In 1986, Murry et al.1 made the landmark observation that brief, nonlethal episodes of myocardial ischemia paradoxically precondition the heart and profoundly reduce infarct size caused by a subsequent, more sustained ischemic insult. This concept of endogenous cardioprotection was, in subsequent years, expanded to encompass the paradigms of postconditioning (with the protective stimulus applied to the heart at the time of reperfusion) and remote conditioning (in which the protective trigger is applied at a remote site, either before, during, or immediately on relief of sustained myocardial ischemia).2–10 Not surprisingly, considerable effort has been invested in substantiating essential criteria for the successful implementation of postconditioning include the appropriate choice of patients (ie, those with large risk regions and negligible collateral flow), timely application of the postconditioning stimulus (immediately on reperfusion), together with proper choice of end points (infarct size, with concomitant assessment of risk region). Remote conditioning has been applied in planned ischemic events (including cardiac surgery and elective percutaneous coronary intervention) and in ST-segment-elevation myocardial infarction patients during hospital transport. Controversies with regard to efficacy have emerged, particularly among surgical trials. These disparate outcomes in all likelihood reflect the remarkable heterogeneity within and among studies, together with a deficit in our understanding of the impact of these variations on the infarct-sparing effect of remote conditioning. Ongoing phase III trials will provide critical insight into the future role of postconditioning and remote conditioning as clinically relevant cardioprotective strategies. (Circ Res. 2013;113:439-450.)

Key Words: myocardial infarction ■ myocardial ischemia ■ ischemic postconditioning ■ remote conditioning ■ reperfusion
the infarct-sparing effect of preconditioning, postconditioning, and remote conditioning in multiple models and species, and in gaining insight into the molecular mechanisms responsible for conditioning-induced cardioprotection. The current challenge—and, indeed, the current mandate—is to capitalize on this wealth of knowledge and exploit the favorable effects of myocardial conditioning to protect the human heart from ischemia-reperfusion injury.11–16

Despite its unquestionable efficacy in limiting myocardial infarct size, the widespread clinical applicability of preconditioning is limited by 2 inherent caveats: (1) preconditioning is, by definition, a pretreatment; and (2) involves the direct and intentional application of brief ischemia to the heart. Emphasis and enthusiasm has, therefore, shifted to efforts aimed at the clinical translation of postconditioning (more amenable to real-world patient care in which treatment is initiated at reperfusion) and remote conditioning (in which protection is initiated by a peripheral and, presumably, benign stimulus). Accordingly, our goals in this review are to provide a critical summary of the progress toward, opportunities for—and caveats to—the successful translation of postconditioning and remote conditioning from the laboratory to the clinic.

Postconditioning: A Paradigm for the Treatment of Lethal Reperfusion Injury

Using the anesthetized canine model, Zhao et al2 demonstrated that postconditioning (ie, brief cycles of ischemia-reperfusion applied immediately after reopening the culprit coronary artery) could reduce myocardial infarct size by 30% to 40%. These results are consistent with the long-held hypothesis that lethal reperfusion injury represents an important component of the final irreversible damage to the heart. In addition, these data underscore the important concept that, in the reperfusion era, final myocardial infarct size is the net result of a 2-component insult: the first (well-accepted) related to ischemia and the second (less known) secondary to reperfusion.17–19 In the ensuing years since this first report by Zhao et al,2 infarct size reduction with postconditioning has been described in most (but not all) experimental studies20 and, despite the lack of complete consensus,21–24 has emerged as a promising cardioprotective intervention.20,26–28 Moreover, the endogenous protection afforded by postconditioning is not limited to heart and can be applied to treat global or regional ischemia-reperfusion injury in other organs or tissues.29–32 Our current focus is, however, specifically on patients with ST-segment–elevation myocardial infarction (STEMI; ie, the population in which most of the clinical evidence has been obtained with respect to postconditioning).

