Impaired leg vasodilation during dynamic exercise in healthy older women

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The purpose of the present study was to test the hypothesis that leg blood flow responses during leg cycle ergometry are reduced with age in healthy non-estrogen-replaced women. Thirteen younger (20–27 yr) and thirteen older (61–71 yr) normotensive, non-endurance-trained women performed both graded and constant-load bouts of leg cycling at the same absolute exercise intensities. Leg blood flow (femoral vein thermodilution), mean arterial pressure (MAP; radial artery catheter), mean femoral venous pressure, cardiac output (acetylene rebreathing), and blood O2 contents were measured. Leg blood flow responses at light workloads (20–40 W) were similar in younger and older women. However, at moderate workloads (50–60 W), leg blood flow responses were significantly attenuated in older women. MAP was 20–25 mmHg higher (P < 0.01) in the older women across all work intensities, and calculated leg vascular conductance (leg blood flow/estimated leg perfusion pressure) was lower (P < 0.05). Exercise-induced increases in leg arteriovenous O2 difference and O2 extraction were identical between groups (P > 0.6). Leg O2 uptake was tightly correlated with leg blood flow across all workloads in both subject groups (r² = 0.80). These results suggest the ability of healthy older women to undergo limb vasodilation in response to submaximal exercise is impaired and that the legs are a potentially important contributor to the augmented systemic vascular resistance seen during dynamic exercise in older women.

There is evidence of an age-associated reduction in cardiac output during submaximal exercise at a given absolute O2 consumption (VO2) in untrained older men (6, 14). In this context, our laboratory (18) and others (15) recently reported that leg blood flow and O2 extraction during light- to moderate-intensity cycling exercise are well preserved in non-endurance-trained older (~60–75 yr) men despite a reduction in cardiac output. Older women also have reduced cardiac output responses during submaximal exercise (6, 14). However, because of their elevated blood pressure, older women typically display higher levels of systemic vascular resistance during submaximal exercise compared with either older men or younger women (6, 8, 14). In addition, arterial compliance (21, 24) and leg vasodilator capacity (11) both appear to decline to a greater degree with advancing age in women vs. men. However, whether these age-related changes in the peripheral circulation are associated with blunted hyperemic or vasodilator responses in exercising muscle of older women has not been investigated.

Therefore, the purpose of the present investigation was to document the active limb blood flow and O2 extraction responses to graded and constant-load upright leg cycling in healthy non-endurance-trained older (compared with younger) women. To avoid the potentially confounding effects of reproductive hormones, which are known to alter vasodilator responses during rest (12) and exercise (8) in women, we only recruited women who were not currently taking any form of hormone therapy. Leg blood flow (femoral vein thermodilution), mean arterial pressure (MAP; radial artery catheter), mean femoral venous pressure (MVP; femoral vein catheter), and leg O2 extraction were measured during graded and constant-load exercise bouts at the same absolute exercise intensities. Cardiac output [acetylene (C2H2) rebreathing] was measured at selected power outputs on a separate day to examine the influence of age on the cardiac output-leg blood flow relationship during exercise. Because of the previously reported attenuation in limb vasodilatory capacity (11), arterial compliance (21, 24), and submaximal cardiac output (6, 14) with age in women, we hypothesized that leg blood flow and vascular conductance responses during submaximal leg cycling would be reduced in older women.

METHODS

Subject Screening

Thirteen younger (20–27 yr) and thirteen older (60–71 yr) women from State College, PA and surrounding communities completed all phases of this study. Each subject was informed of potential risks and discomforts and signed an
Informed consent form approved by the Institutional Review Board of The Pennsylvania State University and the General Clinical Research Center at the University Park campus. All subjects were recreationally active, but none participated in moderate- or high-intensity aerobic exercise >3 days/wk during the past 12 mo or had a treadmill maximal $V_\text{O}_2$ ($V_{\text{O}_2\text{ max}}$) >80th percentile according to age group norms (1). Additionally, lower body strength-trained subjects (>1 day/wk during past 12 mo) were excluded from participation.

