Age and regional specificity of peak limb vascular conductance in men

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Proctor, David N., Khoi U. Le, and Samuel J. Ridout. Age and regional specificity of peak limb vascular conductance in men. J Appl Physiol 98: 193–202, 2005. First published September 3, 2004; doi:10.1152/japplphysiol.00704.2004.—Because of methodological variation in previous studies, age-associated changes in peak limb vascular conductance (VCpeak; a functional index of arterial structure) and its determinants remain poorly defined. The objectives of this study were to describe and compare age-associated changes in peak limb conductance in men, but the magnitude of this effect is reduced in the calf relative to the forearm. This could reflect regional differences in habitual muscle use with aging in normally active men. Additionally, because most studies have compared only two discrete age groups, it is not known whether the decline in peak limb conductance with age, if it occurs, is linear or exponential.

The present study employed a standardized reactive hyperemia test in healthy men across the adult age range to more fully address the question of whether peak limb conductance changes with age. Specifically, we measured peak forearm and calf vascular conductance in response to 10 min of arterial cuff occlusion in 68 normally fit men age 20–79 yr. Aerobic capacity (cycle peak oxygen consumption), arterial health (ankle-brachial index, pulse wave velocity), and limb-specific measures of muscle mass (dual-energy X-ray absorptiometry) and isometric strength (grip, plantar flexion) were also assessed. The relative decline in forearm VCpeak with age (−6.6% per decade; P < 0.001) was greater than the decline in calf VCpeak (−3.4% per decade; P = 0.004). Limb VCpeak per kilogram of muscle declined with age in the forearm (−3.8% per decade; P = 0.004) but not in the calf (P = 0.35). Age, VO2peak and regional muscle mass were significant predictors of peak conductance in both limbs; however, these predictors explained considerably less variance in the calf than in the forearm. These results suggest that healthy aging is associated with a linear decline in limb vasodilator capacity in men, but the magnitude of this effect is reduced in the calf relative to the forearm. This could reflect regional differences in habitual muscle use with aging in normally active men.

Several studies have compared peak limb vascular conductance between groups of healthy younger and older subjects. However, these studies have yielded inconsistent results with reports of reduced (1, 14), preserved (20, 33), or increased (31) peak conductance with age in the calf and of reduced (16) or preserved (12) conductance with age in the forearm. These mixed results could reflect methodological variation between studies with respect to the limb studied (forearm vs. calf and dominant vs. nondominant limbs), the transducer used to measure blood flow (Silastic strain gauge vs. air cuff plethysmography), and the habitual physical activity levels of the subjects studied. In fact, each of these factors has been shown to influence peak limb vascular conductance independent of age (3, 26, 30). The stimulus used to evoke peak limb vasodilatation has also differed widely between studies, with variability in the duration of ischemia (3–10 min) and the addition of muscle contraction (ischemic exercise to fatigue) in some studies, but not others. Given such wide methodological variation between studies, it remains unclear whether there is a primary age-dependent decline in peak limb vascular conductance in humans. Additionally, because most studies have compared only two discrete age groups, it is not known whether the decline in peak limb conductance with age, if it occurs, is linear or exponential.

The present study employed a standardized reactive hyperemia test in healthy men across the adult age range to more fully address the question of whether peak limb conductance changes with age. Specifically, we measured peak forearm and calf vascular conductance in response to 10 min of arterial cuff occlusion in 68 normally fit men age 20–79 yr on two separate occasions. Our primary hypothesis was that healthy aging in the absence of overt disease would be associated with a progressive decline in peak limb vascular conductance in both the forearm and the calf.

There is emerging evidence in the animal literature that the effects of aging on vascular structure and function are not uniform throughout the arterial tree or between muscle groups (37, 42). To the best of our knowledge, the possible influence of age on regional differences in the peripheral vasculature has never been addressed in healthy humans. Therefore, a secondary purpose of the present study was to determine whether age-associated changes in peak conductance differ between the upper and lower extremity in humans. Peak limb conductance is also markedly influenced by habitual physical activity in younger (26, 31, 34), middle-aged (19), and older (12, 18, 26) populations. Moreover, there is evidence for an influence of limb muscle characteristics (40) on peak limb reactive hyper-

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emia in younger subjects. Consequently, our final objective was to identify physiological characteristics, both systemic and limb specific, that modulate peak conductance of the forearm and calf across the adult age range. For this reason, we employed a multiple regression approach to determine whether objective measures of aerobic fitness, arterial health, or limb-specific measures (muscle mass, composition, and strength) explain variation in peak limb conductance after consideration of the influence of age. We hypothesized that the age-associated rate of decline in peak vascular conductance would be greater in the calf than in the forearm because of previous reports of greater age-associated reductions in muscle mass (11) and strength (2) of the lower vs. upper extremity of normally active men.

**METHODS**

**Subjects.** Sixty-eight men between 20 and 79 yr of age completed this study. All subjects, with one exception (70 yr old with resting systolic blood pressure = 142 mmHg), were normotensive (seated resting blood pressure ≤140/90 mmHg). Subjects were free of overt chronic diseases as evaluated by medical history questionnaire, a physical examination, resting ECG, and blood chemistry (i.e., hemoglobin concentration ranged from 13.1 to 16.3 mg/dl; total cholesterol <242 mg/dl). Subjects were nonsmokers and abstained from caffeine, aspirin or ibuprofen, and herbal supplements for at least 12 h before limb blood flow testing. No subjects were taking medications that had significant hemodynamic effects, but seven men over age 50 yr did take baby aspirin on a regular basis. All subjects gave their written, informed consent to participate. This study was approved by the Office for Research Protections and the Institutional Review Board at The Pennsylvania State University.

