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Cardiac output and leg and arm blood flow during incremental exercise to exhaustion on the cycle ergometer

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[1]*Department of Physical Education, University of Las Palmas de Gran Canaria, Spain;* [2]*The Copenhagen Muscle Research Centre, Rigshospitalet, Copenhagen N, Denmark;* [3]*Department of Biomedical Sciences, Panum Institute, Copenhagen N, Denmark;* [4]*Department of Exercise Science, Concordia University, Montreal, Quebec, Canada;* [5]*Centre for Sports Medicine and Human Performance, Brunel University, Uxbridge, United Kingdom*

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Calbet JA, Gonzalez-Alonso J, Helge JW, Søndergaard H, Munch-Andersen T, Boushel R, Saltin B. Cardiac output and leg and arm blood flow during incremental exercise to exhaustion on the cycle ergometer. *J Appl Physiol* 103: 969–978, 2007. First published June 28, 2007; doi:10.1152/japplphysiol.01281.2006.—To determine central and peripheral hemodynamic responses to upright leg cycling exercise, nine physically active men underwent measurements of arterial blood pressure and gases, as well as femoral and subclavian vein blood flows and gases during incremental exercise to exhaustion (Wmax). Cardiac output (CO) and leg blood flow (BF) increased in parallel with exercise intensity. In contrast, arm BF remained at 0.8 l/min during submaximal exercise, increasing to 1.2 ± 0.2 l/min at maximal exercise ($P < 0.05$) when arm O_2 extraction reached 73 ± 3%. The leg received a greater percentage of the CO with exercise intensity, reaching a value close to 70% at 64% of Wmax, which was maintained until exhaustion. The percentage of CO perfusing the trunk decreased with exercise intensity to 21% at Wmax, i.e., to ~5.5 l/min. For a given local $\dot{V}O_2$, leg vascular conductance (VC) was five- to sixfold higher than arm VC, despite marked hemoglobin deoxygenation in the subclavian vein. At peak exercise, arm VC was not significantly different than at rest. Leg $\dot{V}O_2$ represented ~84% of the whole body $\dot{V}O_2$ at intensities ranging from 38 to 100% of Wmax. Arm $\dot{V}O_2$ contributed between 7 and 10% to the whole body $\dot{V}O_2$. From 20 to 100% of Wmax, the trunk $\dot{V}O_2$ (including the gluteus muscles) represented between 14 and 15% of the whole body $\dot{V}O_2$. In summary, vasoconstrictor signals efficiently oppose the vasodilatory metabolites in the arms, suggesting that during whole body exercise in the upright position blood flow is differentially regulated in the upper and lower extremities.

sympatholysis; performance; fatigue; oxygen extraction

ONE OF THE MOST INTRIGUING questions in human integrative physiology is how cardiac output is distributed between skeletal muscles and other vital organs during exercise. The prevalent concept is that this regulation is accomplished in part by engagement of the sympathetic nervous system to increase vascular resistance in the abdominal viscera and nonactive skeletal muscles, preserving most of the available cardiac output for the perfusion of the active skeletal muscles. Exercise-induced sympathoactivation increases as a function of exercise intensity and the muscle mass recruited during exercise (47, 49). In addition, evidence has accumulated during the past 50 years showing that contracting skeletal muscles are less sensitive to sympathetic vasoconstriction (24, 32, 41, 58, 60), an effect that appears to be augmented with exercise intensity (60). A nonidentified metabolically related factor is thought to be responsible for this effect of "functional sympatholysis" in muscle (19, 31, 44), and this area of inquiry remains of substantial importance in systemic and regional vascular control.

Skeletal muscle blood flow may reach values between 2.5 and 4 $l \cdot kg^{-1} \cdot min^{-1}$ in humans depending on training status (2, 39, 40, 42), indicating that during simultaneous arm and leg exercise the pumping capacity of heart is incapable of supplying the capacity for hyperemia if all muscles are simultaneously activated (10). This implies that functional sympatholysis is attenuated in exercise engaging a large fraction of the muscle mass. Otherwise the blood flow capacity of active muscle mass could exceed the pumping capacity of the heart such that blood pressure would drop. Previous studies suggest that during dynamic exercise with the lower extremities, blood flow is not altered by static arm exercise (48, 54) or neck suction (55) (maneuvers that increase sympathetic tone).

In contrast, it has also been reported that superimposing intense arm exercise (oxygen uptake in the arms representing >40% of whole body oxygen uptake) on leg exercise caused a reduction in blood flow and oxygen uptake in the exercising legs with unchanged mean arterial blood pressure, suggesting neurogenic vasoconstriction in the legs (50) and, conversely, superimposing leg cycling at 60% of $\dot{V}O_{2max}$ on arm cranking at 80% of $\dot{V}O_{2max}$ caused also a reduction in arm blood flow (62). Applying a similar model, Strange (54) showed that static and static-ischemic arm exercise, causing a two- to fourfold increase in muscle sympathetic nerve activity and a 15–32% increase in mean arterial blood pressure, reduced leg vascular conductance without a net effect on leg blood flow, indicating a local autoregulatory effect in the contracting muscles when cardiac output is capable of meeting muscle blood flow demands. However, when global muscular work reaches a critical level as seen during incremental exercise to exhaustion, it has been shown that even the flow demands of the respiratory muscles can elicit selective distribution of flow such that leg blood flow and vascular conductance and peak leg $\dot{V}O_2$ are reduced (17, 25). Tanaka et al. (57) measured arm flow with ultrasound Doppler during intense leg exercise on a recumbent cycle ergometer with the arms resting and immobilized to facilitate the placement of Doppler transducers. These authors

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reported that blood flow in the resting arms increases fourfold, suggesting an uncoupling between arm metabolism and perfusion (57). The latter is at odds with previous studies (50, 62). Whether this pattern is exhibited in upright exercise on the cycle ergometer when cardiac output is at its maximum and the arms are clearly known to contribute a stabilizing functional role for leg exercise is unknown.

No study to date has been undertaken to accurately measure arm and leg blood flow simultaneously during incremental exercise under natural volitional cycling to exhaustion. This matter is of importance for establishing both the patterns of flow distribution in limbs differentially engaged and the regulatory processes of blood flow distribution in primary and ancillary muscle vascular beds. During exercise on the cycle ergometer, the arms could contribute to increase the circulatory resistance due to the static nature of the arm exercise during leg cycling, particularly at high intensities. However, it has also been reported that arm sympathetic nerve activity in relaxed arms decreases during low and moderate intensity leg cycling, i.e., below 60% of $\dot{V}O_{2max}$ (13), whereas arm vascular conductance increases (5) curvilinearly with the exercise intensity of the legs (57). The latter is possible because during submaximal exercise and during peak leg exercise in the recumbent position maximal cardiac output is not reached (53), i.e., there is no need to restrain blood flow to the arms to perfuse the legs. Thus it remains unknown which of both effects (vasodilatation or vasoconstriction) predominates in arm circulation during leg cycling (dynamic exercise) combined with the arm static exercise needed to stabilize the trunk during conventional upright leg cycling exercise.

