Vascular and metabolic response to isolated small muscle mass exercise: effect of age

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First published May 8, 2003; 10.1152/ajpheart.00135.2003.—To determine the effect of age on quadriceps muscle blood flow (QMBF), leg vascular resistance (LVR), and maximum oxygen uptake (QVO₂ max), a thermal dilution technique was used in conjunction with arterial and venous femoral blood sampling in six sedentary young (19.8 ± 1.3 yr) and six sedentary old (66.5 ± 2.1 yr) males during incremental knee extensor exercise (KE). Young and old attained a similar maximal KE work rate (WRmax; young: 25.2 ± 2.1 and old: 24.1 ± 4 W) and QVO₂ max (young: 0.52 ± 0.03 and old: 0.42 ± 0.05 l/min). QMBF during KE was lower in old subjects across all work rates, with old subjects demonstrating a significantly lower QMBF/W (old: 174 ± 20 and young: 239 ± 46 ml·min⁻¹·W⁻¹). Although the vasodilatory response to incremental KE was ~142% greater in the old (young: 0.0019 and old: 0.0046 mmHg·min⁻¹·W⁻¹), consistently elevated leg vascular resistance (LVR) in the old, ~80% higher LVR in the old at 50% WR and ~40% higher LVR in the old at WRmax (young: 44.1 ± 3.6 and old: 31.0 ± 1.7 mmHg·min⁻¹·W⁻¹), dictated that during incremental KE the LVR of the old subjects was never less than that of the young subjects. Pulse pressures, indicative of arterial vessel compliance, were ~36% higher in the old subjects across all work rates. In conclusion, well-matched sedentary young and old subjects with similar quadriceps muscle mass achieved a similar WRmax and QVO₂ max during incremental KE. The old subjects, despite a reduced QMBF, had a greater vasodilatory response to incremental KE. Given that small muscle mass exercise, such as KE, utilizes only a fraction of maximal cardiac output, peripheral mechanisms such as consistently elevated leg vascular resistance and greater pulse pressures appear to be responsible for reduced blood flow persisting throughout graded KE in the old subjects.

THE AGE-RELATED DECLINE in vascular function may be responsible for reductions in blood flow to active skeletal muscle (27, 29, 35, 49) and has been documented in both clinical and research settings manifesting as decreased compliance in arteries and arterioles, chronic high blood pressure, and coronary disease (8). The mechanisms responsible for attenuated skeletal muscle blood flow with increasing age have been investigated utilizing several variables, such as exercise modality, baseline fitness level, and varying age ranges to test specific theories that link age to decreased perfusion of skeletal muscle. Because of the complexity and interdependence of both central and peripheral changes that occur with advancing age, a consensus concerning the mechanisms has not been reached.

Studies (3, 35, 49) of whole body exercise have documented ~20–30% lower blood flow during cycle exercise in elderly males (55–74 yr). Poole et al. (33) recently reported that old sedentary subjects (69.3 ± 2.0 yr) had an increasing blood flow deficit in comparison with young control subjects during cycle exercise from ~50% of the maximal work rate (WRmax). Conversely, small muscle mass experiments have shown preserved perfusion in recreationally active older males. Specifically, similar blood flows were recorded in active young and a wide range of active middle-aged to old (44–69 yr) males during one-legged exercise (26), and similar perfusion and vasodilatory capacity were reported in older (60–74 yr) subjects immediately after dynamic handgrip exercise (21). Together, these findings suggest that in aging populations, blood flow to skeletal muscle is limited by central factors and is therefore preserved during small muscle mass exercise. Casting doubt on these interpretations are data indicating that many peripheral vascular and metabolic factors decline with age, such as decreased reactivity to infused vasodilatory stimuli (9) and increased pulse pressures indicative of arterial vessel stiffening (8). Given that blood flow regulation has been reported to match oxygen demand and local metabolic requirements of skeletal muscle (2), others have implicated factors such as attenuated muscle mass that leads to reduced metabolic demand from chronically inactive muscle (13), decreased mitochondrial density, reduced oxidative capacity (7), and reduced citrate synthase activity (6) for the attenuated skeletal muscle blood flow with age.