### Postconditioning in the Reperfusion Era: Statement of Need

Despite the fact that tremendous progress has been made throughout the past 3 decades in the treatment of patients with acute myocardial infarction (MI), there is still a need for improvement.33,34 Although decreasing, the incidence of acute MI and subsequent mortality remains unacceptably high, and ischemia-related heart failure is becoming more frequent.35,36 The epidemiology of cardiovascular risk factors, including obesity, diabetes mellitus, and smoking, together with the aging of the population, will exacerbate these concerns.37

During this 30-year period, reperfusion therapy has come to maturity. For example, significant progress has been made in shortening the delay from onset of chest pain to the time of reperfusion, both in terms of prehospital care and door-to-balloon time.38 Technical improvements in catheterization, stenting, distal protection, and thrombus aspiration have contributed to increase our ability to achieve optimal revascularization in most patients with STEMI. Meanwhile, large-scale trials have helped to refine the use of anticoagulants and antiplatelet agents, as well as statins, to better maintain vessel integrity and patency and prevent rethrombosis in the culprit coronary arteries. Finally, treatment with angiotensin-converting enzyme inhibitors, aldosterone antagonists, β-blockers, and statins has improved the long-term clinical outcome of acute MI patients, likely by limiting the incidence of arrhythmias and attenuating left ventricular (LV) remodeling and heart failure.

Although there is always scope for improvement, it could be argued, on the basis of these advances, that near-optimal management of patients with cardiovascular disease has been realized in the majority of cases. Importantly, however, none of the aforementioned treatments currently used in patients with STEMI have been shown to protect the myocardium from ischemia-reperfusion injury. In other words, although management of the culprit vessel in acute MI is near-optimal, treatment of the acutely injured, ischemic-reperfused myocardium is neglected or absent. The prognosis of patients with STEMI is highly dependent on outcomes directly related to infarct size, namely adverse LV remodeling and heart failure. Further favorable effects on morbidity and mortality can, therefore, be anticipated by targeting and treating ischemia-reperfusion injury. Protection of ischemic-reperfused myocardium warrants attention and therein lies the niche for postconditioning.

### Reduction of Infarct Size With Postconditioning: Proof-of-Concept Clinical Evidence

Proof-of-concept clinical trials have demonstrated that postconditioning can reduce infarct size in patients with STEMI. The first clinical evidence in support of the infarct-sparing effect of postconditioning was reported by Staats et al29a; four 1-minute cycles of angioplasty balloon inflation, each interspersed with 1-minute periods of deflation and initiated within the first minute after reopening of the culprit coronary artery, reduced infarct size by 34%. Twelve small clinical trials (with total enrollments ranging from 25 to 118 patients) have been published to date in patients with STEMI; among these, 10 have confirmed that postconditioning via angioplasty balloon inflation/deflation significantly attenuates lethal reperfusion injury (Figure 1).38 Importantly, Thibault et al40...
demonstrated that this infarct size reduction was maintained at 6 months after MI and was associated with a significant improvement of contractile function in the reperfused territory. Comparison of all positive phase II clinical studies suggests 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.

Integrating Postconditioning Strategies Into Clinical Practice
Phase II trials have demonstrated that postconditioning reduces infarct size in patients with STEMI. However, before postconditioning can be implemented in daily clinical practice, several issues must be addressed, which may have the potential to impact the benefit that patients with STEMI might ultimately derive from this intervention. These issues include (1) the effect of postconditioning on other facets of reperfusion injury, (2) methodological and technical constraints, (3) choice of appropriate end points, (4) the time window for protection, (5) the modalities of reperfusion therapy, (6) comorbidities and cotreatments, and (7) the relative roles of ischemic versus pharmacological postconditioning.

Other Facets of Reperfusion Injury
As mentioned earlier, the only established benefit of postconditioning in patients with STEMI is the attenuation of lethal reperfusion injury and reduction of infarct size (Table 1). The effect of postconditioning on other facets of reperfusion injury (including postischemic myocardial stunning, no reflow, and the incidence of reperfusion arrhythmias) is largely unexplored. For example, although there are experimental data suggesting that postconditioning does not improve myocardial stunning but significantly attenuates life-threatening reperfusion arrhythmias, this has not been investigated in clinical practice.26,41,42 It must, however, be acknowledged that myocardial stunning per se (ie, transient contractile dysfunction of viable myocardium after a reversible ischemic injury), in the absence of infarction, is not a major clinical concern.43 As for reperfusion-induced ventricular tachycardia or ventricular fibrillation, these arrhythmias can typically be managed by standard pharmacological therapies.

There is limited experimental evidence that postconditioning can limit the no-reflow phenomenon.44 In their initial description, Zhao et al2 reported that postconditioning could improve the maximal vasodilator response of the reperfused myocardium to acetylcholine, an index of endothelial function. Although microvascular obstruction has been associated with adverse LV remodeling and poor prognosis in acute MI patients, there is a need to establish whether postconditioning might blunt no reflow and improve microvascular perfusion in patients with STEMI.45,46 A phase II trial by the Ovize group is currently investigating this question.

