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MAXIMAL PERFUSION OF SKELETAL MUSCLE IN MAN

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SUMMARY

1. Five subjects exercised with the knee extensor of one limb at work loads ranging from 10 to 60 W. Measurements of pulmonary oxygen uptake, heart rate, leg blood flow, blood pressure and femoral arterial–venous differences for oxygen and lactate were made between 5 and 10 min of the exercise.

2. Flow in the femoral vein was measured using constant infusion of saline near 0 °C. Since a cuff was inflated just below the knee during the measurements and because the hamstrings were inactive, the measured flow represented primarily the perfusion of the knee extensors.

3. Blood flow increased linearly with work load right up to an average value of 5·7 l min^{-1}. Mean arterial pressure was unchanged up to a work load of 30 W, but increased thereafter from 100 to 130 mmHg. The femoral arterial–venous oxygen difference at maximum work averaged 14·6 % (v/v), resulting in an oxygen uptake of 0·80 l min^{-1}. With a mean estimated weight of the knee extensors of 2·30 kg the perfusion of maximally exercising skeletal muscle of man is thus in the order of 2·5 l $\mathrm{kg}^{-1}\ \mathrm{min}^{-1}$, and the oxygen uptake 0·35 l $\mathrm{kg}^{-1}\ \mathrm{min}^{-1}$.

4. Limitations in the methods used previously to determine flow and/or the characteristics of the exercise model used may explain why earlier studies in man have failed to demonstrate the high perfusion of muscle reported here.

5. It is concluded that muscle blood flow is closely related to the oxygen demand of the exercising muscles. The hyperaemia at low work intensities is due to vasodilatation, and an elevated mean arterial blood pressure only contributes to the linear increase in flow at high work rates. The magnitude of perfusion observed during intense exercise indicates that the vascular bed of skeletal muscle is not a limiting factor for oxygen transport.

INTRODUCTION

Skeletal muscle constitutes the largest mass of tissue in man and may increase its metabolic rate 100-fold (Asmussen, Christensen & Nielsen, 1939). During heavy bicycle or treadmill exercise large demands are placed on the circulation; cardiac output increases linearly up to values of 20–40 l min^{-1} (for references, see Blomqvist & Saltin, 1983). Measured values for muscle blood flow are in the range of 0·6–1·0 l kg^{-1} min^{-1} (Clausen, 1976; Mellander, 1981). Based on these muscle blood flow values, the active muscle mass would have to be much larger than expected in order to account for the observed cardiac output during maximal exercise in healthy man.

The available methods for determining muscle blood flow in man have limitations, and in the type of exercise used it has been difficult to estimate the muscle mass involved (Bonde-Petersen, Henriksson & Lundin, 1975; Wahren & Jorfeldt, 1973; Cerretelli, Marconi, Pendergast, Meyer, Heisler & Piiper, 1984). In the present study an attempt has been made to isolate the exercise to one muscle group, the knee extensors, the volume of which can be closely estimated. Blood flow has been measured with a thermodilution technique adapted for the present experimental conditions. The data define the relationship between blood flow and oxygen uptake of one muscle group in man at various work intensities.

METHODS

Subjects

Five healthy men participated. They were all fully informed of the risks and discomfort associated with the experiments before they volunteered as subjects. Their age was 25 (21–29) years, height 179 (177–181) cm and body weight 70·8 (68·4–72·5) kg. One of the subjects was sedentary and he had a maximal oxygen uptake of 3·45 l min^{-1}, whereas the others were somewhat more fit. Their maximal oxygen uptake averaged 4·68 (4·50–4·87) l min^{-1} in ordinary two-legged bicycle exercise.

Exercise model

We chose the quadriceps femoris muscle group of one leg to perform the exercise because the contractions could readily be limited to this muscle group (Andersen, Adams, Sjøgaard, Thorboe & Saltin, 1985). Also this muscle mass is such that its oxygen uptake should not be limited by the central circulation (Blomqvist & Saltin, 1983; Andersen *et al.* 1985) or by the dimension of the feeding artery (Pedoe, 1978). Sixty dynamic contractions of the knee extensor muscles per minute were performed, using the experimental set-up shown in Fig. 1. The contraction of the quadriceps femoris muscle caused the lower part of the leg to extend from about 90 to 160 deg flexion. Fly-wheel momentum helps to return the relaxed leg. The angle of the hip was fixed to 90 deg. In order to familiarize the subjects with the exercise procedure and establish their performance capacity, they practised about ten times before the actual experiment.

Blood flow

A constant infusion thermodilution technique was developed for this study, in part using principles similar to those of Pávek, Boska & Selecký (1964). The experimental set-up for flow measurements (Fig. 2) consisted of an infusion pump (Harvard, model 2202A) with calibrated glass syringes cooled with ice bags, connected by a 60 cm polyethylene tube to a stainless-steel coil (3·5 m tube, total volume 46 ml). The coil was placed in a thermobox with ice and water just below the seat of the subject, and connected to the venous catheter stopcock by a 20 cm insulated polyethylene tube. This experimental set-up ensured that the temperature of the injectate was close to 0 °C. At the tip of the venous catheter, the injectate temperature varied with time and rate of infusion. The temperature at this point was measured *in vitro*, with the venous catheter submerged in water at 37 °C. The temperature of the injectate was found to be highly reproducible for each rate of infusion used. The venous catheter (soft Teflon, 7 F, 12 cm long, Fig. 2) was provided with four side holes (diameter 0·4 mm) placed in helical formation over a distance of 1 cm, starting 1 cm from the tip. The thermistor catheter (Edslab TD Probe 94-030-2·5F) was inserted through the venous catheter and was advanced into the vein until the thermistor was located at a distance of 12 cm proximal to the infusion holes. The thermistor was connected to an Edslab computer and the temperature signal was recorded continuously (Siemens, Elema Mingograph) for the whole infusion period (12–16 s).

Infusion rates between 90 and 180 g min^{-1} were selected in order to obtain a drop of approximately 1 °C in blood temperature. The total volume of the injectate was below 50 ml for each measurement.

