Effects of Aging, Gender, and Physical Training on Peripheral Vascular Function

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Background. Blood pressure and total peripheral resistance increase with age. However, the effect of age on vasodilatory capacity has not been characterized.

Methods and Results. To delineate the effects of aging, gender, and physical training on peripheral vascular function, we measured blood pressure during submaximal and maximal treadmill exercise and measured blood pressure, calf blood flow, and calf conductance (blood flow/mean blood pressure) at rest and during maximal hyperemia in 58 healthy sedentary subjects (men aged 25±5 and 65±3 years and women aged 27±5 and 65±4 years) and in 52 endurance exercise–trained subjects (men aged 30±3 and 65±4 years and women aged 27±3 and 65±3 years). Systolic and mean blood pressures were higher at rest, during maximal calf hyperemia, and during submaximal exercise of the same intensity in the older than in the younger subjects of the same gender and exercise training status (p<0.01). The magnitude of the age-related effect on blood pressure during exercise was greater in women than in men (p<0.01). Diastolic blood pressure during submaximal exercise was also higher in the older than in the younger subjects (p<0.05) but not in women treated with estrogen replacement. In contrast, systolic and mean blood pressures during submaximal work were lower in physically conditioned subjects than in sedentary age- and gender-matched subjects (p<0.05) but not in older women. Increased age was associated with reduced maximal calf conductance in women (p<0.01) but not in men. However, calf vasodilatory capacity was higher in trained than in untrained subjects (p<0.01), regardless of age and gender. There was a significant inverse relation between maximal calf conductance and systolic, diastolic, and mean blood pressures during submaximal exercise (r=−0.31 to −0.53, p<0.01) and a direct relation between maximal calf conductance and maximal oxygen uptake (r=0.66, p<0.0001).

Conclusions. Thus, for healthy subjects between the ages of 25 and 65 years, there is an interactive effect between age and gender and an independent effect of physical training on peripheral vascular function. (Circulation 1991;84:654–664)

Blood pressure and total peripheral resistance increase with age.1,2 The resistance vasculature provides a significant portion of total peripheral resistance and distributes up to 85% of the cardiac output to the active musculature during intense exercise.3 Thus, blood pressure and total peripheral resistance during exercise may be affected in part by resistance vascular function and peripheral vasodilatory capacity. However, the effect of age on vasodilatory capacity has not been systematically characterized. Hypertension, congestive heart failure, and other forms of cardiovascular disease increase in prevalence with age4 and are associated with impaired function of vascular endothelium and decreased peripheral vasodilatory capacity.5–8 In contrast, physical training enhances vasodilatory capacity9,10 and may reduce blood pressure and total peripheral resistance during exercise.11 Cardiovascular function during exercise is also influenced by gender.12,13 Thus, it is important to evaluate age-related effects on peripheral vascular function in the context of gender and to differentiate effects of aging from those due to cardiovascular disease and reduced physical activity. Accordingly, the purpose of this investigation was to characterize the relative effects of aging, gender, and physical training on blood pressure during exercise and on resistance vascular function.
Methods

