Leg blood flow during submaximal cycle ergometry is
not reduced in healthy older normally active men

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Proctor, David N., Sean C. Newcomer, Dennis W. Koch, Khoi U. Le, David A. MacLean, and Urs A. Leuenberger. Leg blood flow during submaximal cycle ergometry is not reduced in healthy older normally active men. J Appl Physiol 94: 1859–1869, 2003. First published January 24, 2003; 10.1152/japplphysiol.00898.2002.—The purpose of the present study was to test the hypothesis that leg blood flow responses during submaximal cycle ergometry are reduced with age in healthy normally active men. Eleven younger (20–25 yr) and eight older (62–73 yr) normotensive, nonendurance-trained men performed both graded and constant-load bouts of leg cycling at the same absolute and relative [% of peak O2 consumption (Vo2_peak)] exercise intensities while leg blood flow (femoral vein thermodilution), mean arterial pressure (MAP; radial artery), cardiac output (acetylene rebreathing), blood O2 content, and plasma catecholamines were measured. Leg blood flow responses at the same absolute submaximal power outputs (20–100 W) and at a fixed systemic O2 demand (1.1 l/min) did not differ between groups (P = 0.14–0.19), despite lower absolute levels of cardiac output in the older men (P < 0.05). MAP at the same absolute power outputs was 8–12 mmHg higher (P < 0.05) in the older men, but calculated leg vascular conductance responses (leg blood flow/MAP) were identical in the two groups (P > 0.9). At the same relative intensity (60% Vo2_peak), leg norepinephrine spillover rates were approximately twofold higher in the older men (P = 0.38). Exercise-induced increases in leg arterial-venous O2 difference were identical between groups (P > 0.9) because both arterial and venous O2 contents were lower in the older vs. younger men. These results suggest that the ability to augment active limb blood flow and O2 extraction during submaximal large muscle mass exercise is not impaired but is well preserved with age in healthy men who are normally active.

aging; exercise; cardiac output; oxygen extraction; catecholamines

PEAK AEROBIC EXERCISE CAPACITY and the ability to sustain a given absolute submaximal workload decline with advancing age (11, 37). Much of the previous research into the physiological basis of age-related reductions in exercise tolerance has focused on reductions in skeletal muscle mass (i.e., “sarcopenia”), strength, or cardiac function (7, 15). However, many daily physical tasks require a substantial increase in blood flow delivery to the contracting skeletal muscles. An age-related reduction in blood flow to active skeletal muscle has long been postulated as an underlying cause of reduced exercise tolerance in older adults (6, 11, 37, 42). However, technical challenges associated with direct, catheter-based measurements of limb blood flow in exercising older humans have prohibited systematic investigation into this important question. Consequently, there are limited data indicating whether or how active muscle blood flow changes with increasing age (11, 25, 38). This is particularly true for conventional large muscle mass exercise involving the legs. Such information is functionally relevant because most physically demanding activities of daily living involve leg exercise.

The present understanding of potential age-related changes in leg blood flow during exercise is based primarily on studies of highly physically active older adults. For example, we previously reported (34) that leg blood flow and vascular conductance during submaximal leg cycling were lower in chronically endurance-trained older men compared with younger endurance-trained men. Reduced submaximal leg vasodilation in the endurance-trained older men was associated with greater leg arterial-venous (a-v)O2 content difference and, possibly, augmented local sympathetic activity (28, 32, 46). However, it is unclear whether such differences in leg hemodynamics and O2 extraction reflect adaptations associated with aging per se and/or the adaptations to prolonged endurance training. Given that the vast majority of older adults is not highly aerobically trained, studies of leg blood flow in untrained older subjects are particularly relevant.

Therefore, the primary purpose of the present study was to compare the leg blood flow and O2 extraction responses of healthy nonendurance-trained younger (20–30 yr) and older (60–75 yr) individuals during large muscle dynamic exercise (i.e., upright leg cy-
clining). Measurements of leg blood flow (femoral vein thermodilution), mean arterial pressure (MAP; radial artery catheter), leg \( O_2 \) extraction, and leg norepinephrine (NE) spillover were obtained during graded and constant load bouts of leg cycling at the same absolute and relative [60 and 100% of peak \( O_2 \) consumption \((V_{O2\,peak})\) ] exercise intensities. Cardiac output [acetylene (C\(_2\)H\(_2\)) rebreathing] was also measured at selected submaximal power outputs on a separate day to examine the influence of age on the cardiac output-leg blood flow relationship during exercise. Our primary hypothesis was that leg blood flow would be lower at any given absolute submaximal power output in the older (compared with younger) group due to a lower absolute cardiac output response (11, 15, 42) and elevated local sympathetic activity (i.e., leg NE spillover rate).

