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Allometric scaling of maximal metabolic rate in mammals: muscle aerobic capacity as determinant factor

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Abstract

Maximal metabolic rate (MMR) of mammals scales differently from basal metabolic rate (BMR). This is first shown by scrutinizing data reported on exercise-induced $\dot{V}_{O_2}$max in 34 eutherian mammalian species covering a body mass range of 7 g–500 kg. $\dot{V}_{O_2}$max was found to scale with the 0.872 (±0.029, 95% confidence limits 0.813–0.932) power of body mass which is significantly different from the 3/4 power reported for basal metabolic rate. The aerobic scope is higher in athletic than non-athletic species, and it is also higher in large than in small species. Integrated structure-function studies on a subset of 11 species (body mass 20 g–450 kg) show that the variation of $\dot{V}_{O_2}$max with body size is tightly associated with the aerobic capacity of the locomotor musculature: the scaling exponents for $\dot{V}_{O_2}$max, the total volume of mitochondria, and the volume of capillaries are nearly identical. The higher $\dot{V}_{O_2}$max of athletic species is tightly linked to proportionally larger mitochondrial and capillary volumes in animals of the same size class. As a result $\dot{V}_{O_2}$max is linearly related to both total mitochondrial and capillary erythrocyte volumes. We conclude that the scaling of maximal metabolic rate is explained by features and mechanisms different from those determining basal metabolic rate.

Keywords: Allometry, metabolic rate, maximal versus basal; Exercise, aerobic scope; Mammals, several species; Metabolism, maximal versus basal; Oxygen, consumption, maximal; Scaling, metabolic rate, maximal versus basal

1. Introduction

The energy range of a homeothermic animal is characterized by two set points: basal metabolic rate (BMR) which reflects the lowest need of energy achieved at rest in a postprandial state under thermoneutral conditions; and maximal metabolic rate (MMR) achieved under conditions of heavy exercise when most locomotor muscles are working at their sustainable maximum. It is well established that BMR scales allometrically with body size according to the power law BMR $= aM_b^b$, where, for mammals, the exponent b is generally taken to be 3/4 (Kleiber, 1932; Schmidt-Nielsen, 1984). Thus BMR per unit body mass of a 20 g mouse is about six times higher than that of a human. The capacity of animals to raise their metabolic rate upon exercise varies considerably: whereas in most mammals MMR is about

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10-fold greater than BMR this factor can reach 25–50 in athletic species such as dogs or horses. Body size is not the only determinant of MMR and the question must therefore be raised whether MMR scales differently from BMR, and for what reasons.

As a fundamental biological feature the allometric variation of BMR with body mass challenged biologists to find an explanation, preferably from first principles. When Rubner (1883) first discovered this function he found his empirical data to be best described by BMR $= aM_b^{2/3}$, and he interpreted this to mean that BMR served to maintain constant body temperature against heat dissipation across the body surface which varies with $M_b^{2/3}$. Studying a larger group of mammals Kleiber (1932) found his data to be better described by a power law with $M_b^{3/4}$. Even though there was no obvious mechanistic explanation of this exponent it became broadly accepted as the determinant of basal or standard MR dependence on body mass (Schmidt-Nielsen, 1984). The validity of the 3/4 exponent was recently questioned on statistical grounds (Dodds et al., 2001) concluding that an exponent 2/3 cannot be excluded. White and Seymour (2003) on the other hand, criticized that truly basal MR cannot be obtained on mammals that use fermentation in their digestive tract which causes their BMR to be overestimated. If such species, all in the size class >1 kg, are excluded a scaling exponent close to 2/3 results. The population of mammals here considered does not exclude such species so that we must assume an exponent of 3/4 as the more realistic description of BMR scaling for our purposes.

Most of the recent discussions on the variation of BMR with body mass was concerned with finding a mechanistic explanation for the enigmatic mass exponent of 3/4, invoking quantum mechanics (Demetrius, 2000), the effect of topology (Phillips, 2000), or the relation between supply and demand of metabolites in a network structure (Banavar et al., 1999). One widely acclaimed approach has been the attempt to derive scaling relations from the fractal design of the distribution network for metabolites and oxygen which led to the explanation of the "1/4 power law" from first principles (West et al., 1997). This approach appeared so powerful and fundamental that it was declared a "universal" law that could explain the scaling of metabolic rate for animals, at least mammals and birds, from the organism all the way down to the basic building blocks of the cells, such as the cytochrome oxidase molecule (West et al., 2002). It was furthermore suggested that, on the basis of this model, the design properties should be such "that the magnitudes of structures and functions tend to just meet maximal demands" (Brown et al., 2000), the essential postulate of symmorphosis (Weibel et al., 1991, 1992; Weibel, 2000). Hence, this model predicts that maximal metabolic rate is also proportional to $M_b^{3/4}$ in animals of different size. This notion was challenged by Darveau et al. (2002) and Hochachka et al. (2003) who argued that the metabolic rate of the organism results from the summation of different energy consumers that should be different at rest and in exercise. They presented a concept according to which MMR and BMR should scale differently with body mass.

Such different scaling had been noted before (Koteja, 1987; Taylor et al., 1988; Bishop, 1999). When we first studied the relation of MMR or $\dot{V}_{O_2}$max to body size in 1981 we hypothesized that it should be isometric, i.e. directly proportional to body mass, on the grounds that the cost of transportation should be determined by body mass (Taylor et al., 1981). This hypothesis was rejected after a study on wild and domestic mammals ranging in body mass from 0.3 to 300 kg, as the resultant exponent 0.81 was significantly different from 1.0 but not from 3/4 (Taylor et al., 1981). Adding more data in subsequent years brought the exponent to 0.86 which now was significantly larger than 3/4 (Taylor et al., 1988; Weibel et al., 1991). Bishop (1999) scrutinized the database for maximal oxygen consumption and found a scaling exponent larger than 3/4 for both mammals and birds.

There is, indeed, no a priori reason why MMR should scale the same way as BMR with body size. There are distinct differences in the performance of the system under the two conditions:

(a) at BMR O_2 is consumed in all cells mainly for maintenance of cell polarity, protein synthesis etc.; at MMR over 90% of O_2 is consumed in a single organ system, the locomotor muscles, for ATP resynthesis related to work output;
(b) at BMR blood flow is distributed equitably through the (fractal) vascular tree to all organs of the body; at MMR over 90% of blood flow

is preferentially directed to contracting muscle tissue in response to increased energy demand;

(c) among species with similar BMR there are great differences in the capacity to increase MR in support of exercise, e.g. in athletic versus sedentary species (Taylor et al., 1987; Jones et al., 1989).

In this paper we shall first critically review the existing data base for MMR in mammals and derive a statistically well supported scaling exponent for this broad data set. Taking the point of view of system physiology we then ask what factors may be determining MMR and how this will cause the scaling of MMR to be different from that of BMR. An important characteristic of this analysis is that body size is considered only one of several factors determining MR, and that will be considered in discussing the existing models of MR scaling.

