



Why do arms extract less oxygen than legs during exercise?

J. A. L. Calbet, H.-C. Holmberg, H. Rosdahl, G. van Hall, M. Jensen-Urstad and B. Saltin

Am J Physiol Regul Integr Comp Physiol 289:1448-1458, 2005. First published May 26, 2005;
doi:10.1152/ajpregu.00824.2004

You might find this additional information useful...

This article cites 73 articles, 45 of which you can access free at:

<http://ajpregu.physiology.org/cgi/content/full/289/5/R1448#BIBL>

Updated information and services including high-resolution figures, can be found at:

<http://ajpregu.physiology.org/cgi/content/full/289/5/R1448>

Additional material and information about *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* can be found at:

<http://www.the-aps.org/publications/ajpregu>

This information is current as of October 13, 2005 .



Why do arms extract less oxygen than legs during exercise?

J. A. L. Calbet,^{1,2} H.-C. Holmberg,³ H. Rosdahl,⁴ G. van Hall,² M. Jensen-Urstad,⁵ and B. Saltin²

¹Department of Physical Education, University of Las Palmas de Gran Canaria, Canary Islands, Spain;

²The Copenhagen Muscle Research Center, Rigshospitalet, Copenhagen, Denmark; Departments of

³Physiology-Pharmacology and ⁴Cardiology, Karolinska Institute, Stockholm; and ⁵Department of Sport and Health Sciences, University College of Physical Education and Sports, Stockholm, Sweden

Submitted 6 December 2004; accepted in final form 13 May 2005

Calbet, J. A. L., H.-C. Holmberg, H. Rosdahl, G. van Hall, M. Jensen-Urstad, and B. Saltin. Why do arms extract less oxygen than legs during exercise? *Am J Physiol Regul Integr Comp Physiol* 289: R1448–R1458, 2005. First published May 26, 2005; doi:10.1152/ajpregu.00824.2004.—To determine whether conditions for O₂ utilization and O₂ off-loading from the hemoglobin are different in exercising arms and legs, six cross-country skiers participated in this study. Femoral and subclavian vein blood flow and gases were determined during skiing on a treadmill at ~76% maximal O₂ uptake ($\dot{V}_{O_{2\max}}$) and at $\dot{V}_{O_{2\max}}$ with different techniques: diagonal stride (combined arm and leg exercise), double poling (predominantly arm exercise), and leg skiing (predominantly leg exercise). The percentage of O₂ extraction was always higher for the legs than for the arms. At maximal exercise (diagonal stride), the corresponding mean values were 93 and 85% ($n = 3$; $P < 0.05$). During exercise, mean arm O₂ extraction correlated with the P_{O₂} value that causes hemoglobin to be 50% saturated (P₅₀; $r = 0.93$, $P < 0.05$), but for a given value of P₅₀, O₂ extraction was always higher in the legs than in the arms. Mean capillary muscle O₂ conductance of the arm during double poling was 14.5 (SD 2.6) ml·min⁻¹·mmHg⁻¹, and mean capillary P_{O₂} was 47.7 (SD 2.6) mmHg. Corresponding values for the legs during maximal exercise were 48.3 (SD 13.0) ml·min⁻¹·mmHg⁻¹ and 33.8 (SD 2.6) mmHg, respectively. Because conditions for O₂ off-loading from the hemoglobin are similar in leg and arm muscles, the observed differences in maximal arm and leg O₂ extraction should be attributed to other factors, such as a higher heterogeneity in blood flow distribution, shorter mean transit time, smaller diffusing area, and larger diffusing distance, in arms than in legs.

diffusing capacity; fatigue; oxygen extraction; performance; training

MUSCULAR OXYGEN UPTAKE depends on extrinsic factors such as O₂ delivery and the intrinsic factors that regulate both the transfer of O₂ from the erythrocytes to the mitochondria and the subsequent utilization of O₂ in the mitochondria. However, the diffusive transfer of O₂ is not only determined by intrinsic factors, because it also depends on mean capillary O₂ tension. It is currently assumed that during exercise with a small muscle mass, intrinsic factors are the main determinants of peak local muscular \dot{V}_{O_2} , because the O₂ delivery is extraordinary high (3, 44, 61). During exercise with a large muscle mass, the $\dot{V}_{O_2\text{peak}}$ of the lower extremities appears to be O₂ delivery dependent (6, 7, 16, 33, 35, 57). O₂ extraction across the lower extremities may reach maximal values between 90 and 92% of the arterial O₂ content (Ca_{O₂}), and the P_{O₂} in the femoral vein may be close to 10 mmHg in active subjects (6, 7, 16), leaving little room for further extraction. However, in sedentary subjects, the maximal O₂ extraction across the legs lies close to 70% of the Ca_{O₂},

(59), implying that their peak muscular \dot{V}_{O_2} also may be limited by intrinsic factors (20). In physically active but non-arm-trained subjects, a low O₂ extracting capacity has been reported for the arms (1, 11, 51, 70). Moreover, arm training resulted in only a marginal improvement in the O₂ extraction of the arms (51). Therefore, the intrinsic factors may play an important role in limiting the maximal \dot{V}_{O_2} attainable during maximal arm exercise. One of these roles could be differences in muscle capillarization that may affect both mean transit time (MTT) and diffusion conditions in the muscle. Moreover, primarily on the basis of experiments using the isolated hind-limb preparation in rats, it has been shown that mitochondrial oxidative capacity could determine the rate of O₂ utilization and thereby O₂ extraction (22, 37, 58). However, the limiting factor may be different in humans as suggested by the fact that prolonged bed rest decreases mitochondrial oxidative capacity and $\dot{V}_{O_{2\max}}$ without reducing O₂ extraction in humans (13, 62). Moreover, whole body \dot{V}_{O_2} increases by 6% with hyperoxia (fraction of inspired O₂ = 0.5) during arm-cranking exercise (27). This observation is also compatible with a O₂ delivery limitation of arm peak \dot{V}_{O_2} . However, the effect of hyperoxia also could be explained, but only in part, by the increase in the amount of free O₂ in the arterial blood in subjects without exercise-induced hypoxemia. Therefore, we hypothesize that O₂ extraction across the arms is low because of a less efficient O₂ off-loading from the hemoglobin compared with the legs.

The aim of this study was to determine, first, whether O₂ extraction of the arm muscles is lower than that of leg muscles in humans with well-trained arm and leg muscles, at given systemic and regional absolute \dot{V}_{O_2} . Second, we assessed whether the conditions for the O₂ off-loading from the hemoglobin are different for the arms and legs during submaximal and maximal combined arm and leg exercise in arm- and leg-trained humans. Third, we assessed whether differences in muscle oxidative capacity could account for the differences in O₂ extraction between arm and leg muscles. To pursue these aims, we studied a group of well-trained cross-country skiers.

METHODS

Subjects. Six elite cross-country skiers, age 24 (SD 4) yr, height 180 (SD 6) cm, and weight 74 (SD 6) kg, volunteered to participate in the study. One week before the experiment, their maximal O₂ uptake ($\dot{V}_{O_{2\max}}$) was 5.1 (SD 0.3) l/min or 72 (SD 4) ml·kg⁻¹·min⁻¹, assessed during an incremental intensity test to exhaustion. The incremental exercise test was carried out on skiers using the diagonal

Address for reprint requests and other correspondence: J. A. L. Calbet, Departamento de Educación Física, Campus Universitario de Tafira, 35017 Las Palmas de Gran Canaria, Canary Islands, Spain (e-mail: lopezcalbet@terra.es).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

stride technique while skiing uphill with roller skis on a modified treadmill (Refox, Falun, Sweden). This $\dot{V}O_{2\max}$ value is referred to as $\dot{V}O_{2\max}$ DS. All subjects were informed about the possible risks and discomfort involved in the study before they gave their written consent to participate. This study was carried out according to the Declaration of Helsinki and was approved by the Ethical Committee of the Karolinska Institute, Stockholm, Sweden. The reason for choosing cross-country skiers was not only that they have well-trained arm and leg muscles but also that they are able to skillfully perform exercise with the upper or lower extremities, as well as exercise combining the upper and lower extremities in the upright position.

Experiment preparation. All subjects were familiar with the use of roller skis. On the experimental day, the subjects reported to the laboratory at 8:00 AM, and catheters were placed under local anesthesia (2% lidocaine) and advanced to the final position under fluoroscopic guidance, as previously described (9, 69). An 18-gauge catheter (Hydrocath; Ohmeda, Swindon, UK) was inserted percutaneously, using the Seldinger technique, into the left or right femoral artery 2–5 cm below the inguinal ligament and was advanced 5–10 cm in the proximal direction. This catheter was connected to a blood pressure transducer positioned at the height of the fourth intercostal space (T100209A; Baxter, Unterschleissheim, Germany) and was also used to sample arterial blood. A 20-gauge catheter was inserted in the left femoral vein 2 cm below the inguinal ligament and was advanced 5–7 cm in the distal direction for femoral venous blood sampling. In the right femoral vein, a venous catheter with side holes (Radiopack TFE; Cook, Bjaeverskov, 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. Edslab probe; Baxter, Irvine, CA) was inserted through the venous catheter for blood flow measurements by using the constant infusion thermodilution technique (3). An additional 18-gauge catheter also was inserted into the left femoral vein 2–3 cm below the inguinal ligament and was advanced under fluoroscopic guidance until the tip was positioned in the center of the right atrium, to sample blood from the right atrium. The last catheter, a Swan-Ganz triple-lumen catheter (model 132F5 Edslab) was inserted into an antecubital vein and, under fluoroscopic guidance, was advanced into the subclavian vein until the tip was positioned at 5 cm before the merger with the jugular vein. One lumen was used for blood sampling and another for infusion of iced saline solution for blood flow measurements. Infusate temperatures were measured with a thermistor set in a flow-through chamber (model 93-505 Edslab) connected to the venous catheters. All sampling catheters were connected to a three-way stopcock and, along with the thermistor, were sutured to the skin to minimize the risk of movement during exercise.

