EDITORIAL COMMENT
Ischemic Preconditioning in Coronary Heart Disease: A Therapeutic Golden Fleece?*

Ezra A. Amsterdam, MD, FACC, Saul Schaefer, MD, FACC
Sacramento, California

Preconditioning is the process by which brief, repetitive episodes of ischemia reduce the size of a subsequent myocardial infarction. Since the discovery of ischemic preconditioning by Murry et al. (1) almost two decades ago, thousands of studies have pursued its mechanism(s) and sought therapeutic realization of this unique adaptive response to a physiologic stress. Although mechanistic understanding has progressed, translation into clinical utility has been elusive. Indeed, the pursuit of this goal has been akin to a modern version of Jason’s quest for the Golden Fleece.

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Current understanding of preconditioning and unresolved issues have been reviewed recently (2,3). Early studies demonstrated that ischemic preconditioning was unique in comparison with myriad other approaches to limit infarct size. Under controlled conditions in laboratory animals, its effects are singularly profound and consistent. Infarct size is reduced by as much as 70%, arrhythmias decreased, and ST-segment elevation attenuated (1,4). These findings have been reproducible in all mammalian species studied and are not dependent on coronary collaterals. However, cardioprotection is not observed in the absence of coronary reperfusion and the interval, during which protection can occur after induction of the preconditioning stimulus is limited. In the canine heart, for example, there is no reduction in the size of infarction occurring 3 h after induction of preconditioning (1). However, if the delay from preconditioning onset is increased to >24 h, the protective effect is restored. Thus, preconditioning comprises two phases referred to as early, or “classical,” and delayed, or “second window.”

Although not fully clarified, the mechanisms underlying ischemic preconditioning have been unveiled to a considerable extent (2–4). Classical preconditioning appears to involve a complex series of reactions initiated by agonists such as adenosine, formed during ischemia, that activate second messenger pathways involving protein or tyrosine kinases with subsequent opening of mitochondrial adenosine triphosphate (ATP)-sensitive potassium channels ($K_{ATP}$) and reduction in mitochondrial calcium overload (5). Delayed preconditioning, although responding to similar agonists, likely involves activation of nuclear factor-kappa-B and transcription of several mediators, such as Bcl-2, that maintain the mitochondrial transition pore in its closed conformation (6).

There is evidence for ischemic preconditioning in humans in both acute and chronic coronary heart disease. Clinical settings include exercise, coronary artery angioplasty, coronary bypass graft surgery, and acute myocardial infarction (AMI). It is well documented that a second bout of exercise is associated with delayed onset of angina and less ST-segment deviation than occurs with the initial exertion, a finding known as the “warm-up” phenomenon (7,8). Similar results have been observed after sequential cardiac pacing stress (9). These studies suggest that preconditioning can be induced by demand ischemia as well as interruption of coronary blood flow. The latter paradigm applies to coronary angioplasty during which repeated balloon inflations produce a decrease in electrocardiographic and biochemical evidence of ischemia, adaptations that can be simulated or blocked by agonists and antagonists of the adenosine–$K_{ATP}$ channel pathway (10–12). Although results during cardiac surgery have varied, brief periods of aortic cross clamping to induce preconditioning before prolonged cross clamping have yielded biochemical evidence of myocardial protection in some studies (13).

The foregoing experimental and clinical studies provide a background for reports of improved outcome in AMI patients who experience angina preceding the infarction. Compared with those without antecedent angina, patients with angina have had decreases in mortality, pump failure, arrhythmias, and peak cardiac serum enzyme levels as well as enhanced recovery of cardiac contractile function (14–17). In these studies, preinfarct angina has occurred within 24 to 72 h of AMI, consistent with the temporal relations of early and delayed preconditioning.

In this issue of the Journal, Solomon et al. (18) extend our understanding of the complex interrelation between pre-infarct angina, AMI outcome, and the possible role of preconditioning in their investigation of postinfarction left ventricular (LV) remodeling. They studied a subgroup of the Healing and Early Afterload Reducing Therapy (HEART) trial of immediate versus delayed treatment with ramipril in patients with anterior Q-wave infarction. In accord with previous evidence of smaller infarctions associated with preinfarct angina (13), Solomon et al. (18) detected lower peak creatine kinase levels and reduced infarct segment length in their patients with angina preceding AMI. However, theirs is the first report of attenuation of LV remodeling in patients with preinfarct angina, with maintenance of this finding at 90 days after AMI. These results extend previous data showing acute benefits on LV function (19). They also observed that patients with rest angina had less LV remodeling than those with either stable angina or no angina preceding AMI. Furthermore, although previous studies observed cardioprotection when angina preceded infarction...
by one to three days (19,20), Solomon et al. (18) report protective effects with angina occurring up to three months before AMI. In addition, as has been previously reported, angina did not confer a protective effect in their diabetic patients (21).

The findings of Solomon et al. (18) are provocative. Their data suggest a widening of the window within which angina-related cardioprotection can be initiated before AMI and maintained thereafter. Cardioprotective effects associated with preinfarct angina implicate preconditioning as a potential mechanism. The three-month interval by which angina could precede AMI in this study is most interesting because it greatly exceeds the recognized period within which preconditioning is initiated. However, although not specified in the results, it is possible that many of these patients also had angina proximate to their AMI. Additionally, it is also likely that in the patients with rest angina, in whom cardioprotection was greatest, this symptom had a close temporal relation to AMI.

Protective mechanisms other than preconditioning warrant consideration in this study, including augmented coronary collateral vessels, the development of which is favored by the prolonged interval between angina and subsequent AMI. In this regard, it is noted that the angina patients had almost twice the frequency of previous MI than those without angina (21% vs. 11%), consistent with increased coronary collaterals in the former (22). The time to thrombolysis in this study was similar in the angina and nonangina patients. However, there is experimental evidence that preinfarct ischemia can facilitate thrombolysis by the platelet-inhibiting actions of adenosine (23), thereby favoring improved clinical outcome. This potential mechanism would apply to patients with angina proximate to AMI. Although medications did not differ in the angina and nonangina patients at 90 days, it is noteworthy that both aspirin and beta-blocker use on admission were significantly higher in those with angina. These differences could also influence infarct size and subsequent LV remodeling. Finally, it is not known how the various dosing regimens of ramipril related to LV remodeling.

Other than early reperfusion, ischemic preconditioning is the most potent means of limiting infarct size, an essential target in the challenge to reduce mortality from coronary heart disease. The report of Solomon et al. (18) reflects the complexities of considering preconditioning in the clinical setting. However, their provocative findings complement current efforts to better understand this cardioprotective mechanism and contribute to pursuit of this potential therapeutic Golden Fleece.

References