All subjects were nonsmokers and had clinically normal hemoglobin concentrations (11.6–14.8 g/dl) and resting supine ankle-brachial index ratings (>0.90; Refs. 1, 9). All subjects had a body mass index ≈30. No subjects had a history of symptoms of cardiac, vascular, pulmonary, metabolic, or neurological disease. Hypertensive individuals (resting blood pressure ≥140/90 mmHg) were also excluded because their central (5) and peripheral (22) hemodynamic responses to exercise differ compared with normotensive age-matched controls. No subjects were taking medications having significant hemodynamic effects, but one older woman did take aspirin on a regular basis. Subjects underwent a treadmill test to maximal exertion (self-selected walking or running speed, 2 min/stage) to rule out exercise-induced ECG or blood pressure abnormalities and to quantify $V_{\text{O}_2\text{ max}}$.

**Experimental Design**

After screening, subjects came to the laboratory for three cycle ergometer exercise sessions. The primary goal of these sessions was to determine whether the incremental or constant load leg blood flow responses to leg cycling were attenuated in the older vs. younger women. The purpose of session 1 was to familiarize the subject with the cycle ergometer and pulmonary gas-exchange apparatus (i.e., mouthpiece, nose clip, $C_2H_2$ rebreathing bag) and to determine the constant-load power outputs that would be used for each subject during sessions 2 and 3. The primary purpose of session 2 was to noninvasively measure cardiac output and arterial blood pressure responses to leg cycling. During session 3, subjects repeated the session 2 exercise protocol with indwelling catheters for direct measurement of leg blood flow, MAP, MVP, and blood $O_2$ contents. These sessions were generally conducted at the same time of day for a given subject.

During sessions 2 and 3, two protocols were used to fully characterize the leg blood flow responses of these younger and older women and to allow for age group comparisons at the same absolute (protocol 1: 20–60 W; protocol 2: systemic $V_{\text{O}_2}$ ∼0.75 l/min) exercise intensities. Protocol 1 began with subjects pedaling at 20 W for 6 min, during which three leg blood flow, MVP, and MAP measurements were made. The workload was then increased by 10 W every 3 min up to 60 W. Two measurements of leg blood flow, MAP, and MVP were made during each 3-min period. Venous blood was sampled at the end of every workload for measurement of lactate and blood $O_2$ content, whereas arterial blood was sampled at the end of the 30- and 60-W workloads. At the conclusion of protocol 1, each subject was given a 60-min rest period to minimize muscle fatigue. Protocol 2 consisted of 6 min at a workload eliciting a pulmonary $V_{\text{O}_2}$ of 0.75 l/min. Leg blood flow, MAP, and MVP were measured three times during protocol 2, and arterial and venous blood samples were taken 3.5 and 5.5 min into the protocol for measurement of blood gases and lactate.

**Exercise Testing**

Subjects were instructed to abstain from products containing caffeine or aspirin for 12 h before testing. Subjects were provided a standardized dinner the evening before (~1800) and a breakfast the morning of (0600) sessions 2 and 3. Therefore, all subjects were tested in the postabsorptive state. Subjects were also encouraged to drink six to eight glasses of water the day before these sessions.

All exercise testing was performed in the upright posture by using a Lode electronically braked cycle ergometer with aero- clips. A padded forearm rest was attached above the handlebars to prevent the subject from leaning forward and to facilitate blood sampling from the radial artery catheter. Pulmonary gas exchange ($V_{\text{O}_2}$, $CO_2$ production, and minute ventilation) was measured during all three sessions by using the TrueMax 2400 metabolic system (Parvomedics, Salt Lake City, UT; Ref. 3). Heart rate (HR) was recorded from an ECG, and ratings of perceived exertion (RPE) were assessed by using the Borg 6- to 20-point scale. Room temperature was maintained between 19 and 22°C, and subjects were encouraged to drink water between exercise bouts to remain well hydrated.

**Exercise Protocols and Measurements**

**Session 1 (familiarization and initial $V_{\text{O}_2}$ determination).** During the first session, subjects completed an incremental exercise bout to establish submaximal $V_{\text{O}_2}$, HR, and RPE responses. It consisted of three workloads (40, 60, and 80 W) with 5 min of easy pedaling (20 W) between each. Each workload lasted 5 min to allow for steady-state determinations of $V_{\text{O}_2}$, HR, and RPE. The steady-state $V_{\text{O}_2}$ responses from this session were then used to select each subject’s power outputs for sessions 2 and 3.

