Augmented Forearm Vasoconstriction During Dynamic Exercise in Healthy Older Men

J. Andrew Taylor, PhD; Gregory A. Hand, MS; David G. Johnson, MD; and Douglas R. Seals, PhD

**Background.** We tested the hypothesis that the nonactive limb vasoconstriction evoked during large-muscle dynamic exercise becomes augmented with aging in humans.

**Methods and Results.** Sixteen young control subjects (age, 26±1 year) and twelve older (65±1 year) healthy men with similar chronic physical activity levels were studied during supine leg cycling exercise. Both peak work load (1,100±60 versus 1,400±40 kpm/min) and peak %O₂ uptake (1.85±0.10 versus 2.38±0.07 l/min) were lower in the older men (p<0.05). There were no differences in the two groups under conditions of quiet supine (basal) rest. During cycling for 5 minutes each at mild, moderate, and heavy submaximal intensities (45%, 65%, and 85% of peak %O₂ uptake), the increases in arterial blood pressure generally were similar in the young and older subjects; however, heart rate rose less in the older men (p<0.05). Whole forearm blood flow (venous occlusion plethysmography) was lower and vascular resistance was higher (55–90%) in the older men at all loads (p<0.05), but the steady-state forearm skin blood flow responses (laser Doppler velocimetry) were not different in the two groups. The increases in antecubital venous norepinephrine concentrations were greater in the older men at each work load (p<0.05), although the plasma epinephrine responses were similar in the two groups. In other studies, 1) peak whole forearm reactive hyperemia and vascular conductance after sustained circulatory arrest (ischemia) were slightly (20%) but not significantly lower in the older men and 2) the forearm vasoconstrictor and plasma norepinephrine responses to a nonexercise sympathoexcitatory stimulus (limb immersion in ice water) tended to be blunted in the older men.

**Conclusions.** During brief, submaximal, large-muscle dynamic exercise, healthy older men demonstrate augmented forearm vasoconstriction that is probably caused by greater constriction of skeletal muscle resistance vessels; this appears to be mediated, at least in part, by increased sympathetic outflow. These altered sympathetic vasoconstrictor adjustments do not represent a nonspecific hyperresponsiveness to acute stress with human aging. Finally, the regulation of arterial blood pressure appears to be normal in these healthy older men. *(Circulation 1992;86:1789–1799)*

**KEY WORDS** • aging • sympathetic nervous system • arterial pressure, regulation

During large-muscle dynamic exercise in humans, vasoconstriction occurs in the nonactive limbs and the viscera, which contributes to an increase in arterial perfusion pressure and permits redistribution of blood flow to the contracting skeletal muscles. This region-specific vasoconstriction is mediated by increases in the discharge rate of postganglionic sympathetic nerves; the latter is highly correlated with increases in plasma concentrations of the neurotransmitter norepinephrine. Within an individual, the magnitudes of the vasoconstrictor and plasma norepinephrine responses are primarily dependent on the relative exercise intensity (i.e., percent of exercise capacity or peak %O₂ uptake).

It has been reported that the increase in plasma norepinephrine concentration during the same relative intensity of dynamic leg exercise is greater in older compared with young humans, although similar increases have also been observed. The former suggests that sympathetic nervous system activation may be greater in the older person during this type of physical stress. However, it is not known whether this augmented norepinephrine response, when observed, is associated with exaggerated vasoconstriction.

Accordingly, the primary aim of the present study was to test the hypothesis that nonactive limb vasoconstriction is augmented in older healthy humans during large-muscle dynamic exercise. If so, our secondary aims were to determine whether this exaggerated vasoconstriction 1) is due to greater constriction in the skeletal muscle circulation, 2) is associated with greater sympathetic nervous system activation and/or with evidence of structural changes in the resistance vessels, 3) is exercise intensity–dependent, and 4) also occurs in response to a nonexercise stress. Finally, we wished to determine whether altered sympathetic vasoconstrictor adjustments in older humans are associated with obvious changes in the regulation of arterial blood pressure during exercise.
To accomplish these aims, we measured whole forearm blood flow, forearm skin blood flow, arterial blood pressure, and antecubital venous plasma norepinephrine concentrations at rest and during mild, moderate, and heavy submaximal leg cycling exercise in healthy young and older men with similar chronic physical activity levels. Vascular resistance was calculated and used as an index of whole forearm vasoconstrictor tone; the associated skin blood flow responses were used to infer possible age-related differences in skeletal muscle vasoconstriction. The reactive forearm hyperemia in response to sustained circulatory arrest (ischemia) was determined to gain insight into possible differences in resistance vessel structure/function in the two groups. To determine whether the differences in responses were specific for exercise, the same measurements were made in a subset of the subjects during another sympathetic vasoconstrictor stimulus, limb immersion in ice water (cold pressor test).