METHODS

Subject Screening

Eleven younger (20–25 yr) and eight older (62–73 yr) men 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 (GCRC) 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 \( O_2 \) consumption. Subjects were 100% of peak \( O_2 \) consumption. Each protocol was separated by an average of 2 wk, except for five subjects (3 younger, 2 older) for whom the order had to be reversed due to scheduling conflicts. These sessions were generally conducted at the same time of day for a given subject.

The exercise protocols used during sessions 2 and 3 are shown schematically in Fig. 1. During each session, four protocols were used to fully characterize the leg blood flow responses of these younger and older men and to allow for age group comparisons at the same absolute [protocol 1: 20–100 W; protocol 2: systemic \( O_2 \) consumption \((V_{O2})\) ~1.1 min] and relative [protocol 3: ~60% of \( V_{O2\,peak} \); protocol 4: 100% of \( V_{O2\,peak} \)] exercise intensities. Each protocol was separated by a rest or active recovery period to minimize muscle fatigue.

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 using a Lode electronically braked cycle ergometer with toe 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 (\(\dot{V}O_2\), \(\dot{CO}_2\) consumption, and minute ventilation) was measured during all three sessions by using the TrueMax 2400 metabolic system (Parvomedics, Salt Lake City, UT) (4). Heart rate (HR) was recorded from an ECG, and ratings of perceived exertion were assessed by using the Borg 6-20-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 \(\dot{V}O_2\) peak determination). During session 1, subjects completed two incremental exercise bouts to establish submaximal \(\dot{V}O_2\), \(\dot{V}O_2\) peak, HR, and ratings of perceived exertion responses. The first bout consisted of three workloads (40, 80, and 120 W) with 5 min of easy pedaling (20 W) between each. Each workload lasted 5 min to allow for steady-state determinations of \(\dot{V}O_2\), HR, and ratings of perceived exertion. After a 60-min recovery, subjects performed a continuous incremental test (1 min per stage) to maximum exertion for determination of peak power (Fig. 1) by using the \(2\,H_2\) rebreathing technique (45). Subsequently during supine rest and at selected power outputs (Fig. 1) by using the \(2\,H_2\) rebreathing technique (45). Subjects breathed from a 5-liter rubber bag initially containing 0.74 ml·min\(^{-1} \cdot \text{atm}^{-1} \times \text{32} \times \) (32). 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 2** (cardiac output testing). Cardiac output was estimated during supine rest and at selected power outputs (Fig. 1) by using the \(2\,H_2\) rebreathing technique (45). Subjects breathed from a 5-liter rubber bag initially containing a mixture of 0.6\% \(C_2H_2\), 40\% \(O_2\), 10\% helium, and balance nitrogen. A pneumatically controlled three-way stopcock was activated before a normal inspiration, and subjects were asked to empty the bag with each inspiration for six to seven breaths. Helium and \(C_2H_2\) concentrations were monitored at the mouth by using a respiratory mass spectrometer (Perkin-Elmer MGA 1100). End-tidal helium 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 helium 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. (45) and assuming a blood solubility constant for \(C_2H_2\) of 0.74 ml·min\(^{-1} \cdot \text{atm}^{-1} \times \text{32} \times \) (32). 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 (for leg blood flow and venous blood sampling) and the right radial artery (for MAP and blood sampling), as previously described by our group (34). 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, to approximately 8 cm distally for all sampling and saline infusion. A second catheter was inserted ∼5 cm proximally into the femoral vein for introduction of a thermistor (IT-18, Physiostemp 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 right radial artery for MAP measurements and blood sampling.

**Measurement of leg blood flow and arterial pressure.** Whole leg blood flow was measured during exercise by using the constant infusion, femoral vein thermodilution technique as described previously (34). Briefly, iced 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 transducer (Baxter PX-MK099) were displayed, recorded, and analyzed by using WinDaq software. The transducer was zeroed at the aortic arch (intercostal space 4) for each subject. Leg vascular conductance was calculated as leg blood flow/MAP. The timeline for measurements during the leg blood flow study are shown in Fig. 1. In our laboratory, leg blood flow measurements at a given steady-state submaximal power output (60–100 W) are highly reproducible in both younger (average CV = 3.0%) and older (CV = 4.3%) subjects.