2. Materials and methods

The study is based, in its first part, on data collected from the existing literature on the basis of a broad search, as reported in Appendix A; it also includes our own data set. The criterion for inclusion in this study was that the data were obtained using the accepted standardized method for estimating $\dot{V}_{O_2}$max which is to run animals on a treadmill at varying work intensity (speed and incline) measuring $\dot{V}_{O_2}$ and plasma lactate concentration when steady state is achieved (Seeherman et al., 1981); speed is kept constant and is varied between runs. Under such experimental conditions $\dot{V}_{O_2}$max is reached when a further increase in work output does not cause $\dot{V}_{O_2}$ to rise further but the additional energy is provided by anaerobic metabolism as reflected by an increase in plasma lactate concentration. In this sense maximal metabolic rate MMR does not mean maximal muscle work but rather the maximal rate of aerobic metabolism, $\dot{V}_{O_2}$max, elicited mainly by muscle work.

For the analysis of structure–function relation we used data obtained in various studies from our own group on mammals of varying body size because they were consistently obtained by the same approach and methodology. Briefly, the estimation of $\dot{V}_{O_2}$max, further physiological studies, and the morphometric analysis were done on the same animals; the data are therefore directly correlated. To achieve this the animals were sacrificed after completion of the physiological studies, the lungs were fixed by intratracheal instillation of glutaraldehyde and tissue samples of the muscles and various organs were obtained (Hoppeler et al., 1987).

The mammalian species included were the European woodmouse (20 g, Hoppeler et al., 1984), the white rat and the blind mole rat (150 g, Widmer et al., 1997), the guinea pig (580 g, Hoppeler et al., 1995), the arctic fox and the agouti (4 kg, Longworth et al., 1989; Bicudo et al., 1996; Hoppeler and Fluck, 2002), the goat and dog (24 kg, Vock et al., 1996), the pronghorn antelope (28 kg, Lindstedt et al., 1991), the horse and steer (450 kg, Kayar et al., 1989).

For the morphometric study of the locomotor muscle system muscle samples were obtained by a whole body stratified random sampling strategy (Hoppeler et al., 1984). On one half of the animal the musculature was divided into a number of strata; within each stratum three digit random numbers identified the sampling locations (length, circumference, depth) on a 3D coordinate system projected into the stratum. On the other half of the carcass the muscles were carefully dissected and weighed to obtain an estimate of the strata weights and of total muscle mass M_m. The overall mean of the estimates of mitochondrial volume density is obtained as the weighted average $\langle V_V(\mathrm{mt}, f)\rangle$ of the different strata. The total volume of muscle mitochondria is then obtained as:

$$V(\mathrm{mt}) = \frac{M_m \langle V_V(\mathrm{mt}, f)\rangle}{1.06} \quad (1)$$

where the coefficient 1.06 corrects for muscle density (Hoppeler et al., 1984). On the same whole body random samples, the volume density of capillaries was estimated by stereological methods, obtaining the capillary length density from a count of capillary profiles on cross-sections of the muscle, and using a tortuosity factor of 1.24 (Conley et al., 1987). The volume density V_V(c, f) was calculated as the product of length density and capillary cross section area estimated from measurements of capillary circumference (Conley et al., 1987). Total capillary volume V(c) was calculated by substituting the weighted average $\langle V_V(c, f)\rangle$ in Eq. (1).

3. Results

3.1. Scaling of $\dot{V}_{O_2}max$

Reviewing the literature we found 57 estimates of $\dot{V}_{O_2}$max conforming to the above-stated conditions, representing 34 mammalian species ranging in body mass from 7 g, the pigmy mouse, to over 500 kg, the horse, as presented in the Appendix A (Table A.1, all references in this table). It includes a representative range of mammalian species, wild and domesticated. It would have been desirable to have estimates of $\dot{V}_{O_2}$max in the largest terrestrial mammals that can weigh several tons, but even the best estimates of exercise $\dot{V}_{O_2}$ in the elephant are not near their $\dot{V}_{O_2}$max (Langman et al., 1995). However, the available data set covers five orders of magnitude and therefore encompasses the vast majority of terrestrial mammalian species. In this data set some species (mice, rats, dogs, horses) are represented by several studies. To avoid experimental bias species averages were calculated by pooling corresponding data from the different studies (Table 1).

In Fig. 1 $\dot{V}_{O_2}$max is plotted against body mass on a double-logarithmic scale. The dots represent experimental data (Appendix A Table A.1) and the squares species averages calculated from them (Table 1); it can be seen that the original data cluster closely around the species means. The power law regression was calculated for the species data. We find that

$$\dot{V}_{O_2}\text{max} = 118.2 M_b^{0.872\pm0.03} \quad (2)$$

This slope is significantly different ($F = 17.472$, d.f. $= 1, 64$, $P < 0.01$) from 3/4 that char-

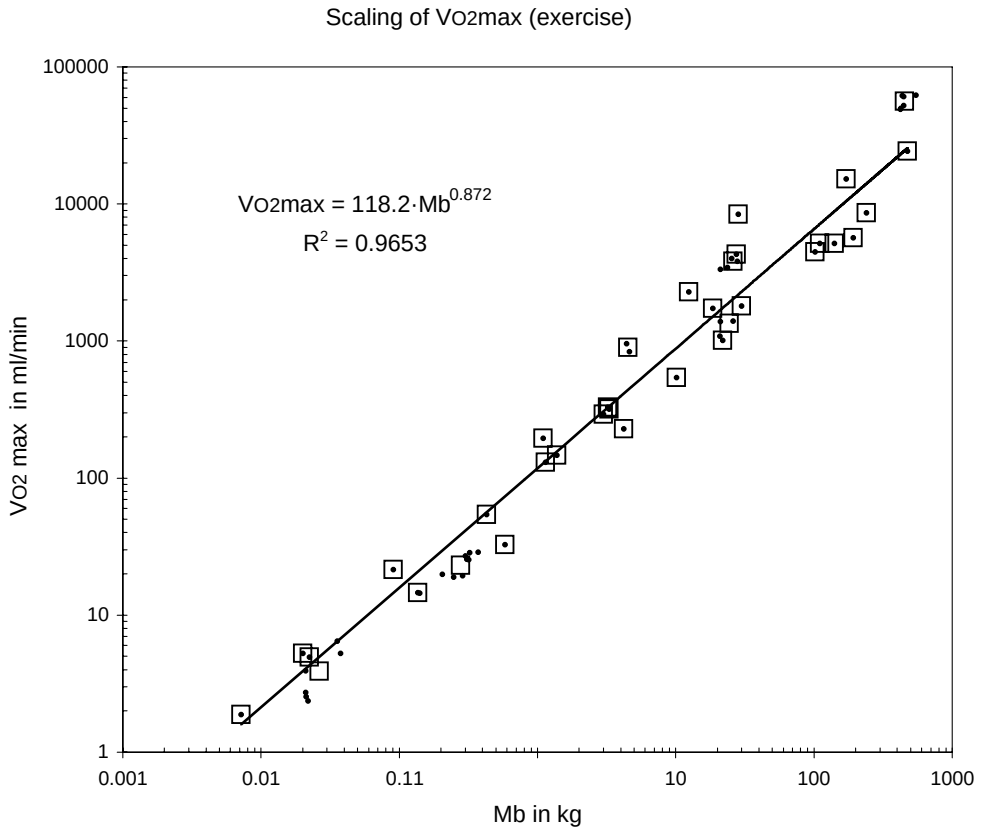

Fig. 1. Allometric plot of maximal metabolic rate $\dot{V}_{O_2}$ and body mass M_b in 34 mammalian species (squares) based on 57 estimates (dots). Species data from Table 1 and original estimates from Appendix A, Table A.1. The slope of 0.872 ± 0.029 has 95% confidence limits of 0.813, 0.932. $F = 890$, d.f. $= 1, 32$, $P < 0.00001$.