A three-lead electrocardiogram (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 thermistors, as well as the infusate temperatures, were recorded simultaneously with the data acquisition system (MacLab 16/s; ADInstruments, Sydney, Australia). Once the catheterization was finished, the subjects lay in the supine position for 180 min. One hour later, muscle biopsies were obtained from the vastus lateralis and, in three subjects, also from the deltoid muscle. Muscle samples were divided into two pieces. One piece was immediately frozen in liquid nitrogen. The other piece was mounted in an embedding medium (Tissue-TEK ACT compound; Miles Diagnostics, Elkhart, IN), frozen in isopentane, cooled to its freezing point in liquid nitrogen, and stored at -80°C . Two hours after catheterization, resting parameters were measured and blood samples were obtained three times, 15 min apart. Femoral and subclavian venous blood flows were measured just before blood sampling and again after sampling.

Exercise protocol. Classic skiing involves different techniques. The diagonal stride technique involves both the arms and the legs and is used uphill (Fig. 1). The double poling technique mainly involves the

upper body (arms) and is used on flat terrain and slightly uphill. Leg skiing is diagonal skiing without poles, which means that, in contrast to diagonal skiing, all the propulsive forces are generated only by the legs. The protocol consisted of 40 min of continuous diagonal stride (referred to as continuous arm + leg) at 77% of $\dot{V}O_{2\max}$ DS, followed without breaks by 10 min of double poling (arm) at 74% of $\dot{V}O_{2\max}$ DS, 10 min of diagonal stride (arm + leg) at 77% of $\dot{V}O_{2\max}$ DS, and 10 min of leg skiing (leg) at 78% of $\dot{V}O_{2\max}$ DS. These conditions elicited a whole body $\dot{V}O_2$ close to 4 l/min. The speed of the treadmill was then reduced, and after 3 min of active recovery, while subjects skied with the diagonal technique at 30–40% of $\dot{V}O_{2\max}$ DS, the speed and slope of the treadmill was increased every minute until subjects reached exhaustion, which occurred within 6–8 min. Blood samples were taken after 21, 24, and 36 min of continuous arm + leg skiing and then ~5–7 min after the start of arm, arm + leg, and leg skiing, respectively.

At the end of the exercise, the position of the subclavian vein and right atrium catheters was checked with fluoroscopy. No catheter was found displaced during the experiment.

Respiratory variables. Whole body $\dot{V}O_2$, CO₂ production, and ventilation were measured continuously using an ergo spirometry system (AMIS 2001; Innovision, Odense, Denmark), which was calibrated with high-precision gases (16.00 ± 0.04% O₂ and 4.00 ± 0.1% CO₂; Air Liquide, Kungsängen, Sweden). During submaximal exercise, the $\dot{V}O_2$ values obtained during the last 4 min were averaged. The $\dot{V}O_{2\max}$ was calculated as the average of the three highest 10-s consecutive measurements of O₂ uptake.

Blood flow. Femoral and subclavian venous blood flow were measured using constant-infusion thermodilution, as described in detail elsewhere (3). Briefly, iced saline was infused (Harvard pump; Harvard Apparatus, Millis, MA) through the femoral and subclavian veins simultaneously at flow rates sufficient to decrease blood temperature at the thermistor by 0.5–1°C. At rest, saline infusions were continued for at least 60 s, whereas during exercise, infusions 15–20 s long were used until femoral vein temperature had stabilized at its new lower value. Blood flow was calculated on the basis of thermal balance principles, as detailed by Andersen and Saltin (3). Resting blood flow and arterial blood pressure were measured six times over 60 min and averaged. During submaximal exercise, blood flow measurements were performed in duplicate. The reported submaximal blood flow values represent the average of at least two measurements. At peak effort, the measurements were made within 1 min of exhaustion.

Leg and Arm $\dot{V}O_2$. Leg and arm $\dot{V}O_2$ values were computed separately using the Fick method, i.e., $\text{leg } \dot{V}O_2 = \text{leg blood flow} \times (\text{Ca}_{O_2} - \text{Cf}_{vO_2})$, and $\text{arm } \dot{V}O_2 = \text{subclavian vein blood flow} \times (\text{Ca}_{O_2} - \text{C}_{svO_2})$, where Cf_{vO_2} represents the O₂ content in the femoral vein and C_{svO_2} represents the O₂ content in the subclavian vein.

Histochemical and enzymatic analysis. Serial transverse sections were stained for myofibrillar ATPase as described by Brooke and Kaiser (5). Muscle capillary density was analyzed, visualized, and quantified as described by Qu et al. (50). Muscle biopsies were analyzed for citrate synthase (CS) and 3-hydroxyacyl-CoA dehydrogenase (HAD) activity (69).

Blood samples and analytical procedures. Blood was sampled anaerobically in heparinized syringes and immediately analyzed for hemoglobin (Hb), O₂ saturation (OSM3 hemoxymeter; Radiometer, Copenhagen, Denmark), blood pH, CO₂, and O₂ tension (ABL5; Radiometer). Blood gases were corrected for measured femoral vein blood temperature (femoral venous and arterial blood gases) and subclavian vein blood temperature (subclavian venous blood gases). Blood O₂ content was computed from the saturation (S_{O₂}) and Hb concentration ([Hb]), i.e., $(1.34 \times [\text{Hb}] \times \text{S}_{O_2}) + (0.003 \times \text{P}_{O_2})$. Another blood sample was taken, and the blood was collected in ice-cold tubes that contained 10 μl of 0.33 M EDTA per milliliter of blood and was immediately centrifuged at 4°C for 10 min and stored at -50°C until analysis. Plasma was analyzed enzymatically for

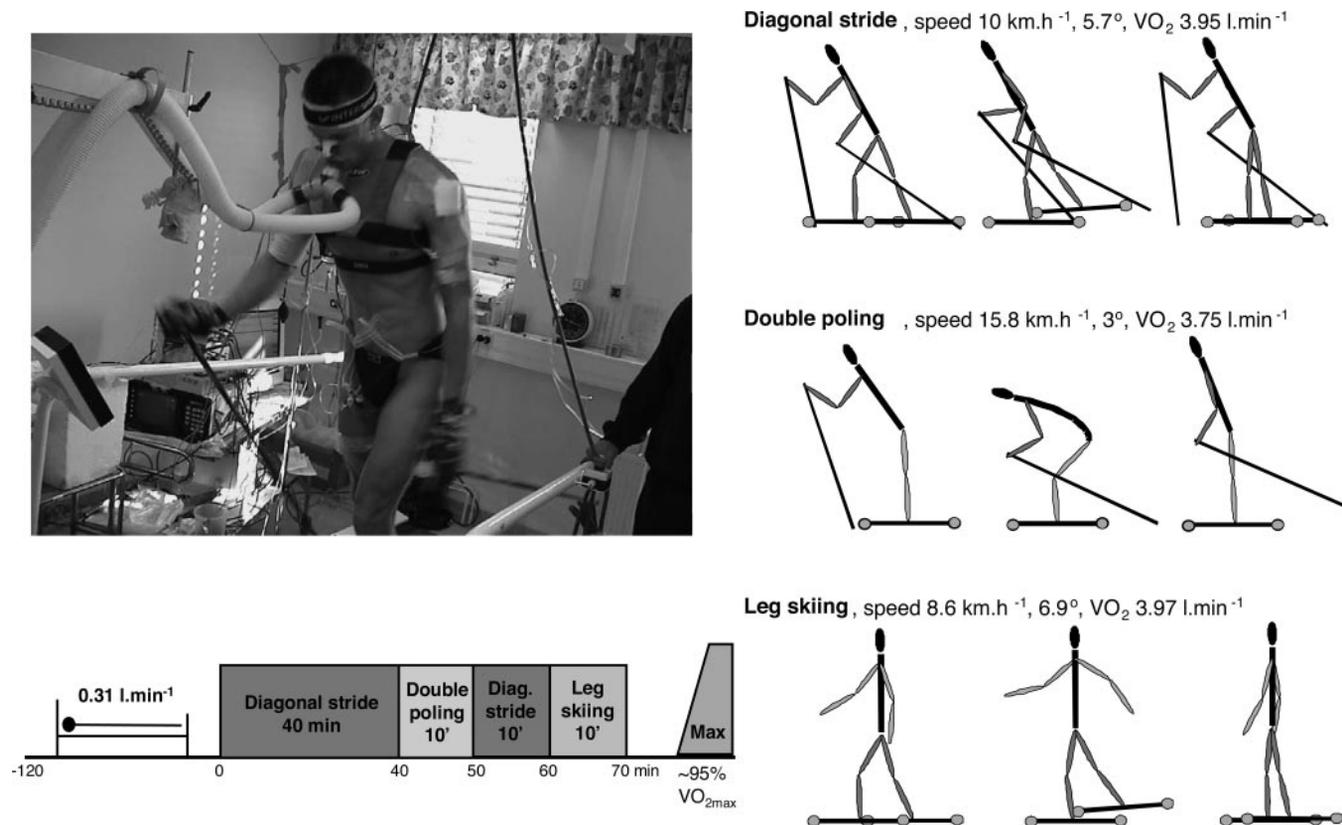


Fig. 1. Experimental protocol indicates speed and inclination of the treadmill during roller skiing. The order in which the different skiing techniques were applied is illustrated at *bottom left*. $\dot{V}O_{2\max}$, maximal O₂ uptake.

lactate (Roche Unikit; Hoffman-LaRoche, Basel, Germany) on an automatic analyzer (Cobas Fara; Roche Diagnostics, Basel, Switzerland). Before biochemical analysis, muscle biopsy samples were freeze-dried and dissected free of connective tissue, visible fat, and blood with the use of a stereomicroscope. The standard P_{50} , defined as the value of P_{O_2} that causes Hb to be saturated by 50% when the O₂Hb equilibration curve is determined at 37°C, pH = 7.40, P_{CO_2} = 40 mmHg, was calculated from the whole set of arterial and venous gases obtained in each experiment. The *in vivo* P_{50} was calculated using Kelman's equation (32). The *in vivo* P_{50} is the P_{O_2} value that causes Hb to be saturated at 50% at the temperature, P_{CO_2} , and pH of the blood in the femoral and subclavian veins during exercise. Arm and leg muscle O₂ conductance and mean capillary P_{O_2} values were determined as previously described by Wagner (71, 73).

Capillary muscle O₂ conductance and mean capillary P_{O_2} . To calculate the diffusing capacity for O₂ (D_{O_2}), we used an iterative numerical integration procedure to find the value of O₂ conductance (i.e., in $ml \cdot min^{-1} \cdot mmHg^{-1}$) that yields the measured femoral muscle venous P_{O_2} . The calculation of D_{O_2} assumes 1) that the intracellular P_{O_2} is negligibly small at $\dot{V}O_{2\max}$ (15, 54), 2) that the O₂ remaining in the femoral and subclavian venous blood is wholly accountable for by diffusion limitation of O₂ from the microcirculation to the mitochondria, and 3) that perfusion/ $\dot{V}O_2$ heterogeneity and perfusional or diffusional shunt are negligible. Mean capillary P_{O_2} is the numerical average of all computed P_{O_2} values, equally spaced in time, along the capillary from the arterial to venous end (49).