**Measurement of blood \(O_2\) content and leg \(O_2\) 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, PO\(_2\), PCO\(_2\), and pH were measured by using an Instrumentation Laboratories blood gas analyzer (Synthesis 15). All blood-gas measurements were made at 37°C and corrected to the femoral vein blood temperature obtained immediately before blood sampling. Blood O\(_2\) content was calculated as (1.39 × corrected hemoglobin concentration × %O\(_2\) saturation) + (0.003 × blood PO\(_2\)), as shown in Ref. 16. Leg (a-v)O\(_2\) difference was calculated as the difference between arterial and venous blood O\(_2\) content. Fractional (%) O\(_2\) extraction by the leg was calculated as leg (a-v)O\(_2\) difference divided by arterial O\(_2\) content.

**Measurement of catecholamines and lactate.** Arterial and venous plasma catecholamine concentrations (5 ml each) were measured by using high-performance liquid chromatography with electrochemical detection (47). Rate of NE spillover (net overflow) from the leg (leg NE spillover) was calculated as described by Savard et al. (39). Arterial and venous lactate concentrations were measured by using a commercially available analyzer (Yellow Springs Instruments 2300 stat-plus). Approximately 150 ml of blood were collected from each subject during the leg blood flow study (session 3). 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 (Hologic QDR 4500-W, software version 9.80D, Waltham, MA) (34). Weekly calibrations were performed on the dual-energy X-ray absorptiometry scanner to ensure accuracy. Leg muscle mass was estimated as (0.692-2 leg lean mass) – (0.019-age) + (0.09-body mass index) – 0.382 (40).

**Data Analysis**

Age group comparisons of subject characteristics (Table 1), constant load responses (Tables 2 and 3), and peak exercise responses were analyzed by using two-sample t-tests, assum-
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Younger Men</th>
<th>Older Men</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>21 ± 1</td>
<td>66 ± 2</td>
<td>0.000</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175.7 ± 2.0</td>
<td>178.5 ± 2.6</td>
<td>0.412</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.1 ± 2.8</td>
<td>85.8 ± 2.5</td>
<td>0.033</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>18.9 ± 1.6</td>
<td>26.2 ± 1.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Total FFM, kg</td>
<td>60.9 ± 2.1</td>
<td>61.7 ± 1.9</td>
<td>0.762</td>
</tr>
<tr>
<td>2-Leg FFM, kg</td>
<td>18.9 ± 0.7</td>
<td>19.6 ± 0.8</td>
<td>0.802</td>
</tr>
<tr>
<td>Arterial hemoglobin, g/dl</td>
<td>15.5 ± 0.3</td>
<td>14.2 ± 0.4</td>
<td>0.025</td>
</tr>
<tr>
<td>Total cholesterol, g/dl</td>
<td>167 ± 6</td>
<td>188 ± 10</td>
<td>0.106</td>
</tr>
<tr>
<td>Arterial norepinephrine, nM</td>
<td>1.54 ± 0.37</td>
<td>2.46 ± 0.59</td>
<td>0.217</td>
</tr>
<tr>
<td>Resting systolic BP, mmHg</td>
<td>127 ± 3</td>
<td>130 ± 4</td>
<td>0.588</td>
</tr>
<tr>
<td>Resting diastolic BP, mmHg</td>
<td>78 ± 2</td>
<td>80 ± 2</td>
<td>0.714</td>
</tr>
<tr>
<td>Resting cardiac output, l/min</td>
<td>7.2 ± 0.3</td>
<td>5.6 ± 0.1</td>
<td>0.000</td>
</tr>
<tr>
<td>Treadmill V̇O₂max, ml·kg⁻¹·min⁻¹</td>
<td>44.5 ± 1.5</td>
<td>31.4 ± 1.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Treadmill V̇O₂max, l/min</td>
<td>3.4 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Values are means ± SE for 11 younger and 8 older men. 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. V̇O₂max, maximal O₂ consumption.

ing unequal variances (Mini-tab version 13.1). Age group comparisons of hemodynamic responses to graded exercise (Figs. 2 and 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 comparisons, but the older men had lower hemoglobin concentrations (P = 0.02) and supine resting cardiac outputs (P < 0.001). Treadmill V̇O₂max was also lower in the older men (P < 0.001).

### RESULTS

**Subject Characteristics and Baseline Resting Values**

The older men weighed more (P = 0.03) and had more total body fat (P = 0.003) than the younger men but had similar leg muscle mass (Table 1). There were no differences between the two groups for resting blood pressure, total cholesterol, or plasma NE concentrations, but the older men had lower hemoglobin concentrations (P = 0.02) and supine resting cardiac outputs (P < 0.001). Treadmill V̇O₂max was also lower in the older men (P < 0.001).

