

EDITORIAL COMMENT

Benefit of an Exercise Program Before Myocardial Infarction*

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In general, we think of exercise as good for the heart. Exercise programs improve exercise tolerance, reduce cardiovascular morbidity and mortality, improve coronary risk factors, and enhance endothelial function (1,2). Exercise promotes weight loss, with the secondary benefits of reduction of metabolic syndrome, diabetes, hypertension, and lipid abnormalities (1). Prior studies showed that exercise-trained animals had smaller myocardial infarctions and better left ventricular function when subjected to ischemia/reperfusion (3–6). Exercise was also shown to restore the ability of ischemic pre-conditioning to reduce ischemic damage in senescent hearts (7). There are some clinical studies that also suggest that older patients who have been physically active are more likely to benefit from a pre-conditioning-like effect of pre-infarct angina (8).

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In coronary artery patients, one episode of acute exercise will pre-condition the patient to a second episode of exercise (9). Thus, when patients undertook two sequential exercise tests with a brief period of rest in between, they were able to exercise longer on the second test before ischemia developed. Also, patients were more resistant to a second episode of percutaneous transluminal coronary angioplasty-induced or pacing-induced ischemia in the catheterization laboratory, than to a first episode (10,11). Experimental studies suggest that exercise induces pre-conditioning and that its mechanism may be related to activation of superoxide dismutase (3).

The study by Freimann et al. (12) in this issue of the *Journal* extends these previous observations by assessing the left ventricle (LV) at four weeks after experimental myocardial infarction in rats that either were sedentary or had undergone a swimming exercise protocol for seven weeks before coronary artery ligation. At four weeks after coronary occlusion, echocardiographic analysis revealed smaller LV volumes and better LV shortening fraction in exercise-trained rats. These less-dilated, better-functioning ventricles also demonstrated a smaller infarct scar and a thicker

noninfarcted interventricular septum. The density of arterioles was also greater in the exercised hearts. Thus the study shows that the benefits of exercise that previously had been described in acute models of ischemia/reperfusion persist for at least one month and translate to less remodeling. Some aspects of these findings are not that surprising—presumably, smaller infarcts in the acute phase in experimental groups would translate to less late remodeling. Other findings are new—including the observation that even four weeks after termination of exercise, there was more muscle mass in the noninfarcted septum of the trained rats with infarcts. Also new are the descriptions of some of the differences in expressed genes, as well as the finding that increased numbers of arterioles persisted in the exercise group even four weeks after termination of exercise.

Although this study suggests that exercise training before the development of coronary occlusion has beneficial effects, we previously observed that swimming exercise in the rat, when performed shortly after coronary artery occlusion, could actually worsen remodeling, leading to a more dilated ventricle and thinner infarct walls (13,14). Presumably, swimming exercise during the early healing phase could increase wall stress and actually thwart early healing. It is also possible that episodes of swimming, during which rats hold their breath, contribute to additional hypoxic damage. Once the infarct is fully healed, exercise is probably safe as long as ongoing ischemia is not present. Also, an episode of heavy physical activity, especially in an untrained individual, may actually trigger acute myocardial infarction.

CHANGES IN GENES WITH ISCHEMIA/INFARCTION

Changes in gene expression can occur rapidly in models of myocardial ischemia. Even brief periods of ischemia—too brief to cause a myocardial infarction—are associated with changes in gene expression patterns. In our experiments, we observed a significant up-regulation of a protective genetic program after applying a brief 20-min ischemic episode in the in vivo rat model of regional ischemia. This protective program included up-regulation in transcripts encoding heat-shock proteins (HSPs 27, 40, 70, 86, and 105), growth factors (brain-derived neurotrophic and vascular endothelial growth factors), serine proteinase inhibitor with anti-apoptotic properties (plasminogen activator inhibitor 1), and cell survivor promoters (growth arrest and deoxyribonucleic acid-damage inducible factor 45-alpha and B-cell translocation gene 2) (15).

A rather different genetic response is observed in models of myocardial infarction. After a permanent coronary occlusion, rat hearts respond with an increased expression of transcripts encoding remodeling and fibrosis-related proteins (e.g., atrial natriuretic peptide, osteopontin, fibronectin, laminin, fibrillin, collagens I and III, and lysyl oxidase) and injury-related proteins as well (e.g., representatives of the complement pathway and vascular cell adhesion

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molecule-1) (16–18). Thus, the duration of ischemia could be an important factor in determining specific changes occurring in the gene expression patterns. Brief nonlethal episode(s) of ischemia promote expression of protective genes, whereas permanent lethal ischemia up-regulates expression of disease and injury-related transcripts.

In the study by Freimann et al. (12), genetic effects of a protective physical exercise program were studied in the in vivo rat model of myocardial infarction. These investigators found that rats subjected to physical exercise (i.e., swimming) demonstrated decreased expression of transcripts for atrial natriuretic peptide and aldolase and increased expression for transcripts encoding cytochrome C oxidase and fatty acid binding protein. These observations expand our knowledge as to what happens to the genetic machinery of the ischemic heart when protective measures are applied. Lethal ischemia up-regulates the expression of transcripts encoding remodeling, fibrosis, and injury-related molecules (16–18). One of the commonly observed up-regulated transcripts includes atrial natriuretic peptide. Although aimed at lowering salt and water retention, reducing systemic vascular resistance and intracardiac filling pressure, and improving myocardial performance, increased production of atrial natriuretic peptide during the post-myocardial period closely correlates with ventricular dysfunction and poor long-term survival in cardiac patients (19). The study shows that protective physical exercise attenuates the increased expression of atrial natriuretic peptide, indicating less wall stress on the LV in trained rats. In addition, physical exercise up-regulates the expression of SERCA-2 transcript (sarcoplasmic reticulum calcium ATPase), an effect that could explain preserved cardiac contractility in trained rats during the period after myocardial infarction.

A recent study by Burelle et al. (20) demonstrated that beneficial effects of regular exercise are associated with a protective metabolic phenotype in the heart. Specifically, these investigators showed that training increases aerobic metabolism, including glucose and fatty acid oxidation, in rat hearts subjected to 20 min of ischemia. The study by Freimann et al. (12) extends this observation and demonstrates that training could also improve aerobic metabolism in models of lethal ischemia, as indicated by increased expression of transcripts for cytochrome C and heart-specific fatty acid binding protein, and decreased expression of aldolase (a representative of anaerobic glucose pathway).

Overall, this study not only confirms the beneficial cardiac effects of regular training but provides us with important details regarding possible mechanisms involved in physical exercise-induced cardiac protection. The readers undoubtedly will appreciate the combination of modern physiological techniques and gene expression profiling platform employed by the authors.

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