One hundred ten subjects participated in the study. On the basis of age, gender, and training status, they were placed in the following eight groups: 16 sedentary men aged 25±5 years, 16 exercise-trained men aged 30±3 years, 10 sedentary women aged 27±5 years, 10 exercise-trained women aged 27±3 years, 16 sedentary men aged 65±3 years, 16 exercise-trained men aged 65±4 years, 16 sedentary women aged 65±4 years, and 10 exercise-trained women aged 65±3 years. Sedentary subjects did not participate in any form of regular leisure-time or work-related exercise requiring strenuous effort but were normally active, community-dwelling citizens. Younger exercise-trained subjects were competitive runners who had been participating in very strenuous exercise for several years and routinely finished in the top 1–3% of all runners of the same gender in large local road races. Older trained men had been competing in road races for 16±6 years and were all top athletes in their age group but had not enjoyed particular athletic success in their youth. Two older exercise-trained women had engaged in strenuous exercise and competitive running for several years. Because no other female competitive runners in this age group could be found, an additional group of eight older women were studied in the final 4 weeks of an 8-month program of progressively more strenuous exercise that culminated in a training intensity nearly equivalent to that of the two older female competitive runners. During this time, they jogged an average of 47 min/day for 4 days/wk at 80–95% of maximal heart rate. All subjects were in good health at the time of the study. A cardiovascular physical examination revealed no abnormalities, including the absence of vascular bruits and symptoms of claudication and the presence of normal lower extremity pulses. Height, weight, percent fat, blood pressure at rest, and exercise capacity data are shown in Tables 1 and 2. Four subjects (two sedentary and two exercise-trained older men) had been diagnosed previously with mild hypertension but were normotensive (resting blood pressure, <140/90 mm Hg) on no medication for at least 3 months before the present investigation. Participants also had a normal 12-lead electrocardiogram and maximal treadmill exercise test based on criteria described below. Urinalysis, complete blood count, and plasma electrolytes were within normal limits, and a chest roentgenogram revealed no acute disease in either group of older sedentary subjects. Individuals screened, but excluded from the study, included one younger sedentary man (abnormal electrocardiogram and seizure disorder), one older exercise-trained man (significant Q waves on resting electrocardiogram), three older exercise-trained women (two for abnormal exercise tests and one for hypertension), and eight sedentary older subjects (five men and three women for abnormal exercise tests in seven instances and hypertension in one instance). Subjects were not receiving medications except for eight older women (four trained and four untrained) who took estrogen replacements and one older sedentary man who was self-medicated with a daily aspirin tablet. No older subjects had used tobacco within at least 1 year of the study. Two younger sedentary subjects (one man and one woman) smoked between one half and one package of cigarettes/day but did not use tobacco on the day that peripheral blood flow studies were conducted. The investigation was approved by the Institutional Human Studies Committee. All subjects

### Table 1. Anthropometric, Resting Blood Pressure, and Exercise Capacity Data for Healthy Sedentary and Endurance Exercise-Trained Younger and Older Men

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Sedentary men aged 18–34 yr</th>
<th>Trained men aged 25–35 yr</th>
<th>Sedentary men aged 60–69 yr</th>
<th>Trained men aged 60–71 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>177.2±8.0</td>
<td>178.7±4.7</td>
<td>178.8±7.6</td>
<td>174.1±5.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.4±20.0</td>
<td>69.0±3.9*</td>
<td>85.7±10.5</td>
<td>67.4±5.5†</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>15.9±8.2 (n=12)</td>
<td>6.0±2.8†</td>
<td>24.9±5.0‡ (n=13)</td>
<td>13.6±4.1 (n=14)‡‡</td>
</tr>
<tr>
<td>Resting blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>109±7</td>
<td>111±9</td>
<td>127±15‡</td>
<td>124±14‡</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>69±9</td>
<td>70±7</td>
<td>74±9</td>
<td>70±7</td>
</tr>
<tr>
<td>Bruce protocol (min)</td>
<td>11.0±1.7</td>
<td>17.8±1.3† (n=13)</td>
<td>8.0±1.1‡</td>
<td>12.4±1.5‡‡ (n=15)</td>
</tr>
<tr>
<td>VO2max (l/min)</td>
<td>3.34±0.56</td>
<td>4.61±0.42†</td>
<td>2.25±0.42‡</td>
<td>3.30±0.41‡‡</td>
</tr>
<tr>
<td>VO2max (ml/kg/min)</td>
<td>43.1±6.9</td>
<td>66.5±4.5†</td>
<td>26.4±3.8‡</td>
<td>49.1±4.1‡‡</td>
</tr>
<tr>
<td>VO2max (ml/kg fat-free mass/min)</td>
<td>51.7±4.5 (n=12)</td>
<td>70.2±4.2†</td>
<td>36.2±4.7‡ (n=13)</td>
<td>57.4±4.4‡‡ (n=14)</td>
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<tr>
<td>Maximal heart rate (beats/min)</td>
<td>194±6</td>
<td>182±8† (n=15)</td>
<td>166±16‡</td>
<td>170±8‡</td>
</tr>
<tr>
<td>Respiratory exchange ratio at maximal exercise</td>
<td>1.13±0.06</td>
<td>1.17±0.05</td>
<td>1.23±0.11‡</td>
<td>1.17±0.07</td>
</tr>
</tbody>
</table>