Statistical analysis. Descriptive statistics were performed on each variable to confirm the assumptions of normality and homoscedasticity. The effect of the skiing technique during submaximal exercise on the dependent variables was assessed using a one-way repeated-measures analysis of variance (ANOVA). 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 Tukey's test. The relationship between muscular O₂ conductance and O₂ extraction was determined using linear regression. Maximal exercise values were obtained in only three subjects. Thus we decided not to perform comparisons between submaximal and maximal exercise. However, to test for differences between arm and leg variables during maximal exercise in these three subjects, we used a paired Student's *t*-test. The significance level was set at $P < 0.05$. Data are expressed as means \pm SD, unless otherwise stated.

RESULTS

O₂ delivery and consumption. During submaximal exercise, whole body $\dot{V}O_2$ was similar during the different exercise conditions at 4 l/min, which represented $\sim 76\%$ of $\dot{V}O_{2\max}$ measured during diagonal skiing ($\dot{V}O_{2\max}$ DS; Table 1). At peak exercise, a $\dot{V}O_2$ close to 95% of $\dot{V}O_{2\max}$ DS was reached. The contribution of the legs to whole body $\dot{V}O_2$ varied between 46% (during double poling) and 67% (during leg skiing). Conversely, for the arms, the corresponding values were 37 and 9%, respectively (Table 1). $\dot{V}O_{2\text{peak}}$ during double poling is a little lower ($\sim 86\%$ of the $\dot{V}O_{2\max}$ DS) (Holmberg et al., unpublished observations). This means that compared with the specific double poling $\dot{V}O_{2\text{peak}}$, the skiers were working at 86% of the double poling $\dot{V}O_{2\text{peak}}$.

Activities of muscle oxidative enzymes. The activities of muscle oxidative enzymes have been previously reported (69) and are summarized in Table 4 together with some additional unpublished data also obtained from cross-country skiers.

O₂ extraction. The effect of the exercise on the blood gases, pH, and lactate is depicted in Table 2. The systemic and leg O₂

Table 1. O₂ delivery and $\dot{V}O_2$

	Resting	Diagonal Skiing	Double Poling	Diagonal Skiing	Leg Skiing	Diagonal Skiing (Maximal)
Systemic O ₂ delivery	1.86 (SD 0.47)	5.22 (SD 0.59)	5.00 (SD 0.56)	4.95 (SD 0.49)	4.99 (SD 0.51)	5.70 (SD 0.95)
2-Leg O ₂ delivery	0.33 (SD 0.12)	2.53 (SD 0.39)*†	2.05 (SD 0.39)*	2.52 (SD 0.27)*†	3.00 (SD 0.24)	3.44 (SD 0.54)
2-Arm O ₂ delivery	0.23 (SD 0.10)	1.10 (SD 0.49)*†	2.02 (SD 0.29)*	1.13 (SD 0.20)*†	0.68 (SD 0.10)	1.27 (SD 0.38)
Pulmonary $\dot{V}O_2$	0.31 (SD 0.05)	3.94 (SD 0.32)	3.74 (SD 0.44)	4.00 (SD 0.29)	3.96 (SD 0.42)	5.07 (SD 0.69)
2-Leg $\dot{V}O_2$	0.08 (SD 0.05)	2.19 (SD 0.37)*†	1.72 (SD 0.42)*	2.27 (SD 0.22)*†	2.64 (SD 0.27)	3.22 (SD 0.61)
2-Arm $\dot{V}O_2$	0.06 (SD 0.02)	0.78 (SD 0.29)*†	1.38 (SD 0.22)*	0.84 (SD 0.12)*†	0.36 (SD 0.07)	1.09 (SD 0.36)

Values are means (SD) (in l/min) for O₂ delivery and O₂ uptake ($\dot{V}O_2$). Maximal exercise values were obtained in only 3 subjects (not included in statistical analysis). **P* < 0.05 compared with leg exercise. †*P* < 0.05 compared with double poling.

content arterial-venous differences (a-vDif) were lower during arm exercise compared with the other exercise modes, whereas the arm O₂ a-vDif was lowest during leg skiing (Fig. 2A). Regardless of the exercise mode, the percentage of O₂ extraction was always higher for the legs than for the arms, even during double poling (Fig. 2B). During diagonal skiing, the femoral vein O₂ extraction values were slightly greater when the exercise was preceded by the double poling bout than during the 40 min of continuous diagonal skiing (Fig. 2B).

The exercise P_{O₂} and O₂ content values were always lower in the femoral vein than in the subclavian vein, whereas the O₂ tension and content values in the blood of the right atrium were in between (Fig. 3, A and B). Even when the subjects used the double poling technique, which elicited a similar $\dot{V}O_2$ in the arms and legs (Table 1), the P_{O₂} and O₂ content values were lower in the femoral vein than in the subclavian vein (Fig. 3, A

and B). Leg O₂ extraction was closely related to arm O₂ extraction during submaximal exercise with the diagonal stride technique (*r* = 0.89, *P* < 0.05). As shown in Fig. 4A, leg mean O₂ extraction correlated closely with mean leg $\dot{V}O_2$ across conditions (*r* = 0.89, *P* < 0.05; *n* = 6), whereas this relationship was not significant at the arm level (*r* = 0.61, *P* = 0.28; *n* = 6). During arm exercise, there also was a close relationship between the mean O₂ extraction and the corresponding P₅₀ value (*r* = 0.93, *P* < 0.05) (Fig. 4B).

O₂ off-loading and arm diffusing capacity. As shown in Table 3, during the 40 min of continuous diagonal skiing, the in vivo P₅₀ value was lower than during the second bout of diagonal exercise, which was performed just after the double poling (33.7 (SD 1.2) and 35.2 (SD 1.5) mmHg, respectively). During combined leg and arm exercise, the blood pH was similar in the femoral and subclavian veins (Fig. 3C). How-

Table 2. Blood gases, pH, and lactate during skiing with different techniques

	Resting	Diagonal Skiing	Double Poling	Diagonal Skiing	Leg Skiing	Diagonal Skiing (Maximal)
P_{O₂}, mmHg						
Femoral artery	101.4 (SD 2.9)	90.9 (SD 7.3)*‡	105.1 (SD 6.6)	95.1 (SD 6.9)‡	93.6 (SD 6.9)‡	87.0 (SD 6.1)
Femoral vein	39.7 (SD 7.1)	15.3 (SD 2.2)*‡	17.5 (SD 3.4)*	13.6 (SD 2.4)*‡	14.6 (SD 2.2)*‡	12.3 (SD 0.9)
Subclavian vein	37.9 (SD 7.6)	22.2 (SD 2.7)*†‡	26.5 (SD 2.0)*	21.7 (SD 2.7)*†‡	27.8 (SD 5.4)*	18.0 (SD 1.4)
Right atrium	42.7 (SD 1.7)	21.3 (SD 3.7)*	22.5 (SD 2.2)*	19.2 (SD 2.0)*‡	19.6 (SD 2.4)*‡	15.8 (SD 0.5)
SO₂, %						
Femoral artery	98.1 (SD 1.5)	96.7 (SD 1.0)*	97.0 (SD 1.2)	96.1 (SD 1.2)*	96.1 (SD 1.7)*	95.1 (SD 1.0)
Femoral vein	74.1 (SD 12.0)	13.0 (SD 3.2)*‡	16.2 (SD 5.9)*	9.2 (SD 3.7)*‡	11.4 (SD 3.9)*‡	7.4 (SD 0.5)
Subclavian vein	71.9 (SD 13.2)	26.5 (SD 6.1)*†	30.8 (SD 8.3)*	24.0 (SD 7.3)*‡	44.8 (SD 10.3)*‡	13.6 (SD 2.8)
Right atrium	80.6 (SD 2.9)	23.4 (SD 5.4)*†	24.7 (SD 4.4)*	18.0 (SD 5.1)*‡	19.6 (SD 4.7)*‡	10.1 (SD 1.6)
O₂ content, ml/l						
Femoral artery	196.2 (SD 4.2)	194.1 (SD 9.8)	192.7 (SD 9.6)	188.8 (SD 9.1)	192.4 (SD 7.3)	190.0 (SD 7.8)
Femoral vein	147.8 (SD 25.0)	26.2 (SD 7.3)*‡	32.3 (SD 12.5)*	18.4 (SD 7.8)*‡	23.4 (SD 7.8)*‡	12.5 (SD 4.2)
Subclavian vein	138.2 (SD 38.7)	54.6 (SD 13.0)*†	61.3 (SD 17.4)*	47.5 (SD 15.7)*†	89.4 (SD 22.3)*‡	27.9 (SD 5.2)
Right atrium	161.7 (SD 5.6)	47.4 (SD 12.0)*†	48.4 (SD 8.3)*	36.0 (SD 10.8)*‡	39.5 (SD 10.0)*‡	20.1 (SD 3.1)
PCO₂, mmHg						
Femoral artery	38.9 (SD 1.2)	38.2 (SD 1.7)†‡	32.9 (SD 2.2)*	34.6 (SD 1.5)*	35.3 (SD 2.4)*‡	34.9 (SD 0.5)
Femoral vein	46.6 (SD 2.2)	64.9 (SD 4.2)*‡	58.3 (SD 2.7)	60.5 (SD 4.2)	63.4 (SD 2.7)*‡	72.2 (SD 6.4)
Subclavian vein	42.7 (SD 5.9)	61.2 (SD 3.2)*†	56.4 (SD 4.9)*	59.0 (SD 8.8)*†	50.0 (SD 7.1)	70.8 (SD 6.1)
Right atrium	44.3 (SD 1.7)	62.2 (SD 3.7)*	57.8 (SD 4.9)*	60.0 (SD 6.1)*	60.1 (SD 4.4)*	70.3 (SD 6.9)
pH						
Femoral artery	7.41 (SD 0.02)	7.36 (SD 0.02)*	7.34 (SD 0.02)*	7.32 (SD 0.05)*	7.35 (SD 0.02)*	7.33 (SD 0.03)
Femoral vein	7.38 (SD 0.02)	7.25 (SD 0.02)*	7.24 (SD 0.02)*	7.23 (SD 0.05)*	7.23 (SD 0.02)*	7.19 (SD 0.05)
Subclavian vein	7.39 (SD 0.02)	7.25 (SD 0.02)*†	7.19 (SD 0.02)*	7.22 (SD 0.07)*†	7.30 (SD 0.05)*‡	7.15 (SD 0.07)
Right atrium	7.39 (SD 0.02)	7.26 (SD 0.02)*†	7.22 (SD 0.02)*	7.23 (SD 0.07)*	7.26 (SD 0.02)*‡	7.17 (SD 0.05)
Lactate level, mmol/l						
Femoral artery	0.6 (SD 0.2)	2.6 (SD 1.0)*†‡	7.5 (SD 1.7)*	6.3 (SD 3.4)*	5.0 (SD 2.0)*‡	8.1 (SD 1.9)
Femoral vein	0.7 (SD 0.2)	2.4 (SD 1.0)*†‡	5.9 (SD 1.7)*	6.1 (SD 2.9)*	5.1 (SD 2.0)*	7.5 (SD 2.3)
Subclavian vein	0.7 (SD 0.2)	3.3 (SD 1.2)*‡	9.0 (SD 2.7)*	6.4 (SD 4.7)*	4.7 (SD 2.0)*‡	10.2 (SD 2.8)
Right atrium	0.6 (SD 0.2)	2.7 (SD 1.0)*†‡	8.6 (SD 2.0)*	6.7 (SD 3.7)*	5.0 (SD 2.2)*‡	8.9 (SD 2.8)

