This Review is part of a thematic series on **Preconditioning**, which includes the following articles:

- Ischemic Preconditioning in Isolated Cells
- The Preconditioning Phenomenon: A Tool for the Scientist or a Clinical Reality?
- The Late Phase of Ischemic Preconditioning
- Myocardial $K_{ATP}$ Channels in Preconditioning

**The Preconditioning Phenomenon**

*A Tool for the Scientist or a Clinical Reality?*

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**Abstract**—The possibility that an innate mechanism of myocardial protection might be inducible in the human heart has generated considerable excitement and enthusiastic research. The potential to enhance myocardial resistance to ischemic injury in patients suffering the consequences of coronary artery disease has led to studies with more direct clinical relevance. However, in common with many other areas of clinical interest based on advances in basic scientific understanding, early enthusiasm may be disproportionate to ultimate therapeutic significance. There can be little doubt that our understanding of the mechanisms underlying the pathogenesis of ischemia-reperfusion injury has been enhanced significantly by the plethora of research stimulated by interest in endogenous myocardial protection. Direct extrapolation of observations in the laboratory to the cardiology clinic or operating theater is tempting but should be avoided. The results of recent clinical experiments that suggest that preconditioning can protect against ischemia, although encouraging, should be interpreted cautiously, with particular attention to the limitations of the end points available. A reasoned evaluation of recent research should prevent unrealistic expectations and allow improved design of future trials so that this potent adaptive phenomenon can be exploited to its maximum potential. *(Circ Res. 2000;87:543-550.)*

**Key Words:** preconditioning n unstable angina n myocardial infarction n coronary angioplasty n coronary bypass surgery

The observation that serial brief episodes of ischemia with intervening reperfusion did not lead to progressive depletion of high-energy phosphates in the canine myocardium led the same group of investigators to examine the response of hearts “preconditioned” with short bursts of sublethal ischemia to a sustained ischemic insult. Their finding that the onset of infarction was delayed in pretreated hearts, with a significant reduction in ultimate myocardial infarct size, resulted in recognition of the concept of ischemic preconditioning, with a proposal that the mechanism responsible involved a slowing of consumption of high-energy phosphates during the prolonged ischemic insult. Since then, this marked limitation of infarction induced by antecedent brief periods of ischemia has been demonstrated in every animal species studied. Subsequent studies have suggested that protection against other end points of injury such as myocardial stunning and reperfusion arrhythmias may also be possible. Characterization of the time frame of protection has demonstrated a biphasic pattern with an initial (“classical” or early) powerful phase that lasts 1 to 2 hours after the preconditioning stimulus and a subsequent “second window” 12 to 72 hours later. It is also important to note that in experimental studies ischemic preconditioning has been found to limit infarction when the duration of the sustained ischemic insult is ~30 to 90 minutes, but is ineffective when this period is extended to 3 hours. This temporal limitation of ischemic preconditioning implies that the protection is only observed when prolonged ischemia is followed by timely reperfusion.

The potential for clinical application of such a powerful protective phenomenon has generated enormous interest in identification of the underlying intracellular signaling path-
ways, with the ultimate aim of pharmacologically exploiting these mechanisms to develop therapeutic strategies that can enhance myocardial tolerance to ischemia-reperfusion injury in patients with coronary artery disease. Extensive research over the past 15 years has gone a long way in elucidating a number of membrane receptor–linked cellular triggers, intracellular signaling cascades, and potential cytoprotective end-effector proteins that may be involved in mediating the protective effects of ischemic preconditioning. However, the application of these findings to the clinical setting depends primarily on proof of safety and efficacy when compared with other strategies of myocardial protection and secondarily on identification of well-defined cohorts of patients who stand to benefit from pretreatment with such cardioprotective agents. Several important issues need to be addressed and are discussed below.

