Oxygen Consumption in Resting Dog Gracilis Muscle Perfused at Varying Oxygen Delivery

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Abstract The different response of O_2 uptake ($\dot{V}_{\text{O}_2}$) of resting skeletal muscle to the changes in blood flow has been thought to reflect a species difference. To scrutinize this notion, we investigated the relation between O_2 delivery (arterial O_2 content multiplied by blood flow) and $\dot{V}_{\text{O}_2}$ in isolated dog gracilis muscle perfused solely with normal hematocrit (Ht) blood ($n=9$), or alternately with normal and low Ht blood ($n=6$), or alternately with normal and high Ht blood ($n=3$) at varying perfusion rates. Eleven out of the 18 preparations showed an autoregulation of blood flow, and the others did not. But, in all preparations, the $\dot{V}_{\text{O}_2}$ was delivery-independent above a critical O_2 delivery ($0.45 \text{ ml}/(\text{min} \cdot 100 \text{ g muscle})$) and showed the constant $\dot{V}_{\text{O}_2}$ of $0.30 \text{ ml}/(\text{min} \cdot 100 \text{ g})$, while below the critical level it turned out to be delivery-dependent. The maximal extraction ratio was 0.67. The same relationship was found with the low and high Ht perfusion. The pattern observed in dog gracilis muscle was essentially the same as that in rat gracilis muscle (KOLÁŘ and JANSKÝ, 1984).

Key words: oxygen uptake, oxygen delivery, autoregulation, blood flow.

Tissue oxidative metabolism is determined not only by the metabolic activity itself but also by blood O_2 supply to tissues. The O_2 supply, in turn, is dependent upon such properties of circulating blood as the O_2 capacity, sigmoid character of the O_2 binding, the O_2 affinity, and the effectors that affect it. Furthermore, blood flow is also an important determinant factor for the O_2 supply. Although many reports (STAINSBY and OTIS, 1964; HONIG *et al.*, 1971; DURÁN and RENKIN, 1974; BOCKMAN *et al.*, 1980) on the fundamental relationship between blood flow and O_2 consumption ($\dot{V}_{\text{O}_2}$) of resting skeletal muscles can be found in the literature, the results are still controversial.

Recently, KOLÁŘ and JANSKÝ (1984) proposed the product of blood flow and arterial O_2 content (O_2 delivery) as the most important determinant of $\dot{V}_{\text{O}_2}$ and

presented the result that $\dot{V}_{O_2}$ of rat gracilis muscle was changed from O_2 delivery-dependent to -independent manner when O_2 delivery was increased. This finding shows that neither blood flow nor arterial O_2 content but the O_2 delivery may be a more pertinent parameter for analyzing the quantitative relationship between blood O_2 supply and tissue aerobic metabolism. The aim of the present study is to evaluate the quantitative relationship between changes in the O_2 delivery by altering blood flow at three different hematocrits (Ht) and changes in $\dot{V}_{O_2}$ in resting canine gracilis muscle under normoxic condition.

We found that in all of the 18 preparations $\dot{V}_{O_2}$ was O_2 delivery-independent above a critical O_2 delivery but delivery-dependent below it. This pattern is essentially the same as that in the rat gracilis muscle (KOLÁŘ and JANSKÝ, 1984).

MATERIALS AND METHODS

Preparation of dogs for perfusion. Mongrel dogs of either sex weighing 7.5 ± 2.6 kg ($n=18$), were anesthetized with pentobarbital sodium (30 mg/kg body weight, i.v.). The animals were ventilated with room air through a cuffed endotracheal tube by means of a respirator at a tidal volume of 15 ml/kg and a frequency of 20/min. Figure 1 shows the setup for perfusion of the gracilis muscle. HONIG *et al.* (1980) had pointed out the importance of keeping all vessels supplying

Fig. 1. Schematic representation of the experimental arrangement. The isolated canine gracilis muscle was perfused via the supply vessels (usually 2 sets). Arterial and venous T-cannula were inserted into the femoral artery and the femoral vein. The blood equilibrated under normoxic condition was stored in reservoir bottles maintained at 27 or 4°C. The perfusion blood was kept at 37°C with dual-tube heat exchanger. The gracilis muscle was perfused either with normal Ht blood alone or alternately with low and normal Ht blood, or high and normal Ht. a: IR lamp regulated via thermistor thermosensor; b: tared glass vessel for measuring the volume of venous effluent; c: mercury manometer for perfusion pressure measurement; d: peristaltic pumps.

