Exercise Training in Coronary Artery Disease and Coronary Vasomotion

S. Gielen, MD; G. Schuler, MD; R. Hambrecht, MD

Abstract—Exercise training has assumed a major role in cardiac rehabilitation, mostly because of its positive effects on myocardial perfusion in patients with coronary artery disease. The mechanisms involved in mediating this key effect have long been debated: both regression of coronary artery stenosis and improvement of collateralization have been suggested as potential adaptations. However, the comparatively minute changes in luminal diameter and myocardial contrast staining do not fully explain the significant changes in myocardial perfusion. During the last decade, endothelial dysfunction was identified as a trigger of myocardial ischemia. The impaired production of endothelium-derived nitric oxide (NO) in response to acetylcholine and flow leads to paradoxical vasoconstriction and exercise-induced ischemia. Recently, it was confirmed in humans that training attenuates paradoxical vasoconstriction in coronary artery disease and increases coronary blood flow in response to acetylcholine. Data from cell-culture and animal experiments suggest that shear stress acts as a stimulus for the endothelium to increase the transport capacity for L-arginine (the precursor molecule for NO), to enhance NO synthase activity and expression, and to increase the production of extracellular superoxide dismutase, which prevents premature breakdown of NO. Exercise also affects the microcirculation, where it sensitizes resistance arteries for the vasodilatory effects of adenosine. These novel findings provide a pathophysiological framework to explain the improvement of myocardial perfusion in the absence of changes in baseline coronary artery diameter. Because endothelial dysfunction has been identified as a predictor of coronary events, exercise may contribute to the long-term reduction of cardiovascular morbidity and mortality. (Circulation. 2001;103:e1-e6.)

Key Words: endothelium ■ exercise ■ coronary disease ■ vasculature ■ microcirculation

Over the last 2 decades, exercise training has assumed a major role in both the primary and secondary prevention of coronary artery disease (CAD). It increases physical performance, lifts the angina threshold in patients with symptomatic CAD, and improves myocardial perfusion. However, which mechanisms mediate the apparent improvement of myocardial perfusion after training therapy is a matter of continuing debate.

Basically, regional myocardial hypoperfusion in CAD results from a combination of 3 pathogenetic components: (1) vascular stenosis, (2) microvascular dysfunction, and (3) microrheology and hemostasis. All 3 components may be affected by exercise training in patients with stable CAD.

Regression of Coronary Atherosclerosis

The first era of clinical research was guided by the concept that the extent of coronary stenosis represented the key determinant of myocardial perfusion. In this phase, which paralleled the expansion of interventional cardiology, the angiographically visible static coronary stenosis was regarded as the therapeutic target. This led to the hypothesis that exercise training would result in a net regression of coronary stenoses. Three prospective, randomized intervention studies have been published assessing the influence of exercise training in combination with cholesterol lowering on the progression of CAD. They share not only the “regression hypothesis,” but also a methodological approach of quantitative coronary angiography.

The Lifestyle Heart Trial analyzed the effect of lifestyle changes, including a strictly vegetarian diet, stress-management techniques, smoking cessation, and 3 hours of exercise training per week, on the degree of coronary artery stenosis. In the intervention group, a regression of coronary artery stenoses from 40±17% to 38±17% was observed; in the control group, stenoses increased from 43±16% to 46±19% (P=0.001). This difference was even more pronounced at 5-year follow-up. At that point, the intervention group had a 3.1% regression of stenoses (in percent of relative coronary stenosis) compared with an 11.8% progression in the usual care group; this regression was associated with a 2.5-fold risk reduction in cardiac events.

In the Stanford Coronary Risk Intervention Project, 300 patients with CAD were randomly assigned to receive either the usual care or multifactorial risk reduction, including a low-fat diet, lipid-lowering medication, and exercise training. Serial coronary angiograms on a yearly basis showed an...
attenuation of disease progression in the intervention arm, with a decline in minimal luminal diameter by 0.024±0.067 mm/year compared with a regression of 0.045±0.073 mm/year in the control group (P<0.02). Over the study period of 4 years, 25 cardiac events occurred in the intervention group and 44 occurred in the control group.

