Vascular and metabolic response to cycle exercise in sedentary humans: effect of age

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Poole, J. G., L. Lawrenson, J. Kim, C. Brown, and R. S. Richardson. Vascular and metabolic response to cycle exercise in sedentary humans: effect of age. Am J Physiol Heart Circ Physiol 284: H1251–H1259, 2003. First published December 19, 2002; 10.1152/ajpheart.00790.2002.—We measured leg blood flow (LBF), drew arterial-venous (A-V) blood samples, and calculated muscle O2 consumption (\(\dot{V}O_2\)) during incremental cycle ergometry exercise [15, 30, and 99 W and maximal effort (maximal work rate, WR\(_{\text{max}}\)] in nine sedentary young (20 ± 1 yr) and nine sedentary old (70 ± 2 yr) males. LBF was preserved in the old subjects at 15 and 30 W. However, at 99 W and at WR\(_{\text{max}}\), leg vascular conductance was attenuated because of a reduced LBF (young: 4.1 ± 0.2 l/min and old: 3.1 ± 0.3 l/min) and an elevated mean arterial blood pressure (young: 112 ± 3 mmHg and old: 132 ± 3 mmHg) in the old subjects. Leg A-V \(\dot{O}_2\) difference changed little with increasing WR in the old group but was elevated compared with the young subjects. Muscle maximal \(\dot{V}O_2\) and cycle WR\(_{\text{max}}\) were significantly lower in the old subjects (young: 0.8 ± 0.05 l/min and 193 ± 7 W; old: 0.5 ± 0.03 l/min and 117 ± 10 W). The submaximally unchanged and maximally reduced cardiac output associated with aging coupled with its potential maldistribution are candidates for the limited LBF during moderate to heavy exercise in older sedentary subjects.

\(\dot{V}O_2\)\(_{\text{max}}\), vascular conductance; skeletal muscle

Although regular physical activity has been demonstrated to be critical for the promotion of normal healthy function as people age (5), persons over 50 yr of age represent the most sedentary segment of the adult population (49). This trend toward inactivity is even more apparent in people 70 yr and above (49). Limited blood flow to active skeletal muscles has been implicated as an important factor that contributes to the decline in physical activity and exercise capacity associated with the aging process (23, 27, 28, 30, 36). With advancing age, changes occur in both the central and peripheral circulation that can affect compliance in arteries and arterioles and blood pressure and ultimately alter the vascular response to exercise (4, 55).

There have only been a few investigations that directly examined local skeletal muscle blood flow in elderly people from submaximal to maximal work intensities (age range: 52–80 yr). Jasperse et al. (23) investigated the effects of age on blood flow during small muscle mass exercise (dynamic handgrip) and demonstrated a preserved peripheral (forearm) blood flow in older subjects compared with their younger counterparts. In the limited number of studies that have examined muscle blood flow during large muscle mass exercise, subjects have typically been elderly recreationally active males (36, 55). During conventional cycle ergometry, this population demonstrated a 20–30% reduction in LBF during several submaximal work rates (WRs) compared with young subjects (36, 55). However, the cardiac output (CO)-to-\(\dot{O}_2\) consumption (\(\dot{V}O_2\)) relationship appears to be well preserved in old subjects (31, 35, 48). In combination, these findings suggest that during exercise in physically active aging subjects, total available blood flow per se (i.e., CO) is not limiting, but rather the ability to direct this blood flow to or within active muscle may be significantly compromised. However, as noted, aging is most commonly associated with a decline in physical activity and as the only available data have been collected from physically active older subjects, the effect of age on skeletal muscle blood flow and metabolism in sedentary individuals remains undocumented.

Therefore, the purpose of the current study was to investigate the vascular and metabolic response of the leg muscles during both submaximal and maximal cycle exercise in two well-matched groups of young and old sedentary subjects. Our primary hypotheses were that the metabolic cost of work as measured by leg muscle \(\dot{V}O_2\) would be similar in both groups, but that this would be achieved by a lower submaximal LBF and elevated arterial-venous (A-V) \(\dot{O}_2\) difference in the old subjects. Ultimately, this limited exercise LBF and the resulting attenuation of \(\dot{O}_2\) delivery would translate into a significantly reduced maximal WR (WR\(_{\text{max}}\)) and maximal muscle \(\dot{V}O_2\) (\(\dot{V}O_2\)\(_{\text{max}}\)) in the older subjects.