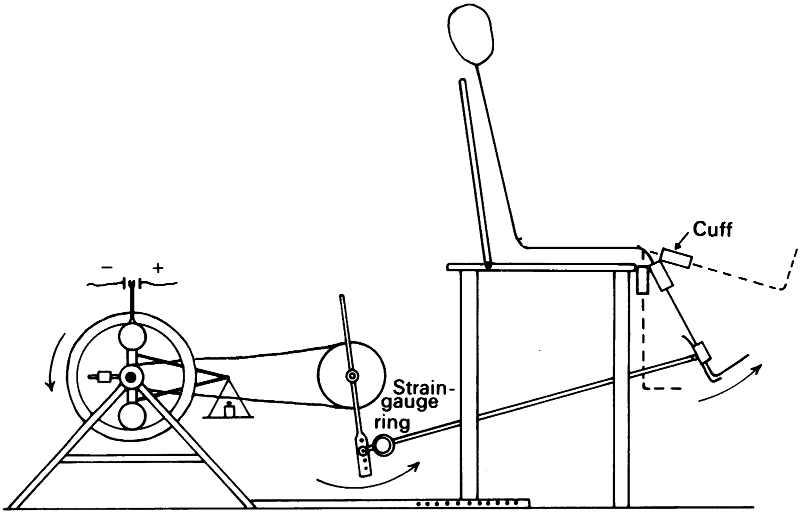

Fig. 1. Schematic drawing of the exercise model used. The subject is kept in place by straps around the hip-joint and distal part of the upper leg. A rod attached to the ankle of the subject and to the crank of the Krogh bicycle ergometer is used to transfer the movement of the lower leg to the bicycle. Fly-wheel momentum returns the relaxed leg.

Flow was calculated according to the equation:

$$(M_B + M_I) \times T_{B2} \times C_{B,I} = M_B \times T_{B1} \times C_B + M_I \times T_I \times C_I,$$

where

M_B and M_I:	mass of blood and infusion solution,
T_{B1}:	blood temperature before infusion,
T_{B2}:	blood temperature during infusion,
T_I:	temperature of infusion solution,
C_B, C_I, $C_{B,I}$:	specific heat of blood, infusion solution and mixed blood and infusion solution (constant values of respectively 0·92, 1·0 and 0·92 are used). Note that flow in volume units is obtained by using a specific gravity of 1·057 for whole blood.

Validity and reproducibility of the method

To test the optimum number and size of the side holes in the infusion catheter at the relevant infusion and flow rates, *in vitro* experiments were performed in which Cardio Green (Indocyanine Green) was added to the injectate solution and infused into a laminar flow of water in a transparent silicone rubber tube (diameter 1 cm). Mixing was evaluated visually using a quartz fibre lamp. The best mixing was attained with four side holes each with a diameter of 0·4 mm.

To validate the method, *in vitro* flow measurements were performed using an experimental set-up designed to imitate the experimental situation (Fig. 3). Among the conditions to fulfil, special care was taken to mimic a pulsatile flow and compression–extension of the vein. A typical temperature recording from the *in vitro* experiment is depicted in Fig. 4 and shows a good similarity with those obtained *in vivo* (cf. Fig. 6). Results obtained from the simultaneous determination of flow by the constant infusion thermodilution technique and by directly measuring flow values were in very good agreement (Fig. 5). The coefficient of variation for all observation was 4·8 % (S.D. in percentage of mean difference) and 3·6 % in the experiments with fluctuations in flow and with manual compression distal to the site of infusion (5–10 and 20 cm). Our results and approach have certain similarities to those in the study by Häggmark, Biber, Sjödin, Winsö, Gustavsson & Reiz (1982),

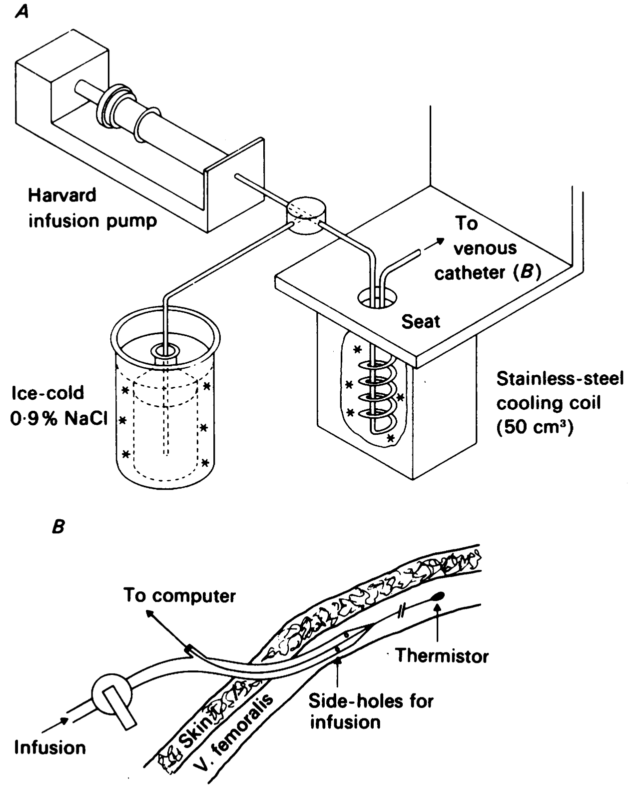

Fig. 2. *A*, schematic illustration of the experimental set-up for blood flow measurements by a constant infusion thermodilution technique. Note that the pump, with its syringe cooled by ice bags, is used to infuse the volume of saline, kept in the stainless-steel cooling coil, into the femoral vein. The coil is submerged in ice water. *B*, an enlargement of the venous catheter set-up, showing the thermistor probe inserted. The end hole of the catheter is closed by the thermistor probe, and the thermistor is located about 12 cm proximal to the side holes of the catheter.

who used and evaluated the constant infusion thermodilution method to measure flow in the portal vein.

The reproducibility of the method in intact man was tested in three of the present subjects at two submaximal levels of work. The coefficient of variation was 4·6 % (mean flow: $\bar{m}$ = 5·1 l min^{-1}). In two sets of additional studies, the reproducibility was further evaluated. In the first series five subjects were tested on different days at a submaximal and a maximal work load. The coefficient of variation during submaximal exercise ws 3·8 % (flow: $\bar{m}$ = 3·4 l min^{-1}) and during maximal exercise, 5·4 % (flow: $\bar{m}$ = 5·8 l min^{-1}). In the second series six subjects were studied repeatedly during 30 min of submaximal exercise between the 10th to 30th minute. The coefficient of variation was 3·4 % (flow; $\bar{m}$ = 5·6 l min^{-1}).

