Differential effects of aging on limb blood flow in humans

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Differential effects of aging on limb blood flow in humans. Am J Physiol Heart Circ Physiol 290: H272–H278, 2006. First published September 23, 2005; doi:10.1152/ajpheart.00405.2005.—Aging appears to attenuate leg blood flow during exercise; in contrast, such data are scant and do not support this contention in the arm. Therefore, to determine whether aging has differing effects on blood flow in the arm and leg, eight young (22 ± 6 yr) and six old (71 ± 15 yr) subjects separately performed dynamic knee extensor [0, 3, 6, 9 W; 20, 40, 60% maximal work rate (WRmax)] and handgrip exercise (3, 6, 9 kg at 0.5 Hz; 20, 40, 60% WRmax). Arterial diameter, blood velocity (Doppler ultrasound), and arterial blood pressure (radial tonometry) were measured simultaneously at each of the submaximal workloads. Quadriceps muscle mass was smaller in the old (1.6 ± 0.1 kg) than the young (2.1 ± 0.2 kg). When normalized for this difference in muscle mass, resting seated blood flow was similar in young and old subjects (young, 115 ± 28; old, 114 ± 39 mL·kg⁻¹·min⁻¹). During exercise, blood flow and vascular conductance were attenuated in the old whether expressed in absolute terms for a given absolute workload or more appropriately expressed as blood flow per unit muscle mass at a given relative exercise intensity (young, 1,523 ± 329; old, 1,340 ± 157 mL·kg⁻¹·min⁻¹ at 40% WRmax). In contrast, aging did not affect forearm muscle mass or attenuate rest or exercise blood flow or vascular conductance in the arm. In conclusion, aging induces limb-specific alterations in exercise blood flow regulation. These alterations result in reductions in leg blood flow during exercise but do not impact forearm blood flow.

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Methods

Subjects and general procedures. Eight young (20–29 yr old) and six old (65–80 yr old) nonsmoking, normally active males participated in the current study. None performed work or recreationally related activities that would result in elevated total physical activity. Subjects were excluded from participation if they were taking any medications that would alter vascular responsiveness or had a history of cardiovascular disease. Informed consent was obtained according to the University of California, San Diego, Human Subjects Protection Program requirements. Health histories and physical examinations were completed on all subjects. In addition, graded exercise tests were required for individuals over 40 years of age. All studies were performed in a thermoneutral environment (21°–22°C). Subjects reported to the laboratory in the 4-h fasted state.

Exercise modalities and exercise protocols. During data collection, subjects were in a semirecumbent position (~60° reclined) for leg measurements or supine for arm measurements. Single-leg, knee extensor exercise (1 Hz) or rhythmic handgrip exercise (0.5 Hz) was performed, as described previously (20, 21, 32, 38). As part of the initial subject screening, incremental knee extensor (leg) and handgrip dynamometer (forearm) exercise tests were performed until failure to establish maximal work rate (WRmax) for each individual in each modality. Heart rate was recorded from a standard three-lead ECG (Logiq 7; GE Medical Systems, Milwaukee, WI). For both arm and leg exercise, absolute submaximal workloads were chosen to be attainable by both groups (forearm, rest, 3, 6, and 9 kg at 0.5 Hz; leg, rest, 0, 3, 6, and 9 W) in addition to several relative workloads (20, 40, 60% WRmax) and handgrip exercise (3, 6, 9 kg at 0.5 Hz; 20, 40, 60% WRmax). Arterial diameter, blood velocity (Doppler ultrasound), and arterial blood pressure (radial tonometry) were measured simultaneously at each of the submaximal workloads. Quadriceps muscle mass was smaller in the old (1.6 ± 0.1 kg) than the young (2.1 ± 0.2 kg). When normalized for this difference in muscle mass, resting seated blood flow was similar in young and old subjects (young, 115 ± 28; old, 114 ± 39 mL·kg⁻¹·min⁻¹). During exercise, blood flow and vascular conductance were attenuated in the old whether expressed in absolute terms for a given absolute workload or more appropriately expressed as blood flow per unit muscle mass at a given relative exercise intensity (young, 1,523 ± 329; old, 1,340 ± 157 mL·kg⁻¹·min⁻¹ at 40% WRmax). In contrast, aging did not affect forearm muscle mass or attenuate rest or exercise blood flow or vascular conductance in the arm. In conclusion, aging induces limb-specific alterations in exercise blood flow regulation. These alterations result in reductions in leg blood flow during exercise but do not impact forearm blood flow.