METHODS

Subjects. Nine healthy sedentary young subjects and nine healthy sedentary old males who were matched in terms of physical characteristics and activity level participated in the study (Table 1). All potential subjects were screened to assess physical activity level using a modified Minnesota Leisure
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Young Subjects</th>
<th>Old Subjects</th>
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<tr>
<td>Age, yr</td>
<td>20 ± 1</td>
<td>70 ± 2</td>
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<tr>
<td>Height, cm</td>
<td>175 ± 2</td>
<td>173 ± 3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74 ± 3</td>
<td>78 ± 4</td>
</tr>
<tr>
<td>Bicycle V(_{02\text{max}}), ml·kg(^{-1})·min(^{-1})</td>
<td>32 ± 2</td>
<td>21 ± 4*</td>
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</table>

Values are means ± SE; n = 9 old subjects and 9 young subjects. V\(_{02\text{max}}\), maximum pulmonary O\(_2\) consumption. *Significantly different from young subjects.

Time Physical Activity questionnaire that correlates well with exercise testing (12, 22, 52). Only those subjects who reported no previous history of physical training or recreational sport and no regular or occasional physical exercise above that required for daily activities were selected. None of the subjects were using any medications that would alter vascular function. Informed consent was obtained according to University of California-San Diego Human Subjects Committee requirements. The older men completed a graded treadmill test with 12-lead electrocardiograph (ECG) and blood pressure monitoring 1–2 wk before the invasive blood flow study to screen for cardiovascular disease. All subjects performed a preliminary graded cycle ergometer exercise test to determine pulmonary V\(_{02\text{max}}\) (Table 1).

Exercise protocol, preliminary screening, and familiarization. All exercise was performed on an electronically braked cycle ergometer (Lode Excalibur Sport, Quinton Instruments; Groningen, The Netherlands) and was restricted to a seated position. Before the main study day, all subjects were familiarized with the testing environment and cycle ergometer by means of a similar graded exercise protocol, but without catheters.

On the main study day after the catheterization procedures, subjects completed one graded cycle ergometer exercise test to maximum in room air. During this test, subjects maintained the predetermined WRs for 2–3 min, after which the WR was incremented. The subjects continued until they were unable to maintain the minimum rpm necessary for the ergometer to maintain a constant WR for the entire work level. Additional criteria such as a respiratory exchange ratio > 1.1 and the achievement of an age-predicted maximum heart rate were used to verify that a true maximum effort was achieved. Comparisons between the young and old subjects were made at the absolute WRs of 15, 30, and 99 W and maximal effort. Data were collected as follows for each incremental WR: 1) 3-ml femoral arterial and venous blood samples were taken for measurements of P\(_{O2}\), P\(_{CO2}\), pH, and arterial (S\(_{aO2}\)) and venous O\(_2\) saturation (S\(_{vO2}\)); and 2) femoral venous blood flow was measured. This series of events was then repeated to allow duplicate measurements. Pulmonary minute ventilation (Ve), V\(_{O2}\), and V\(_{CO2}\) were calculated by a commercially available software package (Consentius Technologies; Salt Lake City, UT) integrated with a Perkin-Elmer MGA 1100 mass spectrometer, a gas mixing chamber, and a Fleisch No. 3 pneumotachograph (Hans-Rudolph; Kansas City, MO). Heart rate, arterial blood pressure, and venous blood pressure were recorded continuously during exercise.