Blood analysis

A fluorometric assay using duplicate 200 μl samples was used to determine lactate concentration (Lowry & Passonneau, 1972).

The blood oxygen saturations (S_{a,O_2} and S_{v,O_2}) were measured on a haemoximeter (OSM-2 Radiometer). The accuracy of the method was verified regularly by determination of oxygen content with a Van Slyke apparatus. P_{O_2} and pH were measured with the Astrup technique (PHM 73 Radiometer). Haemoglobin concentrations in fully oxygenated samples (arterious and venous) were also measured on the haemoximeter: the apparatus was calibrated with several fully oxygenated

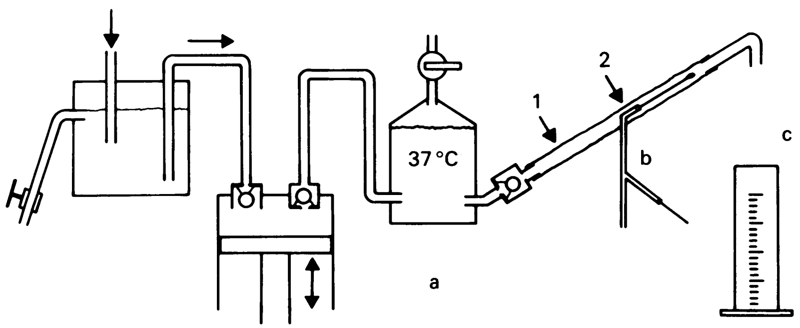

Fig. 3. Schematic illustration of the *in vitro* system used to validate the flow method. The volume of water in the glass bottle (a) and the measuring device (c) were adjusted so that fluctuation in pressure of the rubber tube (b) was similar to that observed in the femoral vein during exercise. A strong pump produced a pulsatile (1 Hz) flow of water (37 °C), which was damped passing through the glass bottle (a). The bicycle rubber tube (diameter 1·4 cm) was compressed rhythmically at a frequency of 60 min^{-1}. This manual compression was either performed close but distal to (2), or approximately 20 cm distal (1) to the infusion site. Point b illustrates the catheter arrangement, which is the same as depicted in Fig. 2*B*. Flow in the rubber tube was measured with the method depicted in Fig. 2, and described in the text and by simultaneous collection of the water outflow (c). In some experiments a stiff silicone rubber tube was used (diameter 1·0 cm) and flow was obtained simply by placing the jar with water (a) well above the arrangement at (b).

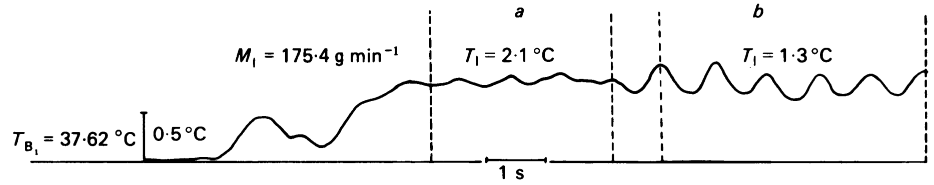

Fig. 4. An original curve depicting lowering of the water temperature in an *in vitro* experiment, which starts with almost stable flow (*a*) and later becomes fluctuating (*b*) due to the compression of the tube distal to the site of the infusion. The water flow was 7·50 l min^{-1} and the thermodilution method gave values of 7·30 (*a*) and 7·48 (*b*) l min^{-1}. See Methods section for explanation of symbols.

blood samples, analysed spectrophotometrically by the cyanmethaemoglobin method (Drabkin & Austin, 1935).

Oxygen uptake

To determine pulmonary oxygen uptake, expired air was collected in Douglas bags, and the volume was measured in a Tissot spirometer. O_2 and CO_2 content were determined with a paramagnetic O_2 analyser (Servomex) and an infra-red CO_2 analyser (Beckman LB-II), regularly calibrated by Scholander analysis.

Thigh volume

Surface measurements of the subjects' thigh length (L) and circumferences (O_1, O_2, and O_3) were performed together with skinfold (S) measurements of the thigh. Thigh volume (V) was then calculated from the formula:

$$V = L \times (12\,\pi)^{-1} \times (O_1^2 + O_2^2 + O_3^2) - (S - 0\cdot4) \times 2^{-1} \times L \times (O_1 + O_2 + O_3) \times 3^{-1}$$

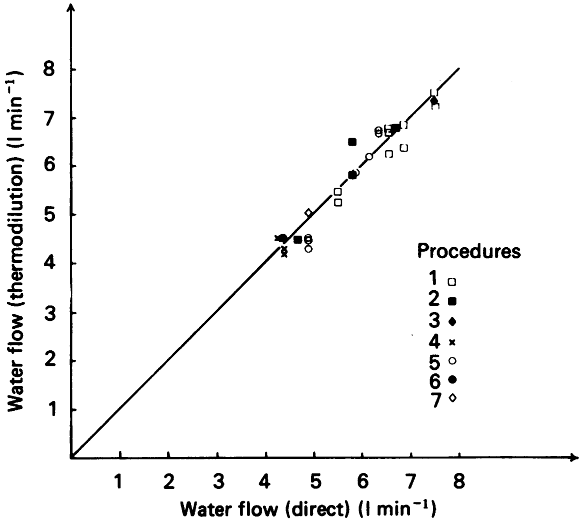

Fig. 5. Results from *in vitro* measurements ($n = 26$), using the set-up depicted in Fig. 3 and comparing directly measured water flow (x axis) with that obtained by the thermodilution method (y axis). Seven different procedures were tried: 1, fluctuation in flow induced by manual compression of the bicycle rubber tube close (but distal) to the site of infusion (as indicated with arrow No. 2); 2, the same as 1, but manual compression approximately 20 cm distal to the site of infusion (arrow 1); 3, fluctuations in flow in the bicycle rubber tube only due to action of the pump; 4, laminar flow in the bicycle rubber tube; 5, the same as in 4, but a stiff silicone rubber tube was used; 6, the same as in 1, but using the silicone rubber tube; 7, laminar flow in the silicone rubber tube with small movements of the thermistor.