Methods

Subjects

Sixteen young men (age, 26±1 year; range, 21–29 years) and twelve older men (age, 65±1 year; range, 60–72 years) healthy men participated in this study. Only male subjects were used to ensure that the interpretation of differences between the two age groups would not be confounded by the possible influence of sex. All subjects were free of any signs or symptoms of overt coronary heart disease based on a medical history and resting and maximal exercise ECGs. Individuals on medications that could affect cardiovascular function and smokers were excluded from the study. To ensure that pulmonary function was within the age-adjusted normative range for each group, subjects performed forced expiratory volume maneuvers on a Collins spirometer. To eliminate possible effects of obesity, only those subjects within 20% of ideal body weight as assessed by body mass index were included in the study. Body fat was assessed using the sum of skinfold thicknesses measured at six body sites. To ensure that differences in chronic physical activity levels would not be a confounding factor in the comparison of responses in the young and older subjects, only individuals who were physically inactive to recreationally active were included in the study; physically trained subjects were excluded from the study because adaptations to training per se could mask any differences caused by aging. The Stanford Physical Activity Questionnaire was used to estimate average daily physical activity levels. Maximal oxygen consumption was determined during graded treadmill exercise to ensure that the aerobic capacities of the young and older subjects were within the normal ranges for men of their respective ages. The nature, purpose, and possible risks of the study were explained to each subject before he gave written consent to participate. The experimental protocol was approved by the Human Subjects Committee at the University of Arizona.

Experimental Procedures

Systemic measurements. Heart rate was measured from a computer-averaged ECG signal. Beat-to-beat arterial blood pressure was measured in the finger by a Finapres blood pressure monitor (model 2300; Ohmeda). The O2 consumption was measured on-line using computer-assisted open-circuit spirometry. The O2 and CO2 fractions in the expired air were determined using Applied Electrochemistry gas analyzers (models S-3A1 and CD-3A), and pulmonary ventilation was measured with a Parkinson-Cowan dry gas meter (model CD-4).

Whole forearm blood flow. Forearm blood flow was measured using venous occlusion plethysmography as described previously. Air-filled, latex plethysmographic cuffs were placed around the mid forearm (right) for recording changes in volume. The limb was positioned above heart level to ensure proper venous drainage. A blood pressure cuff was placed on the upper arm just above the elbow and inflated to =50 mm Hg for 7.5 seconds of every 15 seconds while blood flow to the hand was occluded by a cuff placed around the wrist and inflated to suprasystolic levels (250 mm Hg). Changes in forearm volume were recorded for subsequent calculation of flow expressed in milliliters per 100 ml of tissue per minute.

Forearm skin blood flow. Forearm skin blood flow was estimated using laser Doppler velocimetry (Laserflow blood perfusion monitor, model 403-A, TSI, St. Paul, Minn.) as described previously. A standard laser Doppler probe was attached to the skin on the left forearm in the same position as the latex plethysmographic cuff on the contralateral forearm. Because the laser Doppler signal does not provide absolute units of blood flow, skin blood flow was calculated as percentage of control.

Internal body temperature. Because internal body temperature can influence the autonomic circulatory adjustments to exercise, a subset of the subjects performed the submaximal exercise trial a second time with an esophageal temperature probe (Yellow Springs Instruments, Yellow Springs, Ohio). Only eight subjects (four young, four older) were able to swallow the esophageal probe and therefore participate in this portion of the study. The thermistor was inserted through the mouth and down the esophagus to heart level. Heart level was approximated by inserting the probe to one-fourth the subject’s height.

Plasma catecholamines. To obtain blood samples for subsequent determination of plasma catecholamine concentrations, an indwelling catheter was placed in the left antecubital vein. Samples of approximately 6 ml were drawn and placed in a chilled heparin-containing glass tube for analysis of venous plasma norepinephrine and epinephrine levels. The plasma was separated and stored at −70°C. Analysis (in duplicate) for norepinephrine and epinephrine was made by the single-isotope radioenzymatic technique of Peuler and Johnson. The sensitivity of the assay is ±20–30 pg/ml, with coefficients of variation of 4.8% (intra-assay) and 7.8% (interassay).

Electromyographic activity. To ensure that exercise-induced changes in forearm blood flow were not influenced by involuntary muscle contractions, electromyographic (EMG) activity was measured in the right forearm. Bipolar Ag-AgCl electrodes, 8 mm in diameter, were attached to the surface of the skin =3 cm apart adjacent to the latex plethysmography cuff. Reference electrodes were placed over a bony prominence near the elbow. The electrodes were connected to an isolated...
Preamplifier (Gould), after which the signal was passed through an amplifier for filtering (30 Hz, low; 300 Hz, high) and recording (Gould ES 1000).

Peak reactive hyperemia. Peak reactive forearm blood flow was assessed by measuring the blood flow response in the right forearm after 10 minutes of local ischemia produced by inflating a blood pressure cuff on the upper arm to suprasystolic levels (250 mm Hg).16

Experimental Protocols

Orientation sessions. All subjects were familiarized with the exercise protocol on at least two occasions before participating in the experimental sessions. Subjects were positioned supine on a padded table with both feet strapped to the pedals of an electrically braked cycle ergometer (Quinton Instruments, model 845) and their waist firmly secured to the cycle. The right forearm was supported by a sling attached to the wrist. Subjects then cycled at various work rates while forearm flows and EMG activity were monitored. With sufficient coaching, all subjects were able to perform the exercise without forearm muscle electrical activity.