LBF, heart rate, mean arterial blood pressure and leg vascular conductance. Two catheters (femoral artery and vein, model DSA 400L, Cook; Bloomington, IN) and a thermocouple (femoral vein, model IT-18, Physitkem Instruments; Clifton, NJ) were inserted using sterile techniques as previously reported (14, 42, 44). LBF was determined by the constant infusion thermodilution technique, as originally described by Andersen et al. (3), Saltin et al. (3,14), and used by others (44). Briefly, both venous and infused temperatures were measured continuously during saline infusion (15–20 s), the rate of which was adjusted with a roller pump. The thermistor signals and saline bag weight changes (Grass displacement transducer FT10C) were then displayed on personal computer-based Acknowledge Acquisition System software (Biopac Systems; Santa Barbara, CA), which enabled the real-time observation of each variable. LBF values in this study represent the average of two measurements made between minutes 2 and 3 of each WR, i.e., at a time when steady state was assumed to have occurred at all WRs except maximal effort. Heart rate was obtained from the continuously recorded ECG signal (Lifepak 9A, Lifeline; Santa Barbara, CA). Arterial and venous blood pressures were continuously monitored at the heart level by a pressure transducer (model PX-MK099, Baxter). Mean arterial blood pressure (MABP) was computed by the simple integration of each pressure curve. Leg vascular conductance (LVC) was calculated by dividing LBF by MABP.

Blood analysis and calculations. Hemoglobin concentration, arterial blood Sa\(_{O2}\), and determined systolic blood pressure (11022) was determined spectrophotometrically (IL-682 CO-oximeter; Clayton, NC). Hematocrit, P\(_{O2}\), P\(_{CO2}\), and pH were measured with a blood gas analyzer (IL Synthesis; Clayton, NC) and corrected for measured femoral blood temperature. Blood lactate concentration was measured by a Yellow Springs Instruments 2300 Stat Plus (Yellow Springs, OH).

Blood O\(_2\) content (in ml/dl) was calculated as (1.39 ml O\(_2\)g × [Hb] g/dl × S\(_{aO2}\) ) + [0.003 ml/dl × P\(_{O2}\) (in mmHg)]. Leg V\(_{O2}\) was calculated as the product of the mean LBF and the difference in the A-V O\(_2\) concentration (A-V O\(_2\) difference). Leg O\(_2\) delivery was calculated as the product of LBF and femoral arterial oxygen content (C\(_{aO2}\)). Net venous lactate outflow was calculated as the product of LBF and the difference in the A-V lactate concentration.

Thigh volume measurement. Thigh volume was calculated for each subject using thigh length, circumference, and skinfold measurements (2, 25). It is acknowledged that this method has a tendency to overestimate muscle volume when compared with multiple-slice computer tomography (37). However, as this method was applied in the same fashion to both groups, it allowed a fair comparison of muscle mass to be made between the young and old groups. It should also be recognized that this method does not assess differences in intramuscular fat.

Muscle O\(_2\) transport conductance and mean capillary P\(_{O2}\) calculations. Muscle O\(_2\) transport conductance (D\(_{O2}\)) and mean capillary P\(_{O2}\) were calculated at 100% of WR\(_{max}\), as described previously (53). Briefly, a numerical integration procedure was used to determine that value of D\(_{O2}\), which is assumed constant along the capillary. This value of D\(_{O2}\) is the conductance of O\(_2\) (i.e., in ml·min\(^{-1}\)·mmHg\(^{-1}\)) that yields the measured femoral muscle venous P\(_{O2}\). Additional explicit assumptions of this calculation are as follows: 1) intracellular P\(_{O2}\) is negligibly small at V\(_{O2\text{max}}\) (43); and 2) the only explanation of O\(_2\) remaining in the femoral venous blood is diffusion limitation of O\(_2\) efflux from the muscle microcirculation. Perfusion/V\(_{O2}\) heterogeneity, and perfusional or diffusional shunt, are considered negligible. To the extent that these phenomena contribute O\(_2\) to femoral venous blood, the parameter D\(_{O2}\) is a conductance coefficient that expresses the diffusing capacity that would be required to achieve the measured V\(_{O2\text{max}}\), assuming only diffusion limitation. Although we are working toward the goal of quantifying the contribution of heterogeneity in perfusion/V\(_{O2}\) to the residual O\(_2\) in venous effluent blood (41), this assumption...
cannot be avoided until we can characterize perfusion/\(\dot{V}O_2\) heterogeneity and shunt within exercising human skeletal muscle. Mean capillary \(P_O_2\) is the numerical average of all computed \(P_O_2\) values, equally spaced in time, along the capillary from the arterial to venous end.