Data are mean±SD. Number of subjects in each group is 16 unless noted in parentheses. *p<0.05, †p<0.01 vs. sedentary men of similar age; ‡p<0.01 vs. younger men of similar training status.
<table>
<thead>
<tr>
<th>Table 2. Anthropometric, Resting Blood Pressure, and Exercise Capacity Data for Healthy Sedentary and Endurance Exercise-Trained Younger and Older Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sedentary women</strong></td>
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<tr>
<td><strong>aged 20–35 yr</strong></td>
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<tr>
<td><strong>Height (cm)</strong></td>
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<tr>
<td><strong>Weight (kg)</strong></td>
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<tr>
<td><strong>Fat (%)</strong></td>
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<tr>
<td><strong>Resting blood pressure</strong></td>
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<tr>
<td><strong>Systolic (mm Hg)</strong></td>
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<tr>
<td><strong>Diastolic (mm Hg)</strong></td>
</tr>
<tr>
<td><strong>Treadmill time</strong></td>
</tr>
<tr>
<td><strong>Bruce protocol (min)</strong></td>
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<tr>
<td><strong>VO₂ max (l/min)</strong></td>
</tr>
<tr>
<td><strong>VO₂ max (ml/kg/min)</strong></td>
</tr>
<tr>
<td><strong>Maximal heart rate</strong></td>
</tr>
<tr>
<td><strong>Respiratory exchange ratio</strong></td>
</tr>
</tbody>
</table>

Data are mean±SD. Number of subjects is 16 for sedentary older women and 10 for other groups unless noted in parentheses. *p<0.01, †p<0.05 vs. men of similar age and training status; ‡p<0.01, §p<0.05 vs. sedentary women of similar age; ]p<0.01, ‡p<0.05 vs. younger women of similar training status.

gave voluntary written, informed consent for participation in the study.

**Exercise Testing**

Subjects completed two maximal treadmill exercise tests. An initial evaluation was conducted using the Bruce protocol to exclude those with exercise-induced manifestations of cardiovascular disease and to characterize blood pressure responses to the same standard exercise work rates.14 Exclusion criteria consisted of clinical signs and symptoms of cardiovascular disease (e.g., claudication, chest discomfort, and syncope), flat or downsloping ST segment depression of more than 0.1 mV, cardiac dysrhythmias other than occasional atrial or ventricular premature contractions, and a decrease in systolic blood pressure to a value greater than 20 mm Hg less than that in any previous submaximal exercise stage. Heart rate and blood pressure were determined during the latter 30 seconds of each stage and at peak effort. Heart rate was calculated from three consecutive sinus beats on the electrocardiogram. Blood pressure was measured with a wall-mounted mercury sphygmomanometer.

A second exercise evaluation for quantification of maximal oxygen uptake (VO₂ max) was performed several days later with a progressive protocol 5–10 minutes in duration having an end point of exhaustion.15 Initial treadmill speed was chosen on the basis of the first exercise test. Treadmill grade was then increased in 2% increments every 2 minutes beginning with 0% incline. Oxygen uptake and carbon dioxide production were determined every 30 seconds with an automated on-line system that included a dry gas meter (Parkinson-Cowan, Carl Poe Co. Inc., Houston, Tex.) calibrated against a Tissot spirometer, an oxygen analyzer (model S-3A, Applied Electrochemistry, Inc., Sunnyvale, Calif.), a medical gas analyzer (model LB-2, Beckman Instruments, Fullerton, Calif.) for measurement of carbon dioxide concentration, and a microcomputer for calculation of gas exchange results.15 The system was validated previously against direct assessments of ventilatory volume, oxygen uptake, and carbon dioxide production using the Douglas bag technique. Most subjects attained maximal oxygen uptake, defined as leveling off of oxygen uptake despite further increments in exercise work rate. For the remaining individuals, peak oxygen uptake, defined as the highest oxygen uptake achieved, was reported. Maximal oxygen uptake values were expressed in liters per minute and in terms of total body mass and fat-free mass, the latter determined from skinfold thickness data. The respiratory exchange ratio was calculated as the quotient of oxygen uptake and carbon dioxide production.

**Body Composition and Weight**

To evaluate the possibility that differences in peripheral blood flow among the groups were related to variations in adipose tissue content, we estimated body composition from measurements of skinfold thickness.16 Skinfold thickness was assessed with a Lange Caliper (Cambridge Scientific, Inc., Cambridge, Md.) at the triceps, iliac crest, and thigh in women and at the chest, abdomen, and thigh in men. Percent body fat was derived from the sum of skinfold thicknesses with gender-specific age-corrected equations.17