In addition to supine rest, aging appears to attenuate skeletal muscle blood flow in the leg at submaximal and maximal workloads (2, 14, 21, 27, 29, 36). Again, this reduction may be a consequence of increased vascular resistance in older individuals at a given exercise intensity. Surprisingly, only a single study has examined blood flow as a consequence of exercise in the forearm of young and old individuals. This seminal study by Jasperse et al. (15) was limited to postcontraction hyperemia measurements, but it demonstrated that there was no significant difference between young and old subjects. However, there are currently no data directly comparing arm blood flow in young and old subjects during dynamic forearm exercise.

Despite our growing understanding of vascular changes with age, several gaps in the literature and newly emerging concepts have clouded this area. Specifically, there appear to be significant positional-, limb-, and site-specific differences in terms of vascular responsiveness that may blur the assimilation of some age-related studies (25, 38). As yet unanswered is the question of whether the difference in resting leg blood flow between young and old humans is a consequence of posture, because leg blood flow measurements in human aging studies have always been made while the subject was supine. Is blood flow different between young and old subjects during upper extremity exercise? Furthermore, if arm blood flow and leg blood flow are measured in the same subjects, are the putative age-associated decreases in leg blood flow during exercise also seen in the arm?

Consequently, we tested the following hypotheses: In relation to young controls, older subjects would 1) before exercise, in a seated position, not reveal an attenuated leg blood flow; 2) reveal no difference in blood flow during submaximal forearm exercise; and 3) still exhibit an attenuated blood flow during submaximal leg exercise.
and 60% \(WR_{\text{max}}\). Subjects exercised for 3 min to ensure the attainment of steady-state hemodynamics, and blood velocity and vessel images (Doppler) and arterial blood pressure with automated radial tonometry (Medwave Vasotrac APM205A; BioPac Systems, Goleta, CA) measurements were then taken during the fourth minute. The wrist used to assess blood pressure was always positioned at heart level. To avoid ordering effects, the sequence of arm and leg exercise bouts was randomized.

**Ultrasound Doppler.** The ultrasound system (Logiq 7) was equipped with two linear array transducers operating at an imaging frequency of 7 and 10 MHz. Vessel diameter was determined at a perpendicular angle along the central axis of the scanned area, where the best spatial resolution was achieved. The common femoral artery was insonated distal to the inguinal ligament, \(~2–3\) cm proximal to the bifurcation of the deep and superficial femoral arteries. The brachial artery was insonated approximately midway between the antecubital and axillary regions, medial to the biceps brachii muscle.

The blood velocity profile was obtained through the use of the same transducers with a Doppler frequency of 4.0–5.0 MHz, operated in the high-pulsed repetition frequency mode (2–25 kHz) with a sample depth of 1.5–3.5 cm. Care was taken to avoid aliasing by using scale adjustments, especially during exercise. In duplex mode, real-time ultrasound imaging and the pulse-wave velocity profile were viewed simultaneously. All blood velocity measurements were obtained with the probe appropriately positioned to maintain an insonation angle of 60° or less. The sample volume was maximized according to vessel size and centered, verified by real-time ultrasound visualization of the vessel. With the use of artery diameter and mean blood velocity \(V_{\text{mean}}\), blood flow in the common femoral artery and brachial artery was calculated as

\[
\text{Blood flow} (\text{mL/min}) = V_{\text{mean}} \cdot \pi \cdot (\text{vessel diameter}/2)^2 \times 60.
\]

During the third minute of each exercise level, ultrasound images and Doppler velocity waveforms in the common femoral and brachial artery were obtained. Two ultrasound digital images and velocity spectra segments of \(~30\) s each were recorded and saved to the GE Logiq 7 hard drive for off-line image and waveform analysis. At all sample points, arterial diameter and angle-corrected, time- and space-averaged, and intensity-weighted \(V_{\text{mean}}\) values were calculated on the Doppler system with the use of commercially available software (Logiq 7). In our hands, the coefficient of variation for this Doppler blood flow method in both the arm and leg was <7%.