the muscle intact. Thus, the right gracilis muscle with the main and the other supply vessels from the femoral artery was surgically isolated from the surrounding tissues. The obturator nerve innervating the muscle was cut. The proximal and distal tendinous attachments of the muscle were clamped to eliminate collateral blood flow. The muscle was covered with a sheet of Saran Wrap (Asahikasei). A thermostat-controlled IR-lamp kept the surface of the muscle at 37°C. Before cannulation, heparin (5,000 IU) was administered via the exposed femoral vein. All vessels except the ones directly supplying gracilis muscle (usually 2 sets) from the femoral artery were doubly ligated and cut. A glass T-cannula connected to polyethylene tube (outer and internal diameter: 2.8 and 1.8 mm, or 4.0 and 2.2 mm; catheter volume: 0.56 or 0.79 ml) was inserted into the femoral vein proximal to the main gracilis vein. The proximal portion to the T-cannula was closed with a clamp. An arterial glass T-cannula (outer diameter: 2.5–3.0 mm) was placed in the femoral artery distal to the main gracilis artery. After cannulation, the isolated gracilis muscle was autoperfused for 15 min. The perfusion was started by clamping the femoral artery proximal to the gracilis artery. First, the gracilis muscle was flushed with Ringer-Krebs-Bülbring solution (125 mM NaCl, 4.7 mM KCl, 3.3 mM CaCl₂, 25 mM NaHCO₃, 1.8 mM NaH₂PO₄, 0.2 mM MgCl₂, 7.8 mM glucose) containing 4% bovine serum albumin (pH 7.4; Sigma) to wash out blood in the muscle. The perfusion pressure was always kept below 100 mmHg. The blood flow was adjusted to about 5 ml/(min · 100 g) muscle at the start of the experiment when the following equation (KOHZUKI, 1983) was used to assess the weight of the gracilis muscle (M in g) from the body weight (BW in kg):

$$M = 3.4 \times BW - 9.2 \quad (r = 0.88).$$

Blood reservoir was maintained at 27°C or in later experiments at 4°C so as to keep lower blood lactate level. In the present experiments, mean $\pm$ S.D. of arterial lactate concentration was 3.10 ± 1.16 mM ($n = 27$). The blood was stirred gently with a Teflon-coated magnetic stirrer. The temperature of inflowing blood was kept at 37°C by a dual-tube heat exchanger (volume: 3.5 ml). The flow rate was changed from 0.5 to 28 ml/(min · 100 g) by means of two peristaltic pumps. The steady state perfusion pressure when the flow rate was changed was measured by a mercury manometer. Blood flow was determined by weighing the venous effluent collected for 5 min in a tared glass vessel.

Blood for perfusion. Mongrel dogs of either sex, 8.5 ± 4.3 kg body weight ($n = 18$), were anesthetized with pentobarbital sodium (30 mg/kg body weight, i.v.). The animal was artificially ventilated as stated above. After cannulation of the carotid artery and heparinization (5,000 IU), exsanguination was started. Blood was collected only for the initial 2–3 min, since the lactate level elevated remarkably in the later period of blood-letting. The heparinized blood (10,000 IU) was centrifuged for 5 min at 3,000 rpm. The packed red cells were separated from plasma and the “buffy coat” was removed. The packed red cells were washed twice with Ringer-Krebs-Bülbring solution equilibrated with 95% O₂/5% CO₂ gas mixture

Table 1. Hematological data for the perfusion blood.

	<i>n</i> = 9		<i>n</i> = 6		<i>n</i> = 3	
	Normal Ht	Low Ht	Normal Ht	High Ht	Normal Ht	
Hematocrit (%)	47.5 ± 1.8	27.4 ± 1.8*	45.2 ± 1.8	62.2 ± 1.8*	46.9 ± 1.6	
Ca _{O₂} (dl/ml)	22.14 ± 1.18	13.05 ± 1.13*	21.84 ± 1.22	31.48 ± 1.93*	21.96 ± 0.48	

n value is number of perfused gracilis muscles. Ca_{O₂}, arterial O₂ content. * Significantly different (*p* < 0.05) from the respective Ht group.