**Responses to Graded Submaximal Exercise (Protocol 1)**

Leg blood flow responses during graded leg cycling did not differ between groups (Fig. 2A; P = 0.19). MAP (Fig. 2B) increased linearly in both groups, with the average pressure at any given power output being 8–12 mmHg higher in the older men (P < 0.05). Increases in leg vascular conductance (Fig. 2C) did not differ between groups (P = 0.93).

Arterial O₂ content at rest and during protocol 1 was significantly lower in the older men (Fig. 3A). Femoral venous O₂ content (Fig. 3A) decreased significantly from rest to the first workload (i.e., 20 W) in all subjects and was essentially unchanged from that point onward. Absolute venous O₂ content in the older men was also lower at rest and at any given submaximal workload compared with the younger men, resulting in almost identical leg (a-v)O₂ difference responses (Fig. 3B). Fractional extraction of O₂ by the exercising legs (Fig. 3C) approached peak levels in the older men at a relatively low work intensity (i.e., 72% at 40 W), whereas the younger men demonstrated a further increment in leg O₂ extraction during the peak exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Younger Men</th>
<th>Older Men</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic V̇O₂, l/min</td>
<td>1.08 ± 0.02</td>
<td>1.07 ± 0.03</td>
<td>0.666</td>
</tr>
<tr>
<td>Watts</td>
<td>60 ± 1</td>
<td>65 ± 2</td>
<td>0.052</td>
</tr>
<tr>
<td>RPE</td>
<td>9 ± 1</td>
<td>11 ± 1</td>
<td>0.245</td>
</tr>
<tr>
<td>Femoral venous lactate, mmol/l</td>
<td>1.2 ± 0.3</td>
<td>1.4 ± 0.1</td>
<td>0.374</td>
</tr>
<tr>
<td>Leg blood flow × 2,l/min</td>
<td>5.1 ± 0.3</td>
<td>5.9 ± 0.4</td>
<td>0.140</td>
</tr>
<tr>
<td>Leg (a-v)O₂ difference, ml/dl</td>
<td>13.8 ± 0.5</td>
<td>13.8 ± 0.6</td>
<td>0.953</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>98 ± 4</td>
<td>106 ± 4</td>
<td>0.125</td>
</tr>
<tr>
<td>Leg conductance × 2,l-min⁻¹·mmHg⁻¹</td>
<td>0.053 ± 0.003</td>
<td>0.057 ± 0.004</td>
<td>0.455</td>
</tr>
<tr>
<td>Cardiac output, l/min*</td>
<td>10.2 ± 0.3</td>
<td>9.2 ± 0.3</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Values are means ± SE for 11 younger and 8 older men. RPE, rating of perceived exertion; MAP, mean arterial pressure; V̇O₂, O₂ consumption. Leg vascular conductance was calculated as leg blood flow × 2/MAP. *Cardiac output was estimated by acetylene rebreathing during bike session 2.
Responses did not reach statistical significance, \( P > 0.05 \), compared with the younger (60 W) men (\( P = 0.289 \)) and the older group, but this difference was not statistically significant (\( P = 0.14 \)). There was also a trend toward higher MAP responses in the older men (\( P = 0.13 \)), resulting in similar estimations of leg vascular conductance between groups. Cardiac output was 1.0 l/min lower in the older men (\( P = 0.05 \)). Leg \((a-v)O_2\) difference averaged 13.8 ml/dl in both groups (\( P = 0.95 \)).

## Catecholamine Responses

Although age group differences in catecholamine responses did not reach statistical significance due to the large degree of variability, both plasma NE concentrations and estimated leg NE spillover rates during constant load exercise at 60% \( V_02 \) peak (protocol 3) tended to be higher in the older compared with the younger men (Table 3).

### Relation Between Submaximal Leg Blood Flow and Cardiac Output

The increase in leg blood flow per unit increase in cardiac output (i.e., slope) was 0.32 l/l larger in the older vs. younger men (Fig. 4A), but this difference was not statistically significant (\( P = 0.19 \)). Further analysis (Fig. 4B) revealed that the difference between age groups displayed in Fig. 4A was primarily due to significant age group differences in the % of cardiac output distributed to the legs at the same absolute (65 ± 3 vs. 51 ± 2% of cardiac output; \( P < 0.001 \)), rather than relative (71 ± 5 vs. 62 ± 5% of cardiac output; \( P = 0.21 \)), exercise intensity.