**Oxygen consumption.** During single-leg, knee extensor exercise, minute ventilation and pulmonary oxygen consumption \(V_{O_2}\) and \(V_{CO_2}\) were calculated by a commercially available software and hardware package (TrueMax 2400; ParvoMedics, Sandy, UT) that integrates a gas-mixing chamber, an oxygen and carbon dioxide analyzer, and a Fleisch pneumotachograph 3. Data were obtained at each level after the attainment of steady-state exercise (3–4 min). Leg \(V_{O_2}\) at a given work rate was calculated by subtracting resting \(V_{O_2}\). Such measurements during rhythmic handgrip exercise were not made because pilot studies revealed inadequate signal-to-noise ratio with such a small muscle mass.

**Tissue volume measurements.** Forearm and thigh circumferences (at three sites: distal end, proximal end, and one-third distal-to-proximal end) and length were measured to calculate tissue volume (16). Additionally, central and dorsal skinfold measurements were taken to assess subcutaneous fat and allow an estimation of muscle volume for the thigh and forearm (16). Muscle mass of the complete forearm was then calculated from this anthropometrically measured muscle volume by multiplying by the density of muscle (1.06 g/cm³).

On the basis of both an excellent agreement (±5%) and a high correlation \((r^2 = 0.83)\) between this method and dual energy X-ray absorptiometry (Explorer; Hologic, Waltham, MA) documented in our laboratory, we applied the following regression equation:

\[
\text{Forearm muscle mass (anthropometric)(in kg)} = 1.155 - 0.24 = \text{forearm muscle mass (in kg)}.
\]

The thigh muscle volume was converted to quadriceps muscle mass with the use of the following equation (16):

\[
\text{Thigh muscle volume (in l)} \times 0.307 + 0.353 = \text{thigh muscle mass (anthropometric)(in kg)}.
\]

This anthropometrically determined quadriceps muscle mass, previously revealed to correlate highly with muscle mass assessed by computer tomography \((r^2 = 0.86)\), was then corrected on the basis of this relationship with the following equation (30):

\[
\text{muscle mass (anthropometric)(in kg)} = 0.924 - 0.292 = \text{quadriceps muscle mass (in kg)}.
\]

**Data analysis and statistics.** For each 30-s ultrasound Doppler segment, \(V_{\text{mean}}\) was averaged across the first and last 15 s of the recorded clip. Ultrasound vessel diameter measurements were evaluated during diastole and were in the relaxation phase of muscle contraction during the exercise protocol, with three diameter measurements averaged to accompany each 15-s clip. Statistics were performed with the use of commercially available software (SPSS, Chicago, IL). Data were subsequently analyzed with the use of a combination of parametric or nonparametric statistics, where appropriate, after mathematical confirmation of homoscedasticity or heteroscedasticity with the use of a Shapiro-Wilk test. Specifically, changes in variables with age across exercise intensities were analyzed by a two-factor, repeated-measures ANOVA with Tukey’s post hoc test, whereas Wilcoxon’s and Friedman tests were incorporated as the nonparametric equivalents for simpler comparisons with more limited data sets (e.g., resting blood flow, subject characteristics). Power analyses revealed that in all major variables, the \(\beta\)-value ≤ 0.8. Significance was established at \(P < 0.05\). All group data are expressed as means ± SD.

**RESULTS**

**Subject characteristics.** The older subjects had similar weight but a significantly higher body mass index (BMI) (Table 1). Forearm volume and muscle mass were not significantly different between the age groups (Table 1). Thigh tissue volume and quadriceps muscle mass were significantly lower in the aged subjects (Table 1). The old subjects had a lower \(WR_{\text{max}}\) in both handgrip and knee extensor exercise (Table 1). Maximal knee extensor work rate was positively correlated with quadriceps muscle \((r^2 = 0.64)\), whereas arm \(WR_{\text{max}}\) and forearm muscle mass were not. Resting blood pressure was significantly different between the age groups (Table 1).