(pH 7.4) and then washed once with the same solution containing 4% bovine serum albumin (Sigma). Finally, the packed red cells were resuspended in the original plasma. The Ht was adjusted as desired. The base excess of the blood was adjusted to zero with 7% bicarbonate. The gas equilibration of the perfusion blood (150–300 ml) was performed by a bubble oxygenator (Junkens) for 12–15 min at 37°C with 14% O₂/5% CO₂ balanced with N₂. The final blood gas values were *P*_{O₂} 104.8 ± 3.6 Torr, *P*_{CO₂} 39.8 ± 2.9 Torr, and pH 7.36 ± 0.02 (*n* = 27), respectively.

Measurement of the blood gases and oxygen consumption. Table 1 presents hematological data for the perfusion blood. In the first series of experiments (*n* = 9), normal Ht blood was perfused at various flow rates for a 15-min interval each. In the second (*n* = 6), low and normal Ht blood were alternately perfused for each 15-min interval at various flow rates. In the third (*n* = 3), high and normal Ht blood were perfused in the same manner.

The arterial and venous blood were collected into two glass capillaries (0.5 × 75 and 0.5 × 700 mm). The two samples of blood in each capillary served for measuring *S*_{O₂} with OSM-2 (Radiometer), and pH, *P*_{CO₂}, and *P*_{O₂} with blood gas analyzer (Radiometer, BMS-Mk2), respectively. $\dot{V}_{O_2}$ was calculated by the Fick principle and the blood oxygen content in ml/dl (*C*_{O₂}) was calculated from the relationship

$$C_{O_2} = [\text{Hb}] \times f \times S_{O_2} + 0.0031 \times P_{O_2},$$

where [Hb] is hemoglobin concentration in g/dl, *S*_{O₂} is fractional oxygen saturation, and *P*_{O₂} in Torr. The Hüfner's factor (*f*), theoretically being 1.39, was corrected for the presence of such inactive hemoglobin as HbCO and Hb⁺ (SHIMIZU *et al.*, 1986). In this correction, only the Hb⁺ content was actually measured by a sensitive difference spectrum method (Enoki *et al.*, unpublished), since the HbCO content was fairly constant (0.3%) throughout the animals (SHIMIZU *et al.*, 1986). Average methemoglobin concentration was 0.36 ± 0.29% (*n* = 18). Hematocrit (Ht) was measured with a microhematocrit centrifuge (Kubota, KH-120) and Hb concentration by cyanmetHb method. In each perfusion, $\dot{V}_{O_2}$ was measured at five to nine different flow rates. Lactate concentration was measured enzymatically using Lactate-UV-Test (Boehringer). At the end of each experiment, both the perfused muscle and the corresponding muscle from the contralateral leg were excised and

weighed. Since the perfused muscles (mean $\pm$ S.D., 20.0 ± 8.7 g) weighed a little more than the contralateral non-perfused muscles (mean $\pm$ S.D., 16.9 ± 8.3 g) and the difference was not statistically significant ($p > 0.05$), the contralateral muscle weight was used to calculate the blood flow, O₂ delivery and muscle $\dot{V}_{O_2}$ on 100 g basis. All experimental data were presented as mean $\pm$ S.D. For the statistical comparison, the unpaired *t*-test was used.

RESULTS

Figure 2 shows typical patterns of pressure-flow relationship together with the O₂ delivery to $\dot{V}_{O_2}$ relationship of the gracilis muscles when perfused with the blood of normal Ht. Experiment (a) exhibits an autoregulation of blood flow, i.e. relatively a constant flow upon a large variation of perfusion pressure. In this muscle, $\dot{V}_{O_2}$ is fairly constant at about 0.33 ml/(min $\cdot$ 100 g), and O₂ delivery-independent above a critical O₂ delivery. Experiment (b) shows a weak autoregulation in the initial period of the perfusion but the spontaneous loss was observed in the later period. Nevertheless, $\dot{V}_{O_2}$ of 0.25 ml/(min $\cdot$ 100 g) in this muscle was not delivery-dependent even after the disappearance of autoregulation. Experiment (c) probably represents the fully passive pressure-flow relationship. The $\dot{V}_{O_2}$ was around 0.37 ml/(min $\cdot$ 100 g)

