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CAPILLARY BLOOD TRANSIT TIME IN MUSCLES IN RELATION TO BODY SIZE AND AEROBIC CAPACITY

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Summary

The mean minimal transit time for blood in muscle capillaries (t_c) was estimated in six species, spanning two orders of magnitude in body mass and aerobic capacity: horse, steer, dog, goat, fox and agouti. Arterial (Ca_{O_2}) and mixed venous ($C\bar{v}_{O_2}$) blood O_2 concentrations, blood hemoglobin concentrations ([Hb]) and oxygen uptake rates were measured while the animals ran on a treadmill at a speed that elicited the maximal oxygen consumption rate ($\dot{V}_{O_2max}$) from each animal. Blood flow to the muscles ($\dot{Q}$m) was assumed to be 85 % of cardiac output, which was calculated using the Fick relationship. Total muscle capillary blood volume (Vc) and total muscle mitochondrial volume were estimated by morphometry, using a whole-body muscle sampling scheme. The t_c was computed as Vc/$\dot{Q}$m. The t_c was 0.3–0.5 s in the 4 kg foxes and agoutis, 0.7–0.8 s in the 25 kg dogs and goats, and 0.8–1.0 s in the 400 kg horses and steers. The t_c was positively correlated with body mass and negatively correlated with transcapillary O_2 release rate per unit capillary length. Mitochondrial content was positively correlated with $\dot{V}_{O_2max}$ and with the product of $\dot{Q}$m and [Hb]. These data suggested that $\dot{Q}$m, Vc, maximal hemoglobin flux, and consequently t_c, are co-adjusted to result in muscle O_2 supply conditions that are matched to the O_2 demands of the muscles at $\dot{V}_{O_2max}$.

Introduction

The transit time for blood in muscle capillaries (t_c) represents the time available for oxygen release from the blood to muscle tissue. When an animal exercises at its aerobic

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limit, muscle blood flow is maximized (Armstrong *et al.* 1987) and, consequently, t_c is minimized. As a result, the partial pressure of oxygen in the capillaries is kept high throughout the capillary path, thus ensuring adequate O_2 release to muscle cells at the venous end of the capillaries. We calculated t_c in the muscles of exercising animals with different $\dot{V}_{O_2max}$ to determine whether t_c and aerobic capacity are correlated. Capillary transit time is the product of two independent factors: capillary volume and blood flow rate. At maximal exercise levels, the entire capillary network is recruited, making its volume a fixed quantity that can be computed from capillary anatomy. Blood flow rate, in contrast, can be adjusted during exercise to an upper limit set by maximal heart rate, ventricular size and the maximal volume of blood ejected per cardiac cycle. Thus, testing the correlation between aerobic capacity and t_c also tests the correlations between aerobic capacity and a number of structural and physiological variables.

We previously estimated t_c in individual muscles of animals exercising at $\dot{V}_{O_2max}$ (Kayar *et al.* 1992). Blood flow to selected muscles was estimated by injecting radioactive microspheres into running animals, and muscle capillarity and mitochondrial volume density were estimated by morphometric analysis of preserved samples of these muscles. The present study extends this work by allowing us to estimate t_c for the entire muscle mass of an animal. When an animal exercises at $\dot{V}_{O_2max}$, nearly all of the O_2 is consumed in the muscles (Mitchell and Blomqvist, 1971), making $\dot{V}_{O_2max}$ approximately equal to the sum of the oxygen consumption rates of the individual muscles. At $\dot{V}_{O_2max}$, nearly all of the cardiac output ($\dot{Q}$) perfuses the muscles (Armstrong *et al.* 1987), making cardiac output approximately equal to the sum of the individual muscle blood flows ($\dot{Q}$m). Muscle mass-specific $\dot{V}_{O_2max}$ and muscle mass-specific $\dot{Q}$m are therefore mean values of all muscles, and can be obtained from intact animals. From random and repeated sampling of animal muscles over the entire body, we can use morphometric methods to obtain an estimate of the entire capillary and mitochondrial volume of all the muscles of that animal. Pairing whole-body muscle capillarity with $\dot{V}_{O_2max}$, $\dot{Q}$ and whole-body muscle mitochondrial volume will thus allow us to compare t_c directly with the oxidative capacity of the muscles in intact animals exercising at their maximal aerobic level.

Since mass-specific $\dot{V}_{O_2max}$ is strongly correlated with the size of the animal (Taylor *et al.* 1981), we included species ranging in mass from less than 5 kg to nearly 500 kg. Mass-specific $\dot{V}_{O_2max}$ can also vary considerably within a given size range (Weibel *et al.* 1987); animal species of similar body mass, but greatly differing aerobic exercise capacities, were therefore also included.