**Peripheral Vascular Studies**

Distal lower extremity (calf) blood flow and conductance, the latter defined as blood flow divided by mean blood pressure, were determined by venous occlusion plethysmography at rest and after ischemic
exercise to fatigue as described previously. The plethysmographic system included an air-filled Latex cuff of appropriate size placed around the calf at its maximal circumference and inflated to 4 cm H2O. The cuff was connected by pressure tubing to a low-pressure venous transducer (PM5TC, Statham, Cleveland, Ohio) interfaced with a preamplifier to a PDP MICRO11 computer (Digital, Maynard, Mass.) for storage and analysis of data. Limb volume changes produced proportional alterations in cuff pressure from which calf blood flow was calculated by the slope of the pressure versus time plot displayed on the computer screen. The foot was isolated hemodynamically from the calf circulation by inflation of an ankle tourniquet cuff to 300 mm Hg. Serial blood flow measurements were obtained during intermittent venous occlusion established by inflation of a thigh tourniquet cuff to subdiastolic pressure (50 mm Hg at rest and 80 mm Hg after ischemic exercise). Blood pressure and plethysmographic data were obtained simultaneously. Systolic and diastolic blood pressures were determined with a semiautomatic electrosphygmomanometer (model PE-300, Narco Biosystems, Houston, Tex.) equipped with a sound microphone placed over the brachial artery. Mean blood pressure, defined as [systolic blood pressure + (2 x diastolic blood pressure)]/3, was calculated from these data. Measurements of resting calf blood flow, blood pressure, and calf conductance were obtained after 20–30 minutes of quiet recumbency, and the data were averaged. Subsequently, maximal calf blood flow and conductance were elicited by ischemic exercise. After inflation of the thigh tourniquet cuff to 300–400 mm Hg, subjects performed alternate toe-and-heel raise exercise in the upright posture to an end point of severe fatigue. Immediately after exercise, subjects reassumed the supine posture, and calf blood flow was measured 8–12 times during 2–3 minutes, and blood pressure was determined simultaneously every 30–60 seconds. After ischemic exercise, calf blood flow attains a plateau more than 10-fold higher than the resting value for 60–90 seconds, permitting multiple measurements to be obtained during maximal hyperemia and enhancing reproducibility. Maximal blood flow under these conditions is more than twice that observed after 5 minutes of tourniquet ischemia without exercise. Subjects performed two trials of ischemic exercise separated by 10–15 minutes of rest. Maximal blood flow and conductance were defined as the highest values obtained for each subject in either of the two trials. Results were also expressed as a function of time after ischemic exercise.

Statistics

Data were analyzed with the SAS package as implemented on the SUN computer system of the Division of Biostatistics. Differences between specific subject groups were evaluated with Student's t tests. Analysis of variance was used to determine whether age, gender, and training status had independent or interacting effects on physiological variables. The significance of relations between variables was evaluated by linear and stepwise multiple regression analysis. The interaction term of an analysis of covariance was used to assess whether the relation between two physiological variables differed between subject groups. A p value less than 0.05 was considered significant. Data are expressed as mean±SD.

Results

Body Composition, Resting Blood Pressure, and Exercise Capacity

A 4-decade difference in age was associated with greater skinfold adiposity, higher resting systolic blood pressure, and lower maximal heart rate and exercise capacity, regardless of gender or exercise-training status (all p<0.01, except for adiposity of sedentary women). For men and exercise-trained women, the age-related effect was most pronounced for skinfold adiposity. For sedentary women, differences between younger and older subjects were largest for exercise capacity and only approached significance for skinfold adiposity (p=0.08). The age-related reduction in \( V_{O2\max} \) expressed in milliliters per kilogram per minute was 26% for exercise-trained men, 38–39% for sedentary subjects, and 53% for exercise-trained women. In contrast, the age-related decrement in maximal heart rate was much less, ranging from 7% for exercise-trained men to 19% for sedentary women. Thus, 50–75% of the age-related decline in exercise capacity was related to decreased cardiac stroke volume or arteriovenous oxygen difference at maximal effort. Respiratory exchange ratio and heart rate data were consistent with attainment of maximal exercise in all groups (Tables 1 and 2).