The relative contributions of central versus peripheral factors in modulating blood flow are still contested, and both systems are known to decline with age. Therefore, the purpose of this study was to use the knee extensor exercise (KE) modality to study isolated dynamically exercising skeletal muscle in both young

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and old subjects, thereby investigating the consequences of aging on quadriceps muscle blood flow (QMBF) without the contribution of central factors. Specifically, we had several hypotheses. First, old subjects will demonstrate attenuated skeletal muscle blood flow, increased leg vascular resistance, and decreased vasodilatory capacity due to an age-related decline in vascular function. Second, for any given submaximal WR, maximum quadriceps O$_2$ consumption (QVO$_2$ max) will be similar for young and old subjects. Third, the reduced peripheral blood flow will result in either a compensatory increase in arterial-venous (A-V) O$_2$ difference or a reduction in WR$_{max}$ and muscle QVO$_2$ max in the old.

**METHODS**

**Subjects.** Subjects consisted of six young (18–27 yr) and six old (61–77 yr) randomly selected healthy nonsmoking sedentary males of similar physical activity level (Table 1). As part of the initial subject screening, incremental cycle ergometry tests were performed from WR$_{min}$ of 50 + 25-W increments (young) and 30–50 + 20-W increments (old) until the subjects became fatigued. All subjects were determined to be sedentary by an interview questionnaire similar to that presented in previous work by Jacobs et al. (20) and were excluded from participation if they reported any exercise on a work-related, recreational, or competitive basis. The subjects’ sedentary lifestyle was confirmed by the preliminary cycle data revealing a low pulmonary VO$_2$ max in both groups (Table 1). Health histories and physical examinations were completed. Subjects were not allowed to participate if they were found to be taking any medications that would alter blood flow responsiveness. Informed consent was obtained according to the University of California-San Diego Human Subjects Protection Program requirements.

**Exercise modality and exercise protocol.** Single-leg KE was performed that limited work to the quadriceps muscle group, as originally described by Andersen and Saltin (1), and more recently documented by Richardson et al. (38). The ergometer was adjusted so that contraction of the quadriceps muscles turned a flywheel producing a 90°–170° arc of the lower leg. To provide progressive levels of resistance to the quadriceps muscle, tension was incremented by increasing friction on a belt surrounding the flywheel as a percentage of WR$_{max}$ until the subject could no longer maintain a contraction frequency of 1 Hz. Subjects were allowed sufficient practice during preliminary testing to familiarize with the exercise equipment, ensuring that maximal effort was achieved during the catheter study day. At each WR, data collection proceeded as follows: 1) the subjects were allowed to attain an equilibrium at the given WR, 2) blood samples (3 ml each) were taken from the arterial and venous catheters, 3) blood flow measurements were made, 4) blood sampling and blood flow measurements were repeated, 5) blood pressure readings were taken, and 6) the subject was challenged with the next WR.

**Surgical procedures.** Several days after the familiarization and preliminary testing, subjects returned to undergo the catheter-based study. Two catheters (model DSA 400L, Cook; Bloomington, IN) were inserted: one in the femoral artery and the second in the femoral vein. In addition, a thermocouple (model IT-18, Physitemp Instruments; Clifton, NJ) was placed in the femoral vein ~10 cm proximal to the tip of the venous catheter. All were inserted with the use of a sterile technique as previously described (40) to facilitate blood sampling and the thermodilution blood flow measurement technique.