Values are means (SD). SO₂, O₂ saturation. Maximal exercise values were obtained in only 3 subjects (not included in statistical analysis). **P* < 0.05 compared with resting conditions. †*P* < 0.05 compared with leg exercise. ‡*P* < 0.05 compared with double poling.

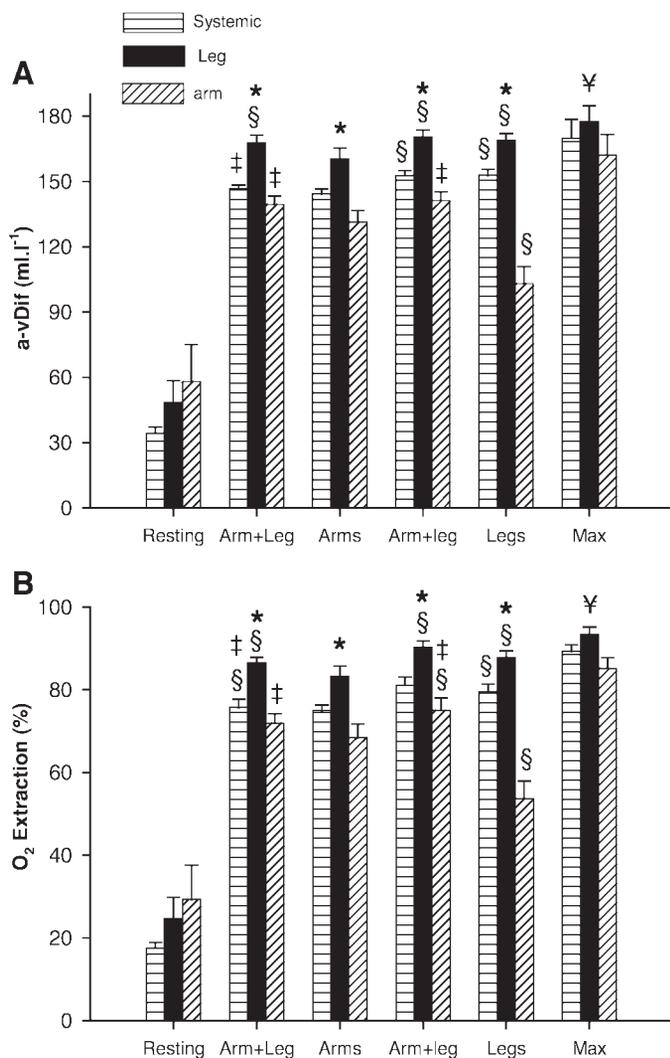


Fig. 2. Systemic, leg, and arm O₂ arterial-venous difference (a-vDif) (A) and O₂ extraction (B) values were measured during exercise with arms and legs (diagonal stride: arm + leg), with only arms (double poling), and with only legs (leg skiing without poles) and during maximal exercise with the diagonal stride technique (max). **P* < 0.05, comparison between legs and arms during the same exercise condition. §*P* < 0.05 compared with double poling. ‡*P* < 0.05 compared with leg skiing. ¥*P* < 0.05, comparison between legs and arms during maximal exercise (*n* = 3). Error bars represent the SE of the mean.

ever, during double poling, the blood pH was lower in the subclavian than in the femoral vein, whereas the opposite was true during leg skiing. The lower extraction capacity of the arm was not related to differences in the variables that regulate the unloading of O₂ from the Hb, because the degree of acidification of blood, blood temperature (not shown), and P_{CO₂} (Fig. 3D) were very similar in the effluent blood from the legs and arms. However, compared with the subclavian vein, a small, but significantly higher blood temperature (+0.6 degrees) and P_{CO₂} (6–10 mmHg) were observed in the femoral vein during leg skiing. Thus the calculated in vivo P₅₀ value was almost the same in the effluent blood from the arm muscles during double poling and the effluent blood from the leg muscles during leg skiing (35.9 (SD 1.7) and 35.8 (SD 1.5) mmHg, respectively, *P* = 0.66) (Table 3). Despite this high P₅₀ value in the arms, which was significantly higher than the 34.6 (SD 1.5) mmHg

observed in the legs, the O₂ extraction was markedly higher in the legs than in the arms during double poling (Fig. 2B).

At maximal exercise with the diagonal technique, the arm and leg in vivo P₅₀ values were 38.8 (SD 4.3) and 37.5 (SD 3.1) mmHg (mean of 3 subjects). In the latter condition, one skier was able to extract 97 and 89% of the O₂ supplied to legs and the arms, respectively. This superb O₂ extraction was achieved with in vivo P₅₀ values of 41.0 and 43.7 mmHg, respectively.

The calculated mean capillary muscle O₂ conductance of the arm muscles during double poling was 14.5 (SD 2.6) ml·min⁻¹·mmHg⁻¹, and the mean capillary P_{O₂} was 47.7 (SD 2.6) mmHg. The corresponding values for the leg muscles during maximal exercise with the diagonal technique were 48.3 (SD 13.0) ml·min⁻¹·mmHg⁻¹ and 33.8 (SD 2.6) mmHg. Arm muscle capillary O₂ conductance tended to correlate with maximal arm O₂ extraction percentage (*r* = 0.76, *P* = 0.08).

DISCUSSION

This study shows that in arms, but not in legs, mean O₂ extraction is closely related to the mean in vivo P₅₀ value. Moreover, for a given P₅₀ value, the upper extremities extract less O₂ than the lower extremities in humans with highly trained arm and leg muscles during exercise. This lower O₂ extraction is associated with a lower O₂ conductance in the upper compared with the lower extremities. Hence, for a given O₂ demand, a greater O₂ delivery is needed for exercising arm than leg muscles, which is the cause of the relatively high blood flow to the arms.

Because O₂ extraction increases with exercise intensity, and the relative intensity during double poling was ~86% of double poling $\dot{V}O_{2\text{ peak}}$, O₂ extraction should have been higher for the arms than for the legs. However, the experimental findings showed higher extraction in the legs than in the arms. This aspect confers additional robustness to our findings.

Arm O₂ extraction in trained and untrained muscles. Rasmussen et al. (51) reported mean axillary vein O₂ saturation values of 38% (extraction: 60%) during arm cranking at an intensity eliciting a heart rate of 170 beats/min. In the current investigation, the subclavian vein saturation during submaximal exercise achieved mean values between 24 and 31% (extraction: 68–75%). The high arm O₂ extraction capacity in the current investigation is likely the result of several years of regular training, given that Rasmussen et al. (51) reported that after 5 wk of intensive arm training (1 h × 5 days/wk), the extraction capacity of the arm muscles was only slightly improved. During maximal exercise, the arm muscles of our skiers extracted 85% of the O₂ supplied, which is higher than reported during maximal cycle ergometry in the leg muscles of untrained people before (59) and even after 9 wk of a training program resulting in a 35% higher $\dot{V}O_{2\text{ max}}$ (59). These skiers attained in their arms the same O₂ extracting values as we have observed in the legs of physically active subjects ($\dot{V}O_{2\text{ max}}$ between 47 and 63 ml·kg⁻¹·min⁻¹) during upright maximal leg cycle ergometry (7, 68). Roca et al. (59) reported maximal leg extraction values of 72% in sedentary subjects that increased to 82% after 9 wk of training. Compared with these values, our skiers also reached remarkably high maximal O₂ extraction values in their legs (93%). However, untrained