Materials and methods

The animals used in this study were the horse (*Equus caballus*, *N*=3), steer (*Bos taurus*, *N*=3), goat (*Capra hircus*, *N*=1), mixed-breed dog (*Canis familiaris*, *N*=2), fox (*Alopex lagopus*, *N*=3) and agouti (*Dasyprocta fuliginosa*, *N*=1). Oxygen consumption rate was measured with an open mask system while animals ran on a treadmill, as described in detail by Jones *et al.* (1989). The $\dot{V}_{O_2max}$ was defined as the O_2 consumption rate at the speed at which further increases in speed elicited no further increase in oxygen

consumption rate; at these higher speeds, the rate of accumulation of plasma lactate increased significantly. The $\dot{V}_{O_2max}$ was used as an approximation of the aerobic capacity of the entire musculature of each animal.

For sampling blood from running animals, catheters were inserted into the carotid and pulmonary arteries as described by Jones *et al.* (1989). Oxygen concentrations in arterial and venous blood samples were measured using a method modified from Tucker (1967) by Karas *et al.* (1987). Blood hemoglobin concentrations were measured spectrophotometrically (Longworth *et al.* 1989).

Cardiac output ($\dot{Q}$) at $\dot{V}_{O_2max}$ was calculated from the Fick relationship:

$$\dot{Q} = \dot{V}_{O_2max}/(Ca_{O_2} - C\bar{v}_{O_2}) . \quad (1)$$

Blood flow to the entire body musculature ($\dot{Q}$m) at $\dot{V}_{O_2max}$ was assumed to be 85 % of the cardiac output (Armstrong *et al.* 1987).

The t_c (in seconds) of blood in muscle capillaries at $\dot{V}_{O_2max}$ was calculated as:

$$t_c = Vc/\dot{Q}m , \quad (2)$$

where Vc is the total capillary internal volume of a muscle (ml), which is taken to be the total volume of capillary blood in a muscle, and $\dot{Q}$m is in ml s^{-1}.

Sampling of muscles for morphometric analysis of capillarity and mitochondrial volume density followed the method of whole-body random sampling described in detail by Hoppeler *et al.* (1984). An animal was divided into general body regions (head, neck, upper and lower trunk, fore- and hindlimbs, pelvis), and 15 samples per animal were collected from randomly selected sites within these regions. The number of sites per body region was weighted for the relative muscle mass in that region, and the precise location of the sampling site within a region was assigned by a series of random numbers (Hoppeler *et al.* 1984).

Muscle total capillary volume was calculated as:

$$Vc = N_A(c,f) \times c(K,0) \times \pi \times (d/2)^2 \times M \times \delta^{-1} , \quad (3)$$

where N_A(c,f) is the number of capillaries per mm^2; c(K,0) is a dimensionless factor for capillary tortuosity (i.e. the extra capillary length due to the deviation of capillaries from straight and unbranching tubes, and is millimeters capillary length per millimeter tissue length); d is capillary inner diameter (in mm); M is muscle mass (in g); and δ is muscle density (1.06×10^{-3} g mm^{-3}; Mendez and Keys, 1960). Capillary density was estimated in muscle cross sections by standard counting procedures (Weibel, 1979). Since the muscle blocks were collected by the whole-body sampling procedure, this capillary density represents an average for all skeletal muscles within a species. A value for c(K,0) of 1.24 has been estimated from a number of muscles and mammalian species, with no indication that this value varies systematically with animal size or oxidative capacity of the muscles (Conley *et al.* 1987; Mathieu-Costello *et al.* 1989). The inner diameter of capillaries was estimated by morphometry (Conley *et al.* 1987; Kayar *et al.* 1992). For all the species in this study, capillary diameter has been estimated to be 4.5×10^{-3} mm, with no systematic differences found between muscle types or animal species (Kayar *et al.* 1992).

Muscle samples were preserved in a buffered glutaraldehyde solution (6.25% in

0.1 mol l^{-1} sodium cacodylate buffer adjusted to 430 mosmol l^{-1} with NaCl) for electron microscopy following standard techniques (Hoppeler *et al.* 1981). For analysis of the capillary density in the whole-body random muscle samples, 15 tissue blocks per animal were cut into ultrathin transverse sections and photographed using a Philips 300 electron microscope. Four randomly selected electron micrographs were analyzed per muscle block, at a magnification of 1500×, yielding an average sample of more than 1000 fibers and capillaries per animal. For analysis of the mitochondrial volume density (volume of mitochondria per unit volume of muscle fibers) of the muscle samples, the same transverse tissue sections were used. Ten randomly selected electron micrographs were analyzed per section, at a magnification of 24 000× using the techniques of Kayar *et al.* (1989).

