Over the past decade, the therapeutic strategies for acute myocardial infarction have changed considerably. Progress in experimental models, as well as noninvasive myocardial imaging techniques, has identified myocardial reperfusion injury as a significant contributor to the final infarct size in human patients. Following 3 decades devoted to the improvement of reperfusion therapy, recent major advances in myocardial protection after reperfusion slowly move the attention from the vessel to the muscle. In the past 20 years, several pharmacologic treatments or techniques applied at early reperfusion have been tested in experimental models and in the clinical setting. Numerous promising therapies in experimental models have failed to show significant benefit in the clinical realm. But to date, ischemic postconditioning applied at the onset of reperfusion is among the most promising therapies to treat reperfusion injury in myocardial infarction patients, with a 35% significant reduction of final infarct size in small groups of patients and different settings. However, clinical evidence in large population studies is still lacking for their widespread usage in the catheter laboratory at the time of reperfusion. After a brief review of the underlying molecular mechanisms of ischemic postconditioning, this review will focus on the clinical studies assessing the postconditioning effect in STEMI patients and review the findings and explore the future of this technique. (Circ J 2013; 77: 1123–1130)

Key Words: Acute myocardial infarction; Ischemic postconditioning; Magnetic resonance imaging; Reperfusion

Therapeutic strategies in acute ST-elevation myocardial infarction (STEMI) patients prior to reperfusion, during reperfusion in the cardiac catheterization laboratory with primary percutaneous coronary intervention (PPCI) and after reperfusion have evolved considerably in the past decade. Both the recommended medications given to patients and the angioplasty procedures are constantly evolving, as illustrated by the recent changes in guidelines. These changes have been associated with significant reductions in cardiac death and cardiovascular morbidity. Most of the progress has been made on ischemia time reduction, coronary thrombosis treatment and prevention, and left ventricular remodeling. Despite this improvement, coronary artery disease remains the leading cause of death in western countries, with a mortality rate near 10% at 1 year for all acute myocardial infarction (AMI) patients. Also, one of the main consequences of infarct size, ischemia-related heart failure, is becoming more frequent.

Steadily, the new frontier in the therapeutic management of AMI is moving from the vessel to the muscle. One of the new therapeutic frontiers in STEMI patient management is the field of infarct size reduction and especially myocardial reperfusion injury. The myocardial reperfusion injury phenomenon was described in experimental models of MI. It causes additional damage to the acutely reperfused myocardium, accounting for up to 40% of the final size.

In human clinical studies, this phenomenon has been brought to light not only by trials aiming at infarct size reduction, but also by the progress in noninvasive cardiac imaging tools. These imaging tools allow the visualization and precise measurement of infarct size, myocardial hemorrhage, myocardial edema and microvascular obstruction, essential components of reperfusion injury. All those different components have been associated with detrimental myocardial remodeling, ventricular arrhythmias and adverse outcomes in MI patients. Nowadays, these techniques enable more precise analysis of different reperfusion strategies to reduce infarct size and reperfusion injury.

Ischemic postconditioning performed at the onset of reperfusion either with a pharmacological agent or by mechanical means has been one of the most explored reperfusion injury-limiting therapeutic techniques. It has a strong and extensive experimental background, and has been tested in several clinical trials. The results from those clinical trials are consistent with a significant reduction in the final infarct size, even if a few recent trials have failed to show significant benefit.
In this review, our objective is to provide a critical summary of the underlying mechanisms, review the clinical translation and evidence, and discuss the future for ischemic postconditioning in “real world” STEMI patients.

**Signaling Pathways Involved in Ischemic Postconditioning**

**Original Description**

Since Zhao’s first report on ischemic mechanical postconditioning in 2003 showing the benefits of postconditioning on infarct size,\(^{14}\) it has been cited more than 600 times and generated a lot of research and debate.

