Enhanced endothelial vasoreactivity in endurance-trained older men

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Enhanced endothelial vasoreactivity in endurance-trained older men. J. Appl. Physiol. 87(6): 2136-2142, 1999.—Using external vascular ultrasound, we measured brachial artery diameter (Diam) at rest, after release of 4 min of limb ischemia, i.e., endothelium-dependent dilation (EDD), and after sublingual nitroglycerin, i.e., non-endothelium-dependent dilation (NonEDD), in 35 healthy men aged 61–83 yr: 12 endurance athletes (A) and 23 controls (C). As anticipated, treadmill exercise maximal oxygen consumption (VO2max) was significantly higher in A than in C (40.2 ± 6.6 vs. 27.9 ± 3.8 ml·kg−1·min−1; respectively, P < 0.0001). With regard to arterial physiology, A had greater EDD (8.9 ± 4.2 vs. 5.7 ± 3.5%; P = 0.02) and a tendency for higher NonEDD (13.9 ± 6.7 vs. 9.7 ± 4.2%; P = 0.07) compared with C. By multiple linear regression analysis in the combined sample of older men, only baseline Diam (β = −2.0, where β is the regression coefficient; P = 0.005) and VO2max (β = 0.23; P = 0.003) were independent predictors of EDD; similarly, only Diam (β = −4.0; P = 0.003) and VO2max (β = 0.27; P = 0.01) predicted NonEDD. Thus endurance-trained older men demonstrate both augmented EDD and NonEDD, consistent with a generalized enhanced vasodilator responsiveness, compared with their sedentary age peers.

endothelial function; exercise; training

IT IS WELL RECOGNIZED that a high level of leisure-time physical activity protects against the development of coronary heart disease (CHD) (23, 28, 38). On the contrary, a sedentary lifestyle is believed to contribute to approximately one-third of deaths caused by CHD (18). It is estimated that nearly 60% of adult Americans get little or no regular exercise (7). Although the benefits of chronic physical activity are indisputable, the mechanisms responsible for this protective effect remain to be identified. Possible contributors include favorable changes seen in lipoprotein profile (36, 56), carbohydrate tolerance and insulin sensitivity (24), neurohormonal release (15, 36), and blood pressure (15, 32). Nevertheless, there is evidence that the beneficial effects of exercise training are in part independent of these important risk factors.

Chronic exercise has been reported to alter both coronary vascular structure and vasomotor reactivity (31, 34, 35, 41, 44, 45, 53). In men with physically active occupations (34) or active lifestyles (31), larger than expected coronary arteries have been reported. Wang et al. (53) recently proposed that the beneficial effects of exercise training on the coronary circulation may reflect enhanced endothelium-dependent vasodilation. Indeed, animal studies suggest that exercise training enhances the vasodilator response to endothelium-dependent stimulation by either acetylcholine or bradykinin (14, 35, 53), as well as enhancing endothelial cell gene expression of nitric oxide (NO) synthase in coronary arterioles (41, 57).

However, despite the supportive data from animal investigations, there are few studies in humans regarding the effects of exercise on endothelial function. Investigations of the release of endothelial NO during acute exercise have produced conflicting results (16, 21, 55). Studies assessing the impact of long-term exercise training on endothelium-dependent vasodilation in young men have also yielded inconsistent results (9, 25, 26). To our knowledge, no studies have addressed the effect of long-term exercise training on endothelial function in older subjects, a population of particular relevance given the well-established age-associated decline in NO-dependent vasoreactivity in humans (6, 8, 10, 48). In the present study, we hypothesized that endurance-trained senior athletes would have significantly greater endothelium-dependent vasoreactivity compared with age-matched sedentary subjects.

METHODS

Population. To determine the effect of chronic aerobic exercise on endothelial function in older adults, we recruited endurance-trained men at least 60 yr old. The athletes were distance runners, racewalkers, cyclists, and swimmers recruited from the Fitness After 50 Program of the University of Maryland. All subjects had trained regularly at least 45 min, three or more times a week for ≥5 yr. In addition, these men fulfilled the following screening criteria: nonsmoker status, no history of hypertension (blood pressure < 160/95 mmHg), no cardiovascular medication, normal resting and exercise electrocardiogram (ECG), and normal exercise thallium scintigraphy. Twelve carefully screened, physically active older individuals met all of these criteria and constituted our athletic group. Ten of the men were runners, averaging 30 mile/ wk, one was a cyclist, and one a swimmer.