Maximal cycling session. Peak work rate and peak O₂ uptake for supine leg cycling were determined on a separate day before the submaximal exercise session. Subjects cycled at an initial work rate of 200 kilopond meters (kpm)/min (older) or 400 kpm/min (young) for 1 minute, after which the work load was increased 100 kpm/min every minute. The pedal frequency was maintained at ≈60 revolutions per minute. The O₂ uptake was determined every 30 seconds throughout the exercise bout. Peak work rate was defined as the intensity at which the subject could no longer perform the required work load and peak O₂ uptake as the highest level attained during the trial. To ensure that maximal voluntary effort was obtained in each subject, a respiratory exchange ratio (CO₂ production/O₂ uptake) (index of hyperventilation) >1.15 was attained in all trials. To determine the reproducibility of these peak exercise measurements, 10 subjects (five young, five older) performed this trial twice. There were no significant differences in either the peak work rate or peak O₂ uptake achieved during the two trials (differences were <10% for both young and older subjects).

Submaximal cycling session. The submaximal exercise trials consisted of 5 minutes of supine cycling preceded by 3 minutes of resting (control) measurements. Cycling was performed at three levels defined as mild, moderate, and heavy (=45%, 65%, and 85% of peak O₂ uptake). In both groups of subjects, exercise was performed in order from the lowest to the highest intensity to minimize the effects of fatigue and to reduce the time required between trials for the various cardiovascular variables to return to normal control levels. Fifteen to 30 minutes of rest occurred between the end of each exercise bout and the start of the next control period to allow the variables to return to their normal baseline levels. Throughout the session, room temperature was maintained at a comfortable thermoneutral level (≈25°C).

During the control and exercise periods, heart rate, arterial blood pressure, skin forearm blood flow, right forearm EMG activity, O₂ uptake, and esophageal temperature were determined continuously, whereas whole forearm blood flow was measured every 15 seconds. A blood sample for determination of plasma catecholamines was drawn 2–3 minutes before the initiation of each exercise bout (control) and 1 minute after the end of exercise because in humans, peak exercise-induced plasma catecholamine levels occur at this time. During the measurement periods, the subjects were continually reminded to relax their forearm, and no sustained EMG activity was observed during any of the submaximal bouts in any subject. After the end of the final exercise trial, peak forearm hyperemia was determined in eight subjects from each group.

Cardiac output session. To determine whether any augmentation in the forearm vasoconstrictor responses to dynamic leg exercise in the older men was associated with a lower level of cardiac output and a higher level of systemic vascular resistance, eight of the young and seven of the older subjects repeated their 45% and 65% of peak exercise cycling trials on a separate day. Cardiac output was measured using the CO₂ rebreathing (indirect Fick) method as described in detail previously. This procedure could not be used at the heavy submaximal exercise intensity because of hyperventilation in some of the subjects. During the resting control and the exercise periods, arterial blood pressure also was measured as described above.

Cold pressor test session. On a separate day, eight young and seven older subjects performed a cold pressor test in the same (supine) position as that used during exercise. This consisted of a 3-minute resting control period followed by immersion of the left foot (up to the malleolus) in 0°C ice water for 2 minutes. Measurements were made as in the submaximal exercise trials (see above). To document that the noxious stimulus was perceived similarly by the young and older subjects, every 30 seconds during immersion, subjects were asked to rate their perceived pain on a pain scale of 6 (not painful) to 20 (very, very painful). A blood sample for determination of plasma catecholamines was drawn 2–3 minutes before immersion (control) and 1 minute after the end of immersion, when peak levels are known to occur.18

Data Analysis

Average values. Control values were taken as the average of the entire 3-minute period. During submaximal exercise, 30-second averages were determined for all variables. For the reactive hyperemia trial, the highest forearm blood flow observed after 10 minutes of circulatory arrest was taken as the peak forearm hyperemia (this was always the first or second flow at the offset of ischemia). For the cold pressor test, average values for all measured variables were determined for each of the 2 minutes of limb immersion. The control value before and the 30-second (exercise) or 1-minute (limb immersion) averages during the interventions were used to calculate the changes in all variables for each individual subject.

Calculations. Mean arterial pressure was calculated as diastolic pressure +1/3(systolic pressure—diastolic pressure). Whole forearm vascular resistance was determined by dividing the values for mean arterial pressure by whole forearm blood flow. Whole and skin forearm vascular conductances were calculated as the inverse of resistance. Systemic vascular resistance was determined by dividing mean arterial pressure by cardiac output.
Statistics. For all variables, differences between groups within a condition were assessed by factorial ANOVA with Scheffe’s post hoc test. Differences between the control and the various exercise (or cold pressor test) time intervals within a group were assessed using ANOVA for repeated measures designs and Scheffe’s post hoc test. Differences were considered to be significant at the \( p < 0.05 \) level. All group data are presented as mean±SEM.