**Does Preconditioning Occur in the Human Heart?**

Ethical considerations restrict the nature of experimental work on the human heart and thereby render the evidence indirect. Numerous approaches have, to some extent, circumvented this problem. Studies in cells derived from isolated human ventricular myocytes and in isolated atrial trabeculae obtained at the time of cardiac surgery suggest that protection can be induced in vitro using metabolic and functional end points, respectively. Moreover, using the same in vitro models, it has been demonstrated that the mechanisms of protection in human tissue closely resemble those observed in many animal species, namely, the involvement of adenosine as an important trigger, protein kinase C as an intermediate intracellular messenger, and the ATP-dependent K⁺ (K<sub>ATP</sub>) channel as a potential end-effector protein.

In the clinical setting, there is some evidence to suggest that preconditioning may occur naturally in patients with coronary artery disease. Patients suffering angina before a myocardial infarction (MI) have a better in-hospital prognosis; a reduced incidence of cardiogenic shock, congestive cardiac failure, and life-threatening ventricular arrhythmias associated with reperfusion; and smaller infarcts as assessed by release of cardiac enzymes. Follow-up studies have suggested that in patients with preinfarction angina, long-term survival is also improved as compared with patients who are asymptomatic before infarction. Whether the protection conferred to these patients as a result of their preceding ischemic symptoms represents a form of myocardial adaptation similar to ischemic preconditioning remains a subject of debate. On the one hand, the issue of enhanced collateral development in patients with preceding anginal symptoms remains unresolved. Another equally attractive hypothesis, although not mutually exclusive from the mechanisms underlying ischemic preconditioning, is facilitation of more rapid reperfusion of the infarct-related artery after thrombolysis in patients with preinfarction angina. This hypothesis is based on the known inhibitory effects of adenosine, released during the brief periods of preinfarction ischemia, on platelet aggregation after activation of A<sub>2</sub> receptors on platelet membranes, which has been suggested to modify thrombus formation and thereby promote earlier reperfusion after thrombolysis. Indeed, in anesthetized open-chest dogs, brief periods of ischemia before a long ischemic insult attenuates platelet-mediated thrombosis and improves vessel patency, and this effect is abolished by inhibition of adenosine receptors.

The phenomenon of “warm-up angina,” in which patients complain that their anginal symptoms are worse in the morning but improve during the course of the day, has been the subject of research over the past few years. This work has provided evidence for increased efficiency of myocardial metabolism, in terms of reduced oxygen consumption at a given workload and a reduction in anginal symptoms and ST-segment changes, during a second period of either exercise or angina resulting from pacing-induced tachycardia. These favorable changes were not accompanied by recruitment of collateral vessels, as evidenced by similar coronary and great cardiac vein blood flow measurements. Similarly, a reduction in electrocardiographic evidence of silent ischemia during successive periods of exercise has been demonstrated. A recent study suggests that the degree of myocardial stunning after exercise-induced myocardial ischemia may also be attenuated if the patient had performed a preceding period of exercise 30 minutes earlier. Studies investigating the temporal profile of warm-up angina have demonstrated that the duration of this phenomenon is 1 to 2 hours after the first period of exercise, a time course that closely parallels that of classic ischemic preconditioning. Moreover, we have recently shown that in addition to immediate protection, patients with stable angina have improved exercise tolerance 24 hours after a period of exercise-induced myocardial ischemia, a finding that may represent delayed preconditioning. However, a recent study using a similar study protocol failed to show enhanced exercise tolerance 24 hours after a period of exercise, thereby arguing against delayed protection in this model. The reasons for the differences between these studies is not immediately obvious and requires further investigation.

These findings suggest that the warm-up phenomenon is at least partly due to metabolic adaptation of myocardium, which induces tolerance to subsequent ischemia, a process that closely resembles ischemic preconditioning. However, studies that have examined the cellular mechanisms mediating warm-up angina do not fully support this hypothesis. For instance, inhibition of adenosine receptors before exercise fails to abolish the warm-up phenomenon. Furthermore, investigation into the role of K<sub>ATP</sub> channels in mediating this form of myocardial adaptation has provided conflicting results. It is therefore not clear at this point whether the adaptation observed during repeated exercise is a representation of the preconditioning phenomenon or whether other mechanisms are involved. Furthermore, despite attempts by some investigators, a major role for recruitment of collateral vessels contributing to this phenomenon has not been ruled out.