**Leg blood flow, heart rate, and blood pressure.** QMBF was measured by the thermodilution technique during KE as previously described (2, 16). Measured blood flow during KE is accepted as a close approximation of QMBF by reason that quadriceps muscles are the sole working muscle mass of the leg during KE (36, 40). Thermistors connected to two digital thermometers (model IT-18, Physitemp Instruments) interfaced to a personal computer (Biopac Systems; Santa Barbara, CA) measured both venous and in situ temperatures during ~15-s saline infusions. QMBF data were collected after a metabolic steady state was achieved at each WR (2–4 min depending on the exercise intensity) and was calculated using a heat-balance equation (1). Heart rate was obtained from a three-lead electrocardiogram signal (Lifepak 9A, Lifeline; Santa Barbara, CA). Femoral arterial and venous blood pressures in the inguinal region were continuously monitored with the use of pressure transducers raised to the level of the heart (model PX-MK099, Baxter). Mean arterial pressure (MAP) and mean venous blood pressures (MVP) were computed by integration of each pressure curve. Leg vascular resistance was calculated as (MAP – MVP)/QMBF. Pulse pressures were calculated as systolic – diastolic pressure.

**Blood analyses.** Total hemoglobin (Hb) and blood O$_2$ saturation were determined spectrophotometrically with a CO-oximeter (model IL-682, Clayton). Hematocrit, POC$_2$, PCCO$_2$, and pH were determined with a blood gas analyzer (IL-Synthesis, Clayton), and the data were temperature corrected to match each subject’s body temperature at each WR. Blood lactate concentration was measured with the use of a lactate analyzer (YSI 2300 Stat Plus, Yellow Springs). Concentration of arterial oxygen (in m/dl) (CaO$_2$) was calculated as 1.39 × [Hb] × O$_2$ saturation + 0.003 × POC$_2$. QVO$_2$ max was calculated as the product of the mean QMBF and the O$_2$ difference between the femoral artery and vein (CaO$_2$ – CVO$_2$). Muscle O$_2$ delivery was calculated as the product of QMBF and CaO$_2$. P50 was calculated as the P0$_2$ at which Hb saturation was equal to 50% using the equation from Perego et al. (32). Net venous lactate outflow, representative of the lactate efflux from the quadriceps muscle, was calculated as the product of QMBF and [arterial lactate] – [venous lactate].

**Estimate of mean capillary P0$_2$ and diffusional conductance.** A Bohr integration technique was used to calculate an estimate of mean capillary (Pcap0$_2$) and diffusional conductance (Dmcox) at WR$_{max}$. Pcap0$_2$ was calculated as described previously (47) as the numerical average of all P0$_2$ values computed equally spaced in time along the capillary as it traverses the muscle bed from the arterial to venous end. This technique has been discussed in detail elsewhere.

**Table 1. Subject characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Old</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>19.8 ± 1.3</td>
<td>66.5 ± 2.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174.5 ± 4.2</td>
<td>174.4 ± 2.1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.2 ± 5.2</td>
<td>76.9 ± 5.0</td>
</tr>
<tr>
<td>Quadriceps muscle mass, kg</td>
<td>2.23 ± 0.09</td>
<td>2.17 ± 0.06</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>27.8 ± 0.6</td>
<td>25.2 ± 1.2</td>
</tr>
<tr>
<td>Cycle QVO$_2$ max, ml/min·kg$^{-1}$</td>
<td>31.6 ± 2.3</td>
<td>20.3 ± 1.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. QVO$_2$ max, maximal O$_2$ consumption. Body mass index determined by weight/height$^2$. Quadriceps muscle mass determined by anthropometrical measurements. *P < 0.05, significant difference between young and old subjects.
(17, 41) based on a proposal by Wagner (48) with the assumption of a homogeneously perfused muscle. Briefly, the drop in Po2 along a capillary is calculated using Fick’s law of diffusion (Eq. 1)

\[ QV_{O2_{max}} = DmO2(PcapO2 - PmitoO2) \]

where PmitoO2 is mitochondrial Po2, which is set at 0 mmHg, only slightly less than that measured in the cytoplasm of canine muscle fibers (14) and in vivo measurements in human muscle (39). DmO2 is an expression of all phenomena that facilitate O2 unloading at the muscle and is useful as a comparison among conditions and subject populations for gas exchange analyses (18, 19).