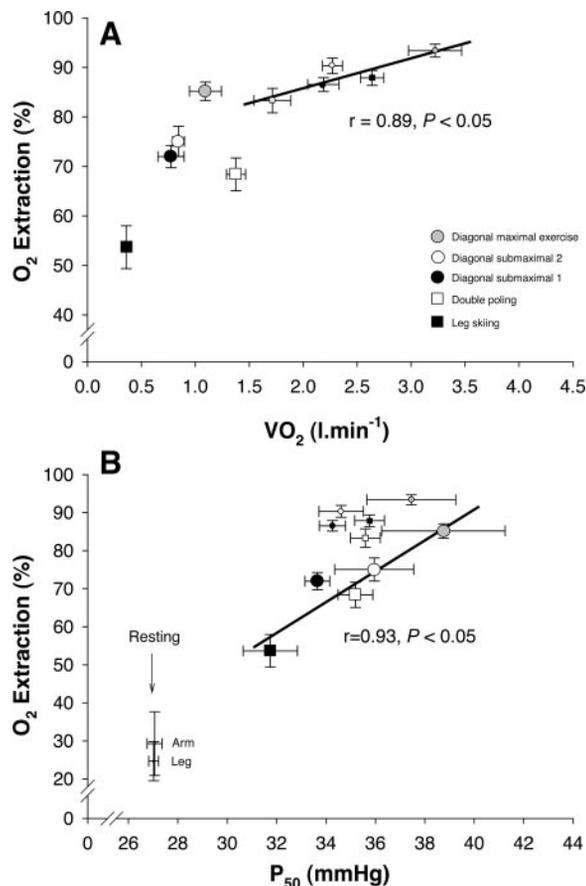
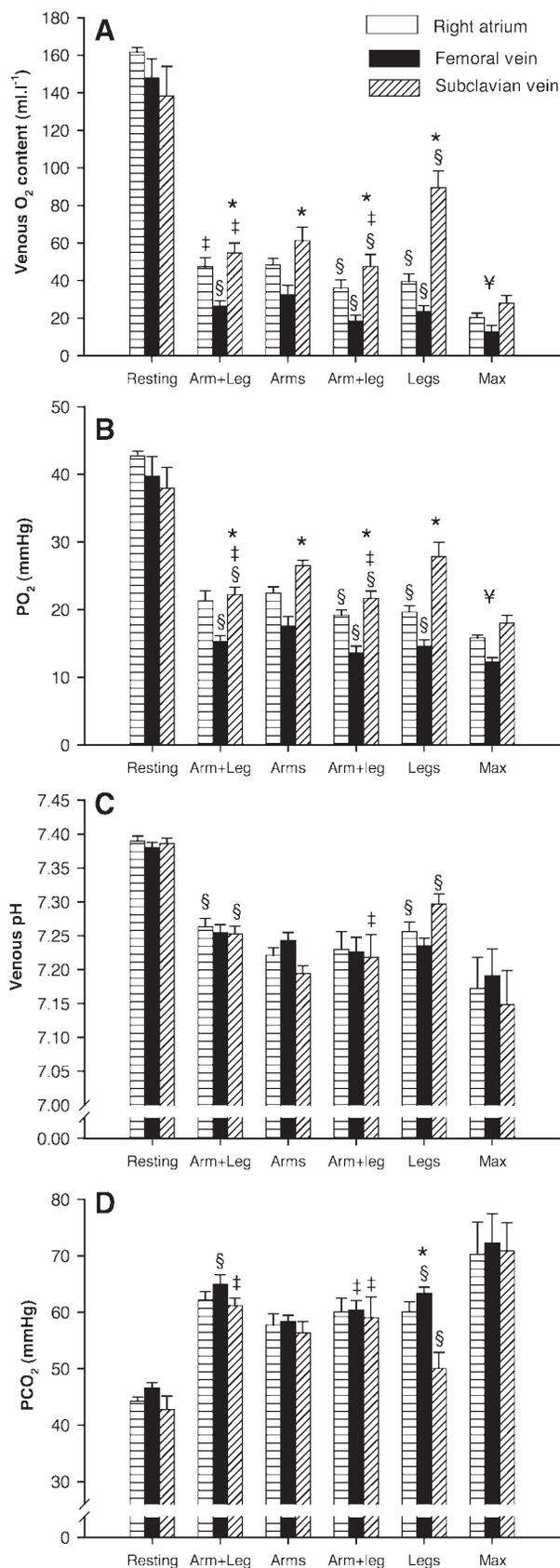


Fig. 4. Relationship between O₂ extraction and limb $\dot{V}O_2$ (A) or P₅₀, the PO₂ value that causes Hb to be saturated by 50% (B). Measurements were performed during exercise with arms and legs (diagonal stride), with only arms (double poling), and with only legs (leg skiing without poles) and during maximal exercise with the diagonal stride technique. Small symbols represent leg values; large symbols represent arm values. It is remarkable that leg O₂ extraction appears to be more dependent on leg $\dot{V}O_2$ than on the P₅₀ value, whereas arm O₂ extraction seems more dependent on the local $\dot{V}O_2$. Error bars represent the SE of the mean.

subjects may reach rather high leg O₂ extractions after bed rest (62) or during ischemic exercise (46).

Several factors may account for the observed differences in muscular O₂ extraction, which depends on the interaction of the following: 1) kinetics of O₂ off-loading from the Hb; 2) capillary muscle O₂ conductance (72); 3) blood flow, mean transit time (47), and degree of mismatch between the metabolic demand and blood flow distribution and/or degree of shunt (48); and 4) muscle maximal oxidative capacity (22) and exercise intensity.

Kinetics of O₂ off-loading from Hb. The off-loading of O₂ from Hb during exercise is facilitated by acidification of the

Fig. 3. O₂ content (A), PO₂ (B), pH (C), and PCO₂ (D) were measured in the right atrium, femoral vein, and subclavian vein. Measurements were performed during exercise with arms and legs (diagonal stride), with only arms (double poling), and with only legs (leg skiing without poles) and during maximal exercise with the diagonal stride technique. **P* < 0.05, comparison between legs and arms during the same exercise condition. §*P* < 0.05 compared with double poling. ‡*P* < 0.05 compared with leg skiing. ¥*P* < 0.05, comparison between leg and arms at maximal exercise (*n* = 3). Error bars represent the SE of the mean.

Table 3. Resting and exercise P₅₀ mmHg in effluent blood of the arm (subclavian vein) and leg (femoral vein)

	Resting	Diagonal Skiing	Double Poling	Diagonal Skiing	Leg Skiing	Diagonal Skiing (Maximal)
Subclavian vein	27.1 (SD 0.7)	33.7 (SD 1.2)	35.9 (SD 1.7)*	35.2 (SD 1.5)†	31.7 (SD 4.4)*‡	38.8 (SD 4.3)
Femoral vein	27.0 (SD 0.5)	34.3 (SD 1.2)	34.6 (SD 1.5)	35.6 (SD 2.2)	35.8 (SD 1.5)‡	37.5 (SD 3.1)

Values are means ± SD (in mmHg) for P₅₀, the P_{O₂} value at which Hb is 50% O₂ saturated. Maximal exercise values were obtained in only 3 subjects (not included in statistical analysis). **P* < 0.05 compared with leg exercise. †*P* < 0.05 compared with the first bout of diagonal skiing. ‡*P* < 0.05 compared with double poling.

blood and the increase of temperature and P_{CO₂} (67). Experiments in dogs have shown that O₂ extraction at $\dot{V}O_{2\max}$ decreases when the P₅₀ of the Hb is reduced from its normal value of 32 to 23 mmHg (24), whereas it increases when the P₅₀ is raised to 53.2 mmHg (56). In agreement, we observed a close correlation between O₂ extraction and P₅₀. Moreover, during diagonal skiing, slightly higher femoral vein O₂ extraction values were observed after than before the double poling bout, which elicited a high degree of blood acidification, despite similar $\dot{V}O_2$ and leg blood flows in both phases of diagonal skiing. The latter implies that for a given $\dot{V}O_2$, facilitating the off-loading of O₂ from the Hb is associated with increased arm and leg O₂ extraction values during exercise. Thus our experiment shows that the conditions for the off-loading of O₂ from the Hb may influence O₂ extraction in the arm and leg muscles. However, despite small differences in blood temperature and the greater release of lactate and protons during the arm exercise (29, 69), the conditions at which the O₂ dissociation curve of Hb operates are similar in the arm and leg muscles (see Fig. 3). Thus the lower arm O₂ extraction capacity cannot be explained by a slower off-loading of O₂ from the Hb in the arms, because the *in vivo* affinity of Hb for O₂ was similar in the arms and legs during both submaximal and maximal exercise.

Capillary muscle P_{O₂} and O₂ conductance. In this investigation we calculated the capillary muscle O₂ conductance by assuming that mitochondrial P_{O₂} is very close to 0–2 mmHg during double poling and during maximal exercise with the diagonal technique. This assumption is likely to be true in muscles working near their maximum (53, 64). Muscle mass is a major determinant of the muscle capillary O₂ conductance. Although it is impossible to know exactly what was the actual muscle mass recruited during the double poling, some estimations can be made. The mean capillary O₂ conductance of the whole arm of our skiers was 14.5 ml·min⁻¹·mmHg⁻¹, i.e., a bit lower than the value of 16.6 ml·min⁻¹·mmHg⁻¹ reported for the leg muscles in 24 sedentary subjects with a mean body weight of 70 kg (including 7 women) (10). Assuming that the mean muscle mass of the skiers arms was 4–5 kg and that the sedentary subjects had a leg muscle mass of 8 kg, it can be estimated that the skiers had ~40–75% higher muscle capillary O₂ conductance in their arm muscles than the sedentary subjects studied by Cardus et al. (10) had in their legs. In physically active subjects we have obtained values of 25 ml·min⁻¹·mmHg⁻¹ during knee extensor exercise (57), 42.2 ml·min⁻¹·mmHg⁻¹ during maximal exercise on the cycle ergometer in physically active subjects (8), and 55 ml·min⁻¹·mmHg⁻¹ in amateur cyclists (16). Together, these data indicate that cross-country skiers have a rather high capillary muscle O₂ conductance in their arms, similar to that observed in the legs of physically active subjects but lower than reported

in the leg muscles of well-trained subjects having almost the same maximal cardiac output as our skiers (16). Using the data obtained at maximal exercise, we calculated that the muscle mass-normalized leg capillary muscle O₂ conductance is at least 50% higher in the leg muscles than in the arm muscles, assuming an arm muscle mass of 4–5 kg and a leg muscle mass of 10–11 kg. These data, combined with the positive relationship observed between the percentage of arm O₂ extraction and capillary muscle O₂ conductance, suggest that the lower arm-to-leg capillary muscle O₂ conductance may explain part of the lower extraction capacity of the arm muscles than the leg muscles in the elite cross-country skiers. However, the question remains, why is capillary muscle O₂ conductance lower in the arm than in the leg muscles?

MTT and heterogeneity in blood flow distribution. A larger MTT may facilitate the transfer of O₂ from the erythrocyte to the mitochondria (47). The MTT of the erythrocytes crossing the muscle capillaries during maximal exercise is estimated as MTT = CBV/MBF, where CBV is the capillary blood volume and MBF is the muscle blood flow. In turn, the capillary volume may be calculated from the capillary density (31). We did not measure the capillary density in the current investigation, but from previous studies in elite cross-country skiers of the same level of performance as the present subjects, it appears that the capillary density is similar in arm and leg muscles (Table 4) (38, 39, 42). With a mean capillary density of 500 capillaries in arm and leg muscles of elite cross-country skiers, a similar MTT through the capillaries is expected in the muscles of the upper and lower extremities. For example, if at maximal exercise the active muscle mass is 4 and 11 kg in the arm and legs, respectively, the calculated MTT values will be 672 and 674 ms, respectively (31). However, the corresponding values will be 1,195 and 1,198 ms if an inner mean capillary diameter of 6.0 μm rather than 4.5 μm is assumed. What these numbers suggest is that MTT is rather high in both upper and lower extremities at maximal exercise. At first sight, MTT does not appear to explain the observed differences in O₂ extraction between the arms and legs. However, heterogeneity in macrovascular MTT has been related to O₂ extraction during low exercise intensity in humans (30). Nevertheless, macrovascular MTT heterogeneity decreases with exercise intensity, but the degree of skeletal muscle capillary MTT heterogeneity existing at maximal exercise remains unknown. In theory, MTT values lying between 0.3 and a little more than 1 s are possible (63).