We hypothesized that during incremental upright leg cycling exercise to exhaustion combined with static arm exercise to stabilize the trunk, as usually performed during conventional stress tests on the cycle ergometer, arm vasodilatation will be prevented to give the perfusion priority to the legs. If our hypothesis holds true, then arm vasodilatation should be attenuated as leg exercise intensity increases.

Thus the main aim of this study is to determine central and peripheral arm and leg hemodynamics during an incremental exercise to exhaustion on the cycle ergometer. Particularly, we aimed to determine whether the vasodilatory response to exercise is similar or not in both muscle territories and to quantify the relative contribution of the upper and lower extremities, as well as the head and trunk to the hemodynamic response to exercise.

METHODS

Subjects

Nine healthy men, age 33 ± 2 yr (range: 24–41 yr), height 178 ± 2 cm, and weight 76 ± 1 kg, volunteered to participate in the study. The subjects had a maximal oxygen uptake ($\dot{V}O_{2max}$) of 3.7 ± 0.1 l/min or 49 ± 1 ml·kg^{-1}·min^{-1} (range: 40–57 ml·kg^{-1}·min^{-1}) assessed during an incremental intensity cycle test to exhaustion (Ergomedic 829E, Monark, Varberg, Sweden). All subjects were informed about the possible risks and discomfort involved before giving their written consent to participate. This study was carried out according to the Declaration of Helsinki and was approved by the Ethical Committee of Copenhagen.

Experimental Preparation

On the experimental day the subjects reported to the laboratory at 8:00 AM, and catheters were placed under local anesthesia (2% Lidocain), as reported elsewhere (Ref. 9; Fig. 1). Briefly, a 20-gauge catheter (Arrow, Ref. ES-14150, Reading, PA) was inserted percutaneously using the Seldinger technique into the right femoral artery, 2–5 cm below the inguinal ligament, and advanced 8 cm in the proximal direction. This catheter was connected to a blood pressure transducer positioned at the height of the parasternal fourth intercostal space (T100209A, Baxter, Unterschleissheim, Germany) and was also used to sample arterial blood. Another 20-gauge catheter was inserted in the right femoral vein, 2 cm below the inguinal ligament and advanced 8 cm in the distal direction for femoral venous blood sampling. This catheter was also connected to a blood pressure transducer positioned also at the height of the fourth intercostal space (T100209A, Baxter) to measure femoral vein pressure. In the same femoral vein, a venous catheter with side holes (Radiopack TFE, Cook, Bjaerverskov, Denmark) was inserted and advanced ~5 cm proximal to the inguinal ligament for the injection of iced physiological saline solution. A thin polyethylene-coated thermistor (model 94-030-2.5F T.D. Probe, Edwards Edslab, Baxter, Irvine, CA) was inserted through the venous catheter for blood flow measurements by the constant infusion thermodilution technique (3). This catheter allowed the measurement of femoral vein blood flow, which includes most of the blood flow perfusing the lower extremity. It should be mentioned that the gluteal muscles receive arterial inflow from the gluteal arteries, which are branches of the hypogastric artery. The corresponding venous outflow drains through the gluteal veins, which are tributaries of the hypogastric vein, i.e., they drain more proximal than the tip of the thermodilution catheter, meaning that the gluteus muscles blood flow is lumped into the trunk. Unfortunately the exact contribution of gluteus maximus and medius to pedalling remains unknown.

A Swan-Ganz triple-lumen catheter (model 132F5, Edwards Edslab) was inserted into an antecubital vein and was advanced into the subclavian vein until the tip was positioned in the midclavicular line (the final position was verified by X-ray). The tip lumen was used for blood sampling and was connected to a blood pressure transducer (T100209A, Baxter) to measure the pressure in the subclavian vein, which was also positioned at the height of the fourth intercostal space. The other lumen of the Swan-Ganz was used for infusion of iced saline solution for blood flow measurements. Infusate temperature was measured with a thermistor set in a flow-through chamber (model 93-505, Edslab) connected to the venous catheters. All these catheters were connected to a three-way stopcock and, along with the thermistor, sutured to the skin to minimize the risk of movement during exercise. An additional venous catheter was inserted into an antecubital vein to inject indocyanine green (ICG, Akorn, IL) for measuring cardiac output, as explained below.

A three-lead ECG was displayed on a monitor during catheterization and the rest of the experimental procedures (Dialogue 2000, Danica, Copenhagen, Denmark). The ECG, blood pressure, and the temperatures registered by the thermistor, as well as the infusate temperatures, were recorded simultaneously with the data-acquisition system (MacLab 16/s ADInstruments, Sydney, Australia).

Respiratory Variables

Pulmonary $\dot{V}O_2$, CO_2 production ($\dot{V}CO_2$), and expired minute ventilation ($\dot{V}E$) were measured continuously using an automated metabolic cart (Quark b^2, Cosmed, Rome, Italy), calibrated before each test according to the specifications of the manufacturer. The respiratory variables were averaged every 30 s. The greatest 30-s averaged $\dot{V}O_2$ value during the test was taken as the $\dot{V}O_{2max}$.

Blood Flow

Femoral and subclavian venous blood flow were measured by constant-infusion thermodilution, as described in detail elsewhere (3). Briefly, iced saline was infused through the femoral and subclavian vein simultaneously at flow rates sufficient to decrease blood temperature at the thermistor by 0.5–1°C. Infusate and blood temperatures were measured continuously during saline infusion (Harvard pump, Harvard Apparatus, Millis, MA) via thermistors connected to the data-acquisition system (MacLab 16/s ADInstruments). Infusate temperatures were measured with a thermistor set in a flow-through chamber (model 93-505, Edslab) connected to the venous catheter. At rest, saline infusions were continued for at least 60 s, while during exercise 15- to 20-s-long infusions were used until femoral vein temperature had stabilized at its new lower value. Blood flow was calculated on thermal balance principles, as detailed by Andersen and Saltin (3). Resting blood flow and pressure were measured two to three times and averaged. At peak effort, the measurements were made within 1 min of exhaustion and repeated again whenever possible until exhaustion every 30–40 s.

Cardiac Output

Cardiac output was measured with the dye-dilution method using indocyanine green as previously reported (6, 12), using the method described by Dow (20).

Vascular Conductances

Systemic vascular conductance was calculated as the cardiac output divided by the mean arterial pressure. Leg vascular conductance was calculated as the quotient between leg blood flow and the pressure difference between the femoral artery and the femoral vein. Arm vascular conductance was calculated as the subclavian vein blood flow divided by the pressure gradient between the mean arterial pressure and subclavian mean vein pressure. All pressures were referred to the fourth intercostal space at its parasternal origin.