Thigh volume measurement. With the use of thigh length, circumference, and skinfold measurements, thigh volume was calculated to allow an estimate of quadriceps femoris muscle mass, as suggested by Jones and Pearson (22), and utilized originally by Andersen and Saltin (2).

Statistical analysis. Data were analyzed post hoc with the use of regression analysis with paired and unpaired t-tests. Statistics were performed with the use of commercially available software (GraphPad, San Diego, CA, and SPSS Software, version 10.1). The data were subjected to a power analysis resulting in a β-value ≥ 0.8 in the majority of variables (e.g., QV_{O2_{max}}, β = 0.74). All data are expressed as means ± SE. Significance was established at a α-level of P ≤ 0.05.

RESULTS

Preliminary testing and subject matching. Both young and old subjects revealed similar height, weight, and activity level (Table 1). In addition, quadriceps muscle mass was not different between young and old, thereby permitting the comparison of data that are not adjusted for muscle mass. Preliminary cycle ergometry testing revealed a significant difference in whole body power output, WR_{max} (young: 181 ± 4 W and old: 131 ± 12 W) and pulmonary VO2_{max} (young: 31.6 ± 2.3 and old: 20.3 ± 1.8 ml·min⁻¹·kg⁻¹). In contrast, during small muscle mass KE, the young and old subjects were equally matched in terms of quadriceps WR_{max} (young: 27.0 ± 2.5 W and old: 24.1 ± 4.0 W; Table 2).

QMBF and vascular pressures. QMBF was initially lower in the old subjects, yet the aging subjects showed a greater vasodilatory response to incremental KE (Fig. 1A and 2C). Specifically, at the initial WR (~3.6 W), QMBF was attenuated in the old (old: 958 ± 52 ml/min and young: 1,711 ± 143 ml/min). While the quadriceps muscles were challenged by progressive increases in KE WR, the corresponding increase in QMBF per watt (~115 ml·min⁻¹·W⁻¹) did not occur between young and old subjects (Fig. 1A). Although the vasodilatory response to incremental KE (change in vascular resistance per watt) was ~142% greater in the old (Fig. 2C), at no point was this response sufficient to overcome the elevated initial LVR in the old, as LVR remained ~80% higher in the old at WR-50%, and ~40% higher at WR_{max} (young: 30.1 ± 1.7 mmHg/ml and old: 44.1 ± 3.6 mmHg/ml; Fig. 2C). MAP was not different between young and old subjects at maximal KE. The driving force on blood across the muscle bed (MAP–MVP) was not different between young and old subjects (young: 0.05 ± 0.01; old: 0.046 ± 0.02 ml·dl⁻¹·W⁻¹) (Fig. 1C).