Table 1
$\dot{V}_{O_2}$max and body mass for 34 mammalian species (see reference list in Appendix A for sources)

Species		n	M_b (kg)	$\dot{V}_{O_2}$max (ml/min)	References
Pygmy mouse	Baiomys taylori	4	0.0072	1.884	Seeherman et al. (1981)
Woodmouse	Apodemus sylvaticus	4	0.020	5.28	Hoppeler et al. (1984)
Deer mouse	Peromyscus maniculatus	211	0.022	4.928	Chappell et al. (2003)
Mouse	Mus musculus	425	0.026	3.884	Kemi et al. (2002), Maxwell et al. (1998), Niebauer et al. (1999), Schefer and Talan (1996)
Chipmunk	Tamias striatus	2	0.090	14.58	Seeherman et al. (1981)
Mole rat	Spalax ehrenbergi	4	0.136	23.13	Widmer et al. (1997)
Rat	Rattus norvegicus	103	0.278	54.44	Abdelmalki et al. (1996), Gonzalez et al. (1998), Gosselin et al. (1997), Lambert et al. (1996), McClelland et al. (1999), Niederhoffer et al. (2000), Seeherman et al. (1981), Tanaka et al. (1997), Widmer et al. (1997)
Dwarf mongoose	Helogale pervula	2	0.430	32.59	Mathieu et al. (1981)
Guinea pig	Cavia porcellus	5	0.584	21.49	Turner et al. (1995)
Rat kangaroo	Bettongia penicillata	2	1.10	194.7	Seeherman et al. (1981)
Banded mongoose	Mungos mungo	1	1.14	130.0	Mathieu et al. (1981)
Genet cat	Genetta tigrina	2	1.38	146.6	Mathieu et al. (1981)
Spring hare	Pedetes capensis	2	3.00	291.6	Seeherman et al. (1981)
Agouti	Agouti paca	1	3.22	328.4	Hoppeler and Fluck (2002)
Suni	Nesotragus moschatus	2	3.30	317.8	Mathieu et al. (1981)
Dik-dik	Madoqua kirkii	2	4.20	228.1	Mathieu et al. (1981)
Fox	Alopex lagopus	5	4.51	897.5	Longworth et al. (1989), Weibel et al. (1983)
Grant's gazelle	Gazella granti	1	10.1	539.3	Mathieu et al. (1981)
Coyote	Canis latrans	2	12.4	2283.3	Weibel et al. (1983)
Pigs	Sus scrofa	2	18.5	1731.6	Seeherman et al. (1981)
African sheep	Ovis aries	2	21.8	1013.7	Mathieu et al. (1981)
Goat	Capra hircus	8	24.3	1344.7	Hoppeler et al. (1987), Mathieu et al. (1981), Vock et al. (1996)
Dog	Canis familiaris	11	25.9	3825	Hoppeler et al. (1987), Seeherman et al. (1981), Vock et al. (1996), Weibel et al. (1983)
Wolf	Canis lupus	2	27.6	4310	Weibel et al. (1983)
Pronghorn	Antilocapra americana	1	28.4	8435	Lindstedt et al. (1991)
Lion	Panthera leo	2	30.0	1800	Seeherman et al. (1981)
Wildebeest	Connochaetes taurinus	1	102	4468	Mathieu et al. (1981)
Waterbuck	Kobus defassa	2	110	5172	Mathieu et al. (1981)
Calf	Bos taurus	3	141	5161	Hoppeler et al. (1987)
Pony	Equus caballus	3	171	15185	Hoppeler et al. (1987)
Zebu cattle	Bos indicus	4	193	5660	Mathieu et al. (1981)
Eland	Taurotragus oryx	1	240	8640	Mathieu et al. (1981)
Horse	Equus caballlus	40	453	56005	Hoppeler et al. (1987), Jose-Cunilleras et al. (2002), Kindig et al. (2001), Lacombe et al. (2001), McKeever and Malinowski (1997), Tyler et al. (1996)
Steer	Bos taurus	3	475	24225	Kayar et al. (1989)

acterizes BMR (Kleiber, 1932; Schmidt-Nielsen, 1984).

Fig. 1 also reveals the great variability of $\dot{V}_{O_2}$max in relation to body mass. For example, in the size class of 25 kg the range of $\dot{V}_{O_2}$max is almost one order of magnitude between the goat on one hand and the pronghorn antelope on the other. This is related to differences in the aerobic exercise capacity of different species, which is higher in athletic mammals, such as horse, dog and pronghorn, compared to the majority

of "normal" or more sedentary species (Taylor et al., 1987; Jones et al., 1989; Lindstedt et al., 1991).

Could the slope be steeper than that of BMR because of the presence of athletic species, which are prevalent in the larger size classes? In Fig. 2 the athletic species are separated from the "normal" on the grounds of their high mass-specific $\dot{V}_{O_2}$max. The regression for the non-athletic species alone is

$$\dot{V}_{O_2}\text{max} = 93.4 M_b^{0.849\pm0.024} \quad (3)$$

with 95% confidence limits 0.799, 0.899. The coefficient a is lower by 20% but the slope b is not different from that of Eq. (2) ($F = 0.265$, d.f. $= 1, 24$, $P = 0.609$). From this we conclude that the difference between the power law slopes of BMR and $\dot{V}_{O_2}$max is not due to the inclusion of athletic species whose MMR scales according $\dot{V}_{O_2}\text{max} = 191 M_b^{0.942\pm0.024}$ which is significantly different from the non-athletic regression both with respect to the exponent b and the coefficient a (see Fig. 2).

