

Ischemic Preconditioning in Humans Models, Mediators, and Clinical Relevance

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Abstract—Ischemic preconditioning, a powerful form of endogenous protection against myocardial infarction, has been demonstrated in several animal species and, recently, in isolated human cardiomyocytes. For both logistic and ethical reasons, no clinical study can meet the strict conditions of experimental studies on preconditioning with infarct size as the end-point. Nevertheless, the demonstration of adaptation to ischemia observed during in vitro studies on human atrial trabeculae, in patients in the setting of coronary bypass surgery, and in the setting of coronary angioplasty in the absence of collateral vessel recruitment strongly suggests that ischemic preconditioning occurs in humans. This notion is further supported by the observation that in these human models, the adaptation to ischemia is influenced by drugs acting on K_{ATP} channels and on purinergic and α -adrenergic receptors, similar to what is observed in accepted experimental models of ischemic preconditioning. This important form of myocardial endogenous protection may also play a role in the warm-up phenomenon and in mediating the beneficial effects of preinfarction angina. The demonstration of ischemic preconditioning in humans and the identification of some of its mediators suggests that in patients at high risk for myocardial infarction, drugs known to block this endogenous form of protection should be used with caution, whereas drugs known to elicit preconditioning might have a relevant therapeutic role. (*Circulation*. 1999;100:559-563.)

Key Words: angina ■ ischemia ■ myocardial infarction

Ischemic preconditioning refers to the ability of short periods of ischemia to make the myocardium more resistant to a subsequent ischemic insult. This term was introduced for the first time by Murry et al, who found in a canine model that 4 consecutive periods of coronary occlusion of 5 minutes were able to reduce the infarct size caused by a subsequent period of occlusion of 40 minutes by as much as 75%.¹ This classic form of ischemic preconditioning has now been observed in several animal species.

Ischemic Preconditioning: Definition and Experimental Models

Although ischemic preconditioning initially referred to the ability of short periods of ischemia to limit infarct size,¹ some investigators extended this definition to include a beneficial effect on ischemia- and reperfusion-induced arrhythmias² and on myocardial stunning.³ It is questionable, however, whether the reduction in the incidence of arrhythmias by ischemic preconditioning is a result of a direct antiarrhythmic effect or a mere consequence of the delay of ischemic cell death.^{1,2} Regarding the beneficial effects of ischemic preconditioning on postischemic contractile dysfunction, Cohen et al³ showed that preconditioning in rabbits can lead to enhanced recovery of contractile function of the myocardial region at risk. Also, in this case, the beneficial effects of preconditioning on

acute recovery of contractile function might be a consequence of the delay of ischemic cell death; indeed, parameters of necrosis extent, ie, infarct size and enzyme leakage, correlate with the enhancement of functional recovery.³

The chain of events which confers resistance to ischemia is only partially understood. Recently, Downey and coworkers have developed the hypothesis that stimulation of a variety of G protein-coupled receptors results in the activation of protein kinase C (PKC). This, in turn, leads to the translocation of PKC from the cytoplasm to the sarcolemma, where it phosphorylates a substrate protein (possibly the ATP-sensitive $K^+[K_{ATP}]$ channel), which confers resistance to ischemia.⁴

It is now well established that the protective effects of preconditioning are transient and last for <2 hours.⁴ However, a so-called second window of protection or delayed ischemic preconditioning has been shown in different species, occurring 24 hours after the preconditioning stimulus and lasting for about 48 hours.⁵ This time course is consistent with the concept that the second window of protection is mediated by the activation of genes encoding for cytoprotective proteins, such as heat shock proteins or antioxidant enzymes.⁵ Similar to the early phase of preconditioning, aside from a delayed anti-infarct effect, a delayed anti-arrhythmic effect following preconditioning has been reported.⁶ Further-

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more, Bolli's group⁷ has recently described a delayed preconditioning against myocardial stunning, independent of ischemic necrosis because the ischemic challenge used was insufficient to induce infarction.

Ischemic Preconditioning in Humans

Experimental findings on ischemic preconditioning cannot be directly extrapolated to humans because its mechanisms are different from other animal species. Unfortunately, for both logistic and ethical reasons, no clinical study can meet the strict conditions of experimental studies on preconditioning in which infarct size is the end-point. Thus, surrogate end-points have been used, including contractile function, electrocardiographic ischemic changes, or biochemical evidence of cell damage. These have to be taken into account in the evaluation of clinical studies on preconditioning, as the mechanisms of such nonclassic forms of ischemic preconditioning may differ from those involved in the reduction of infarct size in the experimental models. Another important limitation of several clinical studies reported is represented by the extent of coronary collateral flow, which, in humans, is a major determinant of the severity of myocardial ischemia during coronary occlusion; it cannot always be accurately quantified.