**Session 2 (cardiac output testing).** Cardiac output was estimated during supine rest and at selected power outputs by using the $C_2H_2$ rebreathing technique (23). Subjects rebreathed from a 5-liter rubber bag initially containing a mixture of 0.6% $C_2H_2$, 40% $O_2$, 10% $H_2$, and balance $N_2$. A pneumatically controlled three-way stopcock was activated to empty the bag with each inspiration for six to seven breaths. He and $C_2H_2$ concentrations were monitored at the mouth by using a respiratory mass spectrometer (model MGA 1100, Perkin-Elmer). End-tidal He and $C_2H_2$ gas concentrations were read from a strip-chart recorder and manually entered into a customized computer program for determination of $C_2H_2$ and He washout curves and computation of cardiac output (l/min). Cardiac output was computed on the basis of breaths 3–6 by using the equations outlined by Triebwasser et al. (23) and assuming a blood solubility constant for $C_2H_2$ of 0.74 ml·ml⁻¹·atm⁻¹ (16). Within-day variability (coefficient of variation) of cardiac output measurements in our laboratory averages 8.5 and 5.5% at rest and during submaximal leg cycling, respectively.

**Session 3 (leg blood flow testing).** Preexercise diet and fluid intake and exercise protocols were the same as in session 2. Preparation for catheter placements typically began between 0700 and 1000. Subjects were instructed on how to shave their right groin region and apply a topical anesthetic (Emla crème). Catheters were placed by using aseptic procedures and local anesthetic (2% lidocaine) in the right femoral vein and the right radial artery as previously described by our group (18). Briefly, a flexible single-lumen catheter (Cook royal flush plus 5.0-Fr angiographic catheter) was inserted just below the right inguinal ligament into the femoral vein and advanced ~10 cm distally for blood sampling, saline...
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Younger Women</th>
<th>Older Women</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>22 ± 1</td>
<td>64 ± 1</td>
<td>0.000</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.5 ± 1.4</td>
<td>163.7 ± 1.4</td>
<td>0.379</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.4 ± 2.5</td>
<td>66.7 ± 1.4</td>
<td>0.147</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>29.8 ± 1.7</td>
<td>35.7 ± 0.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Total FFM, kg</td>
<td>42.6 ± 1.1</td>
<td>42.1 ± 0.7</td>
<td>0.695</td>
</tr>
<tr>
<td>2-Leg muscle mass, kg</td>
<td>10.6 ± 0.3</td>
<td>9.6 ± 0.2</td>
<td>0.012</td>
</tr>
<tr>
<td>Arterial hemoglobin, g/dl</td>
<td>12.7 ± 0.3</td>
<td>12.9 ± 0.3</td>
<td>0.532</td>
</tr>
<tr>
<td>Total cholesterol, g/dl</td>
<td>161 ± 6</td>
<td>204 ± 7</td>
<td>0.000</td>
</tr>
<tr>
<td>Resting systolic BP, mmHg</td>
<td>104 ± 2</td>
<td>123 ± 4</td>
<td>0.000</td>
</tr>
<tr>
<td>Resting diastolic BP, mmHg</td>
<td>67 ± 2</td>
<td>76 ± 2</td>
<td>0.002</td>
</tr>
<tr>
<td>Resting cardiac output, l/min</td>
<td>6.1 ± 0.3</td>
<td>4.9 ± 0.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Treadmill VO2max, ml·kg⁻¹·min⁻¹</td>
<td>35.3 ± 0.7</td>
<td>24.3 ± 1.2</td>
<td>0.000</td>
</tr>
<tr>
<td>VO2max, l/min</td>
<td>7.2 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Values are means ± SE for 13 younger and 13 older women. Body fat %, fat-free mass (FFM), and leg muscle mass were estimated by dual-energy X-ray absorptiometry as described in methods. Resting blood pressure (BP) indicates seated BP (average of 2–3 visits) measured by auscultation. VO2max, maximal O2 consumption.