**Myocardial Adaptation During Revascularization Procedures**

Percutaneous transluminal coronary angioplasty (PTCA) provides a unique opportunity to study the response of the human...
myocardium to brief periods of controlled ischemia and reperfusion. The procedure usually involves repeated intracoronary balloon inflations with intervening periods of perfusion, and in theory the first period of ischemia may enhance the myocardial tolerance to subsequent balloon inflations via classic ischemic preconditioning. Several recent studies have addressed this issue using various indices of myocardial ischemia including clinical, electrocardiographic, metabolic, and hemodynamic measurements. Most of these studies have shown that if the duration of the first balloon inflation is longer than a “threshold” of ≈60 to 90 seconds, all indicators of myocardial ischemia, including chest pain severity, abnormalities of left ventricular regional wall motion, ST-segment elevation, QT dispersion, ventricular ectopic activity, lactate production, and release of myocardial markers such as CKMB, are attenuated during subsequent balloon inflations, which provides evidence for myocardial adaptation induced by the first period of ischemia. As with many studies of ischemic preconditioning in humans, a major confounding factor during successive balloon inflations in PTCA studies is the acute recruitment of collateral vessels. However, studies that have controlled for this effect by angiographic grading of the collateral vessels, measurement of cardiac vein flow, changes in blood flow velocity in the contralateral coronary artery, and, more accurately, by assessment of intracoronary pressure-derived collateral flow index during successive balloon inflations have shown that although collateral recruitment occurs in some patients, it cannot fully explain the myocardial adaptation observed during repeated balloon inflations.

Investigation into the mechanisms underlying this rapid protection of the myocardium during PTCA has provided further support for a preconditioning-like effect. Blockade of KATP channels with oral glibenclamide before angioplasty abolishes the reduction in ischemic indices observed during subsequent balloon inflations, which implies a role for these channels in mediating this form of adaptation. This finding is supported by the observation that opening of these channels with nicorandil reduces the electrocardiographic indices of ischemia during coronary angioplasty. Furthermore, an important role has been demonstrated for adenosine in mediating myocardial adaptation during coronary angioplasty. Inhibition of adenosine receptors by bamiphylline or amiphylline abolishes myocardial adaptation during the second balloon inflation. Conversely, intracoronary infusion of adenosine before PTCA, independent of its vasodilatory effect, attenuates ischemic indices during the first balloon inflation. Two other recent reports have suggested a role for both opioid and bradykinin receptors in mediating myocardial adaptation during PTCA. These studies provide further evidence that myocardial tolerance to further ischemic episodes can be induced by preceding brief periods of ischemia and that this tolerance may be mediated by the same mechanisms as those involved in ischemic preconditioning in animal models.

However, recent experimental evidence has provided grounds for caution when interpreting the results of these PTCA studies, which have mostly used ST-segment elevation on the surface or intracoronary ECG as an end point reflecting the degree of myocardial ischemia, and its attenuation during successive balloon inflations as an indicator of enhanced myocardial resistance to ischemia. Although this assumption was supported by earlier experimental studies of repeated coronary artery occlusion in collateral-deficient pig and rabbit hearts, a recent study clearly indicates a dissociation between ST-segment changes on the ECG and myocardial protection in terms of infarct limitation. The finding of these authors, that the changes in ST-segment voltage during coronary artery occlusion may merely represent an epiphenomenon distinct from the cardioprotective effect of ischemic preconditioning, is particularly pertinent when evaluating or designing mechanistic studies using pharmacological agents to mimic or abolish the cellular signaling mechanisms of ischemic preconditioning. It is imperative that the influence of these pharmacological tools on the sarcolemmal KATP channels, which are thought to modulate ECG voltages, is clearly distinguished from their effect on the mitochondrial KATP channels, which have been proposed as a mediator of cardioprotection.