Statistical analysis. ANOVA was used to determine differences within and between groups at submaximal WRs. Unpaired \(t\)-tests were used to determine differences between groups at maximal exercise. When appropriate, regression analysis was used to assess the relationships between variables. Statistics were performed on commercially available software (GraphPad; San Diego, CA). Significance for all tests was established at an \(\alpha\)-level of \(P < 0.05\), and all data are expressed as means ± SE.

RESULTS

Physical characteristics, activity level, and thigh volume. Matching of subjects based on height and weight resulted in no difference in these variables between the young and old groups (Table 1). Additionally, by design, subject evaluation of activity level on a daily basis was not different between the young and old groups. The anthropometric assessment of thigh volume revealed very similar values for both the young (5.9 ± 0.3 liters) and old group (5.9 ± 0.2 liters). Thus, when converted to muscle mass as suggested by Jones and Pearson (25), both groups were estimated to have ~2.2 kg of quadriceps muscle. As no difference in muscle mass was found between the two groups, functional data were not normalized for muscle mass.

WR and leg \(\dot{V}O_2\). During their progression to WR\(_{\text{max}}\), both groups exercised at several identical absolute submaximal workloads. However, the relative work intensities were significantly different between age groups, with the 15, 30, and 99 W WRs, translating to 13%, 26%, and 84% of maximum in the old group and 8%, 16%, and 47% of maximum in the young group, respectively. The slope of leg \(\dot{V}O_2\)-to-WR relationship over the complete WR range was similar between the two groups (old: 3.7 ± 0.4 ml/W and young: 3.9 ± 0.2 ml/W; Fig. 1C). Leg \(\dot{V}O_2\)\(_{\text{max}}\) was significantly higher in the young subjects, as was the WR\(_{\text{max}}\) (Fig. 1C).

LBF, A-V \(O_2\) difference, and LVC. It should be noted that LBF is presented, as measured, from only one leg. The slope of the LBF-to-WR relationship was significantly different between the young and old subjects (old: 22 ± 1 ml/W and young: 28 ± 2 ml/W), but the intercept of this relationship was not different. Consequently, LBF was similar between groups at the lower submaximal WRs (15 and 30 W; Fig. 1A), whereas at 99 W and WR\(_{\text{max}}\) the old subjects demonstrated an attenuated LBF (Fig. 1A). The A-V \(O_2\) difference rose only modestly with increasing work level in both groups, but this was more notable in the old group, who began with a higher \(O_2\) extraction (the old group rose from 14.4 ± 0.8 to 15.3 ± 0.8 ml/dl and the young group rose from 9.8 ± 0.5 to 12.9 ± 0.9 ml/dl; Fig. 1B). At each comparable absolute WR and WR\(_{\text{max}}\), the leg A-V \(O_2\) difference was significantly higher in the old group (Fig. 1B). In addition to the reduced LBF in the old group, MAP was significantly higher in the old subjects at 99 W and WR\(_{\text{max}}\) compared with their younger counterparts (Fig. 2A). Subsequently, LVC was significantly attenuated at these higher workloads in the old subjects (Fig. 2B).

Major blood-related variables. \(O_2\) delivery to the leg muscles was similar between the two age groups at 15 and 30 W, but at both 99 W and WR\(_{\text{max}}\) \(O_2\) delivery was significantly reduced in the old subjects. Arterial \(P_O_2\), \(S_aO_2\), and \(C_aO_2\) were similar and were maintained across all WRs within normal levels in both age groups (Table 2), indicating that the reduced \(O_2\) delivery in the old subjects was a consequence of LBF. However, femoral \(S_vO_2\) and \(O_2\) content at each power output were significantly lower in the old group (Table 2). [Hb] between age groups was not significantly different and demonstrated only a mild hemoconcentration from submaximal to maximal work intensities (Table 2). Arterial and venous lactate concentrations were not significantly different between the groups at 15 and 30

Fig. 1. Relationship between cycle work rate (WR) and leg blood flow (A), arterial-venous \(O_2\) difference (B), and leg \(O_2\) consumption (\(\dot{V}O_2\); C) in young and old subjects. *Significantly different response at submaximal WRs in old subjects; #significantly different response at maximal WR in old subjects.
W, but differed significantly at 99 W, with the old subjects demonstrating elevated arterial and venous lactate concentrations (Fig. 3B). At WRmax, the young subjects had both a higher arterial and venous lactate concentration. Net lactate release from the leg rose in a similar fashion with increasing WR in both groups; however, at WRmax the old subjects had both a higher arterial and venous lactate concentration. #Significantly different response at submaximal WRs in old subjects. *Significantly different response at maximal WR in old subjects.