**Occupational and physical activity history.** Most of the subjects under 30 yr of age were college students while the majority of the middle-aged (30–65 yr) and older (>65 yr) age groups were professionally employed (primarily desk jobs) and retired, respectively. Only three subjects listed a physically demanding occupation as their primary source of employment (1 assembly line worker, 1 warehouse worker, and 1 retired railroad worker). Subjects also completed a questionnaire to provide information about the type and approximate frequency of their primary recreational and leisure activities, including participation in aerobic or strengthening exercises, during the past 6 mo. Subjects ranged from completely sedentary to moderately active, but none were competitive athletes. In general, men in their 20s, 30s, and 40s listed jogging and stationary exercises (e.g., bike, step machine) as their primary aerobic activities (2–4 days/wk). Resistance exercise (4–5 times/wk) participation in walking and other lower intensity aerobic activities (e.g., bike, stepper machine) as their primary aerobic activities (2–4 days/wk). Participation in walking and other lower intensity aerobic activities (e.g., golf, yard work) was more prevalent in the men over age 50 yr, consistent with national trends (4). Approximately one-third (22 of 68) of the subjects in this study also reported at least occasional (>1 time/wk) participation in strengthening activities. Resistance exercise participation was more prevalent in the younger subjects (40% of subjects under 40 yr) than in the middle-aged and older subjects (24% of subjects over 40 yr), also consistent with recent national surveys (4). Overall, the subjects for this study appear to reflect a normally active sample of American men.

**Peak oxygen uptake test.** Each subject pedaled an electronically braked cycle ergometer (Lode) to maximal exertion to screen for cardiovascular abnormalities and to determine peak oxygen uptake (VO2 peak), as described previously (29). No subjects had evidence of ECG or blood pressure abnormalities during the cycle VO2 peak test that prohibited them from participating in the subsequent limb blood flow studies. All subjects, with one exception (72 yr old with peak respiratory exchange ratio = 1.08), had a peak respiratory exchange ratio >1.20. Subjects achieved an average of 101% of their age-predicted maximum heart rate (38). Only four subjects (20, 37, 41, and 78 yr) had cycle ergometer VO2 peak values that exceeded 85% of age-predicted norms (41), consistent with the fact that most of these subjects were nonathletes who ranged from sedentary to moderately active.

**Body composition.** Total and regional body composition was measured by using dual-energy X-ray absorptiometry (DXA; model QDR 4500W, Hologic, Waltham, MA) with subjects in the supine position wearing a T-shirt, shorts, and no shoes, socks, or jewelry. Region of interest software (version 9.80D, Hologic) was used to determine bone-free lean mass (index of muscle mass) and percent fat for the forearm (from the olecranon process to distal radius or ulna) and the calf (from the proximal tibia to the distal tibia or fibula) of each subject’s nondominant limbs (i.e., nonwriting hand and corresponding leg). All DXA scans were performed and analyzed by the same manufacturer-trained operator who also performed weekly quality control calibrations.

**Strength testing.** Isometric strength of the nondominant hand was measured by using a Jamar handgrip dynamometer (Sammons Preston, AbilityOne). The highest of three maximal efforts, each separated by a 1–2 min rest period, was used as an index of maximal forearm strength. The nondominant hand was chosen over the dominant hand to avoid the possible influence of repetitive use (occupational or leisure activities) on the vasodilator capacity of the dominant forearm (34, 35), thereby enabling an unbiased comparison with the legs, which do not typically display such limb specificity (30). Isometric strength of the plantar flexors of the corresponding leg was measured using an isokinetic dynamometer (Multi-Joint System 3 Pro, Biodex Medical Systems) at 0°/s. Subjects were stabilized using chest, waist, and thigh straps with their knee joint fixed at 180°. Positioning of the ankle relative to the rotational axis of the dynamometer was set at 90° by using a goniometer. The highest of three maximal isometric plantar flexions, each separated by a ~2-min rest period, was used as an index of maximal calf strength.

**Measurement of ankle-brachial index and arterial pulse wave velocity.** Ankle-brachial index (ABI) and pulse wave velocity (PWV) were measured by using the VP2000 vascular profiling machine (Colin Medical) with subjects in the supine position as previously described (5). Ten minutes of quiet rest was given before measurements were taken. Carotid-to-femoral PWV was measured to determine whether age-associated differences in central arterial stiffness contributes to variation in peak forearm or calf conductance. Day-to-day variability (coefficient of variation, %) was assessed in a subset of subjects (n = 33; 30–79 yr) on two separate visits (~7 days apart) and averaged 2.7 and 3.4% for ABI and PWV, respectively.