### Peak Exercise Responses (Protocol 4)

The peak power output achieved during exhaustive graded cycle ergometer exercise varied considerably within each age group (older 132–220 W; younger 150–275 W) but averaged 43 W less (\( P = 0.02 \)) in the older men. Similarly, there was wide variation in \( Vo2 \) peak, with responses averaging 25% lower in the older men (younger men 2.8 ± 0.2 l/min; older men 2.1 ± 0.1 l/min; \( P = 0.001 \)). There was a trend toward lower peak leg blood flow responses in the older men (younger men 12.3 ± 0.7 l/min; older men 10.5 ± 1.0 l/min; \( P = 0.16 \)), although this did not reach statistical significance because of the large variation in peak power output and \( Vo2 \) peak in these groups. Peak leg \((a-v)O2\) differences averaged 1.0 ml/dl lower in the older men (younger men 15.5 ± 0.3; older men 14.5 ± 0.6 ml/dl). Leg \( O2 \) extraction was not significantly different between groups at peak exertion (younger men 71.1 ± 2.1%; older men 74.4 ± 2.1%; \( P = 0.29 \)).

Blood pressure responses during maximal exertion are not reported because excessive hand gripping for stabilization was unavoidable for most subjects, and this artificially elevated MAP measurements to variable degrees. Peak cardiac output could not be measured in most subjects because of dyspnea and difficulty in maintaining a constant rate and depth of \( C2H2 \) rebreathing during maximal exertion.

### DISCUSSION

There are four primary new findings from the present study. First, leg blood flow responses to graded and constant load submaximal leg cycling are not reduced, and may actually be augmented, in healthy older normally active men despite an age-associated reduction in cardiac output. Second, the preserved leg blood flow responses to submaximal leg cycling in these older subjects appear to be achieved with a higher arterial perfusion pressure. Third, exercise-induced increases in leg \((a-v)O2\) difference are preserved with advancing age in normally active men despite modest reductions in arterial \( O2 \) content. Lastly, our results suggest that the distribution of cardiac output to the legs during submaximal exercise in nonendurance-trained men is primarily a function of aerobic fitness not age per se.

### Age and Leg Blood Flow Responses to Submaximal Exercise

The few published studies that have compared exercising leg blood flow responses between younger and older humans have involved highly active (28), chronically endurance-trained (34, 46), or hypertensive (5) subjects and produced mixed results. The physical activity and aerobic fitness levels of the two groups in the present study (~20th–80th percentile for treadmill \( Vo2 \) max) more closely represent a “moderately active”

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**Table 3. Catecholamine responses to constant load cycling at ~60% of peak \( Vo2 \) (protocol 3)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Younger Men</th>
<th>Older Men</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial norepinephrine, nM</td>
<td>4.41 ± 0.89</td>
<td>6.10 ± 1.25</td>
<td>0.292</td>
</tr>
<tr>
<td>Venous norepinephrine, nM</td>
<td>4.40 ± 1.00</td>
<td>6.68 ± 1.77</td>
<td>0.289</td>
</tr>
<tr>
<td>Arterial epinephrine, nM</td>
<td>0.83 ± 0.13</td>
<td>1.05 ± 0.21</td>
<td>0.401</td>
</tr>
<tr>
<td>Venous epinephrine, nM</td>
<td>0.74 ± 0.11</td>
<td>0.87 ± 0.13</td>
<td>0.464</td>
</tr>
<tr>
<td>Estimated norepinephrine clearance, *%</td>
<td>29.8 ± 3.5</td>
<td>22.9 ± 5.4</td>
<td>0.309</td>
</tr>
<tr>
<td>Leg norepinephrine spillover, † nM/min</td>
<td>374 ± 89</td>
<td>594 ± 214</td>
<td>0.378</td>
</tr>
</tbody>
</table>

Values are means ± SE for 8 younger and 6 older men. *Norepinephrine clearance was estimated as 68% of epinephrine clearance (39).† Leg norepinephrine spillover was estimated by using the formula described by Savard et al. (39).
aging population (i.e., nonsedentary and nonendurance trained). We also carefully screened subjects for several additional characteristics that could independently alter hemodynamic responses to exercise, including hypertension, obesity, and cardiovascular medication use. As such, our experimental design should provide a more accurate reflection of the influence of the aging process per se on leg blood flow and its determinants during large muscle dynamic exercise.

Using this approach, we found that leg blood flow responses across a broad range of submaximal power outputs (i.e., 20–100 W) did not differ between the younger and older groups. Maintenance of active limb blood flow with age has also been reported in healthy normally active men in response to small muscle dynamic exercise involving the forearms (25). Together, these studies suggest that active limb blood flow responses to submaximal exercise workloads are well preserved up to ~65–70 yr of age in healthy, nonendurance-trained men.