Vinten-Johansen’s group was the first to describe the concept of postconditioning, reporting that brief episodes of ischemia (30 s repeated 3 times) or “stuttering reperfusion” performed just at the onset of reperfusion following a prolonged ischemic insult significantly reduced infarct size by 40% compared with controls.\(^{13,14}\) Those results obtained with postconditioning were comparable to those obtained with preconditioning, a cardioprotective procedure that had been described 17 years earlier.\(^{15}\)

In this same experimental study, the authors found that postconditioning also significantly reduced myocardial edema and the accumulation of polymorphonuclear neutrophils in the same area by reducing P-selectin on the coronary vascular endothelium.\(^{14,16}\) Therefore, ischemic postconditioning also had anti-inflammatory properties, which is of interest considering the significant role of inflammation in the hours and days following MI and its involvement in adverse cardiac remodeling.\(^{17}\)

In a recent review, Heusch clearly summarized how ischemic postconditioning interacts with various cellular pathways in order to limit myocardial damage following reperfusion.\(^{18}\) Those pathways, shown in Figure 1, are the Reperfusion Injury Salvage Kinase (RISK), the Survival Activating Factor Enhancement (SAFE) pathways and nitride oxide (NO) derivates. Cyclosporin A directly prevents the mPTP opening by inhibiting cyclophilin D, a key molecular component of the mPTP. Thus, through different pathways, ischemic postconditioning exerts a significant cardioprotective effect by limiting the injury induced by reperfusion.

**Figure 1.** Intricate ischemia-reperfusion injury mechanism resulting in myocardial infarction, and the cardioprotective effect of postconditioning. Myocardial infarction results first from ischemic stress for which the principal drivers of infarct size are the size of the myocardial area at risk, the duration of ischemia and the presence of coronary collateral circulation to the ischemic bed. All the mediators of reperfusion injury are planted during the ischemic phase. Brutal reperfusion results in a cascade of events that seem to converge on the opening of the mitochondrial transition pore (mPTP), which results in the irreversible destruction of the cardiomyocyte. Ultimately, reperfusion injury accounts for up to 40% of the infarct size. Ischemic postconditioning, either mechanical (brief repeated episodes of ischemia applied early after the onset of reperfusion) or pharmacological (substance given immediately before reperfusion such as cyclosporine A), has a cardioprotective effect by interacting with the Reperfusion Injury Salvage Kinase (RISK), the Survival Activating Factor Enhancement (SAFE) pathways and nitrite oxide (NO) derivates. Cyclosporine A directly prevents the mPTP opening by inhibiting cyclophilin D, a key molecular component of the mPTP. Thus, through different pathways, ischemic postconditioning exerts a significant cardioprotective effect by limiting the injury induced by reperfusion.
Postconditioning in STEMI

The pattern of mechanical ischemic postconditioning was also determined in rat and rabbit models of myocardial ischemia-reperfusion in which 3 cycles of mechanical postconditioning applied over the first minute of reperfusion optimally reduced infarct size. The extension of the postconditioning algorithm to 6 cycles over the first 2 min of reperfusion did not further reduce infarct size.

The timing of ischemic postconditioning compared with that of ischemia, but also of reperfusion onset, appeared to be critical in experimental models. Applying postconditioning after a short index ischemia was ineffective in a rat model. In the same way, it was initially shown that there was a short period of time following reperfusion to apply ischemic postconditioning and obtain its full cardioprotective effect. This dogma has recently been challenged by Roubille et al, who showed a persistent benefit of postconditioning as much as 90 min after reperfusion. This issue is important for clinical translation to human patients. First, it is not always technically easy to apply angioplasty postconditioning within the first minute of reflow, especially if postconditioning is applied after thrombus aspiration; in this regard, a prolonged window of opportunity could help a larger number of patients to benefit from this protection. Second, nearly 20% of STEMI patients display Thrombolysis In Myocardial Infarction (TIMI) flow of 2–3 on angiography at hospital presentation. It is currently unknown whether these STEMI patients with TIMI 2–3 flow may or may not benefit from “delayed postconditioning”. This question, currently under investigation by our group (the PRIME trial: ClinicalTrials.gov: NCT01483755) is of clinical interest, as it will provide insight into whether the infarct-sparing effects of postconditioning apply to all STEMI patients or only to the TIMI 0–1 subpopulation.