The control group comprised 23 healthy, community-dwelling, generally sedentary men aged 66–83 yr, recruited by and initially evaluated at the General Clinical Research Center of the Johns Hopkins Bayview Medical Center. These men met the same health-screening criteria as the athletes but had not participated in regular aerobic exercise for at least 1 yr. The protocol was approved by the Institutional...
During the exercise tests, oxygen consumption was measured according to either a modified Balke or a Bruce protocol. Each test was performed by all participants from both groups using the Friedewald equation. A maximal treadmill exercise oxygen consumption (i.e., an increase \( \Delta V_{O2} \)) was defined by a plateau of oxygen consumption (i.e., an increase \( \leq 2.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) between the last two exercise stages). Brachial arterial blood pressure was measured by auscultation in the right arm after 20 min of supine rest.

Brachial artery vasoreactivity. Arterial physiology was evaluated on a different day than that of the exercise treadmill test, at least 2 h postprandially. All subjects were studied by the same investigator (TMR) after at least 20 min of supine rest. The brachial artery was studied by using previously described methodology (2–6, 10–12, 47). After the right arm was immobilized in an extended position, blood pressure was measured by auscultation, and brachial arterial diameter and flow velocity were determined by using a 7.5-MHz linear array transducer ultrasound system (Hewlett-Packard Sonos 1000). A 1- to 2-cm segment of artery was consistently located 2–4 cm above the antecubital crease. The image depth was set at 4 cm and gain settings adjusted to optimally delineate the lumen-arterial wall interface. Images were magnified with the resolution box function, leading to a television line width 0.06–0.07 mm (2–4, 47). Doppler flow velocity measurements were obtained by means of range gating, focused on the center of the brachial artery, using an incidence angle of 60° to integrate maximal laminar flow (2, 3, 5, 11, 12, 47). Flow velocity measurements were made in only 18 subjects because they were not routinely obtained at the beginning of the investigation. Throughout each study, all machine settings were kept constant. All images were recorded on videotape for subsequent off-line analysis on the same instrument (11).

After baseline images of brachial arterial diameter and Doppler flow velocity had been obtained, limb flow occlusion was produced by inflating a standard sphygmomanometry cuff on the upper arm to 40 mmHg above systolic blood pressure for 4 min. Prior investigations have demonstrated that the reactive hyperemic increases in brachial artery diameter and forearm blood flow do not differ significantly between occlusions of 3 and 10 min (43). To assess endothelium-dependent dilation (EDD), brachial arterial blood flow velocity was measured within the first 10–20 s after cuff deflation, and brachial arterial diameter was recorded every minute for the next 5 min. The ECG was monitored continuously throughout the study. After a 15-min recovery period, baseline recordings of right brachial arterial diameter and flow velocity were repeated with subsequent administration of 0.4 mg sublingual nitroglycerin (TNG) to assess non-endothelium-dependent dilation (NonEDD). For the next 7 min, brachial arterial diameter and flow velocity were continuously monitored (2, 47). TNG serves as an exogenous source of NO, bypassing the need for endothelial NO production. Multiple investigations (2–6, 12, 39, 47, 52, 54) have demonstrated brachial arterial dilation, typically averaging 12–20%, in response to a 0.4-mg dose, even in individuals with impaired EDD.

Brachial arterial diameter and blood flow were subsequently analyzed off-line from the video recording by a single observer, using electronic calipers. All arterial diameters were obtained at end diastole, defined by the R wave of the ECG. For each cardiac cycle, we measured the brachial arterial diameter, defined from the inner near wall to the inner far wall at three points. A mean of these measurements defined the diameter for that cycle. At each time point, the arterial diameter was determined from the mean of five cardiac cycles (2, 47). To determine EDD, the maximal arterial diameter between 1 and 5 min after release of the cuff occlusion was identified. To evaluate NonEDD, we determined the maximal arterial diameter between 3 and 5 min after TNG administration. Percent change in vessel diameter in response to reactive hyperemia or TNG was determined by dividing the difference between the maximal and baseline diameters by the baseline diameter (2–4, 6, 47). Arterial flow velocities were also averaged from five cardiac cycles. Absolute arterial blood flow was calculated as the mean Doppler flow velocity integrated for each time point, multiplied by the cross-sectional area of the artery (\( \pi r^2 / 4 \), where \( r \) is diameter) and by heart rate (2–5, 47). Percent change in flow was calculated by dividing the difference between posthyperemic flow and baseline flow by the baseline flow.

