke/transient ischemic attack, death.
†MACCE defined as hospitalization for acute coronary syndrome, myocardial infarction, or death because of myocardial infarction.

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**Shifting of the Paradigm**

Despite the many challenges encountered in translating the message implicit in the above-discussed clinical and experimental models of ischemic preconditioning to a more clinically relevant application, our understanding of the basic science of ischemic conditioning has progressed rapidly. The obvious limitation of the PCI model was the application of the stimulus or signal before an observer-controlled induction of sustained ischemia. A broader understanding of the myocardial metabolic pathway(s) involved in the preconditioning response would be necessary to harness the full clinical potential of preconditioning and to develop pharmacological preconditioning mimetics that would be more practical and effective under the less predictable and spontaneous circumstances as occur in the real world. Having established the critical importance of adenosine, bradykinin, opioids, and other agonists acting at the proximal end of a complex network of signaling pathways terminating in the protective phenotype defining preconditioned myocardium in both humans and experimental animals, it became critically important to define those pathways and the end organ that is both necessary and sufficient for preconditioning.
major contributor to adverse clinical outcomes in a STEMI population and varies inversely with, among other factors, the speed and extent of reperfusion. In the context of this review, we need to examine 2 separate but related issues: What degree of myocardial salvage are we currently achieving with contemporary reperfusion therapy? How much opportunity is there for further improvement?

**Postconditioning During Primary PCI for STEMI: The Evidence Base**

For many years, it had been recognized in the surgical literature and, more recently, in the ischemic preconditioning literature that conditions at the onset of reperfusion were strong determinants of the extent of the so-called reperfusion injury and the degree of myocardial salvage after restoration of flow. Gradual, or intermittent, partial reflow of oxygenated blood results in gradual, partial normalization of the acidosis consequent to ischemia and low concentrations of reactive oxygen and nitrogen species. The former, acidosis, is necessary to forestall opening of the mPTP—a mega-channel which when remaining in the open, or activated, state results in cell death via release of proapoptotic elements. The latter, reactive oxygen and nitrogen species, are necessary during early reperfusion to prevent irreversible opening of the mPTP, activate protein kinase C, and serve as second messengers for additional preservation pathways.

Although vital for myocardial salvage, establishment of reflow in a previously occluded vessel may have negative consequences that counteract the beneficial effects of reperfusion. This phenomenon, known as reperfusion injury, is additive to the ischemic cell injury that precedes it and has been estimated to account for as much as 50% of the final IS, despite prompt restoration of flow. It is notable that the extent of myocardial salvage after primary PCI is, on average, approximately half of the area at risk (AAR) and highly dependent, among other factors, on the duration of ischemia. Unlike ischemic injury which beyond a certain period of diminished coronary blood flow is irreversible and results in cell death, reperfusion injury is variable in extent and severity and may be potentially modifiable under specific circumstances. Experts agree that the final common pathway for lethal reperfusion injury is sustained opening of the mPTP and it is at this point where the pathways and signals for ischemic conditioning must converge in properly timed and concerted activation of free radicals, salvage kinases, and antiapoptotic proteins. In this construct, the importance of time and, in particular, ischemic time, and timely activation of salvage pathways, cannot be overstated.

In 2003, Zhao et al demonstrated the cardioprotective effects of a series of brief coronary arterial occlusion/reperfusion cycles in the early moments of reperfusion after a 60-minute occlusion of the left anterior descending artery in a dog model. Notably, the IS was 44% smaller in these postconditioned animals compared with controls, and this degree of cardioprotection was very similar to that conferred by ischemic preconditioning. In contrast to the experience with ischemic preconditioning, the take-up, that is, translation, of these findings by the clinical community was prompt with the first reports of the effects of postconditioning in STEMI patients appearing in 2005.

Table 2 summarizes the results of our systematic review of the literature on randomized controlled clinical trials (RCTs) evaluating ischemic postconditioning as an adjunct to primary PCI versus primary PCI alone. Of note, there is significant variation among the conditioning protocols, the methods for ascertaining of IS/myocardial salvage, and ischemic time. Figure 1 depicts the relationship between the extent of cardiac magnetic resonance (CMR)–derived estimates of myocardial salvage (defined as the AAR, minus the IS normalized to the AAR) and ischemic time from a series of patients undergoing primary PCI for STEMI and is consistent with the known clinical adage that time is muscle. Figure 2 depicts the relationship between estimated IS reduction and ischemic time obtained from the RCTs in Table 2. It can be seen that, in contrast to the expected inverse relationship between the degree of myocardial salvage and ischemic time in the primary PCI experience as seen in Figure 1, no such relationship is evident in these postconditioning trials. Unfortunately, there are too few studies in the postconditioning clinical trial literature with ischemic times <4 hours and, thus, more data are needed to properly compare outcomes after PCI using postconditioning compared with PCI alone within this critical time window.

