Regular Aerobic Exercise Augments Endothelium-Dependent Vascular Relaxation in Normotensive and Hypertensive Subjects: Role of Endothelium-Derived Nitric Oxide

To the Editor:

The recent article by Higashi et al is very intriguing. They showed a connection between long-term aerobic exercise, endothelium-dependent vasorelaxation, and blood pressure reduction in hypertensives. They propose that this training effect may be due to a flow-induced improvement in the stimulated release of nitric oxide (NO).

Dynamic training presents mainly a volume load on the arterial system, and mean arterial pressure is relatively unaffected. Cardiac output is driven up, but total peripheral resistance decreases significantly due to metabolically induced vasorelaxation and the stimulated release of NO to maintain a constant wall shear rate. Average blood flow is increased, but the average wall shear rate may be only slightly elevated above basal levels. It is wall shear rate that drives the regulation of endothelial NO synthase and, with only small acute increases in shear, it may require many months to elicit a significant systemic training response.

During a brief submaximal isometric maneuver, both cardiac output and total peripheral resistance are increased, thus leading to a significant acute increase in wall shear stress on the entire arterial tree. This pressor response continues as long as the isometric contraction is maintained, and it yields small but significant increases in mean arterial pressure during submaximal effort.

Dynamic exercise produces a transient increase in shear, which is offset by the subsequent NO release; this leads to dilatation, decreased shear, and increased flow during the effort. Isometric exercise produces a maintained, increasing shear, which is not completely offset by NO release during the effort. Maintaining an isometric effort for ~1 minute could be a stimulus for the upregulation of endothelial NO synthase through the initiation of signaling events that are activated by shear stress response elements in the endothelium. In fact, this type of training produced significant blood pressure reductions, even in normotensive individuals, when using a simple isometric handgrip regimen over a 4-week period.

Isometrics are generally safe, and isometric handgrip exercises have been used since the early 1900s, mostly as a diagnostic tool. The recent explosion of research regarding NO and its relation to shear stress responses has created an opportunity to investigate controlled isometrics as it relates to a wide array of cardiovascular conditions, such as arteriosclerosis, diabetes mellitus, hypercholesterolemia, hypertension, heart failure, and renal failure. I wish to encourage researchers such as Dr Higashi and colleagues to investigate the use of isometric handgrip training to improve systemic endothelial function.

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Response

We thank Dr Ferguson for his interest in our article on the beneficial effects of chronic aerobic exercise on endothelial function. We agree with Dr Ferguson’s comment that isometric handgrip training is useful for improving endothelial function. In fact, isometric handgrip training enhances endothelium-dependent vasorelaxation of the forearm in patients with chronic heart failure. This regimen is recommended for patients with heart failure or renal failure for whom the degree of physical activity is limited.

Dynamic exercise is associated with beneficial changes in blood pressure, lipid metabolism, glucose metabolism, neurohormonal factors, and body weight rather than with shear stress. These changes may result in the restoration of endothelial function through increased nitric oxide release and an upregulation of endothelial nitric oxide synthase activity. Therefore, it is possible that daily aerobic exercise can prevent the development of atherosclerosis and reduce the risk of cardiovascular and cerebrovascular complications. We think that dynamic exercise augments endothelium-dependent vasodilatation through an increase in shear stress and by means of other exercise-induced beneficial changes. It should be emphasized that aerobic exercise is a useful way to assess endothelial function and it has therapeutic properties in patients with arteriosclerosis, diabetes mellitus, hypercholesterolemia, and hypertension.

Little information exists regarding the effect of long-term isometric exercise on systemic hemodynamics, such as blood pressure, heart rate, and cardiac output; long-term dynamic exercise is generally thought to produce significant blood pressure reductions in patients with essential hypertension. Isometric training over a period of 16 weeks did not alter either blood pressure or heart rate in normotensive individuals. Therefore, whether long-term isometric exercise alters blood pressure is controversial.

We showed that a 12-week aerobic exercise training program consisting of 30-minute sessions performed ≥3 per week at an intensity of 50% of maximal oxygen consumption can augment the forearm vascular response to acetylcholine in patients with essential hypertension. However, the aerobic exercise was performed at only this intensity and duration; further investigation should be performed to determine the intensity and duration of exercise that are most suitable for restoring endothelial function in patients with essential hypertension.

Future studies on the effects of aerobic exercise on arteriosclerosis, hypercholesterolemia, and diabetes mellitus in which endothelium-dependent vasorelaxation is impaired are awaited with great interest.

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