Methodological and Technical Issues
In animal models of myocardial ischemia-reperfusion, the demonstration of the beneficial effect of a protective
intervention requires (1) assessment and appropriate control of the major determinants of infarct size (area at risk, collateral flow, and duration of ischemia), and (2) accurate measurement of infarct size itself. These issues remain quite challenging in patients with STEMI.

It is clear from experimental work that collateral blood flow to the at-risk myocardium is a major determinant of infarct size. For the purpose of this review, we conducted a new, retrospective analysis of previous postconditioning trials by the Ovize group and compared infarct size in a (pooled) subgroup of control patients with visible collateral flow at admission angiography (initially considered eligible but then excluded from the final analysis) to that of control patients without visible collaterals. As depicted in Figure 2, patients with angiographically visible collateral circulation display a 60% reduction of infarct size versus patients with no visible collaterals, demonstrating that patients with collateral perfusion obviously do not need additional protective intervention. In addition, including these patients into the study population would dilute the data and decrease the statistical power of the trial. Because collateral flow cannot be measured under the emergent conditions of acute MI, the only solution is, by design, not to include these patients into any infarct size reduction study (Table 1).

Area at risk is currently the more problematic question. It has long been known that the size of the area at risk is the major determinant of infarct size. As shown in Figure 3, infarct size in patients with STEMI is also dependent on the size of the area at risk. This figure highlights an additional important concept: the larger the area at risk, the greater the magnitude of protection afforded by postconditioning. Patients who benefit the most from postconditioning are those with a large area at risk, and thus, typically those with anterior wall infarcts (ie, in 85% of patients with an area at risk >35% of the total LV, the anterior wall is involved). In contrast, those with a small area at risk develop small infarcts, hence obtain little benefit from the protective intervention. However, the critical question is how can area at risk be assessed in the emergency situation of acute MI?

In animal models, the area at risk is defined as the area of hypoperfusion during the ischemic phase. This implies that risk region must be delineated before reopening the coronary artery. In clinical practice, only technetium-sestamibi administered before reflow, LV angiographic assessment of the extent of the hypokinetic/akinetic region and the Bypass Angioplasty Revascularization Investigation Myocardial Jeopardy Index Score allow this estimation. All these techniques have been used in postconditioning trials. Assessing area at risk after reopening of the culprit coronary artery has also been proposed using edema imaging by T2-weighted cardiac MRI and validated in animal models of infarction. In addition to the limitations introduced by the transient nature and unpredictable time-course of resorption of postreflow myocardial edema, the most critical problem is the influence of the protective intervention per se (ie, postconditioning) on the area at risk measurement. Zhao et al demonstrated in their initial report that postconditioning does reduce myocardial edema. Because infarct size is expressed as a function of area at risk, this introduces the potential to underestimate the benefit of any tested treatment. Indeed, Thuny et al have recently shown that angioplasty postconditioning reduces edema in patients with STEMI, suggesting that T2-weighted assessment of area at risk by MRI should not be used in infarct size reduction trials. In the interim, pending future technical optimization of these imaging techniques, application of the Bypass Angioplasty Revascularization Investigation Myocardial Jeopardy Index Score is expected to serve as a surrogate for area at risk.
Adverse cardiovascular events (including death, heart failure, and reinfarction, unstable angina, stroke, and need for revascularization) at 30 days or several months after acute MI. However, as postconditioning is an intervention specifically targeting myocardial viability, only end points related to infarct size and myocardial damage (such as LV remodeling, occurrence of heart failure, and death) should be used. There is no rationale or published evidence for the use of either recurrent ischemia or infarction, unstable angina, stroke, or need for revascularization; these latter events are related to the pathophysiology of coronary atherothrombosis (not to myocardial ischemia), and there are no current data to support the concept that postconditioning should attenuate their incidence. Indeed, including these criteria into a combined end point introduces the risk of lowering the statistical power of the study and missing the point.