**Venous occlusion plethysmography.** Forearm and calf blood flows (ml·100 ml−1·min−1) of the nondominant limbs were measured using a Hokanson venous occlusion plethysmography system (10). Limb blood flow studies were conducted in a cool, temperature-controlled room (18–20°C) to minimize the contribution of skin blood flow. Subjects sat in a semireclined position on a padded chair with their nondominant forearm and calf elevated 10–20 cm above heart level as necessary to facilitate venous drainage. Mercury-in-Silastic strain gauges were placed around the widest portion of the forearm and calf and calibrated electronically. Venous occlusion cuffs placed around the upper arm and thigh were rapidly inflated to 50 mmHg every 1 s (7 s inflate, 8 s release) during flow measurements. Wrist and ankle cuffs were used to occlude blood flow to the hand and foot, respectively, during all flow measurements.

**Measurement of peak limb vascular conductance.** Plethysmographic measurements of forearm and calf blood flow were obtained during baseline resting conditions and after 10 min of arterial occlusion (i.e., reactive hyperemia) on two occasions, at least 2 days apart. For each study visit, baseline and reactive hyperemia experiments in the forearm were determined first, followed by identical procedures in the calf. After instrumentation (described above), subjects were given 10 min to rest quietly before baseline blood flows were measured (average of 10 flow measurements over 3 min). To familiarize the
were instructed to raise and contract their forearm or calf muscles to performed. Once blood flow returned to baseline (subject with the reactive hyperemia test and to check strain gauge.

Reproducibility of peak limb blood flow and vascular conductance measured during the two study visits. However, test-retest differences of ± 15% for peak flow and conductance were noted in a substantial number of subjects, resulting in an overall coefficient of variation of ~7% for both limbs. Although there was no evidence that the relationship between peak limb flow or peak conductance measured during the first and second visits differed in a systematic way (i.e., slope was not different from 1, intercept was not different from 0), we still decided to define peak flow and vascular conductance for each subject as the highest individual value achieved on the two visits. The use of the highest individual response is a widely used and valid approach in studies evaluating peak physiological capacity. Importantly, the overall relations between age and peak conductance in the forearm and calf were nearly identical for the first and second study visits: forearm conductance = 0.601 – 0.004 × age (visit 1) and 0.629 – 0.004 × age (visit 2); calf conductance = 0.469 – 0.002 × age (visit 1) and 0.462 – 0.002 × age (visit 2).

Statistical analysis. Data grouped by decade (subject characteristics, Table 2) were compared by using an unbalanced one-way ANOVA. Bonferroni’s post hoc test was used to determine the specific age decades that were significantly different from the youngest subjects (i.e., 20- to 29-yr-old group). Line fitting of limb-specific characteristics (Fig. 1) and hemodynamic variables (Figs. 2 and 3) vs. age were performed by using simple linear regression. Comparison of slope differences between the forearm and calf were assessed by using the F-test.

Pearson correlations were calculated to assess the relation between peak limb conductance and other measured variables in the entire sample of subjects (Table 3). Forward stepwise multiple linear regression (best-subsets method with P < 0.15 to enter) was then performed to determine which combination of variables explained the most variance in forearm and calf peak conductance (Table 4) with age entered in both models. Each model was checked for the existence of influential data points. These points did not influence the variance of any models (forearm and calf), and so these data were retained in the regression analysis.

All data are presented as means ± SE. Statistical significance was accepted at P < 0.05. Minitab version 14 was used for all statistical analyses.

RESULTS

Subject characteristics (Table 2). There were no significant age group differences in body weight or body mass index, although a reduced height was observed in the oldest subjects (70–79 yr). An age-related increase in total cholesterol and percent body fat became apparent for the subjects beginning in their 50s and 60s, respectively. By design, there were no age-group differences in resting systolic or diastolic blood pressures (obtained during baseline rest before reactive hyperemia testing). PWV and ABI, however, were significantly elevated in the oldest men (70–79 yr). Cycle VO2 peak declined an average of −7.7% per decade in these men.

Limb characteristics (Fig. 1). Limb characteristics as a continuous function of age are displayed in Fig. 1. In the

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>P Value</th>
<th>CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak blood flow, ml/100 ml−1·min−1</td>
<td>60</td>
<td>37.0±1.3</td>
<td>38.2±1.2</td>
<td>0.23</td>
<td>6.4</td>
</tr>
<tr>
<td>Peak conductance, ml/100 ml−1·min−1·mmHg−1</td>
<td>60</td>
<td>0.41±0.02</td>
<td>0.43±0.02</td>
<td>0.08</td>
<td>7.2</td>
</tr>
<tr>
<td>Calf</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak blood flow, ml/100 ml−1·min−1</td>
<td>64</td>
<td>35.1±1.1</td>
<td>35.0±0.9</td>
<td>0.55</td>
<td>6.7</td>
</tr>
<tr>
<td>Peak conductance, ml/100 ml−1·min−1·mmHg−1</td>
<td>64</td>
<td>0.39±0.01</td>
<td>0.39±0.01</td>
<td>0.51</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. CV, coefficient of variation.
forearm, age-associated declines were observed for limb circumference (−1.2% per decade), muscle mass (−3.5% per decade), and grip strength (−4.8% per decade). In the calf, age-associated declines averaged −0.8, −2.2, and −3.0% per decade for limb circumference, muscle mass, and plantar flexor strength, respectively. There was a progressive increase in percent fat with age in the forearm (percent fat = 7.2 + 0.088 × age; \( P = 0.01 \)), but not in the calf (percent fat = 17.5 + 0.036 × age; \( P = 0.47 \)).