Blood Samples and Analytical Procedures

Blood was sampled anaerobically in heparinized syringes and immediately analyzed for hemoglobin (Hb), oxygen saturation (OSM3 haemoxymeter, Radiometer, Copenhagen, Denmark), blood pH, CO_2, O_2 tension, lactate, and hematocrit (ABL700, Radiometer). Blood gases were corrected for measured femoral vein blood temperature (femoral venous and arterial blood gases) and subclavian vein temperature (subclavian venous blood gases). Blood O_2 content (Ca_{O_2}, Cfv_{O_2}, and Csv_{O_2}) was computed from the saturation and [Hb], i.e., $(1.34\times[Hb]\times So_2) + (0.003\times Po_2)$.

Calculations

Arteriovenous O_2 difference (a-vO_2diff) was calculated from the difference in femoral arterial and the venous O_2 content in the femoral (leg) or subclavian vein (arm). This difference was then divided by arterial concentration to give O_2 extraction. Systemic oxygen delivery was computed as the product of cardiac output and Ca_{O_2}. Likewise, leg and arm oxygen delivery was calculated as the product of leg and arm blood flow and Ca_{O_2}, respectively. Leg $\dot{V}o_2$ was computed as the product of leg blood flow and the ($Ca_{O_2} - Cfv_{O_2}$), and arm $\dot{V}o_2$ as the product of arm blood flow and ($Ca_{O_2} - Csv_{O_2}$). Trunk and head blood flow was computed as the difference between cardiac output and twice the arm and leg blood flow, and included into a lumped parameter the blood flow directed to the head, neck, heart, abdominal viscera, kidneys, respiratory muscles, and gluteal muscles.

Exercise Protocol

An aluminum frame was built to host two Monark cycle ergometers on top of each other. The lower cycle ergometer was used for leg cycling whereas the top cycle ergometer was conveniently adapted for arm cranking (Fig. 1). During leg exercise, the height of the upper cycle ergometer was adjusted such that the position of the trunk was vertical and the shoulder was at the height of the crank. Thus, during leg cycling, the arms were positioned at the height of the heart, with the elbows slightly flexed. The exercise protocol started with a prolonged warm up of 90 min of combined arm and leg exercise (the legs working at 60% of their $\dot{V}o_{2peak}$ and the arms at 20% of their $\dot{V}o_{2peak}$). This was followed by 1 h of rest and then an incremental exercise to exhaustion was performed with the arms or the legs randomly. This was followed by 30 min of rest, and the incremental exercise was repeated with the other extremity, i.e., the subject who carried out first the incremental arm cranking test later did the leg cycling test and vice versa. Similar responses were observed in the cardiovascular variables in the subjects regardless of the order of the incremental exercise test. The leg incremental exercise started with unloaded pedalling, which was increased by 40–60 W every 2 min until exhaustion. In this paper, only the data collected during the incremental leg exercise are reported.

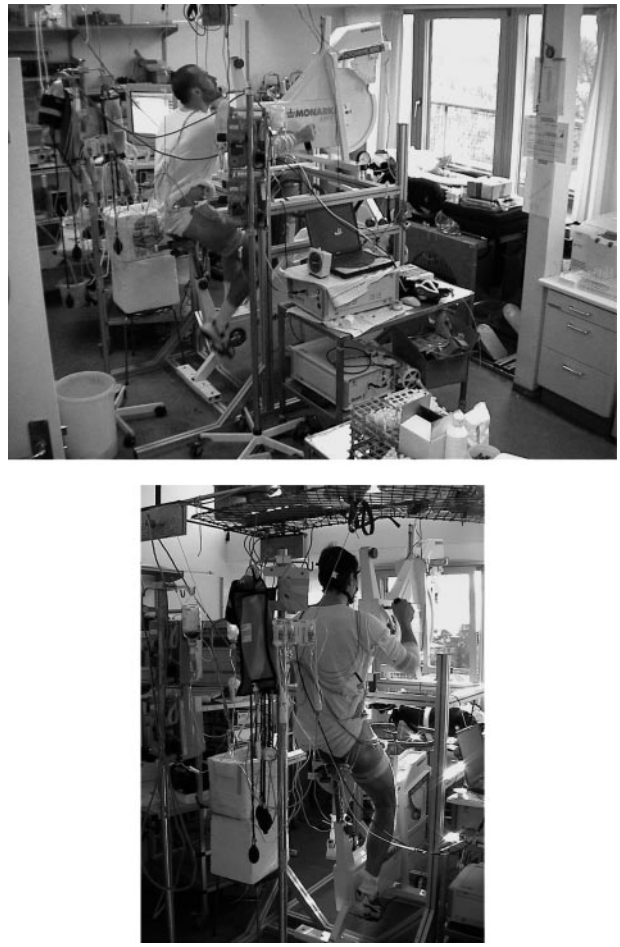

Fig. 1. Cycle ergometers used in the experiments. Note the pedalling position of the trunk and arms.

Statistical Analysis

Descriptive statistics were performed on each variable to confirm the assumptions of normality and homoscedasticity. The effect of exercise on the dependent variables was assessed using a one-way repeated measures analysis of variance. The Mauchly's test of sphericity was run before the ANOVA and in case of violation of the sphericity assumption the degrees of freedom were adjusted according

to the Huynh and Feldt test. Pairwise comparisons were carried out with the Tukey's test. Linear regression analysis was used to test for the existence of a linear relationship between cardiovascular variables an exercise intensity. The relationship between vascular conductance and $\dot{V}O_2$ was also determined by linear regression. Parabolic functions to describe the relationships among variables were only applied when resulting in a lower mean squared error than a linear fit. Repeated measures ANOVA of vascular conductance with $\dot{V}O_2$ as a covariate was used to determine if there was any difference between arms and legs in the vasodilatory response to exercise for a given $\dot{V}O_2$. The significance level was set at $P < 0.05$. Data were expressed as means ± SE, unless otherwise stated.

RESULTS

Oxygen Uptake

Oxygen uptake of the leg increased linearly with exercise intensity and represented ~80% of the whole body $\dot{V}O_2$ at intensities ranging from 38 to 100% of the maximal exercise intensity (Fig. 2; $r = 0.99$, $P < 0.001$). Arm $\dot{V}O_2$ increased at low exercise intensities (from 0.09 ± 0.02 to 0.10 ± 0.02 l/min from unloaded pedalling to 64% of Wmax, $P < 0.05$) doubling the resting value at Wmax ($P < 0.05$). Arm $\dot{V}O_2$ contributed between 7 and 10% to the whole body $\dot{V}O_2$. The head and trunk $\dot{V}O_2$ increased slightly with exercise intensity from 0.30 ± 0.05 to 0.53 ± 0.11 l/min at Wmax ($n = 5$, $P < 0.05$). The head and trunk $\dot{V}O_2$ represented 25% of the whole body $\dot{V}O_2$ during unloading pedalling. From 19% to Wmax, the $\dot{V}O_2$ of the head and trunk represented between 14 and 15% of the whole body $\dot{V}O_2$.