Possibly the most direct evidence for preconditioning in humans comes from studies that have examined the effect of preconditioning protocols in patients undergoing cardiac surgery in which resistance to global ischemia is assessed, a setting that is not confounded by changes in collateral recruitment. In this respect, we reported a prospective study examining the effects of a preconditioning protocol of 2 cycles of 3 minutes of global ischemia (induced by intermittently cross-clamping the aorta and pacing the heart at 90 bpm) followed by 2 minutes of reperfusion before a 10-minute period of global ischemia and ventricular fibrillation. Patients subjected to this protocol had better preservation of ATP levels in myocardial biopsies during a subsequent 10-minute global ischemic period. These metabolic changes were almost identical to those seen in dogs by Reimer et al. However, total myocardial ATP content may not reflect local turnover within subcellular compartments and certainly does not provide information about the efficiency of cellular metabolism in terms of ATP requirements. In a more recent study involving a larger group of patients, serum levels of troponin T were used as an indicator of myocardial cell necrosis. Using this end point, patients subjected to the same preconditioning protocol suffered less necrosis as determined by release of troponin T. Of considerable interest, however, was the finding that the ATP levels did not differ between preconditioned and control groups. This emphasizes the need for multiple end points to be used, especially in studies in which small differences in myocardial viability without overt clinical effects are expected.

On the other hand, studies that have used other cardioprotective strategies during the prolonged period of ischemia, such as hypothermia or cardioplegia, have not consistently demonstrated additional protection by ischemic preconditioning. For instance, the use of similar preconditioning protocols of one 3-minute episode of aortic cross-clamping before the onset of cardioplegic arrest failed to show any beneficial effects compared with the control group; in fact, the preconditioned group of patients had more creatine kinase release compared with case-matched controls. Similarly negative
results have been reported by another group.60 These divergent results have led to the hypothesis that in the setting of coronary artery bypass surgery, the additional protection conferred by ischemic preconditioning may only be demonstrable in cases in which a potential for suboptimal myocardial protection increases the risk of perioperative infarction.61 However, this hypothesis is not supported by recent studies that indicate improved myocardial preservation by ischemic preconditioning during coronary bypass or valve surgery despite optimal protection with hypothermia and cardioplegia.62,63 Resolution of these discrepancies is obviously required before brief antecedent ischemia can be advocated as a means of prophylactic therapy.

**Which Patients May Benefit?**

Although it would appear from the evidence outlined above that the human myocardium is amenable to preconditioning, this does not imply that clinical benefit will automatically follow. Prompt reperfusion will always remain the most effective method of infarct size limitation and is therefore the most important determinant of prognosis. Preconditioning, by virtue of delaying myocardial necrosis, prolongs the time window during which revascularization therapies can be effectively instituted. However, the use of brief antecedent ischemia as a means of prophylactic induction of this protection is not desirable or feasible in most circumstances. On the other hand, the use of pharmacological agents capable of mimicking the protective effects of preconditioning, in lieu of brief ischemia, may provide a more benign approach for eliciting cardioprotection. However, even with the development of pharmacological agents that may be capable of mimicking the protection, timing of administration remains a critical limiting factor.

First, deployment of pharmacological preconditioning strategies necessitates pretreatment; the pathophysiology of the preconditioning phenomenon dictates that the myocardium must be preconditioned before the onset of a potentially lethal ischemic insult. This depends on identification of a relatively well-defined cohort of patients who are at high risk of acute coronary occlusion and stand to benefit from preconditioning or from pretreatment with agents that trigger or augment myocardial preconditioning.

The acute coronary syndromes (ACSs) comprise a spectrum of pathophysiological conditions spanning unstable angina, non–ST-elevation MI, and acute ST-elevation MI. In patients with acute MI with persistent ST elevation, early reperfusion to re-establish epicardial blood flow is well established as the standard of care, be it with early fibrinolytic therapy or, where the facilities and expertise are available, with intravenous or oral nitrates, it is possible that the vasodilatory properties of nicorandil. As far as pharmacological preconditioning strategies are concerned, these patients are unlikely to benefit from such treatment, and their management should focus on early restoration of coronary artery patency and potential strategies to minimize reperfusion injury. On the other hand, non–ST-elevation ACSs, including unstable angina and non–Q-wave MI, mark the transition from stable coronary artery disease to an unstable state and constitute the leading cause of hospital admission in patients with coronary artery disease. This group of patients is at a high risk of progression to acute coronary occlusion, and >10% die or suffer a MI (or reinfarction) within 6 months, with about one half of these events occurring during the acute early phase.65