(cf. Jones & Pearson, 1969). The quadriceps femoris muscle mass (M) was then calculated as:

$$M = 0{\cdot}307 \times V + 0{\cdot}353 \ (n = 12,\ r = 0{\cdot}93,\ P < 0{\cdot}001),$$

(autopsy study, O. Halskov, personal communication).

Experimental protocol

The subjects arrived at the laboratory in the morning after a light breakfast. Anthropometric measurements for the calculation of thigh volume were made in the supine position. The femoral artery and vein were cannulated 2 and 4 cm, respectively, distal to the inguinal ligamentum. The arterial catheter was advanced 10 cm up-stream and connected to a Siemens blood-pressure transducer. The venous catheter (Fig. 2) was also directed proximally (3–4 cm in the vein). The thermistor catheter (Edslab PD-Probe) was advanced until the thermistor was located 12 cm proximal to the infusion holes. Blood samples could be drawn from both venous and arterial catheters. After placing the catheters, the subject rested for at least 30 min in the supine position and then sat in the knee-extension chair. The equipment was connected and tested for proper function. Each session started with exercise at 10 W, increased by 10 W increments until exhaustion (drop in frequency of contractions). For final adjustment of the maximal load ($\dot{W}_{\text{max}}$) 5 W increments were used. The work time was 10 min at the lower loads and 5½–6½ min at the highest work loads. After 20 min rest and a 5 min warming-up period, work at a load of only 5 W higher than the $\dot{W}_{\text{max}}$ was performed until exhaustion.

To diminish admixture of blood from the lower leg, a 7 cm broad cuff was placed just below the knee of the working leg. It could be inflated instantaneously to 280 mmHg from a pressure chamber operated by electromagnetic valves. The lower leg cuff was kept inflated (280 mmHg) during the last 2–2½ min of work at each load. During this period venous and arterial blood samples were taken

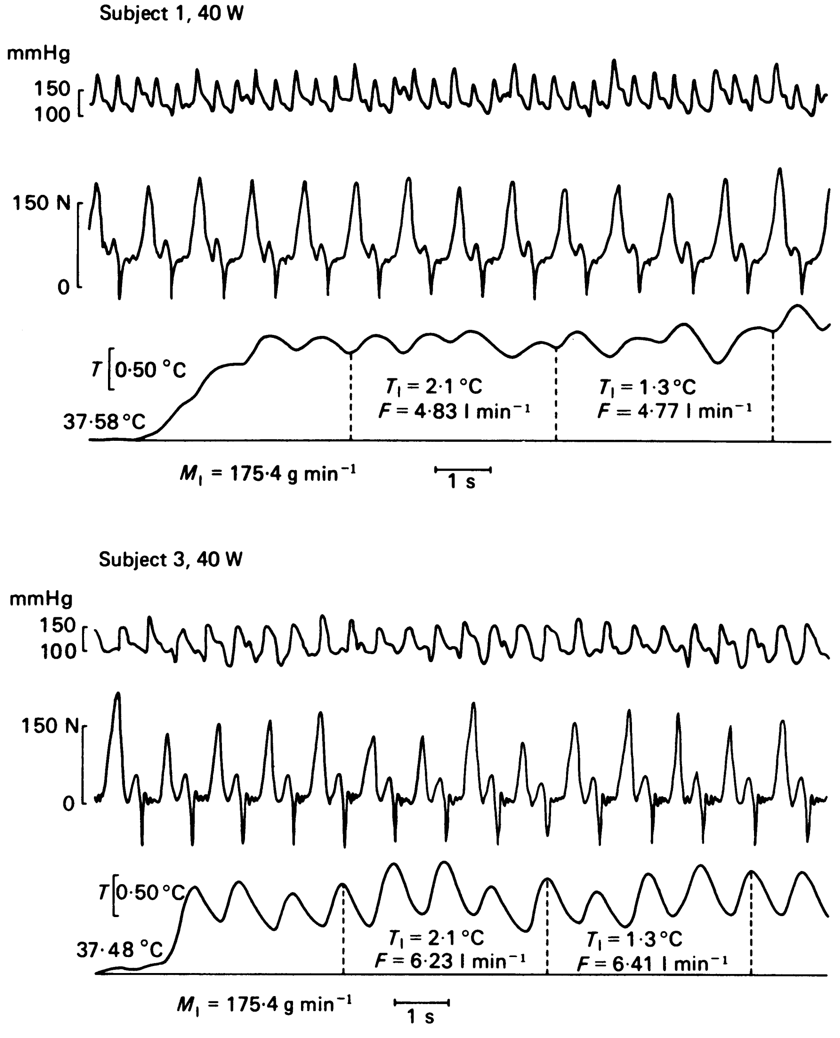

Fig. 6. Original curves from two flow (F) measurements are depicted. In both examples are shown the blood pressure, the force tracing and lowering of the femoral vein temperature during dynamic concentration with the knee extensors when ice-cold saline is infused. Appropriate calculations are given in the Figure. See Methods section for explanation of symbols.

simultaneously and venous flow, blood pressure, and pulmonary oxygen uptake were measured. Mean arterial blood pressure was calculated as diastolic pressure plus one-third of pulse pressure. Heart rate was obtained from the pressure curve.

Examples of venous blood temperature, force, and blood-pressure registrations are shown in Fig. 6. Mean flow is calculated from two 4 s periods (4–8 s, and 8–12 s after onset of infusion), including two times four whole cycles of the varying flow. For each of these periods the mean blood temperature (T_{B2}) was obtained by planimetric integration.