Male subjects were taller and heavier but had a lower percent body fat and higher exercise capacity than women (all p<0.01, except for body weight of older exercise-trained subjects). The gender-related difference in \( V_{O2\max} \) was eliminated in younger subjects by expression of results in terms of fat-free mass, but differences in percent body fat did not account for the lower exercise capacity of older women compared with older men. Resting blood pressure was not significantly related to gender except in younger sedentary female subjects, who had lower systolic blood pressures (p<0.01). Exercise capacity was invariably greater (p<0.01) and skinfold adiposity was nearly always lower (p<0.01, except p=0.08 for older women) in trained than in untrained subjects. \( V_{O2\max} \) (ml/kg/min) was 54–86% higher and estimated body fat was 45–62% lower in exercise-trained than in untrained younger and older men and younger women (all p<0.01). Older exercise-trained women also had a 29% higher \( V_{O2\max} \) (p<0.01) than their sedentary age-matched peers. A lower maximal heart rate was associated with exercise training in younger (p<0.01) but not in older subjects.
Exercise Blood Pressure

All groups of older subjects had higher systolic blood pressures than younger subjects of corresponding gender and training status (p<0.01) during submaximal exercise of the same intensity (Bruce protocol stages 1 and 2, Figure 1). However, there was a significant interactive effect of age with gender on blood pressure during exercise. The age-related increase in systolic blood pressure at the same submaximal work rate was approximately twice as great in woman as in men (35–42% versus 18–21%, respectively; p<0.01). At peak effort, the difference was even more pronounced (22% versus 3% for women and men respectively, p<0.01). These effects partly reflected the lower systolic pressures in younger women than in younger men (p<0.01). For male subjects, the effect of age on systolic blood pressure during submaximal work was less in the exercise-trained than in the untrained group (11–18% versus 24–25%, p<0.01). This effect was not observed in women. At peak effort, systolic blood pressure was higher in all groups of older than in younger subjects (p<0.01) except exercise-trained men. Mean and diastolic blood pressures were also higher at all exercise intensities in older than in younger subjects (p<0.05) except exercise-trained women, for whom...
diastolic blood pressure during very strenuous effort was not influenced by age. The age-related increase in mean blood pressure at the same submaximal work rate was 17–21% for men and 24–31% for women \((p<0.05)\).

To evaluate the possibility that the interaction between age and gender has a hormonal basis, blood pressures at rest and during exercise were compared in estrogen-treated and untreated older women (Figure 2). Diastolic and mean blood pressures were lower at rest and were particularly lower during exercise in the estrogen group \((p<0.05\) versus nonestrogen group), and a similar trend was observed for systolic blood pressure \((p=0.12)\). Increased age was associated with higher diastolic blood pressures in the nonestrogen group \((p<0.01)\) but not in the estrogen group. Mean blood pressures of older estrogen-treated women were intermediate between those of younger women and untreated older women (all differences at least \(p<0.05)\).

An association between exercise training and lower systolic blood pressure during submaximal work was most evident in older men. Systolic blood pressure was 15–18% lower in the conditioned group \((p<0.01)\). The same effect was less marked in younger subjects (7–12% difference, \(p<0.05\) and was not evident in older women. In contrast, younger exercise-trained subjects had higher systolic pressures at peak effort than younger untrained subjects (10–11%, \(p<0.05\) but at much greater work intensities (Bruce protocol treadmill time, 62–67% longer, \(p<0.01)\). This effect was not evident in older subjects. Diastolic blood pressure was lower at submaximal and peak effort in exercise-trained than in sedentary younger men \((p<0.05)\) but otherwise was not influenced by training status. At the same treadmill stage, mean blood pressure of physically conditioned men was 10–14% less than that of their unconditioned counterparts \((p<0.01)\), regardless of age, which is consistent with lower total peripheral resistance. A similar effect was not observed in women. At peak effort, exercise-trained younger women developed a 9% greater mean blood pressure than their sedentary peers \((p<0.01)\) but at a much higher work rate \((p<0.01)\).

**Calf Blood Flow and Conductance**

For sedentary men and exercise-trained women, increased age was associated with higher resting calf blood flow, conductance, and mean blood pressure \((p<0.01, \text{Figure } 3)\). However, calf blood flow and conductance were lower at rest in conditioned than in the sedentary older men \((p<0.05)\), and significant age-related effects on mean blood pressure and limb vascular dynamics at rest were not observed in exercise-trained men.

