Impaired aerobic capacity in hypercholesterolemic mice: partial reversal by exercise training

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1Section of Vascular Medicine, Division of Cardiovascular Medicine and 2Division of Pediatric Cardiology, Stanford University, and 3Department of Pathology, Veterans Administration Hospital, Stanford University, Stanford, California 94305; and 4Department of Cardiology, Heart Center, University of Leipzig, 04289 Leipzig, Germany

Niebauer, Josef, Andrew J. Maxwell, Patrick S. Lin, Philip S. Tsao, Jon Kosek, Daniel Bernstein, and John P. Cooke. Impaired aerobic capacity in hypercholesterolemic mice: partial reversal by exercise training. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H1346–H1354, 1999.—The present study assessed whether impaired aerobic capacity previously observed in hypercholesterolemic mice is reversible by exercise training. Seventy-two 8-wk-old female C57BL/6J wild-type (+, n = 42) and apolipoprotein E-deficient (−, n = 30) mice were assigned to the following eight interventions: normal chow, sedentary (E−, n = 17); E−, n = 8) or exercised (E−, n = 13; E−, n = 7) and high-fat chow, sedentary (Echol−, n = 6; Echol−, n = 8) or exercised (Echol−, n = 6; Echol−, n = 7). Mice were trained on a treadmill 2 × 1 h/day, 6 days/wk, for 4 wk. Cholesterol levels correlated inversely with maximum oxygen uptake (r = −0.35; P < 0.02), which was blunted in all hypercholesterolemic sedentary groups (all P < 0.05). Maximum oxygen uptake improved in all training groups but failed to match E−. Vascular reactivity and nitric oxide (NO) synthesis correlated with anaerobic threshold (r = 0.36; P < 0.025) and maximal distance run (r = 0.59; P < 0.007). We conclude that genetically induced hypercholesterolemia impairs aerobic capacity. This adverse impact of hypercholesterolemia on aerobic capacity may be related to its impairment of vascular NO synthesis and/or vascular smooth muscle sensitivity to nitrovasodilators. Aerobic capacity is improved to the same degree by exercise training in normal and genetically hypercholesterolemic mice, although there remains a persistent difference between these groups after training.

apolipoprotein E-deficient mice; atherosclerosis; nitric oxide; oxygen uptake; vascular reactivity

WE SHOWED PREVIOUSLY (13) in sedentary mice that both diet-induced and genetically determined hypercholesterolemia lead to an early impairment of aerobic capacity during maximal treadmill testing. This impairment in aerobic capacity significantly correlated with a reduction in endothelium-dependent relaxation, endothelial nitric oxide (NO) production, and urinary nitrate excretion. Conversely, there is accumulating evidence that exercise-induced increase in blood flow induces the expression of mRNA for NO synthase (NOS), augments NO activity, and enhances endothelium-dependent vasodilation (6, 11, 14, 24, 27). It was the aim of this study to examine the effect of exercise training on vascular reactivity and aerobic capacity in the presence of a broad spectrum of diet-induced and/or genetically determined cholesterol levels; to assess whether exercise training could reverse the cholesterol-induced impairment of aerobic capacity; and to further determine the role of NO during aerobic adaptation to exercise training in the hypercholesterolemic state.

METHODS

Animals. Eight-week-old female wild-type (n = 42) and apolipoprotein E (apoE)-deficient (n = 30) C57BL/6J mice (Jackson Laboratories, Bar Harbor, ME) were entered into experimental protocols after 1 wk of acclimation in the housing facilities of the Stanford Department of Comparative Medicine. All mice were inspected before the study by their veterinarians and monitored daily by technicians and investigators. All experimental protocols were approved by the Administrative Panel on Laboratory Animal Care of Stanford University and were performed in accordance with the recommendations of the American Association for the Accreditation of Laboratory Animal Care. Mice were housed three to four per cage under standard conditions in conventional cages. They were maintained on a 12:12-h light-dark cycle and given unlimited access to food and water for the duration of the study. All mice were handled daily and taught to run on a treadmill with shock plate incentive (Exer-4 Treadmill, Columbus Instruments, Columbus, OH) but were otherwise confined to cages for the duration of the study.

The apoE-deficient mice were generated from targeted disruption of the apoE-deficient gene in the 129 embryonic stem cell line. Germ-line chimeras were mated and back-crossed for 10 generations with C57BL/6J wild-type mice (19).