Results

Subject Characteristics

Table 1 shows selected characteristics of the young control subjects and the older men. The average age difference was \( \approx 40 \) years. There were no significant differences in height, body weight, or body mass index; however, the older subjects did have a greater percentage of body fat (\( p < 0.05 \)). The older men had a lower aerobic capacity than the young men (\( p < 0.05 \)), but the estimated average daily energy expenditure was not different in the two groups. Pulmonary function was similar to the respective age-adjusted normative values in both groups (98±4% and 100±3% of normal for forced vital capacity and 100±3% and 99±5% of normal for forced expiratory volume in 1 second in the young and older men, respectively).

Peak Exercise Responses

The peak work rate attained during supine cycling was lower in the older subjects than in the young men (1,100±60 versus 1,400±40 km/min, \( p < 0.05 \)). Because of the lower peak work rate, the peak \( O_2 \) uptake of the older subjects was less than that for the young subjects (1.85±0.10 versus 2.38±0.07 l/min, \( p < 0.05 \)). The peak heart rate of the older men also was lower than that for the young men (143±4 versus 171±2 beats per minute, \( p < 0.05 \)).

Resting Control Levels

During the initial resting control period (i.e., before the mild exercise level), there were no differences between the two groups in any variable (Table 2; time point 0 in Figure 1). Heart rate and whole forearm blood flow were higher during the final control period compared with the initial control period in both groups (\( p < 0.05 \)), whereas arterial blood pressure was higher during the middle and final control periods compared with the initial control period in the older group (\( p < 0.05 \)).

Adjustments to Submaximal Exercise: Same Relative Work Loads

\( O_2 \) uptake. The three submaximal work loads represented 45±1%, 67±1%, and 84±2% and 49±2%, 71±2%, and 84±3% of peak cycling \( O_2 \) uptake in the young and older men, respectively (Figure 2). These three exercise intensities were different from one another within each subject group (\( p < 0.05 \)); thus, the exercise stimulus was graded. The percent of peak \( O_2 \) uptake at any of the three submaximal exercise levels was not different in the young and older subjects; therefore each submaximal exercise level represented the same relative stress for both groups. Because peak \( O_2 \) uptake was lower in the older men, their absolute (liters per minute) level of \( O_2 \) uptake (i.e., whole-body energy expenditure) during each of the three exercise intensities also was lower (\( p < 0.05 \); Figure 2).

Arterial blood pressure and heart rate. Arterial blood pressure increased above baseline within the first minute of each submaximal exercise level and tended to plateau by the end of the second minute in both groups (Figure 3); the increases were proportional to the exercise intensity. In general, the absolute levels of diastolic arterial pressure were not significantly different in the young and older subjects during any work load; however, mean and systolic arterial pressure

### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Subject Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body mass index (kg/m²)</th>
<th>Estimated body fat (%)</th>
<th>Maximal oxygen consumption (ml/kg⁻¹·min⁻¹)</th>
<th>Estimated energy expenditure (Kcal/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young (n=16)</td>
<td>25.9±0.7</td>
<td>177.7±1.8</td>
<td>74.7±2.5</td>
<td>15.3±1.0</td>
<td>47.4±0.8</td>
<td>2,825±132</td>
</tr>
<tr>
<td>Older (n=12)</td>
<td>65.0±0.8*</td>
<td>178.4±2.2</td>
<td>80.0±3.5</td>
<td>22.6±1.1*</td>
<td>32.1±1.0*</td>
<td>3,071±178</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *\( p < 0.05 \) vs. young group.

### Table 2. Baseline Values Before Three Levels of Supine Leg Cycling

<table>
<thead>
<tr>
<th>Exercise level</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Systolic arterial pressure (mm Hg)</th>
<th>Diastolic arterial pressure (mm Hg)</th>
<th>Heart rate (beats per minute)</th>
<th>Plasma norepinephrine (pg/ml)</th>
<th>Plasma epinephrine (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>93±2</td>
<td>135±2</td>
<td>72±2</td>
<td>68±2</td>
<td>186±14</td>
<td>37±5</td>
</tr>
<tr>
<td>Older</td>
<td>94±3</td>
<td>143±5</td>
<td>70±2</td>
<td>65±4</td>
<td>178±15</td>
<td>51±14</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>90±2</td>
<td>131±2</td>
<td>69±2</td>
<td>69±3</td>
<td>170±12</td>
<td>32±4</td>
</tr>
<tr>
<td>Older</td>
<td>99±3*†</td>
<td>151±5*†</td>
<td>73±2</td>
<td>65±4</td>
<td>199±16</td>
<td>47±11</td>
</tr>
<tr>
<td>Heavy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>91±2</td>
<td>132±2</td>
<td>71±2</td>
<td>75±3†</td>
<td>187±16</td>
<td>37±5</td>
</tr>
<tr>
<td>Older</td>
<td>103±3*†</td>
<td>155±5*†</td>
<td>77±3</td>
<td>70±4†</td>
<td>189±14</td>
<td>56±11</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *\( p < 0.05 \) vs. young, †\( p < 0.05 \) vs. initial control value; \( n = 16 \) (young), \( n = 12 \) (older).
tended to be higher in the older men. The magnitudes of the increases in mean and diastolic arterial pressure from control to exercise were almost identical in the two groups during all levels of cycling. The increases in systolic arterial pressure were more variable: slightly greater in the older men during the last 2 minutes of mild exercise \( (p<0.05) \), not different during moderate exercise, and somewhat smaller in the older men during heavy exercise \( (p<0.05) \).