Time Window for Protecting Against Reperfusion Injury
In the mouse model of MI, Roubille et al have recently challenged the long-standing dogma that postconditioning is only protective if applied during the first minute of reflow. Specifically, a persistent benefit of postconditioning was achieved even when the stimulus was applied as long as 90 minutes after reopening of the culprit artery. This issue is, for many reasons, of major clinical relevance. First, it is not always technically easy to apply angioplasty postconditioning within the first 60 seconds of reflow; in this regard, a prolonged window of opportunity would help a larger number of patients to benefit from this protection. Second, a large number of patients with STEMI display thrombolysis in myocardial infarction (TIMI) flow of 2 to 3 on angiography at hospital presentation, in all likelihood reflecting spontaneous reperfusion of the initially occluded coronary artery at some point between initial treatment and admission to the catheterization laboratory. In other words, reperfusion injury may have already occurred when the interventional cardiologist is prepared to apply the postconditioning protocol. It is currently unknown whether these patients with STEMI with TIMI flow of 2 to 3 may or may not benefit from delayed postconditioning (Table 1). This question, currently under investigation by the Ovize group in the Postconditioning Retardé au Cours de l’Infarctus du Myocarde Reperfusé study, requires further investigation.

Figure 3. Relationship between infarct size and risk region. A, Peak creatine kinase (CK) release (a surrogate for infarct size) is plotted as a function of the circumferential extent of abnormally contracting segments (abnormally contracting segments [ACS]; a surrogate for area at risk) in control and postconditioned (PostC) ST-segment–elevation myocardial infarction (STEMI) patients. In the control group, area at risk size is a major determinant of infarct size. Postconditioned patients developed smaller infarcts than controls; however, the magnitude of cardioprotection varied according to the size of the risk region, with the greatest benefit achieved in patients with the largest volume of at-risk myocardium (ie, typically those with left anterior descending occlusions). Data are pooled from References 39, 40, 49 and 50. B, Area at risk (ACS) and peak CK in control and postconditioned STEMI patients, presented as mean±SE. The size of the area at risk was comparable in the 2 groups, yet postconditioned patients developed significantly smaller infarcts. LV indicates left ventricle.

Choice of Appropriate End Points
Postconditioning is, first and foremost, an intervention that reduces infarct size (Table 1). Accordingly, for clinical studies in which the primary end point is different (eg, contractile function), infarct size should nonetheless be measured to ensure the efficacy of postconditioning in the population under investigation. Cardiac enzyme release (creatine kinase or troponins), single-photon emission computed tomography imaging, or MRI (gadolinium hyper-enhancement) are straightforward and established methods.

For phase III trials, cardiologists typically report major adverse cardiovascular events (including death, heart failure, reinfarction, unstable angina, stroke, or need for revascularization) at 30 days or several months after acute MI. However, as postconditioning is an intervention specifically targeting myocardial viability, only end points related to infarct size and myocardial damage (such as LV remodeling, occurrence of heart failure, ventricular arrhythmias, and death) should be used. There is no rationale or published evidence for the use of either recurrent ischemia or infarction, unstable angina, stroke, or need for revascularization; these latter events are related to the pathophysiology of coronary atherothrombosis (not to myocardial ischemia), and there are no current data to support the concept that postconditioning should attenuate their incidence. Indeed, including these criteria into a combined end point introduces the risk of lowering the statistical power of the study and missing the point.

Time Window for Protecting Against Reperfusion Injury
In the mouse model of MI, Roubille et al have recently challenged the long-standing dogma that postconditioning is only protective if applied during the first minute of reflow. Specifically, a persistent benefit of postconditioning was achieved even when the stimulus was applied as long as 90 minutes after reopening of the culprit artery. This issue is, for many reasons, of major clinical relevance. First, it is not always technically easy to apply angioplasty postconditioning within the first 60 seconds of reflow; in this regard, a prolonged window of opportunity would help a larger number of patients to benefit from this protection. Second, a large number of patients with STEMI display thrombolysis in myocardial infarction (TIMI) flow of 2 to 3 on angiography at hospital presentation, in all likelihood reflecting spontaneous reperfusion of the initially occluded coronary artery at some point between initial treatment and admission to the catheterization laboratory. In other words, reperfusion injury may have already occurred when the interventional cardiologist is prepared to apply the postconditioning protocol. It is currently unknown whether these patients with STEMI with TIMI flow of 2 to 3 may or may not benefit from delayed postconditioning (Table 1). This question, currently under investigation by the Ovize group in the Postconditioning Retardé au Cours de l’Infarctus du Myocarde Reperfusé study, requires further investigation.
trial (PRIME; ClinicalTrials.gov: NCT01483755) is of both scientific and clinical interest, as it will provide insight into whether the infarct-sparing effects of postconditioning apply to all patients with STEMI or only the subpopulation with TIMI flow of 0 to 1.