Pulmonary ventilation and pulmonary VO₂. Pulmonary ventilation was similar in both the young and old subjects until the 99-W workload, at which point it was significantly elevated above that of the young subjects (Fig. 3A). However, at maximal exercise, pulmonary ventilation was significantly lower than that attained by the young group (Fig. 3A). Pulmonary VO₂ was only statistically different between the young and old groups at maximal exercise (Tables 1 and 2).

Capillary PO₂ and DO₂. Calculated capillary PO₂ at maximal exercise was not different between the young and old groups (young: 43 ± 2 mmHg and old: 42 ± 3 mmHg). However, the average DO₂ was reduced by ≈50% in the old subjects (12 ± 3 ml O₂·min⁻¹·mmHg⁻¹) compared with the young subjects (24 ± 2 ml O₂·min⁻¹·mmHg⁻¹; see Fig. 3).

DISCUSSION

The major finding of this research is that at relatively light submaximal cycling efforts (below ≈54 W or ≈55% of maximum effort for the old subjects), LBF was preserved in sedentary old subjects compared with similarly sedentary young subjects. However, as submaximal exercise intensity increased from 54 to 99 W, the LBF-to-WR relationship was significantly attenuated in the old subjects. Muscle VO₂ at the more taxing submaximal work level (99 W) was similar to the young subjects but was achieved in the old subjects by an elevated A-V O₂ difference. However, O₂ delivery at 99 W and maximal effort, VO₂ max and WRmax were significantly reduced compared with their younger counterparts. Despite the elevated O₂ extraction in the old subjects, the normoxic muscle DO₂ was reduced, indicative of either an O₂ transport limitation from blood to muscle cells or potentially a mitochondrial O₂ demand limitation. Therefore, it is likely that the limited perfusion of exercising muscle during moderate to heavy exercise in these old sedentary subjects was directly responsible for the lower WRmax and VO₂ max associated with the aging process. However, the reduced muscle DO₂ provides evidence that the diffusive component of O₂ transport may also play a role in attenuating the maximal exercise capacity of older people. Thus it is possible that if LBF were restored, the benefit may be attenuated by this apparent reduction in muscle DO₂.

Potential mechanisms for the attenuated LBF and LVC response. Older people often exhibit a reduction in muscle mass (13), which could help to explain a reduction in absolute LBF and LVC. This was not the case in the current subjects, where both young and old men had similar leg muscle volumes as assessed by the limited method of anthropometry (see METHODS).

Certainly, the finding that during incremental cycling exercise, both LBF and LVC become progressively compromised in older subjects, which could be explained by a failing CO. However, although maximal CO is clearly diminished (16, 21), it has most commonly been documented that the CO-to-VO₂ relationship during submaximal exercise is well maintained with advancing age (35, 48).

Thus it is more likely that a maldistribution of CO is responsible for the attenuated increase in perfusion to the exercising leg. Ho et al. (20) demonstrated that older men experience less visceral sympathetic vasoconstriction (spleen and kidneys) during exercise than younger men. In young healthy subjects, LBF and leg VO₂ can be reduced by competition from the respiratory muscles due to an increased work of breathing (17). In young healthy subjects, the work of breathing accounts for ~10% of pulmonary VO₂ at VO₂ max (1). Previously, we have documented that elderly chronic obstructive lung disease patients (65 ± 2 yr), whose work of breathing is doubled, improved their cycle WRmax from a reduction in respiratory muscle work by helium
It is tempting to recognize the similarity between the blood flow response (Fig. 1A), a variable that typically responds to absolute WR, and that of ventilation and arterial lactate (Fig. 3, A and B), responsive to relative WR. Perhaps the increased ventilation is indirectly modulating LBF via this blood flow steal phenomenon. However, pulmonary VO$_2$ at 99 W in the old subjects was not elevated compared with the young subjects, which would be expected if there was a significantly elevated cost of ventilation. Although the amount of work necessary for ventilation may be greater in the older subjects, the arterial PO$_2$ and SA$_{O_2}$ were maintained throughout the cycle exercise, suggesting normal lung function (Table 2). This concept of a maldistribution of CO is also sup-