Relation between age and limb blood flow (Fig. 2). Baseline resting blood flow decreased with advancing age in the forearm (\( P < 0.001 \)), but not calf (\( P = 0.45 \)). Peak reactive hyperemic blood flow decreased with advancing age in both limbs. The relative age-associated decline in peak blood flow was greater in the forearm (−6.2% per decade, \( P < 0.001 \)) than the calf (−3.1% per decade, \( P = 0.009 \)).

Relocation between age and peak limb conductance (Table 3). Both forearm and calf peak conductance decreased significantly (\( P < 0.001 \) and \( P = 0.004 \), respectively) as a function of increasing age. The overall decline in peak forearm conductance (\( r = 0.65 - 0.0043 \times \text{age}; \ r^2 = 0.38 \)) and peak calf conductance (\( r = 0.49 - 0.0017 \times \text{age}; \ r^2 = 0.12 \)) were best described as a linear function of age. The slope of the age-associated decline in peak conductance was significantly steeper in the forearm (−6.6% per decade) than the calf (−3.4% per decade; \( F\text{-test} = 10.60, \ P < 0.005 \)). The age-associated declines in peak forearm and calf conductance were proportional to reductions in peak forearm and calf blood flow (−6.2% per decade, \( P < 0.001 \) and −3.1% per decade \( P = 0.009 \), respectively), because the MAP response during peak reactive hyperemia was similar across age in both the forearm and calf (\( P = 0.18 \) and 0.64, respectively). When peak vascular conductance was normalized to muscle mass for each limb (ml blood flow−1 × 100 ml tissue−1 × 1 min−1 × mmHg−1 × kg muscle−1), the age-associated decline was attenuated in the forearm (−3.8% per decade; \( P = 0.004 \)) and abolished in the calf (\( P = 0.352 \)).

Predators of limb-specific peak vascular conductance. Table 3 shows the univariate correlations between age, peak limb conductance, and selected physical characteristics. It is important to note that age was significantly correlated with all of the systemic (i.e., \( \text{VO}_2\text{peak}, \text{PWV}, \text{and ABI} \)) and forearm-specific variables. Correlations with age were lower for calf-specific variables, with only calf muscle mass and peak conductance achieving statistical significance. Forward stepwise linear regression analysis was then performed on potential predictors of peak conductance in the forearm and calf. The variables entered were age, cholesterol, \( \text{VO}_2\text{peak}, \text{PWV}, \text{ABI}, \) and limb-specific measures of isometric strength, muscle mass, and percent fat. Limb circumference was not included in these models due to its strong association with limb muscle mass (Table 3) and because plethysmographic flows (and therefore peak conductance) are already normalized to limb circumference.

Table 4 shows the simple and stepwise multiple regression models describing the variance in peak conductance of the forearm and calf. Chronological age, by itself, was a statistically significant predictor of peak conductance in both limbs (both \( P < 0.01 \)). In the forearm, age was the strongest overall predictor of peak conductance. \( \text{VO}_2\text{peak} \) and forearm muscle mass were the second and third factors to enter the equation, improving \( r^2 \) from 0.37 to 0.50. In the calf, \( \text{VO}_2\text{peak} \) was the strongest overall predictor of peak conductance. Calf muscle mass was the only additional factor that signficantly improved the model \( r^2 \) (i.e., from 0.10 to 0.15). Age did not enter the multiple regression model for peak calf conductance unless \( \text{VO}_2\text{peak} \) was excluded.

Relationships between peak limb conductance, \( \text{VO}_2\text{peak} \), and age. \( \text{VO}_2\text{peak} \) (ml·kg−1·min−1) was significantly correlated with peak conductance in the forearm (\( r = 0.61 \)) and calf (\( r = 0.41 \)) for our overall sample (Table 3). Because of the strong association (colinearity) between age and \( \text{VO}_2\text{peak} \) (\( r = 0.689, \ P < 0.001 \)), we also determined the marginal contribution of \( \text{VO}_2\text{peak} \) to reducing error variance in peak limb conductance in two discrete age categories (20–39 yr and 60–79 yr) by using coefficients of partial determination. With calf muscle mass entered in the model, \( \text{VO}_2\text{peak} \) contributed an additional 34% to reducing the variation in peak calf conductance in subjects aged 20–39 yr. However, in subjects aged 60–79 yr, the reduction in error associated with adding \( \text{VO}_2\text{peak} \) to the model was only 6%. The contribution of \( \text{VO}_2\text{peak} \) to reducing error variance in peak conductance in the forearm (with forearm muscle mass in the model) was also significant but less age
dependent (i.e., 17 and 15% in younger and older groups, respectively) than it was in the calf.