Modalities of Reperfusion Therapy

One intriguing question is whether lethal reperfusion injury, and hence protection by postconditioning-like interventions, is dependent on the method used to reintroduce blood flow (thrombolysis versus coronary angioplasty). Obviously, angioplasty postconditioning cannot be applied when lysis is the chosen treatment. However, this question is relevant in the application of pharmacological postconditioning and important because thrombolysis remains the preferred reperfusion therapy in many countries. It is usually thought that reflow is achieved in a more gradual or smooth manner after thrombolysis than with balloon angioplasty. Although this remains to be demonstrated in humans, experimental evidence suggests that controlled reperfusion per se (using low pressure or low oxygen tension) might attenuate reperfusion injury.64,65

In this regard, Ghaffari et al66 have recently reported that administration of cyclosporine before thrombolysis provided no added benefit, that is, did not reduce infarct size nor improve clinical outcome, in patients with STEMI due to anterior descending coronary artery occlusion. Unfortunately, coronary angiography was performed in only 70% of patients, at 4 days after thrombolysis, and neither collateral flow nor area at risk was assessed in the study. Additional trials are, therefore, needed to assess whether pharmacological postconditioning can be applied when thrombolysis is used as the reperfusion therapy.

Two other conditions of reperfusion may influence the response to postconditioning: (1) thrombus aspiration, and (2) microembolization. Thrombus aspiration has become routine practice in patients with STEMI.67 Although several reports have shown beneficial effects of thrombus aspiration on infarct size, others report no effect on various parameters of reperfusion-induced myocardial injury and clinical outcomes.66–71 In clinical practice, the use of a thrombus aspiration device may require several minutes, thereby delaying the application of the postconditioning protocol and allowing some reperfusion injury to develop. Thus, in theory, thrombus aspiration might alter the efficiency of postconditioning: additional analyses or trials are needed to answer this question.

Distal embolization of athero-thrombotic debris dislodged as a consequence of dilatation and stenting of the culprit coronary artery lesion may represent a significant component of lethal reperfusion injury.72,73 In all trials conducted by the Ovize group, particular care was taken to apply the repeated inflations and deflations of the angioplasty balloon at low pressure and upstream of the culprit lesion to avoid inadvertent microembolization during the postconditioning procedure.39,40,49 In contrast, Freixa et al.74 who reported a detrimental effect of postconditioning on microvascular obstruction and infarct size, performed the postconditioning protocol at the site of the index lesion where the thrombotic mass is maximal. This maneuver has the potential to enhance thrombus dislodgement and, therefore, distal embolization, which in turn could exacerbate the final myocardial damage.75

Impact of Comorbidities and Concurrent Treatments

Comorbidities and concomitant medications may, in theory, modify both the tolerance of the heart to ischemia-reperfusion and the efficacy of cardioprotection achieved by postconditioning. In experimental models, the effects of increased age, diabetes mellitus, hypertension, and hyperlipidemia on myocardial tolerance to ischemia-reperfusion injury are equivocal.76 The clinical relevance of observations made in these models has been questioned,60 and there are no conclusive data on whether these comorbidities affect the tolerance to ischemia-reperfusion in patients with STEMI.

As for the response to a protective intervention, accumulating evidence indicates that aged, diabetic, obese, hypertensive, and hyperlipidemic animals display some resistance to ischemic postconditioning.76–87 The mechanism for this impaired responsiveness remains unknown. Moreover, there are no current data on whether this loss in efficacy also applies to postconditioning-mimetic drugs (ie, cyclosporine) that target downstream effectors such as the mitochondrial permeability transition pore. Whether patients have a variable response to ischemic postconditioning according to comorbidities remains unknown. This issue is potentially important, as most patients with STEMI display ≥2 cardiovascular risk factors and are comparatively older than the young adult animal models typically used in laboratory studies.39 The outcome of a recent meta-analysis of 10 European postconditioning trials suggested that male sex, young age (and direct stenting) may improve the response to angioplasty postconditioning;86,87 however, additional studies are required to substantiate this finding and interrogate the role of specific comorbidities on the response to postconditioning.

Some animal studies suggest that statins, angiotensin-converting enzyme inhibitors, and β-blockers may modify both infarct size and the response to ischemic postconditioning.89–92 These drugs have been established to improve clinical outcome and thus are standard of care for patients with STEMI. However, despite the possible effects of these concurrent treatments on infarct size, clinical trials have demonstrated that the infarct-sparing effect of angioplasty postconditioning is manifest with these agents on board.

