Exercise and Endothelial Function

To the Editor:

We have interest in the recent article by Higashi et al., which found that in both normotensive and hypertensive subjects, 12 weeks of walking increased forearm vasodilator responses to acetylcholine but that responses to Nω-monomethyl-L-arginine were unchanged. These data concur with cross-sectional data from our group comparing elite athletes and sedentary controls, and in both studies, the increase in responsiveness to acetylcholine after training correlated with lipid differences.2 The extent to which dietary variation may have contributed is not clear in either study. In particular, the study by Higashi et al2 provides no objective evidence that a training response was achieved, and the reduction in LDL is more consistent with a dietary modification than a brisk walking program. Despite this limitation, both studies and previous animal studies suggest that training for periods of ≥12 weeks increases endothelium-dependent vasodilator reserve. With 4 weeks of cycle training in both normal1 and hypercholesterolemic subjects, however, Nω-monomethyl-L-arginine vasoconstrictor responses are enhanced and the production of nitrates and nitrites from the forearm increases, but neither acetylcholine responses nor the lipid profile is modified.3 These latter data are consistent with enhanced basal production of nitric oxide. The importance of endothelial function as a risk marker and the potential benefits of training in this regard make it important to reconcile these data.

One unifying hypothesis is that the differences in findings reflect progressive adaptation in the nitric oxide system to the trained state. We showed that a single cycling bout increases forearm shear stress and would thus be expected to upregulate endothelial nitric oxide synthase. This results in increased nitric oxide production and vasodilation between exercise bouts in the first few weeks after the commencement of a training program.3,4 If training is continued for several months, it is possible that adaptations to meet increased metabolic demands will evolve from nitric oxide–mediated vasodilation in the short-term to metabolic enzyme and vascular structural modification. The enhanced endothelium-dependent vasodilator reserve that develops with training over months is most likely related to lipid profile modification. This adaptation may be particularly important in the setting of coronary and peripheral vascular disease.

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Response

We thank Dr Kingwell and colleagues for their interest in our article concerning the beneficial effects of a 12-week aerobic exercise program on endothelial function in normotensive and hypertensive subjects.1 Their hypothesis that although short-term exercise over a few weeks augments endothelium-dependent vasodilation through an increase in nitric oxide (NO), enhanced endothelium-dependent vasodilatation due to long-term exercise is most likely related to lipid profile modification and structural vascular changes is interesting and well-conceived but speculative. There is no direct evidence that long-term exercise is not associated with the endothelial NO synthase–NO pathway. The observations are consistent in that long-term exercise over a period of several months augments the endothelium-dependent vasodilatation evoked by acetylcholine and does not change responses to Nω-monomethyl-L-arginine (L-NMMA).1,2 Although the mechanisms by which chronic exercise restores endothelial function are unknown, an exercise-induced reduction in LDL (oxidized LDL), which interferes with the formation of NO and enhances vascular structure by a chronic increase in shear stress, may contribute to acetylcholine-stimulated NO release. After 4 weeks of exercise in normal subjects, a lower dose of L-NMMA (2 μmol/min) reduced basal forearm blood flow (FBF). However, no differences existed in basal FBF between the training group and the sedentary group at a higher dose of L-NMMA (4 μmol/min). In hypercholesterolemic patients, a slight but significant difference existed in basal FBF response to L-NMMA between the training group and sedentary group (79.3±3.4% vs 69.9±6.8%; P=0.05).3,4 In addition, it is possible that a 4-week cycle training regimen is not sufficient to augment FBF response to acetylcholine.3,4 Thus, the data of FBF response to L-NMMA and acetylcholine after short-term exercise should be carefully construed at present. We suggest that enhanced endothelium-dependent vasodilation with both short- and long-term exercise may be mainly due to an increase in NO release.

In our study, hypercholesterolemic patients were excluded. Subjects were divided randomly into an exercising group and a sedentary group to avoid study bias. In addition, to confirm the evidence of exercise and maintenance of lifestyle modification, we checked the exercise performance sheet, measured sodium and potassium intake, and conducted interviews every 4 weeks. We believe that dietary modification and brisk walking do not have a dramatic effect on lipid metabolism, including LDL.
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