infusion, and MVP. A second catheter was inserted ~5 cm proximally into the femoral vein for introduction of a thermistor (model IT-18, Physitemp Instruments, Clifton, NJ). This catheter was then removed, leaving the thermistor in the vein. Subsequently, a 20-gauge Teflon catheter (Arrow arterial catheterization set RA-04020) was inserted into the vein. Subsequently, a 20-gauge Teflon catheter was inserted into the femoral vein for introduction of a thermodilution technique as described previously (18). Briefly, icod saline (3–5°C) was infused for 10–15 s until femoral vein temperature had decreased to a stable level. The rate of saline infusion was adjusted with a roller-pump controller to achieve an ~1°C drop in femoral vein temperature at each workload. Thermistor signals and saline bag weight changes were displayed on personal computer-based WinDaq software, which enabled real-time observation of each measurement. Leg blood flow was calculated by using the thermal balance equation detailed by Andersen and Saltin (2) and doubled to give two-leg blood flow (l/min). Simultaneous recordings from the radial artery pressure and femoral vein transducers (model PX-MK999, Baxter) were displayed, recorded, and analyzed by using WinDaq software. The arterial transducer was zeroed at the aortic arch (intercostal space 4) for each subject, and the venous transducer was zeroed at the greater trochanter of the femur. Leg perfusion pressure was estimated by correcting the measured MAP for the hydrostatic gradient between the arterial and venous catheters and then subtracting the MVP. Leg vascular conductance was calculated as leg blood flow × 2/leg perfusion pressure.

Measurement of blood O2 content and leg O2 extraction. Arterial and venous blood samples (1 ml each) were collected in heparinized syringes, placed on ice, and analyzed within 5–10 min. Total hemoglobin, percent oxyhemoglobin saturation, P50, P2CO2, and pH were measured by using an Instrumentation Laboratories blood-gas analyzer (model 15, Synthesis). All blood-gas measurements were made at 37°C and corrected to the femoral vein blood temperature obtained immediately before blood sampling. Blood O2 content was calculated as (1.39 × corrected hemoglobin concentration × %O2 saturation) + (0.003 × blood PO2), as shown in Ref. 7. Leg (a-v)O2 difference was calculated as the difference between arterial and venous blood O2 content. Fractional (%) O2 extraction by the leg was calculated as leg (a-v)O2 difference divided by arterial O2 content.

Measurement of lactate. Arterial and venous lactate concentrations were measured by using a commercially available analyzer (model 2300 stat-plus, Yellow Springs Instruments). No blood was collected during sessions 1 or 2.

Body Composition

Total body fat, fat-free mass, and leg tissue composition were estimated by using dual-energy X-ray absorptiometry (DXA: Hologic QDR 4500-W, software version 9.80D, Waltham, MA). Weekly calibrations were performed on the DXA scanner to ensure accuracy. Leg muscle mass was estimated as (0.692·2·leg fat-free soft tissue mass) − (0.019·age) + (0.09·body mass index) − 0.382 on the basis of a recently published study (19) that reported a strong association between this estimate and magnetic resonance imaging-derived leg muscle mass (r² = 0.89, minimal bias) in a large sample of healthy men and women. The predictive accuracy (SE of the estimate) of this DXA-based estimate of leg muscle mass is ±1.02 kg (19).

Data Analysis

Age group comparisons of subject characteristics (Table 1) and constant-load responses (Table 2) were analyzed by using two-sample t-tests, assuming unequal variances (Minitab version 13.1). Age group comparisons of hemodynamic responses to graded exercise (Fig. 1 and see Fig. 3) were analyzed by using a general linear mixed effects model procedure (Proc Mixed, SAS version 8.2) with age group as the fixed effect, exercise workload as a covariate (first-order autoregressive structure), and repeated measures of subjects over time. The relationships between cardiac output and systemic VO2 (Fig. 2A), between cardiac output and watts (Fig. 2B), and between leg blood flow and leg VO2 (Fig. 3D) were evaluated by using a linear regression model (Proc REG, SAS version 8.2) with age group as an indicator vari-

Table 2. Responses to constant-load cycling at the same systemic absolute VO2 (protocol 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Younger Women</th>
<th>Older Women</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic VO2, l/min</td>
<td>0.78 ± 0.02</td>
<td>0.75 ± 0.01</td>
<td>0.201</td>
</tr>
<tr>
<td>Watts</td>
<td>41 ± 2</td>
<td>39 ± 1</td>
<td>0.276</td>
</tr>
<tr>
<td>RPE</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>0.580</td>
</tr>
<tr>
<td>Femoral venous lactate, mmol/l</td>
<td>1.1 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>0.090</td>
</tr>
<tr>
<td>Leg blood flow × 2, l/min</td>
<td>4.2 ± 0.2</td>
<td>3.9 ± 0.3</td>
<td>0.415</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>88 ± 2</td>
<td>114 ± 4</td>
<td>0.000</td>
</tr>
<tr>
<td>LPP, mmHg</td>
<td>93 ± 3</td>
<td>113 ± 5</td>
<td>0.003</td>
</tr>
<tr>
<td>Leg conductance × 2, ml·min·mmHg⁻¹</td>
<td>46 ± 2</td>
<td>37 ± 4</td>
<td>0.060</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>8.4 ± 0.2</td>
<td>7.4 ± 0.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Leg arteriovenous O2 difference, ml/dl</td>
<td>11.6 ± 0.3</td>
<td>11.4 ± 0.5</td>
<td>0.661</td>
</tr>
</tbody>
</table>

