VASCULAR AND METABOLIC RESPONSE TO CYCLE EXERCISE IN SEDENTARY HUMANS: THE EFFECT OF AGE

Authors: J.G. Poole
L. Lawrenson
J. Kim
C. Brown
R.S. Richardson

Institution: Department of Medicine,
University of California San Diego,
La Jolla, CA 92093.

Mailing address:
Russell S. Richardson
Department of Medicine
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0623

Telephone: (858) 534-9841
Fax: (858) 534-4812
e-mail: rrichardson@ucsd.edu

Running Head: Cycle exercise and aging
ABSTRACT:
We measured leg blood flow (LBF), drew arterial-venous (a-v) blood samples, and calculated muscle O₂ consumption (VO₂), during incremental cycle ergometry exercise (15, 30, 99 W, and maximal effort (WRmax)), in 9 sedentary younger (Y, 20 ± 1 yrs) and 9 sedentary older (O, 70 ± 2 yrs) males. LBF was preserved in the older subjects at 15 and 30 Watts. However, at 99 W and at maximal effort, leg vascular conductance was attenuated because of a reduced LBF (Y= 4.1 ±0.2; O= 3.1 ± 0.3l/min) and an elevated mean arterial blood pressure (Y= 112 ± 3; O= 132 ± 3 mmHg) in the older subjects. Leg a-v O₂ difference changed little with increasing WR in the older group, but was elevated compared to the younger subjects. Muscle VO₂max and cycle WRmax were significantly lower in the older subjects (Y= 0.8 ± 0.05 l/min, 193 ± 7 W; O=0.5 ± 0.03 l/min, 117 ± 10 W). The submaximally unchanged and maximally reduced cardiac output associated with aging coupled with its potential maldistiribution are candidates for the limited LBF during moderate to heavy exercise in older sedentary subjects.

Key Words: VO₂max, vascular conductance, skeletal muscle, aging.
INTRODUCTION:

Although regular physical activity has been demonstrated to be critical for the promotion of normal healthy function as people age (5), persons over 50 years of age represent the most sedentary segment of the adult population (49). This trend toward inactivity is even more apparent in people 70 years 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, 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 yrs). 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 when compared to 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 WR’s when compared to younger subjects (36, 55). However, the cardiac output (CO) to VO2 relationship appears to be well preserved in older 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 cardiac output) 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 has 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 older sedentary subjects. Our primary hypotheses were that the metabolic cost of work as measured by leg muscle VO$_2$ would be similar in both groups, but that this would be achieved by a lower submaximal LBF and elevated a-v O$_2$ difference in the older subjects. Ultimately, this limited exercise LBF and the resulting attenuation of O$_2$ delivery would translate into a significantly reduced WR$_{\text{max}}$ and muscle VO$_{2\text{max}}$ in the older subjects.
METHODS:

Subjects: Nine healthy sedentary young and 9 healthy sedentary older 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 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 the 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 weeks before the invasive blood flow study to screen for cardiovascular disease. All subjects performed a preliminary graded cycle ergometer exercise test to determine pulmonary VO$_{2\text{max}}$.

Exercise Protocol, Preliminary Screening and Familiarization: All exercise was performed on an electronically braked cycle ergometer (Lode Excalibur Sport, Quinton Instruments Inc. Groningen, The Netherlands) and was restricted to a seated position. Prior to 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 following the catheterization procedures, subjects completed one graded cycle ergometer exercise test to maximum in room air. During this test, subjects maintained the predetermined work rates for 2-3 minutes, after which the work rate was incremented. The subjects continued until they were unable to maintain the minimum rpm
necessary for the ergometer to maintain a constant work rate for the entire work level. Additional
criteria such as an RER > 1.1 and the achievement of age predicted maximum heart rate were
used to verify that a true maximum effort was achieved. Comparisons between the young and
older subjects were made at the absolute work rates of 15W, 30W, 99W, 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 PO2, PCO2, pH, and arterial and venous O2
saturation (SaO2)), 2) femoral venous blood flow was measured. This series of events was then
repeated to allow duplicate measurements. Pulmonary Ve, VO2, VCO2, 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 pneumotachograph #3 (Hans-Rudolph, Kansas City, Missouri). Heart rate, arterial blood
pressure, and venous blood pressure were recorded continuously during exercise.

