Alveolar oxygen uptake and femoral artery blood flow dynamics in upright and supine leg exercise in humans

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MacDonald, Maureen J., J. Kevin Shoemaker, Michael E. Tschakovsky, and Richard L. Hughson. Alveolar oxygen uptake and femoral artery blood flow dynamics in upright and supine leg exercise in humans. J. Appl. Physiol. 85(5): 1622–1628, 1998.—We tested the hypothesis that the slower increase in alveolar oxygen uptake (V˙O2) at the onset of supine, compared with upright, exercise would be accompanied by a slower rate of increase in leg blood flow (LBF). Seven healthy subjects performed transitions from rest to 40-W knee extension exercise in the upright and supine positions. LBF was measured continuously with pulsed and echo Doppler methods, and V˙O2 was measured by breath by breath at the mouth. At rest, a smaller diameter of the femoral artery in the supine position (P < 0.05) was compensated by a greater mean blood flow velocity (MBV) (P < 0.05) so that LBF was not different in the two positions. At the end of 6 min of exercise, femoral artery diameter was larger in the upright position and there were no differences in V˙O2, MBV, or LBF between upright and supine positions. The rates of increase of V˙O2 and LBF in the transition between rest and 40 W exercise, as evaluated by the mean response time (time to 63% of the increase), were slower in the supine [V˙O2 = 39.7 ± 3.8 (SE) s, LBF = 27.6 ± 3.9 s] than in the upright positions [V˙O2 = 29.3 ± 3.0 s, LBF = 17.3 ± 4.0 s; P < 0.05]. These data support our hypothesis that slower increases in alveolar V˙O2 at the onset of exercise in the supine position are accompanied by a slower increase in LBF.

kicking exercise; Doppler velocimetry; echo Doppler; leg blood flow

AT THE ONSET OF SUBMAXIMAL EXERCISE in the supine position, the rate of increase in alveolar oxygen uptake (V˙O2) is slower than when the same exercise work rate is completed in the upright position (1, 2, 7, 11). It has been speculated that this slower rate of increase in V˙O2 might be due to a slower rate of increase in the supply of O2 to the working muscles (3, 7). Blood flow is one component of oxygen delivery that is altered at the onset of exercise and may be an important modulator for oxidative phosphorylation in this situation (6). Information on the dynamics of the muscle blood flow response at the onset of large-muscle-mass exercise is lacking.

Recently, it has become possible to monitor the changes in skeletal muscle blood flow in the transition from rest to exercise and to determine the relationship between O2 delivery and O2 utilization (23, 24). Grassi et al. (5) used thermodilution techniques to monitor blood flow in combination with direct femoral vein samples to determine O2 extraction and found that the time courses of increases in muscle blood flow and muscle V˙O2 were similar during upright cycle ergometry. Hughson et al. (9), who used Doppler ultrasound technology, observed a close correlation between the rate of increase in blood flow to the forearm muscles and the muscle V˙O2. They further noted that both flow and muscle V˙O2 adapted slower when the exercising forearm was above, rather than below, the heart.

The rationale for this study was to incorporate manipulations in perfusion pressure in a leg exercise model to examine the effect of leg blood flow delivery at the onset of large-muscle-mass exercise. To study this, we have used combined pulsed and echo Doppler methods to continuously quantify the femoral artery blood flow in the transition from rest to submaximal knee extension and flexion exercise in both the supine and the upright positions. We tested the hypothesis that the slower rate of increase in alveolar V˙O2 at the onset of supine exercise would be accompanied by slower increases in leg blood flow (LBF) in the same posture.

METHODS

The experiments were carried out on seven healthy young volunteers (5 men and 2 women, age 27 ± 5, height 180 ± 5 cm, and weight 75 ± 9 kg). After reading a description of the methods and possible risks, each signed a consent form approved by the Office of Human Research at the University of Waterloo. Each subject practiced the exercise to become familiar with the activity so that high-quality cardiorespiratory and Doppler signals could be obtained in both positions at rest and during exercise. This was important because complete relaxation of knee extensors during knee flexion was necessary to achieve optimal blood flow between extension periods and to reduce motion artifact in the Doppler signals. On the data-collection day, subjects reported to the laboratory at least 2 h after their last meal. They were asked to avoid caffeine and alcohol ingestion and strenuous exercise for 24 h before the test.

Experimental design. Testing was performed on an electrically braked knee extension and flexion ergometer. In this study, the ergometer was configured so that subjects worked against a resistance on both extension and flexion and maintained a knee extension and flexion cadence of ~44 cycles per leg per minute at a work rate of 40 W. The ergometer had an adjustable backrest that allowed the subjects to sit with a hip angle of 120° during the upright tests, whereas the hips were completely extended (180°) during the supine tests. Aside from the hip angle, the exercise task was identical in both positions. The exercise intensity of 40 W was selected because it provided a signal (V˙O2 and LBF) of sufficient amplitude that curve fitting to the time course could be accomplished with some confidence.