A steeper allometric slope of $\dot{V}_{O_2}$max compared to BMR suggests that larger mammals have a greater relative capacity to increase metabolic rate above the resting state than small mammals. The so-called factorial aerobic scope (fAS) is defined as the ratio of $\dot{V}_{O_2}$max to BMR and is commonly thought to be of order 10. We have calculated fAS as the ratio of measured $\dot{V}_{O_2}$max (Table 1) to BMR predicted from the regression of Kleiber (1932)

$$\text{BMR(K)} = 11.3 M_b^{3/4} \quad (4)$$

and we find that fAS shows a positive power slope with body mass with exponent 0.122 ± 0.029 ($F = 17.297$, d.f. $= 1, 32$, $P < 0.001$). We note that fAS(K) averages about 10 for a 1 kg animal but it can be as high as 50 in horses and pronghorns, and as low as

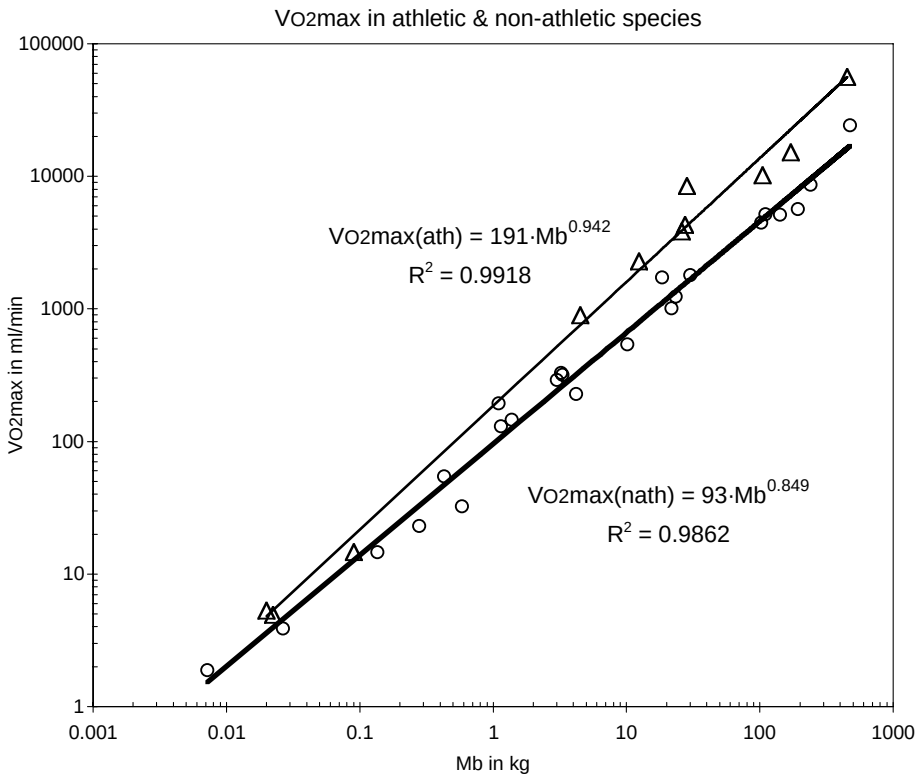

Fig. 2. $\dot{V}_{O_2}$max plotted against body mass for the 34 mammalian species of Table 1 separated into athletic and non-athletic species. The two curves differ by a factor of 2 in the coefficient a. The mass exponent of the athletic species of 0.942 has 95% confidence limits 0.889, 0.995, $F = 1609$, d.f. $= 1, 9$; that of non-athletic species is 0.849 (95% confidence limit 0.799, 0.900; $F = 1231$, d.f. $= 1, 21$), $P < 0.00001$ for both. The slope of athletic species is significantly larger than that for the non-athletic species ($F = 38.3$, d.f. $= 1, 32$, $P < 0.00001$).

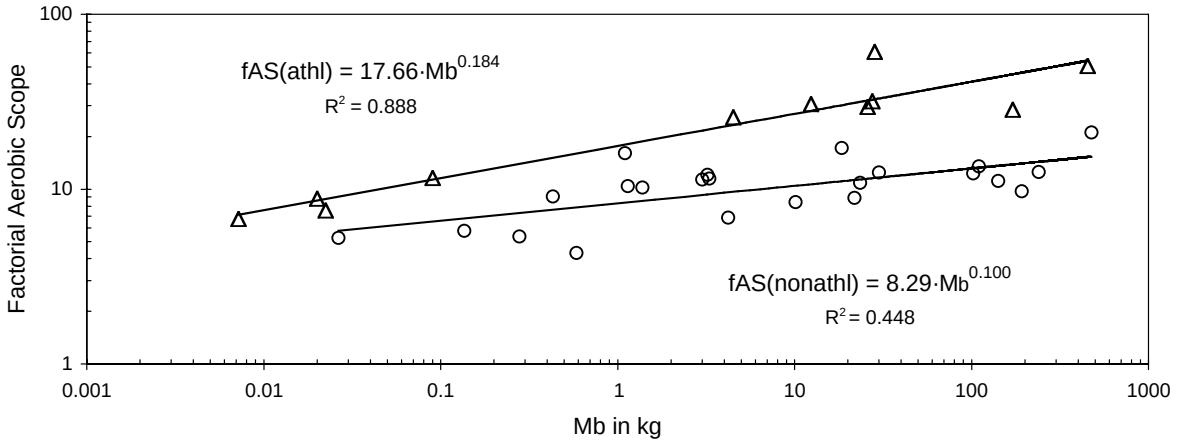

Fig. 3. Factorial aerobic scope (fAS): $\dot{V}_{O_2}$max divided by BMR $\sim M^{3/4}$ for the 34 mammalian species of Table 1 separated into athletic (triangles) and non-athletic species (circles). The higher fAS of athletic species scales with 0.184 (95% confidence limits 0.133, 0.233; $F = 71.4$; d.f. = 1, 9; $P < 0.0001$) compared with 0.0997 (95% confidence limit 0.0495, 0.1499; $F = 16.82$; d.f. = 1, 21; $P < 0.001$) for non-athletes. The latter is still larger than 0 (95% confidence limits 0.0495, 0.1499; $F = 16.823$, d.f. = 1, 21, $P < 0.001$) so that fAS increases with body mass in both groups.

six in mice. In Fig. 3 fAS is plotted separately for athletic and non-athletic mammals; the shallower slope for non-athletic species with power 0.100 (±0.024) is still significantly larger than 0 (95% confidence limits 0.0495, 0.1499; $F = 16.823$, d.f. = 1, 21, $P < 0.001$). The factorial aerobic scope is therefore related both to body mass and to aerobic capacity, and the range of fAS is greater in large than small mammals.

3.2. $\dot{V}_{O_2}$max and muscle aerobic capacity

The apparent discrepancy between the scaling of BMR and $\dot{V}_{O_2}$max suggests that different factors set the conditions for basal and maximal metabolism. Considering that $\dot{V}_{O_2}$max is elicited by muscle work we must first look for characteristics of the locomotor muscle system that could cause the variation of $\dot{V}_{O_2}$max to be partly independent of BMR, as suggested by the concept of Darveau et al. (2002). Essential factors to consider are muscle mass and aerobic capacity of muscle fibres.