Results

Whole-body sampling of muscles indicated that, in each of the three size classes of animals studied, the active species (horse, dog, fox) had a greater muscle capillary density and mitochondrial volume density than the inactive species (steer, goat, agouti) (Table 1). Neither capillary density nor mitochondrial volume density was a direct function of body size (Table 1). These animals were not similarly constructed in terms of the relative proportions of muscle mass to body mass (Table 1).

In each size class, total capillary volume, muscle blood flow and $\dot{V}_{O_2max}$ were greater in active species than in inactive species (Student's *t*-test, $P<0.05$, Table 2). Arterio-venous O_2 extraction and [Hb] were higher in the horse and dog than in the steer and goat respectively, but lower in the fox than in the agouti ($P<0.05$, Table 2). The t_c ranged from a maximum of 1 s in the steer to a minimum of 0.28 s in the fox (Table 2).

Since the animals in this study did not have similar proportions of muscle mass relative

Table 1. *Body mass, whole-body muscle mass, mean capillary density and mitochondrial volume density of muscles from the animals used in this study*

	Body mass (kg)	Muscle mass (kg)	Muscle mass (% body mass)	N_A(c,f) (mm^{-2})	V_V(mt,f) (%)
Horse (N = 3)	447±36	191±16	42.7±0.2	926±36	7.46±0.5
Steer (N= 3)	474±12	165±3.0	34.8±0.9	727±6	3.56±0.3
Dog (N = 2)	26.0±0.5	11.3±0.26	43.6±0.1	1140±140	8.10±0.8
Goat (N = 1)	25.3	8.15	32.2	631	3.80
Fox (N = 3)	4.40±0.19	1.65±0.10	37.4±0.8	826±41	12.4±0.6
Agouti (N = 1)	3.24	1.31	40.7	581	5.62

Data were obtained from a whole-body random sampling scheme.
N_A(c,f), mean capillary density; V_V(mt,f), mitochondrial volume density.
Values are means ± 1 S.E.M.

Table 2. *Blood hemoglobin concentration, total skeletal muscle capillary volume, arterio-venous blood O_2 extraction, whole-body maximal O_2 consumption rate, total muscle blood flow and mean capillary transit time in mammals exercising at their aerobic maxima*

	[Hb] (g ml^{-1})	Vc (ml)	$Ca_{O_2} - C\bar{v}_{O_2}$ (ml O_2 ml^{-1})	$\dot{V}_{O_2max}$ (ml O_2 s^{-1})	$\dot{Q}$m (ml s^{-1})	t_c (s)
Horse (N = 3)	0.197±0.008[1]	3280±230	0.219±0.014	1010±51[1]	3930±263	0.84±0.08
Steer (N = 3)	0.139±0.004[1]	2230±37	0.155±0.001	406±17[1]	2230±79	1.00±0.02
Dog (N = 2)	0.188±0.002[2]	240±35	0.161±0.006[2]	59.0±0.4	312±1.9	0.77±0.11
Goat (N = 1)	0.107±0.002[2]	95.7	0.103±0.003[2]	17.3	143	0.67
Fox (N = 3)	0.153±0.002[3]	25.3±2.7	0.150±0.008[3]	15.9±1.6	90.6±9.9	0.28±0.03
Agouti (N = 1)	0.172	14.2	0.185	6.07	27.8	0.51

[1]Jones *et al.* (1989); [2]Karas *et al.* (1987); [3]Longworth *et al.* (1989).

[Hb], hemoglobin concentration; Vc, volume of capillaries; Ca_{O_2}, arterial blood oxygen concentration; $C\bar{v}_{O_2}$, venous blood oxygen concentration; $\dot{V}_{O_2max}$, maximal oxygen consumption rate; $\dot{Q}$m, total muscle blood flow; t_c, mean capillary transit time.

Values are means ± 1 S.E.M.