breathing (45). Healthy older subjects fall somewhere in between these young healthy and old smoking populations, as lung compliance and airway resistance both increase with normal aging (8, 9) and exercise highlights these pulmonary deficiencies (24, 29), making them good candidates for a respiratory muscle “steal” from locomotor muscle.

Additionally, as illustrated in the current data, ventilation is coupled tightly to arterial blood lactate levels (Fig. 3, A and B), which change in response to relative exercise intensity. Hence, for a given absolute WR (e.g., 99 W), ventilation is significantly elevated in the old subjects compared with the young subjects (Fig. 3A), setting the stage for an exaggerated respiratory muscle ‘steal’ of blood flow from the locomotor muscles.

<table>
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<td>15 W</td>
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<td>30 W</td>
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<td>90 W</td>
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<td>Maximum</td>
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<table>
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<tr>
<th>Leg blood flow, l/min</th>
<th>1.3 ± 0.1</th>
<th>1.2 ± 0.2</th>
<th>4.1 ± 0.2</th>
<th>6.1 ± 0.3</th>
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<tr>
<td>A-V O$_2$, ml/dl</td>
<td>9.8 ± 0.5</td>
<td>10.6 ± 0.4</td>
<td>10.3 ± 0.6</td>
<td>12.9 ± 0.9</td>
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<tr>
<td>O$_2$ delivery, l/min</td>
<td>0.26 ± 0.01</td>
<td>0.34 ± 0.03</td>
<td>0.83 ± 0.05</td>
<td>1.26 ± 0.1</td>
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<tr>
<td>Pulmonary VO$_2$, l/min</td>
<td>0.68 ± 0.03</td>
<td>0.94 ± 0.05</td>
<td>1.50 ± 0.15</td>
<td>1.64 ± 0.02</td>
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<tr>
<td>Pulmonary Ve, l/min</td>
<td>23 ± 2</td>
<td>26 ± 1</td>
<td>41 ± 3</td>
<td>104 ± 2</td>
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<td>Arterial PO$_2$, Torr</td>
<td>107 ± 2</td>
<td>107 ± 3</td>
<td>106 ± 3</td>
<td>115 ± 3</td>
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<td>Venous PO$_2$, Torr</td>
<td>22 ± 1</td>
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<td>23 ± 1</td>
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<td>Cao$_2$, ml/dl</td>
<td>20.2 ± 0.2</td>
<td>19.9 ± 0.04</td>
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<td>20.7 ± 0.4</td>
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<tr>
<td>Cvo$_2$, ml/dl</td>
<td>10.2 ± 0.5</td>
<td>9.2 ± 0.4</td>
<td>9.9 ± 0.5</td>
<td>7.7 ± 0.5</td>
</tr>
<tr>
<td>Sa$_{O_2}$, %</td>
<td>98.7 ± 0.1</td>
<td>98.7 ± 0.1</td>
<td>98.5 ± 0.2</td>
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<tr>
<td>Hb, g/dl</td>
<td>36.3 ± 1.9</td>
<td>33.1 ± 1.5</td>
<td>35.2 ± 1.8</td>
<td>26.5 ± 1.8</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>95 ± 6</td>
<td>101 ± 5</td>
<td>132 ± 5</td>
<td>184 ± 5</td>
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</table>

Values are means ± SE; n = 9 young subjects and 9 old subjects. A-V, arterial-venous; Cao$_2$ and Cvo$_2$, arterial and venous O$_2$ content, respectively; Sa$_{O_2}$ and Sv$_{O_2}$, arterial and venous O$_2$ saturation, respectively. Maximal work rate was 193 W for younger subjects and 117 W for older subjects. *Significantly different response at maximal work rate in old subjects; †significantly different response at submaximal work rates in old subjects.

