

What is the evidence that preconditioning occurs in man?

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Preconditioning has been shown to be a powerful technique for reducing infarct size in every animal model tested. There is now evidence that the human heart can be preconditioned by ischemia and pharmacologic agents. Humans can adapt rapidly to brief ischemic insults, as shown by “warm-up” or “walk-through” angina pectoris. In vitro analysis of human tissue, angioplasty literature, and studies of preinfarction angina have also shown the reality of preconditioning in humans. The mechanisms whereby preinfarction angina confers benefit has been an area of considerable discussion. Preconditioning-like drugs might be administered to produce a cardioprotective effect in patients undergoing open heart procedures, or in patients with unstable angina pectoris or threatened myocardial infarction. Whether these agents could play any role during evolving myocardial infarction is less clear.

Cardiovascular disease remains the major killer of men and women in the Western world. In the United States, 1.5 million people a year develop myocardial infarctions; 500 000 die of myocardial infarctions; and 250 000 die within the first hour of onset of symptoms. There is no question that major progress has been made in the treatment of myocardial infarction and coronary artery disease. Lifestyle modifications with reduction in risk factors may play an important role, but so does better therapy for coronary artery disease. Decrease in in-hospital mortality for acute myocardial infarction is related to early reperfusion by either thrombolytic therapy or angioplasty. Early reperfusion salvages myocardium and improves cardiac function and survival. However, despite these advances in the early treatment, in-hospital mortality still averages about 7%. What other maneuvers and treatments might salvage ischemic myocardium?

Over the course of 25 years there have been numerous attempts at trying to reduce myocardial infarct size. Various drug therapies have been attempted, including β -blockers, calcium channel blockers, fluorocarbons, anti-inflammatory agents, and antineutrophil agents, with varying success, in both experimental as well as clinical trials. In experimental studies,

there only have been a small number of maneuvers that have consistently reduced myocardial infarct size. These include early coronary reperfusion, ischemic preconditioning, and hypothermia. Preconditioning has been shown to be such a powerful technique for reducing myocardial infarct size in every animal model tested that there has been considerable interest in the possibility that it could be applied to the ischemic human myocardium. If the mechanism whereby ischemic preconditioning worked could be identified, then pharmacologic agents involved in possible mechanisms might be applied to human coronary events. The purpose of this review is to discuss the evidence that the human heart can be preconditioned in relationship to both ischemic and pharmacologic preconditioning.

EVIDENCE FROM THE ANGIOPLASTY LITERATURE

One of the earliest findings suggesting that preconditioning might occur in man actually comes from the angioplasty literature. Several clinical reports described that sequential angioplasty balloon inflations were associated with decreasing chest pain, decreasing degrees of ST-segment elevation, and reduced amount of lactate production, on subsequent

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compared to the initial inflation.^{1,2} This observation was made without any increase in coronary flow in one study,¹ but may have been associated with recruitment of coronary collaterals in some, but not all, patients in another study.² Over the past few years, there has been growing evidence that some of the same pathways involved in infarct size reduction in animal studies may also play a role in ischemic preconditioning during angioplasty procedures in man. For example, the K_{ATP} channel blocker glibenclamide will block the beneficial effects of repetitive balloon inflation in humans, just as it blocks the ability of ischemic preconditioning to reduce infarct size in animal models.^{3,4} Infusion of adenosine can mimic the cardioprotective effects of repetitive balloon inflation, just as adenosine agonists can reduce myocardial infarct size in animal experiments.^{5,6}

Adenosine antagonists will block the beneficial effects of repetitive balloon inflation, just as they block the ability of ischemic preconditioning to reduce myocardial infarct size in some animal models.⁷ There is a practical clinical implication that may be derived from the preconditioning-like effect of repetitive coronary artery angioplasty balloon inflation. Patients with coronary stenoses within arteries that supply large territories of the ventricles and patients with difficult and complex lesions might benefit from repetitive balloon inflations in order to precondition the myocardium prior to lengthy angioplasty procedures. In general, the duration of the initial inflation needed to achieve a protective effect appears to be 90 seconds.¹ Alternatively, pretreatment prior to angioplasty with an agent such as adenosine or perhaps a K_{ATP} channel opener might achieve the same benefit.