DISCUSSION

Previous studies have provided evidence both for and against an age-associated reduction in peak limb vascular conductance in healthy adults (1, 12, 14, 16, 20, 31, 33). We speculated that inconsistencies in the literature were due to wide methodological variation between previous studies. The present investigation attempted to control for many of these factors and provides the first direct comparison of peak vascular conductance between the upper and lower extremities of healthy humans across a broad, continuous age range. The present study also appears to be the first to employ a multiple regression approach to examine and compare possible predictors of the peak conductance response between limbs. The major new findings are as follows. First, there is an overall decline in peak vascular conductance with age in both the forearm and calf of healthy, normally active adult men. The decline in peak conductance with age is linear, reproducible, and limb specific, with a blunted decline in the calf relative to the forearm. Second, normalization of peak conductance to limb-specific muscle mass abolishes the age-associated decline in the calf but not in the forearm. Third, chronological age, \( V_\text{O}_2 \text{peak} \), and regional muscle mass are significant predictors of peak conductance in both limbs; however, these predictors explain considerably less variance in the calf than in the forearm. Collectively, the findings of the present study indicate that limb vasodilator capacity declines with advancing age in healthy men, but the magnitude of this effect is limb specific.

Age and peak forearm vascular conductance. To the best of our knowledge, only two previous studies in the literature have directly assessed the effect of age on peak reactive hyperemia in the forearm. In apparently healthy men aged 20–69 yr, Lind et al. (16) reported an inverse relationship (\( r = -0.52; P < 0.01 \)) between age and peak hyperemia after 3 min of cuff occlusion. Jasperse et al. (12), by contrast, observed no differences in peak blood flow or vascular conductance after ische-
mic handgrip exercise between younger (20–29 yr) and older (60–74 yr) men who were closely matched for forearm size and chronic physical activity. In the present study, we observed a progressive decline in peak forearm reactive hyperemia and vascular conductance with age in a healthy, normally active sample of men. Several methodological differences between our study and that of Jasperse et al. could explain the disparate results, including differences in the limb studied (nondominant vs. dominant, respectively), the transducer used to measure blood flow (strain-gauge vs. Dohn air cuff, respectively), and the stimulus used to evoke peak forearm hyperemia (cuff occlusion alone vs. cuff occlusion + handgrip contraction). Additionally, although the subjects in both studies were normotensive and described as “sedentary to recreationally active,” the older men in the study of Jasperse et al. had well preserved dynamic handgrip exercise capacity (and presumably isometric grip strength), whereas our subjects exhibited a decreased grip strength with age. We have no information...
about the dynamic exercise capacity of our subjects’ forearms, or the occupational history of the subjects studied by Jaspers et al., making it difficult to ascertain whether differences in habitual forearm activity (exercise or occupational) contributed to the disparate results between studies. Nevertheless, the present study suggests that normal aging, with the attendant declines in grip strength and forearm muscle mass, is associated with a progressive decline in forearm vasodilator capacity in men.

Peak forearm conductance was reduced by an average of 6.6% per decade in the present study. When peak conductance was normalized to forearm muscle mass (Fig. 3), the age-associated decline was reduced by approximately one-half (−3.8% per decade; P = 0.004). This finding indicates that a significant component of the decline in peak forearm conductance with age in our sample of men was secondary to the loss of muscle mass, possibly reflecting sarcopenia. The mechanisms responsible for the decline in normalized peak conductance with age are unknown. One possibility is that this residual decline in normalized conductance is secondary to an age-related change in forearm composition (replacement of muscle with fat). Although there is some evidence for a relationship between forearm composition and peak reactive hyperemia in the literature (40) and in the present study (Table 3), forearm percent fat did not contribute to variance in absolute or normalized peak conductance in our overall sample. Taken together, these observations suggest that there is an age-associated reduction in the intrinsic ability of the forearm musculature in men to vasodilate. This presumably reflects reductions in the size of the arteriolar bed (vascular density and/or number) because under normal circumstances the peak reactive hyperemic response is independent of sympathetic tone (34) and nitric oxide (NO)-mediated vasodilation (7). To the best of our knowledge, direct information about arteriolar morphology in human skeletal muscle is not available. However, arterial vascular beds in younger and older rats do exhibit an age-associated reduction in resistance artery number in some limb muscles (6).

Why is the decline in peak calf conductance with age blunted relative to the forearm? We originally hypothesized that reductions in peak limb conductance with age would be greater in the calf compared with the forearm because of previous reports that showed a greater age-related loss of muscle mass and strength in the leg than in the arms of healthy men (2, 11). In contrast to our expectations, peak conductance and regional muscle mass exhibited less rapid declines in the calf than in the forearm. Blunted age-associated reductions in calf muscle mass and vasodilator capacity in our older subjects could reflect an age-associated change in the frequency or intensity of lower body activity relative to the arms and/or a shift in the types of recreational (exercise) or daily activities that men participate in as they age. We cannot address the first possibility because we did not quantify the intensity or duration of daily activities of our subjects. However, the types of exercise activities reported by our younger and older age groups differed. Specifically, the younger subjects were more likely to