Table 2. Comparison of blood, heart rate, and pulmonary measurements for the old versus young subjects during cycle exercise
ported by the elegant work of Beere et al. (4), who demonstrated that the ratio of LBF to CO was significantly increased in older subjects as a consequence of exercise training, indicating a reversal of this maldistribution with regular exercise.

Alternatively, it is possible that a more local phenomenon such as age-related dysfunctional peripheral vasodilatation plays a role in the inability to increase LBF with increasing exercise intensity. This mechanism is, perhaps, mediated by the endothelium (7, 10, 50). In this scenario, a failure to reduce leg vascular resistance may limit the ability to increase LBF. Consequently, perfusion in the exercising limb is unable to keep up with the rising demand for O2 transport, and muscle metabolism becomes limited as a result.

Submaximal exercise and aging. Although our submaximal WRs of 15 and 30 W (13% and 28% of WRmax for the old subjects) appear to be minimal power outputs, they compare favorably in terms of the relative physical challenge performed by older active subjects in previous research (70 W or ~30% of WRmax (36)). Additionally, in practical terms, an average heart rate of 96 ± 7 beats/min (66% of the maximal heart rate) was recorded during the old group’s prescreening treadmill test at a reasonable walking speed of 1.7 ± 0.2 mph (zero grade), which equates to the same heart rate recorded at the 15-W cycle WR. Therefore, such exercise challenges (15 and 30 W) are reasonable models of “real life” physical exertion in a sedentary population.

Previously, it has been reported that LBF during submaximal cycle ergometry was substantially reduced in endurance-trained older men relative to their younger counterparts (4, 36, 55). However, these studies were, by design, focused on exercise-trained older subjects and physically active younger subjects with the goal of removing activity level as a confounding factor between age groups. Typically, even healthy aging is associated with a decrease in physical activity and subsequent changes in cardiovascular function (19, 38, 47), whereas the maintenance of endurance exercise in older subjects attenuates these modifications and results in an aerobic power of nearly twice that of sedentary individuals (11, 18, 34). Consequently, our approach was avoid the issue of exercise-induced adaptations by matching sedentary young with sedentary old subjects.

The sedentary young and old subjects in this study had the same LBFs at the lower WRs, but demonstrated a similarly elevated O2 extraction response to that observed in a previous study of endurance-trained older subjects (36). Therefore, the sedentary subjects’ acute response appears somewhat inefficient, in terms of maintaining an elevated A-V O2 difference while being apparently able to preserve LBF. Although leg VO2 was not statistically elevated compared with the young subjects, there was a tendency for this to be the case (P = 0.1). It should be recognized that small reciprocal changes within the Fick principle equation [VO2 = Q(CaO2 – CvO2), where Q is blood flow and CvO2 is venous O2 content] may account for the statistical significance of the A-V O2 difference, which, when combined with a similar LBF response, results in similar leg VO2 values. However, there is certainly a suggestion of either a tendency for a lower LBF or a metabolic inefficiency in the old subjects at these submaximal WRs.

The change in the A-V O2 difference across progressive submaximal levels of cycle exercise was different between the young and old groups (Fig. 1B). As noted, the old subjects began the exercise with an already elevated O2 extraction compared with the young group and maintained this A-V O2 difference at a relatively

Fig. 3. Relationship between cycle WR and pulmonary ventilation (A), arterial lactate concentration (B), and net venous lactate outflow (C) in young and old subjects. #Significantly different response at submaximal WRs in old subjects; *significantly different response at maximal WR in old subjects.
constant level throughout the incremental changes in WR. In fact, neither group of subjects demonstrated the hyperbolic elevation from submaximal to maximal effort that is typically seen in physically fit young subjects (26, 44). Even the young sedentary subjects demonstrated only a modest increase in the A-V O2 difference (increasing the WR from 16% to 80% resulted in a 10.6–11.5 ml/dl A-V O2 increase). Whereas the A-V O2 difference in the exercise-trained subjects studied by Knight et al. (26) increased far more quickly (a 20–80% increase in WR resulted in a 12.6–15.7 ml/dl A-V O2 increase). It is also interesting to note that the A-V O2 difference in the aged endurance-trained subjects measured by Proctor et al. (36) was also elevated at the lower WR levels, but rose in a similar fashion to their young exercise-trained control group. Again, this highlights the different physiological responses to exercise between both aging and activity level.