The reproducibility of EDD was investigated in four volunteers. Arterial vasoreactivity was determined serially, separated by 20 min of rest. There were no differences between tests with regard to baseline arterial diameter (4.23 ± 0.11 mm vs. 4.22 ± 0.1 mm, \( P = 0.61 \)) or maximal arterial diameter after hyperemia (4.33 ± 0.14 mm vs. 4.34 ± 0.12 mm, \( P = 0.66 \)).

Statistical analysis. The following baseline characteristics were compared between the athletes and the control group: age, height, weight, BMI, serum cholesterol (total, LDL, and HDL cholesterol), triglycerides, \( V_{O2\max} \), resting heart rate, and systolic and diastolic pressures. From the brachial arterial study, baseline arterial diameter and maximal EDD and NonEDD responses and posthyperemic flow rates were compared between groups. Intergroup comparisons were made by using the unpaired \( t \)-test. The Pearson correlation coefficient was employed to identify univariate correlations between continuous variables. Multiple linear-regression analysis was used to determine the independent predictors of endothelium-dependent and -independent responses. The strongest models were identified by using stepwise methods according to the adjusted \( R^2 \). Multicollinearity among independent variables was evaluated by examining the variance inflation factors; a value < 10 was considered satisfactory. For all analyses, a two-tailed \( P \) value < 0.05 was required for statistical significance. Values are expressed as means ± SD unless otherwise noted. All analyses were done in the Statistical Analysis System (SAS).

RESULTS

From October, 1995, to March, 1997, we tested 12 senior athletes aged 61–83 yr and 23 sedentary older men aged 66–83 yr. Baseline characteristics are presented in Table 1. The two groups showed no differences in age, blood pressure, or total or LDL cholesterol. However, the senior athletes had lower body weight, BMI, resting heart rate, and serum triglycerides levels.
Neither cholesterol levels (total, HDL, and LDL) were directly related to V˙O2max. These correlations were also directionally similar in the two groups of men. The positive relationship between EDD and V˙O2max is shown in Fig. 1A. Neither cholesterol levels (total, HDL, and LDL) nor triglycerides were significantly correlated with V˙O2max. Only a modest correlation between EDD and V˙O2max (r = 0.36, P = 0.04) was observed. The independent predictors of EDD were determined from multiple linear regression analysis, including BMI, HDL cholesterol, V˙O2max, and baseline brachial artery

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Senior Athletes</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>70.4 ± 4.6</td>
<td>71.2 ± 5.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175.0 ± 3.1</td>
<td>171.8 ± 6.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.9 ± 7.7</td>
<td>80.0 ± 8.8</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.1 ± 2.5</td>
<td>27.1 ± 2.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>50 ± 7</td>
<td>63 ± 8</td>
<td>0.0002</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>124 ± 14</td>
<td>119 ± 13</td>
<td>0.3</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>69 ± 9</td>
<td>68 ± 7</td>
<td>0.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>188 ± 35</td>
<td>170 ± 25</td>
<td>0.1</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>123 ± 30</td>
<td>111 ± 20</td>
<td>0.2</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>48 ± 15</td>
<td>35 ± 8</td>
<td>0.0002</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>82 ± 30</td>
<td>130 ± 65</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = no. of subjects. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Boldface indicates significant difference (P < 0.05).

Height and HDL cholesterol were significantly greater in athletes compared with controls. As anticipated, V˙O2max was much higher in the endurance-trained subjects. With regard to arterial physiology (Table 2), the baseline brachial artery diameter and arterial blood flow velocity were similar in the two groups. The vasodilator response to the endothelium-dependent stimulus of reactive hyperemia, however, was ~50% higher in athletes compared with sedentary subjects (8.9 ± 4.2 vs. 5.7 ± 3.5%, respectively, P = 0.02). In contrast, the increase in posthyperemic brachial arterial flow, responsible for distention of the artery, was similar between the respective groups (475 ± 151 vs. 549 ± 168%, P = 0.5). There was a trend of borderline significance toward a greater vasodilator response to the NonEDD stimulus in athletes than in controls.