The test protocol consisted of at least 5 min of baseline rest. To begin a trial, the flywheel of the ergometer was hand cranked by an assistant and the subjects were issued a verbal command to start 6 min of exercise at 40 W. Each subject performed two trials in each posture, separated by at least 15–20 min of rest. The order of postures was assigned randomly.
Data acquisition. Breath-by-breath ventilation and gas exchange were measured with a computerized system (First Breath, St. Agatha, ON, Canada). Fractional concentrations of O₂, CO₂, and N₂ were measured with a mass spectrometer (model MGA-1100, Marquette Electronics, Milwaukee, WI), and inspired and expired volumes were measured with a volume turbine (VMM-110, Alpha Technologies, Laguna Beach, CA). Calibration of the mass spectrometer was performed before each test by using two gas tanks of known concentration. Volume was calibrated by manually pumping a 3-liter syringe at a flow rate similar to that of respiration during the exercise test. VO₂ was corrected on a breath-by-breath basis for changes in lung gas stores due to altered lung volume or alveolar composition, as described previously (8). Matching of fractional gas concentrations with the appropriate volume was done by accounting for the sum of the transport lag plus the instrument response time.

LBF to the exercising legs was obtained with combined pulsed and echo Doppler ultrasound to measure mean blood velocity (MBV) and femoral artery diameter, respectively, from a site 2–3 cm distal to the inguinal ligament. MBV and diameter measured at this site do not reflect MBV and diameter at the level of the resistance vessels in the exercising muscles. However, LBF calculated from femoral MBV and diameter reflects total LBF. Blood velocity was obtained on a beat-by-beat basis from the left leg with the pulsed Doppler system (model 500V, Multigon Industries, Mt. Vernon, NY) by using a flat 4-MHz probe with a fixed angle of insonation of 45°. The spectrum of audio-range signals reflected from the moving blood cells was processed online by a Doppler signal processor to yield instantaneous MBV (16). The velocity signal was recorded at 100 Hz on a computer system along with the electrocardiograph so that the data could be analyzed beat by beat. Calibration signals in the Doppler-shift frequency range were generated from the Doppler signal processor. A handheld linear-array 7.5-MHz probe was used to obtain B-mode echo images of the right femoral artery by using a medical diagnostic ultrasound system (model SSH140A, Toshiba, Tochigi-Ken, Japan). The images of the artery were recorded on VHS videotape and analyzed for artery diameter with on-screen calipers. Vessel diameter was measured three times during rest, each 10 s during the first minute of exercise, and then at 1-min intervals to the end of exercise. The diameter data were fit with a linear or exponential regression to obtain an average response and reduce random error. Mean LBF was calculated on a beat-by-beat basis by multiplying the MBV with the estimated diameter from the regression equation for each time point.

Mean arterial pressure was measured with a pneumatic finger cuff (Ohmeda 2300, Finapres, Englewood, CO). The hand was placed at the level of the femoral artery to give an estimate of perfusion pressure.

Kinetic analysis. Breath-by-breath values for VO₂ were linearly interpolated between breaths to give values at 1-s intervals. The time course data for VO₂ and LBF collected from both trials in each condition were ensemble averaged to produce a single data set for each variable, for each subject, in each test condition. The time course of changes in VO₂ and LBF were analyzed by fitting an exponential curve to the average results of the trials. A two-component exponential model was fit to the data by using a least squares procedure. As previously described (7), the model had a baseline component (G₀), two amplitude terms (G₁ and G₂), two time constants (τ₁ and τ₂), and two time delays (TD₁ and TD₂):
The MRT of the LBF response was faster than that of the \( \dot{V}O_2 \) in both upright and supine positions (Table 2). The similar temporal responses of the slower LBF and the slower \( \dot{V}O_2 \) were evident in the supine position (Fig. 3).

**DISCUSSION**

The primary finding of this study was that both LBF and alveolar \( \dot{V}O_2 \) increased more slowly at the onset of exercise in the supine compared with the upright posture. The time course of change, given by the MRT, was 35% slower for \( \dot{V}O_2 \) and 60% slower for LBF in supine exercise compared with that for the same exercise performed in the upright position. These data suggest that \( O_2 \) supply at the onset of exercise might alter metabolic control and limit the rate of increase in muscle \( \dot{V}O_2 \). Thus these data support our hypothesis that, in the supine position, the slower rate of increase in alveolar \( \dot{V}O_2 \) observed frequently at the onset of exercise (1, 2, 7, 11, 12) was a consequence of a delayed adaptation in LBF.