<table>
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<th>Characteristic</th>
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<th>Old</th>
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<tr>
<td>Age, yr</td>
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<td>Height, cm</td>
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<td>Weight, kg</td>
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<td>Body mass index, kg/m²</td>
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<td>Forearm muscle mass, kg</td>
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<td>0.84±0.2</td>
</tr>
<tr>
<td>Quadriceps muscle mass, kg</td>
<td>2.1±0.2</td>
<td>1.6±0.1*</td>
</tr>
<tr>
<td>Systolic blood pressure, supine, mmHg</td>
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<td>129±7*</td>
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<tr>
<td>Diastolic blood pressure, supine, mmHg</td>
<td>70±8</td>
<td>82±10*</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>62±8</td>
<td>70±7*</td>
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<td>Maximum handgrip, kg</td>
<td>51±5</td>
<td>28±5*</td>
</tr>
<tr>
<td>Maximum knee extensor, W</td>
<td>61±11</td>
<td>31±17*</td>
</tr>
</tbody>
</table>

Values are means ± SD. *\(P < 0.05\) young vs. old subjects.
significantly higher in the older subjects compared with the young but was still within the normotensive range (Table 1).

Resting limb blood flow. Seated, resting absolute leg blood flow was 26% lower in old subjects than in their young counterparts (young, 296 ± 74; old, 218 ± 74 ml/min; P = 0.06) but was not different when expressed most appropriately as blood flow per kilogram of quadriceps muscle mass (young, 115 ± 28; old, 114 ± 39; ml·kg⁻¹·min⁻¹). There were no significant age-related differences in resting arm blood flow when blood flow was expressed in absolute terms or normalized for muscle mass.

Absolute leg blood flow versus absolute workload. At any given absolute submaximal exercise intensity (0, 3, 6, and 9 W), absolute leg blood flow was attenuated in the older subjects (Fig. 1A). This attenuated leg blood flow in the aged subjects could be attributed to an attenuated leg vascular conductance when compared with young subjects at each absolute submaximal workload (Fig. 1B). Old subjects exhibited augmented mean arterial pressure across these submaximal exercise workloads when compared with the younger subjects (Fig. 1C). Leg VO₂ was similar in young and old subjects at each absolute submaximal workload (Fig. 1B).

Leg blood flow normalized for muscle mass versus workload. When leg blood flow was normalized for muscle mass, the recorded differences in blood flow and conductance per absolute workload (0, 3, 6, and 9 W) were abolished (Fig. 2, A and B, left). However, the older subjects still revealed an attenuated leg blood flow and vascular conductance for a given relative workload (20, 40, and 60% WRmax) (Fig. 2, A and B, right), work rates that should have activated a similar proportion of quadriceps muscle mass in young and old subjects. There was a trend toward higher leg VO₂ per kilogram of quadriceps muscle mass in the older subjects than at any given absolute workload in young subjects (P = 0.10) (Fig. 3B, left). As would be expected, absolute leg VO₂ was greater in the young subjects at any given relative work rate, because this corresponds to a greater absolute work rate in this group (Fig. 3A, right). Leg VO₂ per kilogram of quadriceps muscle mass was not different with respect to relative workloads (Fig. 3B, right).

Absolute forearm blood flow versus absolute workload. At each of the absolute exercise intensities (3, 6, and 9 kg), forearm blood flow was similar in young and old subjects (Fig. 4A). Vascular conductance was similar in young and old subjects at these absolute workloads (Fig. 4B). Mean arterial pressure was augmented in the old subjects across these absolute exercise workloads (Fig. 4C).

Forearm blood flow normalized for muscle mass versus workload. When forearm blood flow was normalized to forearm muscle mass, the older subjects tended to have higher

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Fig. 1. Effects of aging on blood flow (A), vascular conductance (B), and mean arterial pressure (C) during leg exercise across a series of submaximal absolute workloads in young and old subjects. *Significant difference (P < 0.05).

Fig. 2. Effects of aging on blood flow per kilogram of quadriceps muscle mass (A) and vascular conductance per kilogram of quadriceps muscle mass (B) during leg exercise across a series of submaximal absolute and relative workloads in young and old subjects. *Significant difference (P < 0.05).
blood flow and vascular conductance compared with the young subjects at any given absolute workload (3, 6, and 9 kg at 5 Hz), but this did not achieve significance \( (P = 0.19) \) (Fig. 5A, left). At relative exercise workloads (20, 40, and 60% WR\(_{\text{max}}\)), normalized forearm blood flow and vascular conductance did not differ with respect to age (Fig. 5A, right).