In a series of in-depth studies performed for other purposes (Hoppeler et al., 1984; Kayar et al., 1989; Lindstedt et al., 1991; Bicudo et al., 1996; Vock et al., 1996; Widmer et al., 1997; Hoppeler and Fluck, 2002) we obtained correlated data on muscle structure and $\dot{V}_{O_2}$max in a set of mammals ranging from the woodmouse of 20 g to the horse and steer of 500 kg (Table 2). We first find muscle mass M_m to be 36% of body mass on average, ranging from 25% in the goat to 45% in the pronghorn but without any dependence on body size as M_m scales with $M_b^{1.01}$ ($r^2 = 0.997$). Interestingly, the smallest animal, the woodmouse, had one of the highest relative muscle masses: 42%.

It has been noted for a long time that the higher aerobic capacity of athletes is related to the mitochondrial content of the locomotor muscles, as well in humans (Hoppeler et al., 1973) as in athletic mammals (Hoppeler et al., 1987). This suggests the hypothesis that the mitochondria of muscle could determine $\dot{V}_{O_2}$max also with respect to allometric variation. To test this hypothesis requires a study design where the physiological and morphometric measurements are congruent, i.e. relate to the same compartment and are obtained on the same animals. In quadrupedal mammals running at $\dot{V}_{O_2}$max nearly the entire muscle mass is engaged and oxidative phosphorylation accordingly occurs in all muscles; this may be different in bipedal locomotion in humans (Hoppeler, 1990). The estimate of muscle mitochondrial content must therefore reflect the musculature of the whole body. This is achieved

Table 2
Body mass M_b, muscle mass M_m, $\dot{V}_{O_2}$max, mean mitochondrial volume density V_V(mt, f), total muscle mitochondrial volume V(mt), mean capillary length density J_V(c, f), total muscle capillary length J(c), total muscle capillary volume V(c), hematocrit Hct, and total muscle capillary erythrocyte volume V(ec), obtained by whole body muscle sampling in 11 mammalian species

Species		n	M_b (kg)	$\dot{V}_{O_2}$max (ml/min)	M_m (kg)	M_m/M_b (kg/kg)	Vv(mt, f) (ml/ml)	V(mt) (ml)	J_V(c, f) (m/m^2)	J(c) ($\times 10^5$ cm)	V(c) (ml)	Hct (ml/ml)	V(ec) (ml)	Reference
European woodmouse	Apodemus sylvat.	4	0.020	5.28	0.00836	0.418	0.1197	0.94	1575	12.4	0.197	0.42	0.083	a
Mole rat	Spalax ehrenbergi	3	0.129	13.61	0.0351	0.272	0.0883	2.93	1757	61.2	0.973	0.42	0.4	b
White rat	Rattus norvegicus	4	0.148	15.55	0.0511	0.347	0.0604	2.91	1346	62.3	0.991	0.42	0.425	b
Guinea pig	Cavia porcellus	21	0.595	33.20	0.178	0.299	0.0609	10.23	1018	171	2.72	0.5	1.36	c
Agouti	Agouti paca	1	3.22	328.44	1.31	0.407	0.0562	69.5	720	883	14.04	0.42	5.897	c
Fox	Alopex lagopus	3	4.4	955.7	1.67	0.380	0.1272	200.4	1025	1615	25.68	0.42	10.786	d
Goat	Capra hircus	3	21.0	1386.0	5.40	0.257	0.0412	209.8	1255	6393	101.6	0.299	30.38	e
Dog	Canis familiaris	3	23.7	3455.5	8.65	0.365	0.0864	705.1	1750	14280	227	0.5	113.5	e
Pronghorn	Antilocapra amer.	1	28.4	8434.8	12.79	0.450	0.0785	947.5	1537	18545	294.9	0.456	134.47	f
Horse	Equus caballlus	3	446	60745.2	191	0.428	0.0747	13460.1	1150	207216	3295	0.55	1812.25	g
Steer	Bos taurus	3	475	24225.0	165	0.347	0.0356	5541.5	901	140250	2230	0.4	892	g

Data sources: (a) Hoppeler et al. (1984); (b) Widmer et al. (1997); (c) Hoppeler and Fluck (2002); (d) Bicudo et al. (1996); (e) Vock et al. (1996); (f) Lindstedt et al. (1991); (g) Kayar et al. (1989).

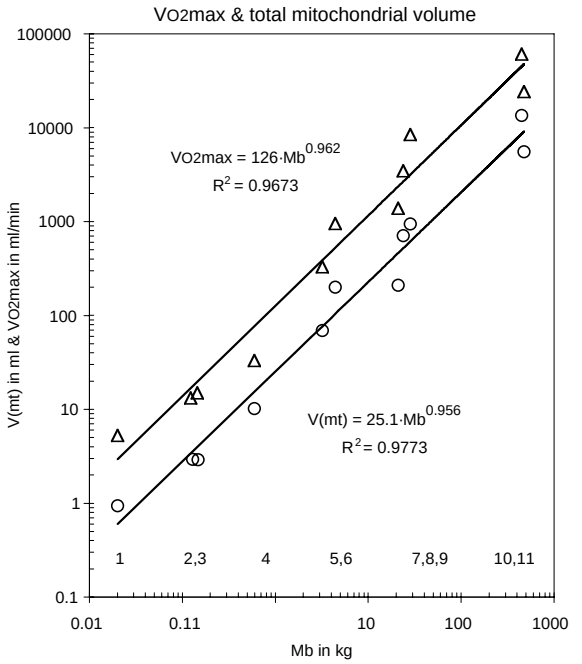

Fig. 4. $\dot{V}_{O_2}$max (triangles) and morphometric estimate of total volume of muscle mitochondria V(mt) (circles) in 11 species based on whole body sampling. The slope is 0.962 for $\dot{V}_{O_2}$max (95% confidence limits 0.829–1.096; $F = 265$, d.f. $= 1, 9$, $P < 0.00001$), and 0.956 for V(mt) (95% confidence limits 0.846–1.066; $F = 388$, d.f. $= 1, 9$, $P < 0.00001$); the two regressions are identical ($F = 0.168$, d.f. $= 1$, $P = 0.683$). Numbers at the bottom identify species: (1) woodmouse, (2) mole rat, (3) white rat, (4) guinea pig, (5) agouti, (6) fox, (7) goat, (8) dog, (9) pronghorn, (10) horse, (11) steer.

by the stratified random sampling scheme discussed above.

Estimates of whole body muscle mitochondrial volume V(mt) have been obtained in 11 mammalian species for which $\dot{V}_{O_2}$max was also estimated on the same animals (Table 2). Fig. 4 shows these data in a log–log plot against body mass. We note that $\dot{V}_{O_2}$max and V(mt) are proportional in all instances: the overall regression lines have identical slope of 0.96 ($F = 0.168$, d.f. $= 1, 44$, $P = 0.683$), and the data points for athletic species are consistently higher in both data sets.