The exercise model. Exercise required contractions of both the knee extensor and flexor muscles of both legs.
This is different from the knee-extension-only exercise employed by other researchers (18, 19, 21). We use this mode of exercise to involve a relatively large muscle mass while focusing the activity within muscles served by the femoral artery. There is very little, or no, involvement of muscles of the hips or above in both the upright and supine positions, and there was no difference in the work done against gravity. Although it is possible that slightly different recruitment of muscles in the two postures might have accounted for the differences in LBF and \( \dot{V}O_2 \) kinetics, we do not believe this to be the case, because no difference was observed in the steady-state metabolic cost. Rather, the legs were exercised in exactly the same manner in both postures, and the discussion is based on a constant metabolic demand in both the transition and steady state in the two different body positions.

The work rate was clearly of light to moderate intensity for all subjects. The heart rate response in the upright position showed a slight overshoot in the first seconds after the onset of exercise (Fig. 1), and, for both upright and supine positions, exercise heart rate was only 82–86 beats/min. Furthermore, the alveolar \( \dot{V}O_2 \) and LBF had MRT values of <40 s, even in supine exercise, indicating that the steady state was achieved in <4 min, in all tests. Richardson et al. (19, 21) have shown that the peak work rate for single-leg, knee-extension-only exercise was in excess of 100 W in trained cyclists. Our subjects were not trained, but they used flexor and extensor muscles of both legs during exercise at 40 W. Further studies in our laboratory have confirmed that 40 W represents only about one-third of the peak work rate reached in incremental exercise on this ergometer (150 W) in typical female and male subjects (unpublished observations).

Doppler blood flow measurements have only recently been applied to the study of blood flow during quadriceps muscle exercise (18, 23, 28). In a recent comparison between Doppler and the thermodilution techniques during one-leg knee-extension exercise, similar blood flow values were observed with the two methods across a wide range of work rates (18).

Steady-state exercise. There were no differences in the steady-state values of \( \dot{V}O_2 \) or LBF at rest, or at 40 W, between the upright and supine postures in this study. Similar levels of \( \dot{V}O_2 \) are expected during exercise at the same absolute power output if, as in our study, modifying body position does not alter the work done against gravity (12). It is well established that cardiac output is greater in the supine compared with the upright position at rest and during lighter intensities of exercise (12), but the increase in stroke volume at the onset of exercise in the upright position reduces the difference.
There have been few studies of leg muscle blood flow in the different body positions. We found that the LBF at rest was not different between body positions as a consequence of a significantly smaller femoral artery diameter and a greater MBV in the supine compared with the upright position (Table 1). Leyk et al. (13) also found a significantly smaller diameter and a greater peak systolic blood velocity in the supine position. However, their calculated resting LBF was significantly greater in the supine than the upright posture. Leyk et al. kept their subjects in a seated posture so that the legs were above heart level, whereas our subjects were supine with the thigh muscles at heart level and the calf muscles below the heart. Consistent with our observations of no differences in blood flow to the exercising muscle with body position, both Van Leeuwen et al. (27) and Leyk et al. (13) observed no difference in LBF in upright compared with supine seated positions during calf muscle exercise. The similar levels of LBF were achieved in the face of significantly lower mean arterial pressure at the level of the exercising muscle in the supine exercise. This must mean that greater local vasodilation occurred in the exercising muscles in the supine position.

Cardiovascular responses at the onset of exercise. In selecting knee extension and flexion exercise, we realized that it was not possible to isolate the blood flow to only the working muscles. The femoral artery flow supplies the active quadriceps and hamstring muscles groups, as well as inactive lower leg muscles and skin. Therefore, at the onset of exercise, it is not clear how blood flow is distributed between working and nonworking muscles. Most of the initial increase in blood flow would be expected to go to working muscles because the mechanical effects of the muscle pump and local vasodilation combine to increase vascular conductance (13, 22, 26). As is evident in the biphasic response of the LBF (see Fig. 3) in both the supine and upright postures, further dilation occurs after 15–20 s so that steady-state blood flow for light-to-moderate-intensity exercise is achieved within 1–3 min (9, 24). This progressive dilation is consistent with negative-feedback control required to supply appropriate flow for the metabolic demands.

The within-active muscle distribution of blood flow is also influenced by the interactions between the muscle pump and local, metabolically induced vasodilation. During submaximal exercise, only a fraction of the fibers contract, yet these fibers are distributed so that tension developed throughout the muscle will act as the pump to eject blood from the venules and veins. On muscle relaxation, the pressure gradient across the capillary bed is increased so that blood flow increases. Flow within the muscle would be increased by the muscle pump mechanism, without regard to the local distribution of active vs. nonactive muscle fibers. In the upright position, the greater initial increase in flow (G1 of the exponential-fitting model; see Table 2) may be a consequence of a greater increase in arterial-to-venous pressure gradient because gravity would have filled the veins at rest. As activity continues, local vasodilation may occur in the vicinity of the active fibers, whereas vasoconstriction will probably occur near inactive fibers where blood flow may have increased out of proportion to the metabolic demands.