In fact, the evidence from these contemporary postconditioning trials indicates variability in treatment effect and variability in the means of estimating IS (biomarker-derived estimates of IS, myocardial perfusion imaging–derived estimates of IS, CMR-derived estimates of IS/salvage) which range from benefit (normalized treatment effect >0%) to harm (normalized treatment effect <0%). Figures 3 and 4 demonstrate the results from a random effects meta-analysis of those trials in Table 2 using biomarker assessment of IS as the outcome and stratified on direct versus remote postconditioning (see below). It can be seen that heterogeneity is substantial and the overall estimated treatment effect is marginally statistically significant (P=0.042). Figures 5 and 6 demonstrate the results from a random effects meta-analysis of trials using CMR-derived estimates of IS. Notable again is significant heterogeneity, an overall estimated treatment effect that is not statistically significant and the possibility of harm with adjunctive postconditioning.

The source(s) of disagreement between biomarker-assessed and CMR-assessed outcome measures are not immediately obvious, although in contrast to the qualitative similarity of results using biomarker-derived estimates of differences in the timing of CMR studies, precision in the estimate of the AAR, conduct of the postconditioning protocol itself, composition of patient population, and total ischemic time are all potential sources of variability among studies. CMR estimates of myocardial salvage index are exquisitely time dependent, as is the case for IS assessment, and may also vary with the extent of infarction and AAR. Postconditioning may not be appropriate for all-comers and greater benefit may be limited to the largest evolving infarcts. Given that controversy still exists on the precision and timing of the estimation of AAR using CMR methodology, until these issues are resolved the opportunity for improvement in myocardial salvage with adjunctive postconditioning rests heavily on short ischemic times, that is, <4 hours, and a standardized postconditioning protocol applied in patients most likely to benefit. Even small degrees of
intermittent reperfusion in STEMI patients before arrival in the catheterization laboratory may mitigate, or preclude, detection of incremental benefit by virtue of the postconditioning inherent in such episodic reperfusion. Such considerations do not, however, provide explanation for the concerning signals of harm or null effect in the studies using CMR assessment of IS/salvage.
The variability in treatment effect in these trials also supports lingering concerns in the experimental literature on the lack of reproducibility of the postconditioning response across species\textsuperscript{69–72} and inconsistencies in the RISK-SAFE pathway paradigm of postconditioning cardioprotection.\textsuperscript{73–75} Thus, despite the extent of preclinical data on the beneficial effects of postconditioning during reperfusion, concerns remain on our understanding of the postconditioning paradigm. The clinical trial data reviewed herein are also conflicting. The evidence base is limited to either indirect measures of IS (biomarkers) or still-in-evolution CMR methodology. Of most importance from a clinical trial standpoint, there are insufficient numbers of hard clinical outcomes. In the 902 patients participating in the trials summarized in Table 2, there were <50 hard outcome events reported. Given the current decreasing rates of in-hospital STEMI-associated death and reinfarction in patients undergoing reperfusion therapy, coupled with a baseline myocardial salvage index of, on average, 0.5,\textsuperscript{48} larger scale RCTs designed to detect a least clinically meaningful difference between treatment arms will be necessary. In addition,
a reduction in IS, if accurately measured, from 20 to 10 g is unlikely to have significant clinical relevance. Although unlikely to be independent of absolute IS reduction, the clinical benefit derived from postconditioning also may not be apparent until weeks or months have transpired. Activation of the various salvage and antiapoptotic pathways identified with postconditioning may contribute to favorable remodeling in the late term and may mitigate longer term risks. Thus, hard clinical end points which capture the risk of heart failure or hospital readmission should be considered in more suitable study designs (eg, large-scale, simple RCTs).76

The role of adjunctive pharmacological agents given at the time of primary PCI is beyond the scope of this review and has been discussed elsewhere.26 However, in view of the continuing, and to date unsuccessful, search for a clinically effective pre/postconditioning mimetic agent, the known inhibitory effect of cyclosporine on the mPTP offers much promise. When administered at the time of primary PCI, lessened creatinine kinase release and smaller CMR-derived IS at 5 days (37 versus 46 g of tissue) in patients who received cyclosporine77 support the critical role of the mPTP in reperfusion injury. These promising results are undergoing more rigorous testing in a much larger scale, multicenter trial.