There were no statistically significant age group differences in leg blood flow in the present study. However, there are several indications that leg blood flow responses to submaximal cycling were actually greater in the older compared with younger men. Leg blood flow (2 legs) averaged 0.6 l/min higher in the older men at any given power output during graded exercise (protocol 1; \( P = 0.19 \)). The trend for higher flows in the older men was also observed during constant load cycling at a systemic \( \dot{V}O_2 \) of 1.1 l/min (protocol 2; 0.8 l/min higher vs. young; \( P = 0.14 \)), although part of this difference could be explained by the slightly higher power output (i.e., 65 vs. 60 W) required for the older men to achieve the same whole body \( \dot{V}O_2 \). A post hoc comparison of leg blood flow between the older (\( n = 4 \)) and younger (\( n = 10 \)) men who were tested at the identical power output (i.e., 60 W) for protocol 2 did reveal a smaller age group difference (i.e., 5.5 vs. 5.1 l/min, old vs. young, respectively; \( P = 0.65 \)). However, statistical power analysis indicated that 32 subjects per group would be necessary to detect an age group difference of this magnitude. Unfortunately this number of subjects per group is impractical given the invasive and costly nature of these studies. Augmented leg blood flow responses in our older subjects, if present, would probably reflect a higher \( O_2 \) cost of pedaling (i.e., lower mechanical efficiency) rather than more blood flow per liter of leg \( O_2 \) consumed (see Fig. 3D). These issues are deserving of further investigation.

The finding that leg blood flow responses to submaximal leg cycling are preserved or possibly augmented in normally active older men contrasts what we (34) and others (46) previously reported in cross-sectional comparisons of younger and older chronically endurance-trained men. In those studies, leg blood flow responses during submaximal leg cycling were 10–25% lower in the older groups. However, leg (a-v)\( O_2 \) differences during submaximal cycling were \( \sim 20\% \) higher (\( \sim 2.0–2.5 \) ml/dl) in the trained older men (34) compared with the subjects in the present study. This comparison suggests that the attenuated increases in leg blood flow during submaximal leg cycling in chronically endurance-trained older men are not due to physiological aging per se but may reflect peripheral adaptations to prolonged endurance training that reduce the overall demand for leg blood flow during submaximal exercise. The augmented leg \( O_2 \) extractions seen in endurance-trained older men may reflect the extensive capillary

![Fig. 2](https://jap.physiology.org/)

Fig. 2. Leg blood flow (A), mean arterial pressure (B), and leg vascular conductance (C) during graded submaximal leg cycling (protocol 1) in younger (○) and older (●) men. Values are means ± SE for 11 younger and 8 older men. *Significant difference vs. young men (\( P < 0.05 \)).
supply and/or high oxidative enzyme activities of their trained leg muscles, as was previously demonstrated by our group (35).

In summary, the findings of the present study clearly indicate that leg blood flow responses to submaximal leg cycle ergometry are not reduced in healthy, normally active older men, an effect that is markedly different from what is observed in their chronically endurance-trained peers.

Age and Cardiac Output Responses to Submaximal Exercise

Absolute levels of cardiac output were lower in the older men at all workloads for which measurements were taken, consistent with most previous comparisons of nonendurance-trained younger and older men (15, 42). The magnitude of the age group difference was also consistent with previous studies, both at rest (1.6 l/min lower in the older men; Ref. 21) and during upright submaximal leg cycling at a given systemic VO₂ (1.0 l/min lower in older men) (18, 29). The lower absolute cardiac outputs during exercise in the older men were due to the combined effects of a lower HR (7–10 beats/min) and stroke volume (6 ml/beat) compared with the younger men. These reductions, in turn, were likely mediated by age-related impairments in β-adrenergic stimulation of HR and left ventricular systolic function, respectively. An age-related decline in total blood volume could also contribute to the attenuated stroke volume and cardiac output responses observed in nonendurance-trained older men. This is unlikely in the present study, however, considering that total fat-free mass, which is strongly and positively related to blood volume and stroke volume in healthy men (3, 21), did not differ between groups (Table 1).

When the significant age-associated reduction in submaximal cardiac output is considered, it was surprising to find that leg blood flow responses were so well maintained in these older men. However, our results also suggest that more of the total cardiac output during submaximal exercise is distributed to the legs in older compared with younger normally active men (Table 2 and Fig. 4A). Further analysis (Fig. 4B) revealed that this group difference was primarily due to a significantly higher percent distribution to the legs at a given absolute, but not relative, exercise intensity. Collectively, these results suggest that the higher % distribution of cardiac output to the legs of our older subjects during submaximal exercise at the same absolute exercise intensity is primarily a function of aerobic fitness, not age per se. Moreover, these findings do not support our original hypothesis that the age-associated reduction in submaximal cardiac output limits the rise in leg blood flow during light or heavy submaximal exercise (up to 100 W) in men.