Leg blood flow, heart rate, and 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, Physitemp Instruments, Clifton, NJ) were inserted
using sterile technique as previously reported (14, 42, 44). LBF was determined by the constant
infusion thermodilution technique, originally described by Andersen & Saltin (3, 14, 44).
Briefly, both venous and infusate temperatures were measured continuously during saline
infusion (15-20s) 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 System, Santa
Barbara, CA) which enabled the real-time observation of each variable. LBF values in this study
represent the average of 2 measurements made between minutes 2-3 of each WR, i.e. at a time when steady-state was assumed to have occurred at all WR’s 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 heart level by a pressure transducer (Baxter, PX-MK099). 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, and blood O2 saturation were determined spectrophotometrically (IL-682 CO-oximeter Clayton, NC). Hematocrit, PO2, PCO2, 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 YSI 2300 Stat Plus (Yellow Springs, OH).

Blood O2 content (ml/dl) was calculated as (1.39 mlO2/g x [Hb] g/dl x O2 saturation) + (0.003 ml/dl x PO2 mmHg). Leg VO2 was calculated as the product of the mean LBF and the difference in the arterial-venous O2 concentration (a-v O2 difference). Leg O2 delivery was calculated as the product of LBF and femoral arterial oxygen content (CaO2). Net venous lactate outflow of was calculated as the product of LBF and the difference in the venous-arterial lactate concentration.

Thigh Volume Measurement: Thigh muscle 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 older groups. It should also be recognized that this method does not assess differences in intramuscular fat.

**Muscle $O_2$ transport conductance and mean capillary $PO_2$ calculations:** Muscle $O_2$ transport conductance ($DO_2$) and mean capillary $PO_2$ were calculated at 100% of maximum work rate, as described previously (53). Briefly, a numerical integration procedure is used to determine that value of $DO_2$ which is assumed constant along the capillary. This value of $DO_2$ is that conductance of $O_2$ (i.e., in ml/min/mmHg) which yields the measured femoral muscle venous $PO_2$. Additional explicit assumptions of this calculation are: 1) intracellular $PO_2$ is negligibly small at $VO_{2\text{max}}$ (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/$VO_2$ heterogeneity, and perfusional or diffusional shunt are considered negligible. To the extent that these phenomena contribute $O_2$ to femoral venous blood, the parameter $DO_2$ is a conductance coefficient that expresses the diffusing capacity that would be required to achieve the measured $VO_{2\text{max}}$, assuming only diffusion limitation. Although we are working toward the goal of quantifying the contribution of heterogeneity in perfusion/$VO_2$ to the residual $O_2$ in venous effluent blood (41), this assumption cannot be avoided until we can characterize perfusion/$VO_2$ heterogeneity and shunt within exercising human skeletal muscle. Mean capillary $PO_2$ is the numerical average of all computed $PO_2$ values, equally spaced in time, along the capillary from the arterial to the venous end.

**Statistical Analysis:** Analysis of variance was used to determine differences within and between groups at submaximal work rates. 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 (Graph Pad, San Diego, CA, USA). Significance for all tests was established at an alpha level of
$P < 0.05$, and all data are expressed as mean ± SE.
RESULTS:

**Physical characteristics, activity level, and thigh Volume:** Matching of subjects based upon 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 l) and older group (5.9 ± 0.2 l). Thus when converted to muscle mass as suggested by Jones and Pearson (25) both groups were estimated to have approximately 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 O\(_2\) consumption:** 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 work rates translating to 13, 26, and 84% in the older and 8, 16, and 47% of maximum in the younger group, respectively. The slope of leg VO\(_2\) to work rate relationship over the complete work rate range was similar between the two groups (old = 3.7 ± 0.4 ml/watt; young = 3.9 ± 0.2 ml/watt, Figure 1C). Leg VO\(_{2\text{max}}\) was significantly higher in the younger subjects, as was maximal work rate (Figure 1C).