Hemodynamics

Blood flow and cardiac output. Cardiac output and leg blood flow increased in parallel with exercise intensity according to a parabolic function ($r^2 = 0.995$ and $r^2 = 0.998$, both $P < 0.001$, respectively). Between 38 and 84% of Wmax cardiac output rose with a mean slope of 155 ml/min exercise intensity (in %). However, from 84 to 100% of Wmax, the rate of increase of cardiac output was significantly reduced to 75 ml/min exercise intensity (in %). In contrast to cardiac output

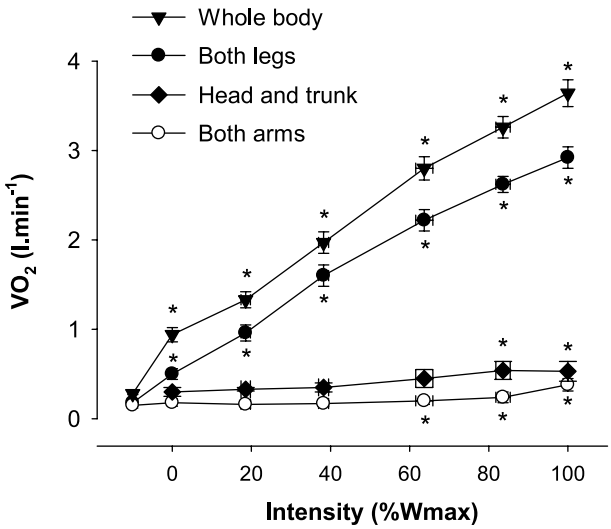

Fig. 2. Whole body and regional oxygen uptake ($\dot{V}O_2$) during incremental leg cycling to exhaustion. The "0" value corresponds to unloaded pedalling. The value prior to 0 is that recorded under resting conditions, seated on the cycle ergometer prior to the start of the test. *$P < 0.05$ compared with resting.

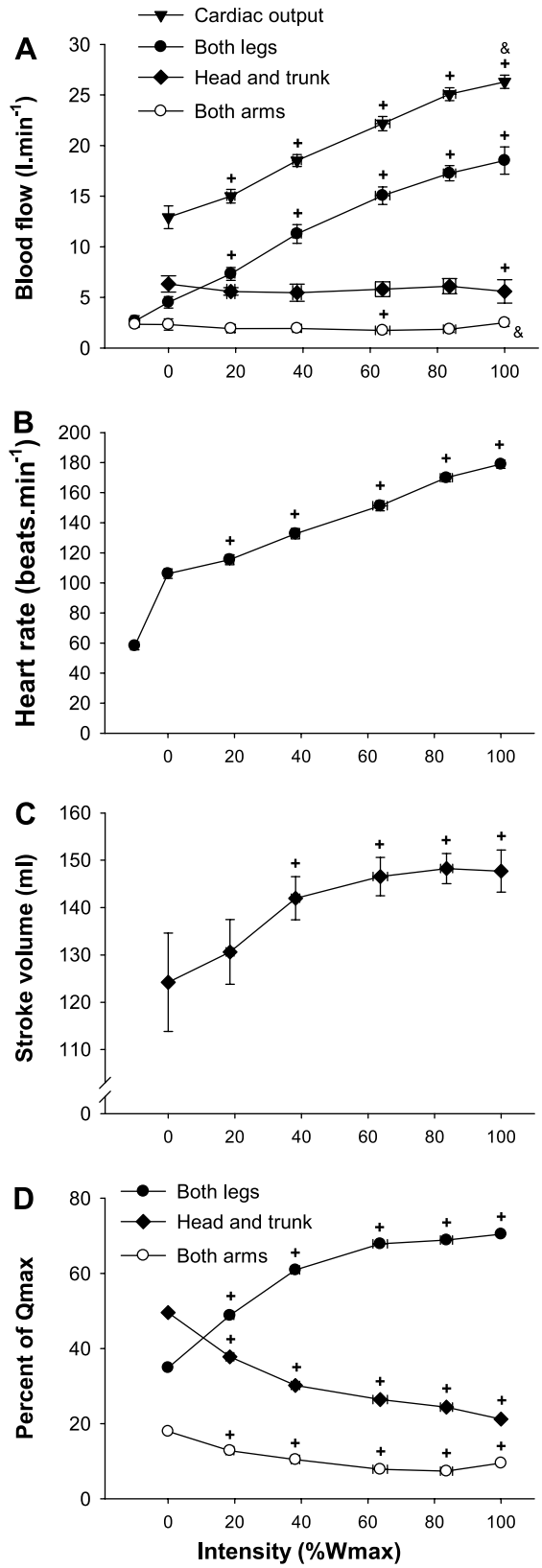

Fig. 3. Cardiac output and regional blood flow, heart rate, stroke volume, and distribution of cardiac output during incremental exercise to exhaustion on the cycle ergometer. The 0 value corresponds to unloaded pedalling. The value prior to 0 is that recorded under resting conditions, seated on the cycle ergometer prior to the start of the test. +$P < 0.05$ compared with unloaded pedalling; &$P < 0.05$ compared with 84% of exercise to exhaustion (Wmax).

and leg blood flow, arm blood flow remained at 0.8 l/min during submaximal exercise, increasing to 1.2 ± 0.2 l/min, at maximal exercise ($P < 0.05$, 100% Wmax compared with 84% Wmax; Fig. 3*A*). Heart rate increased linearly with exercise intensity ($r^2 = 0.995$, $P < 0.001$; Fig. 3*B*). Stroke volume increased also with exercise intensity reaching peak values already at 64% of Wmax ($P < 0.05$, compared with previous values), remaining at this level until exhaustion (Fig. 3*C*). With increasing exercise intensity, the distribution of cardiac output was modified such that the leg received a greater percentage of the cardiac output, with exercise intensity reaching a value close to 70% at 64% of Wmax, which was maintained until exhaustion. The percentage of cardiac output perfusing the trunk decreased with exercise intensity to 21% at Wmax, i.e., ~5.5 l/min at Wmax ($P < 0.05$, compared with resting values). Likewise, the percentage of cardiac output perfusing the arms was reduced with exercise intensity from 18% in unloaded pedalling to 7% at 84% of Wmax ($P < 0.05$) and 10% at Wmax (Fig. 3*D*; $P < 0.05$).

Blood pressure and vascular conductances. Mean arterial pressure increased slightly with exercise intensity from 92 ± 4 mmHg with unloaded pedalling to 108 ± 5 mmHg at 84% of Wmax (Fig. 4*A*; $P < 0.05$). Then, mean arterial pressure increased to reach maximal values at Wmax (122 ± 5 mmHg, $P < 0.05$ compared with 84% of Wmax). The double product increased exponentially with exercise intensity ($r^2 = 0.998$; $P < 0.001$; Fig. 4*B*).