After ischemic exercise to fatigue, distal lower limb blood flow and conductance rose more than 10-fold higher than resting values in all groups and attained a plateau that remained stable for 60–90 seconds, which is consistent with achievement of maximal vasodilatation (Figure 4). By comparison, the increase in mean blood pressure was very modest \((11–19%, \ p<0.01)\) and was not influenced by age, gender, or exercise-training status (Figure 3). However, because of higher resting values, mean blood pressures under these conditions were greater in all groups of older than in younger subjects \((p<0.01)\). The smallest increments in indexes of vasodilatation were observed in older sedentary subjects \((11 \text{ to } 13\text{-fold})\), and the largest occurred in younger exercise-trained women \((32\text{-fold})\). However, maximal calf blood flow and conductance were greater in all of the exercise-trained than in the untrained groups, regardless of age and gender \((\text{all } p<0.01, \text{ except } p<0.05 \text{ for older men})\). Differences in maximal blood flow between physically conditioned and sedentary older women. Data are mean±SD. Peak, peak exercise. \(*p<0.01\) vs. younger women. \(\dagger p<0.01, \ddagger p<0.05\) vs. nonestrogen-treated women.
and sedentary subjects were 23% for older men, 40% for older women, and 53–54% for younger individuals. As was observed for systolic and mean blood pressures during submaximal exercise, there was an interactive effect between age and gender on maximal lower limb vasodilatory capacity. Thus, vascular conductance during maximal hyperemia was lower in older than in younger women (p<0.05) but was not influenced by age in men. Maximal conductance of women receiving estrogen tended to be higher than in untreated women (21%, p=0.11), but the difference was not significant, possibly because only eight subjects were in the estrogen-treated group. There was no significant difference in estimated percent body fat between estrogen-treated and untreated older women (28.5±3.5 versus 31.3±7.1%, respectively).

**Relations Between Calf Vascular Dynamics and Blood Pressure, Body Composition, and Exercise Capacity**

Resting systolic and mean blood pressures were directly, but weakly, correlated with resting calf blood flow (r=0.31 and 0.27; p<0.001 and p<0.01, respectively) but not with resting calf conductance. In contrast, systolic, diastolic, and mean blood pressures during submaximal treadmill exercise were all inversely correlated to both maximal hyperemic calf blood flow and conductance (blood flow: r=-0.22 to -0.34, p<0.05; conductance: r=-0.31 to -0.53; p<0.001). These effects were not influenced by age or gender but were highly significant in trained subjects (p<0.0001) and only marginally significant for sedentary individuals (p<0.05). At peak treadmill exer-
However, vasodilatory capacity (r= -0.50, p<0.0001) was directly, but weakly, correlated with both resting calf blood flow and conductance (r=0.32 and 0.27, respectively; p<0.01) and more strongly, but inversely, correlated to maximal calf vasodilatory capacity (maximal calf blood flow: r=-0.50, p<0.0001; maximal conductance: r=-0.57; p<0.0001). However, the latter effect was dependent on the close inverse correlation between subcutaneous adiposity and Vo2max (r=-0.88, p<0.0001). By stepwise multiple regression analysis, only Vo2max was independently correlated with calf vasodilatory capacity (r=0.66, p<0.0001, Figure 5). Thus, nearly half of the variability in Vo2max could be accounted for by differences in maximal limb conductance (r2=0.44). The relation was not significantly influenced by age or gender but was closer in exercise-trained than in untrained subjects (r=0.57 and 0.26, respectively; p<0.001 and p=0.05, respectively).

**Discussion**

Major new findings of this study are that the age-related increase in blood pressure during exercise is greater in women than in men and that calf vasodilatory capacity is reduced with aging only in women. Because of the longer life expectancy of women, we were somewhat surprised by these results. However, the shorter life expectancy of men is largely related to the development of cardiovascular disease. The greater prevalence and severity of atherosclerosis in middle-aged men18,19 can easily obscure a difference in the effect of aging per se on peripheral vascular function of men and women. All of our subjects were in good health, had no major cardiovascular risk factors, no abnormalities on physical examination, and a normal resting electrocardiogram and maximal treadmill stress test. Thus, the prevalence of occult cardiovascular disease in this population is likely to have been low even though it was not excluded by invasive evaluation. Although an

**FIGURE 4.** Plot of calf blood flow at rest and at various times after ischemic exercise to fatigue in sedentary and trained younger and older men. Similar plot for corresponding groups of women was nearly identical to that for men except for differences in resting and hyperemic plateau blood flow values.