Values are means ± SE for 13 younger and 13 older women. VO2 consumption; RPE, rating of perceived exertion; MAP, mean arterial pressure. Leg perfusion pressure (LPP) was calculated as MAP corrected for hydrostatic gradient between arterial catheter and greater trochanter femoral venous pressure. Leg vascular conductance was calculated as leg blood flow × 2/LPP. Cardiac output was estimated by C4H2 rebreathing during bike session 2.
able. All data are presented as means ± SE. Statistical significance was accepted at $P \leq 0.05$.

RESULTS

Subject Characteristics and Baseline Resting Values (Table 1)

The younger and older women did not differ in height, weight, total fat-free mass, leg fat-free mass, or arterial hemoglobin. However, older women had a larger percent body fat ($P < 0.01$) and less leg muscle mass ($P = 0.01$) compared with younger women ($P < 0.01$). Blood cholesterol concentration and resting blood pressure were both higher ($P < 0.01$), whereas resting cardiac output and treadmill $\dot{V}_O_2$ max were lower, in older than in younger women ($P < 0.01$).

Hemodynamic Responses to Exercise (Figs. 1 and 2, Table 2)

Leg blood flow responses to leg cycling did not differ between groups at light workloads ($P = 0.17–0.42$). However, at 50–60 W, LBF responses were significantly lower in the older compared with younger women ($P < 0.05$). MAP increased with workload in both groups, with the average pressure at any given power output being ~20–25 mmHg higher in the older women ($P < 0.01$). Estimated leg perfusion pressure was significantly higher and leg vascular conductance was lower in older women at all workloads except for 20 W.

Although systemic $\dot{V}_O_2$ was nearly identical across workloads, cardiac output was ~1 l/min lower in the older women (Fig. 2A). The percent distribution of cardiac output to the legs was similar between age groups across all workloads studied (Fig. 2, B and C).

$O_2$ Extraction Responses (Fig. 3)

Younger and older women had similar arterial and venous $O_2$ contents both at rest and during exercise. In both age groups, arterial $O_2$ content remained stable throughout the study, whereas femoral venous $O_2$ content decreased significantly from rest to the first workload (i.e., 20 W) in all subjects and was essentially unchanged from that point onward (Fig. 3A). This resulted in identical leg $O_2$ extraction (Fig. 3B) and (a-v)$O_2$ differences at all workloads. At 60 W, leg $\dot{V}_O_2$ was lower in the older women due to their attenuated leg blood flow response (Fig. 3C). Finally, there was a close linear relationship ($r^2 = 0.80–0.86$) between leg blood flow and leg $\dot{V}_O_2$ in both age groups (Fig. 3D).

DISCUSSION

The major new findings from the present investigation are as follows. First, the rise in leg blood flow during light, but not more intense (e.g., 50–60 W) submaximal leg cycling is preserved in healthy older (compared with younger) women. Second, the rise in leg vascular conductance during incremental exercise is attenuated in older women. Third, these altered vascular responses to exercise in older women are not
associated with age group differences in total leg muscle mass. Finally, exercise-induced increases in leg (a-v) O₂ difference during graded and constant load leg cycling were nearly identical in these two groups of women.