TABLE 1. Pulmonary O_2 uptake ($\dot{V}_{O_2}$), mean arterial blood pressure, muscle blood flow and O_2 uptake, arterial (a) and femoral venous (v) O_2 saturation (S_{O_2}%) and haemoglobin (Hb) concentration at rest and during exercise with the knee extensors. Mean values (±1 S.E. of mean)

				Muscle		S_{O_2} (%)		Hb (g 100 ml^{-1})	
Load (W)	n	Pulmonary $\dot{V}_{O_2}$ (l min^{-1})	Mean arterial blood pressure (mmHg)	Blood flow (l min^{-1})	$\dot{V}_{O_2}$ (l min^{-1})	a	v	a	v
Rest	5	—	—	—	—	97·4 (0·2)	70·8 (5·3)	14·5 (0·6)	14·5 (0·5)
10	5	0·56 (0·02)	100 (3)	2·60 (0·44)	0·28 (0·02)	97·9 (0·1)	42·3 (2·6)	14·7 (0·4)	14·7 (0·4)
20	5	0·68 (0·02)	101 (3)	3·27 (0·22)	0·41 (0·02)	98·0 (0·1)	37·2 (2·5)	14·7 (0·5)	14·8 (0·5)
30	5	0·83 (0·02)	105 (3)	3·94 (0·48)	0·51 (0·04)	97·9 (0·1)	32·9 (2·2)	14·8 (0·5)	14·9 (0·5)
40	5	0·99 (0·03)	116 (6)	4·72 (0·42)	0·65 (0·04)	98·1 (0·2)	30·6 (1·6)	15·0 (0·5)	15·0 (0·5)
55	4	1·39 (0·07)	128 (4)	5·58 (0·33)	0·82 (0·06)	98·5 (0·2)	27·0 (2·5)	15·0 (0·5)	15·1 (0·5)

TABLE 2. Individual values are given for knee extensor muscle mass and maximal work loads and various variables obtained during the maximal exercise with the knee extensor muscle

			Oxygen uptake				
Subject	Muscle mass (kg)	Load (W)	Pulmonary (l min^{-1})	Muscle (l min^{-1})	Blood flow (l min^{-1})	Heart rate (beats min^{-1})	Mean arterial blood pressure (mmHg)
1	2·12	40	0·99	0·69	4·83	156	135
2	2·32	60	1·39	0·96	6·18	131	127
3	2·37	60	1·47	0·92	7·34	155	136
4	2·41	55	1·54	0·70	5·12	153	138
5	2·30	55	1·46	0·75	5·02	135	120
Mean	2·30	54	1·37	0·80	5·70	146	131
S.E. of mean	0·05	4	0·10	0·06	0·47	5	3

RESULTS

Femoral vein blood flow increased linearly with work intensity in all subjects (Fig. 7 and Table 1). Maximal blood flow varied between 4·8 and 7·3 l min^{-1} for the five subjects with a mean of 5·7 l min^{-1} (Table 2). There was some interindividual variation in the absolute values at a given work intensity and one subject deviated rather markedly by exhibiting high flow values. He had a low arterial oxygen content due to a low haemoglobin concentration (12·2 g 100 ml^{-1}). The value of oxygen supplied by the femoral artery (flow times arterial oxygen content) was quite similar for all subjects at any given work intensity. Arterial oxygen saturation was close to 98 % over the entire range of work intensity (Fig. 8 and Table 1). Due to haemoconcentration, the arterial oxygen content ($C_{a,\,O_2}$) increased from 19·2 % (v/v) at rest to 19·6 % (v/v) at 10 W, and to 20·1 % (v/v) at the highest performed work load. At the onset of exercise, femoral vein blood oxygen content ($C_{v,\,O_2}$) dropped substantially from 13·8 % (v/v) at rest to 8·2 % (v/v) at 10 W, and 6·1 % (v/v) at maximal exercise. The corresponding values for femoral vein blood oxygen saturation were 70·8 % at rest, 42·3 % at 10 W, and 29·5 % at the maximal work load. In three subjects P_{O_2} was also measured and it followed the pattern of S_{O_2}. In the femoral vein, P_{O_2} was 45 mmHg at rest, and 28 mmHg at 10 W. It fell slightly at higher loads, but never below 24 mmHg. Oxygen delivered to the knee extensors could be calculated from arterial oxygen content and venous blood flow, corrected for loss of water over the capillary

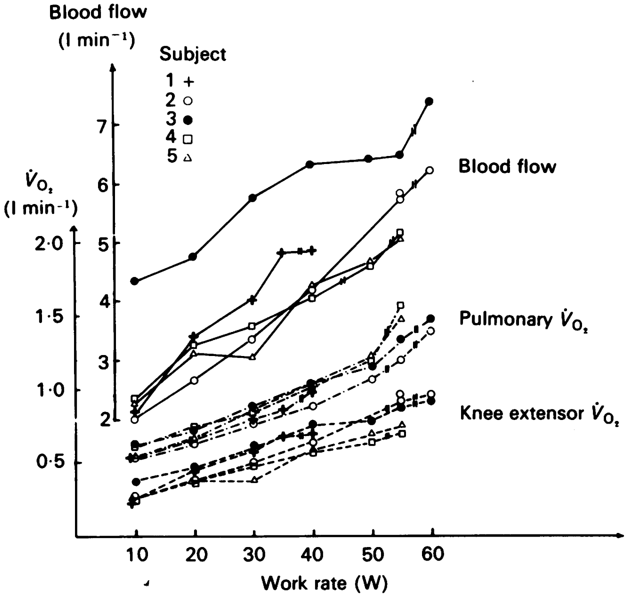

Fig. 7. Individual values for pulmonary oxygen uptake, femoral vein blood flow and knee extensor oxygen uptake at various work levels. The vertical double bars indicate that 20 min of rest followed by a 5 min warm-up period, were inserted between work loads. Note that the subject with a high blood flow (filled circle) had a low haemoglobin concentration (12·2 g 100 ml^{-1}).

bed based on arterial and venous haemoglobin concentrations. The amount of oxygen extracted (muscle $\dot{V}_{O_2}$; y in l min^{-1}) was calculated as oxygen delivered minus femoral vein oxygen outflow, and this estimated value was closely related to the oxygen delivered (x in l min^{-1}) to the knee extensors ($y = 0{\cdot}78x - 0{\cdot}09$; $r = 0{\cdot}98$; S.D. of $x = 0{\cdot}26$; S.D. of $y = 0{\cdot}21$). Mechanical efficiency for the knee-extension work was 24 % based on an observed mean increase in knee extensor $\dot{V}_{O_2}$ of 0·54 l min^{-1} with an increase in work load from 10 W to 55 W.