**Leg blood flow, a-v O\(_2\) difference, and leg vascular conductance:** It should be noted that LBF is presented, as measured, from only one leg. The slope of the LBF to work rate relationship, was significantly different between the young and older subjects (old = 22 ± 1 ml/watt and young = 28 ± 2 ml/watt), but the intercept of this relationship was not different. Consequently, LBF was similar between groups at the lower submaximal work rates (15 and 30W Figure 1A), while at
99W and WR\textsubscript{max} the older subjects demonstrated an attenuated LBF (Figure 1A). A-v O\textsubscript{2} difference rose only modestly with increasing work level in both groups, but this was more notable in the older group who began with a higher O\textsubscript{2} extraction (old rose from 14.4 ± 0.8 to 15.3 ± 0.8 ml/dl; young rose from 9.8 ± 0.5 to 12.9 ± 0.9 ml/dl, Figure 1B). At each comparable absolute work rate and WR\textsubscript{max}, leg a-v O\textsubscript{2} difference was significantly higher in the older group (Figure 1B). In addition to the reduced LBF in the older group, MABP was significantly higher in the older subjects at 99W and WR\textsubscript{max} compared to their younger counterparts (Figure 2A). Subsequently, LVC was significantly attenuated at these higher workloads in the older subjects (Figure 2B).

**Major blood related variables:** O\textsubscript{2} delivery to the leg muscles was similar between the two age groups at 15 and 30 Watts, but at both 99 watts and WR\textsubscript{max} O\textsubscript{2} delivery was significantly reduced in the older subjects. Arterial PO\textsubscript{2}, O\textsubscript{2} saturation, and CaO\textsubscript{2} were similar and were maintained across all WR’s within normal levels in both age groups (Table 2) indicating that the reduced O\textsubscript{2} delivery in the older subjects was a consequence of LBF. However, femoral venous O\textsubscript{2} saturation and O\textsubscript{2} content at each power output were significantly lower in the older 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 30W, but differed significantly at 99W with the older subjects demonstrating elevated arterial and venous lactate concentrations (Figure 3B). At WR\textsubscript{max}, 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 work rate in both groups, however at WR\textsubscript{max} the older subjects had an attenuated net
lactate release (Figure 3C). Heart rate was not different between the young and old, until WR_{max} when the maximum heart rate of the older subjects was attenuated by approximately 40 b/min.

**Pulmonary ventilation and pulmonary VO_{2}:** Pulmonary ventilation was similar in both the young and older subjects until the 99 Watt workload at which point it was significantly elevated above that of the younger subjects (Figure 3 A). However, at maximal exercise, pulmonary ventilation was significantly lower than that attained by the younger group (Figure 3 A). Pulmonary VO_{2} was only statistically different between the young and older group at maximal exercise (Table 1 and 2).

**PcapO_{2} and DO_{2}:** Calculated PcapO_{2} at maximal exercise was not different between the young and the older group (young = 43 ± 2 mmHg; Old = 42 ± 3 mmHg). However, the average DO_{2} was reduced by ≈ 50% in the older subjects (12 ± 3 ml O_{2} /min/mmHg) compared to the younger subjects (24 ± 2 ml O_{2} /min/mmHg).
DISCUSSION:

The major finding of this research is that at relatively light submaximal cycling efforts (below \( \approx 54 \) Watts or \( \approx 55\% \) of maximum effort for the older subjects) LBF was preserved in sedentary older subjects when compared to similarly sedentary younger subjects. However, as submaximal exercise intensity increased from 54 to 99 Watts, the LBF to WR relationship was significantly attenuated in the older subjects. Muscle VO\(_2\) at the more taxing submaximal work level (99W) was similar to the younger subjects, but was achieved in the older subjects by an elevated a-v O\(_2\) difference. However, O\(_2\) delivery at 99 watts and maximal effort, VO\(_{2\text{max}}\), and WR\(_{\text{max}}\) were significantly reduced in comparison to their younger counterparts. Despite the elevated O\(_2\) extraction in the older subjects, the normoxic muscle DO\(_2\) was reduced, indicative of either an O\(_2\) transport limitation from blood to muscle cell or potentially a mitochondrial O\(_2\) demand limitation. Therefore it is likely that the limited perfusion of exercising muscle during moderate to heavy exercise in these older sedentary subjects was directly responsible for the lower WR\(_{\text{max}}\) and VO\(_{2\text{max}}\) associated with the aging process. However, the reduced muscle DO\(_2\) provides evidence that the diffusive component of O\(_2\) 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 DO\(_2\).