Table 3. Pearson correlation coefficients

<table>
<thead>
<tr>
<th>Forearm</th>
<th>Peak G</th>
<th>Age</th>
<th>Rest BF</th>
<th>Circ</th>
<th>Regional % Fat</th>
<th>MM</th>
<th>Str</th>
<th>% Fat</th>
<th>V˙O2peak</th>
<th>PWV</th>
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<tr>
<td>Age</td>
<td>−0.619*</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rest BF</td>
<td>0.359*</td>
<td>−0.468*</td>
<td>0.385*</td>
<td></td>
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<tr>
<td>Circ</td>
<td>0.423*</td>
<td>−0.368*</td>
<td>0.385*</td>
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<tr>
<td>Regional % Fat</td>
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<td>0.299*</td>
<td>0.049</td>
<td>−0.017</td>
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<tr>
<td>MM</td>
<td>0.482*</td>
<td>−0.443*</td>
<td>0.342*</td>
<td>0.777*</td>
<td>−0.384*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Str</td>
<td>0.524*</td>
<td>−0.625*</td>
<td>0.355*</td>
<td>0.621*</td>
<td>−0.226</td>
<td>0.601*</td>
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<tr>
<td>% Fat</td>
<td>−0.470*</td>
<td>0.335*</td>
<td>−0.038</td>
<td>−0.020</td>
<td>0.722*</td>
<td>−0.271*</td>
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<td>V˙O2 peak</td>
<td>0.612*</td>
<td>−0.689*</td>
<td>0.216</td>
<td>0.149</td>
<td>−0.430*</td>
<td>0.263*</td>
<td>0.445*</td>
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<td>PWV</td>
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<td>0.594*</td>
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<td>0.352*</td>
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<tr>
<td>ABI</td>
<td>−0.416*</td>
<td>0.612*</td>
<td>−0.295*</td>
<td>−0.474</td>
<td>0.176</td>
<td>−0.352*</td>
<td>−0.505*</td>
<td>0.161</td>
<td>−0.387*</td>
<td>0.370*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calf</th>
<th>Peak G</th>
<th>Age</th>
<th>Rest BF</th>
<th>Circ</th>
<th>Regional % Fat</th>
<th>MM</th>
<th>Str</th>
<th>% Fat</th>
<th>V˙O2peak</th>
<th>PWV</th>
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<tbody>
<tr>
<td>Age</td>
<td>−0.344*</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Rest BF</td>
<td>0.352*</td>
<td>−0.093</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Circ</td>
<td>0.320*</td>
<td>−0.225</td>
<td></td>
<td>0.162</td>
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<td>Regional % Fat</td>
<td>−0.072</td>
<td>−0.090</td>
<td>0.233</td>
<td>0.383*</td>
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<tr>
<td>MM</td>
<td>0.189</td>
<td>−0.301*</td>
<td>−0.036</td>
<td>0.645*</td>
<td>−0.213</td>
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<tr>
<td>Str</td>
<td>0.071</td>
<td>−0.172</td>
<td>0.117</td>
<td>0.339*</td>
<td>0.072</td>
<td>0.340*</td>
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<tr>
<td>% Fat</td>
<td>−0.238</td>
<td>−0.335*</td>
<td>0.208</td>
<td>0.254*</td>
<td>0.686*</td>
<td>−0.218</td>
<td>0.050</td>
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<tr>
<td>V˙O2 peak</td>
<td>0.409*</td>
<td>−0.689*</td>
<td>−0.011</td>
<td>−0.037</td>
<td>−0.377*</td>
<td>0.159</td>
<td>0.085</td>
<td>−0.626*</td>
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</tr>
<tr>
<td>PWV</td>
<td>−0.250</td>
<td>0.594*</td>
<td>−0.065</td>
<td>−0.034</td>
<td>−0.054</td>
<td>−0.083</td>
<td>0.101</td>
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<td>−0.538*</td>
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<tr>
<td>ABI</td>
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<td>0.612*</td>
<td>−0.076</td>
<td>−0.167</td>
<td>−0.047</td>
<td>−0.118</td>
<td>−0.235</td>
<td>0.161</td>
<td>−0.387*</td>
<td>0.370*</td>
</tr>
</tbody>
</table>

Peak G, peak vascular conductance; Rest BF, resting blood flow; Circ, circumference; Regional % Fat, region-specific fat percentage (forearm or calf); MM, region-specific muscle mass (forearm or calf); Str, region-specific strength (grip or plantar flexion); % Fat, total body fat percentage; V˙O2peak, whole body V˙O2 peak; ABI, nondominant ABI. *P < 0.05

Table 4. Regression analysis of peak vascular conductance of the forearm and calf

<table>
<thead>
<tr>
<th>Limb</th>
<th>Dependent Variable</th>
<th>Predictors</th>
<th>Cumulative r², %</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Forearm</td>
<td>Peak conductance</td>
<td>Age</td>
<td>38.3</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Peak conductance</td>
<td>V˙O2 peak</td>
<td>43.4</td>
<td>0.013</td>
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<tr>
<td></td>
<td></td>
<td>Muscle mass</td>
<td>50.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Calf</td>
<td>Peak conductance</td>
<td>Age</td>
<td>11.8</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Peak conductance</td>
<td>V˙O2 peak</td>
<td>10.2</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle mass</td>
<td>14.5</td>
<td>0.096</td>
</tr>
</tbody>
</table>

Simple regression (vs. age alone) and multiple regression (forward stepwise) models for peak conductance of the forearm and calf.
list activities involving the arms and upper body, whereas walking and other lower body aerobic activities were more common among older men, consistent with national trends (4). Even short-term participation in upper and lower body aerobic activities have been shown to result in augmented peak conductance in the forearm (34) and calf (39), respectively, of previously sedentary men. Thus regional differences in habitual muscle use with advancing age could explain the blunted decline in calf vs. forearm peak conductance seen in the present study.