Heart rate increased above control during the first minute at each level of exercise in both groups \( (p<0.05, \text{ Figure 4}) \); the magnitude of the increase during cycling was greater with increasing exercise intensity. At all time points during all three intensities, both the absolute levels and the magnitudes of the increases in heart rate were less in the older men \( (p<0.05) \).

**Regional hemodynamics.** Whole forearm blood flow decreased below control by the second minute of each exercise intensity in both groups \( (p<0.05) \) and remained at this reduced level (Figure 1). The absolute levels were lower in the older subjects than in the young men throughout each intensity of exercise \( (p<0.05) \). Because there was a tendency (NS) for the control value to be lower in the older subjects, the decreases from control during exercise were not significantly different for the two groups. Whole forearm vascular resistance increased above control in both groups by the second minute of each exercise level \( (p<0.05) \); the increases were proportional to the exercise intensity (Figure 1). Both the absolute levels during exercise and the magnitude of the increases from control were greater in the older subjects during all work intensities, with the greatest differences observed at the highest load \( (p<0.05) \). The same differences were observed when the responses were expressed as forearm vascular conductance, i.e., the older men maintained lower absolute levels and demonstrated greater decreases than the young men at all work loads.

At the initiation (first 30 seconds) of exercise at all three loads, forearm skin blood flow decreased slightly in the young men \( (2-6\% \text{ below control}) \) but increased slightly \( (1-3\% \text{ at the two lowest loads}) \) to moderately \( (23\% \text{ at the highest load}) \) above control levels in the older men. However, thereafter, skin blood flow increased gradually and similarly at all loads in both groups, typically attaining steady-state levels by the second or third minute of exercise. Peak steady-state levels were 26–42\% above control in young control subjects versus 27–40\% above control in older men (NS between groups).

**Plasma catecholamines.** Venous plasma norepinephrine concentrations increased above control levels only in the older subjects in response to mild exercise \( (p<0.05) \) but rose in both groups during moderate and heavy exercise \( (p<0.05, \text{ Figure 5}) \); the response tended to be graded with increasing exercise intensity. Both the absolute concentrations of plasma norepinephrine at end exercise and the magnitudes of the increases from control were greater in the older subjects at all exercise levels, with the most marked differences observed at the

---

**Figure 1.** Plots of whole forearm blood flow (bottom panels) and vascular resistance (top panels) before (0 time point) and during the three submaximal levels of cycling in the young control subjects \( (n=16) \) and the older men \( (n=12) \). Forearm blood flow was lower and vascular resistance was higher in the older men during each level of exercise. \( *p<0.05 \) vs. young control subjects.

**Figure 2.** Bar graphs show \( \text{O}_2 \) uptake \( (\dot{V}_{O_2}) \) during three submaximal levels of leg cycling in the young control subjects \( (n=16) \) and older men \( (n=12) \). At the same level of exercise, the young and older men were working at a similar percentage of their peak \( \dot{V}_{O_2} \) uptake, i.e., at a similar relative exercise stress (top panel). However, because of their lower peak \( \dot{V}_{O_2} \) uptake, at the same level of exercise the older men were performing less work and thus had a lower absolute level of whole-body \( \dot{V}_{O_2} \) uptake (i.e., energy expenditure) (bottom panel). \( *p<0.05 \) vs. young control subjects.
highest intensity ($p<0.05$). Plasma epinephrine concentrations did not change from control levels in response to mild exercise in either group, increased slightly with moderate exercise in the young subjects only ($p<0.05$), and were substantially elevated in response to heavy exercise in both groups ($p<0.05$) (Figure 5); the changes tended to be greater with increasing exercise intensity. There were no differences in either the absolute levels at end exercise or the magnitudes of changes from control at any work load in young and older subjects.

**Internal body temperature.** In general, during the mild- and moderate-intensity exercise trials, esophageal temperature remained within $0.1^\circ$C of control levels in both

---

**Figure 3.** Plots show increases above resting control values for arterial blood pressure during the three submaximal levels of cycling in the young control subjects ($n=16$) and the older men ($n=12$). In general, the regulation of arterial pressure appeared to be similar in the two groups although there were some differences in the systolic blood pressure response, primarily at the highest work load. *$p<0.05$ vs. young control subjects.*

**Figure 4.** Plots show increases above resting control values for heart rate during the three submaximal levels of cycling in the young control subjects ($n=16$) and the older men ($n=12$). The increase in heart rate (bpm, beats per minute) was less in the older men during each level of exercise. *$p<0.05$ vs. young control subjects.*

**Figure 5.** Bar graphs show increases above control values for plasma norepinephrine (top panel) and epinephrine (bottom panel) at the end of the three submaximal levels of exercise in the young control subjects ($n=16$) and the older men ($n=12$). Plasma norepinephrine increased more in the older men in response to each level of exercise. In contrast, there were no group differences in the plasma epinephrine responses to exercise. Note the different scaling in the upper and lower panels. *$p<0.05$ vs. young control subjects.*
uptake of 1.59 l/min; NS versus young men) were compared (Figure 6). At this common absolute exercise intensity, the age-related differences in the whole forearm blood flow, whole forearm vascular resistance, and plasma norepinephrine responses were much greater than that observed at the same relative cycling loads.