Table 2. Arterial physiology in athletes and controls

<table>
<thead>
<tr>
<th></th>
<th>Senior Athletes</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>V˙O2max, ml·kg⁻¹·min⁻¹</td>
<td>40.2 ± 6.6</td>
<td>27.9 ± 3.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Brachial artery diameter, mm</td>
<td>4.7 ± 0.6</td>
<td>5.1 ± 0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Hyperemic flow increase, %</td>
<td>475 ± 151</td>
<td>549 ± 168</td>
<td>0.5</td>
</tr>
<tr>
<td>EDD, %</td>
<td>8.9 ± 4.2</td>
<td>5.7 ± 3.5</td>
<td>0.02</td>
</tr>
<tr>
<td>NonEDD, %</td>
<td>13.9 ± 6.7</td>
<td>9.7 ± 4.2</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Values are means ± SD. V˙O2max, maximal oxygen consumption; EDD, endothelium-dependent vasoactivity; NonEDD, non-endothelium-dependent vasoactivity. Boldface indicates significant difference (P < 0.05).

Table 3. Univariate correlates of arterial function

<table>
<thead>
<tr>
<th></th>
<th>EDD</th>
<th>NonEDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>-0.13</td>
<td>-0.32</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>-0.44</td>
<td>-0.14</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>-0.50</td>
<td>-0.25</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>-0.21</td>
<td>0.35</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>-0.14</td>
<td>0.11</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>-0.05</td>
<td>0.23</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>0.30</td>
<td>0.27</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>-0.09</td>
<td>0.15</td>
</tr>
<tr>
<td>Brachial artery diameter, mm</td>
<td>0.46</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Boldface indicates significant difference (P < 0.05).
diameter. As presented in Table 4, $V_O^{2max}$ was a positive independent predictor of EDD, whereas baseline arterial diameter was a negative predictor. Together, these two variables were a strong predictor of endothelial response to reactive hyperemia ($R^2$ adjusted = 0.34, $P = 0.0009$). Neither BMI ($P = 0.36$) nor HDL cholesterol ($P = 0.78$) contributed significantly to the final model. In a similar analysis, including age, heart rate, $V_O^{2max}$, and brachial artery diameter, only the latter two variables independently predicted NonEDD. Analagous to the results for EDD, $V_O^{2max}$ was an independent positive predictor of the arterial response to TNG, whereas baseline diameter was a negative predictor (Table 4). Collinearity among independent variables was tested by the variance inflation factor for both EDD and NonEDD models and confirmed to be within an acceptable level (i.e., $<10$).

**DISCUSSION**

The effect of endurance training on human endothelial function has received only minimal attention, particularly in the elderly. Therefore, this study was designed to determine whether endurance-trained older men exhibit enhanced endothelial function relative to their age peers who were sedentary. Our endurance-trained men showed $>50\%$ greater endothelium-dependent vasoreactivity compared with sedentary individuals. By multiple linear-regression analysis, aerobic capacity, as measured by $V_O^{2max}$, was an independent predictor of EDD as well as NonEDD.

Impairment of endothelial function is a well-known phenomenon in many pathophysiological states such as hypertension (49), diabetes mellitus (54), heart failure (40), and overt CHD (13, 29) and is associated with CHD risk factors such as hypercholesterolemia (2, 52), smoking (3), and male gender (6, 10). In some of these conditions, the endothelial dysfunction appears to be reversible. Lowering of the cholesterol levels (52), cessation of smoking (3), and treatment with angiotensin-converting enzyme inhibitors (30) improve EDD, whereas normalization of high blood pressure (30, 39) has produced conflicting results.

Several studies have reported a progressive decline in EDD with advancing age in healthy volunteers (6, 8, 10, 48). Using ultrasound techniques, Corretti et al. (10) compared brachial artery dilation due to reactive hyperemia in subjects $>40$ and $\leq 40$ yr old. They found that younger men had a $70\%$ greater vasodilator response compared with older men, whereas there was only a modest trend for an enhanced response in younger vs. older women. Celermajer et al. (6) demonstrated that aging is associated with progressive impairment in endothelial function in both genders; a steep decline commenced at about age 40 yr for men but approximately a decade later in women. Similar data were reported by Taddei et al. (48), who observed a strong negative correlation between acetylcholine-induced vasodilatation of the brachial artery, measured by strain-gauge plethysmography, and age. Chauhan et al. (8) observed a significant negative relationship between age and the increase in coronary blood flow during intracoronary infusion of acetylcholine.