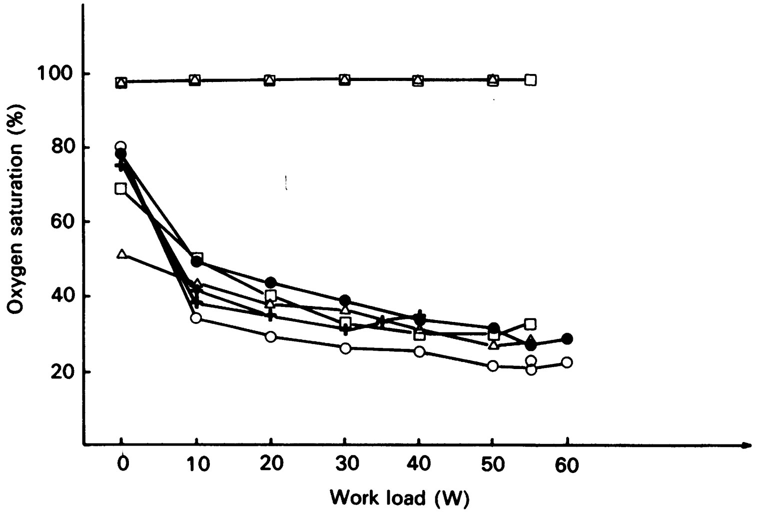

Fig. 8. Individual values for femoral vein oxygen saturation at various exercise levels performed with the quadriceps femoris muscle. Included in the graph is also the mean arterial oxygen saturation, which varied within 2 %. In this and subsequent Figures each subject is represented by a different symbol.

Maximal knee extensor muscle $\dot{V}_{O_2}$ averaged 0·80 l min^{-1} (Table 2), and when the mean value for the mass of the quadriceps femoris muscle was taken into account, it was $0{\cdot}35 \pm 0{\cdot}023$ l min^{-1} kg^{-1}. Over the studied range from very light to maximal exercise, individual values for knee extensor $\dot{V}_{O_2}$ were closely related to the corresponding venous blood flow values, when both variables were expressed as a percentage of the observed maximal oxygen uptakes and blood flows, respectively (Fig. 9).

Pulmonary oxygen uptake increased linearly with increasing loads up to 50 W (Fig. 7), and tended to parallel the increase in knee extensor $\dot{V}_{O_2}$ at a higher level of approximately 0·4 l min^{-1}. At the heaviest work loads there was a further steep increase in pulmonary $\dot{V}_{O_2}$. Heart rate increased in a linear fashion from 83 beats min^{-1} at 10 W to 144 beats min^{-1} at 55 W.

With an increase in work intensity from 10 to 55 W, diastolic pressure increased from 81 to 105 mmHg and systolic pressure from 136 mmHg at 10 W to 176 mmHg. Mean arterial pressure therefore increased from 100 mmHg at 10 W to 128 mmHg at 55 W (Table 1, Fig. 10). Only a small increase in blood pressure was noted at the lower work rates whereas the higher work rates produced a greater increase. Calculated leg vascular resistance (Fig. 10) decreased from 41 u. at 10 W ($n = 5$) to 23 u. at 55 W ($n = 4$). The subjects with the highest maximal flow values exhibited the lowest leg resistance.

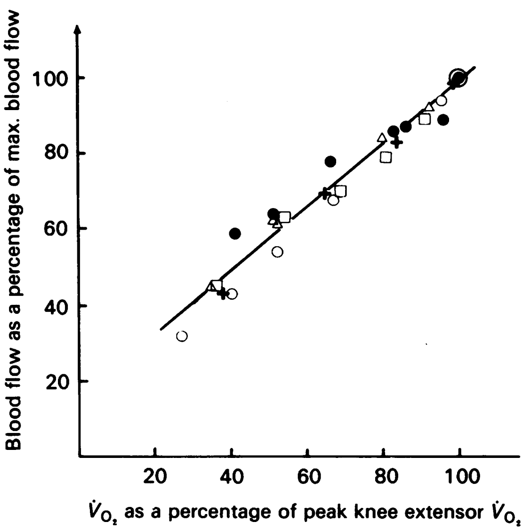

Fig. 9. Individual values for relative work intensity of the knee extensor in relation to relative values for blood flow. Individual values are expressed as a percentage of highest attained values, for knee extensor muscle oxygen uptake and blood flow respectively. The values fit the equation: $y = 0{\cdot}83x + 15{\cdot}36$; $r = 0{\cdot}98$.

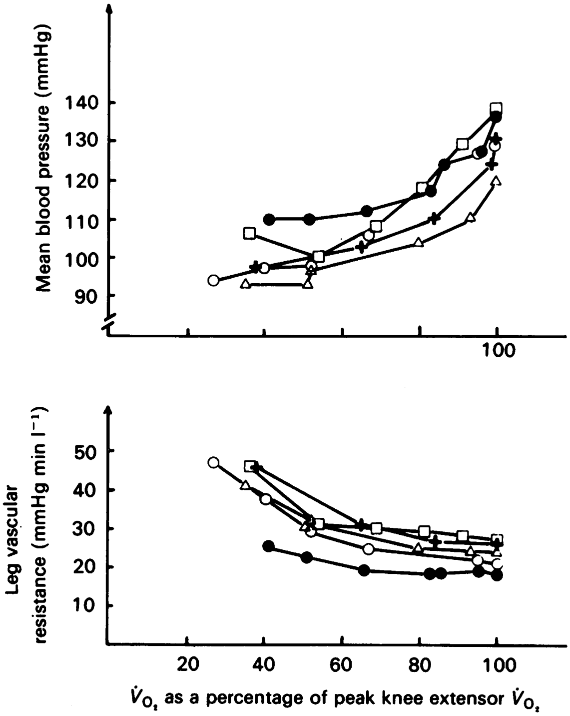

Fig. 10. Individual values for mean blood pressure and leg vascular resistance in relation to the relative work intensity, i.e. observed muscle oxygen uptake × (maximal muscle oxygen uptake)$^{-1}$ × 100.

At rest the arterial lactate concentration was 0·81 mmol l^{-1} and the venous concentration 0·05 mmol l^{-1} higher. At the lowest work load (approximately 40 % of $\dot{V}_{O_2}$ max) no arterial–venous difference was observed (Fig. 11). However, at 20 W (approximately 50 % of $\dot{V}_{O_2}$ max) the venous lactate concentrations were slightly higher than the arterial. Thereafter, a more pronounced difference was noted, especially for relative loads above 70 % of $\dot{V}_{O_2}$ max. At the highest work intensities the lactate concentrations were 1·5–2·0 mmol l^{-1} higher in the femoral vein than in the artery. With blood flow values of 4·8–7·3 l min^{-1} during the most intense exercise, the lactate release reached 10 mmol min^{-1}.