Potential Mechanisms of Preserved Leg Blood Flow in Older Normally Active Men

Several factors could explain the well-preserved submaximal leg blood flow responses in these older men, independent of age or fitness differences in cardiac output or its distribution. The lack of an age group difference in leg muscle mass (Table 1) is one possibility. To explore this issue further, we compared leg blood flow responses at a fixed workload (60 W) between a subgroup of younger (n = 6) and older subjects (n = 6) who differed in leg muscle mass by 10%, which
The preserved leg blood flow responses in our older men during submaximal exercise would appear, therefore, to be primarily determined by the O$_2$ demand of the contracting muscles, as it is in younger men. This is suggested by the similar relationship between submaximal leg blood flow and leg VO$_2$ in the two groups as shown in Fig. 3D. These findings support the concept that limb O$_2$ demand is the major determinant of active limb blood flow during dynamic exercise (33). The strong association between these variables in both groups also suggests that aging in normally active men does not substantially alter the proportion of leg blood flow perfusing less-metabolically active components of the legs (i.e., adipose tissue, bone, skin), at least during submaximal leg cycling.

It is important to note that the leg blood flow responses in the older men were achieved with an augmented arterial perfusion pressure relative to that of the younger controls. The older group maintained a significantly higher MAP during graded submaximal cycling (8–12 mmHg) and a trend toward higher pressures (8 mmHg; $P = 0.12$) during constant load cycling at a similar absolute systemic O$_2$ uptake (i.e., protocol 2). Average increases in estimated leg vascular conductance during graded submaximal cycling (protocol 1) were nearly identical between groups. These findings suggest that the well-preserved leg blood flow responses in the untrained older men were mediated by augmented arterial perfusion pressure rather than by an augmented local vasodilatory response.

The preserved leg vascular conductance responses observed in our older subjects were unexpected considering the putative age-related reductions in endothelium-dependent limb vasodilation (12, 30) and increases in muscle sympathetic vasoconstrictor tone (13). We have no data with which to address the first possibility. For the second possibility, although we do not have catecholamine data at a similar absolute power output, plasma NE concentrations and leg NE spillover rates during exercise at 60% VO$_2$ peak tended to be higher in the older men (Table 3), suggestive of augmented systemic and local sympathetic outflow, respectively. Because the younger men were at a higher absolute workload at 60% VO$_2$ peak, this trend should be even stronger if younger and older men were
compared at the same absolute workload. If sympathetic outflow to the legs during submaximal exercise is in fact augmented with advancing age, preserved leg blood flow responses could be explained by attenuated peripheral vasoconstrictor responsiveness with advancing age (10).

**Age and Leg O₂ Extraction Responses**

Femoral venous O₂ content was significantly lower in the older compared with younger men at all submaximal workloads (Fig. 3A) and tended to be lower in the older men during maximal cycling (i.e., 5.1 vs. 6.3 ml/dl; P = 0.10). The greater exercise-induced reduction in femoral venous O₂ content during submaximal work in these older men was probably necessary to compensate for their reduced arterial O₂ content, as discussed above. During peak cycle ergometer exercise, however, full compensation for the age difference in arterial O₂ content was less apparent because peak leg (a-v)O₂ differences averaged 1.0 ml/dl lower in the older compared with younger men.

The fractional extraction of O₂ by the legs (% of arterial O₂ content extracted by the tissues) was higher in the older men at any given submaximal workload. In fact, the older men essentially reached their peak leg O₂ extraction at a very low power output (e.g., 72% at 40 W), whereas the younger men demonstrated a further increment during the peak exercise bout (i.e., protocol 4). The early attainment of peak limb O₂ extraction in the older men could result from an earlier and more extensive recruitment of muscle capillaries at similar absolute but higher relative workloads compared with the younger men.

