Exercise and Cardiovascular Health
Get Active to “AKTivate” Your Endothelial Nitric Oxide Synthase
Stefanie Dimmeler, PhD; Andreas M. Zeiher, MD

Epidemiological studies have clearly documented that regular physical exercise promotes cardiovascular health and reduces the risk in patients with established coronary heart disease.\(^1,2\) The mechanisms mediating the atheroprotective effects of exercise are not clearly defined. Multiple possible mediators have been suggested, including various physiological adaptations, altered autonomic function, and metabolic adjustments. Regular physical activity is associated with favorable modification of cardiovascular risk factors such as hypertension, diabetes, obesity, and hypercholesterolemia.\(^3\) However, the beneficial effects of regular physical activity cannot be accounted for solely by reduction of risk factors, because with associated reduction with mortality is independent of other coronary risk factors.\(^4\) In recent years, it has become apparent that exercise directly affects the functional activity of the vascular endothelium.\(^4\) By increasing the mechanical shear forces on the luminal surface of the endothelial monolayer, exercise-induced increases in blood flow enhance the vasodilatory capacity of the arteries in animal models and in patients.\(^5,6\) The endothelium not only plays a pivotal role in controlling vascular tone but exerts several important antiatherosclerotic functions, such as preventing platelets and inflammatory cells from adhering to the vascular surface. Indeed, the functional integrity of the endothelium to respond to increased blood flow is the major independent predictor of atherosclerotic disease progression and clinical outcome in patients at risk for coronary artery disease.\(^6\) Thus, the improvement of endothelial function by exercise is most likely to be of major importance for the atheroprotective effects of regular physical activity.

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In the present issue of Circulation, Hambrecht et al\(^7\) now provide some mechanistic insights into the molecular mechanisms underlying the enhanced endothelial vasodilator function in response to exercise in patients with coronary artery disease, namely the increased production of NO. Previous experimental studies demonstrated that endothelial NO bioavailability is regulated by at least 3 different mechanisms, as follows: (1) transcriptional upregulation of the endothelial NO synthase (eNOS),\(^8\) (2) posttranscriptional activation of the eNOS,\(^9,10\) and (3) reduction of reactive oxygen species–mediated breakdown of NO by increasing the antioxidative defense mechanisms.\(^11,12\) Using tissue specimens of the left internal mammary artery harvested during coronary bypass surgery, Hambrecht et al\(^7\) demonstrate that transcriptional and posttranscriptional mechanisms indeed contribute to exercise-induced improvement of endothelial function in patients with coronary artery disease. In detail, the authors link the effect of regular exercise training to an increase in eNOS protein expression and activation of eNOS enzyme activity via Akt-dependent phosphorylation, thereby providing direct evidence for the clinical relevance of the previous cell culture and animal experiments.\(^5\)

Phosphorylation of the amino acid Ser1177 (bovine Ser1179) within the eNOS by the serine/threonine kinase Akt (protein kinase B) has been shown to be critical for activation of the eNOS in various in vitro studies.\(^9,10\) Shear stress–induced stimulation of Akt is responsible for the prolonged, calcium-independent activation of the eNOS and, thus, acts in addition to the short-term calcium-mediated stimulation of eNOS. Meanwhile, additional kinases have been postulated to phosphorylate eNOS at Ser1177, including AMP-activated protein kinase\(^13\) and protein kinase A.\(^14\) Whereas AMP-activated protein kinase does not appear to be involved in shear stress–mediated eNOS phosphorylation and activation, the data regarding the contribution of Akt and protein kinase A for shear stress–induced phosphorylation of eNOS at Ser1177 are conflicting.\(^9,14,15\) However, all studies agree that inhibition of Akt blocks shear stress–induced NO synthesis and that Akt activates the enzymatic activity of eNOS.\(^9,14,15\) To make it even more complex, eNOS recently has been shown to be phosphorylated at various other residues, thereby either promoting (Ser617 and Ser635) or inhibiting (Ser116 and Thr495) eNOS enzyme activity.\(^16,17\) Particularly, shear stress has been reported to phosphorylate Ser635 of the bovine eNOS (equivalent to human Ser633) with a slower kinetic than that of Ser1177.\(^18\) Additionally, eNOS is regulated by protein-protein interaction, acetylation, and translocation.\(^19\) Thus, the somehow conflicting data probably reflect a complex and not yet fully defined array of pathways regulating eNOS activity. Although the limitation of the clinical setting does not allow for studying the causal contribution of the different kinases for eNOS phosphorylation and activation, the highly significant correlation of Akt phosphorylation and eNOS Ser1177 phosphorylation observed by Hambrecht et al\(^7\) supports an important and dominant role for Akt in exercise-induced activation of eNOS in humans.