In the Heidelberg Regression Study, 113 patients with documented CAD were randomly assigned to a bifactorial intervention with a low-fat diet and regular physical exercise or to a control group. This regimen was effective in halting the progression of coronary atherosclerosis. After 1 year, the mean luminal diameter was unchanged in the training group (0.0±0.038 mm), but it decreased in the usual care group by 0.13±0.045 mm (P<0.05). At 6-year follow-up, the progression of CAD was still significantly retarded in the training group. In a retrospective analysis, a correlation between exercise-associated energy expenditure and change in minimal stenosis diameter revealed that a regression of coronary stenoses may only be expected when using >2200 kcal/week, which is equivalent to 5 to 6 hours of regular physical exercise per week. This finding makes the regression of coronary stenoses an unlikely mechanism to explain the improved myocardial perfusion in the majority of patients who undergo exercise training.

In summary, multifactorial lifestyle changes, including reducing cholesterol and improving exercise training, can attenuate the progression of coronary stenoses. However, the comparatively small morphometric changes observed in coronary diameter make it difficult for this factor to explain the substantial increase in myocardial perfusion and angina threshold associated with training interventions. From today’s perspective, it may be that the use of intravascular ultrasound, which permits a more accurate assessment of plaque volume and 44 occurred in the control group.

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Formation of Collaterals

As with epicardial vessels, the first scientific approach to the microcirculation was led by the search for a morphological correlate: collateral formation. Evidence from animal studies suggested that long-term intensive physical exercise led to an improvement in coronary collateralization. Neill et al found an increase in collateralization after 5 to 8 weeks of training in dogs on the basis of microsphere injections. However, no difference in epicardial collaterals was apparent angiographically.

In humans, data derived from clinical studies are equally controversial. In a subgroup analysis of an 8-week exercise training trial in ischemic cardiomyopathy involving 23 patients, Belardinelli et al found a significant increase in coronary collateralization as quantified by visual classification of the retrograde filling of the infarct-related vessel.

In the Heidelberg Regression Study, which involved patients with stenotic CAD and preserved left ventricular function, however, no increase in angiographically visible collateralization was observed in long-term follow-up after 1 year of exercise training. It may well be that (1) angiography is not sensitive enough to detect the formation of small intramyocardial collateral vessels that will be recruited only during exercise and (2) the stimuli for collateralization are different in patients with stenotic CAD and stable angina pectoris and postinfarction patients with complete vessel occlusion and reduced left ventricular function.

Endothelial Dysfunction in Coronary Conduit Vessels

The last decade witnessed a paradigm shift in the pathophysiological concept of CAD. With the growing knowledge about endothelial function came the awareness that the luminal diameter of epicardial vessels is highly dynamic in response to mechanical (flow-related) or agonist-mediated (endogenous or pharmacological) stimuli.

Alterations in coronary vascular endothelial function were first described in 1986, when Ludmer et al observed a paradoxical vasoconstriction of atherosclerotic segments after infusing acetylcholine into the left coronary artery of patients with atypical chest pain. The observation that major coronary risk factors are associated with coronary endothelial dysfunction even before circumscript stenoses are visible has led to the concept that endothelial dysfunction occurs at the early stages of atherosclerosis as a condition sine qua non for atherogenesis.

Pathophysiology of Endothelial Dysfunction

Coronary vasomotion is influenced by mechanical and agonist-mediated stimuli, both of which converge on endothelial nitric oxide (NO) synthesis/release as the final common pathway. Endothelial dysfunction occurs as a result of decreased bioactive NO concentrations at vascular smooth muscle cells.

NO concentrations can be affected by alterations at the following different steps of its pathway: (1) availability of the precursor molecule L-arginine; (2) alterations of NO synthesis rate, as determined by endothelial NO synthase (eNOS) conformational changes, expression, or genetic polymorphism; and (3) differences in NO breakdown velocity related to reactive oxidative species (ROS) once it is released.

L-Arginine

The availability of L-arginine at the active site of eNOS depends on several factors: (1) exogenous supply with L-arginine or endogenous L-arginine synthesis; (2) intracellular accumulation of L-arginine, which depends on active cytokine-regulated transmembranous transport; (3) intracellular degradation of L-arginine by arginase to ornithine and urea; and (4) the presence of the antagonist asymmetric dimethyl arginine, which blocks NO synthesis from L-arginine. Asymmetric dimethyl arginine is present in patients with peripheral vascular disease and chronic renal failure. To date, it remains unclear which of these mechanisms are involved in the development of endothelial dysfunction in coronary atherosclerosis, and clinical data are also contradictory.