It is unclear whether the age-associated reduction of endothelial function can be attenuated. Exercise training, known for its beneficial modulatory effects on CHD risk factors, is a promising intervention to improve endothelial dysfunction. Several studies have assessed the impact of exercise training on endothelial function in animals (35, 37, 41, 53). Most of them demonstrated significant improvement in the coronary arterial response to an endothelium-dependent stimulus (35, 37, 41), although the effect appeared to depend on artery size. In coronary resistance vessels (35), exercise stimulates enhanced NO-dependent vasodilation, whereas there is minimal effect in large coronary arteries (37). Additionally, Sinoway et al. (44, 45) have demonstrated enhanced forearm peak hyperemic blood flow after forearm training, an effect that appears to be an early adaptation to exercise training (27, 37).

Only a few clinical studies have examined the impact of aerobic exercise training on endothelial function, and all of these involved young individuals. In men aged 17–24 yr, Clarkson et al. (9) reported that 10 wk of combined aerobic and anaerobic exercise training was associated with a nearly $70\%$ increase in flow-mediated EDD of the brachial artery. The enhanced arterial response was not related to levels of LDL or HDL cholesterol. These latter authors did not observe any exercise-induced changes in NonEDD, in contrast to our present findings. These conflicting results may be due to age differences between the two population samples. In a cross-sectional study, Kingwell et al. (26) compared endothelial function in 10 young male endurance athletes with that in 10 sedentary men; mean $V_O^{2max}$ values in the two groups were 68.1 and 39.3 ml·kg$^{-1}$·min$^{-1}$, respectively. There was an $\sim 30\%$ greater reduction in forearm vascular resistance to acetylcholine, an endothelium-dependent stimulus, in the trained individuals. This reduction in vascular resistance was directly related to $V_O^{2max}$ ($r = 0.42$, $P = 0.05$). However, multivariate analysis suggested that the lower mean level of plasma cholesterol in the trained group was a major contributor to their enhanced vascular responsiveness. In the present study, endurance-trained individuals had similar or slightly higher total and LDL cholesterol levels than did seden-

| Table 4. Multivariate predictors of endothelium-dependent and -independent dilation |
|---------------------------------|---|---|
|                                | β  | 95% CI          | P   |
| EDD                            |    |                 |     |
| $V_O^{2max}$, ml·kg$^{-1}$·min$^{-1}$ | 0.21 | 0.07–0.36 | 0.006 |
| Brachial artery diameter, mm   |    | −1.9 to −3.63   | 0.006 |
| NonEDD                         |    |                 |     |
| $V_O^{2max}$, ml·kg$^{-1}$·min$^{-1}$ | 0.27 | 0.06–0.48 | 0.01  |
| Brachial artery diameter, mm   |    | −4.0 to −1.48   | 0.003 |

For EDD, adjusted model $R^2 = 0.34$, $P = 0.0009$, by multiple regression analysis; for NonEDD, adjusted model $R^2 = 0.38$, $P = 0.0003$, by multiple-regression analysis. CI, confidence interval; β, regression coefficient. Boldface indicates significant difference ($P < 0.05$).
ary controls. However, EDD was ~50% higher in the athletes. Multiple regression analysis demonstrated that VO$_{2max}$ was a strong independent determinant of endothelial function, whereas LDL and HDL cholesterol exerted no significant effect.

In a crossover study of 13 subjects aged 24 ± 6 yr by Kingwell et al. (25), endothelial function in the forearm arteries was evaluated after 4 wk of endurance training. Although there was an increase in basal release of NO after training, EDD remained unchanged. The discrepancy between our findings and previous reports may be due to age differences in the studied cohorts as well as in study design. Furthermore, the 4-wk exercise intervention used by Kingwell et al. (25) may have been of insufficient duration for the endothelial adaptations to be fully utilized. In addition, both of Kingwell’s studies (25, 26) evaluated a relatively small number of subjects, raising the possibility of type 2 statistical error.