Recently, Grassi et al. (5) stated that their observation of no decline in femoral venous PO2 within the first 15 s of exercise was evidence that leg muscle VO2 was not constrained by bulk delivery of O2. In the absence of information about the potential transient mismatching of blood O2 supply to O2 demand or of the effect of blood pooled in the leg veins while at rest, this interpretation needs to be viewed with caution, especially because muscle VO2 continues to increase over the first 1–2 min of exercise (Fig. 3). It is unlikely that the complex pattern of flow distribution will be resolved in studies of human muscle with currently available techniques.

The central cardiovascular responses at the onset of exercise appeared to be similar in each of the upright and supine positions. Heart rate increased very rapidly, with an overshoot in some tests. This overshoot is a consequence of very rapid vagal withdrawal in excess of that required to achieve the steady-state heart rate (25). In Fig. 1, it is apparent that mean arterial pressure decreased by ~10 mmHg at the onset of exercise, presumably because of a rapid reduction in peripheral resistance (25). Mean arterial pressure recovered rapidly as a consequence of the increase in cardiac output and modifications in total peripheral resistance.

LBF and metabolism. The slower alveolar VO2 response observed when femoral artery blood flow also adapted more slowly at the onset of supine exercise suggests a link between O2 transport and utilization. There is, however, no evidence in the upright position that VO2 is rate limited by the increase in LBF at the onset of exercise. At least for the supine position, the rate of increase in O2 supply (LBF) appeared to limit the rate at which VO2 increased. The consequence of this was that energy not supplied by oxidative metabolism must be supplied by anaerobic glycolysis, with net accumulation of lactate and utilization of stored high-energy phosphates. However, in both body positions, the MRT for LBF was faster by ~10–12 s than that for VO2 (Table 2). There are two possible explanations for these findings. First, it might be that the change in body position induced a change in the dynamics of both VO2 and LBF. As we discussed previously, this is unlikely, because the position of the legs remained constant while the body rotated at the hips in the two different postures. A second explanation could be related to the issue of within-muscle blood flow distribution as considered above. That is, the muscle pump increases flow within a muscle without regard for metabolic requirements. It is only with continued exercise and the effects of negative feedback on local vascular responses that this flow is redistributed to achieve optimal matching of O2 supply to metabolic demand.

Classically, VO2 has not been viewed as a limiting factor in the process of oxidative phosphorylation because one-half maximal rate occurs at an intracellular...
PO$_2$ of 0.03 Torr in studies of isolated mitochondria (4). However, the affinity of cytochrome c for VO$_2$ varies with the energy state of the cell, and an intracellular PO$_2$ value below ~25 Torr (~40 μM) could have an impact on the intracellular concentrations of metabolic substrates required to drive the oxidative mechanisms at a given rate of ATP production (4, 29). Given this argument, it is understandable that the intracellular PO$_2$ does not have to reach zero to contribute to the metabolic balance that establishes the rate of oxidative phosphorylation (6, 10). That is, a relative hypoxia in the rest-to-exercise transition might cause a temporary slowing of muscle VO$_2$ while the intracellular environment adapts to this PO$_2$. Indeed, Richardson et al. (20) presented evidence from proton magnetic resonance spectroscopy that intracellular PO$_2$ decreases to 3.1 Torr during calf muscle exercise at 50% maximum work rate.

The consequences of a slow adaptation of the oxidative metabolic processes at the onset of exercise are now more apparent. When LBF (24) and alveolar VO$_2$ (17) increased more rapidly at the onset of submaximal exercise after a short-term period of exercise training, there were less marked reductions in intracellular phosphocreatine and smaller increases in blood and muscle lactate (17).

Conclusions. These are the first estimations of LBF dynamics that have been measured simultaneously with alveolar VO$_2$ during transients in work rate in upright and supine leg exercise. A reduction in perfusion pressure in the supine position appears to have been responsible for the slower increase in LBF and, therefore, the O$_2$-delivery response at the onset of exercise. These findings are in support of the hypothesis that O$_2$ availability can, under certain conditions, play a limiting role in the adaptation of muscle VO$_2$. The results further suggest that local vascular regulatory factors might be important in determining the time-dependent pattern of blood flow within exercising muscles.

This research was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada. M. J. MacDonald and J. K. Shoemaker were supported by NSERC Graduate Scholarships.

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Received 3 July 1997; accepted in final form 9 July 1998.

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