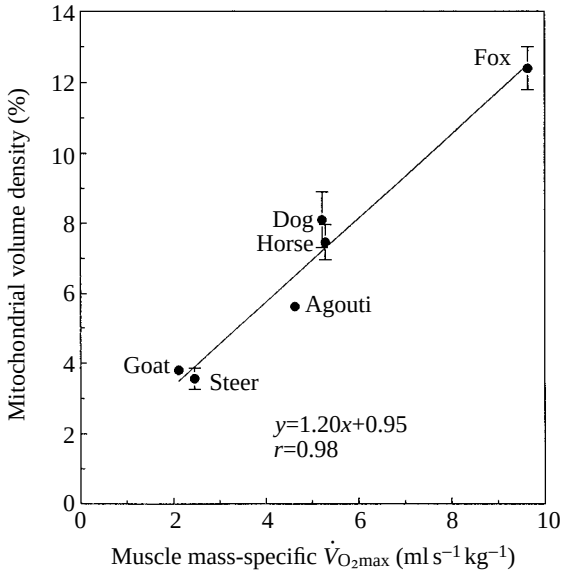

Fig. 1. Muscle mass-specific maximal oxygen consumption rate of animals exercising at their aerobic maxima *versus* mean volume density of mitochondria from a whole-body random sampling of muscles. In this and all other figures, values are means ± S.E.M., values of N are given in Table 1.

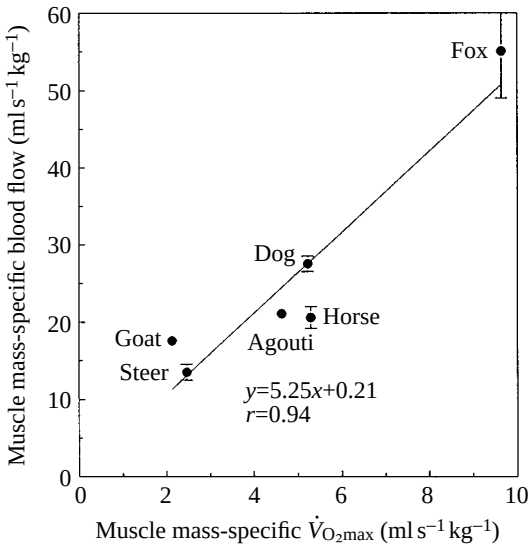

Fig. 2. Muscle mass-specific maximal oxygen consumption rate *versus* muscle mass-specific blood flow in muscles of animals exercising at their aerobic maxima.

to body mass, the various variables for oxidative capacity, blood flow and capillary volume were calculated per unit muscle mass. The muscle mass-specific $\dot{V}_{O_2max}$ of the various animal species was significantly positively correlated with the mitochondrial volume density of the muscles (Fig. 1; r=0.98, P<0.01) and with total muscle blood flow ($\dot{Q}$m) (Fig. 2; r=0.94, P<0.05). There was a significant negative correlation between t_c and muscle mass-specific blood flow (Fig. 3; r=−0.81, P=0.05), and a negative

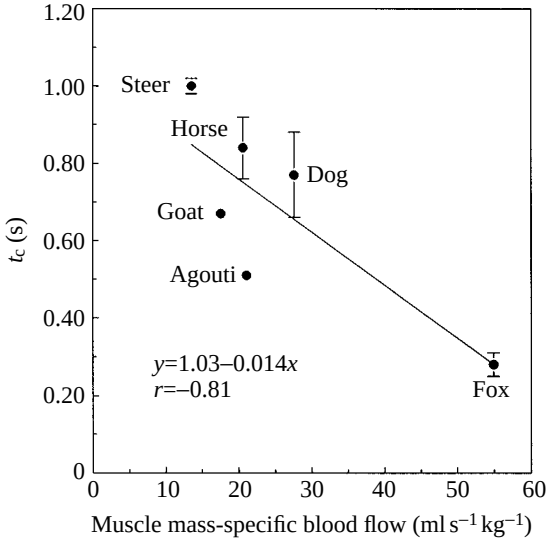

Fig. 3. Muscle mass-specific blood flow *versus* mean minimal transit time (t_c) for blood in muscle capillaries of animals exercising at their aerobic maxima.

correlation between t_c and muscle mass-specific $\dot{V}_{O_2max}$ ($\dot{V}_{O_2max}$/Mm) that was not statistically significant (t_c=1.02−0.069$\dot{V}_{O_2max}$/Mm; r=−0.73; P=0.10).