Recent data suggest that antiplatelet agents may also modify infarct size. Specifically, observations made by in the Downey laboratory using 2 different animal models indicated that platelet P2Y12 receptor inhibitors had an infarct-sparing effect that was not explained by inhibition of platelet aggregation but, rather, may be because of upregulation of the signaling pathways involved in postconditioning.93 As a follow-up to this work, the Ovize group conducted a retrospective analysis of their postconditioning trials to examine whether clopidogrel was able to affect infarct size and modify the postconditioning-induced protection seen in patients with STEMI. In support of this concept, control patients who had received clopidogrel (but not glycoprotein IIb IIIa antagonists) displayed smaller infarcts. Moreover, the beneficial effect of clopidogrel was additive to that of postconditioning.94

Pharmacological Versus Ischemic Postconditioning

Although postconditioning, applied at reperfusion, has been shown to reduce infarct size, the administration of
pharmacological postconditioning mimetics may provide some clinical advantages. Despite the fact that the Ovize group never observed adverse effects with angioplasty post-conditioning, it is not always technically feasible and, as discussed previously, could carry a risk of microembolization if not performed appropriately. In contrast, the use of a safe drug as a postconditioning agent is fairly easy, provided it is available in an intravenous formulation and can be administered in a way to cover the time window for protection against lethal reperfusion injury. The Ovize group has reported that cyclosporine, administered as a single intravenous injection immediately before reperfusion, can reduce infarct size in patients with STEMI and Lønborg et al have recently provided similar evidence of cardioprotection. Various agents, tested in phase II trials before the advent of postconditioning, are being reevaluated, including adenosine (the Myocardial Protection with Adenosine during Primary Percutaneous Coronary Intervention in Patients with STEMI [PROMISE]; ClinicalTrials.gov: NCT00781404) and metoprolol (the Effect of Metoprolol in Cardioprotection during Acute Myocardial Infarction - Centro Nacional de Investigaciones Cardiovasculares trial [METROCARD-CNIC]; ClinicalTrials.gov: NCT01311700). New pharmacological agents are being developed specifically as postconditioning mimetics, and there is no doubt that the very active preclinical research in the field will soon yield novel compounds aimed at attenuating lethal ischemia-reperfusion injury.

A second logistic advantage of pharmacological postconditioning is that it could be used in clinical conditions where access to coronary artery is difficult or impossible. One such example is cardiac arrest, which may be considered as a condition of global ischemia-reperfusion with potential multi-organ damage. In a rabbit model of cardiac arrest, the Ovize laboratory recently demonstrated that cyclosporine could improve cardiac functional recovery and limit remote organ damage. The Ovize group is currently running a large-scale clinical trial (ClinicalTrials.gov Identifier: NCT01595958) to determine whether cyclosporine, administered at the onset of resuscitation, may prevent the postcardiac arrest syndrome and improve outcomes. Finally, one might speculate that maximal protection against ischemia-reperfusion injury will, in the future, be obtained by the combination of pharmacological agents and of ischemic plus pharmacological postconditioning.

Remote Conditioning: Protection at a Distance

In the classic paradigm of ischemic preconditioning, both the antecedent protective stimulus and the subsequent sustained ischemic insult are, by definition, applied in the same vascular territory (ie, brief periods of circumflex occlusion-reperfusion reduce infarct size in the circumflex bed, whereas, similarly, brief bouts of left anterior descending occlusion-reperfusion precondition the left anterior descending territory). However, in 1993, Przyklenk et al made the intriguing observation that brief regional ischemia rendered remote, naive myocardium resistant to infarction, an effect presumably “...mediated by factor(s) activated, produced or transported throughout the heart.”

After an initial period of skepticism, this concept of remote preconditioning was expanded beyond the prototype of intracardiac transfer of protection to encompass (1) other remote triggers; (2) other target organs; and (3) variations in the timing of the remote stimulus, with brief episodes of ischemia applied in kidney, liver, mesentery and skeletal muscle having been demonstrated to initiate a cardioprotective phenotype. Second, although our focus is on heart, multiple tissues and organs (including brain, kidney, liver, pancreas, intestine, and muscle flaps) are susceptible to ischemia-reperfusion injury and responsive to the favorable, protective effects of remote conditioning. Finally, pretreatment is not a requirement for efficacy: application of a remote ischemic stimulus during sustained coronary occlusion (remote perconditioning) and at the time of reflow (remote postconditioning) have both been shown to reduce myocardial infarct size. Despite the interest and importance of these aforementioned observations, the pivotal finding that elevated remote conditioning from laboratory curiosity to potential clinical relevance was provided by Kharbanda et al, who, using the pig model, revealed that brief periods of limb ischemia, achieved noninvasively by simple application of a tourniquet or blood pressure cuff on 1 or 2 limbs, served as a potent trigger for cardioprotection.