In Vitro Human Studies

In vitro human studies, in which confounding effects due to coronary collateral flow can be overcome, have shown that human cardiomyocytes can be preconditioned.⁸⁻¹¹ Yellon and his coworkers⁸ showed that isolated, superfused, isometrically contracting human atrial trabeculae can be preconditioned against a combined hypoxic and substrate depletion challenge by simulated ischemia and by A₁ and A₃ adenosine receptor activation. The same group has also demonstrated that protection against contractile dysfunction caused by a combined hypoxic and substrate depletion challenge can be induced by activation of PKC and by the opening of K_{ATP} channels, and the protection induced by PKC activation and preconditioning can be blocked by blockade of K_{ATP} channels.⁹

Very recently, Cleveland et al¹⁰ have shown that in this model protection is not evident when the myocardium is obtained from diabetic patients exposed to long-term oral hypoglycemic agents, thus suggesting important clinical implications. Finally, Morris and Yellon¹¹ have shown in human atrial trabeculae that angiotensin-converting enzyme inhibitors can potentiate the protective effects of a subthreshold preconditioning stimulus, possibly because of bradykinin degradation inhibition resulting in enhanced B₂-bradykinin receptor activation. Such a demonstration may help explaining the mechanisms involved in the reduction of fatal ischemic events in patients treated with angiotensin-converting enzyme inhibitors.

Limitations of the model of isolated, superfused, isometrically contracting human atrial trabeculae include the use of hypoxia rather than ischemia to initiate protection, recovery of contractile function as surrogate end-point, and the use of atrial rather than ventricular tissue.

Coronary Artery Bypass Surgery

Intermittent ischemia achieved by aortic cross-clamping in a fibrillating heart during coronary artery bypass grafting has been used as a clinical model of ischemic preconditioning. In this model, the confounding effects due to collateral flow are overcome by using global instead of regional ischemia. Recently, Yellon et al¹² examined the effect of two 3-minute ischemic episodes, where each was followed by 2-minute reperfusion on high energy phosphate metabolism during 10-minute cross-clamping. Distal coronary anastomosis was performed during the cross-clamping. Myocardial biopsies taken after the 10-minute ischemic insult exhibited a significantly higher ATP content than was found in controls not previously exposed to brief ischemic episodes, thus proving that the human myocardium shows the typical biochemical features of preconditioning observed by Murry et al¹ in their classic canine model of ischemic preconditioning. Yet, Perrault et al¹³ have recently reported that 3-minute aortic cross-clamping followed by 2-minute reperfusion before warm-blood cardioplegic arrest during coronary artery bypass surgery fails to provide any beneficial effect. Nevertheless, evidence that preconditioning may offer patients protection against irreversible myocyte injury comes from another study by Yellon and coworkers.¹⁴ They showed a reduction of troponin T release in patients exposed to two 3-minute periods of myocardial ischemia at the beginning of the revascularization operation. Furthermore, it has been shown that in the setting of coronary artery bypass surgery, adenosine¹⁵ and acadesine¹⁶ are effective in improving postoperative left ventricular function. Taken together, these findings suggest that ischemic preconditioning appears to occur in this human model with potentially relevant beneficial clinical effects.

Coronary Angioplasty

The first formal study aimed at assessing adaptation to ischemia during coronary angioplasty was reported by Deutsch et al¹⁷ and involved 12 patients with an isolated obstructive stenosis in the left anterior descending coronary artery; they underwent 2 sequential 90-second balloon inflations. In comparison with the initial balloon occlusion, the second occlusion was characterized by less subjective anginal pain, less ST-segment shift, and lower mean pulmonary artery pressure, despite a reduction in cardiac vein flow and unchanged coronary wedge pressure. These findings have been observed in several other angioplasty studies,¹⁸⁻²² thus confirming an adaptive response of the myocardium to repeated ischemic episodes, akin to ischemic preconditioning. Of note, some angioplasty studies failed to show adaptation to ischemia during repeated coronary occlusions, probably because they neglected some crucial methodological aspects, eg, short balloon inflations of < 90 seconds, preinflation ischemia, or inadequate end-points.²³

Mechanisms of Adaptation to Ischemia

The adaptation to ischemia that was observed after repeated coronary balloon occlusions may be a result of both progressive collateral recruitment and ischemic preconditioning. In order to determine the role of collateral recruitment, we

recently assessed changes in blood flow velocity in the contralateral coronary artery during repeated balloon occlusions by using a Doppler guide wire.²² We found that coronary blood flow velocity significantly increased from baseline to the end of the first inflation, whereas it exhibited a modest increase during the second inflation in $\approx 20\%$ of the patients, which failed to predict the changes in ST-segment shift or cardiac pain severity. These findings are in agreement with those of Kyriakidis et al,²⁴ who assessed collateral recruitment by using ipsilateral and contralateral injections of contrast medium.