As depicted in Fig. 4*C*, leg vascular conductance increased linearly with exercise intensity ($r^2 = 0.986$; $P < 0.001$). In contrast, arm vascular conductance decreased curvilinearly, with exercise intensity reaching a nadir around 64–84% of Wmax and then increased again following a parabolic function ($r^2 = 0.89$; $P < 0.01$) until exhaustion (Fig. 4*C*). At peak exercise, arm vascular conductance was not significantly different than at rest or during unloaded pedalling. The vascular conductance of the trunk also decreased linearly with exercise intensity ($r^2 = 0.69$; $P < 0.01$). For a given metabolic rate ($\dot{V}O_2$), vascular conductance was higher in the arms than in the legs, but the difference between extremities was narrowed with exercise intensity. At peak exercise, the level of vascular conductance for a given metabolic rate was similar in both extremities (Fig. 4*D*). Leg vascular conductance for a given metabolic rate was maintained from 64 to 100% of Wmax; however, it followed a decreasing pattern with exercise intensity in the arm ($P < 0.05$).

Regional O_2 delivery and extraction. Oxygen delivery paralleled the pattern of blood flow (Fig. 5*A*). Leg fractional O_2 extraction increased linearly with exercise from 38 to 100% of Wmax ($r^2 = 0.99$, $P < 0.05$), to reach 83 ± 2% at Wmax. Likewise, trunk oxygen extraction increased linearly with exercise intensity ($r^2 = 0.91$, $P < 0.01$), to reach a maximal value of 54%. Arm fractional O_2 extraction also increased with exercise intensity but followed an exponential function ($r^2 = 0.99$, $P < 0.001$) to reach a maximal value of 73 ± 3% ($P < 0.05$, compared with the leg).

Exercise venous P_{O_2} was lower in the femoral than in subclavian vein ($P < 0.05$), but the differences narrowed at 84% of Wmax and disappeared at Wmax (20.0 ± 1.3 and 21.5 ± 1.8 mmHg, respectively).

Metabolites and electrolytes. Arterial and venous pHs were reduced by 0.11 units at the start of exercise ($P < 0.05$).

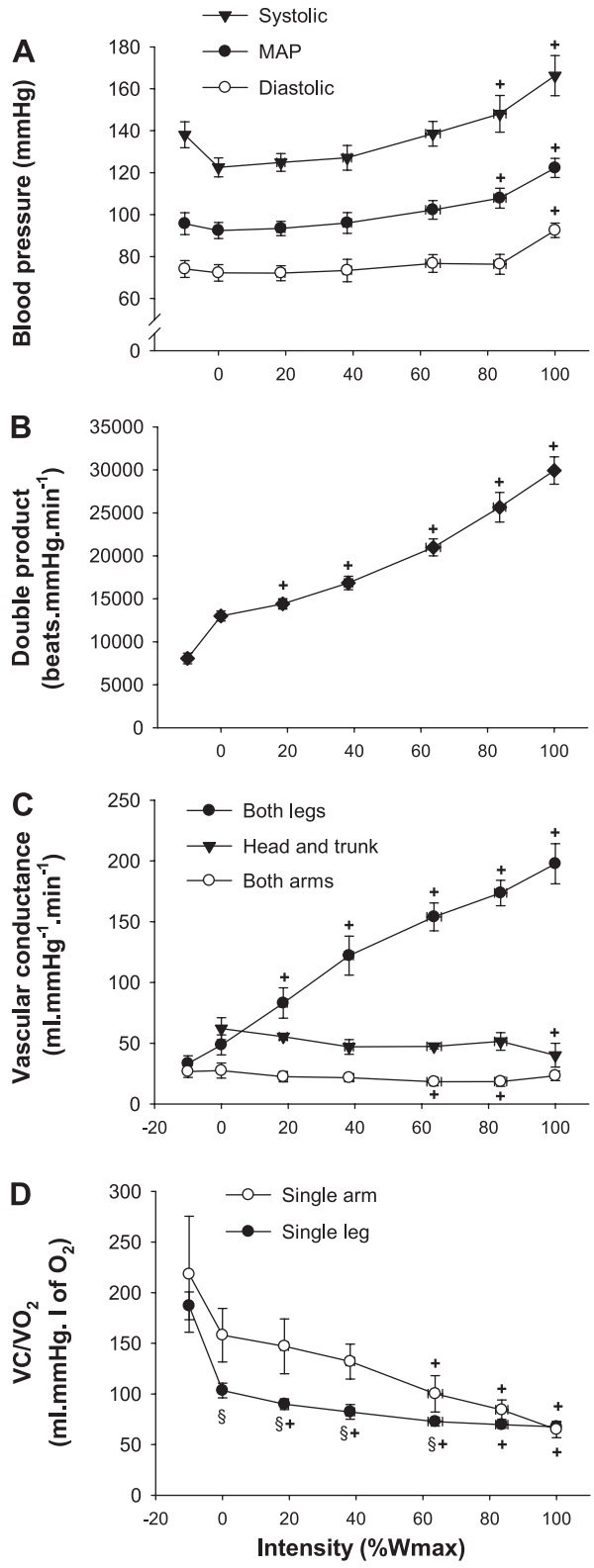

Fig. 4. Blood pressure, double product, regional vascular conductances, and $\dot{V}O_2$-normalized leg and arm vascular conductances during incremental exercise to exhaustion on the cycle ergometer. The 0 value corresponds to unloaded pedalling. The value prior to 0 is that recorded under resting conditions, seated on the cycle ergometer prior to the start of the test. +$P < 0.05$ compared with unloaded pedalling; §$P < 0.05$ leg vascular conductance compared with arm vascular conductance.