EVIDENCE FROM PREINFARCTION ANGINA STUDIES

Another clinical observation that supports the notion that ischemic preconditioning occurs in man comes from studies of preinfarction angina. Experimental studies have clearly demonstrated that brief periods of nonlethal ischemia (usually of the order of 2 to 10 min) prior to a prolonged episode of ischemia (usually of the order of 30 to 90 min), will markedly reduce the size of the myocardial infarction. Many patients are known to have anginal attacks prior to their myocardial infarction. Assuming that these anginal attacks are brief (less than 20 min), then one could postulate that these brief nonlethal episodes of ischemia prior to myocardial infarction might actually be protective in humans. While this concept is seductive, there are some complicating features of patients with histories of angina prior to myocardial infarction. These patients tend to have more multivessel coronary disease, may have more risk factors, and may be on more antianginal medicines than patients without prior histories of angina pectoris. Indeed, some studies have suggested that patients with long histories of prior angina have a poorer long-term prognosis.⁸

MILIS, TIMI 4 and 9, GUSTO, and other studies

This was especially the case in studies from the prethrombolytic era. We performed an analysis on patients who had entered one such prethrombolytic trial called the Multicenter Investigation of the Limitation of Infarct Size (MILIS) trial,⁹ which showed that there was no overall reduction in infarct size

assessed by creatine kinase (CK) curves in patients with versus patients without a history of preinfarction angina. This came as no surprise, since animal studies have shown that ischemic preconditioning will only reduce myocardial infarct size if there is reasonably early reperfusion—within 60 to 90 min of the prolonged coronary occlusion. Thus, ischemic preconditioning would not be expected to work in the situation of permanent coronary occlusion. However, in the MILIS trial, there was a group of patients who probably had early spontaneous reperfusion, as suggested by early peaking of their CK curves. In this group of patients, those who had histories of preinfarction angina had lower total CKs, suggesting smaller infarct sizes compared with patients with early reperfusion, but no history of preinfarction angina.

In the Thrombolysis In Myocardial Infarction (TIMI) 4 trial,¹⁰ which was a thrombolytic trial, we observed that patients who had a history of preinfarction angina had lower total CK release as well as fewer Q waves on their ECG, compared with patients who had no history of preinfarction angina. Patients with preinfarction angina also had better in-hospital survival and less congestive heart failure and/or shock. Coronary angiograms did not reveal more collaterals in the preinfarction angina group. The benefits of preinfarction angina were not related to differences in medicines between the two groups. The benefit of preinfarction angina occurred despite the fact that patients with preinfarction angina had more multivessel coronary disease and had a longer duration from onset of angina to administration of thrombolytic. There was a downside to having preinfarction angina—these patients had a trend toward more postinfarction angina.



This probably was due to the fact that these patients had more multivessel coronary disease.

Recently, we analyzed the findings of another large thrombolytic trial, the TIMI 9 trial.¹¹ In this trial, the benefits of preinfarction angina were only manifest when the history of preinfarction angina occurred within 24 hours of onset of the infarction. Patients who had preinfarction angina during this time were more likely to have lower peak CKs and a lower incidence of in-hospital death, shock, and/or heart failure. However, in patients who had onset of angina more than 24 h prior to onset of infarction, there was no protective effect. This trial suggested that for preinfarction angina to have a beneficial effect there must be a close temporal relationship between the brief ischemic episodes and the myocardial infarction. A time course of 24 h would allow for mechanisms of either classic preconditioning or the second window of protection to play a role. The benefits of preinfarction angina were not related to antianginal medication.

