EDITORIAL COMMENT

Preinfarct Angina and Exercise: Yet Another Reason to Stay Physically Active*

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In the past, angina has been considered something bad. Though I still maintain that any ischemia is something the heart should avoid if possible, several studies suggest that preinfarct angina paradoxically may have protective effects (1–7). Our group observed this phenomenon in the Thrombolysis In Myocardial Infarction (TIMI-4) (1) study and then in the TIMI-9 study (2). Preinfarct angina reduced in-hospital death and congestive heart failure/shock and was associated with a smaller myocardial infarct size as measured by creatine kinase-MB fraction (CK-MB) release. In the second study, TIMI-9 (2), it appeared that for the benefit to be manifest, the preinfarct angina had to occur temporally close to the MI. Several other groups have observed benefits of preinfarct angina—ranging from a reduction in enzymatically determined myocardial infarct size to improved long-term survival, to improved left ventricular function, to reduction in arrhythmia (3–7). These studies were primarily ones in which myocardial infarcts were reperfused with thrombolytic therapy. In a study that analyzed preinfarct angina from the prethrombolytic era, there did not appear to be an overall benefit of preinfarct angina (8). However, in a subgroup of patients who had presumed spontaneous thrombolysis (early peaking CK), angina did appear to be associated with smaller infarcts. Thus, for preinfarct angina to have a benefit, it appears that thrombolysis must eventually occur.

What are the potential mechanisms for this phenomenon of a benefit of preinfarct angina? One very obvious one is ischemic preconditioning (9). The brief episodes of transient ischemia (angina) that occurred temporally close to the infarct could have rendered the heart resistant to the subsequent severe and prolonged ischemia associated with the coronary artery occlusion of acute MI (AMI). Ischemic preconditioning is a phenomenon that has been observed in virtually every species that has been tested (10). Brief periods of ischemia render the heart resistant to a longer duration of ischemia through a complex series of second messenger pathways, culminating in activation of an effector, which some investigators believe is the mitochondrial K_{ATP} channel.

There are other potential mechanisms whereby preinfarct angina could benefit outcome. Andreotti et al. (11) suggested that preinfarct angina might enhance thrombolysis. This phenomenon might be related to the release of adenosine during angina and its effect on inhibiting platelet aggregation (12).

Another concept is that preinfarct angina, especially chronic angina, could result in enhanced collateral blood flow, which would then limit myocardial infarct size. However, some of the preinfarct angina studies that investigated the presence of coronary collateral vessels did not observe an increase in at least the visible epicardial collateral vessels in patients with preinfarct angina (1,3,5,6). Also, in some patients, the angina was of new onset prior to infarction, and presumably it would not have been present long enough to stimulate the growth of new vessels (13).

The exact mechanism whereby preinfarct angina has protective effects remains to be determined, but based on observations from experimental studies, some aspects of the phenomenon certainly suggest preconditioning as a potential mechanism (i.e., the time course, the effect on infarct size, the effect on arrhythmias, and the fact that reperfusion eventually must occur for the benefit to be observed).

Some experimental studies have shown that ischemic preconditioning does not work or is less effective in the elderly heart (14–17). Several clinical reports also suggest that preinfarct angina is not protective in elderly patients (18,19). This might be considered another parallel to ischemic preconditioning. However, not all preconditioning studies in elderly animals or patients have been negative (20–22). In a TIMI-4 substudy (23) we analyzed the effect of preinfarct angina in patients >60 years of age versus those who were younger. As expected, older patients had a worse outcome, as has been observed in numerous AMI studies. Those >60 years of age had higher rates of death as well as the combined end point of death, heart failure/shock and/or reinfarction versus younger patients. However, older patients with preinfarct angina had lower rates of death, heart failure/shock and/or reinfarction (11%) versus older patients without angina (23%; p = 0.04). Elderly patients with preinfarct angina had lower median CK units (144 vs. 153; p = 0.05).

Another recent study by Jimenez-Navarro et al. (13) showed that the presence of angina within one week of AMI protected elderly patients. Patients >64 years of age (n = 143) who had prodromal angina had less in-hospital death (6%) versus those without prodromal angina (20.4%; p = 0.02), had less heart failure (10.0%) than those without prodromal angina (23.7%; p = 0.07) and had less of the combined end point of in-hospital death and/or heart failure.

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(14%) than those without prodromal angina (32.3%; \(p = 0.01\)). Preinfarct angina in the elderly was associated with better left ventricular function and fewer arrhythmias. Peak CK ± SD was 1,748 ± 1,433 IU/l in elderly patients with prodromal angina versus 2,500 ± 2,190 IU/l in elderly patients without prodromal angina (\(p = 0.01\)). Hence, both this study and the TIMI-4 study suggested that preinfarct angina in the elderly was still protective.

These findings differ from previous reports by Abete et al. (18) and Ishihara et al. (19), neither of which observed a benefit of preinfarct angina in elderly patients with MIs. The present study by Abete et al. (24) may offer a potential explanation for differences in findings among these studies. In the present study, Abete et al. (24) described the intriguing observation that a high level of physical activity was associated with decreased in-hospital mortality in elderly patients with preinfarction angina (defined here as angina within 24 h of infarction) but not in those without preinfarct angina. In addition, older patients who had a high level of physical activity appeared to demonstrate other benefits of preinfarct angina: less cardiogenic shock, more non–Q-wave MI, lower CK-MB peak and less ventricular arrhythmia.

In older patients with no preinfarct angina, a high physical activity score was not protective. Logistic regression analysis showed that preinfarct angina was protective in older patients with the highest physical activity score. While speculative, it is possible that the elderly patients in the TIMI-4 study (23) and that of Jimenez-Navarro et al. (13) were more physically active than those from the earlier study of Abete et al. (18). These patients would then have demonstrated the expected protective effect of preinfarct angina; and this might be a possible explanation for the different observations among studies.

There is good news from the Abete et al. (24) study published in this issue of the Journal, namely the concept that preinfarct angina can still benefit the aged heart in individuals who are physically active. These investigators previously showed in a rat model that exercise training restored the protective effect of ischemic preconditioning in the aging heart (25). They postulated that exercise training restored the ability of the senescent heart to release norepinephrine during global ischemia and reperfusion. It has been shown by our group as well as by others that brief exposure of catecholamines can trigger preconditioning (26). By restoring the ability of the heart to release norepinephrine during stress, physical exercise training may restore preconditioning to the old heart.

There have been other attempts to restore the ability of senescent hearts to precondition. McCully et al. (21) showed that adenosine in concert with ischemic preconditioning enhanced posts ischemic function and reduced infarct size in the elderly heart. The McCully et al. study (21) as well as the experimental study of Abete et al. (25) and the clinical study of Abete et al. (24) show that there is hope for the aging heart. The fact that an elderly heart has the potential to exhibit benefit from preinfarct angina is, of course, an important finding, especially as our population is aging. However, for the aging heart to reap the benefit of preinfarct angina—whether this be through preconditioning or some other mechanism—the patient needs to stay physically active. Thus, here is yet another reason to remain physically fit.

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REFERENCES