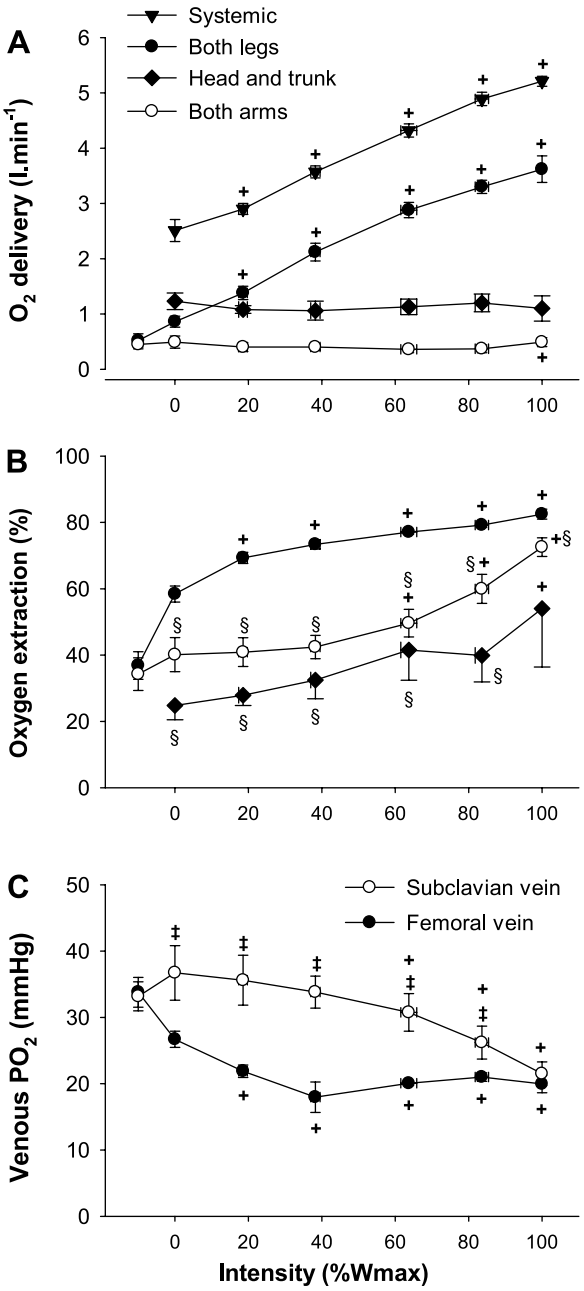

Fig. 5. Systemic and regional oxygen delivery, O_2 extraction, and venous P_{O_2} during incremental exercise to exhaustion on the cycle ergometer. The 0 value corresponds to unloaded pedalling. The value prior to 0 is that recorded under resting conditions, seated on the cycle ergometer prior to the start of the test. $+P < 0.05$ compared with unloaded pedalling; §$P < 0.05$ compared with leg O_2 extraction. ‡$P < 0.05$ compared with femoral vein P_{O_2}.

During exercise, arterial pH remained close to 7.35 until 84% of Wmax (7.35 ± 0.01), dropping thereafter to 7.31 ± 0.01 ($P < 0.05$, compared with 84% of Wmax). Likewise, subclavian vein pH remained ~7.32 up to 84% of Wmax and declined to 7.30 ± 0.01 at Wmax ($P < 0.05$, compared with 84% Wmax). From 0 to 40% of Wmax, the femoral vein pH was similar to the subclavian vein pH, thereafter femoral vein pH decreased with exercise intensity to 7.14 ± 0.02 at Wmax.

Arterial and subclavian vein P_{CO_2} were reduced at the start of exercise by 5 mmHg ($P < 0.05$, compared with resting values), remaining at ~36 and 42 mmHg between 0 and 64% of Wmax. Then, arterial P_{CO_2} was reduced to 34 ± 1 mmHg at Wmax ($P < 0.05$, compared with 64% of Wmax). In contrast, subclavian vein P_{CO_2} increased to 46 ± 3 mmHg at Wmax ($P < 0.05$, compared with 64% of Wmax). Femoral vein P_{CO_2} remained at resting levels (48–49 mmHg) up to 38% of Wmax, thereafter it increased linearly ($r^2 = 0.98$, $P < 0.01$) to 75 ± 2 mmHg at maximal exercise (Fig. 6*A*).

At low exercise intensity, arterial and venous lactate was maintained at the pre-exercise level, but then arterial and femoral vein lactate increased to maximal values of 9.9 ± 0.7 and 10.6 ± 0.7 mM at Wmax, respectively. Subclavian vein lactate started to increase from 64% of Wmax, reaching a peak value of 6.5 ± 0.7 mM.

As illustrated in Fig. 6*B*, the plasma concentration of potassium increased with exercise intensity following a parabolic function in the three vessels ($r^2 > 0.99$, $P < 0.05$). While the femoral vein and femoral artery $[K^+]$ increased from the start of exercise in parallel, the subclavian vein $[K^+]$ did not begin to increase until 64% of Wmax, reaching at exhaustion a value of 4.9 ± 0.3 meq/l, which was lower than the value observed in the femoral vein (6.4 ± 0.2 meq/l, $P < 0.05$).

Leg vascular conductance increased curvilinearly with $[K^+]$ according to the function $VC = 177.7 \cdot [K^+] - 14.2 \cdot [K^+]^2 -$

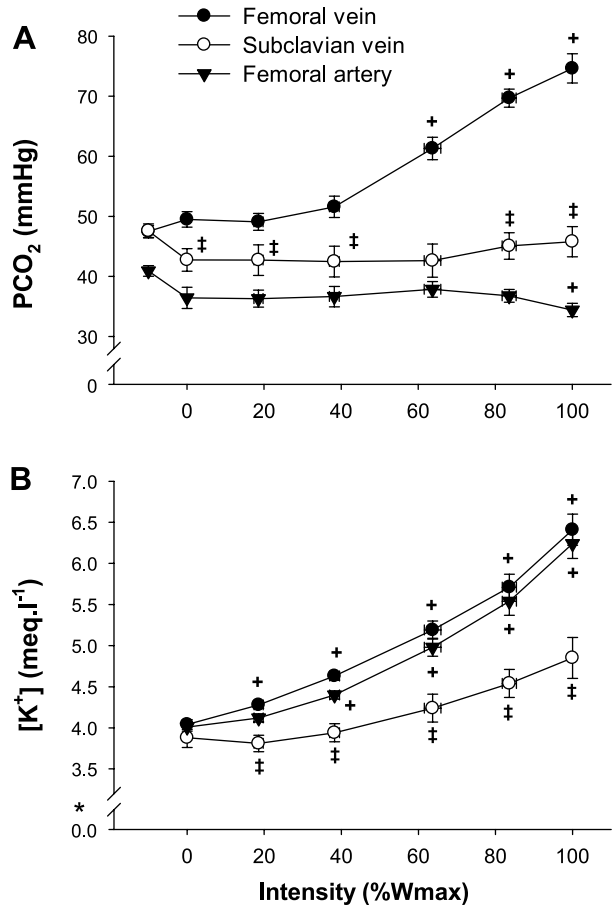

Fig. 6. P_{CO_2} and potassium concentrations in arterial and venous blood during incremental exercise to exhaustion on the cycle ergometer. *$P < 0.05$ subclavian vein compared with femoral vein. The 0 value corresponds to unloaded pedalling. The value prior to 0 is that recorded under resting conditions, seated on the cycle ergometer prior to the start of the test. $+P < 0.05$ compared with unloaded pedalling; ‡$P < 0.05$ compared with femoral artery and vein.