If $\dot{V}_{O_2}$max is plotted against V(mt) it becomes evident that the two variables are tightly associated (Fig. 5). The "noise" in the allometric relations due to the presence of athletic and sedentary species in all size classes (Fig. 4) disappears and all data points lie tightly around the linear regression

$$\dot{V}_{O_2}\text{max} = 4.876 V(\text{mt})^{1.01}.$$

A Spearman test on residuals reveals that $\dot{V}_{O_2}$max and V(mt) show a high positive association (Spearman $R = 0.909$, $t = 6.547$, d.f. $= 9$, $P < 0.001$) independent of their relation to M_b. This result also means that, in all mammalian species considered—whether athletic or sedentary, whether small or large—1 ml mitochondria consumes 4.9 ($\pm$0.43) ml O_2 per minute at $\dot{V}_{O_2}$max, confirming the observation of Hoppeler and Lindstedt (1985).

3.3. $\dot{V}_{O_2}$max and capillary blood supply

The rate of mitochondrial oxidative phosphorylation depends crucially on the supply of O_2 from capillary blood to the extent that this can be a limiting factor for aerobic metabolism. Since $\dot{V}_{O_2}$max varies with the level of athletic prowess and with body size we must ask whether the design of muscle microvasculature is matched to the varying demand.

In previous studies comparing athletic with sedentary mammals whose $\dot{V}_{O_2}$max differs by a factor of 2.5 it was found that the volume of the capillary network was higher in the athletic species, but only by a factor of 1.7. However, athletic species have a 1.8 times greater hematocrit (Conley et al., 1987; Kayar et al., 1994) so that, as a consequence, the volume of capillary erythrocytes in the musculature is 2.5 times larger in athletic species, hence matched to their higher $\dot{V}_{O_2}$max (Weibel et al., 1991).

How are capillaries related to $\dot{V}_{O_2}$max when comparing mammals of different body size? Table 2 shows the estimates of the total length of the capillary network in the locomotor muscles, estimated by the whole-body random sampling approach (see above). It amounts to 12 km in the mouse and 200,000 km in the horse (sic!). The total volume of these capillaries is plotted in Fig. 6 against body mass and we note that the scaling exponent of 0.98 does not differ from those for $\dot{V}_{O_2}$max and the volume of muscle mitochondria. Table 2 shows that the hematocrit is invariant with body mass averaging 0.42 whereas it is higher in the athletic species. We find that the volume of capillary erythrocytes and $\dot{V}_{O_2}$max are linearly related across the entire size range (Fig. 7). In all mammalian species whether small or large, athletic or sedentary,

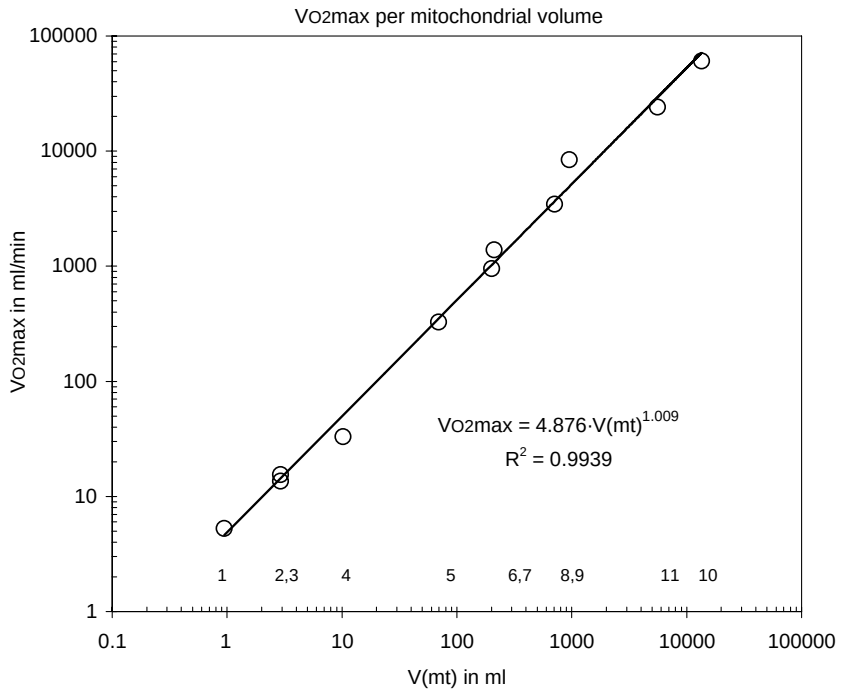

Fig. 5. $\dot{V}_{O_2}$max plotted as function of total muscle mitochondrial volume V(mt) in 11 species. The exponent is 1.009; 95% confidence limits 0.949, 1.068; $F = 1463$, d.f. = 1, 9; $P < 0.00001$. Numbers at the bottom identify species as in Fig. 4.

one ml of capillary erythrocytes delivers 45 ml O_2 per min at $\dot{V}_{O_2}$max. We also note that muscle tissue contains about 1 ml of erythrocytes in capillaries for every 10 ml of mitochondria in the muscle fibres.

4. Discussion

This study demonstrated unequivocally that, in mammals, maximal metabolic rate MMR scales differently with body mass than basal metabolic rate BMR. The data set used for this analysis covers five orders of magnitude of mammals from 7 g to 500 kg. We found that maximal metabolic rate scales with an exponent of 0.872 with confidence limits on the exponent of 0.813–0.932 (see Table 3 for a summary on statistics). This is significantly larger than the exponent of 0.75 observed for BMR and confirms earlier reports (Koteja, 1987; Taylor et al., 1988; Bishop, 1999). A mechanistic explanation of the scaling of

Table 3
Summary of statistics of the power law regressions

Figure	Regression	Coefficient, a	Exponent, b	S.E.	95% confidence limits	F	d.f.	P
1	$\dot{V}_{O_2}$max per M_b	118.2	0.872	0.029	0.8130–0.9320	890	1, 32	<0.00001
2a	$\dot{V}_{O_2}$max non-athletes	93.42	0.849	0.024	0.7989–0.8996	1231.6	1, 21	<0.00001
2b	$\dot{V}_{O_2}$max athletes	190.8	0.942	0.024	0.8887–0.9950	1608.7	1, 9	<0.00001
3a	fAS non-athletes	8.29	0.100	0.024	0.0495–0.1499	16.82	1, 21	<0.001
3b	fAS athletes	17.66	0.184	0.022	0.1334–0.2327	71.4	1, 9	<0.0001
4 and 6	$\dot{V}_{O_2}$max	126.4	0.962	0.059	0.8287–1.0960	265.3	1, 9	<0.00001
4	V(mt) per M_b	25.1	0.956	0.049	0.8463–1.0658	388.3	1, 9	<0.00001
5	$\dot{V}_{O_2}$max per V(mt)	4.876	1.009	0.0026	0.9490–1.0680	1463	1, 9	<0.00001
6	V(c) per M_b	6.731	0.984	0.033	0.9090–1.0559	916	1, 9	<0.00001
7	$\dot{V}_{O_2}$max per V(ec)	44.9	0.975	0.041	0.8832–1.0674	574.3	1, 9	<0.00001