Table 2. Maximal blood gas and exercise variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young</th>
<th>Old</th>
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</thead>
<tbody>
<tr>
<td>Work, watts</td>
<td>27.0 ± 2.5</td>
<td>24.1 ± 4.0</td>
</tr>
<tr>
<td>Quadriceps muscle blood flow, l/min</td>
<td>3.95 ± 0.10</td>
<td>3.32 ± 0.32</td>
</tr>
<tr>
<td>Quadriceps muscle VO2, l/min</td>
<td>0.52 ± 0.03</td>
<td>0.42 ± 0.05</td>
</tr>
<tr>
<td>pHH</td>
<td>7.38 ± 0.01</td>
<td>7.38 ± 0.01</td>
</tr>
<tr>
<td>pHl</td>
<td>7.23 ± 0.01</td>
<td>7.23 ± 0.01</td>
</tr>
<tr>
<td>[Hb], g/dl</td>
<td>14.1 ± 0.4</td>
<td>15.1 ± 0.6</td>
</tr>
<tr>
<td>CaO2, ml/dl</td>
<td>19.7 ± 0.52</td>
<td>20.9 ± 0.81</td>
</tr>
<tr>
<td>CVO2, ml/dl</td>
<td>6.5 ± 0.8</td>
<td>8.3 ± 0.6</td>
</tr>
<tr>
<td>PaO2, mmHg</td>
<td>123 ± 6</td>
<td>116 ± 3</td>
</tr>
<tr>
<td>PvO2, mmHg</td>
<td>24.0 ± 1.5</td>
<td>27.7 ± 1.5</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>98.8 ± 0.2</td>
<td>98.3 ± 0.2</td>
</tr>
<tr>
<td>SvO2, %</td>
<td>32.9 ± 4.2</td>
<td>39.1 ± 2.8</td>
</tr>
<tr>
<td>O2 del l/min</td>
<td>0.78 ± 0.02</td>
<td>0.69 ± 0.06</td>
</tr>
<tr>
<td>(CaO2 – CVO2), ml/dl</td>
<td>13.2 ± 0.9</td>
<td>12.7 ± 0.8</td>
</tr>
<tr>
<td>Lactate outflow, mmol/min</td>
<td>5.5 ± 1.6</td>
<td>4.2 ± 1.1</td>
</tr>
<tr>
<td>Leg vascular resistance, mmHg-min·ml⁻¹</td>
<td>27.2 ± 2.0</td>
<td>43.1 ± 4.5</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>136 ± 7</td>
<td>138 ± 6</td>
</tr>
<tr>
<td>Arterial-venous pressure, mmHg</td>
<td>120 ± 4</td>
<td>121 ± 7</td>
</tr>
<tr>
<td>PcapO2, mmHg</td>
<td>42.5 ± 0.9</td>
<td>46.3 ± 2.1</td>
</tr>
<tr>
<td>DmO2, l·min⁻¹·mmHg⁻¹</td>
<td>12.5 ± 1.0</td>
<td>10.4 ± 1.0</td>
</tr>
</tbody>
</table>

Values are means ± SE for 6 young and 6 old subjects. [Hb], total hemoglobin concentration; CaO2, total oxygen content of arterial blood; CVO2, oxygen concentration of venous blood; SaO2, arterial oxygen saturation; SvO2, venous oxygen saturation; PaO2, arterial PO2; PvO2, venous PO2; PcapO2, mean capillary PO2; DmO2, oxygen diffusion conductance. Subscripts a and v denote arterial and venous, respectively. Blood gas measurements from femoral arterial and venous sampling during maximal single leg dynamic knee extensor exercise; quadriceps blood flow measured by thermodilution method. *P < 0.05, significantly different between young and old subjects.
DISCUSSION

There are several major findings of this study. First, QMBF measurements during KE revealed a consistently attenuated blood flow (~500 ml/min) in old sedentary subjects when compared with young sedentary subjects of similar quadriceps muscle mass. Second, LVR was elevated in the old throughout KE, and, as the driving force on blood across the muscle bed (A-V pressure) was similar for both groups, elevated LVR was responsible for reduced QMBF in the old subjects. Third, the vasodilatory response to incremental KE (fall in LVR W⁻¹) was elevated in the old subjects, indicating that the vasodilatory pathways activated in response to incremental KE are capable of producing a greater change in LVR from the initial WR of 3 W to WRmax. These changes, however, were insufficient to overcome the initially elevated LVR in the old subjects, who therefore always had a greater absolute LVR than the young subjects. Finally, old and young sedentary subjects of equal quadriceps muscle mass achieved similar WRmax and QVO₂ max during small muscle mass KE. During cycle exercise, the old subjects revealed lower WRmax and pulmonary VO₂ max, indicating an age-related central limitation to maximal whole body exercise. When taken together, these findings indicate that when central limitations are minimized during small muscle mass KE, peripheral factors usually associated with declining vascular function, including elevated LVR, elevated pulse pressures, and reduced QMBF persist in the old subjects throughout KE. Perhaps in compensation for the initially reduced QMBF and elevated LVR, the old subjects revealed a greater vasodilatory response to incremental KE, which, when coupled with the elevated A-V O₂ difference documented in the old subjects, facilitate the attainment of equal O₂ uptake and power output to the young subjects during maximal isolated skeletal muscle exercise.