Potential mechanisms for the attenuated LBF and LVC response: Older people often exhibit a reduction in muscle mass (13) that could help to explain a reduction in absolute LBF and LVC. This was not the case in the current subjects, where both young and older 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 could be explained by a failing cardiac output. However, although maximal cardiac output is clearly diminished (16, 21), it has most commonly been documented that the cardiac output to VO₂ relationship during submaximal exercise is well maintained with advancing age (35, 48).

Thus, it is more likely that a maldistribution of cardiac output 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 approximately 10% of pulmonary VO₂ at VO₂max (1). Previously, we have documented that elderly COPD patients (65±2 yrs), whose work of breathing is doubled, improved their cycle WRmax from a reduction in respiratory muscle work by helium breathing (45). Healthy older subjects fall somewhere in between these young healthy and older 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 (Figure 3A 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 older subjects when compared with the young subjects (Figure 3A), setting the stage for an exaggerated respiratory muscle steal of blood flow from the locomotor muscles.
It is tempting to recognize the similarity between the blood flow response (Figure 1A), a variable that typically responds to absolute WR, and that of ventilation and arterial lactate (Figure 3A 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 99W in the older subjects was not elevated in comparison to the younger 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 P$_a$O$_2$ and S$_a$O$_2$ were maintained throughout the cycle exercise suggesting normal lung function (Table 2). This concept of a maldistribution of cardiac output is also supported by the elegant work of Beere et al. (4) who demonstrated that the ratio of LBF to cardiac output 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 O$_2$ transport and muscle metabolism becomes limited as a result.

Submaximal exercise and aging: Although our submaximal work rates of 15 and 30 W (13 and 28% of WR$_{max}$ for the aged 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 (70W or ~30% of WR$_{max}$ (36)). Additionally, in practical terms, an average HR of 96 ± 7 b/min (66% of HR$_{max}$) was recorded during the older group’s pre-screening
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 15W cycle WR. Therefore, such exercise challenges (15 and 30W) 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 upon 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), while 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 older subjects in this study had the same LBFs at the lower WR’s, but demonstrated a similarly elevated O₂ extraction response to that observed in a previous study of endurance trained aged 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 in comparison to the younger 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 – CₐO₂), may account for the statistical significance in of 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 older subjects at these submaximal WR’s.

The change in a-v O₂ difference across progressive submaximal levels of cycle exercise was different between the young and older group (1B). As noted, the older subjects began the exercise with an already elevated O₂ extraction compared to the younger group and maintained this a-v O₂ difference at a relatively constant level throughout the incremental changes in work rate. 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 younger sedentary subjects demonstrated only a modest increase in a-v O₂ difference (increasing WR from 16 to 80% resulted in a 10.6 to 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% to 80% increase in WR resulted in a 12.6 to 15.7 ml/dl a-vO₂ 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 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 99W, where the aged subjects are working at ~84% of their maximal effort, leg arterial and venous lactate levels are significantly higher than the younger subjects who are working at only ~47% of their maximum (Figure 3A and 3B. 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 older 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. 3B and 3C).