Do We Need Another Conditioning Paradigm?

Given the effort invested in the clinical application of post-conditioning, together with the encouraging outcomes obtained to date in patients with STEMI, one could ask: what unique features does remote conditioning bring to the field of cardioprotection? Focusing on remote conditioning triggered by inflation-deflation of a blood pressure cuff, the most compelling aspects of this paradigm are its simplicity and safety. Specifically, in contrast to postconditioning, direct manipulation of the culprit coronary artery and imposition of an additional ischemic burden on the heart are not required.

As discussed previously, cardioprotection in patients with STEMI remains a major unmet need. In this regard, there is emerging evidence for a role of remote conditioning (in particular, perconditioning applied during transport to hospital) in the treatment of this cohort. However, the majority of clinical studies conducted to date have focused on the application of remote conditioning in planned ischemic events (ie, on cardiac surgery and, to a lesser extent, in elective PCI). It could be argued that the development and implementation of novel cardioprotective strategies in these settings is not warranted, as postprocedure mortality rates are low (ie, in the order of 1% to 3% at 30 days after coronary artery bypass grafting [CABG]) and continue to decline. Nonetheless, the proportion of patients exhibiting postprocedural release of cardiac enzymes—a variable associated with poor short-term and long-term outcomes—has been estimated at 30% after elective PCI and 40% to 90% after CABG surgery, with 12% to 19% of CABG patients developing Q-wave or non-Q-wave infarction. These data demonstrate that, as with STEMI, there remains considerable scope for augmenting cardioprotection in clinical instances of planned ischemia-reperfusion.

Cardioprotection With Remote Conditioning: Proof-of-Concept Clinical Evidence

Three landmark phase II studies provided compelling proof-of-concept evidence for cardioprotection achieved via remote
conditioning. First, in patients undergoing elective CABG, Hausenloy et al.\textsuperscript{113} found a significant, 43% reduction in postoperative serum troponin T concentration in patients randomized to receive transient arm ischemia (three 5-minute inflations of a blood pressure cuff positioned on the upper arm) when compared with placebo-controls (blood pressure cuff positioned but not inflated). Similar results were described by Hoole et al.\textsuperscript{46} in patients undergoing elective PCI; postprocedural troponin T elevation was attenuated in the cohort assigned to undergo remote conditioning (three 5-minute periods of transient arm ischemia) versus controls. Finally, Bøtøk et al.\textsuperscript{55} demonstrated that four 5-minute cycles of arm ischemia, applied during ambulance transport, increased myocardial salvage in patients with STEMI. In all 3 settings (cardiac surgery, elective PCI, and STEMI), there is recent preliminary evidence of persistent benefit with remote conditioning.\textsuperscript{115-117} Taken together, these data may provide grounds for cautious optimism that remote conditioning may yield clinical benefit.

**Future of Remote Conditioning: Establishing the Determinants of Efficacy**

There are, at present, 25 published phase II trials that have investigated the clinical efficacy of remote conditioning.\textsuperscript{16} Among these, 13 reported statistically significant cardioprotection, 5 showed a positive trend that did not achieve significance (possibly because of small n values and inadequate statistical power), whereas the remaining 7 found either no significance (possibly because of small n values and inadequate statistical power), whereas the remaining 7 found either no benefit or exacerbated myocardial injury with remote conditioning (Figure 1). These disparate outcomes underscore the importance of establishing the criteria that impact the efficacy of this conditioning paradigm.

Of the 2 publications focused on patients with STEMI, both reported that remote conditioning reduces myocardial infarct size.\textsuperscript{35,111} Despite this early consensus, future trials investigating remote conditioning in this cohort should be designed with the understanding that efficacy will be affected by many of the factors discussed in detail for postconditioning and summarized in Table 1. For example, key issues will undoubtedly include an appropriate choice of end points (focusing on indices of myocardial damage), due consideration of the primary determinants of infarct size (risk region, collateral perfusion, and duration of ischemia), and potential confounding effects of comorbidities and concurrent medications—themes that will also be relevant to the future application of remote conditioning in elective PCI.