Experimental protocol. Wild-type mice and apoE-deficient mice were randomized at 8 wk of age to eight groups with the following diet and exercise interventions (Fig. 1): wild-type mice on normal mouse chow, sedentary (E−, n = 17) or exercised (E−, n = 13); wild-type mice on a high-fat chow, sedentary (Echol−, n = 6) or exercised (Echol−, n = 7); and apoE-deficient mice on a high-fat chow, sedentary (Echol−, n = 8) or exercised (Echol−, n = 7). We showed previously (13) in sedentary mice that both diet-induced and genetically determined hypercholesterolemia lead to an early impairment of aerobic capacity during maximal treadmill testing. This impairment in aerobic capacity significantly correlated with a reduction in endothelium-dependent relaxation, endothelial nitric oxide (NO) production, and urinary nitrate excretion. Conversely, there is accumulating evidence that exercise-induced increase in blood flow induces the expression of mRNA for NO synthase (NOS), augments NO activity, and enhances endothelium-dependent vasodilation (6, 11, 14, 24, 27). It was the aim of this study to examine the effect of exercise training on vascular reactivity and aerobic capacity in the presence of a broad spectrum of diet-induced and/or genetically determined cholesterol levels; to assess whether exercise training could reverse the cholesterol-induced impairment of aerobic capacity; and to further determine the role of NO during aerobic adaptation to exercise training in the hypercholesterolemic state.

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In our previous report (13) we assessed the influence of hypercholesterolemia on aerobic capacity in wild-type and apoE-deficient mice at the age of 8 and 12 wk. Mice were
Maximal oxygen uptake is defined as oxygen uptake attained by the animal before exhaustion. The respiratory exchange ratio is the carbon dioxide production/oxygen uptake at any given time and, at exercise intensities above anaerobic threshold, is used as an indirect indicator of lactic acid production. At high work rates, anaerobic work supplements aerobic work. Lactic acid, produced from anaerobic metabolism, is buffered by serum bicarbonate, resulting in a stoichiometric increase in carbon dioxide output over oxygen uptake (32). Thus the respiratory exchange ratio begins to rise after anaerobic threshold is attained and continues to rise with increasing workload until exhaustion (28).

The anaerobic threshold for each individual mouse is expressed in units of oxygen uptake and was determined from computer analysis of carbon dioxide production/oxygen uptake plots by the V-slope method of Beaver et al. (2). In situations when the slope of carbon dioxide production/oxygen uptake did not increase at higher work rates, the maximum oxygen uptake was taken as the anaerobic threshold (2).

Distance run until exhaustion was measured during maximal treadmill testing. The change in distance run to exhaustion between baseline and end of the study (distance run until exhaustion at 12 wk – distance run until exhaustion at 8 wk) is taken as an approximate measure of the change in overall work performance during the study course.

Aerobic work capacity was determined by the summation of minute oxygen uptake above the basal rate over the course of treadmill running until exhaustion. This was multiplied by the constant 20 J/ml O2 to convert oxygen uptake to aerobic work (29).

Vascular reactivity. One 7-mm segment of thoracic aorta (measured proximal from the diaphragm) was dissected free of connective tissue and immediately placed in cold physiological saline solution (PSS) composed of (mM) 118 NaCl, 4.7 KCl, 2.5 CaCl2, 1.2 MgSO4, 25 NaHCO3, 0.026 Na2EDTA, 11.1 dextrose, and 0.1 L-arginine. Aortic segments were quickly mounted on wire stirrups, hung from force transducers, and submerged in oxygenated PSS at 37°C. Over the course of 60 min, the segments were progressively stretched to the optimum point of their length-tension relationship (determined previously to be 3 g). Subsequently, the EC50 of norepinephrine (NE) was determined by exposing the segments to increasing concentrations of NE (in half-log increments from 10−10 to 10−4 M). Once a maximal response was obtained, the segments were washed repeatedly with fresh PSS for 60 min.
until the tension returned to the previous baseline value. Responses to the vasodilators nitroglycerine and acetylcholine were studied after precontracting the segments with the EC50 of NE. After a stable contraction was obtained, the segments were exposed to increasing doses of vasodilator.

Measurement of nitrogen oxides. A 7-mm segment from the abdominal aorta (measured proximal from the iliac bifurcation) was stored at −80°C for measurement of nitrogen oxides (NOx). NOx in the incubation medium was measured with a commercially available chemiluminescence apparatus (model 2108, Dabsi, Glendale, CA) as previously described (25). The samples (100 μl) were injected into boiling acidic vanadium(III) chloride. This technique utilizes acidaic vanadium(III) chloride at 98°C to reduce both NO2− and NO3− to NO, which is then detected by the chemiluminescence apparatus after reacting with ozone. Signals from the detector were analyzed by computerized integration of curve areas. Standard curves for NaNO2/NaNO3 were linear over the range of 50 pM to 10 nM. In these small segments of tissue, there is significant variability, which is a limitation of this technique.