**Attenuated QMBF in old subjects throughout KE.** QMBF was consistently lower (~500 ml/min) in the old subjects during KE. These data differ from previous findings obtained with a similar KE model that revealed similar perfusion between young and middle-aged to older subjects (26). This disparity in findings is perhaps explained by the difference in age range and activity levels between the subjects in Magnusson’s study compared with the present research. Whereas Magnusson studied a wide range (44–69 yr) of middle-aged to old men who were regularly physically active, the current study focused on sedentary old subjects (66 ± 2.5 yr).

Findings from the current study also revealed that at maximal KE, older subjects have attenuated QMBF. This is not in agreement with the data presented by Jasperse et al. (21), who reported similar perfusion.
between young and old subjects immediately after sub-maximal and maximal dynamic handgrip exercise. The subjects in the Jasperse study were reported to be “chronically physically active” possibly increasing forearm vascular conductance and accounting for the similarities in conductance and the equalization of blood flow. On the basis of mounting evidence implicating endurance exercise in modifying certain aspects of vascular function, such as improved vessel compliance (46) and improved vascular reactivity to infused pharmacological agents (9), one should use caution when comparing data from trained subjects and sedentary subjects. In addition, blood flow measurements presented by Jasperse et al. (21) were made directly after each level of exercise and may not be representative of the pathways controlling blood flow that are activated during dynamic exercise. It is also possible that the vasculature in the upper and lower extremities respond differently to the aging process.

The current data, however, are in accordance with previous studies (23, 49) that have documented reductions in skeletal muscle blood flow in aging subjects during exercise. In a related study from our laboratory, Poole et al. (33) reported an attenuated increase in blood flow to leg muscles in sedentary aging subjects during whole body cycle exercise from 50% of WR_{max} to WR_{max}, suggestive of a progressive maldistribution of blood flow with increasing exercise intensity, which was responsible for the attenuated leg blood flow in the old subjects. If central limitations were solely responsible for reduced muscle perfusion during cycle exercise in the old, it would be expected that when these central limitations are minimized (as in KE) perfusion in the old subjects should reach equal values to young subjects.

Fig. 2. A: mean arterial pressure (MAP)-mean venous pressure (MVP) measured with femoral arterial and venous pressure transducers. B: pulse pressures measured in femoral artery. C: leg vascular resistance calculated as (MAP – MVP)/QMBF versus WR. All values recorded during incremental single leg knee extensor exercise. *Significantly different slope and y-intercept between young and old subjects.
subjects at the same WR. The finding of a lower QMBF suggests that in the old subjects, peripheral vascular limitations during isolated small muscle mass exercise persist and are responsible for the attenuated blood flow in the old subjects. Possible mechanistic explanations for these observations may be the previously documented augmentation of α-adrenergic vasoconstriction (11) and/or the decreased ability of insulin to alter blood flow to skeletal muscle (30). Although resting QMBF data were not collected in the current study, we cannot discount the possibility that low resting QMBF resulting from attenuated vasodilatory factors at rest in the old subjects (e.g., nitric oxide via an endothelial nitric oxide synthase mechanism) may persist during exercise and may be responsible for the consistently attenuated QMBF recorded throughout incremental KE (12, 15, 50).