Fig. 2. Presentation of three typical types of steady state pressure-flow curves (upper panels), together with O₂ consumption ($\dot{V}_{O_2}$)-O₂ delivery relationships (lower panels), in the resting gracilis muscles perfused with normal Ht blood. Closed square symbols in Expt. (b) indicate measurements of pressure-flow and $\dot{V}_{O_2}$ -O₂ delivery relation after a spontaneous loss of vascular reactivity.

Fig. 3. Relationship between $\dot{V}_{O_2}$ and O_2 delivery in the resting gracilis muscles perfused with blood of normal Ht. The results for rat gracilis (KOLÁŘ and JANSKÝ, 1984) were inserted for comparison (dashed line).

and was not delivery-dependent above a critical level of the delivery, but below the critical level, it was O_2 delivery-dependent. Six of nine preparations perfused with normal Ht blood showed more or less an autoregulation behavior. One of these exhibited complete absence of the autoregulation. In the other two the active pressure-flow relation in the early phase disappeared later.

Figure 3 shows a summary of the $\dot{V}_{O_2}$ in the resting gracilis muscles perfused with blood of normal Ht. $\dot{V}_{O_2}$ remained nearly constant at 0.30 ± 0.04 ml/(min · 100 g) (0.21–0.38) and delivery-independent over O_2 delivery range from 0.45 to 3.10 ml/(min · 100 g), while it turned out to be less and delivery-dependent below a critical O_2 delivery of 0.45 ml/(min · 100 g). The mean $\dot{V}_{O_2}$ in the O_2 delivery range from 0.45 to 0.90, 0.90 to 1.80, and 1.80 to 3.10 ml/(min · 100 g) were 0.28 ± 0.04 , 0.30 ± 0.04 , and 0.31 ± 0.05 ml/(min · 100 g), respectively, and were statistically not different from each other (Table 2). Figure 4 (a) and (b) are results for muscles perfused alternately with the low and normal Ht blood ($n=6$), and high and normal Ht blood ($n=3$), respectively. The results were almost similar to those in the normal Ht perfusion (Fig. 3). Two out of the six perfusions with the blood of low and normal Ht and two of the three perfusions with the blood of high and normal Ht exhibited an autoregulation of blood flow during the perfusion. The critical O_2 delivery was 0.45 ml/(min · 100 g) and it was not different from that in the normal Ht perfusion (Figs. 3 and 4). The mean $\dot{V}_{O_2}$ for the low and high Ht perfusion

Table 2. Effect of O₂ delivery on the resting O₂ consumption ($\dot{V}_{O_2}$) in 18 isolated dog gracilis muscles perfused with blood of 3 different hematocrits (Ht).

O ₂ delivery range (ml/(min · 100 g))	Oxygen consumption (ml/(min · 100 g))					
	n = 9		n = 6		n = 3	
	Normal Ht	Low Ht	Normal Ht	High Ht	Normal Ht	Normal Ht
0.00–0.45	0.17 ± 0.09 (7)	0.13 ± 0.08 (4)	(0)	0.15 (1)	(0)	(0)
0.45–0.90	0.28 ± 0.04 (17)	0.27 ± 0.03* (12)	0.29 ± 0.02 (6)	0.28 ± 0.03 (7)	0.29 ± 0.03 (3)	0.29 ± 0.03 (3)
0.90–1.80	0.30 ± 0.04 (24)					
1.80–3.10	0.31 ± 0.05 (12)	0.27 ± 0.03* (19) [†]	0.30 ± 0.05 (15) [†]	0.31 ± 0.04 (7) [†]	0.30 ± 0.04 (8) [†]	0.30 ± 0.04 (8) [†]
3.10–	0.22 (2)	(0)	(0)	(0)	(0)	(0)
0.45–3.10	0.30 ± 0.04 (53)	0.27 ± 0.03* (31)	0.30 ± 0.04 (21)	0.29 ± 0.04 (14)	0.30 ± 0.03 (11)	0.30 ± 0.03 (11)

O₂ delivery (ml O₂/(min · 100 g muscle)) is the product of blood flow (ml blood/(min · 100 g muscle)) and arterial oxygen concentration (ml O₂/ml blood). *Significantly different ($p=0.05$) from the respective normal Ht group. Numbers in parentheses indicate number of observations collected at each O₂ delivery range for each perfused gracilis. [†]Values collected in the O₂ delivery range from 0.90 to 3.10. *n* value is number of perfused gracilis muscles.