**Peak Reactive Hyperemia**

After 10 minutes of forearm ischemia, the older subjects attained peak levels of whole forearm blood flow (35.9±3.2 ml/100 ml per minute) and vascular conductance (0.39±0.05 units) that were ≈20% lower on average than the levels observed in the young men (43.3±4.1 ml/100 ml per minute and 0.50±0.05 units); however, the differences were not statistically significant. The same nonsignificant trend was observed when the responses were expressed in terms of vascular resistance.

**Cardiac Output Trial**

During supine rest, cardiac output was 5.6±0.2 versus 5.2±0.3 l/min and systemic vascular resistance was 16.6±0.6 versus 18.9±1.8 units in the young and older subjects, respectively (both NS). Cardiac output increased and systemic vascular resistance decreased in proportion to increases in exercise intensity in both groups of subjects. At 45% and 65% of peak O₂ uptake, respectively, cardiac output tended to be lower (11.7±0.9 versus 12.6±0.6 l/min and 14.1±0.6 versus 15.4±0.9 l/min) and systemic vascular resistance higher (10.2±0.7 versus 8.8±0.3 units and 9.2±0.6 versus 7.7±0.4 units) in the older compared with the young men (NS).

**Cold Pressor Test**

There were no significant differences between the young and older subjects for any variable before the cold pressor test (Table 3). The cold stimulus was perceived as “very painful” by both the young and older subjects (perceived pain ratings of 16±1 versus 15±1 units, respectively; NS). There were no significant differences in the cardiovascular responses to limb immersion in the two groups, although the increases in mean arterial pressure and whole forearm vascular resistance tended to be smaller in the older men (Figure 7). The older subjects demonstrated lesser increases in both plasma norepinephrine (p<0.07) and plasma epinephrine (p<0.05) concentrations compared with the young subjects (Figure 7). Thus, in contrast to dynamic exercise, there was a tendency for the sympathoadrenal forearm vasoconstrictor adjustments to local cold stimulation to be attenuated in the older men.

### TABLE 3. Baseline Values Before 2-Minute Cold Pressor Test

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Systolic arterial pressure (mm Hg)</th>
<th>Diastolic arterial pressure (mm Hg)</th>
<th>Heart rate (beats per minute)</th>
<th>Forearm blood flow (ml per 100 ml/min)</th>
<th>Forearm vascular resistance (units)</th>
<th>Plasma norepinephrine (pg/ml)</th>
<th>Plasma epinephrine (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>94±4</td>
<td>133±5</td>
<td>77±4</td>
<td>70±3</td>
<td>5.2±0.5</td>
<td>19.4±2.1</td>
<td>232±24</td>
<td>73±20</td>
</tr>
<tr>
<td>Older</td>
<td>93±3</td>
<td>143±3</td>
<td>73±3</td>
<td>63±3</td>
<td>5.5±0.6</td>
<td>18.3±2.1</td>
<td>308±55</td>
<td>40±13</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n=8 (young), n=7 (older).
FIGURE 7. Bar graphs show increases above resting control levels for the measured variables during the second minute of a 2-minute cold pressor test (foot immersion in 0° C water) in a subset of the young control subjects (n=8) and the older men (n=7). In contrast to large-muscle exercise, the older subjects tended to have blunted forearm vasoconstrictor and plasma norepinephrine responses to this stimulus. \( \text{Beats per minute} \). *p<0.05 vs. young control subjects.

Discussion

The primary new conclusion from this study is that compared with young men, older healthy men demonstrate greater forearm vasoconstriction during brief submaximal dynamic leg exercise that appears to be mediated primarily by augmented constriction in the skeletal muscle circulation. This response is associated with greater increases in plasma norepinephrine concentrations, suggesting augmented sympathetic neural activation is a key mechanism. The greater sympathetic vasoconstrictor adjustments to dynamic leg exercise in the older men do not represent a nonspecific hyperreactivity to all forms of acute stress because augmented responses were not observed during a nonexercise sympathoexcitatory stimulus. Compared with the young control subjects, the regulation of arterial blood pressure during this type of exercise appears to be essentially normal in these older healthy men.