Discussion

The advantage of using this method to estimate t_c is that, by using a combination of physiological data obtained from exercising animals and morphometric data obtained later for the size of the capillary bed, we could estimate t_c in animals known to be exercising at their aerobic maxima. Isolated muscle preparations may not succeed in reaching true $\dot{V}_{O_2max}$ conditions of either blood flow or oxygen extraction (Honig *et al.* 1980; Hudlicka *et al.* 1982). By estimating bulk blood flow and net oxygen extraction through the entire capillary bed, we eliminated the considerable problems of calculating mean capillary length (Sarelius, 1986) and estimating a flow-weighted mean blood transit time from the 'sojourn times' of individual erythrocytes (Duling and Damon, 1987). By using the whole-body random sampling approach, we also eliminated the bias inherent in selecting individual muscles for analysis (Kayar *et al.* 1992). In this whole-body approach, it is unimportant that all of the muscles, or all of the capillaries in any one muscle, are not participating equally or maximally, since it is an average value per animal that is sought. The $\dot{V}_{O_2max}$ and $\dot{Q}$m values used here represent approximations of the sum of the oxygen consumption rates and blood flows of all of the muscles. Thus, muscle mass-specific $\dot{V}_{O_2max}$ and muscle mass-specific $\dot{Q}$m are average values for the muscles, ignoring the variance between muscles. The whole-body random-sampled capillarity and mitochondrial volume densities represent, likewise, an average value for all of the muscles in an animal and ignore any variance between the muscles.

The main disadvantage to our methodology is that it requires a number of assumptions, which impose some limitations. (1) We assumed that, under conditions of maximal oxygen uptake, all capillaries in all muscles are being perfused. This is an overestimation of an unknown magnitude. However, the majority of muscles in running quadrupeds receive blood flows substantially elevated over resting levels (Armstrong *et al.* 1987) and, in activated muscles, 95–99 % of all capillaries contain moving erythrocytes (Damon and Duling, 1985). (2) We assumed that all oxygen release from the blood is in the capillaries. It has been demonstrated (Duling and Berne, 1970) that, under resting blood flow conditions, small arterioles leak a substantial amount of oxygen from the precapillary circulation. However, with the elevated blood flows during exercise, the precapillary loss of oxygen is thought to be slight (Roth and Wade, 1986). (3) We computed a capillary blood flow that represents the average flow of whole blood, not the flow of erythrocytes. These two flow rates are not identical; there is a complex relationship between plasma velocity, erythrocyte velocity, capillary and erythrocyte dimensions, and blood viscosity. Erythrocyte velocity may exceed whole-blood mean velocity by up to a factor of 2 in theory, but probably more realistically by a factor of approximately 1.25 for vessels 4.5 μm in diameter (Chien *et al.* 1984). (4) We assumed that, at maximal oxygen uptake, all oxygen consumption is occurring in the skeletal muscles, which is likely to be an overestimation. The oxygen consumption of the muscles is thought to be approximately 90 % of whole-body oxygen consumption at $\dot{V}_{O_2max}$ (Mitchell and Blomqvist, 1971).

Table 3. *Partial pressure of O_2 in arterial and mixed venous blood, percentage saturation of arterial and mixed venous blood and computed mean O_2 consumption rate of mitochondria in muscles of mammals exercising at their aerobic maxima*

	Pa_{O_2} (mmHg)	$P\bar{v}_{O_2}$ (mmHg)	Sa_{O_2} (%)	$S\bar{v}_{O_2}$ (%)	Mitochondrial $\dot{V}_{O_2max}$ (ml O_2 min^{-1} ml^{-1})
Horse (N = 3)	87.2±0.7[1]	15.8±1.8[1]	93.7±1.0[1]	15.7±2.2[1]	4.53±0.45[2]
Steer (N = 3)	99.0±5.0[1]	18.9±1.0[1]	92.0±1.5[1]	8.0±0.8[1]	4.40±0.44[2]
Dog (N = 3)	101±1.7[3]	26.7±1.2[3]	92.6±1.1[4]	28.6±2.8	4.12±0.36
Goat (N = 3)	123±2.8[3]	34.4±1.4[3]	95.0±2.1[4]	23.0±2.1	3.55
Fox (N = 3)	120±4.3[5]	37.4±2.5[5]	92.6±2.6[5]	20.4±4.2[5]	4.94±0.50
Agouti (N = 1)	111.8	29.9	94.1	18.7	5.21

[1]Jones *et al.* (1989); [2]Kayar *et al.* (1989); [3]Karas *et al.* (1987); [4]Taylor *et al.* (1987); [5]Longworth *et al.* (1989).

Pa_{O_2}, partial pressure of oxygen in arterial blood; $P\bar{v}_{O_2}$, partial pressure of oxygen in mixed venous blood; Sa_{O_2}, percentage saturation of oxygen in arterial blood; $S\bar{v}_{O_2}$, percentage saturation of oxygen in mixed venous blood; $\dot{V}_{O_2max}$, maximal oxygen consumption rate.