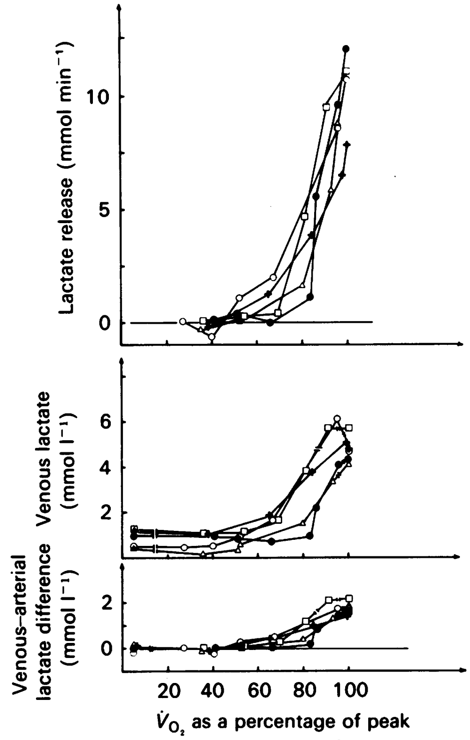

Fig. 11. Individual values for femoral venous lactate concentration, the venous–arterial difference for lactate over the knee extensors as well as the release of lactate from the knee extensors at rest and at various exercise rates expressed in relative terms, i.e. observed muscle oxygen uptake × (maximal muscle oxygen uptake)$^{-1}$ × 100.

DISCUSSION

Quadriceps muscle blood flow increased linearly with increasing work rate without levelling off at heavier work rates. During maximal work, blood flow was 5·7 l min^{-1} and 2·5 l min^{-1} kg^{-1} when expressed in relation to the muscle mass of the knee extensors.

The high value for muscle flow is the anticipated one in view of the actual work performed. Mean maximal work rate amounted to 55 W. In ordinary two-legged bicycle exercise at this intensity, oxygen uptake ranged from 0·7–0·9 l min^{-1} at an apparent mechanical efficiency of 23 % (Åstrand, 1960). The mechanical efficiency of the knee extensors was in the same range (24 %). Thus, with an observed arterial–venous oxygen difference over the knee extensors of 14·0–15·0 % (v/v) and an oxygen demand of 0·7–0·9 l min^{-1}, blood flows in the range of 5–7 l min^{-1} are needed. Of note is also that knee extensor exercise conforms to ordinary whole body exercise in regard to the relation between elevation in blood flow and oxygen uptake. Systemic cardiac output is increased with 5 l min^{-1} per litre of oxygen consumed in the exercise (Rowell, 1974; Lewis, Taylor, Graham, Pettinger, Schutte & Blomqvist, 1983). Knee extensor exercise lies in exactly the same range.

To measure flow to an exercising limb we have chosen a method based on the tracer-dilution principle. However, most tracer-dilution methods are not directly applicable to the present study. Some of the concerns we had were that in flow measurements using bolus injections of tracer or cold saline (Hosie, 1962; Jorfeldt, Juhlin-Dannfelt, Pernow & Wassén, 1978; Sørlie & Myhre, 1977; Klausen, Secher, Clausen, Hartling & Trap-Jensen, 1982) one obvious general problem is the fluctuations in blood flow during dynamic exercise. Multiple randomized measurements which are averaged may compensate for this. The bolus thermodilution techniques are further complicated by a thermistor response time of 0·5–1 s, which is quite long in comparison to the transit time of the cold wave, which in turn varies with blood flow. This factor is not taken into account in the commonly used computerized programs which are only able to compute curves of a predictable shape. Therefore, we preferred to apply a constant infusion technique, and as tracer we used cold saline instead of a dye to avoid problems with recirculation and mixing (Wahren & Jorfeldt, 1973). Our *in vitro* measurements revealed very good validity (Fig. 5) and the reproducibility was very high. Although the flow values are reliable, there is a problem with how large an area is drained by the vein (v. iliaca externa) where the thermistor probe is placed. In addition to a drainage of blood from the thigh, some flow comes from smaller veins joining the main vein just distal and proximal to the inguinal ligament.

Flow to the lower leg can be disregarded, since a cuff was inflated just below the knee. Most of the hamstrings and part of the gluteal muscles as well as the skin of the thigh are drained through the femoral vein. No electromyographic (e.m.g.) activity could be seen in either the hamstrings or the gluteal muscles, during exercise with the knee extensors (cf. also Andersen *et al.* 1985). Thus, no exercise-induced hyperaemia needs to be attributed to these muscles. Whether flow is increased because of the elevated blood pressure at the higher work rates is unknown, but it appears likely that there is a compensating vasoconstriction in the vascular tree of these muscles as with other inactive muscles (Shepherd, 1963) Skin blood flow is elevated, but the total flow from the skin of the thigh may amount at the most to 0·2–0·3 l min^{-1}. This together with the flow in the hamstrings is unlikely to exceed 0·5 l min^{-1}, which is less than 10 % of the observed mean maximal flow rates. This assumption is substantiated by results from experiments where flow has been observed to be in the range of 0·15–0·45 l min^{-1} at rest and when the other leg is exercising submaximally. Thus, we feel certain that the knee extensors during exercise receive 2 l min^{-1} kg^{-1} or more.

Exercise-induced muscle hyperaemia as large as the present has never before been reported in man. Four of our five subjects were physically fit, but one was sedentary. Even in this subject the maximal perfusion was in the range of 2 l min^{-1} kg^{-1}.

Further, Sørlie & Myhre (1977), using the thermodilution technique (bolus injection), have found flows in calf muscle during maximal dynamic plantar flexion of 2–3 l min^{-1}. They did not report the mass of these muscles, but reported values for cross-sectional areas and length of the calf muscles suggest a muscle mass of approximately 1–1½ kg. Thus, there is good agreement between their data and our results. In muscles of other species with a similar degree of muscle capillarization to that of man, muscle blood flows as high or higher than found in man have been observed (Laughlin & Armstrong, 1982; Mackie & Terjung, 1983).