DISCUSSION

This study has provided new insight into the effects of aging on peripheral limb blood flow at rest and during exercise. First, aging does not attenuate resting leg blood flow per unit muscle mass when subjects are in an upright, seated position. This suggests that the impact of postural adjustments on the vasculature may be responsible for age-related differences seen in previous studies with supine subjects. Second, aging is associated with an attenuation of leg blood flow and vascular conductance during leg exercise, whereas there was no such deficit in the same old subjects during forearm exercise, indicating that some of the processes that alter skeletal muscle vascular tone with aging are limb specific. Taken together, these findings reveal that the age-related attenuation of leg muscle blood flow during seated upright exercise is not a consequence of differences that persist from rest and that these age-related vascular changes in the leg do not occur in the arm.

Leg blood flow at rest. Resting muscle blood flow is dependent upon metabolic rate and \( \text{VO}_2 \) (6, 17), which is dictated almost exclusively by muscle mass. With age, there is a progressive loss of muscle mass, termed sarcopenia (10). However, even when normalized for muscle mass, aging is associated with lower resting supine leg blood flow in both men and women (6, 7, 24). On the basis of these disparate findings, it is conceivable that age-related differences in supine blood flow may not persist in upright seated humans, especially because older subjects exhibit reduced arterial baroreflex gain (13, 33) and blunted leg vasoconstriction to exogenous adrenergic agonists (4, 34). When appropriately normalized for the difference in muscle mass between the young and old subjects, the current data support this hypothesis, with no difference in resting leg blood flow. In addition, it is interesting to note that seated, resting blood flow values in the current study are significantly lower than values published from studies in the supine position (7). Although garnered from different studies, these data imply a more pronounced increase in leg vascular...
reduced vascular conductance during leg exercise (Fig. 1). These differences were apparent despite greater vascular conductance for a given absolute exercise intensity (Fig. 1A). Thus aged individuals exhibited a lower leg blood flow per kilogram of forearm muscle mass (Fig. 5) and vascular conductance per kilogram of forearm muscle mass (Fig. 5). Consequently, when muscle masses differ between groups of subjects, work rates should be normalized to percentage of WRmax and perfusion should be expressed per unit of muscle mass (1, 19, 31). When these normalizations were performed on the current data, the older subjects once again revealed an attenuated leg blood flow and vascular conductance at a given percentage of WRmax (Fig. 2A, right). Independent measurements of absolute leg VO2 and the effect of normalizing for muscle mass support this concept of muscle recruitment and work rate (Fig. 3). There was no difference between absolute VO2 at an absolute work rate in the young and old (Fig. 3A, left), but there was a clear difference when compared at relative work rates (Fig. 3A, right). However, this difference in VO2 at a relative work rate was no longer evident when leg VO2 was normalized for muscle mass (Fig. 3B, right) and there was a trend toward an elevated VO2 per kilogram of quadriceps muscle mass in the old across absolute work rates (P = 0.1) (Fig. 3B, left).

To our knowledge, this study is the first to evaluate leg blood flow both at rest and during exercise in the same young and old subjects. A previous aging study from our laboratory (21) lacked resting muscle blood flow, so we were unable to discount the possibility that low exercising muscle blood flows were the result of attenuated vasodilatory factors at rest in the old subjects (e.g., nitric oxide) that may persist during exercise (9, 11, 37). In the present study, the attenuated leg blood flow per kilogram in the old at a given relative work rate (Fig. 2A, right) cannot be attributed to differences at rest, because resting quadriceps muscle blood flow per unit muscle mass was not different between the young and old. This is supportive of the concept that the exercise response per se is responsible for the attenuated muscle blood flow with age and that it is not the consequence of an underlying deficit present at rest.

It is of interest to note that underlying differences in subject characteristics such as BMI and blood pressure often correlate significantly with alterations in vascular function (3, 22) and may play a role in the leg blood flow differences between young and old observed in the current study. Whereas blood pressure was not well related to blood flow during exercise expressed as blood flow per unit muscle mass at the higher

tone in the young subjects on assuming an upright position, with a diminished response in the old that would account for the equal resting leg blood flow and leg vascular conductance while seated.

Leg blood flow during exercise. In the present study, normally active older subjects exhibited a lower leg blood flow than young subjects for a given absolute exercise intensity (Fig. 1A). These differences were apparent despite greater systemic arterial blood pressure in the older individuals at each exercise intensity (Fig. 1C). Thus aged individuals exhibited reduced vascular conductance during leg exercise (Fig. 1B). These data are in agreement with the majority of studies that have assessed absolute leg blood flow during exercise in young and old subjects (2, 21, 27–29).