Values are means ± 1 S.E.M.

(5) We assumed that, at maximal oxygen uptake, 85 % of the cardiac output goes to the muscles in all species. This estimation was based on blood flow studies in running pigs (87 % of $\dot{Q}$; Armstrong *et al.* 1987) and running dogs (85 % of $\dot{Q}$ in untrained and 91 % of $\dot{Q}$ in trained animals; Musch *et al.* 1987). (6) Our analysis estimates only a mean transit time and cannot estimate between-muscle, within-muscle or between-capillary flow heterogeneity. It has been demonstrated that this capillary flow heterogeneity is at least as important to oxygen delivery as mean capillary flow (Popel, 1982). (7) We made several assumptions regarding capillary geometry. These have been discussed in detail elsewhere and are not expected to have introduced systematic bias (Kayar *et al.* 1992).

It is clear that, for an analysis of the oxidative capacity of the muscles, the variable of choice is muscle mass-specific $\dot{V}_{O_2max}$, rather than the more commonly used body mass-specific $\dot{V}_{O_2max}$. The animals we selected did not have similar proportions of muscle mass; the more athletic species are generally more muscular (Table 1; S. L. Lindstedt and H. Hoppeler, unpublished observations). The body mass-specific $\dot{V}_{O_2max}$ is therefore biased because differing amounts of body mass may be contributing to the $\dot{V}_{O_2}$ of an exercising animal. The relative oxidative capacity of an animal is directly related to its relative muscle composition. Body mass-specific $\dot{V}_{O_2max}$ was not significantly correlated with t_c for the whole-body muscle estimates of this study (P>0.10) or for single-muscle estimates in a previous study (Kayar *et al.* 1992). Muscle mass-specific $\dot{V}_{O_2max}$ increased in direct proportion to the mitochondrial volume density (Fig. 1). This necessarily means that, at $\dot{V}_{O_2max}$, the volume of O_2 consumed per unit volume of mitochondria is constant

for all these species (Table 3). We computed the $\dot{V}_{O_2max}$ of the mitochondria by dividing the muscle mass-specific $\dot{V}_{O_2max}$ by the volume density of muscle mitochondria and correcting for muscle density. In all quadrupedal mammals studied to date, mitochondrial $\dot{V}_{O_2max}$ has been estimated to be in the range 3–5 ml O_2 min^{-1} ml^{-1} mitochondria (Hoppeler *et al.* 1984; Conley *et al.* 1987). Muscle mass-specific $\dot{V}_{O_2max}$ also increased in direct proportion to the muscle mass-specific total blood flow (Fig. 2). This also necessarily means that, at $\dot{V}_{O_2max}$, the volume of O_2 consumed per unit volume of blood is constant for all the species we studied; a value we compute to be 0.19 ml O_2 ml^{-1} blood (1/5.25 ml O_2 ml^{-1} blood; Fig. 2).

The mitochondrial content of the muscles was also highly positively correlated with the maximal flow rate of hemoglobin, which we computed from the product of muscle mass-specific $\dot{Q}$m and hemoglobin concentration (Fig. 4). This suggests that, at $\dot{V}_{O_2max}$, there is a close match between our tissue-level index of oxidative capacity and the maximal potential supply rate of O_2 in the capillary blood. This further supports the relationships illustrated in Figs 1 and 2.

The t_c was negatively correlated with muscle mass-specific $\dot{Q}$m (Fig. 3). In any animal, capillary transit time must become shorter with increasing blood flow because blood flow increases continuously with exercise intensity up to $\dot{V}_{O_2max}$, while capillary recruitment causes Vc to reach maximal anatomical limits at some lower exercise intensity. This negative correlation between t_c and muscle mass-specific $\dot{Q}$m also exists between these animal species at $\dot{V}_{O_2max}$, given the close correlations between oxidative capacity, blood flow and hemoglobin flux among species at $\dot{V}_{O_2max}$ (Figs 2 and 4). Thus, it is probably incorrect to suggest that short transit times limit the time available for O_2 release, thereby making t_c a limiting factor to $\dot{V}_{O_2max}$. Such a limitation was proposed by Saltin *et al.* (1986), on the basis of studies of human exercise. Instead, we found that t_c depends on a