Although L-arginine supplementation improves vascular function in hypercholesterolemia and chronic heart failure, it has no effect in patients with stable CAD.
**eNOS**
The activity of eNOS can be altered in response to short-term stimuli by conformational changes. Michel and Ferriol proposed that eNOS association with caveolin suppresses the enzyme activity in the unactivated endothelial cell. Agonist activation increases intracellular calcium concentration via cGMP-dependent mechanisms, thus promoting calmodulin binding to eNOS and dissociation from caveolin. The activated eNOS-calmodulin complex synthesizes NO until [Ca^{2+}]] decreases below a level necessary to sustain calmodulin binding. Calmodulin dissociates, and the inhibitory eNOS-caveolin complex reforms.

Because NO is released via plasmalemmal caveolae, eNOS is targeted to this subcellular compartment by enzyme acylation, which may occur as reversible palmitoylation or irreversible myristoylation. Prolonged eNOS activation leads to depalmitoylation of the enzyme, translocation away from the caveolae, phosphorylation, and rebinding of the inhibitory caveolin. It remains unclear how this regulation of enzymatic activity is affected by the pathological conditions of endothelial dysfunction.

More is known about long-term conditions like exposure to high levels of tumor necrosis factor-α, oxidized LDL, and hypoxia, all of which have been shown to lower eNOS expression in cultured endothelial cells. In atherosclerosis, eNOS expression is significantly reduced, indicating that this downregulation may be an important factor for the pathogenesis of endothelial dysfunction.

Genetic polymorphisms of eNOS were recently described as prevalent in certain patients (e.g., in hypertensive Japanese). However, whether polymorphisms of eNOS result in alterations of enzyme activity remains controversial.

### NO Breakdown
Atherosclerosis and endothelial dysfunction are associated with increased levels of ROS (ie, ·OH, H₂O₂). These highly reactive radicals accelerate the extracellular degradation of secreted NO by forming peroxynitrite. Adventitial NADPH oxidases produce quantities of superoxide high enough to affect endothelial function. This mechanism has been confirmed in CAD in intervention studies with antioxidants. For example, in patients with CAD, the long-term administration of ascorbic acid (vitamin C), a natural radical scavenger, reverses endothelial dysfunction.

However, the underlying mechanism is more complex. Vascular smooth muscle cells produce and set free a potent antioxidative enzyme, the extracellular superoxide dismutase (ecSOD), which is reduced in CAD and correlates with flow-dependent vasodilation of the radial artery in vivo. In human aortic smooth muscle cell cultures and organoid cultures of mouse aorta, the NO donor diethylamine-NO (DETA-NO) enhances ecSOD expression in a time- and dose-dependent fashion. This finding is consistent with the hypothesis that endothelium-derived NO stimulates the expression and release of ecSOD from vascular smooth muscle cells. Training seems to have similar effects on ecSOD.

### Shear Stress and Endothelial Function: Experimental Data
Shear stress is an important component of exercise, and it affects vascular NO concentrations on all 3 levels responsible for the development of endothelial dysfunction discussed above.

### L-Arginine
Shear stress increases the velocity of the endothelial high-affinity/low-capacity transport system for L-arginine. This ensures substrate availability as the rate-limiting step of eNOS, which generates ROS in the absence of L-arginine.

### eNOS
As early as 60 minutes after the initiation of shear stress, bovine aortic endothelial cells produce 13 times more NO compared to baseline conditions. This increase seems to be mediated by both short-term enhancement of eNOS activity and the activation of eNOS expression. Shear stress leads to eNOS phosphorylation on serine residues independent from increases in [Ca^{2+}], which may modulate enzyme activity.

Recently, a shear-stress-activated signal transduction cascade involving phosphatidylinositol-3-kinase and the serine/threonine kinase Akt has been identified; it causes [Ca^{2+}]-independent eNOS phosphorylation and activation.

A considerable increase of eNOS expression has been demonstrated in endothelial cell-culture experiments after 6 hours of exposure to laminar shear stress. This is consistent with animal studies of exercise training in dogs, which documented increased eNOS expression and NO production in coronary conduit mice and resistance vessels. Increases in eNOS expression are proportional to the extent of laminar shear stress applied, but they are abolished by turbulent flow.