This cohort of patients with non–ST-elevation ACS forms a reasonably well-defined high-risk group that might benefit from pretreatment with agents that trigger or augment myocardial preconditioning over a period of several days or weeks and could therefore effectively maintain the myocardium in a protected or “preconditioned” state. A number of these patients who suffer a MI after unstable symptoms may be “naturally” preconditioned by their preceding ischemic episodes. Recent evidence, however, suggests that this natural protection is limited to those patients in whom the episodes of preinfarction angina occur during a narrow time window in relation to the infarct.20,21

Second, even when prior treatment with the pharmacological preconditioning agent is feasible, the duration of the protection afforded is limited. The temporal profile of the protective effects of preconditioning in humans is unknown but, according to experimental evidence in laboratory animals, it is unlikely to exceed 48 to 72 hours.66,67 Therefore, unless the onset of an ischemic event can be predicted with accuracy, repeated dosing with the potential preconditioning drug will be necessary in these high-risk patients to maintain the preconditioned state. Early experimental evidence suggested that the protective effects of classic ischemic preconditioning are lost after prolonged periods of repetitive ischemia68 or chronic pharmacological preconditioning with selective adenosine A1 agonists.69 However, recent encouraging evidence indicates that tachyphylaxis could be overcome by exploiting the prolonged time course of the second window of protection. Intermittent treatment of conscious rabbits with an optimal dosing regimen of pharmacological preconditioning with selective adenosine A1 receptor agonists maintains the animals in a preconditioned state over a period of several days and results in a significant reduction in infarct size.70,71

Very few studies have evaluated a protective role for pharmacological preconditioning strategies in patients with non–ST-elevation ACS. In this regard, a recent report suggests that opening of KATP channels with nicorandil, in addition to standard aggressive medical therapy for unstable angina, results in a significant reduction in the incidence of myocardial ischemic events and tachyarrhythmias.72 This may purely represent an anti-ischemic effect due to the vasodilatory properties of nicorandil. However, because the patients in this study were already on maximal antianginal therapy, and in particular a significant proportion were treated with intravenous or oral nitrates, it is possible that the protection observed in the nicorandil group, be it only using soft end points of myocardial injury, may at least partially be due to a preconditioning-like effect.73 These encouraging findings, coupled with very recent experimental evidence indicating that nicorandil specifically activates the mitochondrial rather than the sarcolemmal KATP channels in rabbit ventricular myocytes,74 provide a promising new approach to myocardial protection in patients with unstable angina.
Although the conditions of the majority of patients with non–ST-elevation ACS will stabilize with effective anti-ischemic medications, ~50% of such patients will require coronary angiography and revascularization because of failure of medical therapy assessed by recurrence of ischemic symptoms at rest or demonstration of provokable ischemia during stress testing. The optimal timing of revascularization procedures in patients with ACS is under debate, although recent evidence points to the benefit of early intervention. However, the complication rate associated with revascularization procedures in unstable patients is appreciably higher than that in patients with stable coronary artery disease. For example, emergency PTCA in patients with refractory unstable angina is associated with a periprocedural mortality rate of 1% to 3% and nonfatal infarction occurs in a further 6% to 10%, with a need for emergency surgery in up to 12%. The potential for and the time course of any protection conferred by preceding anginal episodes in this situation is not known, although some evidence suggests that unstable symptoms occurring in the 6 to 12 hours before PTCA may have a preconditioning-like effect. Conversely, the Thrombolysis in Myocardial Ischemia (TIMI) IIIB study suggested that emergency PTCA performed within 24 hours of enrollment was the most powerful predictor of periprocedural death and MI. Although the risk associated with the procedure diminishes if a patient is allowed to “cool off” and the plaque is at least partly healed, this longer waiting period carries the risk of progression to MI and death. These patients may therefore have the most to benefit from pretreatment with agents that mimic preconditioning or augment the protection afforded by naturally occurring ischemic preconditioning, thereby reducing the degree of myocardial injury in the event of periprocedural complications associated with PTCA. At the other end of the spectrum are patients with stable angina undergoing elective PTCA, who have a relatively low risk of complete coronary artery occlusion and MI (<5%). However, as more high-risk procedures are performed, and considering the potential benefits associated with this potent mode of cardioprotection, it is possible that application of pharmacological preconditioning agents may find a place routinely before elective angioplasty.