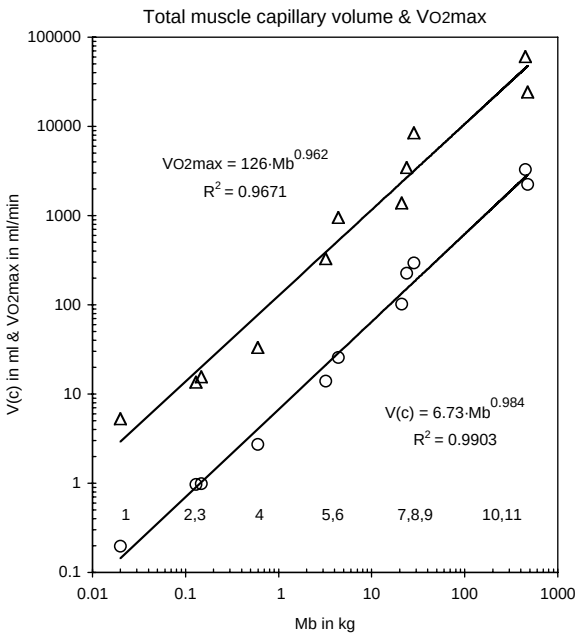

Fig. 6. $\dot{V}_{O_2}$max (triangles) and morphometric estimate of total volume of muscle capillaries V(c) (circles) in 11 species based on whole body sampling. The slope is 0.962 for $\dot{V}_{O_2}$max (95% confidence limits 0.829–1.096; $F = 265$, d.f. $= 1, 9$, $P < 0.00001$), and 0.984 for V(c) (95% confidence limits 0.909–1.056; $F = 916$, d.f. $= 1, 9$, $P < 0.00001$); the two regressions are identical. Numbers at the bottom identify species as in Fig. 4.

MMR therefore cannot be a simple extrapolation from that of BMR as different factors come into play, particularly such associated with locomotor musculature. This notion is reinforced by the observation that the presence of species with very different athletic prowess leads to considerable scatter in the data for $\dot{V}_{O_2}$max such that for the same size class the highest value of MMR can be five times greater than the lowest.

We have also noticed that the ratio of MMR/BMR, the factorial aerobic scope, is larger in large than in small mammals. This is only partly due to the fact that athletic species are more prevalent in the large size classes: after exclusion of athletic species MMR still scales steeper than BMR.

In this study we have defined $\dot{V}_{O_2}$max as the oxygen consumption elicited by maximal muscle work. The values of MMR thus achieved are higher than those elicited by cold exposure, sometimes called peak $\dot{V}_{O_2}$. In a similar study Hinds et al. (1993) used cold exposure to elicit peak $\dot{V}_{O_2}$ in a similar range of mammals. They also observed a scaling of peak metabolic rate with an exponent 0.85, similar to the value observed here.

Basal and maximal metabolic rates are set points of the lower and upper limit of the range of metabolic activities in which homeothermic animals, in our case terrestrial mammals, can engage. They reflect functional states that are relatively well controlled under experimental conditions, but they are very rarely, or almost never, achieved in nature. The natural energetic needs are better reflected by the field metabolic rate (FMR) as estimated in free-ranging animals by the doubly labelled water technique, a method that measures the production of CO_2 over prolonged periods. Nagy et al. (1999) have studied FMR in a large spectrum of free-ranging species, mammals, reptiles and birds, and found it to be predominantly determined by body size, but there was a large effect of taxonomic differences as well as effects of diet and habitat. For eutherian mammals they found FMR to scale with the 0.772 power of body mass, but this includes marine mammals that have a high FMR and are in the larger size classes. It is not easy to interpret the relation of FMR to the two limiting conditions BMR and MMR as it is undoubtedly determined by "basic" energetic needs, but in highly active animals there will also be a significant contribution from locomotory activity. This needs to be worked out.

The advantage of concentrating on exercise-elicited $\dot{V}_{O_2}$max lies in the fact that under these conditions over 90% of oxygen is consumed in muscles and 90% of blood flow is directed to the musculature (Mitchell and Blomqvist, 1971). This facilitates the search for an explanation of MMR scaling in the size-dependent variation of muscle properties.

On a subset of 11 mammalian species ranging in body mass from 20 g to 450 kg we have obtained detailed data on $\dot{V}_{O_2}$max and a number of functional and structural characteristics of locomotor muscles which are all tightly related as they were obtained on the same animals. In addition, these data reflect the whole muscle mass of the body which, in quadrupeds, is active when the animal works at MMR. We have found the scaling exponent of MMR to be steeper in this subset namely 0.96 instead of 0.87 for the entire population. The confidence limits of the two

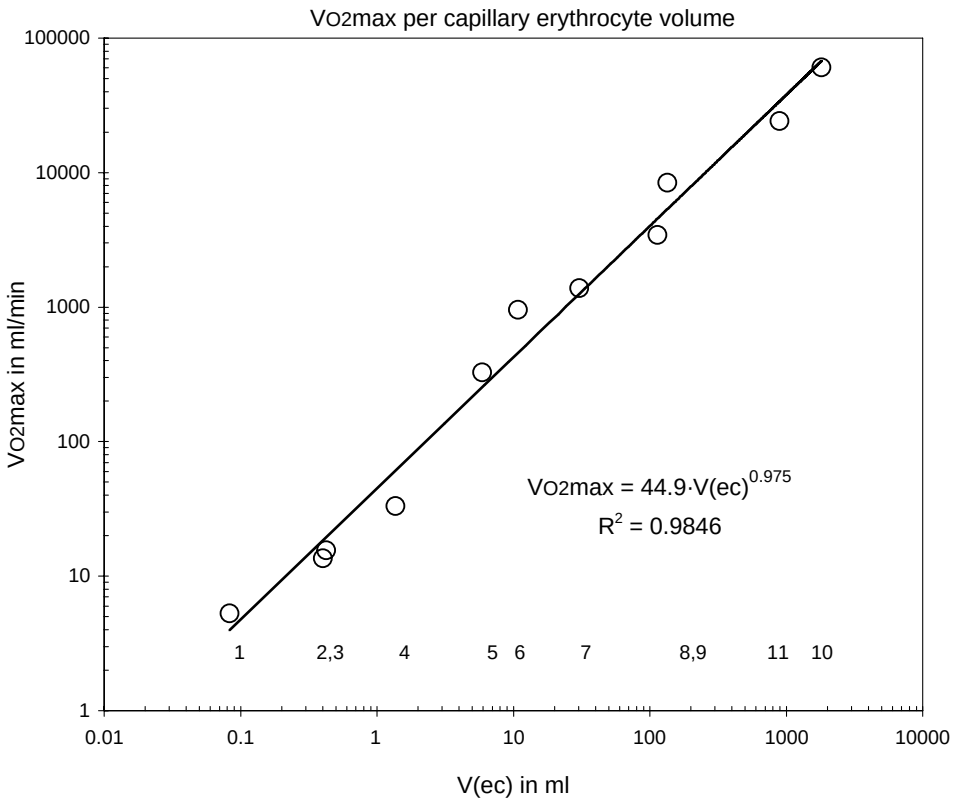

Fig. 7. $\dot{V}_{O_2}$max plotted as function of total muscle capillary erythrocyte volume V(ec) in 11 species. The exponent is 0.975; 95% confidence limits 0.893, 1.074; $F = 604$, d.f. $= 1, 9$; $P < 0.00001$. Numbers at the bottom identify species as in Fig. 4.

exponents (0.829–1.096 versus 0.813–0.932) overlap (see Table 3).