Enhanced NonEDD in endurance-trained subjects has been demonstrated in several investigations. Haskell et al. (22) observed that coronary arterial dilation capacity to TNG was 120% greater in distance runners 39–66 yr old compared with sedentary controls. The magnified dilatory response was positively related to aerobic capacity, consistent with our findings. In one of the studies by Kingwell et al. (26), there was a nearly 20% greater reduction in forearm vascular resistance in young athletes compared with controls during a high-dose infusion of sodium nitroprusside, although this failed to reach statistical significance. In endurance-trained men aged 30.5 ± 2 yr, Snell et al. (46) demonstrated 36% greater peripheral vasodilator capacity, measured by vascular conductance of the brachial artery, compared with sedentary controls. There was a high correlation between VO$_{2max}$ and vascular conductance, computed from blood flow by venous plethysmography and mean arterial pressure in trained individuals (r = 0.81, P = 0.002). Similar findings were reported by Martin et al. (33), who observed 25 and 21%, respectively, longitudinal enhancement of vasodilatory capacity in men and women aged 64 ± 3 yr who performed aerobic exercise regularly for more than 6 mo. Although made with the use of different methodologies, these prior studies are consistent with our present finding that NonEDD vasodilator capacity may be enhanced by long-term endurance training.

The mechanisms of enhanced endothelial function associated with endurance training are unclear but may involve chronic exercise-induced increases in shear stress and pulsatile flow. Chronic increases in blood flow induced by exercise may exert their effect on EDD by modulating the expression of NO synthase (36). The expression of mRNA for NO synthase is upregulated in cultured bovine aorta endothelial cells exposed to increased laminar flow (50). Animal studies have documented short-term (53) and long-term (41, 53) exercise-induced increases in the mRNA expression of NO synthase, augmented NO activity, and enhanced EDD in coronary arteries. With regard to NonEDD, the chronic, intermittent increases in pulse pressure with training might also exert a beneficial effect on arterial structure, as suggested by the lower pulse-wave velocity and carotid artery augmentation index in another subset of these older athletes studied in our laboratory (51). It is also possible that the augmented EDD and NonEDD in older athletes compared with their sedentary age peers results from enhanced sensitivity to NO, whether endothelium derived or exogenous.

Study limitations. Certain limitations of the present study should be recognized. From its cross-sectional design, it is not possible to determine to what extent genetic or environmental factors other than endurance training contributed to the enhanced endothelial function in master athletes compared with sedentary control subjects. Whether neurohormonal changes caused by chronic exercise training influence NO-dependent arterial dilation is also unclear. Our exclusion of young subjects and women from this study limits conclusions regarding the arterial responses to endurance training in these groups.

Although the increase in brachial artery diameter during reactive hyperemia is thought to be endothelium dependent, the extent to which this response is mediated by NO is not clear. Other mediators of this vasodilation include prostaglandins and ischemic metabolites (17). The administration of arginine analogs to inhibit the generation of NO would have helped to elucidate the specific contribution of NO to the enhanced EDD observed in our older athletes. It is possible that mechanisms other than enhanced shear stress led to the increased EDD of the athletes; Silber et al. (42) demonstrated a 50% increase in reactive hyperemic forearm blood flow after 4 wk of training on a leg ergometer, a stimulus not expected to increase shear stress in the upper extremities. Finally, it should be recognized from Fig. 1 that the modest correlations between VO$_{2max}$ and both EDD and NonEDD, although statistically and probably biologically significant, do not allow accurate prediction of an individual’s vasodilator responses.

Implications. The augmented EDD in these older endurance-trained men relative to their sedentary peers suggests that the chronic increases in blood flow and shear stress that accompany regular aerobic exercise may enhance endothelial function. High shear stress is known to inhibit the progression of atherosclerosis, whereas low shear force within an artery defines locations more likely to develop atherosclerosis (20). In addition, endurance training-mediated augmentation of NO activity would be expected to increase arterial vasoreactivity and to antagonize key processes involved in atherogenesis, such as monocyte adherence and chemotaxis, platelet adherence and aggregation, and vascular smooth muscle proliferation (1, 19). Thus we speculate that a beneficial impact of endurance exercise on upregulating the availability of NO might contribute in part to the favorable effect of such exercise on cardiovascular morbidity and mortality.

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REFERENCES