Hematology and biochemistry. Blood samples were collected at the time of death. These were immediately centrifuged at 3,000 rpm for 15 min. The serum was separated and stored at −80°C until analysis. Total serum and high-density lipoprotein cholesterol were analyzed using an enzymatic method (1).

Tissue preparation. At death the heart was excised and placed in PSS, pH 7.2, for 5 min. It was then embedded in optimum cutting temperature compound (Fischer Chemical, Santa Clara, CA), snap-frozen on dry ice, and kept at −80°C until being cryosectioned.

Histochemistry. Sectioning and lesion evaluation was performed following the protocol of Paigen et al. (18). The basal portion of the heart and the proximal ascending aorta were sectioned transversely into 10-μm-thick slices. Serial sections were collected on polylysine-coated slides and stored at −80°C. Lipid deposits were identified by use of oil red O with hematoxylin and light green counterstain (18). For each animal, five sections separated by 50 μm (12) were quantified. The first and most proximal section to the heart was taken 80 μm beyond the distal extent of the aortic sinus. Histologic cross-sections were viewed by light microscopy with ×10 magnification and quantitated by using a grid in the eyepiece. The area of oil red O staining in each section was determined by an experienced observer blinded to the treatment group, and the mean lesion area per section per animal was calculated for each individual and group of animals.

Scanning electron microscopy. The base of the heart with the attached aorta was fixed without distension in 1.5% glutaraldehyde buffered to pH 7.2 and then dissected longitudinally to allow visualization of the luminal surface of the aorta and the aortic sinus (Fig. 2). Samples were dehydrated in graded ethanol, dried by the critical point method using carbon dioxide, spatter coated with gold and examined with an ISI 40 scanning electron microscope (International Scientific Instruments, Santa Clara, CA) operating at 10 kV with ×50 magnification for morphological features of the endothelium.

Drugs. All solutions were prepared in distilled water except for oxalacetic acid (OAA) and 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB), which were prepared in 0.1 M and 1 M Tris·HCl, respectively. Acetyl coenzyme A, DTNB, OAA, norepinephrine bitartrate, acetylcholine, calcium ionophore A-23187, N-nitro-L-arginine, and L-arginine were purchased from Sigma Chemical (St. Louis, MO), whereas nitroglycerin was obtained from DuPont Chemicals (Wilmington, DE).

RESULTS

Body weight and serum cholesterol. At 8 wk of age baseline body weight was comparable in wild-type and apoE-deficient mice (19.1 ± 0.6 vs. 19.9 ± 0.6 g) (Table 1). After 4 wk of study, apoE-deficient mice on a high-fat diet had greater body weight in comparison to all other groups (all P < 0.05).

Total serum cholesterol levels were significantly higher in the high-fat compared with the normal diet groups (wild type: normal diet vs. Thomas-Hartfroft, P < 0.0001; apoE-deficient: normal chow vs. western-type diet, P < 0.0001). High-density lipoprotein cholesterol levels were not significantly different between groups (P = not significant [NS]). Exercise training did not lead to significant changes in body weight or cholesterol levels in wild-type or apoE-deficient mice.

Basal aerobic capacity. We previously reported (13) that at the age of 8 wk wild-type and apoE-deficient mice showed comparable exercise performance. In particular, there were no significant differences in maximum oxygen uptake, respiratory exchange ratio, anaerobic threshold, or aerobic work capacity. Only distance run until exhaustion was 27% greater in the apoE-deficient mice.

Aerobic capacity after exercise training. After 4 wk of study, sedentary wild-type mice on a normal chow ran farther than at baseline (8 wk of age), whereas corresponding values remained unchanged in Echol mice and decreased significantly in E− mice (P < 0.05) (Table 2, Fig. 3). Maximal running distance to exhaustion improved in all training groups, reaching statistical significance in E− mice (all P < 0.05). Changes in maximal running distance between baseline and 4 wk of study were inversely correlated to total serum cholesterol (r = 0.75, P < 0.0001).