Over the last 3 years, there have been a number of published studies that have confirmed the concept that preinfarction angina is protective. These include reports that preinfarction angina reduces myocardial infarct size as measured by CK curves, improves ventricular function, reduces the frequency of clinical congestive heart failure, reduces arrhythmias, and reduces the likelihood of ventricular rupture.¹²⁻¹⁵ One preliminary study suggested that preinfarction angina that occurs within 24 h of infarction improves long-term survival.¹⁶ Not all such studies have been positive. For example, a preliminary study from the GUSTO group (Global Utilization of Streptokinase and

TPA for Occluded arteries) did not observe a benefit of preinfarction angina.¹⁷ However, their study included patients with angina that may have been more remote from the time of infarction.

What are the possible mechanisms?

The mechanisms whereby preinfarction angina confer early benefit in these studies have been an area of considerable discussion. Obviously, one likely explanation is that preconditioning caused the benefit. Another potential explanation is that intramural collaterals developed in patients with previous angina. Small vessels might not be visualized on angiography, so that studies would not necessarily describe an increase in collateralization among patients with previous angina. An intriguing new theory regarding the benefit of preinfarction angina was suggested by Andreotti et al.¹⁸ They showed, in a small cohort of patients, that previous angina was associated with earlier and more complete reperfusion by thrombolysis. This unique concept suggests that ischemic preconditioning may protect the large epicardial coronary arteries, making them more susceptible to thrombolytic agents. Hata and Przyklenk¹⁹ in our laboratory have observed a similar finding in a canine model of partial coronary artery stenosis, in which brief episodes of ischemia improve vessel patency and reduce cyclic flow variation due to transient platelet plugs.

Clinical and therapeutic implications

Could the knowledge that preinfarction angina confers beneficial effects have practical clinical or therapeutic implications? Patients with myocardial infarction who present with a history of

angina of recent onset may have early in-hospital benefits. However, the clinician should know that these patients may have more multivessel coronary artery disease, and therefore may be more likely to present with recurring ischemia. It is tempting to think that preconditioning-like drugs (such as adenosine, adenosine agonists, and K_{ATP} channel openers) might be administered early during the course of myocardial infarction and produce a cardioprotective effect as occurs with preconditioning. Whether these drugs could be administered early enough to have a benefit in patients already evolving substantial tissue necrosis is not yet known. However, it might be possible to administer preconditioning-like drugs that stimulate the pathways of preconditioning without causing ischemia in patients with either threatened acute myocardial infarction or in patients with unstable angina pectoris. It is more likely that the practical benefits of giving ischemic preconditioning-like drugs will be most useful in controlled clinical settings, in which the drugs can be given in a pretreatment fashion prior to a known ischemic insult. An obvious situation to consider would be administration of such agents prior to coronary artery bypass surgery or any cardiopulmonary bypass procedure. In a recent report, Mentzer et al²⁰ attempted pharmacologic preconditioning in patients undergoing open heart procedures. Placebo or various doses of adenosine were given to the patients prior to undergoing cardiopulmonary bypass. Patients who received high doses of adenosine had improved regional wall motion and had less need for inotropic support. This is one of the first studies of which I am aware where a preconditioning-mimetic agent was shown to have direct clinical benefit.

EVIDENCE FROM “WARM-UP” OR “WALK- THROUGH” ANGINA

Another clinical situation in which preconditioning may occur is in the situation of so-called “warm-up” or “walk-through” angina pectoris. Most clinicians have seen the patient who develops angina while walking, stops for a few minutes, and then continues to walk without chest pain. This “warm-up” phenomenon may be related to ischemic preconditioning. Patients are able to exercise for a longer duration before developing ischemia during a second stress test compared to a first test, if there is a brief rest period between the first and second tests.²¹ In another related study, patients with coronary artery disease who were undergoing cardiac catheterization were rapidly paced during two finite periods, with a period of nonpacing in between. There was less ST-segment deviation and less lactate production during the second compared to the first pacing period.²² Interestingly, there was no increase in coronary flow during the second test compared to the first test. There was, however, a reduction in myocardial oxygen demand during the second test compared to the first, suggesting a possible mechanism for this benefit. Maybaum et al²³ reported the effect of three sequential exercise tests, separated by a period of 30 min. They observed a longer time to development of ST-segment depression during the second and third tests compared to the first. In addition, the exercise duration was improved in the second and third tests and these were associated with a higher rate-pressure product. In summary, it does appear that humans can adapt rapidly to brief ischemic insults. A practical take-home message for the clinician is to suggest a warm-up phase of

exercise in those coronary disease patients that are physically active. It is also useful to know that exercise tolerance in these patients may vary from time to time depending on whether there was a warm-up phase.