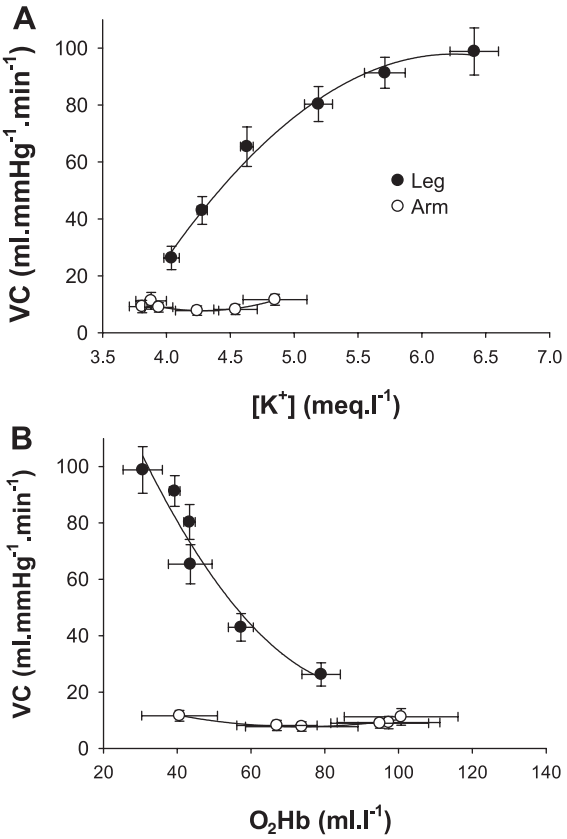

Fig. 7. Relationship between vascular conductance and venous potassium concentration in the femoral vein and subclavian vein during the incremental exercise to exhaustion (*A*). Relationship between vascular conductance and the concentration of hemoglobin bound oxygen in the venous blood of the femoral and subclavian veins during the incremental exercise to exhaustion (*B*).

457.4 ($r^2 = 0.99$, $P < 0.05$). In contrast, there was no relationship between subclavian vein potassium concentration and arm vascular conductance. In fact, at the maximal [K^+] achieved in the subclavian vein, vascular conductance was six times greater in the leg than in the arm (Fig. 7*A*; $P < 0.05$). There was no relationship between vascular conductance and the venous P_{CO_2}, P_{O_2}, and [H^+] in the legs nor in the arms. However, in the legs, vascular conductance increased as femoral vein S_{O_2} decreased according to a parabolic function ($r^2 = 0.98$, $P < 0.05$; Fig. 7*B*). In contrast, there was no relationship between subclavian vein S_{O_2} and VC. In fact, when the S_{O_2} was 28% in the subclavian and femoral vein, vascular conductance was five times greater in leg than in the arm.

DISCUSSION

There are three main findings in this study. First, we demonstrate that during incremental exercise to exhaustion on the cycle ergometer, vasoconstrictor signals efficiently oppose the metabolic vasodilatory stimuli in the arms. This vasoconstrictor influence also affects the trunk where vascular conductance decreases slightly with exercise intensity, despite that coronary and respiratory muscle vascular conductances should be increasing with exercise intensity. In contrast, leg vascular conductance increases linearly with exercise intensity. Second, this study shows that for a given concentration of vasodilatory metabolites and for a given degree of venous hemoglobin desaturation, the vascular conductance of the arm is five to sixfold lower than the vascular conductance of the leg (a difference that remains high even after accounting for differences in muscles mass; data not shown), implying that vasoconstricting signals are able to oppose very efficiently metabolic vasodilatation in the arms. This enhanced vasoconstrictor tone forces the arms to extract O_2 maximally (10, 63), as reflected by the fact that at exhaustion the P_{O_2} was the same in the effluent blood of the arms and legs. Third, our data show that during incremental exercise to exhaustion blood flow to the trunk remains between 6.5 and 5.5 l/min, likely due to a concomitant increase of blood flow in the coronaries, respiratory muscles, and gluteal muscles coupled with falling renal and splanchnic flows. Consequently, the contribution of the trunk to the whole body $\dot{V}_{O_2}$ remains ~14–15% of the $\dot{V}_{O_2}$ for intensities ranging between 38 and 100% of the Wmax. In addition, this study indirectly supports the concept that in humans, $\dot{V}_{O_{2max}}$ is limited by cardiac output and skeletal muscle blood flow (45). In fact, task failure is preceded by an increase of MAP that is accompanied by a reduction in the rate of increase in cardiac output (12), which limits the ability to match oxygen delivery to oxygen demand in the main locomotory muscles but also in the less active arm muscles, as reflected by the high levels of oxygen extraction and some activation of the anaerobic metabolism.

Our results differ from those of Tanaka et al. (57), who reported an increase in arm vascular conductance with leg exercise of increasing intensity, whereas we did not observe any significant change in arm vascular conductance at peak leg exercise. This disagreement may be attributed to differences in the experimental model, exercise intensities, and body positions (upright vs. semi-recumbent). Another factor that could contribute to these discrepancies is that in contrast to Tanaka et al., who measured humeral artery blood flow, we measured subclavian blood flow, i.e., the blood flow perfusing the whole upper extremity (shoulder included). The measurements performed by Tanaka et al. might have been influenced by the changes in the cutaneous circulation of the forearm.

Distribution of Blood Flow: Vasodilator Stimuli

During exercise, skeletal muscle blood flow is regulated depending on metabolic, humoral, mechanical, and neural mechanisms (14). Evidence has accumulated in recent decades suggesting that skeletal muscle blood flow is regulated during exercise depending on the oxygen content of blood, in such a way that oxygen delivery is tightly coupled to $\dot{V}_{O_2}$ (43, 46; see Refs. 8, 11 for review). Recent theories propose that skeletal muscle blood flow is regulated by intracellular and extracellular oxygen sensing mechanisms that elicit the appropriate change in the vascular tone. Experimental evidence is accumulating, suggesting that hemoglobin itself functions as an O_2 sensing mechanism in blood and initiates, via conformational and redox transitions, activation (or release) of vasodilatory regulators, namely nitric oxide, S-nitrosylated thiols, nitrite, and ATP (7, 52). In vitro experiments have shown that these substances are released from the erythrocytes on hemoglobin deoxygenation (4, 15, 21, 29, 30). This study appears to confirm a role for hemoglobin deoxygenation in the regulation of skeletal muscle blood flow during exercise, since there was a close relationship between femoral venous hemoglobin sat-

uration and femoral venous blood flow. However, the arms were almost unresponsive to changes in subclavian vein hemoglobin saturation. The latter may indicate reduced responsiveness to vasodilators released on hemoglobin deoxygenation. Alternatively, a mechanical hindrance to flow due to the isometric nature of the muscle contractions in the arms could also have limited vascular conductance. However, given the parabolic pattern exhibited by arm vascular conductance with nadir values at 64–84% of Wmax, mechanical hindrance could hardly explain our results.

Distribution of Blood Flow: Vasoconstricting Stimuli

Our findings indicated that the vasodilatory responses arising from the hemoglobin on deoxygenation are counteracted by vasoconstricting signals in the arms. In agreement with this interpretation, forearm bier block with bretylium, which inhibits norepinephrine release at the neurovascular junction and in the process causes a "pharmacologically induced sympatholysis," increases arm blood flow and $\dot{V}O_2$ during incremental handgrip exercise (34). Alternatively, our results could also indicate that the close relationship observed in vivo between deoxygenation and the increase of blood flow is an epiphenomenon caused by the close relationship that exists between skeletal muscle blood flow, $\dot{V}O_2$, and metabolism.