Fig. 4. Relationship between $\dot{V}_{O_2}$ and O_2 delivery in the resting gracilis muscles perfused with blood of low and normal Ht alternately (a), and blood of high and normal Ht alternately (b). $\circ$, the results with normal Ht; $\bullet$, low and high Ht.

above the critical O_2 delivery were 0.27 ± 0.03 and 0.29 ± 0.04 ml/(min $\cdot$ 100 g), respectively. Figure 5 shows the oxygen partial pressure of venous effluent (P_{vO_2}) as related to the O_2 delivery in the resting muscles. The P_{vO_2} was decreased as lowering O_2 delivery. The P_{vO_2} at which the $\dot{V}_{O_2}$ becomes O_2 delivery-dependent was read in Fig. 5. The values for the normal, low and high Ht perfusions were 35, 41, and 34 Torr, respectively. Table 2 summarizes the data for the resting gracilis muscles perfused with blood of the three different Ht. Mean $\dot{V}_{O_2}$ in the low Ht perfusions was slightly lower as compared to that in the same muscle perfused with the normal Ht blood in the same O_2 delivery range, and this difference was statistically significant ($p < 0.05$).

DISCUSSION

The present perfusion study indicated that the resting $\dot{V}_{O_2}$ in the vascularly isolated dog gracilis muscles was O_2 delivery-independent above a critical O_2 delivery and delivery-limited below this level (Fig. 3 and Table 2). It should be also noted that the general pattern was not influenced by the change in blood Ht (Fig. 4).

Fig. 5. Oxygen partial pressure of venous effluent (P_{vO_2}) in relation to O_2 delivery in the resting gracilis muscles perfused with blood of normal Ht (a), blood of low and normal Ht (b), and blood of high and normal Ht (c). Symbols are the same as in Fig. 4. Dashed vertical line indicates the critical O_2 delivery of $0.45 \text{ ml}/(\text{min} \cdot 100 \text{ g})$.

These findings are essentially the same as those observed recently in the rat skeletal muscle (KOLÁŘ and JANSKÝ, 1984). Although the general patterns were essentially the same, the maximal $\dot{V}_{O_2}$ in resting rat gracilis was remarkably higher than that in dogs (Fig. 3). This difference reflects the general situation that the resting metabolic rate is higher in smaller animals (KLEIBER, 1961). The initial slope in which $\dot{V}_{O_2}$ is delivery-dependent represents O_2 extraction ratio by the tissue at rest. This figure for dogs (0.67) in the present study was similar to that for rats (0.63) as observed by KOLÁŘ and JANSKÝ (1984). DURÁN and RENKIN (1974) also found a similar value for dogs (0.71).

Relationships between $\dot{V}_{O_2}$ and blood flow in the dog gracilis muscle were intensively investigated by DURÁN and RENKIN (1974). They showed that the resting $\dot{V}_{O_2}$ were either dependent upon or independent of the blood flow which was changed from 2 to $10 \text{ ml}/(\text{min} \cdot 100 \text{ g})$. They also suggested that the flow-independent $\dot{V}_{O_2}$

might be associated with the vascular "autoregulation." Their results, however, should be reconsidered in view of the fact that the widely different arterial oxygen contents (12.7 to 20.2 ml/dl) resulted in the widely different O_2 delivery even though the flow was the same. The vascular "autoregulation" has been sometimes used as an explanation for the phenomenon that the resting muscular $\dot{V}_{\text{O}_2}$ is independent of the blood flow down to very low perfusion rate (WHALEN *et al.*, 1973; GLADDEN and YATES, 1983). This, however, is doubtful in view of the present results (Fig. 2). The $\dot{V}_{\text{O}_2}$ - O_2 delivery relationship of the resting dog gracilis muscle was not associated with the autoregulation. As for the dog gastrocnemius-plantaris muscle, STAINSBY and OTIS (1964) reported that the oxygen uptake was not altered by changes in the blood flow except below a critical value.