Another important aspect that has been explored in experi-

Figure 2. Different aspects of reperfusion injury explored by contrast-enhanced cardiac magnetic resonance imaging (MRI) in an acute anterior STEMI patient. Cardiac MRI performed in the first week following myocardial infarction enables assessment of myocardial edema using T2-weighted sequences (A, white arrows), myocardial hemorrhage using T2-star sequences (B, red arrow), first-pass myocardial perfusion (D) and microvascular obstruction on early (3 min) and late (10 min) gadolinium enhancement sequences (C, E, F, black arrows).
Applying Ischemic Postconditioning to STEMI Patients

The Right Endpoint in the Right Setting
In animal models of myocardial ischemia-reperfusion, the beneficial effect demonstration of a protective intervention requires the assessment and appropriate control of the major determinants of infarct size (ie, area at risk, collateral flow, duration of ischemia). The second requirement is accurate quantification of infarct size itself, the principal endpoint of ischemic microembolization, which could be potentiated by several angioplasty balloon inflations at the site of the index lesion during mechanical postconditioning. This could account for the negative results found by Freixa et al in a recent clinical trial. In an experimental model of ischemia-reperfusion, Skyschally et al recently showed that controlled microembolization interfered with mechanical postconditioning and induced additional damage.
postconditioning. These issues remain quite challenging in STEMI patients.

In order to accurately assess the effect of ischemic postconditioning, it is compulsory to use an infarct size quantification method that is robust, applicable to all patients and with good reproducibility. It is also necessary to study ischemic postconditioning in a clinical setting where the principal determinants of infarct size are adjusted for. Any clinical study not accounting for those determinants and with inaccurate principal endpoint choice will ultimately run the risk of negative results.33

The development of new, noninvasive imaging tools such as gadolinium enhanced cardiac magnetic resonance imaging (MRI) have considerably helped the purpose of demonstrating the benefits of cardioprotective techniques34–37 (Figure 2). However, the most used method of assessing infarct size has been myocardial enzyme release of total creatine kinase, creatine kinase muscle brain isoenzyme and troponin I.18

**Infarct Size Reduction With Mechanical or Pharmacological Postconditioning: Phase II Clinical Trials**

Two ischemic postconditioning protocols performed at the onset of reperfusion have been tested with success in clinical phase II trials (Figure 3). Other postconditioning protocols with remote conditioning have been tested in AMI,38 but that is not the focus of this review.

Between 2004 and 2007, our group was the first to perform proof-of-concept small-size phase II clinical trials showing that (1) ischemic postconditioning with 4×1-min cycles of angioplasty balloon inflation, each interspersed with 1-min periods of deflation and initiated within the first minute of re-opening the culprit coronary artery significantly reduced infarct size by 40% in a dog model of ischemia-reperfusion as described for the first time by Zhao et al.14 (B) In the first clinical postconditioning trial, ischemic postconditioning significantly reduced infarct size as assessed by the area under the curve (AUC) of creatine kinase (CK) release by 36% compared with controls.39 PTCA, percutaneous transluminal coronary angioplasty. (Adapted from Zhao et al14 and Staat et al39 with permission.)

**Figure 4.** Significant infarct size reduction effect of ischemic postconditioning transposed from experimental models to human patients. (A) Ischemic postconditioning applied at reperfusion significantly reduced infarct size on pathology by 40% in a dog model of ischemia-reperfusion as described for the first time by Zhao et al.14 (B) In the first clinical postconditioning trial, ischemic postconditioning significantly reduced infarct size as assessed by the area under the curve (AUC) of creatine kinase (CK) release by 36% compared with controls.39 PTCA, percutaneous transluminal coronary angioplasty. (Adapted from Zhao et al14 and Staat et al39 with permission.)

As shown in Figure 5, those results were confirmed in majority, by several small clinical trials (with total enrollments ranging from 25 to 118 patients) in STEMI patients; among these, 10 have confirmed that postconditioning via angioplasty balloon inflation/deflation significantly attenuates lethal reperfusion injury.