Age and Active Limb Blood Flow Responses in Women

We are unaware of any studies in the literature that have systematically investigated the influence of age on blood flow to exercising muscle in women. The present results suggest that blood flow (and O₂ delivery) to the legs is well preserved during light-intensity exercise involving a large muscle mass, during both graded and constant-load conditions. However, as exercise intensity increased to moderate levels (50–60 W), there was an attenuated rise in leg blood flow in the older women. Possible contributors to this attenuated hyperemic response include age-associated reductions in cardiac output, limb muscle mass, local perfusion pressure, or vasodilation (25). Although the rise in cardiac output (Fig. 2, A and B) and the percentage of cardiac output diverted to the legs (Fig. 2C) were similar in younger and older subjects, there was a lower absolute level of cardiac output at any given Vo₂ or workload in the older women (~1.0 l/min less). Consequently, it is possible that the lower absolute cardiac output response observed in the older women contributed to their attenuated leg blood flow response. Part of the attenuated leg blood flow response in the older women could also be attributable to their reduced leg muscle mass. When leg blood flow was normalized to leg muscle mass (data not shown), blood flow differences between the younger and older women at the higher workloads were abolished (P > 0.35 at 50 and 60 W). However, a subgroup comparison of seven younger and seven older women matched for leg muscle mass revealed an age-associated reduction in leg blood flow across these workloads (i.e., ~15%) that was similar to that seen in the full sample (i.e., ~14%). This suggests that total leg muscle mass is not a major determinant of the attenuated leg blood flow response during submaximal exercise in older women. We cannot exclude the possibility that differences in leg muscle recruitment (i.e., active leg muscle mass) contributed to the blunted hyperemic response in the older women. A final potential contributor to the observed leg blood flow responses in the older women is impaired local vasodilation, as evidenced by their markedly augmented leg perfusion pressure (Fig. 1C) and reduced leg vascular conductance (Fig. 1D).

Possible Mechanisms of Impaired Leg Vasodilation in Older Women

At all workloads studied, estimated leg vascular conductance was reduced by 14–30% in the older women relative to their younger counterparts. This suggests there was a relative vasoconstriction in the exercising
limbs of these older women that was independent of work intensity. The rise in leg conductance during graded exercise was also reduced in the older vs. younger women (i.e., 40–60 W), suggesting attenuated vasodilator responsiveness. The older women’s impaired vasodilator responses to leg cycling are not likely to be the result of a smaller metabolic “signal” for vasodilation relative to the younger women because the rise in lactate across these workloads tended to be larger in the older women. This would suggest that the metabolic signal for vasodilation was similar, or possibly higher, in the older women.

Local vasoregulatory mechanisms that could contribute to augmented vasoconstriction and blunted vasodilation in healthy older women include elevated α-adrenergic vasoconstrictor tone, myogenic tone, and release of vasoconstrictor substances (i.e., endothelin-1 or thromboxane A₂), or reduced release of endothelium-derived vasodilator substances (i.e., nitric oxide, prostacyclin, or hyperpolarizing factor). The present study did not directly address whether the observed leg vascular responses seen in the older women resulted from vasoregulatory adaptations. In this context, Moreau et al. (12) reported elevations in muscle sympathetic nerve activity in sedentary older (vs. younger) women under resting conditions that were not associated with age group differences in leg blood flow or vascular conductance. However, whether sympathetic outflow or vascular responsiveness is augmented in the limbs of older women during exercise has not been determined. Therefore, augmented sympathetic vasoconstriction in the legs of older women cannot be dismissed as a possible mechanism contributing to their impaired leg vasodilator response to exercise. We also cannot discount the possibility that myogenic mechanisms might be involved in the attenuated vasodilator responses observed in the older women. However, recent evidence in rat muscle arterioles suggests that myogenic responsiveness is blunted, rather than augmented, with advancing age (13). Age-related alteration in the vascular endothelium, which can modulate sympathetic or myogenic responsiveness, is a more likely mechanism of altered vascular control of limb perfusion in older women. For example, nitric oxide-mediated vasodilation in the resting forearm (4) and flow-induced vasodilator responsiveness in rat muscle arterioles (13) are reduced with advancing age. If such age-related changes are also present in the legs of older women, this could contribute to their attenuated vasodilator response to exercise. Finally, elevations in plasma endothelin-1, which have recently been documented in healthy older women under resting conditions (10), could contribute to the relative vasoconstrictor state observed in the exercising legs of these older women.

Although we cannot address this issue directly, it is also possible that the older women were approaching a mechanical or structural limit to peripheral vasodilation at moderate work intensities. Recent research suggests that, under resting conditions, femoral artery diameter and compliance do not change with age in sedentary women (12, 21). However, this finding does not exclude the possibility that there are mechanical limits to leg artery distensibility during vasodilator states such as exercise. Experimental support for a structural limitation comes from the study of Martin et
al. (11), who reported that peak calf vascular conductance after fatiguing ischemic exercise is reduced in healthy sedentary older compared with younger women. Under such conditions, vascular conductance is thought to provide an index of the maximum arterial cross-sectional area (20).