Similar complications may arise during cardiac surgery. In patients with unstable angina undergoing coronary artery bypass grafting (CABG), perioperative mortality rates of 3.7% and infarction rates of 9.9% have been reported, which are considerably higher than those associated with elective surgery. Even in patients with stable coronary artery disease, despite carefully controlled intraoperative ischemic periods and hypothermia, sensitive markers of tissue injury such as troponin T indicate that discrete necrosis occurs. Moreover, as surgeons undertake more complex and higher-risk operations, the need for better preservation methods increases. In a situation such as CABG, the administration of an agent before surgery that could enhance myocardial defenses would reduce susceptibility to focal necrosis during surgery and permit the extension of the intraoperative ischemic period. High-risk patients with poor preoperative left ventricular function, extensive coronary artery disease, or severe left ventricular hypertrophy could certainly benefit from the degree of protection were improved by invoking endogenous cellular adaptive mechanisms. The possibility that organ preservation before transplantation might be amenable to the same improved protection, as suggested by some experimental evidence, is also of significant interest. This might allow an extension of the “cold ischemic time” between harvesting and implantation, facilitating optimal matching of recipient to donor, as well as affording a potential improvement in early myocardial function.

What Are We Trying to Improve Upon?

It seems that techniques utilizing endogenous myocardial protection are suited to application in patients with unstable angina and non–Q-wave MI and in those undergoing planned procedures such as PTCA and CABG. In non-ST-elevation ACS there is a substantial risk of progression to acute MI or reinfarction and death. Development of effective medical therapies for these patients, including use of aspirin, heparin, nitrates, β-adrenergic receptor antagonists, and calcium channel antagonists, has markedly reduced these event rates. The more widespread use of more effective antithrombotic agents, such as low-molecular-weight heparin, and antiplatelet therapy with glycoprotein IIb–IIIa inhibitors are likely to result in further improved outcome in these patients. Furthermore, percutaneous coronary interventions are frequently used in these patients. Periprocedural complication rates in patients with non-ST-elevation ACS undergoing PTCA are higher than those in patients with stable angina but are still acceptable in view of the overall higher risk for adverse events in these patients. The introduction of intracoronary stents has further improved both the short-term and long-term outcomes as compared with PTCA alone. Ongoing studies of new angioplasty balloons, stent coatings, and optimal adjunctive antithrombotic therapies are likely to improve the success rate of these procedures even more and to further reduce the risk of death or nonfatal MI. The potential protection conferred by pharmacological preconditioning in this setting may add to the currently available means of reducing the complications associated with these procedures and result in improved outcome for the patients but must be viewed in the context of these existing protective strategies.

Similarly, in the surgical setting, effective strategies of myocardial preservation have already been developed, including the use of various cardioplegic solutions. In general, the rationale behind the use of cardioplegic techniques includes rapid diastolic arrest, membrane stabilization, hyperosmolarity (to prevent intracellular edema), acid buffering, and hypothermia. Additional strategies such as continuous coronary perfusion, warm instead of cold cardioplegia (to avoid cold injury), and the use of blood instead of crystalloid solutions (to improve oxygen delivery) have all added to the choices available to the cardiac surgeon. The potential use of endogenous myocardial protection must be seen in the context of these pre-existing efficacious techniques.

How Can We Measure Our Success?