Similar to the earlier-discussed remote preconditioning studies, there has been keen interest in the application of remote postconditioning protocols to STEMI patients before arrival in the cardiac catheterization laboratory for primary PCI. Although there have been numerous studies of remote ischemic conditioning (mostly preconditioning) in the cardiac surgical setting,18,19 there are insufficient data in the STEMI setting at this time. Our systematic review and meta-analysis of postconditioning for primary PCI identified only 2 RCTs, as seen in Figures 3 and 4. In a well-designed, RCT study from Denmark78 using prehospital remote ischemic conditioning (perconditioning), myocardial perfusion imaging–derived estimates of myocardial salvage and IS failed to achieve the study’s primary end point when analyzed as intention to treat. However, consistent with the majority of clinical studies of remote postconditioning in nonacute clinical venues, there was a trend toward reduced biomarker evidence of myocardial necrosis. This study also highlights the above-noted issues surrounding the precision and timing of ancillary imaging in this specific setting.

In summary, the outcome of attempting to effect the translation of this most potent and basic cardioprotective response to the clinical environment has been somewhere between frustrating and disappointing.26,79 The frustration stems from misperceptions regarding the additional time required for the ischemic preconditioning stimulus during elective or emergent PCI in the non-STEMI setting and the so what response to the many reproducible studies demonstrating significant reductions in post-PCI biomarker release. The absence of evidence of a treatment effect is not the same as evidence for the absence of a treatment effect, and we contend that, at least for ischemic preconditioning, additional opportunity exists for demonstration of improvement in clinical outcomes in high-risk subsets of patients undergoing PCI. The disappointing lack of consistency, as well as the paucity of nonsurrogate measures of

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD [95% Conf. Interval]</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freisies</td>
<td>0.423 [-0.084, 0.931]</td>
<td>39.41</td>
</tr>
<tr>
<td>Lomborg</td>
<td>0.354 [-0.377, 0.026]</td>
<td>22.48</td>
</tr>
<tr>
<td>Sorensen</td>
<td>0.120 [-0.330, 0.570]</td>
<td>20.77</td>
</tr>
<tr>
<td>Tarantini</td>
<td>0.546 [-0.079, 1.001]</td>
<td>20.51</td>
</tr>
<tr>
<td>Thurye</td>
<td>-0.223 [-1.196, 0.750]</td>
<td>17.92</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.37 [-0.73, 0.01]</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Figure 4.** Forest plot for studies shown in Figure 3. There is, overall, only a borderline statistically significant reduction in biomarker-assessed infarct size with postconditioning in 16 (14 direct, 2 indirect) randomized controlled trials of the efficacy of postconditioning during primary percutaneous coronary intervention. SMD indicates standardized mean difference.

**Figure 5.** Meta-analysis of randomized clinical trials using cardiac magnetic resonance (CMR) estimates of infarct size. Significant heterogeneity of treatment effect (standardized mean difference in CMR-estimated size of infarct size) exists across the 5 trials. CI indicates confidence interval; and SMD, standardized mean difference.
Clinical benefit in the clinical postconditioning literature, is of concern given that the STEMI setting, the highest risk setting in clinical cardiology, represents the greatest potential for benefit. Although it may be true that the observations in animal model(s) are simply not translatable to the clinical situation, we doubt this simplistic explanation. More likely, the disappointment in the clinical realm is the result of uncertainty on the correct postconditioning stimulus, the absolute mandate for application of this adjunct during the first several minutes of the reestablishment of flow in the previously occluded artery, uncertainty in the measurement of the duration of the index ischemia, and, of course, the failure to intervene within what seems to be an even narrower window of opportunity than for PCI, in general. Given the potential to minimize the adverse sequelae of uncontrolled reperfusion, we advocate for a more concerted effort to conduct large, simple randomized trials in real-world settings. The large stems from the need to acquire a study sample with robust statistical power to observe differences confidently between treated and control groups in clinically relevant outcomes, whereas the simple stems from the need to observe such differences without intensive logistical, laboratory, or technological requirements. The beauty of ischemic conditioning derives from its universality and the directness of its effect. The transition from laboratory to clinic will rest, as it always does in clinical medicine, on the identification of the appropriate patient (eg, large anterior wall myocardial infarction, the right time; a duration of index ischemia <4 hours, and the right treatment protocol; and direct versus remote conditioning with a standardized set of inflation-deflation cycles). To date, ineffective translation of an extensive body of experimental knowledge to the acute myocardial infarction setting in humans reflects our still-limited understanding of the biological pathways, kinetics, and modifiable elements of ischemic conditioning in humans.

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Disclosures
None.

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35. Downey JM, Cohen MV. We think we see a pattern emerging here. Circulation. 2005;111:120–121.


**Key Words:** ischemic preconditioning  ■ ischemic postconditioning