Elevated LVR and pulse pressures in old subjects. The driving force on blood through the muscle bed (MAP – MVP) was not different in the old subjects. Similarly, MAP at WRmax was not different between young and old. LVR was elevated in the old subjects throughout incremental KE and is therefore responsible for decreased QMBF in the old subjects. LVR is largely determined by two age-dependent factors, arteriolar cross-sectional area, and compliance of the arterial wall. Previous studies have documented multiple factors that contribute to elevated vascular resistance in aging populations, including decreased arterial and arteriolar diameter as a result of arterial wall thickening (10), arterial stiffening (25), insulin resistance (30), age-related reductions in tonic nitric oxide-mediated vasodilation (31, 44), and increases in endothelin-1-mediated vasoconstriction (4). Offering further mechanistic insight into elevated LVR in the old are the elevated pulse pressures seen throughout KE. Elevated pulse pressures are indicative of large artery stiffness (8, 25) and decreased vessel conductance both leading to reduced QMBF. These findings of elevated pulse pressures in the old are supported by research presented by Dinenno et al. (10), who concluded that age-associated femoral arterial wall thickening was due to increased α-adrenergic vasoconstriction. In addition, Kass et al. (24) implicated glycation end products and their interference with long-lived arterial collagen and elastin fibers as a mechanism underlying age-associated vessel wall stiffening.

Greater reduction in LVR to graded KE in old subjects. Our findings of increased vasodilatory response to KE in the old subjects are in accordance with studies conducted by Jasperse et al. (21), which revealed greater peak increases in forearm vascular conductance in the old subjects. Because the vasodilatory pathways are responding more dramatically in old subjects, it appears that a basal limitation to QMBF is continually and equally dampening the vasodilatory efforts of the smooth muscle reactive pathways across all WRs (Fig. 2C). Because the old subjects begin with a high LVR, it is perhaps simply by necessity that they have a greater reduction in LVR than the young subjects, permitting the required blood flow response to achieve an equal WRmax.

The present data, documenting an increased vasodilatory response to incremental KE (Fig. 2C), may at first appear to conflict with the findings of several other research groups who have reported age-related declines in endothelium-dependent vasodilation (5, 9, 45). However, it must be remembered that much of this research has been performed at rest when the role of the endothelium in mediating vasodilation may be most significant. During exercise, as in the current study, diminished endothelial function may be overcome by other vasodilatory mechanisms such as metabolite concentrations. In addition, when data presented by DeSouza et al. (9) are examined more closely, it appears that from baseline to the intra-arterial infusion of 1 μg ACh/100 ml tissue that there is a difference between the vasodilatory response in young and old. However, from this point on, the slopes of the two lines (change in conductance per microgram of ACh infusion) are remarkably similar for young and old subjects suggestive of similar vasodilatory capabilities in young and old subjects. This result was not recognized in the study by DeSouza et al. (9). Although resting pharmacological intervention studies have contributed significantly to the current understanding of blood flow regulation by offering a specific insight into select pathways, they may produce different results from the current study because they are designed to evoke responses from a specific pathway from the many regulatory mechanisms that may govern blood flow during exercise and cannot account for the complex combination of mechanical and metabolic changes that influence vascular resistance during exercise. Finally, studies involving dynamic muscle contraction reveal how muscle blood flow is affected by the combination of naturally occurring stimuli in a situation
much more akin to those occurring in everyday life, and, in such a scenario, the older subjects do not reveal a diminished vasodilatory response to incremental KE (Fig. 2C).

Limitations to maximal exercise. A hallmark of the aging process appears to be a fall in maximal exercise capacity (3, 33, 35). Although this attenuation of maximal exercise was apparent in the current subjects during the prescreening bicycle exercise testing (Table 1), when exercise was isolated to a relatively small muscle mass in the form of KE, the difference between young and old was lost. In support of these findings, variables reflecting relative stress, such as venous lactate outflow and pH, were nearly identical between young and old subjects during submaximal and maximal KE (Table 2). These findings are in agreement with Jasperse et al. (21), who documented a similar WRmax in young and old physically active males during small muscle mass dynamic handgrip exercise. However, it should be recognized that a statistical analysis of QVO2max revealed marginally acceptable power β = 0.74 and a P value of 0.14 (two-tailed paired t-test). Thus the potential of a type II error as a consequence of the limited sample size cannot be ruled out.