It could also be argued that limb differences in peak vascular conductance as a function of age are secondary to differences in limb circumference (baseline effect) and/or composition (percent muscle) between the forearm and calf. Plethysmographic measurements of blood flow are normalized to a standardized volume of limb tissue (ml·100 ml⁻¹·min⁻¹), so this should negate any effect of limb size on our results. However, plethysmography does not account for differences in the relative composition of the limbs, which differed as a function of age in this study, because percent fat increased progressively in the forearm but not in the calf. Despite limb differences in percent fat with age, this variable did not contribute to explaining the variance in absolute or normalized peak conductance in either limb. Therefore, it is doubtful that the blunted decline in peak conductance of the calf relative to the forearm can be explained by differences in limb size or percent composition.

Is there a primary effect of age on peak vasodilator capacity in the forearm or calf? In the forearm, chronological age was the strongest predictor of peak conductance, explaining 38% of its variance. \( VO_2 \text{peak} \) and forearm muscle mass improved the model \( r^2 (0.50) \), and normalizing for forearm muscle mass diminished the age-associated decline in peak forearm conductance (Fig. 3). These findings indicate that the decline in forearm vasodilator capacity with age is modulated by declines in aerobic fitness and muscle mass. Because these variables (\( VO_2 \text{peak} \) and forearm muscle mass) are strongly influenced by age, it is difficult to determine whether aging is exerting a primary or secondary effect on forearm vasodilator capacity. The strongest evidence favoring a primary effect of age in the forearm is the fact that a significant age-associated decline of 5% per decade in forearm conductance persists even when we controlled for fitness by examining conductance changes within a \( VO_2 \text{peak} \)-matched (~30–32 ml·kg⁻¹·min⁻¹) subsample of our subjects (21–74 yr, \( n = 25 \)). However, peak forearm conductance normalized to muscle mass did not decrease with age (\( P > 0.001 \)) in this \( VO_2 \text{peak} \)-matched subgroup. Therefore, it appears that muscle atrophy is a substantial component of the age-associated decline in forearm vasodilator capacity in healthy men. It should be acknowledged, however, that at least half of the variance in peak forearm conductance remains unexplained and could be, as discussed above, due to a primary effect of age on intrinsic dilator capacity of the remaining muscle.

Age was also a significant predictor of peak conductance in the calf (Table 4). However, when \( VO_2 \text{peak} \) was entered into the model, age dropped out. This suggests collinearity between age and \( VO_2 \text{peak} \). To determine whether the effects of aging on peak calf conductance are exerted indirectly via reductions in aerobic fitness or directly, we repeated the analysis of peak conductance in \( VO_2 \text{peak} \)-matched subjects, this time for the calf. Controlling for fitness abolished the age-associated decline in peak conductance of the calf (\( P = 0.64 \)), in contrast to what was seen in the forearm. This finding, along with the multiple regression results, suggests that aerobic fitness (\( VO_2 \text{peak} \)) has a stronger influence on vasodilator capacity in the calf than age itself (i.e., secondary effect of age). However, \( VO_2 \text{peak} \) matching also abolishes the age-associated reduction in calf muscle mass, making it difficult to isolate the effects of reduced \( VO_2 \text{peak} \) from reduced muscle mass. Nevertheless, the fact that peak normalized calf conductance is preserved with age in our overall sample (Fig. 3, bottom right) suggests that muscle atrophy, whether caused by reduced aerobic fitness or aging per se, is the primary mediator of the age-associated decline in calf vasodilator capacity in healthy men.

Why is substantially less variance explained in peak calf conductance relative to the forearm? It was surprising that only 15% of the variance in peak calf conductance could be explained given the broad range of possible physiological predictors that were measured. Although between-day variability in peak limb conductance was substantial (±15% in one-third of our subjects), there was no systematic bias with increasing age, and the test-retest reliability in the calf was similar to that of the forearm (coefficient of variation = 7.2%: Table 1). However, there was higher between-subject variability in calf peak conductance, as indicated by a twofold higher interquartile range for the calf compared with the forearm in the subjects over 40 yr (data not shown). This increased variability, coupled with the smaller overall decline in calf conductance with age, could account for the smaller error variance explained in the calf (\( r^2 = 15\% \)) vs. forearm (\( r^2 = 50\% \)) regression models. The degree to which limb expansion accurately reflects arterial inflow, and the extent to which strain gauge plethysmography accurately quantifies arterial inflow in the calf relative to the forearm, are methodological issues that have not been systematically studied and therefore should not be discounted. It is also possible that systemic \( VO_2 \text{peak} \), regional muscle mass, and information about the type and frequency of habitual physical activities are less reflective of the daily demands for vasodilation in the calf compared with the forearm. However, we expected just the opposite to be true given the leg-specific nature of our \( VO_2 \text{peak} \) test (i.e., leg cycle ergometer). The most likely explanation for the lower explained variance in the calf is the fact that chronological age is not as strong a predictor of peak conductance in the calf as it is in the forearm.