Present values for the average maximal $\dot{V}_{\text{O}_2}$ (0.30 ± 0.04 ml/(min $\cdot$ 100 g)) observed in the delivery-independent region are in almost the similar range of, but a little higher than, the value from 0.22 to 0.29 for the same muscle by previous workers (COSTIN *et al.*, 1971; DURÁN and RENKIN, 1974, 1976; NELLIS *et al.*, 1980; HONIG and ODOROFF, 1981; STEFFEN *et al.*, 1982). The reasons for the present higher value are as follows. 1) Difference in perfusion method. The temperature for the perfusion was varied from 35°C in one experiment (NELLIS *et al.*, 1980) to 38°C in the other (COSTIN *et al.*, 1971). The different temperature should apparently influence the metabolic rate ($\dot{V}_{\text{O}_2}$). However, $\dot{V}_{\text{O}_2}$ of 0.30 ml/(min $\cdot$ 100 g) in the present perfusions at 37°C is a little higher than 0.28 ml/(min $\cdot$ 100 g) at 38°C (COSTIN *et al.*, 1971). Whether the gracilis nerve is cut or kept intact will not induce the change in $\dot{V}_{\text{O}_2}$ (HONIG *et al.*, 1971; DURÁN and RENKIN, 1974). In all the experiments except HONIG and ODOROFF (1981) and the present one, only the main gracilis artery and vein served for the perfusion, and the other supply vessels were ligated. According to HONIG and ODOROFF (1981), if only the main gracilis vessels were used, anoxic regions could arise in the distal third of the muscle during exercise. This may explain the reduced $\dot{V}_{\text{O}_2}$ in some of the experiments although it is not clear that it may decrease the oxygen uptake in the resting muscle. 2) A possible effect of arterial lactate. In the present experiments, mean arterial lactate concentration (3.10 ± 1.16 mM) was higher than the previously reported value, 1–2 mM (GRAHAM *et al.*, 1976; BARBEE *et al.*, 1983; GLADDEN and YATES, 1983). When lactate was infused and maintained at a higher level in dogs (about 11 mM), $\dot{V}_{\text{O}_2}$ of the resting gastrocnemius-plantaris muscle increase by 26% (GLADDEN and YATES, 1983). Arterial lactate concentrations in the present perfusions were not such a high value but it is most likely a cause of the slightly higher $\dot{V}_{\text{O}_2}$. 3) The animal body size and muscle size. HUDLICKÁ (1975) reported an inverse relationship between the muscle weight and the resting $\dot{V}_{\text{O}_2}$ in feline soleus muscles. The dogs used in the present experiments weighed 4.6–15.3 kg, and the mean weight of gracilis muscles was 16.9 ± 8.3 g. These values are smaller than those in some of the above-cited investigations (DURÁN and RENKIN, 1976; NELLIS *et al.*, 1980; HONIG and ODOROFF, 1981). If the situation in cats is applicable to dogs, it possibly explains the slightly higher $\dot{V}_{\text{O}_2}$ in the present results.

The mean $\dot{V}_{O_2}$ in perfusion with the low Ht blood was significantly lower than that with the normal Ht blood. The O₂ delivery to the muscle is apparently enough and the venous oxygen tension (P_{vO_2}) is higher than that of the normal Ht. Consequently these can be excluded as the cause of the lowered $\dot{V}_{O_2}$. The needed capillary supply in accord with tissue O₂ demand during the perfusion period of the normal Ht blood will be less than that with the low Ht blood. When Ht of the perfusion blood is acutely changed from normal to low, the tissue oxygenation will be reduced if capillary recruitment is not increased promptly. Also the local blood flow inhomogeneity in muscle (PIIPER *et al.*, 1985) may be more increased in resting state owing to the higher perfusion rate needed during the low Ht perfusion to maintain the same O₂ delivery. These will explain the higher critical P_{vO_2} value (Fig. 5) and the slightly decreased $\dot{V}_{O_2}$.

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