Interestingly, none of the aforementioned studies has identified a measurable sarcopenia and thus their data have been expressed in terms of absolute blood flow. In contrast, the current subjects fall more in line with the findings of larger aging studies (10), with the older group having a smaller quadriceps muscle mass with increasing age. Acknowledging the relation between muscle mass and resting blood flow (6, 17), it is tempting to speculate that the smaller quadriceps muscle mass of the old (Table 1) may account for the attenuated exercising blood flow in this study. However, unlike rest, during exercise this would be a vast oversimplification of a complex process based on Henneman’s (12) muscle recruitment theory. Specifically, during submaximal exercise, only a portion of the potentially active muscle mass is working (31), and thus at a given absolute work rate, leg blood flow is preferentially distributed to active muscle fibers (1, 19). Therefore, if leg blood flow in the aged population were represented as blood flow per unit muscle mass, this would be an overestimate because each absolute workload for the old subjects represents a greater percentage of their WRmax (Fig. 2A, left). If the aged are working at a greater percentage of their WRmax, it is likely that these subjects recruit and perfuse a greater proportion of their quadriceps muscle mass to perform an absolute work rate (1, 19, 31). This concept was supported by the correlation between quadriceps muscle mass and maximal knee extensor workload (r2 = 0.64), with the oldest subjects achieving the lowest WRmax and having the smallest quadriceps (Table 1).

Fig. 5. Effects of aging on blood flow per kilogram of forearm muscle mass (A) and vascular conductance per kilogram of forearm muscle mass (B) during leg exercise across a series of submaximal absolute and relative workloads (handgrip at 0.5 Hz) in young and old subjects.

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relative exercise intensities ($r^2 = 0.1$), BMI was significantly correlated with blood flow expressed in this fashion ($r^2 = 0.6$). Thus these data support the concept that BMI or factors associated with increasing BMI (e.g., plasma lipid profile) may be associated with the lower levels of muscle blood flow in the legs of older people, perhaps mediated by endothelial dysfunction.

**Forearm blood flow at rest and during exercise.** In contrast to the leg, there were no age-associated differences in resting or exercising forearm blood flow and vascular conductance, whether expressed absolutely (Fig. 4, A and B) or normalized for muscle mass and examined at both absolute and relative exercise intensities (Fig. 5, A and B). These findings are qualitatively similar to the only other study that has compared young and old arm blood flow associated with exercise, by Jaspers et al. (15), who documented no difference in postconstriction hyperemia between young and old subjects.

**Age-related limb differences.** In agreement with an increasing number of recent reports (25, 38), this study illustrates that vascular function is not uniform across limbs, which may be of particular significance as we attempt to better understand the complexity of cardiovascular changes with age (26). The apparently nonuniform limb vascular response certainly raises some important questions regarding alterations that take place in the aged vasculature of the leg that appear not to take place in the arm. Recent data from Newcomer et al. (26) in resting subjects utilizing pharmacological interventions suggest that vasodilation in the leg is preserved with advancing age, whereas forearm vasodilation in the same aged subjects is reduced; although collected at rest, these data imply that endothelial dysfunction is not a likely mechanism for the age-related reduction in leg blood flow during exercise. Although the current data do not identify a specific mechanism, the fact that leg blood flow and vascular conductance are reduced in specific conditions (supine and exercise) with age, whereas the arm is not affected, may be indicative of age-related and limb-specific changes in vessel structure or alterations in vascular tone. These findings may be mediated by factors such as sympathetic nervous system control (7, 18), endothelin (8), or other potent vasoconstrictors.

In conclusion, this study has documented that resting, upright, seated muscle blood flow when normalized for muscle mass is not attenuated with age. During single-leg knee extensor exercise, older subjects exhibit a reduced leg blood flow and vascular conductance that were still evident when differences in muscle mass and muscle recruitment were taken into account. In contrast, arm blood flow and vascular conductance during forearm exercise were not influenced by age and were not complicated by differences in muscle mass. Therefore, this study has revealed that the attenuated leg blood flow during exercise with age is not a remnant of reduced blood flow at rest in the same upright seated position and that this age-associated reduction in blood flow during exercise is not uniform across limbs.

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**GRANTS**

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