The current controversies lie primarily in the outcomes obtained in cardiac surgery, where recent failures have raised concerns and undermined enthusiasm for the application of remote conditioning.\textsuperscript{119-122} We propose that 2 interrelated issues contribute to these apparent discrepancies. The first is heterogeneity, both within and among protocols. For example, some studies enrolled only stable patients undergoing CABG, whereas others included valve surgeries, patients with unstable coronary disease, and high-risk patients (ie, double and triple valve surgeries, mitral valve surgery, and combined CABG and valve surgery).\textsuperscript{16,98,123-125} Attempting to draw conclusions from mixed populations is problematic, as it assumes that the effects of remote conditioning will be comparable among all cohorts—an assumption that has not been tested and may be flawed. Additional sources of variation among studies include the choice of anesthetic and cardioplegic agents, the inclusion versus exclusion of patients with diabetes mellitus, and the temporal aspects of the remote conditioning algorithm. Among these, the 2 most important confounders might potentially be the anesthetic regimen (in particular, the use of propofol),\textsuperscript{123,126} together with variability in the time at which the remote stimulus was applied (after induction of anesthesia but before the first surgical incision versus after the first incision but before cardiopulmonary bypass).\textsuperscript{120,121,123-125} However, this raises the second issue: we have limited insight into the consequences of this variability. In contrast to pre- and postconditioning, which underwent exhaustive and systematic preclinical investigation,\textsuperscript{127} our understanding of the biology of remote conditioning is derived from a relatively small number of basic science studies together with 1 recent report based on analysis of human cardiac biopsy samples.\textsuperscript{98,128} This deficit in knowledge hampers our ability to gauge the impact of administering propofol, varying the number of cuff inflations, applying the stimulus on arms versus legs and 1 limb versus 2, modifying the time interval between the remote stimulus and the onset of myocardial ischemia, etc, on the efficacy of remote conditioning. The future success of exploiting the cardioprotective properties of remote conditioning for clinical benefit may critically depend on the resolution of these fundamental issues.

**Next Step: Moving From Phase II to Clinical Outcome Trials**

Can postconditioning and remote conditioning provide benefit beyond initial cardioprotection and yield a sustained improvement in clinical outcome? A large-scale trial is currently underway to address this issue. The Danish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction-3 study (DANAMI-3; ClinicalTrials.gov Identifier: NCT01435408) will compare the combined end point of cardiac death, reinfarction, and heart failure among 3 groups of patients with STEMI submitted to conventional PCI (immediate stent implantation), angioplasty postconditioning, or primary PCI with deferred (48 hours) stent implantation. The Ovize group is conducting the Does Cyclosporine Improve Clinical Outcome In ST Elevation Myocardial Infarction Patients trial (CIRCUS; ClinicalTrials.gov: NCT01502774), the objective of which is to determine in a randomized, double-blind, placebo-controlled, multicenter trial, whether a single intravenous dose of cyclosporine, immediately prior to PCI reperfusion, reduces the incidence of the combined end point of total mortality, heart failure, and LV remodeling (defined as an increase in LV end-diastolic volume >15%) at 1 year postinfarction in a population of patients with anterior infarcts. Two additional phase III trials are focused on remote preconditioning in cardiac surgery: the Effect of Remote Ischemic Preconditioning on Clinical Outcomes in CABG Surgery trial (ERICCA; ClinicalTrials.gov: NCT01247545, with the combined end point of major cardiac and cerebral events) and the Remote Ischemic Preconditioning for Heart Surgery (RIPHeart-Study; ClinicalTrials.gov: NCT01067703, with the combined end point of all-cause mortality, nonfatal MI, and any new stroke and acute renal failure).\textsuperscript{129,130} Within the next 2 years, these and other studies will provide critical
insight into the fate of postconditioning and remote condition-
ing as clinically relevant cardioprotective strategies in patients with STEMI and cardiac surgery.

**Sources of Funding**

Clinical trials by the Ovize group39,40,49,50 were funded by the Program Hospitalier de Recherche Clinique research program of the French government.

**Disclosures**

Dr Przyklenk serves on the Scientific Advisory Board of Infarct Reduction Technologies, Inc. The other authors report no conflicts.

**References**


**Ovize et al Myocardial Conditioning**


48. Reimer KA, Jennings RB. The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest. 1979;40:633–644.


Myocardial Conditioning: Opportunities for Clinical Translation
Michel Ovize, Hélène Thibault and Karin Przyklenk

Circ Res. 2013;113:439-450
doi: 10.1161/CIRCRESAHA.113.300764
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/113/4/439

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/