Finally, previous studies have demonstrated that estrogen can influence both vascular regulation and structure (4, 11, 12). Because the older women in the present study were not on any form of hormone replacement therapy, it cannot be determined whether the differences observed were due to aging per se or to the normal estrogen-deficiency in older women after menopause.

Physiological Implications

The reduced leg blood flow response observed in the older women during moderate-intensity leg cycling (60 W) has important metabolic implications because it was associated with an attenuated rise in whole limb O2 uptake (Table 2) due to similar leg (a-v)O2 difference between groups. It is unclear why a compensatory increase in O2 extraction across the leg did not occur to allow for maintenance of leg VO2 in the older women. However, it is possible that non-endurance-trained older women, like their male counterparts (15, 18), reach near maximal levels of limb O2 extraction at very low power outputs, with limited capacity for augmentation at higher workloads. It is also possible that the attenuated rise in leg O2 uptake during moderate-intensity exercise in the older women could simply reflect greater blood flow and/or O2 extraction by gluteal or stabilizing muscles that would not be detected by femoral venous measurements. Some evidence in support of this possibility is the observation that non-leg VO2 was significantly higher in the older compared with younger women at 60 W (Fig. 3C). Regardless of the precise cause or nature of this limitation (vascular or metabolic), the attenuated rise in leg VO2 would likely limit older women’s submaximal exercise tolerance.

The results of this study also have important implications for blood pressure regulation during submaximal exercise, during which older women typically display higher levels of systemic vascular resistance compared with either older men or younger women (6, 8, 14). Elevated systemic blood pressure (Fig. 1B) and reduced cardiac output (Fig. 2B) both contributed to this elevation in vascular resistance in older women. Furthermore, the age group difference in systemic blood pressure was greater at all workloads studied (20–25 mmHg) than at rest (12 mmHg), and this difference persisted even after correction was made for the relative work intensity (percentage of peak VO2; data not shown). These results are suggestive of an age-related impairment in systemic vasodilation, and the markedly attenuated leg vascular conductance (elevated leg vascular resistance) responses observed in the older women in the present study suggest that active skeletal muscle is a significant contributor to this systemic response.

Are These Responses Unique to Older Women?

The present results differ in several respects from our recent studies in younger and older non-endurance-trained men (18). In those studies, leg blood flow and vascular conductance were well preserved with age across a broad range of submaximal cycling power outputs. We cannot exclude the possibility that the blunted hyperemic and vasodilator responses seen in the present group of older women were due, at least in part, to their low aerobic fitness level. However, this is unlikely for at least two reasons. First, the older women had similar normative values for VO2 max compared with the older men in our previous study (i.e., 20th to 80th percentile) (1). Second, exercising leg perfusion tends to be augmented, rather than blunted, in the untrained vs. endurance-trained state (17). The previous study also differed from the present one in that leg muscle mass was identical in younger and older men (18), whereas older women had ~9% less leg muscle mass compared with younger women in the present study. However, total leg muscle mass does not appear to be a major determinant of the attenuated leg blood flow responses during submaximal exercise in older women or the well-preserved leg blood flow responses observed in non-endurance-trained older men (18).

The most striking hemodynamic difference between the present group of women and our previous studies in men was the age difference in the absolute MAP during exercise (18). Direct measurement of MAP was 20–25 mmHg higher at any given power output in the older vs. younger women, which was more than twice the age difference observed in men (8–12 mmHg). The higher MAP in older women was the major contributor to the blunted leg vascular conductance seen across workloads, and particularly at light work intensities (i.e., 20–40 W). In contrast, the moderately augmented arterial pressure in older men was associated with slightly (although nonsignificantly) higher leg blood flow responses, such that leg vascular conductance was identical to those observed in younger men. The reduced ability of older women to augment exercising limb blood flow despite augmented perfusion pressure could be due to reduced arterial compliance (i.e., mechanical limitation), reduced arterial diameter (i.e., structural limitation), reduced vasodilatory responsiveness, and/or augmented vasoconstrictor tone relative to older men or younger women. Finally, as discussed above, none of the older women in the present study was on any form of hormone replacement therapy, and whether similar responses would be observed in hormone-replaced older women is deserving of further investigation.

Conclusions

The results from the present study suggest that healthy older non-estrogen-replaced women are lim-
ited in their ability to augment leg blood flow and vascular conductance in response to submaximal large-muscle dynamic exercise and that the legs are a potentially important contributor to the augmented systemic vascular resistance previously reported during exercise in older women.

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