Another major concern regarding the angioplasty model of preconditioning is that the electrocardiographic changes do not actually reflect ischemic preconditioning. Shattock et al²⁵ addressed this problem by measuring ST-segment changes in open-chest pigs subjected to 2 cycles of 8-minute ischemia, induced by occlusion of left anterior descending coronary artery and 8-minute reperfusion followed by 1-hour ischemia and 2-hour reperfusion. They found that in the absence of a significant increase in collateral flow, ST-segment changes during the first 3 minutes of ischemia were smaller during the second and third ischemic cycle than during the first, and they concluded that ST-segment changes provide a reliable index of preconditioning during the first few minutes of coronary occlusion. More recently, in an open-chest rabbit model, Cohen et al²⁶ found that the administration before repeated periods of coronary occlusions of drugs known to induce or prevent the classic form of preconditioning abolishes the attenuation of ST-segment changes.

Mechanisms of Ischemic Preconditioning

To establish whether the reduction of myocardial ischemia observed in humans during coronary angioplasty after repeated balloon inflations is a result of activation of K_{ATP} channels, we randomized 20 consecutive patients undergoing 1-vessel coronary angioplasty to receive 10 mg oral glibenclamide, a selective K_{ATP} channel blocker, or placebo.¹⁸ We found that in glibenclamide-treated patients, the mean ST-segment shift on the intracoronary ECG during the second balloon inflation was similar to that observed during the first inflation, and the severity of cardiac pain was even greater. Conversely, in placebo-treated patients, both the mean ST-segment shift and cardiac pain severity during the second inflation were less than those during the first inflation. Because the adaptation to ischemia observed during brief repeated coronary occlusions was completely abolished by pretreatment with glibenclamide, we suggested that in this human model it is predominantly a result of ischemic preconditioning and is mediated by K_{ATP} channels.

Adenosine receptors also appear to play an important role in preconditioning during coronary angioplasty. In fact, adenosine antagonists have been shown to prevent the adaptation to ischemia during repeated balloon inflations,^{19,20} whereas adenosine, independently of its vasodilatory effect, is able to mimic it.²¹ Recently, we have shown that adaptation to ischemia during coronary angioplasty is abolished by phentolamine in the absence of collateral recruitment, thus suggesting that it is also mediated by α -adrenergic receptors.²²

Finally, early results suggest that opioid receptors also seem to play a role in preconditioning during coronary angioplasty. In fact, morphine sulfate²⁷ and naloxone²⁸ have, respectively, been shown to mimic and prevent the adaptation to ischemia during repeated balloon inflations.

Exercise-Induced Ischemia (Warm-Up Phenomenon)

The warm-up phenomenon usually refers to the improved performance exhibited by more than half of patients with coronary artery disease following a first exercise test.^{29,30} However, the mechanisms underlying the warm-up phenomenon are still only partially known and somewhat controversial.

Mechanisms of Adaptation to Exercise-Induced Ischemia

Okazaki et al²⁹ demonstrated that in patients with a single lesion of the left anterior descending coronary artery, great cardiac vein flow is similar during the first and second exercise stress test, thus suggesting that the warm-up phenomenon is not accompanied by an increase in total myocardial blood flow. Interestingly, myocardial oxygen consumption was reduced during the second test, suggesting increased metabolic efficiency, a feature of preconditioning. A role for preconditioning is also supported by the demonstration that the time course of the warm-up phenomenon is consistent with that of classic ischemic preconditioning (lasting no longer than between 60 and 90 minutes).³⁰ Indeed, we found that in patients with stable angina undergoing 3 consecutive exercise tests, the warm-up phenomenon observed within minutes of a first exercise test is a result of adaptation to ischemia, whereas warm-up phenomenon observed 2 hours after the second exercise test is a result of a training effect caused by peripheral mechanisms.³⁰

Mechanisms of Ischemic Preconditioning

Adenosine receptors do not seem to play a major role in the setting of the warm-up phenomenon. In fact, bamiphylline, a selective antagonist of A_1 adenosine receptors, at a dose previously shown to block adaptation to ischemia during coronary angioplasty,²⁰ failed to prevent the warm-up phenomenon.³¹

The involvement of K_{ATP} channels in the warm-up phenomenon is uncertain. In fact, K_{ATP} channel blockade by glibenclamide, given in the attempt to prevent the warm-up phenomenon at a dose previously shown to block adaptation to ischemia during coronary angioplasty,¹⁸ has yielded conflicting results.^{32,33} It is possible, therefore, that different mechanisms of ischemia might trigger the preconditioning state in different ways.