Taken together, these phase II clinical trials indicate that, on average, one-third of the infarcted myocardium can be preserved by application of a relatively simple protective strategy – postconditioning – at the time of reperfusion.31,37,39–48

**Integrating Postconditioning Strategies Into Clinical Practice**

Phase II trials have demonstrated that postconditioning reduces
There is a significant beneficial effect of postconditioning on infarct size, but this is not enough yet to get a clinical recommendation. However, it is interesting to compare the fate of ischemic postconditioning to that of thrombus aspiration, the latter having become current practice in the management of STEMI patients in the past 4 years. Only 1 significant clinical trial, the TAPAS trial, published in 2008 by Svilaa et al. was sufficient to establish this technique as routine in catheter laboratories. This large, open-label monocentric randomized study in over 1,000 STEMI patients showed that manual thrombus aspiration with an industry-specific catheter significantly improved myocardial blush grade (primary endpoint) compared with conventional PCI. Those results were soon backed up by clinical follow-up results of this initial cohort showing significant improvement in clinical outcomes after 1 year of follow-up. In less than 1 year, this concept was integrated into the management of PPCI STEMI patients, with approximately 70% of patients being treated with thrombus aspiration. What are the other underlying reasons for this rapid success in comparison with ischemic postconditioning that was reported before? Industry support and publicity, simple pathophysiological concept, broad application to STEMI patients, easy and logical integration into the PCI workflow, immediate gratification when extracting macroscopic thrombotic material and absence of side effects are the other reasons for the success of thrombus aspiration during PPCI. Those results were soon backed up by clinical follow-up results of this initial cohort showing significant improvement in clinical outcomes after 1 year of follow-up. In less than 1 year, this concept was integrated into the management of PPCI STEMI patients, with approximately 70% of patients being treated with thrombus aspiration.

What Is Preventing Us From Applying Ischemic Postconditioning to All STEMI Patients in Clinical Practice?

First and foremost, the absence of a large pivotal study with significant clinical endpoints holds in abeyance the advent of ischemic postconditioning in the catheter laboratory for routine STEMI patients’ management. Until a solid prospective randomized clinical study showing a significant benefit of ischemic postconditioning on clinical outcomes in STEMI patients is performed, there is currently no significant evidence supporting its systematic use in STEMI patients. The first study assessing the effect of ischemic postconditioning on clinical outcomes, the CIRCUS trial (NCT01502774), is underway and results should be presented in 2015. All the clinical trials that have been performed up to now, whether positive or negative (Figure 5), have only focused on surrogate endpoints (myocardial biomarker release, infarct size by cardiac MRI or SPECT, ST-segment regression) in relatively small samples of selected STEMI patients. There is a significant beneficial effect of postconditioning on infarct size, but this is not enough yet to get a clinical recommendation.

However, it is interesting to compare the fate of ischemic postconditioning to that of thrombus aspiration, the latter having become current practice in the management of STEMI patients in the past 4 years. Only 1 significant clinical trial, the TAPAS trial, published in 2008 by Svilaa et al. was sufficient to establish this technique as routine in catheter laboratories. This large, open-label monocentric randomized study in over 1,000 STEMI patients showed that manual thrombus aspiration with an industry-specific catheter significantly improved myocardial blush grade (primary endpoint) compared with conventional PCI. Those results were soon backed up by clinical follow-up results of this initial cohort showing significant improvement in clinical outcomes after 1 year of follow-up. In less than 1 year, this concept was integrated into the management of PPCI STEMI patients, with approximately 70% of patients being treated with thrombus aspiration.

What are the other underlying reasons for this rapid success in comparison with ischemic postconditioning that was reported before? Industry support and publicity, simple pathophysiological concept, broad application to STEMI patients, easy and logical integration into the PCI workflow, immediate gratification when extracting macroscopic thrombotic material and absence of side effects are the other reasons for the success of thrombus aspiration during PPCI. All of this despite questioning of thrombus aspiration benefit by recent clinical trials and the absence of significant effect on infarct size.

There are many steps to climb before ischemic postconditioning, an academic-driven research effort, becomes part of the routine management of STEMI patients. As stated previously, the main step is clinical demonstration of its efficacy on clinical outcomes. Other questions will have to be addressed,
Conclusion

First developed and demonstrated in animal models of ischemia-reperfusion, ischemic postconditioning, either with a pharmacologic agent or with sequential short reocclusions of the culprit coronary artery, has emerged as a promising therapeutic technique to treat myocardial reperfusion injury. However, the complex mechanisms involved and the rapid evolution of therapeutic strategies in acute STEMI patients that could interfere with the postconditioning effect have not allowed us to apply this therapy to all STEMI patients. Ongoing phase III trials will provide important insight into the role of ischemic postconditioning as a clinically relevant cardioprotective strategy.

References