Forearm Vasoconstriction During Exercise

In the present study, augmented forearm vasoconstriction was observed in the older subjects at all three submaximal exercise levels, indicating that these age-related differences are independent of the stimulus intensity. Because whole forearm blood flow is determined primarily by flow in the forearm skin and skeletal muscle circulations and because the steady-state skin blood flow responses were similar in the two groups during exercise, the greater increases in whole forearm vascular resistance in the older subjects probably were mediated by greater vasoconstriction in the skeletal muscle. This was associated with larger increases in plasma norepinephrine levels, suggesting greater exercise-evoked sympathetic nervous system activation in the older subjects. The interpretative limitations of plasma norepinephrine concentrations as an index of sympathetic nervous system activity are well documented.\(^\text{19,20}\) However, \( \approx 50\% \) of the antecubital venous plasma norepinephrine concentration is derived from skeletal muscle sympathetic nerve release\(^\text{21,22}\) and is well correlated with muscle sympathetic nerve activity both at rest\(^\text{23}\) and during large-muscle dynamic exercise.\(^\text{4}\) Therefore, the greater increases in antecubital venous plasma norepinephrine concentrations in the older subjects are consistent with the postulate that their heightened level of vasoconstriction was mediated at least in part by greater sympathetic outflow to resistance vessels in skeletal muscle. However, recent reports of age-related decreases in presynaptic \( \alpha_2 \)-adrenergic receptor inhibition of norepinephrine release,\(^\text{24}\) in norepinephrine reuptake by sympathetic nerve terminals (personal communication, Dr. Murray Esler), and possibly in norepinephrine clearance\(^\text{25}\) suggest that peripheral factors may have also contributed to the higher plasma norepinephrine concentrations.

There are other mechanisms that may have been involved in the augmented vasoconstrictor responses in the older subjects. Although not statistically significant, we found that compared with the young control subjects, the older subjects tended to demonstrate a lower peak reactive hyperemia and maximal vascular conductance (increased minimal vascular resistance) after sustained forearm ischemia, which suggests possible structural changes in the resistance vessels.\(^\text{16}\) Such an interpretation is consistent with known age-related alterations that result in increased arterial wall thickness and decreased arterial elasticity.\(^\text{26,27}\) In hypertensive animals and humans, qualitatively similar but more severe structural changes are associated with exaggerated constriction in response to neural or pharmacological stimuli.\(^\text{28}\) Therefore, the greater vasoconstrictor responses observed in our older subjects could be due in part to this structural "amplifier" effect.

Altered vascular responsiveness to adrenergic receptor stimulation is another potential contributor to these age-associated differences. In general, there is little or no evidence for changes in tissue sensitivity to \( \alpha \)-adrenergic stimulation with age.\(^\text{29}\) However, \( \beta \)-adrenoceptor-mediated vasodilation appears to decrease with human aging.\(^\text{29}\) Therefore, the similar exercise-induced increases in epinephrine levels in our young and older subjects may have had lesser vasodilatory effect to counteract \( \alpha \)-adrenergic vasoconstriction in the older subjects.

There is some experimental support for neurally mediated (sympathetic cholinergic) vasodilation of forearm skeletal muscle during leg exercise in humans; thus, this neural response could have been attenuated in our older subjects. However, in humans, the influence of this mechanism on forearm blood flow is thought to be restricted to the initiation (e.g., first minute) of exer-
Because the largest differences in forearm vascular resistance in our young and older subjects were after the initial minute of exercise, it is unlikely that this mechanism was involved.

Therefore it appears that the augmented forearm vasoconstrictor response to dynamic exercise in older humans could be mediated by the collective influence of 1) increased neurotransmitter concentrations (increased central sympathetic outflow and possibly peripheral factors), 2) structural changes in the vasculature, and 3) decreased β-adrenergic vascular responsiveness. However, the fact that the older men did not demonstrate exaggerated forearm vasoconstriction in response to a stress that failed to produce an augmented norepinephrine response (i.e., local cold) suggests that sympathetic nervous system stimulation of norepinephrine release was the key mechanism involved.

**Specificity of Age-Related Differences in Sympathetic Vasoconstrictor Adjustments to Exercise**

The augmented forearm vasoconstrictor response to dynamic leg exercise in the older subjects could be a nonspecific, age-related phenomenon observed with all sympathoexcitatory stimuli. As mentioned above, this did not appear to be the case because the older men demonstrated a tendency for blunted rather than augmented forearm vasoconstrictor and plasma norepinephrine responses to a cold pressor test. In fact, the exaggerated responses appear to be quite specific for large-muscle dynamic exercise because we have recently demonstrated that the nonactive limb vasoconstrictor and antecubital venous plasma norepinephrine responses to small-muscle isometric exercise are not different in these young and older men. There are at least two other points concerning specificity that deserve mention.

One such issue is whether this age-associated augmented vasoconstriction during large-muscle dynamic exercise is observed only in skeletal muscle or whether it occurs in other regional circulations as well. Our data indicate that it does not necessarily occur in all vascular beds because there were no obvious differences in the steady-state skin blood flow responses to exercise in the young and older subjects. However, sympathetically mediated vasoconstriction in the viscera is an important circulatory adjustment to large-muscle dynamic exercise, and it is possible that older humans may demonstrate a greater vasoconstrictor response in this or other regions.