Vasodilator capacity of older arms vs. legs: possible physiological significance. In the younger groups (ages 20–39 yr), we observed ~20% higher peak conductance in the forearm than in the calf (Fig. 3), consistent with previous studies in younger non-endurance-trained (24) and non-strength-trained (27) men. This limb difference was not seen in our middle-aged subjects and exhibited a strong trend in the opposite direction (i.e., calf tended to be higher than the forearm) in our older groups (Fig. 3). The physiological significance of these age-group differences is not immediately obvious. A smaller age-associated decline in peak vascular conductance in the legs of older men would translate into the potential for a better preserved skeletal muscle blood flow response at any given arterial perfusion pressure during exercise. An important unanswered question is whether there are differential declines in skeletal muscle vasodilator capacity and cardiac pump function
with advancing age. If so, this could lead to a mismatch between the rise in active muscle vascular conductance and cardiac output during exercise in older adults that would require augmented sympathetic restraint to maintain systemic blood pressure. In this context, our laboratory has previously shown that the exercising legs of healthy older men exhibit augmented vasoconstrictor responses to acute sympathetic stimulation (13).

The overall age-associated reductions in peak calf reactive hyperemia and conductance we observed might appear at odds with our laboratory’s recent report of well-preserved leg blood flow and vascular conductance responses to graded leg cycling in older (compared with younger) normally active men (29). However, leg perfusion during exercise involving a large muscle mass is subject to sympathetic restraint and would therefore not be expected to be as high as that seen during small muscle reactive hyperemia (19). Therefore, a diminished vasodilator capacity in the legs of older men could still pose a structural limit to muscle perfusion during small-muscle dynamic exercise (15).

**Experimental considerations.** Venous occlusion plethysmography does not distinguish between blood flow to the various tissues within arms and legs (i.e., muscle, skin, fat, etc.). Because reactive hyperemic responses to limb occlusion are also observed in cutaneous (17) and subcutaneous adipose (25) vascular beds, it is likely that plethysmographic measurements of limb reactive hyperemia do not solely reflect increased blood flow to skeletal muscle. However, the relative contribution of nonmuscle vascular beds to the early (peak) phase of the reactive hyperemic response is thought to be minimal compared with skeletal muscle (33, 35). Additionally, we attempted to minimize the contribution of cutaneous dilation during reactive hyperemia, and the possible effect of age on this response (17), by testing our subjects in a cool environment. Therefore, it is reasonable to assume that blood flow through skeletal muscle resistance vessels accounts for most of the peak hyperemic response to 10 min of limb occlusion in the present study.

Peak limb vascular conductance is thought to primarily reflect the size of the arterial bed [vascular density, number, and/or geometry (16, 32, 36)]. The fact that pulse wave velocity did not contribute to reducing error variance in peak limb conductance in the present study is further evidence, albeit indirect, favoring a structural rather than mechanical basis (i.e., arterial stiffness) for this measurement. We cannot rule out the possibility that functional changes in the arterial vasculature with advancing age contributed to the diminished peak limb conductance in our older men. However, an alternation in myogenic responsiveness, a major component of the early (i.e., peak) reactive hyperemic response to arterial occlusion, is unlikely to have influenced our results for at least two reasons. First, peak blood pressure responses were similar across age groups. This would reduce the likelihood of an age-associated increase in the myogenic constrictor response to the sudden increase in intravascular pressure after release of the occlusion cuff. Second, there is recent evidence that myogenic responsiveness is diminished, rather than augmented, in hindlimb muscles of older rats (23). Finally, although there are well-established reductions in NO-mediated vasodilation in the forearm with age, it is unlikely that this would play a significant role in the diminished conductance with age we observed because the role of NO in mediating the peak reactive hyperemic response is thought to be minimal (7). Endothelium-derived vasoactive substances are more likely to be involved in sustaining hyperemia after cuff occlusion due to time-dependent activation of shear-stress mechanisms.

A possible confounding influence on our results is the fact that approximately twice as many of our younger subjects (40%) participated in strengthening activities compared with our older groups (24%). Because strengthening exercises typically emphasize upper body movements, this could artificially augment the age-associated rate of decline in forearm peak conductance relative to the calf. However, we do not believe that the strength training history of our subjects contributed significantly to our results for the following reasons. First, almost all of the younger subjects who reported participation in strengthening activities also participated occasionally in traditional “whole body” aerobic activities (jogging, stationary exercise machines); this combination of activities would be expected to elevate blood flow and maintain vascular adaptation in both the arms and legs (9, 19, 36). Second, the peak isometric grip strength of our younger subjects (20–30 yr; 112% of age predicted) was not higher than that of our oldest age groups [60–79 yr; 130% of predicted (21)]. This suggests that the forearms of our younger subjects were not stronger relative to their age-matched peers than our older subjects. Finally, when all the subjects who reported engaging in strengthening exercises (22 of 68 subjects) were excluded from the regression analysis (data not shown), there was still observed a twofold steeper rate of decline in forearm peak conductance with age (−7.2% per decade) compared with the calf (−3.7% per decade). Consequently, we do not think the higher prevalence of strength training participation in the younger subjects we studied explains the more rapid decline in vasodilator capacity with age in the forearm vs. calf.

**Conclusions.** The results of the present study suggest that healthy aging is associated with a decline in limb vasodilator capacity in men, but the magnitude of this effect is reduced in the leg relative to the forearm. This could reflect regional differences in habitual muscle use with advancing age. These findings have important implications for age-associated changes in flow-mediated vasodilation based on the premise that the primary stimulus for conduit artery dilation is the peak dilator response of the downstream resistance vasculature (8). The hemodynamic significance of the differential decline in upper and lower extremity dilator capacity with advancing age is unclear and requires further investigation.

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REFERENCES