**FIGURE 5.** Plot of linear relation between calf conductance during maximal hyperemia and maximal oxygen uptake during treadmill exercise in sedentary older women (△), trained older women (●), sedentary younger women (◇), trained younger women (▼), sedentary older men (○), trained older men (●), sedentary younger men (□), and trained younger men (■). Regression equation presents data for all subjects depicted.
interaction between age and gender has not been described previously, our results are consistent with earlier observations regarding the effects of aging and gender on exercise blood pressure. \textsuperscript{1,2,12} Julius et al\textsuperscript{8} demonstrated that increased age is associated with higher systolic and mean blood pressures, similar cardiac output, and greater total peripheral resistance at the same exercise work rate. Hossack and Bruce\textsuperscript{12} reported that blood pressure and total peripheral resistance during exercise are higher in women than in men. Other investigators have shown that left ventricular ejection fraction and cardiac output are lower in women than in men and in older than in younger subjects, particularly women, during intense exercise.\textsuperscript{12,13,20} These results may be related in part to the age-related reduction in peripheral vasodilatory capacity of older women and increased blood pressure and peripheral resistance during exercise in older subjects in general.

Exercise capacity was lower in female than in male subjects in this investigation, which is consistent with observations in earlier studies of sedentary women.\textsuperscript{12,21} Thus, we cannot entirely rule out the possibility that our results reflect gender differences in level of physical activity, particularly for older trained subjects. However, our sedentary subjects maintained a normal level of physical activity despite their lack of engagement in regular strenuous exercise. Maximal oxygen uptake values of these subjects were similar to values reported in previous studies of healthy sedentary age-matched men and women.\textsuperscript{12,21,22} The age-related reduction in VO\textsubscript{2}max of sedentary subjects was nearly identical for men and women, which suggests that the women did not decrease their level of activity to a greater extent with aging. Although exercise-training duration was not equivalent for physically conditioned older men and women, the difference in calf vasodilatory capacity between exercise-trained and -untrained subjects was not influenced by gender, and the age-related effect was not significantly different in sedentary and exercise-trained women. Thus, a disparity in level of physical activity is unlikely to explain greater age-related effects on blood pressure during exercise and on calf vasodilatory capacity in women, even in the exercise-trained group.

Similarly, it is difficult to completely exclude differences in adiposity and resting blood pressure as contributing factors to age- and training-related effects on peripheral vascular function. However, the disparity in adiposity of older compared with younger subjects was as great for men as for women, yet an age-related effect on maximal calf conductance was observed only in women. For sedentary women, the age-related increase in adiposity only approached significance ($p=0.08$). Longitudinal studies have demonstrated much greater effects of training on calf vasodilatory capacity than on percent body fat or blood pressure at rest.\textsuperscript{9,23} In the present investigation, blood pressure at rest was not significantly different in older exercise-trained compared with untrained subjects and in women compared with men. Thus, differences in adiposity and blood pressure at rest appear unlikely to be major explanations for age- and training-related effects on peripheral vascular function.

The lower blood pressure during exercise and tendency for vasodilatory capacity to be higher in estrogen-treated older women suggest that these effects have a hormonal basis. However, the number of subjects in the estrogen-treated group was small, and these women had a slightly lower blood pressure at rest. Nevertheless, our data are supported by the recent observation of a lower blood pressure during exercise in post-menopausal women, 48–50 years old, after estrogen treatment\textsuperscript{24} and by other evidence that estrogen may influence endothelium- and non-endothelium-dependent vasodilation in coronary arteries of experimental animals.\textsuperscript{25,26} The applicability of these results to the peripheral circulation of human subjects is uncertain, but these findings suggest that estrogen modulates vascular tone. Further investigation of this effect appears warranted.

Calf vasodilatory capacity was greater in exercise-trained than in sedentary subjects regardless of age or gender. The magnitude of the disparity tended to be smaller in older than in younger subjects, but the difference was not significant. Exercise and vasodilatory capacities of younger and older competitive runners who have been training for several years are likely to approach the upper physiological limits for subjects of similar age and gender. Such data are useful in evaluating the true age-related effect that might otherwise be obscured by the influence of physical deconditioning. In this context, a previous study from our laboratory demonstrated that the age-related rate of decline in VO\textsubscript{2}max of highly trained older men was approximately half that of older sedentary subjects.\textsuperscript{27} However, in a recent study,\textsuperscript{28} we observed that after only several months of exercise training, lower extremity vasodilatory capacity of previously sedentary older subjects increased to a level equivalent to that of the highly trained older competitive runners who participated in the present investigation but had an exercise capacity more than 30% higher. These results suggest that physical conditioning of the resistance vasculature occurs fairly rapidly and is more closely related to physical activity per se than to a high exercise capacity. In contrast, the very high VO\textsubscript{2}max values of older competitive runners in the present study may be partly due to their many years of strenuous training and partly due to genetic endowment, despite their lack of a successful athletic history in their youth.