We previously reported (13) in sedentary mice that after 4 wk of study maximum oxygen uptake remained essentially unchanged in E+ (8 wk vs. 12 wk: 107 ± 4 vs. 109 ± 5, P = NS), whereas there was a trend toward

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Fig. 2. Varying degrees of endothelial damage in wild-type and apoE-deficient mice after 4 wk of study. A: normal endothelial surface distal to aortic cusp of a wild-type, normocholesterolemic mouse. (Endothelial surface of aortas from wild-type animals on high-fat diet was not appreciably different from those on a normal diet.) B: endothelial surface with mild alterations in a sedentary apoE-deficient mouse on normal chow. Note detachment of occasional endothelial cells. C: endothelial surface of a sedentary apoE-deficient mouse on a high-fat chow with focal severe damage, endothelial detachment, and leukocyte adherence.
deterioration of maximum oxygen uptake in hypercholesterolemic mice (Echol, 8 wk vs. 12 wk: 107 ± 4 vs. 101 ± 9 mL O₂·min⁻¹·kg⁻¹, P = 0.07) and a significant reduction in apoE-deficient mice on normal chow (103 ± 1 vs. 98 ± 6, P < 0.004) as well as high-fat diets (103 ± 1 vs. 97 ± 6, P < 0.0006). In this study, exercise training led to significant improvement in all groups, but values reached by trained apoE-deficient mice on normal as well as high-fat diets were not above those of sedentary wild-type mice.

Highest values for anaerobic threshold were documented in sedentary and trained wild-type mice on normal chow. Although apoE-deficient mice on either chow still showed significant improvement over values reached by their sedentary littersmates (all P < 0.05), results were significantly worse than those observed in Echol (P < 0.05). In addition, respiratory exchange ratio was significantly higher in apoE-deficient mice than in wild-type mice (P < 0.05), and values did not change with exercise training.

Exercise training led to significantly higher aerobic work capacity in all training groups compared with their respective sedentary groups (P < 0.05). Neverthe-
less, mice in the training groups that received high-fat diets reached significantly lower levels of aerobic work capacity than mice on normal chow (P < 0.05).

Aerobic work capacity may be influenced by cardiac mass. However, cardiac mass was slightly higher in apoE-deficient mice compared with wild-type mice (all P < 0.05), so this cannot explain the lower aerobic work capacity in the apoE-deficient mice.

Because body weight is the denominator for anaerobic threshold, aerobic work capacity, and maximum oxygen uptake, ANCOVA was performed. Significance remained when anaerobic threshold, aerobic work capacity, and maximum oxygen uptake of 1) all mice and 2) exercised mice only were adjusted for body weight, suggesting that increasing body weight is not the cause for declining aerobic capacity.

Vascular reactivity. Maximal vasoconstriction to NE and ECA₉₀ was not different between groups (data not shown). Endothelium-dependent vasorelaxation was impaired in Echol and Echol-ex mice (Fig. 4). When apoE-deficient mice underwent exercise training, endothelium-dependent relaxation in Echol-ex was comparable to Echol and Echol-ex, whereas vasorelaxation in Echol-ex was not different from Echol.

Endothelium-independent relaxation in response to nitroglycerin was attenuated in apoE-deficient mice (P < 0.0001), and this was not altered by exercise training. There was significant inverse correlation between endothelium-independent relaxation and total plasma cholesterol (r = 0.44, P < 0.005), dietary fat content (r = −0.35, P < 0.027), and body weight (r = −0.33, P < 0.044).

NO release was significantly higher in all wild-type mice compared with apoE-deficient mice (P < 0.05); the difference in NO release between wild-type and apoE-deficient mice was not abolished by exercise training (P = NS). NO release correlated inversely with total serum cholesterol levels (r = −0.42, P < 0.001) and

### Table 1. Heart and body weight and metabolic variables

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<th>Sedentary (n = 42)</th>
<th>Exercise (n = 30)</th>
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<td>E₁</td>
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<td>BW-TT, g</td>
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<td>21.8 ± 1.2</td>
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<td>Heart wt, mg</td>
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<td>120 ± 10</td>
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<td>Chol, mg/dl</td>
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<td>180 ± 80</td>
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<td>HDL, mg/dl</td>
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<td>60 ± 90</td>
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<td>Non-HDL, mg/dl</td>
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<td>120 ± 90</td>
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Values are means ± SD; n, no. of mice. E¹, sedentary wild-type; E₁, sedentary apolipoprotein E (apoE) deficient; Echol, high-fat diet E¹; Echol-ex, exercised apoE deficient; Echol-ex, high-fat diet exercised wild-type; Echol-ex, high-fat diet exercised apoE deficient; BW-TT, body wt at treadmill testing; Chol, total cholesterol; HDL, high-density lipoprotein cholesterol. Superscripted nos. refer to no. of groups that differed significantly from indicated group (all P < 0.05).

