Editorial Comment

Ischemic Preconditioning: The Issues of Refractoriness and Tolerance*

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This issue of the Journal contains two articles (1,2) that offer further insight into the issues of refractoriness and tolerance in ischemic preconditioning. Brief episodes of ischemia just before a prolonged coronary artery occlusion can markedly reduce myocardial infarct size (3). The phenomenon of ischemic preconditioning has been documented in virtually every species studied, and there is now compelling evidence for ischemic preconditioning in humans (4). As the duration of reperfusion between the last episode of brief ischemia and the prolonged coronary occlusion is increased, the beneficial effects of preconditioning wane. In rats, rabbits, dogs and pigs, separation of the brief preconditioning ischemic episodes from the long occlusion by 60 to 120 min results in complete or nearly complete loss of preconditioning's powerful infarct size-limiting effect (5–8). However if this duration is extended to 24 to 72 h, infarct size again will be reduced (9). Hence there is a distinct first (or classic) as well as a second (or delayed) phase of protection.

Why the effect of ischemic preconditioning wanes after 60 to 120 min of reperfusion and reappears at 24 h is the subject of considerable interest. It has been postulated that different mechanisms may be involved to explain the second window compared with the first window of protection. The first window may involve release of adenosine during ischemic preconditioning, stimulation of adenosine A1-receptors and, through G proteins and second-messenger pathways, phosphorylation of some unknown effector, perhaps the KATP channel. The second window may also involve adenosine, nitric oxide, oxygen free radicals and production of new proteins such as heat shock protein. The exact pathways involved are complex and may vary by species.

Our group (10) has shown that in rats, the early protective effect that is lost after 1 to 2 h of reperfusion can be recaptured by introducing another brief ischemic episode at the end of 60 min of reperfusion, just before a 90-min occlusion. Similar results were reported in the rabbit (11). In these two species the lost effects of the first window of ischemic preconditioning could be recaptured by reawakening the memory with another brief period of ischemia. However, studies in the pig (12) suggested that a true refractory period exists. A second episode of ischemic preconditioning 1 h after the first episode failed to reduce myocardial infarct size. What is the mechanism of refractoriness in this model? Vogt et al. (1) in this issue of the Journal have again confirmed the fact that a second preconditioning cycle at 60 min after the first is ineffective in the pig model. They postulated that the refractory period might be due to a reduction in intramyocardial adenosine levels, and apparently they were correct. Adenosine content increased only during the first brief preconditioning coronary occlusion but not on sequential coronary occlusions. When an adenosine A1-receptor agonist was infused directly into the refractory myocardium, infarct size again was reduced. Therefore, at least in the pig model, refractoriness appears to be related to a decrease in endogenous adenosine and can be counteracted by an exogenous adenosine agonist. Whether this phenomenon holds true in other species is not clear. As previously mentioned, in the rat and rabbit the early phase of ischemic preconditioning can be re instituted by another brief period of ischemia (10,11). It is possible that in these species the brief episode of ischemia is again able to cause an increase in intramyocardial adenosine levels. However, whether preconditioning can be recaptured by an intramyocardial injection of an adenosine agonist in these models remains to be determined. Although, it is clear that adenosine plays a role in preconditioning in the rabbit model, its role in the rat is controversial (12). There are now data suggesting that adenosine may play a role in humans. In one study (13), adenosine infusion before percutaneous transluminal coronary angioplasty (PTCA) reduced ST segment elevation during balloon inflation. In another study (14), pretreating patients with adenosine before cardiopulmonary bypass was associated with improved cardiac function and reduced use of inotropic agents. In summary, the study by Vogt et al. (1) suggests that in the pig model, refractoriness to the early phase of preconditioning exists, is probably due to reduced adenosine production and can be reversed with an adenosine A1-receptor agonist.

Recent studies from Tsuchida et al. (15) and Cohen et al. (16) suggested that tolerance to ischemic preconditioning may limit its potential usefulness. In a chronically instrumented conscious rabbit model, they showed that 40 to 65 five-minute occlusions over a period of 3 to 4 days resulted in a loss of the benefit of ischemic preconditioning. They also showed that a prolonged infusion of an adenosine A1-receptor agonist for 72 h resulted in a loss of protection that could not be recaptured with a 5-min coronary occlusion. These results suggest that there is tachyphylaxis to the benefits of preconditioning that may be due to a desensitization of the A1-receptor on the myocyte. Whether less frequent but repetitive occlusions could maintain the effect of preconditioning is not known. The issue of whether the heart can be maintained in a chronic state of preconditioning is important from a therapeutic standpoint.
For example, if a preconditioning mimetic drug were administered to a patient with angina, would tolerance develop (much like what occurs with long-term nitrate therapy)?

Dana et al. (2) have addressed this issue of whether tolerance occurs to the second window of preconditioning when repeated doses of an adenosine A1-receptor agonist are administered to conscious rabbits. They gave an adenosine agonist or vehicle every 48 h five times and then 48 h later subjected the animals to a 30-min coronary occlusion and reperfusion. This regimen of adenosine agonist administration was associated with a smaller infarct size than that with vehicle. In other words, they were able to maintain these hearts in a chronic preconditioned state. Whether this same regimen would preserve the first window (classic preconditioning) of protection was not studied. Obviously, the way in which the agonist was administered (once every 48 h in this study) versus the way in which it was administered in the study by Tsuchida et al. (15) (continuous intravenous infusion over 72 h) may also help explain the differences between these two studies. The important findings of the report by Dana et al. (2) do provide a reason to be optimistic regarding the issue of whether pharmacologic preconditioning can result in long-term protection. A clinical implication of this study is that therapies that simulate the second window of protection may be administered long term and still have benefit.

However, in the present investigation by Dana et al. (2) it is not clear whether more frequent administration of the adenosine agonist (for example every few hours) might have caused tolerance to the second window of protection. There probably is some optimal dosing regimen that affords maximal protection without the development of tolerance. A dose every 48 h does not cause tolerance. This finding parallels to some degree the situation of nitrate tolerance. Continuous nitrate therapy without a nitrate-free interval is associated with rapid development of tolerance, whereas intermittent nitrate therapy with a nitrate-free interval is not. The same may be true for stimulation of adenosine A1-receptors. Continuous stimulation may result in their downregulation and desensitization, whereas intermittent stimulation may not. If intermittent stimulation is spaced appropriately, it may chronically precondition to the second window of protection (and possibly the first window as well, although this remains to be fully tested).

Over the past 11 years, much has been learned about the biology of preconditioning. The two fine studies by Vogt et al. (1) and Dana et al. (2) have extended this knowledge by showing that refractoriness and tolerance to preconditioning can be overcome.

References