During peak exercise, fractional O₂ extraction across the leg did not differ between groups (i.e., older 74 ± 2.1% vs. younger 71 ± 2.0%; P = 0.29). Fractional O₂ extraction is determined by the ratio between regional O₂ diffusion capacity and blood flow (26). Therefore, the well-preserved peak leg O₂ extractions in the older men could reflect a better maintenance of muscle O₂ diffusion capacity (limited by capillary-to-muscle fiber surface area) relative to that of peak leg blood flow (limited by peak cardiac output) with advancing age in healthy men. Such adaptations could preserve peak leg fractional O₂ extraction with age by maintaining or prolonging the mean transit time of red blood cells through the leg muscle capillaries. Indirect support for this hypothesis comes from studies demonstrating similar capillary-to-fiber area ratios (8, 35) in older vs. younger normally active men. As discussed above, even higher leg O₂ extractions have been reported during strenuous leg cycling in endurance-trained older men (34, 37). Taken together, these results suggest that fractional leg O₂ extraction is well maintained during both submaximal and peak cycle ergometry, at least to an age of ~65–70 yr in healthy men.

It was surprising to find that most of the reduction in femoral venous O₂ content and the widening of the leg (a-v)O₂ difference in both groups of subjects occurred during very mild exercise (e.g., 20 W), with little further adjustment at higher submaximal workloads (Fig. 3A). Average leg (a-v)O₂ differences during graded submaximal cycling (protocol 1) were similar to those observed during constant load submaximal cycling (i.e., protocol 2), suggesting that this unexpected pattern of limb O₂ extraction was not protocol specific. These results appear contrary to the idea that active limb (a-v)O₂ difference increases progressively with increasing workloads. However, this assumption has been based primarily on the responses of young endurance-trained men (36) across a much broader range of absolute power outputs (up to 300–350 W), which may differ from responses seen in less active or sedentary subjects.

**Physiological Significance**

The results of the present investigation, which demonstrate well-preserved leg blood flow and O₂ extraction responses to exercise in healthy older men, could be used to argue against the idea that leg O₂ delivery and extraction contribute to age-related declines in submaximal exercise tolerance in humans. Although we did not measure submaximal endurance per se, there was no indication that a relatively brief period (i.e., 6 min) of constant load cycling at a given absolute systemic O₂ demand (i.e., 1.1 l/min) evoked significantly more physiological strain in our older compared with younger subjects (Table 2). However, it should be noted that the older men did utilize a higher percentage of their leg O₂ extraction “reserve capacity” to achieve this submaximal level of VO₂. For submaximal exercise bouts of longer duration (e.g., >6 min), this could gradually lead to an increased sense of effort and more rapid fatigue. For gradually increasing work intensities, this means that the older adult would become progressively more “blood flow limited” and depend to a greater extent on their ability to augment leg blood flow because further widening of their leg (a-v)O₂ difference appears to be limited. Fortunately, the lower absolute level of cardiac output in these subjects does not appear to limit the rise in leg blood flow, even during moderately intense submaximal leg cycling (e.g., 100 W). However, competition for blood flow by other regional circulations could, under certain conditions (i.e., exercise in the heat, combined arm/leg exercise, and so forth), attenuate the rise in leg blood flow of exercising older adults, particularly because a higher percentage of their available cardiac output is distributed to their working muscles at a given absolute power output or VO₂.

The present results also have implications for age-related differences in systemic cardiovascular regulation during exercise. To maintain a higher MAP in the face of a lower cardiac output during submaximal exertion, the older men would need to maintain a higher level of systemic vascular resistance compared with their younger counterparts. The similarity of leg vascular conductance responses between age groups (Fig. 2C) suggests that the exercising legs are not the major sites of augmented vasoconstriction in the older men.
under these conditions. It is more likely that augmented vasoconstriction occurred in the arms (44), postural/stabilizing muscles (28), and/or in the splanchnic/renal circulations of these older, nonendurance-trained men to generate the augmented MAP response. Although previous age group comparisons during exercise at the same relative intensities (% of $\dot{V}O_2_{\text{peak}}$) in hot ambient conditions argue against augmented splanchnic and renal vasoconstriction in healthy older men (20), there is evidence of augmented splanchnic vasoconstriction during exercise at the same absolute intensity in younger men when cardiac output was acutely reduced by systemic $\beta$-adrenergic blockade (31) and in senescent dogs (compared with young dogs) during treadmill exercise (19).

In conclusion, the results of the present study suggest that the ability to augment active limb blood flow and $O_2$ extraction during submaximal exercise involving the legs is not impaired by the aging process per se in humans. The leg blood flow responses to submaximal exercise in healthy, normally active older men appear to be largely regulated according to the $O_2$ demand of the exercising limbs, as in younger adults. However, the maintenance of active leg vasodilation during exercise in these subjects is achieved with an elevated arterial perfusion pressure, possibly due to a sympathetically mediated increase in non-leg vasoconstriction to compensate for the age-associated reduction in cardiac output. These findings have implications for systemic blood pressure regulation, limb mechanical efficiency, and submaximal and peak exercise tolerance in healthy older adults.

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