### Table 2. Aerobic capacity

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<td>E</td>
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<td>Δdist, m</td>
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<td>23 ± 72</td>
<td>0.8 ± 33</td>
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<td>diste, m</td>
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<td></td>
<td>23 ± 72</td>
<td>251 ± 33</td>
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<td>AT, ml O₂·min⁻¹·kg⁻¹</td>
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<td>103 ± 8</td>
<td>92 ± 11</td>
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<td>AWC, J/g</td>
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<td>6.6 ± 2.7</td>
<td>5.8 ± 3.0</td>
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<td>RER</td>
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<td>0.91 ± 0.04</td>
<td>0.94 ± 0.04</td>
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<td>VO₂max, ml O₂·min⁻¹·kg⁻¹</td>
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<td>109 ± 5</td>
<td>101 ± 9</td>
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Values are means ± SD; n, no. of mice. AT, anaerobic threshold; AWC, aerobic work capacity; diste, distance run to exhaustion; Δdist, distance run to exhaustion at 12 wk – 8 wk; RER, respiratory exchange rate; VO₂max, maximal oxygen uptake. Superscripted nos. refer to no. of groups that differed significantly from indicated group (all P < 0.05).
As expected, high-fat diet and/or apoE deficiency led to increased levels of total serum cholesterol that remained essentially unchanged despite 4 wk of training. High-density lipoprotein cholesterol levels were not significantly different between groups. The observed increase in total serum cholesterol levels was caused by non-high-density lipoprotein cholesterol (i.e., very low-density lipoprotein plus immediate-density lipoprotein fraction; Ref. 20). Although exercise training leads to an increase in high-density lipoprotein cholesterol in humans (30), this effect was not observed in the mice.

Aerobic exercise capacity. During exercise the rate at which oxygen is consumed and carbon dioxide is produced in the muscle is greatly increased. The capacity of the heart and lungs to respond to the stress of physical exercise is often used as a measure of their physiological health. Of the various gas exchange measures obtained during exercise testing, maximum oxygen uptake is the most accurate, reproducible, and thus most commonly used measure of cardiopulmonary function. However, other variables including anaerobic threshold, aerobic work capacity, and distance run until exhaustion derived from exercise testing with gas exchange measurements can provide valuable additional information regarding the capacity of the heart and lungs to deliver oxygen to the working muscle during exercise (15). We reported previously (13) that diet-induced or genetically induced hypercholesterolemia induced a decline in aerobic work capacity, anaerobic threshold, distance run until exhaustion, and maximum oxygen uptake. In the present study, exercise training led to improvement of these measures in hypercholesterolemic mice compared with their sedentary littermates. However, values reached failed to equal those of sedentary normocholesterolemic mice, and in the genetically induced hypercholesterolemic mice, measures of aerobic capacity remained significantly worse than those of normocholesterolemic trained mice. Maximum oxygen uptake and anaerobic threshold were inversely correlated to total serum cholesterol, suggesting an inhibitory effect of cholesterol.

In the sedentary groups, apoE-deficient mice experienced the largest decline in running distance over the 4-wk study period. Conversely, apoE-deficient mice that were trained improved their running distance to a similar extent as wild-type mice. Because apoE-deficient mice showed the largest decline in maximum oxygen uptake and anaerobic threshold despite a similar increase in distance run until exhaustion, it may be assumed that they initiated anaerobic metabolism (reached anaerobic threshold) early, so that there was a greater contribution of anaerobic metabolism to the overall work capacity.

It is well known that maximum oxygen uptake, anaerobic threshold, and aerobic work capacity increase with exercise training (8). Because body mass is the denominator for these variables, it could be speculated that simply the increase in body weight during the study period is responsible for the attenuated

**DISCUSSION**

The salient findings of this study are that 1) genetically induced hypercholesterolemia impairs NO-mediated vasodilatation and vascular NO elaboration; 2) the impairment of vasorelaxation is associated (and correlated) with an impairment of aerobic exercise capacity; 3) the impairment of endothelium-dependent vasorelaxation and aerobic exercise capacity induced by genetically determined hypercholesterolemia is partially reversed by exercise training; and 4) exercise training caused a similar percentage increase in maximum oxygen uptake of all groups, although a persistent difference remained between the normal and genetically hypercholesterolemic groups.