EVIDENCE FROM IN VITRO ANALYSIS OF HUMAN MYOCARDIAL TISSUE

While this review has focused on examples of clinical preconditioning, there are a number of studies that support the concept that the human heart can be preconditioned that have relied upon in vitro analysis of human tissue. Ikonomidis et al²⁴ observed enhanced survival of cultured human cardiomyocytes exposed to simulated prolonged ischemia when they were preconditioned with prior episodes of brief ischemia. Yellon's group performed a series of studies in human atrial trabeculae that were exposed to ischemia and reperfusion, and measured contractile function of these strips of muscle.^{25,26} They observed that adenosine receptor activation enhanced recovery of function from simulated ischemia, as did the K_{ATP} channel opener cromakalim and stimulation of protein kinase C.

POTENTIAL APPLICATIONS OF PRECONDITIONING IN MAN

In some but not all animal models preconditioning appears to have a beneficial effect on arrhythmias. Takano et al²⁷ suggested that this may hold true in humans. They investigated the incidence of ventricular arrhythmias during ischemic attacks in relationship to the previous ischemic period. The incidence of ventricular premature beats, couplets, and ventricular tachycardia was reduced when the

previous ischemic attack occurred within 5 h, compared to when the previous attack occurred at an interval that was greater than 5 h.

One of the first studies that suggested that human cardiac tissue could be preconditioned comes from a study in which serial biopsies were obtained from ventricular myocardium for ATP levels. In this study, patients undergoing coronary bypass surgery received a 10-min period of ischemia induced by aortic cross-clamp defibrillation. Some of the patients were preconditioned with two episodes of 3 min of ischemia induced by aortic cross-clamping. Patients who were preconditioned demonstrated less degradation of ATP during the test period of ischemia.²⁸ The same group showed that ischemic preconditioning prior to placement of a coronary artery bypass graft reduced serum troponin T concentrations.²⁹ Could ischemic preconditioning be used to protect the myocardium during cardiopulmonary bypass procedures? While various cardioplegic techniques are commonly used, they are often associated with some degree of myocardial stunning.³⁰ There is a need for better cardioprotective techniques. As already mentioned, one study suggested that pretreatment with the preconditioning-mimetic adenosine could improve postoperative cardiac function, despite the use of cardioplegics. The author has heard anecdotes in which a cardiac surgeon has preconditioned a territory of the anterior wall of the left ventricle by actually clamping the coronary artery for a few min, reperusing, and then proceeding to a coronary bypass of the artery. Certainly, with the advent of minimally invasive surgery, there is a need to consider newer ways of protecting the heart during the period of the anastomosis.



CONCLUSION

Based on the studies discussed above as well as numerous other studies (for more detailed reviews, see references 31, 32, and 33), it is very likely that the human heart can be preconditioned. What remains to be determined from a clinical standpoint is whether the basic science information resulting from the exploration of the mechanism of ischemic preconditioning will result in preconditioning-mimetic drugs that do not cause ischemia but do cause cardioprotection. Likely clinical situations in which preconditioning could be harnessed to protect the ischemic myocardium include pretreatment with preconditioning-mimetics prior to minimally invasive cardiac surgery, routine cardiac surgery, prior to difficult coronary angioplasty cases, and administration of such agents to donor hearts to preserve them prior to heart transplant. It is also conceivable that preconditioning-mimetics might be assessed for efficiency in patients with threatened myocardial infarction or unstable angina pectoris. Whether these agents could play any role during evolving myocardial infarction is less certain. What is certain is that ischemic preconditioning is one of the most powerful techniques that experimentalists have observed for reducing myocardial infarct size. Understanding its mechanism will improve our overall understanding of myocardial ischemia and hopefully provide future therapies.

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