In terms of convective O2 transport, the old subjects demonstrated a consistently reduced QMBF, but the tendency toward an elevated CaO2 resulted in a similar O2 delivery in the young and old subjects. Thus both the young and old achieved the same WRmax, A-V O2 difference, and QVO2max. These findings are starkly different from the 30% reduction in both WRmax and pulmonary VO2max exhibited by the same old subjects during the bicycle exercise test. These data suggest a central limitation in aging persons resulting in disparities between young and old subjects during centrally taxing exercise (e.g., maldistribution of cardiac output), which are resolved during a small dynamic muscle mass exercise such as KE.

When the diffusional component of O2 transport is assessed by the calculation of a normoxic DmO2, the young and old subjects appear similar in terms of the movement of O2 from blood to muscle cell (Fig. 3). Recently published data (33) collected in our laboratory during maximal cycle exercise in nine sedentary young and nine sedentary old subjects revealed a significantly lower maximal quadriceps muscle DmO2, pulmonary VO2max, and QVO2max in the old subjects. It is possible that the decreased DmO2 and QVO2max reported during cycle exercise results from central limitations (e.g., inappropriate distribution of a finite cardiac output) that are not present when the quadriceps muscle bed is now the sole muscle with high metabolic demand. It is noteworthy that both the young and old subjects show a greatly reduced DmO2 compared with data collected from young endurance trained subjects performing KE in our laboratory (37; Fig. 3). These findings suggest that both DmO2 and QVO2max are much more strongly associated with a sedentary lifestyle rather than simply age.

The finding of similar quadriceps mass, WRmax, and QVO2max appears to disagree with reports that normal aging brings about a general reduction in muscle mass of up to 25–30% by age 70 (6, 13, 42) and a concomitant 30–40% reduction in muscle strength (34). In addition, others have shown ~50% lower oxidative capacity per unit volume resulting from decreased ATP per mitochondria recorded during MRI twitch studies (7) and decreased muscle metabolic capacity, as represented by an age-related decline in pulmonary VO2max, citrate synthase, and phosphocreatine (28). On the basis of these latter findings, it would be expected that for a similar muscle mass, aging subjects should have ~50% lower WRmax and QVO2max. Perhaps resolving this disparity are studies showing that typically persons >50 years of age remain the most sedentary segment of the population, with persons >70 years of age being extreme examples of this inactive group (43), and that this progressive decline in activity level causes the concomitant fall in strength, blood flow, metabolic capacity, etc. Typically, young sedentary volunteers are most likely more active than their older counterparts due to daily routine and leisure activities, tending to magnify the apparent aging effect. The subject selection criteria for this study were strict and many young subjects were rejected for participation in any exercise, even if only on an occasional recreational basis.

In summary, six equally matched sedentary young and old subjects who differed significantly in terms of maximal cycle exercise capacity achieved similar QVO2max and WRmax when tested during KE. Submaximally, the old subjects revealed an elevated A-V O2 difference, and attenuated QMBF, yielding a similar QVO2max to the young subjects across all WRs. Elevated LVR is likely responsible for the attenuation in QMBF in the old subjects and may be the result of factors present at rest, which persist during incremental KE, such as decreased arterial cross-sectional area, decreased vasodilatory stimuli, such as endothelial nitric oxide, increased α-adrenergic vasoconstriction, and decreased arterial compliance resulting in increased pulse pressures that contribute to the obstruction of blood flow in the old subjects. However, these differences did not hinder the vasodilatory response to incremental KE (measured as a change in LVR per watt), which was greater in the older subjects. In addition, diffusional O2 transport in this small muscle mass condition appeared to be uncompromised in the old subjects.

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DISCLOSURES

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