Endothelium-derived NO exerts a plethora of antiatherosclerotic functions. Acting in an autocrine manner on the
endothelial cell itself, NO inhibits endothelial cell apoptosis, suppresses inflammatory activation, and increases the activity of oxygen radical–scavenging enzymes.12,20 The paracrine effects of NO include inhibition of platelet aggregation via luminal release from the endothelium as well as inhibition of vascular smooth muscle cell proliferation and promotion of positive arterial remodeling via abluminal release.21 Thus, linking exercise to Akt-mediated activation of eNOS does indeed provide important and significant insights into the mechanisms involved in the atheroprotective effects of exercise in patients with coronary artery disease.

However, in addition to mediating eNOS activation, Akt performs several NO-independent functions, which are very likely to contribute to restoring normal endothelial function and, thereby, limiting the clinical manifestation of atherosclerotic disease (Figure). Akt-mediated signaling plays a pivotal role for endothelial cell survival, migration, and proliferation, all of which are intimately involved in angiogenesis and vascular repair.22 In addition, Akt-dependent mechanisms promote mobilization and functional activity of bone marrow–derived endothelial progenitor cells, which contribute crucially to neovascularization of ischemic tissue.23,24 Thus, the close correlation between Akt phosphorylation (and thus activation) and physical activity reported by Hambrecht et al7 may not only translate into improved endothelial NO–mediated vasodilator function of arterial conductance vessels prone to atherosclerotic lesion development, but may also enhance neovascularization of ischemic tissue and vascular repair processes. Indeed, regular physical activity is well established to enhance blood flow to critically ischemic tissue in both the coronary and the peripheral circulation.3

If exercise does translate into improved endothelial function via Akt-dependent mechanisms, other interventions that activate Akt might also be expected to have demonstrable effects on endothelial function. Available evidence clearly supports this hypothesis. Lipid-lowering therapy with statins not only activates the Akt-eNOS pathway25 but also rapidly improves endothelial NO production and, most importantly, decreases cardiovascular events in patients at risk for coronary artery disease. Thus, it is reasonable to speculate that activation of the Akt-eNOS signaling pathway by exercise—as reported by Hambrecht et al7—will eventually translate into inhibition of atherosclerotic disease progression. Interestingly, however, the effects of exercise on Akt-mediated eNOS activation observed by Hambrecht et al7 appear to be superimposed on the effects of statin therapy, given that 88% of the patients studied were chronically receiving statins.

The study by Hambrecht et al,7 however, does not answer the question how much exercise is needed to activate the Akt-eNOS signaling pathway in human arteries. Moreover, the exercise regimen applied is rather unconventional, with 6 sessions of short-term physical activity 10 minutes each day for 4 weeks. Thus, the findings reported by the authors might be specific for frequent but short-term bouts of increases in blood flow rather than reflecting the effects of regular physical activity, which is recommended in most cardiac rehabilitation programs, with 5 to 6 exercise sessions of 20 to 30 minutes each per week. In addition, the number of patients studied was relatively small, and only male patients were included. Notwithstanding these limitations, the findings of Hambrecht et al7 not only disclose a molecular signaling pathway illuminating the therapeutic effects of regular physical activity but also represent an excellent demonstration of translational research from bench to bedside to decipher insights gathered from epidemiological evidence.

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References


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