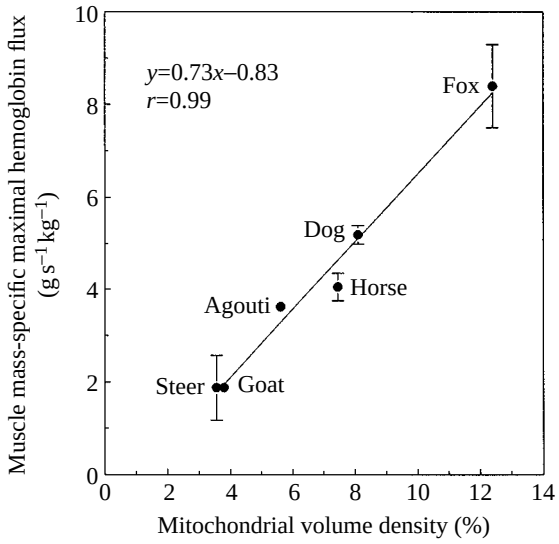

Fig. 4. Mean mitochondrial volume density *versus* muscle mass-specific hemoglobin flux in muscle capillaries of animals exercising at their aerobic maxima.

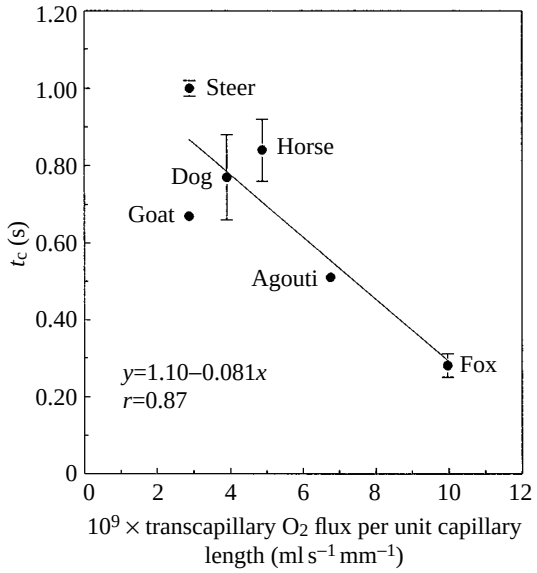

Fig. 5. Transcapillary O_2 flux per unit capillary length *versus* mean minimal transit time (t_c) for blood in muscle capillaries in animals exercising at their aerobic maxima.

number of covariant physiological and anatomical factors that are all matched to maximal oxidative capacity. Short t_c will indeed limit the time available for O_2 release, but is also a necessary condition for enhancing O_2 unloading. The t_c must become shorter with increasing oxidative capacity to satisfy all of the conditions of blood flow, blood volume and oxygen flux. To illustrate this point, we examined the relationship between t_c and transcapillary O_2 flux per unit capillary length, which we computed from muscle mass-specific $\dot{V}_{O_2max}$ divided by capillary density and capillary tortuosity, and corrected for muscle density; we obtained a significant negative correlation (Fig. 5; r=0.87, P<0.05). This suggests that $\dot{V}_{O_2max}$ is perfusion-limited in these animals, but does not preclude the

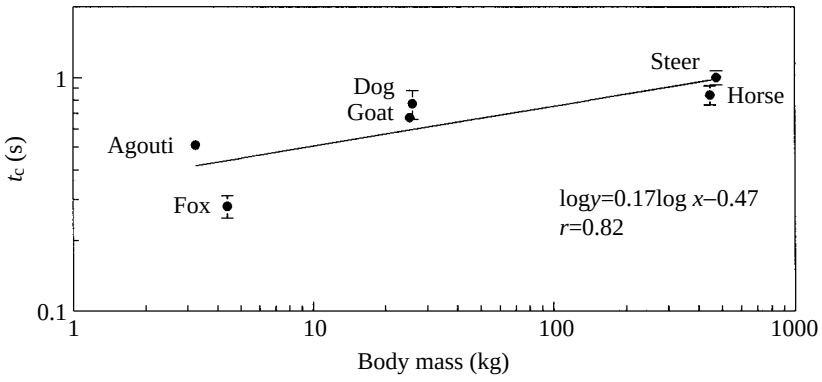

Fig. 6. Body mass *versus* mean minimal transit time for blood in muscle capillaries (t_c) in animals exercising at their aerobic maxima.

possibility that there is also a simultaneous diffusion-limitation of a similar magnitude in these tissues.