The large discrepancies between our values of maximal human muscle blood flow and those from most of the earlier studies, may be related to the method of determining flow and to the choice of exercise model. Ceretelli *et al.* (1984) have shown that the xenon clearance method may underestimate muscle blood flow by as much as 2-fold. From the results reported by Clausen and associates (Clausen, Klausen, Rasmussen & Trap-Jensen, 1973; Secher, Clausen, Klausen, Noer & Trap-Jensen, 1977; Klausen *et al.* 1982) it appears that when a large percentage of the muscle mass is involved in the exercise (arm work added to leg work or two-legged instead of one-legged exercise) resistance in vessels of the exercising limbs is also increased.

Some vasoconstriction may be present when maximally exercising the knee extensor muscles of one leg. However, it is likely that the conditions for obtaining maximal flow values are better than with other known exercise models. An indication that this may be true is the finding that during maximal exercise in two-legged bicycle exercise, venous effluent values of S_{O_2} and P_{O_2} from the exercising limbs, lower than 15% and 15 mmHg, respectively, are frequently observed (Saltin, Blomqvist, Mitchell, Johnson, Wildenthal & Chapman, 1968; Saltin, Nazar, Costill, Stein, Jansson, Essén & Gollnick, 1976), whereas the corresponding values in the present study were around 25% and 25 mmHg, respectively. It is true that the sampling site for the venous blood is proximal to the entrance of the saphenous vein and this contains blood from the skin. However, in the studies just cited the location of the venous sampling is identical to the one in the present study. The explanation for the high oxygen content in the femoral vein in the present study may be related to quite short mean transit times. Capillary counts in the present subjects were in the normal range, with a mean of around 400 capillaries mm^{-2}. Assuming a mean capillary diameter of 6 μm, and an arrangement in parallel with muscle fibres, the capillaries occupy approximately 1% (v/v) of muscle. Assuming a flow in all capillaries when the muscle blood flow was 2·5 l min^{-1} kg^{-1} the estimated mean transit time is in the order of only 300 (200–400) ms. It is apparent from the temperature variations observed in the femoral vein blood when the cold saline is infused (as depicted in Fig. 6) that there are marked fluctuations in flow, which are related to mechanical hindrance to flow in the capillary bed due to the muscle contraction, compression of the vessel and respiration. Estimations of the variation in flow are not made, because the thermistor inside the polyethylene catheter has a rather long response time (approximately 1 s). It is likely that true peak flow may be up to 50% higher than mean blood flow. Thus, estimated mean transit time is probably larger than the *in vivo* mean transit time. These short estimated mean transit times may explain the rather small extraction of oxygen observed in the maximally exercising knee extensor muscles, and support the notion that flow is not limiting for muscle oxygen uptake in this exercise model.

In contrast to several earlier studies (Grimby, Häggendahl & Saltin, 1967; Clausen & Lassen, 1971; Wahren, Saltin, Jorfeldt & Pernow, 1974) a linear elevation of muscle flow with the exercise was observed in the present study. This occurred with only a minor increase in systemic pressure until the work approached maximal level (Fig. 10). Thus, up to 70% of the peak oxygen uptake of the knee extensors the leg vascular resistance declines gradually, whereas at higher relative exercise intensities, no further reduction in leg vascular resistance is observed (Fig. 10). Instead systemic pressure becomes elevated.

The question that arises is to what extent the observed changes in resistance and pressure are regulated by central or peripheral factors. Of the local chemical compounds usually thought to play a role in vasodilatation (for reference see Sparks, 1980), we have measured oxygen, lactate (osmolarity) and pH. The P_{O_2} tensions in the venous effluent changed the most going from rest to light exercise, but not much thereafter. In contrast, lactate accumulation in the muscle was small until quite heavy work levels were reached. It is not obvious why this anaerobic energy liberation suddenly occurs, since muscle flow and oxygen uptake showed linear increases with work load for the whole range of loads (Fig. 9 and Table 1). Further, the onset of increased lactate release coincided with the load ($>$ 30 W) when the lowest peripheral resistance had already been attained. Therefore, our results suggest only a minor role for lactate (osmolarity) and pH in intact man as a cause for lower peripheral resistance in the muscle. In this respect our conclusion differs from those of Lundvall (1972) and Stowe, Owen, Andersson, Haddy & Scott (1975).

The chemical factors mentioned above can hardly directly affect the larger arterioles going to the thigh muscles, but might rather contribute to the distribution of flow within the muscle. The larger vessels may, however, respond to a reflex elicited in the muscle. Such a reflex has been postulated to contribute to the elevation of both heart rate and blood pressure during exercise, and the stimuli could be of chemical origin (Alam & Smirk, 1937, 1938; and Mitchell, Kaufman & Iwamoto, 1983). Whether one can also assign a role for such a reflex in contributing to a selective vasodilatation of vessels supplying the exercising limbs is an intriguing possibility. We know that oxygen uptake of muscle is well regulated and so is oxygen delivery to the exercising muscles. As arterial oxygen content is constant at the various exercise intensities, venous oxygen content is a dependent variable and simply becomes the result of other regulations.

Finally, the present data can shed some light on the classical question of what limits pulmonary oxygen uptake in man. For many years, the central circulation was thought to be the limiting factor (Åstrand, 1952; Mitchell, Sproule & Chapman, 1958; Rowell, 1974) until findings, such as that of Kaijser (1970), that breathing air at 10 atm did not cause a rise in maximal oxygen uptake, and that muscle mitochondrial enzymes were markedly elevated with training (Holloszy, 1967), gave rise to speculation over the possibility for a peripheral limitation of maximal oxygen uptake. The fact that a mass of 2–3 kg of knee extensor muscles can accommodate a flow of 5–7 l min^{-1} and consume approximately 0·8 l O_2 min^{-1} suggests, however, that the capacity of the skeletal muscles by far exceeds the capacity of the central circulation for supplying it with blood and oxygen, when a large fraction of the muscle mass is actively engaged in the exercise. In fact, in sedentary man it seems that only one-third of the muscle mass needs to be involved in intense exercise for the heart to reach its upper limit of cardiac output.

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