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 VO₂max (32, 50). In the present study the attenuated WRₘₐₓ and LBF in the older subjects was accompanied by an exaggerated rise in MABP (Fig. 2A). This resulted in an attenuated LVC in the older subjects at maximal exercise, consistent with age associated changes in the vasculature. As already eluded to, another potential explanation is limited sympathetic vasoconstriction of blood flow to other regions of the body (e.g. intestinal viscera and respiratory muscles) during exercise, which could attenuate LBF (17, 20). Whatever the mechanism, the result was a severely reduced O₂ delivery to the leg muscles of the older subjects. A reduction in convective O₂ transport has a clear negative impact on muscle VO₂max (40), although it should be recognized that the sensitivity to such changes may be somewhat attenuated in sedentary 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 VO₂max 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 PcapO₂ 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 VO₂max is invariant with variations in PcapO₂ they are deemed to be limited by mitochondrial
capacity and a single value for DO\textsubscript{2} can still be calculated for each condition (39, 54). Although the current data set does not provide repeated PcapO\textsubscript{2} values resulting from variations in inspired O\textsubscript{2}, recognizing the inherent limitations of calculating DO\textsubscript{2} in a single condition (normoxia), this type of evaluation can certainly offer some insight into the limitations experienced by the young and older subjects at maximal exercise (Figure 4). From this analysis the older subjects appear to have a significantly diminished DO\textsubscript{2} in comparison to their younger counterparts who in turn have a much diminished DO\textsubscript{2} in comparison to active young subjects (Figure 4). Thus, these analyses imply that an attenuated DO\textsubscript{2} may play a significant role in diminishing O\textsubscript{2} transport and subsequently maximal metabolic capacity with inactivity that is compounded by the aging process. It should again be indicated that the current analysis can not distinguish whether the reduced DO\textsubscript{2} is simply a consequence of altered O\textsubscript{2} transport or a metabolic limitation, this will require further investigation.

Bearing in mind that the older subjects exhibited a consistently elevated O\textsubscript{2} extraction, these inferences about a diminished DO\textsubscript{2} may at first seem counter intuitive. However it should be recognized that O\textsubscript{2} extraction (e) is not a pure reflection of factors that determine “peripheral” O\textsubscript{2} transport (DO\textsubscript{2}) as it incorporates other “central” factors (namely blood flow (Q) and the shape of the Hb-O\textsubscript{2} dissociation curve (β) (O\textsubscript{2} extraction = 1-\text{e}^{-\text{DO}_{2}/(\beta \cdot Q)}), (33)). Therefore it is important that differences in O\textsubscript{2} extraction (e.g. elevated O\textsubscript{2} extraction in the older subjects) are not wrongly interpreted as an indication of either O\textsubscript{2} transport or metabolic capacity. In this scenario, as the relationship between VO\textsubscript{2} and WR was not different between the young and old, the elevated O\textsubscript{2} extraction in the older subjects at maximal exercise was simply a consequence of the attenuated LBF and not a reflection of greater metabolic capacity or O\textsubscript{2} transport from blood to cell.
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 cardiac output. 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 O$_2$ delivery may account for some of the diminished exercise capacity associated with aging, however other variables such as the reduced DO$_2$ (which at present may be a consequence of either limitations to O$_2$ conductance from blood to cell or a mitochondrial limitation) reported in this study may also play an important role.
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FIGURE AND TABLE LEGENDS:

Table 1: Subject characteristics. Values are given as means ± SE for 9 older subjects and 9 younger subjects. VO2max, maximum pulmonary oxygen consumption; * significantly different from young subjects.

Table 2. Comparison of blood, heart rate and pulmonary measurements for the older vs. younger subjects. Values are given as means ± SE for 9 older subjects and 9 younger subjects. # significantly different response at submaximal work rates in the older subjects. * significantly different response at maximal work in the older subjects.

Figure 1. The relationship between cycle work rate and leg blood flow (A), arterial-venous oxygen difference (B), and leg oxygen consumption (C) in the young and older subjects. # significantly different response at submaximal work rates in the older subjects. * significantly different response at maximal work in the older subjects.

Figure 2. The relationship between cycle work rate and mean arterial blood pressure (A), LVC (B), and LVR (C) in the young and older subjects. # significantly different response at submaximal work rates in the older subjects. * significantly different response at maximal work in the older subjects.

Figure 3. The relationship between cycle work rate and pulmonary ventilation (A), arterial lactate concentration (B), and net venous lactate outflow (C) in the young and older subjects.
# significantly different response at submaximal work rates in the older subjects. * significantly
different response at maximal work in the older subjects.

Figure 4. Evidence of proportionally attenuated maximal oxygen consumption (VO2) and
peripheral muscle O2 diffusing capacity (DO2) with age and inactivity. The additional young
exercise trained data (46) are included to illustrate that although both VO2 and DO2 are greatly
attenuated in the old compared with their sedentary young counterparts, there is also a sharp
contrast between the sedentary young subjects and their exercise trained counterparts. *
Significantly different from young sedentary subjects.
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Figure 1.
Figure 2.
Figure 3.
Figure 4.