In our experimental conditions, where exercise is performed at maximal intensity, there is no reason to suspect a mismatch, shunt, or differences in capillary length between the perfused and the active fibers (72) in arm and leg muscles (14, 26). However, we cannot rule out a greater degree of heterogeneity in the distribution of blood flow between muscles in the arms

Table 4. $\dot{V}O_{2\max}$, capillary density, CS activity, HAD activity, % ST, and capillary index of cross-country skiers

Muscle	$\dot{V}O_{2\max}$, ml·kg ⁻¹ ·min ⁻¹	<i>n</i>	Capillary Density, cap/mm ²	CS Activity, $\mu\text{mol}\cdot\text{g dry wt}^{-1}\cdot\text{min}^{-1}$	HAD Activity, $\mu\text{mol}\cdot\text{g dry wt}^{-1}\cdot\text{min}^{-1}$	%ST	Mean Fiber Area, μm^2	Cap/Fiber	Capillary Index	Reference
Vastus lateralis	76	3 ^a	654	88	74	72	5,200	3.4	0.0133	Saltin et al. ^d
Vastus lateralis	76	4 ^b	553	82	66		5,600	3.1	0.0116	Saltin et al. ^d
Vastus lateralis	72	6 ^b		51	38					Van Hall et al. (69)
Deltoid (posterior)	76	3 ^a	582	76	61	61	5,300	3.1	0.0118	Saltin et al. ^d
Deltoid (posterior)	76	4 ^b	560	68	60		5,400	3.0	0.0115	Saltin et al. ^d
Deltoid (posterior)	72	3 ^b		38	22					Van Hall et al. (69)
Gastrocnemius (lateral)	72	8 ^b	596	74	49	60	4,800	2.7	0.0110	Mizuno et al. (38)
Triceps (lateral)	72	8 ^b	492	59	34	45	6,400	3.1	0.0108	Mizuno et al. (38)
Triceps (lateral)	71	9 ^b	415	55	43	61	7,500	3.2	0.0104	Terzis et al. ^d
Vastus lateralis	76	10	422	49	31	69	6,100	2.5	0.0090	Mygind et al. (39)
Triceps (lateral)	76	10	373	39	20	51	7,400	2.7	0.0089	Mygind et al. (39)
Rectus femoris		17 ^c	411					2.9		Parsons et al. (42)
Triceps (lateral)		17 ^c	536					4.9		Parsons et al. (42)

$\dot{V}O_{2\max}$, maximum O₂ uptake; CS, citrate synthase; HAD, 3-hydroxyacyl-CoA dehydrogenase; %ST, percentage of slow-twitch fibers; Cap, no. of capillaries. Capillary index is the mean no. of capillaries around each fiber per mean muscle fiber perimeter; *n* represents the no. of cross-country skiers: ^atop-level skiers, ^bclose to elite-level skiers, ^c7 women and 10 men skiers ($\dot{V}O_{2\max}$ not reported). ^dUnpublished data.

than in the legs. In fact, electromyographic activity data show large interindividual differences in the degree of recruitment of upper arm muscles during double poling (25). Lower O₂ extraction may be expected in the muscles that are less activated, hence also contributing to a low mean O₂ extraction of the whole extremity. Moreover, upper compared with lower extremities differ in degree of freedom of movement. Leg flexion and extension is performed in a rigid back and forward pattern with only minor variation in the activation of the different muscles and their functional portions. Arm and shoulder muscles, on the other hand, perform their movements in different positions, resulting in larger variation in the degree of muscle recruitment. Hence the mass of active muscles in the arm and shoulder region may be overestimated in cross-country skiing. In turn, the actual MTT across the active arm muscles may be shorter than the calculated value of 672 ms if flow is passing through a smaller capillary bed. In case of a lower active muscle mass in the upper extremity than assumed in this study, the real skeletal muscle O₂ conductance of the arms would have been underestimated. However, as explained below, this fact cannot explain alone the observed differences in muscle O₂ conductance between arms and legs.

The transfer of O₂ from the Hb to the mitochondria should overcome the resistance imposed by the elements interposed between the Hb molecule and the mitochondrial matrix. It seems that most of the resistance to the diffusion of O₂ from the Hb to the mitochondria relies on the capillary wall (23, 24, 56). Increasing the number of capillaries around each fiber (i.e., the amount of capillary-to-muscle fiber exchange surface) is likely the most efficient way to improve the muscle conductance for O₂ (72). In fact, endurance training induces an increase in the number of capillaries (2). Capillary proliferation appears more accentuated in elite endurance athletes (60, 63, 65) and the longer the time of sport participation (60). Conditions in which the conductance of O₂ has been lowered by reducing the mitochondrial oxidative capacity (36) or by eliminating the presence of myoglobin in the sarcoplasm (18) are associated with capillary proliferation as a compensation mechanism. Although it seems that capillary density is similar in the leg and arms muscles of cross-country skiers (Table 4), the capillary-to-fiber perimeter index (mean number of capil-

laries around each fiber/mean muscle fiber perimeter) is slightly higher in the leg than in the arm muscles because of the higher mean fiber cross-sectional area of the arm muscles. Using the data in Table 4, we have calculated a mean capillary index of 0.011 and 0.010 capillaries per micrometer of capillary perimeter in the leg and arm muscles, respectively. Thus the available morphometric data suggest that the diffusional area is lower and the diffusional distance longer in the arm than in the leg muscles.

Muscle oxidative capacity. Despite the great amount of training performed by these subjects with the arm muscles, deltoid muscle oxidative capacity was lower than vastus lateralis oxidative capacity, as reflected by the 25 and 11% lower CS and HAD activities in the deltoid compared with the vastus lateralis muscles of our skiers (69). However, no relationship was observed between capillary muscle O₂ conductance and the activities of CS and HAD. Previous studies also have reported lower CS and HAD activities in the triceps brachii than in the vastus lateralis in cross-country skiers (39) (Table 4). It is difficult to establish to what extent the role of this reduced oxidative capacity may be in the lower O₂ extraction capacity of the arms, but some animal in vitro experiments support this possibility (22, 37, 58) while others do not (36). In humans, however, prolonged bed rest results in reduced mitochondrial volume and muscle oxidative enzyme activities while O₂ extraction during maximal exercise is elevated (13, 62). In addition, the fact that $\dot{V}O_{2\max}$ increases with hyperoxia in the trained quadriceps of elite athletes (52) and patients with restricted physical activity due to respiratory insufficiency (55) suggests that humans, regardless of trained status (21), do not use their maximal mitochondrial oxidative capacity even when exercising at $\dot{V}O_{2\max}$ with a small muscle mass (27). In fact, it has been estimated that only 20% of the muscle mass has to be recruited to tax the maximal oxidative capacity in humans (4). This corresponds well with the observation made in rats that maximal muscle O₂ extraction remains unchanged despite a 45 and 30% reduction in cytochrome oxidase and of CS activity, respectively (36). Despite the fact that the arm oxidative capacity of the elite cross-country skiers is lower than their leg muscle oxidative capacity (39), it is likely far in excess of their respective maximal O₂ demand (4). In support, we can argue

that rowing $\dot{V}O_{2\max}$ increases with hyperoxia in elite rowers, a discipline in which there is a substantial contribution of the arms to the exercise $\dot{V}O_{2\max}$ (41, 45). In addition, Clausen et al. (11) showed that after 5 wk of leg training, the whole body $\dot{V}O_2$ during maximal arm cranking increased by 10%, whereas the arm arterial-venous difference in O₂ content remain unchanged. Thus our data and those summarized in Table 4 suggest that the small difference in oxidative capacity between arm and leg muscles has a minor role, if any, in the lower maximal arm O₂ extraction capacity.

Increased arm vascular reactivity? Under resting conditions, the forearms have higher vasodilatory responsiveness to acetylcholine, substance P, nitroprusside (40), and isoproterenol (28) and lower vasoconstricting responsiveness to phenylephrine (α_1 agonist) (43). These functional differences between arms and legs suggest increased ability to maintain vasodilation in the arms than in the legs under some level of ongoing sympathetic activation. Thus our data could be interpreted to indicate that the lower O₂ extraction in the arms only reflects a compensation for the relatively greater perfusion of the arms compared with the legs. However, if the reason for the lower O₂ extraction of the arms was that the arms vasodilated in excess, then O₂ extraction should have been similar in arms and legs at peak exercise with the diagonal style, because during this condition, perfusion of the arm and legs is limited by the pumping capacity of the heart (9). Nevertheless, peak arm blood flow reached a much lower value during maximal combined arm and leg exercise than during double poling, while O₂ extraction remained at a lower level in the arms than in the legs. Although the reported higher vascular reactivity of the forearm at rest may facilitate the vasodilatory response in the arms during combined arm and leg exercise, it remains unknown whether vascular reactivity remains higher in the arm than in the leg muscles during exercise. It may be that it does not, given that vascular reactivity during exercise is modulated by the compound action of several vasodilating and vasoconstricting agents (12). For example, 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 the 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 (66). This mechanism will give the perfusing priority to the main locomotory muscles. However, in case of competition for blood flow between the leg muscles and the respiratory muscles, the perfusion priority is likely given to the respiratory muscles (19).