Any clinical trial involving the use of a pharmacological agent designed to mimic the protection of ischemic preconditioning will have to demonstrate its value in terms of...
relevant clinical end points such as preservation of left ventricular function, attenuation of stunning, need for inotrope/balloon support, incidence of clinically detectable MI, left ventricular failure, and periprocedural death. However, studies so far have concentrated on low-risk patients with good preprocedural status who would be expected to do well in any event. The benefit derived from ischemic or pharmacological preconditioning in this group of patients is therefore likely to be marginal. In the studies of preconditioning during coronary angioplasty, the end points used are indirect markers of myocardial ischemia, namely ST-segment shifts on ECG, pain scores, and metabolic end points such as coronary sinus lactate levels during balloon inflations. Likewise, the end points used in surgical studies so far are “blunt tools” that provide us with indirect information with respect to myocardial viability and are no substitute for direct measurement of infarct size. Measurement of total myocardial ATP content is not universally accepted as a sensitive marker of cell viability, and the concept of a “critical” level of ATP, below which cell death occurs, is now known to be incorrect.\(^8\) If it were possible to measure subcellular levels of ATP within different compartments (such as the mitochondrial fraction) and thereby assess local turnover, then more useful information might be available. More sensitive and specific markers of myocardial injury and death are now available, and there is considerable interest in the use of serum troponin T (or troponin I) assays.\(^79\)\(^80\) However, although these surrogate markers of myocardial injury have been used as a means of providing evidence for the concept of preconditioning in the human myocardium or to demonstrate the safety and tolerability of various pharmacological preconditioning agents in low-risk patients, they are by no means a substitute for hard end points of clinical outcome. It is only with direct evidence for an improved clinical outcome after ischemic and/or pharmacological preconditioning, which is more likely to be achieved in studies conducted in high-risk groups of patients, that preconditioning treatments may become a clinical reality.

Conclusions and the Future
Fifteen years of extensive research and publication of in excess of 1500 papers in the field of ischemic preconditioning have vastly extended our understanding of the mechanisms underlying the pathogenesis of ischemia-reperfusion injury. There can be little doubt that the elucidation of the pathophysiology and the cellular mechanisms of the phenomenon of ischemic preconditioning has taught us the means of protecting the myocardium in the experimental setting. Clinical studies in this field, while fraught with limitations, have pointed to the fact that the human myocardium may respond in a way similar to that seen in the experimental laboratory and may be amenable to protection by ischemic preconditioning. This evolving field however, has so far failed to provide any direct evidence that this plethora of experimental and clinical research may one day translate into a clinical reality that would ultimately benefit patients with coronary artery disease. Despite this, the knowledge gained as a result of this research has provided us with tools for protecting the myocyte and has enabled us to identify several classes of pharmacological agent that may be able to mimic the protection conferred by ischemic preconditioning. These include agents aimed at triggering the preconditioning phenomenon such as adenosine or its more selective analogues, bradykinin/angiotensin-converting enzyme inhibitors and opioids, and those that target the putative distal mediator of preconditioning (mito-K\(_{ATP}\) channels) such as nicorandil. A number of studies in routine (low-risk) patients have been performed with the aim of proving the concept of pharmacological preconditioning in humans and to establish the safety and tolerability of these agents using indirect end points to detect myocardial ischemia, small differences in myocardial viability, and extent of microinfarction. These findings provide some basis for optimism that a beneficial and clinically detectable improvement in myocardial protection may yet be possible. However, this goal can only be achieved when carefully designed clinical studies using hard end points of clinical outcome have been undertaken in appropriate subsets of patients at short-term risk of coronary artery occlusion. These studies have as yet not been undertaken. In our opinion, whereas further research in the basic laboratory continues to identify the next steps in the signaling cascade mediating myocardial preconditioning, it is timely that large-scale trials of high-risk patients at multiple centers were performed with the currently available preconditioning-mimetic agents, with comparisons against pre-existing myocardial protective strategies. Such studies need to focus on the high-risk groups of patients outlined in this review, with particular emphasis on those subsets with features predictive of a worse outcome, who stand to gain the most benefit from additional cardioprotective strategies.\(^8\) The cohorts randomized in these studies may include patients with non-ST-elevation ACS presenting with persistent ST-segment depression on ECG, elevated serum troponin levels, or impaired left ventricular function, whether treated medically or with early revascularization. These patients must be randomized to preconditioning-mimetic agents versus placebo, in addition to standard therapy, and evaluated in terms of robust end points of clinical outcome. Similarly, high-risk patients undergoing elective revascularization procedures need to be included in studies evaluating the clinical efficacy of preconditioning-mimetic treatments in terms of reduction in periprocedural infarct size, heart failure, and mortality. It is only with demonstration of improved outcome in such large-scale studies that the past 15 years of research may translate into a clinical reality.

References


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