Preinfarction Angina

Recent studies have shown that patients with myocardial infarction preceded by angina have smaller infarcts and a better in-hospital outcome after thrombolytic therapy than patients without preinfarction angina.^{34–36}

At least 3 mechanisms may explain this difference between infarctions that are preceded by angina and those that are not: (1) coronary collaterals, (2) reperfusion rate, and (3) ischemic preconditioning.

Mechanisms of the Beneficial Effect of Preinfarction Angina

Kloner et al³⁴ found that patients with angina within 48 hours of myocardial infarction had a lower in-hospital death rate and a smaller infarct size than patients without angina, despite a similar development of coronary collateral vessels assessed at angiography 90 minutes after myocardial infarction. This suggests that preconditioning by preinfarction angina might render the myocardium more resistant to infarction from the subsequent prolonged ischemic episode.

Another attractive hypothesis about the protective role of preinfarction angina has been suggested by Andreotti et al.³⁵ They compared the infarct size of patients with or without unstable angina during the week before myocardial infarction, taking into account the speed of recanalization. Interestingly, in patients with preinfarction angina, as compared with those without, thrombolytic therapy resulted in more rapid reperfusion and smaller infarcts, thus suggesting that the benefit of preinfarction angina on infarct size might depend on a speedier coronary thrombolysis in addition to, or perhaps instead of, preconditioning. Ishihara et al³⁶ confirmed that reperfusion was more frequently achieved in patients with than in those without prodromal angina in the 24 hours before infarction, thus suggesting a more efficient response of the infarct-related artery to thrombolytic therapy in the former. However, they also demonstrated that prodromal angina in the 24 hours before infarction, but not angina occurring at an earlier time, was independently associated to a better 5-year outcome, thus suggesting a role for ischemic preconditioning.

Clinical Implications

The demonstration of preconditioning in humans has several important clinical implications. For instance, the increased mortality from cardiovascular causes observed in diabetic patients on sulfonylureas in the UGDP trial³⁷ and the worse outcome of patients who are on sulfonylureas at the time of acute myocardial infarction³⁸ might be due to blockade of preconditioning. These findings, if confirmed in prospective studies, might suggest that the treatment of diabetes in some high-risk coronary patients should be shifted from sulfonylureas to insulin. Similarly, the demonstration that adenosine receptor antagonists prevent ischemic preconditioning during coronary angioplasty^{19,20} and in vitro human⁸ studies suggests that methylxanthines should be used with caution in those patients with ischemic heart disease in whom ischemic preconditioning is likely to play an important cardioprotective role (ie, those with unstable angina and those who are undergoing coronary artery bypass surgery or coronary angioplasty).

Concerning the potential therapeutic applications of pharmacologic preconditioning, both K_{ATP} channel openers and adenosine or its analogues might limit the detrimental effects of myocardial ischemia. They may also have the potential to be used as cardioprotective agents during cardiac surgery and in the attempt to improve the preservation of explanted hearts before transplantation.

A tantalizing clinical application of pharmacologic preconditioning is in patients with acute myocardial infarction, in the attempt to slow down the progression of myocardial

necrosis, thus increasing the time available for effective reperfusion. The exploitation of preconditioning, however, depends on the possibility of administering preconditioning drugs before ischemia, thus making this approach difficult in patients at low risk of myocardial infarction, such as those with chronic stable angina. Conversely, it is well known that patients with unstable angina or with a recent myocardial infarction have a higher risk of myocardial infarction in the few months after the initial ischemic episode.³⁹ In this group of patients, the administration of drugs mimicking ischemic preconditioning in the period at increased risk might slow necrosis rate in those patients who will eventually develop an acute myocardial infarction, thus increasing the time available for reperfusion therapy. The myocardium of patients with unstable angina, however, might already be preconditioned by prior ischemic episodes, thus limiting the potential advantages of preconditioning drugs. Yet, it is reassuring that in the animal, preconditioning can be reinstated after the initial protection has waned.⁴⁰ Another theoretical problem may be the development of tachyphylaxis to preconditioning agents. Indeed, Tsuchida et al⁴¹ have shown in a rabbit model that continuous infusion of a selective A_1 adenosine receptor agonist led to downregulation of the signaling mechanism and loss of protection. However, more encouraging data have been obtained recently using a different dosing schedule, in which the same drug was administered to rabbits by intermittent dosing over a 10-day period with persistence of myocardial protection assessed 48 hours after the last dose.⁴²

Finally, early reports have shown that the administration of preconditioning drugs as an adjunct to thrombolytic therapy may reduce infarct size⁴³ and the incidence of tachyarrhythmias and myocardial ischemic episodes in unstable angina.⁴⁴

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