A final point is whether the increased sympathetic outflow during this type of exercise in older humans is region specific or more systemic in nature. We did find that plasma norepinephrine concentrations increased more at any exercise level in the older men. However, there was no obvious augmentation of sympathetic nervous stimulation of epinephrine release from the adrenal medulla because the plasma concentrations were not different in the young and older subjects at any level of exercise. These latter observations agree with previous findings during brief, graded dynamic leg exercise. In contrast, Hagberg et al actually reported a lesser increase in plasma epinephrine concentration during prolonged, submaximal treadmill exercise in healthy older men compared with young men. Thus, the greater venous plasma norepinephrine response in older humans does not appear to represent a generalized heightened sympathoadrenal reactivity to this stress.

**Physiological Significance for the Control of Arterial Blood Pressure During Exercise**

Why would older humans demonstrate an augmented vasoconstrictor response to large-muscle dynamic exercise? It is widely accepted that arterial blood pressure is a key regulated variable during exercise in humans. Furthermore, the relative (i.e., percentage of maximum) work load is the primary determinant of the level of arterial blood pressure attained during dynamic exercise.

In the present study, because of their lower peak cycling work rate, whole-body O₂ uptake was lower in the older men at each relative exercise intensity (Figure 1). Because cardiac output is primarily a function of whole-body O₂ uptake during large-muscle dynamic exercise, in the present study one would predict that cardiac output would be = 0.7, 1.6, and 2.7 l/min lower in the older subjects than in the young control subjects at the three exercise levels, respectively. Consistent with our prediction, cardiac output was, on average, 0.9 and 1.4 l/min lower in the older subjects at the mild and moderate exercise intensities, respectively. Because cardiac output is one of the two systemic hemodynamic determinants of arterial blood pressure, attaining a similar level of arterial pressure during exercise with a lower cardiac output would necessitate a greater level of systemic vascular resistance in the older men. We speculate that because the skeletal muscle circulation is so large and exerts such an important influence on systemic vascular resistance, this region would serve as an important source for additional vasoconstriction in the older men. This would necessitate a greater increase in sympathetic nerve activity to skeletal muscle, explaining the larger exercise-induced increases in antecubital venous plasma norepinephrine concentrations in the older subjects. We cannot rule out the possibility, however, that at least part of the reason for the augmented plasma norepinephrine levels in the older men was related to an age-associated decrease in tissue responsiveness to this neurotransmitter.

It is possible that the augmented forearm vasoconstrictor responses in the older men could somehow have been related to the fact that they were exercising at lower absolute levels of whole-body O₂ uptake and cardiac output compared with the young control subjects at the same relative work intensity. This question was addressed by comparing the responses of the young and older men during cycling at the same level of whole-body O₂ uptake (Figure 6). At this common "absolute" exercise intensity, however, the age-related differences in forearm vascular resistance and plasma norepinephrine concentrations were even greater than those observed at the same relative cycling loads. Thus, the augmented sympathetic vasoconstrictor adjustments to dynamic exercise observed in the older men do not appear to be attributable to this factor.

**Influence of Aging on Sympathoadrenal Cardiovascular Function in Resting Humans**

We did not find any differences in plasma catecholamine concentrations or in any of the cardiovascular variables during baseline supine resting conditions (i.e.,
before the initial exercise trial) in our young and older subjects. Several previous studies have reported higher plasma norepinephrine concentrations and little or no change in plasma epinephrine levels with advancing age under the same conditions.25,34,35 Our norepinephrine data agree with those of Fleg and colleagues,5 who studied populations of young and older healthy humans similar to those in the present investigation. Regarding cardiovascular function, it is generally thought that arterial blood pressure increases with age, at least in industrialized societies.26,36 The present data are consistent with previous findings obtained in a similar population of older humans37 and suggest that increases in arterial pressure in healthy older subjects, when observed, appear to be confined primarily to systolic pressure, probably as a consequence of age-associated structural changes in the arterial system.26,27 Thus, the present findings and those from other recent investigations suggest that many of the sympathoadrenal cardiovascular changes previously attributed to the aging process may not occur in healthy, active older humans.

Conclusions

We found that older men demonstrated augmented forearm vasoconstriction during submaximal dynamic leg exercise that is probably mediated by greater constriction in the skeletal muscle circulation. Increased muscle sympathetic outflow appears to be a key mechanism in this response, although several peripheral factors may also contribute. These age-related differences were observed over a wide range of submaximal exercise intensities but did not occur in response to a nonexercise sympathoexcitatory stimulus, indicating a stress-specific alteration. Although an exaggerated sympathetic forearm vasoconstrictor response was evident in our older subjects, their regulation of arterial blood pressure appeared to be normal. Our finding of a lower level of cardiac output at the same relative work load in the older men indicates that the augmented vasoconstriction in nonaerobic skeletal muscle (and possibly other regional circulations) may be necessary for older humans to attain the appropriate increase in arterial (perfusion) pressure required by large-muscle dynamic exercise.

Acknowledgments

The authors thank Mary Jo Reiling, Martha Elkin, Omar Suwarno, and Sara Julka for their technical assistance.

References

Augmented forearm vasoconstriction during dynamic exercise in healthy older men.
J A Taylor, G A Hand, D G Johnson and D R Seals

Circulation. 1992;86:1789-1799
doi: 10.1161/01.CIR.86.6.1789

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/86/6/1789

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/