The t_c was significantly positively correlated with body mass (Fig. 6; r=0.82, P=0.05). We had intentionally selected species of sufficient diversity to ensure that muscle mass-specific $\dot{V}_{O_2max}$ was not correlated with body size. Thus, we propose that the correlations between t_c, body mass and muscle oxidative capacity reflect two separate phenomena: (1) a higher oxidative capacity necessitates a greater blood flow which, in turn, shortens t_c; (2) smaller animals have a systematically shorter t_c than larger animals for some reason unrelated to oxidative capacity. We propose that the correlation of t_c with body size is related to the systematic decrease in the affinity of hemoglobin for O_2 in smaller mammals (Schmidt-Nielsen and Larimer, 1958).

The blood gas data from these species support these suggestions (Table 3). The arterio-venous O_2 partial pressure differences are similar in all species. In all three size classes, a higher oxygen release rate to muscles is accounted for by differences in arterial blood O_2 concentration and/or blood flow but not by differences in arterio-venous O_2 partial pressures or greater venous O_2 extractions (Conley *et al.* 1987). The smaller animals have slightly higher values of Pa_{O_2} and $P\bar{v}_{O_2}$ for similar Sa_{O_2} and $S\bar{v}_{O_2}$ values in the larger animals (Table 3). These observations suggest that the hemoglobin O_2-affinity is systematically lower in the smaller species. Longworth *et al.* (1989) made a detailed model of t_c in the lungs of foxes; they concluded that a high mixed venous oxygen tension (but similar O_2 saturation) suggested a hemoglobin with a particularly low oxygen affinity in this species. In a study of a greater number of mammalian species, Schmidt-Nielsen and Larimer (1958) reported that smaller animals have slightly higher P_{50} values than larger animals. This is apparently a function of the concentration of 2,3-diphosphoglycerate (DPG) in their erythrocytes and the sensitivity of their hemoglobin to DPG (Nakashima *et al.* 1985). Lower-affinity hemoglobin would favor O_2 unloading in the tissues of smaller animals, and this may account for the shorter t_c at the same O_2 release rate per unit volume of blood in smaller animals. We note that the slope of the regression in Fig. 6 is opposite in sign and near in value to the slope of the regression presented by Schmidt-Nielsen and Larimer (1958) for P_{50} *versus* body mass.

Table 4. *Mean transit time for blood in capillaries of lungs and the ratio of* t_c *in muscle to* t_c *in lung in mammals exercising at their aerobic maxima*

	Lung t_c (s)	Muscle t_c/lung t_c
Horse	0.40[1]	2.10
Steer	0.49[1]	2.04
Human	0.4[2]	1.75*
Dog	0.29[3]	2.66
Goat	0.47[3]	1.43
Fox	0.13[4]	2.15

[1]Constantinopol *et al.* (1989); [2]Mochizuki *et al.* (1987); [3]Karas *et al.* (1987); [4]Longworth *et al.* (1989).

*Muscle t_c estimated for a 70 kg human from Fig. 6 as 0.7 s.

t_c, mean capillary transit time.

We can predict t_c for an animal species two orders of magnitude smaller in body size than the fox and agouti. For a 17 g woodmouse, $\dot{V}_{O_2max}$ is 0.0744 ml s^{-1} (Hoppeler *et al.* 1984) and total capillary volume of the muscles is 0.110 ml (Hoppeler *et al.* 1984; S. R. Kayar, unpublished data). Assuming a blood oxygen extraction of 0.15 ml O_2 ml^{-1} blood (Table 2), we obtain a t_c of 0.26 s. This is in reasonable agreement with the value of 0.17 s which can be obtained by extrapolation from Fig. 6 for a 17 g animal.

The t_c for blood in the lungs at $\dot{V}_{O_2max}$ has been estimated for some of the same animals for which we estimated the t_c in muscles (Table 4; also included for comparison is an estimate of t_c for the human lung (Mochizuki *et al.* 1987) and t_c for the muscles of a 70 kg human that was estimated from the regression in Fig. 6). The t_c in muscle is consistently longer than lung t_c by a factor of approximately 2 (Table 4). We speculate that this difference in the potential time available for loading O_2 into the blood in the lungs *versus* unloading O_2 from the blood into the muscles is related to the resistance to oxygen diffusion imposed by the muscle tissue.

We conclude that transit time for capillary blood in the muscles of animals exercising at their aerobic maxima is significantly positively correlated with body size, but decreases with increasing transcapillary O_2 flux. Muscle blood flow and hemoglobin flux are positively correlated with muscle oxidative capacity. These observations support the hypothesis that muscle blood flow, hemoglobin flux and capillary blood volume all scale in proportion to $\dot{V}_{O_2max}$ and that, as a consequence of these interrelationships, t_c is negatively correlated with oxidative capacity.

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