Potential limitations. Although limited by the fact that O₂ extraction at maximal exercise intensity was not determined during isolated exercise with either the upper and the lower extremities, our results are clear: O₂ extraction across the upper extremities is lower than oxygen extraction across the lower extremities at a given absolute and relative exercise intensity. Given the fact that venous effluent blood from either extremity drains blood principally coming from the active muscles, the skin, and the bone marrow, the calculated extraction values represent the mean extraction capacity of the whole extremity. In theory, the skeletal muscles of both extremities could have a similar O₂ extraction capacity if the degree of “venous

admixture,” i.e., the amount of blood coming from the bone marrow and the cutaneous circulation at the sampling point, is higher in the arms than in the legs. However, the magnitude of the differences in fractional O₂ extraction between legs and arms is too high to be accounted for by different degrees of venous admixture. Of all potential contributors to venous admixture, skin blood flow is quantitatively the most important. Skin blood flow increases with body temperature. In these experiments we took measurements of venous Po₂ and O₂ extraction after 12 min of diagonal skiing, and they were repeated after 24 and 36 min of diagonal skiing (data not shown). During this period, exercise intensity was constant, but body temperature increased significantly from 38.1 to 38.6°C. Despite this increase in body temperature, and likely in skin blood flow (17), no increase in venous Po₂ or reduction in O₂ extraction was observed in arms or legs. This suggests that the degree of admixture is small and is not accentuated by a condition that increases skin blood flow. Moreover, we have calculated that during double poling, venous admixture in the upper extremities should have been at least 1.1 l/min greater than in the lower extremities in case the skeletal muscle O₂ extraction values in arm muscles during double poling were similar to the O₂ extraction in the leg muscles during leg skiing. This means that total venous admixture should have been 2.2 l/min higher in the upper than in the lower extremities, which does not seem reasonable because it would imply an impossible regional difference in cutaneous vasodilation between the upper and the lower extremities (34). Moreover, forearm exercise experiments were performed in the 1960s with venous catheters placed in deep forearm veins (under X-ray control) to avoid skin contamination and with a cuff inflated around the wrist at >200 mmHg to exclude the circulation of the hand (74). In these experiments, maximal exercise extraction values were lower than reported in the current investigation for the whole upper extremity (74).

Even with our state-of-the-art technology it is impossible to know the accurate amount of muscle mass activated during arm or leg exercise. Even worse, it is not possible to know to what extent the motor units are activated. The latter limitation also applies to human models of localized exercise such as the leg extension model. This problem holds for both extremities. The only way to circumvent this limitation is by using animal preparations, which may be stimulated electrically to activate maximally all motor units. However, these preparations show lower D_{O₂} values than reported in vivo simply because with these preparations $\dot{V}O_{2\text{ peak}}$ values in most models are ~50% of the real in vivo $\dot{V}O_{2\text{ peak}}$ values. Our lower D_{O₂} values agree well with the observation of lower O₂ extraction capacity for the arms. For an active muscle mass of 5 and 11 kg in arms and legs, a local muscle $\dot{V}O_2$ of 138 and 147 ml/kg muscle mass can be calculated in the arms during double poling and in the legs during maximal diagonal stride, respectively. The corresponding “muscle-mass-normalized D_{O₂}” is 2.9 and 4.4 ml·min⁻¹·mmHg⁻¹·kg muscle mass⁻¹. Arm muscle mass-normalized D_{O₂} would have matched leg muscle-mass-normalized D_{O₂} for an active muscle mass of 3.3 kg in the arms and 11 kg in the legs. This proportion 3.3/11 (arm/leg active muscle mass) allows for a match in muscle mass-normalized D_{O₂} between arm and leg muscles but is simply impossible, because the $\dot{V}O_{2\text{ peak}}$ per kilogram of active muscle mass would have been 209 and 147 ml/kg, i.e., 42% higher in the arm than in leg

muscles. Thus only a lower value of muscle mass-normalized D_{O₂} in the arm muscles fits both our results and the current scientific knowledge.

In summary, the present investigation shows that O₂ extraction is closely related to the in vivo P₅₀ during arm exercise in humans with highly endurance trained arm and leg muscles. However, for a given P₅₀ value, the arms have lower O₂ extraction and lower capillary muscle O₂ conductance values than the leg muscles. Because the conditions for the O₂ off-loading from the Hb are similar in leg and arm muscles, the observed differences in maximal arm and leg O₂ extraction should be attributed to other factors, such as a higher diffusing distance and higher heterogeneity in the distribution of blood flow between muscles or functional portions of the same muscle, or lower mean transit time and lower diffusing area in the arms than in the legs. These findings have implications to explain the differences in the cardiorespiratory response to arm vs. leg exercise, because the lower the muscular extraction capacity, the greater should be the blood flow, and hence the cardiovascular effort, to maintain a given metabolic rate.

ACKNOWLEDGMENTS

We highly appreciate help from the staff and the use of facilities at the Department of Cardiology and Clinical Physiology, Karolinska Hospital, Sweden. We also acknowledge the excellent technical assistance provided by Birgitte Jessen and Karen Juel.

GRANTS

This study was supported by grants from the Swedish Olympic Committee, Team Danmark, and the Sport Research Council of the Ministry of Culture. The Copenhagen Muscle Research Center is funded by Danish National Research Foundation Grant 504-14.

REFERENCES

- Ahlborg G and Jensen-Urstad M. Arm blood flow at rest and during arm exercise. *J Appl Physiol* 70: 928–933, 1991.
- Andersen P and Henriksson J. Capillary supply of the quadriceps femoris muscle of man: adaptive response to exercise. *J Physiol* 270: 677–690, 1977.
- Andersen P and Saltin B. Maximal perfusion of skeletal muscle in man. *J Physiol* 366: 233–249, 1985.
- Blomstrand E, Radegran G, and Saltin B. Maximum rate of oxygen uptake by human skeletal muscle in relation to maximal activities of enzymes in the Krebs cycle. *J Physiol* 501: 455–460, 1997.
- Brooke MH and Kaiser KK. Three “myosin adenosine triphosphatase” systems: the nature of their pH lability and sulfhydryl dependence. *J Histochem Cytochem* 18: 670–672, 1970.
- Calbet JA. Oxygen tension and content in the regulation of limb blood flow. *Acta Physiol Scand* 168: 465–472, 2000.
- Calbet JA, Boushel R, Radegran G, Sondergaard H, Wagner PD, and Saltin B. Determinants of maximal oxygen uptake in severe acute hypoxia. *Am J Physiol Regul Integr Comp Physiol* 284: R291–R303, 2003.
- Calbet JA, Boushel R, Radegran G, Sondergaard H, Wagner PD, and Saltin B. Why is $\dot{V}O_{2\max}$ after altitude acclimatization still reduced despite normalization of arterial O₂ content? *Am J Physiol Regul Integr Comp Physiol* 284: R304–R316, 2003.
- Calbet JA, Jensen-Urstad M, Van Hall G, Holmberg HC, Rosdahl H, and Saltin B. Maximal muscular vascular conductances during whole body upright exercise in humans. *J Physiol* 558: 319–331, 2004.
- Cardus J, Marrades RM, Roca J, Barbera JA, Diaz O, Masclans JR, Rodriguez-Roisin R, and Wagner PD. Effects of F_{IO₂} on leg $\dot{V}O_2$ during cycle ergometry in sedentary subjects. *Med Sci Sports Exerc* 30: 697–703, 1998.
- Clausen JP, Klausen K, Rasmussen B, and Trap-Jensen J. Central and peripheral circulatory changes after training of the arms or legs. *Am J Physiol* 225: 675–682, 1973.
- Clifford PS and Hellsten Y. Vasodilatory mechanisms in contracting skeletal muscle. *J Appl Physiol* 97: 393–403, 2004.
- Ferretti G, Antonutto G, Denis C, Hoppeler H, Minetti AE, Narici MV, and Desplanches D. The interplay of central and peripheral factors in limiting maximal O₂ consumption in man after prolonged bed rest. *J Physiol* 501: 677–686, 1997.
- Fuglevand AJ and Segal SS. Simulation of motor unit recruitment and microvascular unit perfusion: spatial considerations. *J Appl Physiol* 83: 1223–1234, 1997.
- Gayeski TE and Honig CR. O₂ gradients from sarcolemma to cell interior in red muscle at maximal $\dot{V}O_2$. *Am J Physiol Heart Circ Physiol* 251: H789–H799, 1986.
- Gonzalez-Alonso J and Calbet JA. Reductions in systemic and skeletal muscle blood flow and oxygen delivery limit maximal aerobic capacity in humans. *Circulation* 107: 824–830, 2003.
- Gonzalez-Alonso J, Calbet JA, and Nielsen B. Muscle blood flow is reduced with dehydration during prolonged exercise in humans. *J Physiol* 513: 895–905, 1998.
- Grange RW, Meeson A, Chin E, Lau KS, Stull JT, Shelton JM, Williams RS, and Garry DJ. Functional and molecular adaptations in skeletal muscle of myoglobin-mutant mice. *Am J Physiol Cell Physiol* 281: C1487–C1494, 2001.
- Harms CA, Babcock MA, McClaran SR, Pegelow DF, Nickle GA, Nelson WB, and Dempsey JA. Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol* 82: 1573–1583, 1997.
- Haseler LJ, Lin AP, and Richardson RS. Skeletal muscle oxidative metabolism in sedentary humans: ³¹P-MRS assessment of O₂ supply and demand limitations. *J Appl Physiol* 97: 1077–1081, 2004.
- Henriksson J and Reitman JS. Time course of changes in human skeletal muscle succinate dehydrogenase and cytochrome oxidase activities and maximal oxygen uptake with physical activity and inactivity. *Acta Physiol Scand* 99: 91–97, 1977.
- Hepple RT, Hagen JL, and Krause DJ. Oxidative capacity interacts with oxygen delivery to determine maximal O₂ uptake in rat skeletal muscles in situ. *J Physiol* 541: 1003–1012, 2002.
- Hepple RT, Hogan MC, Stary C, Bebout DE, Mathieu-Costello O, and Wagner PD. Structural basis of muscle O₂ diffusing capacity: evidence from muscle function in situ. *J Appl Physiol* 88: 560–566, 2000.
- Hogan MC, Bebout DE, and Wagner PD. Effect of increased Hb-O₂ affinity on $\dot{V}O_{2\max}$ at constant O₂ delivery in dog muscle in situ. *J Appl Physiol* 70: 2656–2662, 1991.
- Holmberg HC, Lindinger S, Stöggl T, Eizlmeyer E, and Mueller E. Biomechanical analysis of double poling in elite cross-country skiers. *Med Sci Sports Exerc* 37: 807–818, 2005.
- Honig CR, Odoroff CL, and Frierson JL. Active and passive capillary control in red muscle at rest and in exercise. *Am J Physiol Heart Circ Physiol* 243: H196–H206, 1982.
- Hopman MT, Folgering HT, Groothuis JT, and Houtman S. The effect of inspired oxygen fraction on peak oxygen uptake during arm exercise. *Eur J Appl Physiol* 90: 120–124, 2003.
- Jacob G, Costa F, Shannon J, Robertson D, and Biaggioni I. Dissociation between neural and vascular responses to sympathetic stimulation: contribution of local adrenergic receptor function. *Hypertension* 35: 76–81, 2000.
- Jensen-Urstad M and Ahlborg G. Is the high lactate release during arm exercise due to a low training status? *Clin Physiol* 12: 487–496, 1992.
- Kalliokoski KK, Knuuti J, and Nuutila P. Blood transit time heterogeneity is associated to oxygen extraction in exercising human skeletal muscle. *Microvasc Res* 67: 125–132, 2004.
- Kayar SR, Hoppeler H, Jones JH, Longworth K, Armstrong RB, Laughlin MH, Lindstedt SL, Bicudo JE, Groebe K, Taylor CR, and Weibel ER. Capillary blood transit time in muscles in relation to body size and aerobic capacity. *J Exp Biol* 194: 69–81, 1994.
- Kelman GR. Digital computer subroutine for the conversion of oxygen tension into saturation. *J Appl Physiol* 21: 1375–1376, 1966.
- Knight DR, Schaffartzik W, Poole DC, Hogan MC, Bebout DE, and Wagner PD. Effects of hyperoxia on maximal leg O₂ supply and utilization in men. *J Appl Physiol* 75: 2586–2594, 1993.
- Kondo N, Takano S, Aoki K, Shibasaki M, Tominaga H, and Inoue Y. Regional differences in the effect of exercise intensity on thermoregulatory sweating and cutaneous vasodilation. *Acta Physiol Scand* 164: 71–78, 1998.
- Koskolou MD, Roach RC, Calbet JA, Radegran G, and Saltin B. Cardiovascular responses to dynamic exercise with acute anemia in humans. *Am J Physiol Heart Circ Physiol* 273: H1787–H1793, 1997.