**Metabolic studies.** It was previously reported that hypercholesterolemia is strongly associated with an impairment of endothelium-mediated increases in coronary blood flow and that this is found even in the early stages of atherosclerosis (4, 21, 31). To study the effects of exercise training on vascular reactivity in the hypercholesterolemic state, we chose the mouse model because apoE-deficient mice have been shown to develop the entire spectrum of atherosclerotic lesions similar to those seen in humans and are considered a suitable model for the study of atherogenesis (20). To assess changes in vascular reactivity before formation of obstructive atherosclerotic lesions, mice were studied at the young age of 8–12 wk. The overall number as well as extent of lesions visualized by oil red O staining were too modest to allow quantitative comparison between groups. With scanning electron microscopy occasional endothelial detachment was detected in apoE-deficient mice only, which was more pronounced in those on a high-fat diet. No qualitative difference was detected between sedentary and trained groups (Fig. 2).
exercise performance. However, ANCOVA revealed that body weight was not a significant determinant of the group difference in aerobic capacity.

Vascular reactivity. A strong correlation has been reported between total serum cholesterol and the impairment of endothelium-mediated increases in coronary blood flow in hypercholesterolemic animals and humans (26, 31). We hypothesized that a training-induced increase in blood flow and thus laminar shear stress could overcome the detrimental effect of hypercholesterolemia and then result in improved endothelium-dependent vasodilation via increased endothelial NO synthesis. Indeed, training-induced changes in vascular reactivity have been observed in the coronary arteries of dogs after 8 wk of exercise (3). Also, in healthy young men (5) as well as patients with congestive heart failure (9), an enhanced endothelial function has been demonstrated in the brachial artery after chronic exercise training even in the presence of cardiovascular risk factors (5). These findings are consistent with observations from animal studies in which exercise increased the mRNA expression of NOS, augmented NO activity, and enhanced endothelium-dependent vasodilation in coronary arteries (14, 24, 27). The mechanism by which flow augments the expression of NOS probably involves shear stress responsive elements within the promoter region of the gene encoding NOS (23).

Fig. 4. Maximal endothelium-dependent vasorelaxation after 4 wk of study. Maximal endothelium-dependent vasorelaxation (acetylcholine 10^{-7} M) was impaired in E^- (B) and E_{ex} (D) mice. When apoE-deficient mice underwent exercise training, endothelium-dependent relaxation in E_{ex} mice was comparable to that in E^- and E_{ex} mice (B), whereas vasorelaxation in E_{min} mice was not different from that in E_{ex} mice (D). Endothelium-independent vasodilation in response to nitroglycerin was attenuated slightly in apoE-deficient mice (A and C). There was a significant inverse correlation between endothelium-independent relaxation and total serum cholesterol.
In keeping with current literature, in this study total serum cholesterol was inversely correlated with endothelium-dependent vasorelaxation and with NO release. These data suggest that hypercholesterolemia exerts an NO-antagonizing effect that leads to endothelial dysfunction, which could possibly result in an impaired oxygen transport capacity. Additionally, there was also an impairment of endothelium-independent vasorelaxation to nitroglycerin, indicating an impaired sensitivity of the vascular smooth muscle to NO. Although endothelium-dependent relaxation was improved with exercise, response to nitroglycerin was not. Because maximum oxygen uptake is in part determined by the ability to direct blood flow to the active muscles (15), these alterations in vascular reactivity could lead to a subsequent reduction in aerobic capacity.

Increases in blood flow may also effect the elaboration of prostacyclin, which has not been assessed in this study. Koller et al. (11) demonstrated in a rat model that the sensitivity of gracilis muscle arterioles to wall shear stress was upregulated after short-term daily exercise, which resulted in an augmented dilator response, probably caused by an increased release of both endothelium-derived NO and prostacyclin. Hecker et al. (7) observed continuous release of NO and prostacyclin from the endothelium that was enhanced by an increase in shear stress. However, in conduit arteries the contribution of prostacyclin to flow-mediated vasodilation appears negligible because NO plays the major role (10).

In summary, the present study shows that 4 wk of exercise training enhances aerobic capacity in normal mice. Aerobic capacity is attenuated by genetically induced hypercholesterolemia and only partially restored by exercise training. The training-induced improvement in aerobic capacity is associated with an improvement in endothelial vasodilator function. Hypercholesterolemia-induced impairment of NO-mediated vasodilation may play a role in the lipid-induced attenuation of aerobic capacity.

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