

Preconditioning

A New Concept About the Benefit of Exercise

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Case presentation: A 45-year-old man with coronary artery disease is found to be in good condition after his annual medical checkup, and his doctor advises him to continue with the same drugs, a prudent diet, entertainment, and regular exercise; however, the patient is afraid that he will not have time to exercise regularly.

Benefits of Exercise

Clinicians have learned about the beneficial effects of several factors that may prevent a myocardial infarction (MI), including avoidance of smoking; treatment of high blood pressure, diabetes, dyslipidemia, and obesity; and regular performance of exercise. This last factor is based on epidemiological observations such as a decrease in the incidence of MI in men who perform heavy work^{1,2}; however, it is only in the last few years that the beneficial effect of exercise has obtained plausible explanations of its own, that is, apart from its effect on other risk factors. There are at least 3 distinct mechanisms for this benefit: (1) Improvement of endothelial function, thereby preventing atherosclerosis and coronary occlusion³; (2) prevention of remodeling after MI through the ex-

pression of oxidative metabolism-related genes⁴; and (3) delaying acute ischemic injury after a coronary occlusion by preconditioning.

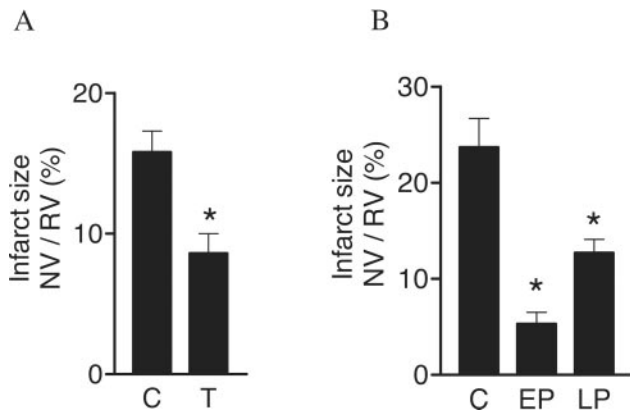
Since the discovery of ischemic preconditioning by Murry et al⁵ in 1986, studies have appeared in the literature searching for its mechanisms and for alternative ways to trigger it. The concept that 1 or 2 episodes of brief ischemia (≈ 5 minutes in duration each), induced a few minutes or a few hours (early preconditioning) or 24 to 72 hours (late preconditioning or second window) before a prolonged coronary occlusion, followed by reperfusion substantially decreases the speed of the ischemic injury and limits infarct size is firmly established in all animal species studied in the experimental laboratory.⁶ It is one of the most powerful means of protecting the myocardium with the exception of early reperfusion. Several lines of evidence in coronary patients suggest but do not prove that the human myocardium is also protected by ischemic preconditioning. For example, preinfarction angina is associated with a smaller infarct size; a lower incidence of congestive heart failure, shock, and ventricular arrhythmias; and decreased mortality.⁷⁻⁹ The ST-segment eleva-

tion observed during angioplasty decreases after subsequent occlusions,¹⁰ which suggests that each occlusion provides preconditioning for the ischemic effect of the next one. Protocols of ischemic preconditioning before coronary artery bypass grafting preserve ATP levels during the subsequent global ischemic period¹¹ and decrease serum levels of troponin T, thereby suggesting a smaller infarct size.¹² Finally, the progressive decrease in the magnitude of ischemia during several consecutive episodes of exercise in patients with demand angina (warm-up phenomenon) suggests the preconditioning effect of each episode.¹³

The protective effect of ischemic preconditioning can be reproduced by several drugs, thus avoiding the necessity of ischemic periods to induce it. Pharmacological preconditioning is potentially a strong therapeutic tool. For example, the opening of mitochondrial ATP-sensitive potassium channels appears to be an important mediator of ischemic preconditioning. The administration of a mitochondrial ATP-sensitive potassium channel opener before planned procedures that involve a potentially ischemic insult (such as coronary artery surgery or angioplasty in the presence of a non-

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Effect of tachycardia (A) and exercise (B) on myocardial infarct size in dogs. C indicates control; T, preconditioning with tachycardia; EP, early preconditioning with exercise; LP, late preconditioning with exercise; and NV/RV (%), infarct size expressed in terms of necrotic region volume as percent of the risk region volume. **P* at least <0.05. Modified from Domenech et al¹⁵ (A) and Domenech et al¹⁹ (B).

ST-elevation acute coronary syndrome that includes unstable angina) has been proposed to “buy time” before proceeding to reperfusion.⁶ Thus, pharmacological preconditioning may be considered “insurance” to protect the heart against ischemia.⁶

Among the maneuvers that induce preconditioning is exercise. Experiments in pigs¹⁴ and dogs¹⁵ showed that brief episodes of tachycardia that do not induce ischemia before a prolonged coronary occlusion decrease the infarct size (Figure) by a mechanism similar to that of ischemic preconditioning and that is mediated through modifications of sarcoplasmic reticulum and mitochondrial ATP-sensitive potassium channels.^{16,17} Subsequent experiments in rats¹⁸ and in dogs¹⁹ showed, as expected, that brief episodes of exercise also induced preconditioning of the infarct size. Interestingly, exercise induces early as well as late preconditioning and the magnitude of reduction in infarct size observed in dogs is much larger than that obtained with ischemic and tachycardia preconditioning (Figure). As yet, there are no studies that show this effect of exercise in humans. In light of these findings, the need for well-designed studies in humans to search for evidence of myocardial preconditioning by exercise is clear.

Regular moderate exercise activity may protect against the effect of myo-

cardial ischemia if a plaque rupture in a coronary artery occurs in an individual with or without previous clinical and laboratory evidence of coronary artery disease, delaying the injury, providing more time for revascularization, and thus yielding a smaller infarct size. Regular exercise may constitute a physiological “insurance policy” against the progression of ischemia. From a physiological point of view, it may be speculated that the myocardium is being preconditioned regularly by common daily physical activity. If tachyphylaxis exists for this protective action, as described for ischemic and pharmacological preconditioning, then episodes of moderate or heavy exercise should be needed to promote the late preconditioning effect.

Clinical Recommendations

Accordingly, the recommendation for the patient under discussion should be to perform exercise that is at least of moderate magnitude but that is performed regularly,²⁰ not only to obtain the beneficial effects of exercise on cardiovascular risk factors but also to obtain the “insurance” it provides.

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Disclosures

None.

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