At the same submaximal exercise intensity, cardiac output is similar regardless of age, gender, or training status.\textsuperscript{1,11,13} Thus, the effects of these factors on blood pressure during exercise are primarily related to differences in total peripheral resistance. The resistance vasculature provides a significant portion of systemic resistance and distributes up to 85% of
the cardiac output to active muscles during strenuous exercise.\textsuperscript{3} Therefore, we hypothesized that blood pressure during exercise would be closely related to vasodilatory capacity in muscles that are active during treadmill exercise. Although this relation was highly significant ($r = -0.30$ to $-0.50$, $p < 0.001$), differences in calf vasodilatory capacity only accounted for 10–25\% of the variability in blood pressure during exercise. The age-related increase in blood pressure during exercise was not accompanied by a decrease in calf vasodilatory capacity of men. Lower blood pressure during exercise in trained men occurred in conjunction with increased calf vasodilatory capacity, but the same relation was not found in women. These findings emphasize the complexity of the relation between resistance vascular function and blood pressure during exercise. Recent studies provided evidence that greater systolic and mean arterial blood pressures in older subjects and experimental animals may be a manifestation of increased aortic characteristic impedance.\textsuperscript{28,29} Sympathoadrenal activity is reported to be higher in older than in younger subjects and may also contribute to the age-related rise in blood pressure during exercise.\textsuperscript{30} In contrast, plasma catecholamines and heart rate responses of young subjects to submaximal work are markedly attenuated by even a few weeks of regular, strenuous exercise.\textsuperscript{31} Thus, blunted blood pressure responses of older exercise-trained men may be partly a result of a reduction in sympathoadrenal activity during exercise. Our results suggest that vasodilatory capacity of active muscle groups plays a role but is not the major determinant of blood pressure during exercise. Further studies will be necessary to delineate the mechanisms of age, gender, and training-related effects on blood pressure during exercise.

A possible limitation of our findings is that blood pressure during exercise and reactive hyperemia was obtained in the arm by an indirect technique. Nevertheless, blood pressures were very similar to those observed in previous studies in which measurements were obtained directly with an indwelling catheter.\textsuperscript{1,12} Thus, our results are unlikely to be explained by use of a noninvasive technique. It can be argued that during leg exercise, systolic pressure is higher in the arm than in the aorta because of vasoconstriction in nonactive tissue and, therefore, is not representative of systemic blood pressure. However, Rowell et al\textsuperscript{32} observed nearly identical mean blood pressures and a similar pattern in the rise of systolic pressure in both the aorta and arms during treadmill exercise. Although we cannot rule out disparate effects of aging, gender, or training on blood pressure during exercise in the arms and aorta, this has not been reported. Thus, despite the acknowledged limitation of measuring blood pressure in the arm by indirect techniques, there is no good evidence that our findings can be explained on this basis.

We cannot entirely exclude the possibility that our older subjects were genetically endowed with superior health because more than 50\% of men in this age range would be expected to have atherosclerotic heart disease.\textsuperscript{19} However, a major purpose of this investigation was to differentiate effects of aging from those of other confounding factors such as cardiovascular disease and decreased physical activity. Exercise capacity and other physiological characteristics in the sedentary groups of older subjects were similar to those reported for healthy untrained individuals of the same age and gender.\textsuperscript{12,21,22} Despite having an increased exercise capacity reflecting their history of strenuous activity, older trained subjects did not have a history of athletic success in their youth and only began exercising after the age of 50 years. In addition, they were compared with younger competitive runners who are likely to have an equal genetic endowment in terms of cardiovascular performance and exercise capacity. Longitudinal studies beginning in childhood and continuing for several decades will be necessary to unequivocally characterize the effects of aging. Excluding the acknowledged limitations of a cross-sectional investigation, there was no reason to suspect that our results reflect differences in inheritance.

In summary, the major conclusions of this study are 1) the age-related increase in blood pressure during exercise is greater in women than in men, 2) calf vasodilatory capacity is reduced in older compared with younger women but not men, 3) exercise training is associated with lower blood pressure during submaximal exercise in men and in younger but not in older women and is associated with enhanced calf vasodilatory capacity regardless of age or gender, and 4) differences in maximal exercise capacity and in blood pressure during submaximal exercise are related in part to calf vasodilatory capacity. Thus, there is an interactive effect between age and gender and an independent effect of physical training on peripheral vascular function.

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