However, the presence of 2 alleles of the eNOS gene seems to be necessary to increase eNOS expression in response to exercise training. In mice heterozygotic for a loss of the eNOS gene, no increased eNOS protein expression could be observed in the aorta, whereas wild-type eNOS mice had a 2.5±0.4-fold increase.

### NO Breakdown
It has long been enigmatic why exercise training, which increases total oxygen uptake and in turn the production of ROS, can improve endothelial function. As mentioned above, it was recently shown that endothelium-derived NO increases the expression of ecSOD in vascular smooth muscle cells. In the same publication, the authors demonstrated that exercise training increased both eNOS and ecSOD in wild-type mice, whereas ecSOD remained unchanged in mice lacking eNOS. This suggests that the effect of training on ecSOD is mediated by endothelium-derived NO.

### Effects of Exercise Training on Endothelial Dysfunction in Conduit Vessels
In a recently published prospective clinical study, 19 patients with coronary endothelial dysfunction, as documented by acetylcholine-induced vasoconstriction, were prospectively randomized to a training (10 patients) or control group (9 patients). At baseline and after 4 weeks, endothelium-
mediated vasodilation was assessed after intracoronary infusions of acetylcholine (0.072, 0.72, and 7.2 µg per minute). The average peak flow velocity was measured using a Doppler wire, and vessel diameter was assessed by quantitative coronary angiography.

At baseline, both groups had similar constrictive responses to acetylcholine. After 4 weeks of intensive physical training, acetylcholine-induced coronary artery constriction was attenuated by 54% after the administration of 7.2 µg/min acetylcholine (from $-0.41 \pm 0.05$ to $-0.19 \pm 0.07$ mm; $P < 0.05$ versus control). In training patients, the change in average peak flow velocity in response to 7.2 µg/min acetylcholine increased from 78±16% at the initial study to 142±28% after 4 weeks ($P < 0.01$ versus control). This trial documented, for the first time, that exercise training attenuates paradoxical vasoconstriction in response to acetylcholine and improves the endothelial function of coronary conduit vessels in patients with CAD.

While the study by Hambrecht et al.44 enrolled patients with nonocclusive stable CAD, Griffin et al.45 used an animal model of subacute coronary occlusion by amaroid constrictor in pigs to assess the effects of 16 weeks of exercise training on endothelium-dependent vasorelaxation after long-term coronary occlusion. Even in artery segments distal to the constrictor, they observed a markedly enhanced NO-mediated relaxation, which basically confirmed the results in patients with nonstenotic CAD.

**Coronary Resistance Vessels and Microcirculation**

**Microvascular Dysfunction in CAD**

Small coronary arteries with an internal diameter <300 µm are a major component of the regulation of coronary vascular resistance and the distribution of coronary flow. It has been shown that the responsiveness to endothelium-derived relaxing factors changes from the proximal to the distal part of dog coronary arteries. cGMP-mediated vasodilators like NO, nitrates, and atrial natriuretic peptide preferentially dilate proximal conductance arteries. Resistance arteries—in contrast to epicardial conduit arteries—are exposed to more than just circulating or platelet-derived neurohormones. The vascular motor state of the distal microvasculature is influenced by the dominant effects of local myocardial metabolic demands.46 Altman et al.47 reported that N\textsuperscript{G}-nitro-L-arginine, a NO synthase inhibitor, did not substantially impair the coronary vasodilation associated with the increased myocardial oxygen requirements produced by exercise in conscious dogs. Under these conditions, adenosine, which is a by-product of the breakdown of ATP, the main energy source of myocardial contraction, is formed at an accelerated rate.48 Among all metabolic factors described so far, adenosine seems to be the most relevant clinically.

**Effects of Exercise Training on the Microcirculation**

Exercise training increases resistance vessel sensitivity and maximal responsiveness to adenosine in dogs in vivo.49 These results also suggest that training alters the responses of coronary artery smooth muscle to metabolic vasodilators. In line with this hypothesis, Muller et al.50 found an increased myogenic response of coronary resistance arteries from exercise-trained swine for intraluminal pressures >40 mm Hg. After exercise training, adenosine-mediated arteriolar permeability for porcine serum albumin increased by 65%, indicating a higher vascular permeability.51

Long-term exercise training induces functional and morphological changes in the microvasculature. White et al.52 conclusively showed in a porcine model of exercise training that training increases the total vascular bed cross-sectional area by up to 37% after 16 weeks. As a consequence, vascular resistance decreases and maximal flow reserve rises.