It is not surprising that at the third submaximal level of 99 W, where the old subjects are working at ~84% of their maximal effort, leg arterial and venous lactate levels are significantly higher than the young subjects, who are working at only ~47% of their maximum (Fig. 3, A and B). However, it is clear that this elevation in arterial lactate level is not a simple consequence of net venous lactate outflow from the working legs, as net venous lactate outflow is equal or even lower in the old group. It is possible that other hard-working muscle groups (i.e., respiratory muscles) in the old subjects may have also contributed to the elevated arterial lactate levels. It is interesting to note that in both groups, the elevated arterial lactate levels may contribute to an attenuated net venous lactate outflow at levels of work approaching maximum, an observation that has been documented previously during small muscle mass exercise when the work of other muscle groups was superimposed (42) (Fig. 3, B and C).

Maximal exercise and aging. Changes in vascular compliance with age (15, 51) have been associated with an elevation in blood pressure and a reduction in maximal peripheral blood flow, peak heart rate, and ultimately VO2 max (32, 50). In the present study, the attenuated WR max and LBF in the old subjects was accompanied by an exaggerated rise in MABP (Fig. 2A). This resulted in an attenuated LVC in the old subjects as a consequence of a reduced mitochondrial capacity (6).

A commonly used method of assessing the interplay between the convective and diffusive determinants of VO2 max in humans is to perform multiple maximal exercise tests while breathing varied levels of inspired O2 (6, 39, 40, 54). If a subject or group of subject’s VO2-to-capillary PO2 relationship varies proportionately with this treatment, their exercise capacity is labeled as limited by O2 supply and the slope of this relationship describes DO2. Conversely, if their VO2 max is invariant with variations in capillary PO2, they are deemed to be limited by mitochondrial capacity and a single value for DO2 can still be calculated for each condition (39, 54). Although the current data set does not provide repeated capillary PO2 values resulting from variations in inspired O2, recognizing the inherent limitations of calculating DO2 in a single condition (normoxia), this type of evaluation can certainly offer some insight into the limitations experienced by the young and old subjects at maximal exercise (Fig. 4). From this analysis, the old subjects appear to have a significantly diminished DO2 compared with their younger counterparts, who in turn have a much diminished DO2 compared with active young subjects (Fig. 4). Thus these analyses imply that an attenuated DO2 may play a significant role in diminishing O2 transport and subsequently the maximal metabolic capacity with inactivity that is compounded by the aging process. It should again be indicated that the current analysis cannot distinguish whether the reduced DO2 is simply a consequence of altered O2 transport or a metabolic limitation; this will require further investigation.

Bearing in mind that the old subjects exhibited a consistently elevated O2 extraction, these inferences about a diminished DO2 may at first seem counterintuitive. However, it should be recognized that O2 extraction (e) is not a pure reflection of factors that
determine “peripheral” O2 transport (DO2) as it incorporates other “central” factors (namely, blood flow (Q) and the shape of the Hb-O2 dissociation curve (β); O2 extraction = 1 – e^{-DO2/(6Q)} (33)). Therefore, it is important that differences in O2 extraction (e.g., elevated O2 extraction in the old subjects) are not wrongly interpreted as an indication of either O2 transport or metabolic capacity. In this scenario, because the relationship between VO2 and WR was not different between the young and old subjects, the elevated O2 extraction in the old subjects at maximal exercise was simply a consequence of the attenuated LBF and not a reflection of greater metabolic capacity or O2 transport from blood to cells.

In summary, these data clearly indicate a limited vascular conductance within the exercising leg of older subjects that is apparent at moderate to heavy exercise. These data, coupled with previous work in the literature, suggest a possible mechanism could be the maldistribution of what would otherwise appear to be an appropriate CO. It is likely that blood is being directed toward respiratory muscles and other viscera instead of toward the active muscle mass. This limited LBF and O2 delivery may account for some of the diminished exercise capacity associated aging; however, other variables such as the reduced DO2 (which at present may be a consequence of either limitations to O2 conductance from blood to cells or a mitochondrial limitation) reported in this study may also play an important role.

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