We recently showed that combined maximal vascular conductance of arms and legs outweighs the maximal pumping capacity of the heart, implying that the muscular vasodilatory response during maximal exercise must be restrained to maintain perfusion pressure (10). This means that when leg and arm muscles are active, the vasodilatory response to exercise must be blunted in the arms, the legs, or in both territories. The present investigation provides evidence for a blunted vasodilatory response to exercise in the arms, given the perfusing priority to main locomotor muscles (the legs). This conclusion is based on the following facts. First, for a given metabolic demand ($\dot{V}O_2$) vascular conductance in the arms showed a linear reduction with exercise intensity. In contrast, leg vascular conductance (normalized for $\dot{V}O_2$) remained almost at the same level between 64 and 100% of Wmax. This implies that the main mechanism/s responsible for the regulation of blood flow in the legs is tightly coupled to metabolism, while in the arms the metabolic signals are progressively overridden by a vasoconstricting signal(s). In agreement, it has been shown that muscle sympathetic activity increases with exercise intensity (16, 59). In addition, despite the low metabolic rate of the arms, O_2 extraction increased to values even above those observed during maximal arm cranking exercise (63), suggesting insufficient perfusion as observed during ischemic exercise (56). Moreover, for a given concentration of H^+, K^+, or lactate, vascular conductance was much higher in the legs than in the arms, even after accounting for differences in local $\dot{V}O_2$ and venous P_{O_2}. In fact, arm vascular conductance was not related to the concentration of any of these vasodilators. In contrast, leg vascular conductance increased with $[K^+]$ in the femoral vein, particularly at $[K^+]$ below 5.5 meq/l.

Distribution of Blood Flow: Balance Between Vasodilating and Vasoconstricting Stimuli

Under resting conditions the forearms have higher vasodilatory responsiveness to acetylcholine, substance P, nitroprusside (36), and isoproterenol (28), suggesting that the arms may be more sensitive to the action of vasodilators than the legs. In addition, the forearms have lower vasoconstricting responsiveness to phenylephrine (α_1-agonist) than the legs (38), meaning that the arms may be less responsive to a given sympathetic tone.

Thus, if the arms are more sensitive to vasodilators and less sensitive to adrenergic vasoconstriction, how was arm vascular conductance maintained at this low level during incremental exercise with the legs? There are several possible explanations. First, this study is compatible with a lower sensitivity of the arms to vasodilatory agents released on hemoglobin deoxygenation. Second, it may be a consequence of a differential regulation of the sympathetic tone in arms and legs, with a much stronger signal (or greater innervation) in the arms than in the legs during simultaneous arm and leg exercise. In fact, a regional differentiation in sympathetic nervous system outflow has been described (22). Animal experiments showed that α-adrenergic blockade with phentolamine produces increased blood flow in the fast-twitch, low-oxidative muscle of rats, whereas blood flow to the high-oxidative muscle was unchanged (33). Moreover, sympathetic excitation in cats reduced vascular conductance more in the fast-twitch gastrocnemius than in the slow-twitch soleus muscle (27). If during maximal exercise with the legs, arms and legs are submitted to the same sympathetic tone, then our findings could be explained by a superior sympatholytic capacity of the legs, as previously suggested (9). The alternative explanation, i.e., an increased sensitivity to α_1-agonists in the arms than in the legs has been disproved (38). However, it remains unknown whether vascular reactivity remains higher in the arm than in the leg muscles during exercise. Moreover, despite a similar sympathetic activation in arms and legs in response to the cold pressor test, vascular resistance increases in the arms but not in legs (28). Thus it is possible that during near maximal combined arm and leg exercise the exercise-induced elevation of muscle sympathetic nerve activity is likely more efficiently counteracted in the legs than in the arms, i.e., reducing the vasodilatory response of the arms more than that of the legs (54). In fact, maneuvers that are associated with increased sympathetic tone, like neck suction to stimulate the carotid sinus baroreceptors, fail to reduce leg blood flow during heavy exercise (55). This mechanism will give the perfusing priority to the main locomotor muscles, maintain mean arterial pressure (10), and promote muscle oxygen extraction (61). In agreement with this view, the P_{O_2} in effluent blood of the arms reached the same low level as that observed in the legs, i.e., ~20 mmHg. This value is similar to that achieved in the subclavian vein by elite cross-country skiers during maximal skiing with the diagonal technique, which involves both arms and legs (9). Similarly low venous P_{O_2} values are likely reached in the hepatosplanchnic (37) and coronary circulation (23) during intense exercise. However, in the case of blood flow competition between the locomotory and the respiratory muscles, the priority is likely given to the respiratory muscles (1, 17, 18, 25, 51).

Cardiac Output and Stroke Volume

As previously reported by Mortensen et al. (35), cardiac output increased curvilinearly with exercise intensity up to 84% of Wmax, then it tended to level off. In fact, between 84

and 100% of Wmax cardiac output was only increased by 1.2 l/min. This flattening in the cardiac output exercise intensity relationship was due to the stabilization of stroke volume, which reached maximal values at 64% of Wmax, remaining at this level until exhaustion. In contrast, Mortensen et al. (35) observed a reduction of stroke volume at high exercise intensities. The discrepancy between Mortensen et al. (35) and the current investigation may be explained by two reasons. First, the higher MAP in the study by Mortensen et al. (35) could have contributed to reduce stroke volume (26). Second, differences may be accounted for by the exercise protocol. In this study, the ramp of the load increments was always the same, while in Mortensen et al. (35) the load was increased by 20% of Wmax every minute until 80% of Wmax and the last minutes by 10 and 5% of the Wmax. This reduction in the rate of increase in exercise intensity may have facilitated the plateau in cardiac output and the decline in stroke volume reported by Mortensen et al. (35).

In summary, during incremental exercise to exhaustion on the cycle ergometer, task failure is preceded by an increase of mean arterial pressure that is accompanied by a reduction in the rate of increase in cardiac output. The fact that stroke volume remained at maximum values from 64% to maximal exercise intensity indicates appropriate venous return and ventricular filling. Thus, close to task failure, cardiac output appears to be insufficient to match oxygen delivery to oxygen demand in the main locomotory muscles but also in the less active arm muscles, as reflected by the high levels of oxygen extraction and the activation of the anaerobic metabolism in legs and arms. However, vasoconstrictor signals efficiently oppose the vasodilatory metabolites in the arms as reflected by a progressive reduction in arm vascular conductance for a given metabolic rate. Thus, during whole body exercise in the upright position, blood flow is differentially regulated in the upper and lower extremities. Finally, this study supports, although indirectly, the concept that in healthy humans $\dot{V}O_{2max}$ is limited by cardiac output and skeletal muscle blood flow.

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