36. **McAllister RM, Ogilvie RW, and Terjung RL.** Impact of reduced cytochrome oxidase activity on peak oxygen consumption of muscle. *J Appl Physiol* 69: 384–389, 1990.
37. **McAllister RM and Terjung RL.** Acute inhibition of respiratory capacity of muscle reduces peak oxygen consumption. *Am J Physiol Cell Physiol* 259: C889–C896, 1990.
38. **Mizuno M, Juel C, Bro-Rasmussen T, Mygind E, Schibye B, Rasmussen B, and Saltin B.** Limb skeletal muscle adaptation in athletes after training at altitude. *J Appl Physiol* 68: 496–502, 1990.
39. **Mygind E.** Fibre characteristics and enzyme levels of arm and leg muscles in elite cross-country skiers. *Scand J Med Sci Sports* 5: 76–80, 1995.
40. **Newcomer SC, Leuenberger UA, Hogeman CS, Handly BD, and Proctor DN.** Different vasodilator responses of human arms and legs. *J Physiol* 556: 1001–1011, 2004.
41. **Nielsen HB, Madsen P, Svendsen LB, Roach RC, and Secher NH.** The influence of P_aO₂, pH and S_aO₂ on maximal oxygen uptake. *Acta Physiol Scand* 164: 89–87, 1998.
42. **Parsons D, McIntyre K, Schultz W, and Stray-Gundersen J.** Capillarity of elite cross-country skiers: a lectin (*Ulex europaeus* I) marker. *Scand J Med Sci Sports* 3: 89–98, 1993.
43. **Pawelczyk JA and Levine BD.** Heterogeneous responses of human limbs to infused adrenergic agonists: a gravitational effect? *J Appl Physiol* 92: 2105–2113, 2002.
44. **Pedersen PK, Kiens B, and Saltin B.** Hyperoxia does not increase peak muscle oxygen uptake in small muscle group exercise. *Acta Physiol Scand* 166: 309–318, 1999.
45. **Peltonen JE, Rantamaki J, Niittymaki SP, Sweins K, Viitasalo JT, and Rusko HK.** Effects of oxygen fraction in inspired air on rowing performance. *Med Sci Sports Exerc* 27: 573–579, 1995.
46. **Pernow B, Saltin B, Wahren J, Cronstrand R, and Ekstrom S.** Leg blood flow and muscle metabolism in occlusive arterial disease of the leg before and after reconstructive surgery. *Clin Sci Mol Med* 49: 265–275, 1975.
47. **Piiper J.** Perfusion, diffusion and their heterogeneities limiting blood-tissue O₂ transfer in muscle. *Acta Physiol Scand* 168: 603–607, 2000.
48. **Piiper J and Haab P.** Oxygen supply and uptake in tissue models with unequal distribution of blood flow and shunt. *Respir Physiol* 84: 261–271, 1991.
49. **Poole JG, Lawrenson L, Kim J, Brown C, and Richardson RS.** Vascular and metabolic response to cycle exercise in sedentary humans: effect of age. *Am J Physiol Heart Circ Physiol* 284: H1251–H1259, 2003.
50. **Qu Z, Andersen JL, and Zhou S.** Visualisation of capillaries in human skeletal muscle. *Histochem Cell Biol* 107: 169–174, 1997.
51. **Rasmussen B, Klausen K, Clausen JP, and Trap-Jensen J.** Pulmonary ventilation, blood gases, and blood pH after training of the arms or the legs. *J Appl Physiol* 38: 250–256, 1975.
52. **Richardson RS, Grassi B, Gavin TP, Haseler LJ, Tagore K, Roca J, and Wagner PD.** Evidence of O₂ supply-dependent $\dot{V}_{O_{2max}}$ in the exercise-trained human quadriceps. *J Appl Physiol* 86: 1048–1053, 1999.
53. **Richardson RS, Newcomer SC, and Noyszewski EA.** Skeletal muscle intracellular PO₂ assessed by myoglobin desaturation: response to graded exercise. *J Appl Physiol* 91: 2679–2685, 2001.
54. **Richardson RS, Noyszewski EA, Kendrick KF, Leigh JS, and Wagner PD.** Myoglobin O₂ desaturation during exercise. Evidence of limited O₂ transport. *J Clin Invest* 96: 1916–1926, 1995.
55. **Richardson RS, Sheldon J, Poole DC, Hopkins SR, Ries AL, and Wagner PD.** Evidence of skeletal muscle metabolic reserve during whole body exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 159: 881–885, 1999.
56. **Richardson RS, Tagore K, Haseler LJ, Jordan M, and Wagner PD.** Increased $\dot{V}_{O_{2max}}$ with right-shifted Hb-O₂ dissociation curve at a constant O₂ delivery in dog muscle in situ. *J Appl Physiol* 84: 995–1002, 1998.
57. **Roach RC, Koskolou MD, Calbet JA, and Saltin B.** Arterial O₂ content and tension in regulation of cardiac output and leg blood flow during exercise in humans. *Am J Physiol Heart Circ Physiol* 276: H438–H445, 1999.
58. **Robinson DM, Ogilvie RW, Tullson PC, and Terjung RL.** Increased peak oxygen consumption of trained muscle requires increased electron flux capacity. *J Appl Physiol* 77: 1941–1952, 1994.
59. **Roca J, Agusti AG, Alonso A, Poole DC, Viegas C, Barbera JA, Rodriguez-Roisin R, Ferrer A, and Wagner PD.** Effects of training on muscle O₂ transport at $\dot{V}_{O_{2max}}$. *J Appl Physiol* 73: 1067–1076, 1992.
60. **Rodriguez LP, Lopez-Rego J, Calbet JA, Valero R, Varela E, and Ponce J.** Effects of training status on fibers of the musculus vastus lateralis in professional road cyclists. *Am J Phys Med Rehabil* 81: 651–660, 2002.
61. **Saltin B.** Hemodynamic adaptations to exercise. *Am J Cardiol* 55: 42D–47D, 1985.
62. **Saltin B, Blomqvist G, Mitchell JH, Johnson RL Jr, Wildenthal K, and Chapman CB.** Response to exercise after bed rest and after training. *Circulation* 38, Suppl 5: VII1–VII78, 1968.
63. **Saltin B and Gollnick PD.** Skeletal muscle adaptability: significance for metabolism and performance. In: *Handbook of Physiology. Skeletal Muscle*. Bethesda, MD: Am Physiol Soc, 1983, sect. 10, p. 555–631.
64. **Severinghaus JW.** Exercise O₂ transport model assuming zero cytochrome P_{o2} at $\dot{V}_{O_{2max}}$. *J Appl Physiol* 77: 671–678, 1994.
65. **Sjogaard G.** Muscle morphology and metabolic potential in elite road cyclists during a season. *Int J Sports Med* 5: 250–254, 1984.
66. **Strange S.** Cardiovascular control during concomitant dynamic leg exercise and static arm exercise in humans. *J Physiol* 514: 283–291, 1999.
67. **Stringer W, Wasserman K, Casaburi R, Porszasz J, Maehara K, and French W.** Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol* 76: 1462–1467, 1994.
68. **van Hall G, Calbet JA, Sondergaard H, and Saltin B.** The re-establishment of the normal blood lactate response to exercise in humans after prolonged acclimatization to altitude. *J Physiol* 536: 963–975, 2001.
69. **Van Hall G, Jensen-Urstad M, Rosdahl H, Holmberg HC, Saltin B, and Calbet JA.** Leg and arm lactate and substrate kinetics during exercise. *Am J Physiol Endocrinol Metab* 284: E193–E205, 2003.
70. **Volianitis S and Secher NH.** Arm blood flow and metabolism during arm and combined arm and leg exercise in humans. *J Physiol* 544: 977–984, 2002.
71. **Wagner PD.** Algebraic analysis of the determinants of $\dot{V}_{O_{2max}}$. *Respir Physiol* 93: 221–237, 1993.
72. **Wagner PD.** Diffusive resistance to O₂ transport in muscle. *Acta Physiol Scand* 168: 609–614, 2000.
73. **Wagner PD.** Gas exchange and peripheral diffusion limitation. *Med Sci Sports Exerc* 24: 54–58, 1992.
74. **Wahren J.** Quantitative aspects of blood flow and oxygen uptake in the human forearm during rhythmic exercise. *Acta Physiol Scand Suppl* 269: 1–93, 1966.