Hambrecht et al.44 assessed changes in microvascular function by measuring the coronary flow reserve ratio in response to adenosine. Training patients had a 29% increase in coronary flow reserve after exercise training (from 2.8±0.2 to 3.6±0.2; $P < 0.01$ versus control), which also indicated an enhanced sensitivity of the coronary microcirculation to adenosine.

**Microrheology and Platelet Function**

Blood viscosity can be reduced and microrheology improved by exercise training in healthy subjects and patients with peripheral vascular disease.53 However, in patients with CAD and impaired left ventricular function, training failed to have any significant effect on blood viscosity.54 The reasons for the different responses to exercise in these subgroups remain obscure.

Short-term bouts of strenuous exercise may have thromboembolic side effects because platelet number and activity are increased.55 Long-term exercise training, however, attenuates this potentiation of platelet function and increases platelet cGMP content.56 Physical training seems to suppress coagulability, as indicated by the decrease in fibrinogen, factor VIII.C, von Willebrand factor, factor VII.C, and thrombin-antithrombin III complex and the prolongation of activated partial thromboplastin time. The decrease of anticoagulatory factors like plasminogen, tissue plasminogen activator antigen, α\textsubscript{2}-plasmin inhibitor, plasminogen activator inhibitor-1, and plasmin-α 2PI complex after physical training may result from decreased coagulability.57 In summary, a net reduction of thrombogenic risk in CAD by exercise training has been documented.

**Future Aspects**

Despite the encouraging results of high-intensity exercise training on coronary endothelial function, any training intervention must be embedded in a comprehensive risk factor management as a secondary prevention strategy. In most cases, the pathogenesis of endothelial dysfunction can be linked to the presence of one or more of the following coronary risk factors, all of which have been shown to be associated with impaired endothelium-dependent vasodilation: diabetes mellitus,58 hypercholesterolemia,59 arterial hypertension,60 and smoking (both active61 and passive62). Given the prevalence of these risk factors, it still must be determined if adequate therapy for the risk factor (eg, statins for hypercholesterolemia) is effective in restoring endothelial
dysfunction to normal or whether additive effects are to be expected in combination with training.

A further open question that might influence future guidelines of exercise training in CAD is the dose-response relationship between the training intensity and the effects on coronary vasomotion. Is there a threshold of either training intensity/duration or trained muscle mass that must be surmounted to achieve improved endothelium-dependent vasodilation?

Recently, the first reports about a possible association between endothelial dysfunction and the frequency of clinical events were published. Further prospective studies are needed to establish whether endothelial dysfunction is an independent prognostic marker. If so, exercise training may be promoted from a symptomatic intervention to a preventive strategy with long-term prognostic benefits.

**Conclusion**

Protagonists of exercise training in patients with coronary atherosclerosis have long faced the dilemma of how to explain the improvement of myocardial perfusion. Regression of coronary atherosclerosis and collateral formation have been favorite theories. However, angiographic techniques have thus far failed to document any significant increase in coronary collaterals at rest. Although the net regression of stenotic lesions may be achieved with high-intensity exercise training, it is unlikely that plaque regression causes the significant improvement in myocardial perfusion, which is seen much earlier than changes in baseline luminal diameter.

Keeping these limitations in mind, exercise training enhances myocardial perfusion by increasing both eNOS and ecSOD expression, thus attenuating the premature breakdown of NO by ROS. These increases in both local NO production and half-life improve endothelium-dependent vasodilation in response to flow or acetylcholine. It is reasonable to suppose that these functional changes occur rather rapidly after the initiation of an exercise training program, although no studies are available on their precise time course. Anatomic changes like augmentation of the capillary bed and slowing of the progression of coronary atherosclerosis will require more extended periods of training (Figure).
55. Prisco D, Francalanci I, Filippini M, et al. Physical exercise and hemo-
56. Wang JS, Jen CJ, Chen HL. Effects of exercise training and decondi-
58. Johnstone MT, Creager SJ, Scales KM, et al. Impaired endothelium-
59. Chowienczyk PJ, Watts GF, Cockcroft JR, et al. Impaired endothelium-
dependent vasodilation of forearm resistance vessels in hypercholester-
61. Nitenberg A, Antoni I, Foult JM. Acetylcholine-induced coronary vaso-
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