We first observe that the total volume of mitochondria in the locomotor musculature scales with the same exponent of 0.96 and is strictly proportional to $\dot{V}_{O_2}$max for all species. In the allometric plot we note that the values for both $\dot{V}_{O_2}$max and V(mt) of athletic species are shifted to the same degree from the regression line. This led to the conclusion that the ratio of $\dot{V}_{O_2}$max/V(mt) is 4.9 ml/min ml for all mammalian species, whether small or large, athletic or non-athletic which confirms the observation of Hoppeler and Lindstedt (1985). It should be noted however that this important invariant value does not reflect the maximal metabolic capacity of mitochondria. Higher values are obtained in vitro (Schwerzmann et al., 1989) and slightly higher metabolic rates are also obtained in vivo with blood doping (Ekblom et al., 1976), that is by increasing to some degree oxygen supply to the mitochondria. This limitation may reflect the fact that the process of oxidative phosphorylation at the mitochondrial inner membrane is constrained by various cellular factors, such as oxygen diffusion to and into the mitochondria, substrate flux through the Krebs cycle, or high energy phosphate cycling.

Using mitochondrial volume as a primary reference is correct only in first approximation. A better parameter would be the surface of the inner mitochondrial membrane where the enzyme system of oxidative phosphorylation resides. In previous studies we have observed that the density of inner membrane in the mitochondrial volume is invariant over the range of mammalian species studied here (Hoppeler and Lindstedt, 1985; Schwerzmann et al., 1989). We should however note that this may not be acceptable for example in very small animals with extremely high energy demand such as in the Etruscan shrew or in the hummingbird where it was found that the inner

membranes are more tightly packed into the mitochondria (Suarez et al., 1991; Bicudo and Zerbinatti, 1995).

Mitochondrial oxidative phosphorylation depends on adequate oxygen supply from the capillaries in proportion to demand. We find that the volume of capillaries is proportional to both MMR and V(mt) in the species of the restricted data set. When considering the fact that hematocrit is higher in athletic than non-athletic species the correlation is improved with the result that the volume of erythrocytes in capillaries is linearly proportional to both V(mt) and MMR. We therefore conclude that the structural parameters that determine oxygen supply to the mitochondria scale in proportion to oxygen needs under the conditions of MMR.

Mitochondria and capillary blood together determine the aerobic capacity of muscle. It is interesting and highly significant that both are related to body size in strict proportion to the maximal metabolic rate an animal can achieve.

Is it justified to generalize these findings obtained on a subset of species to the entire range of mammals for which MMR was found to scale with the 0.87 power of body mass? We believe so, for several reasons. First, the scaling exponent of the subset is not statistically different from that of the overall population. Second, the subset is evenly distributed over nearly the entire size range, but it excludes the smallest species of the overall set. Furthermore the subset includes both athletic and non-athletic species, but with a slight overweight of athletic species in the larger size classes. In addition, we have obtained approximate estimates of muscle mitochondrial and capillary volume in 10 additional mammalian species with a similar result. We therefore conclude that the scaling of the aerobic capacity of locomotor muscle is strictly proportional to the scaling of $\dot{V}_{O_2}$max.

It must next be asked whether and how the functional and structural properties of the heart are matched to the variation in O_2 supply to muscle microcirculation with variations in body size. The two key parameters of blood flow, heart frequency and stroke volume, must be considered. Stroke volume is proportional to heart size which is known to be larger in athletes but invariant with body mass (Prothero, 1979). In contrast, heart frequency depends on body size as it is higher in small than large species. At BMR heart frequency is found to scale with body mass to the power −0.25. Resting heart frequency therefore scales in parallel with mass specific basal metabolic rate. Upon exercise, heart frequency increases to reach a maximum at $\dot{V}_{O_2}$max. We find that maximal heart frequency scales with an exponent −0.15 (Bishop, 1999; Weibel and Hoppeler, 2004) which agrees with the scaling of mass specific MMR for which we obtain an exponent −0.13 from Fig. 1. It is thus evident that cardiac output is also adjusted to the needs of working muscle in animals of varying body mass. This is only partly the case in the lung as this organ at the interface to the environment maintains variable excess capacity for O_2 uptake so that the scaling of its diffusing capacity does not follow the simple relations observed in the internal parts of the respiratory pathway (Weibel et al., 1991; Weibel, 2000).

5. Conclusions

On the basis of these integrated findings on the relation between structure and function of the pathway for oxygen in mammals of varying body size we can attempt some conclusions on the mechanistic explanation of the scaling exponents. The cascade model of Darveau et al. (2002) and Hochachka et al. (2003) conceives that the scaling exponent of metabolic rate is a resultant of the weighted partial scaling of the sequential functions that determine metabolic rate. At BMR all organ systems must be considered, but at MMR elicited by exercise the major oxygen consumer is the locomotor musculature. The sequential steps in this case would be the mitochondria as sites of oxidative phosphorylation, the capillaries as oxygen supplier, the blood and the heart as oxygen carriers, and finally the lungs as organ of oxygen uptake (Weibel, 2002). We have shown here that the relevant scaling exponents for all these steps, except the lung, are identical and also the same as the scaling exponent for $\dot{V}_{O_2}$max. Most significantly we have found that the scaling of $\dot{V}_{O_2}$max is tightly correlated with the aerobic capacity of the locomotor muscles determined by the complex of mitochondria and capillary blood. These are stressed to the limit at $\dot{V}_{O_2}$max. The heart is also adjusted to the needs for oxygen supply determined by this aerobic capacity of muscle: it does so by increasing heart frequency in proportion to the factorial

aerobic scope of the animal which is larger in large than in small animals.

The mechanistic explanation of the scaling of MMR appears easy because it relates to conditions where metabolism occurs predominantly in one functionally homogenous compartment, the locomotor musculature, which is dominant in the sense that under these conditions this organ system receives 90% of the blood flow and consumes over 90% of the oxygen taken up in the lung. And since the key elements of all the steps between the lung and the muscle cells show tightly related scaling relations this may explain the observed scaling of the overall MMR.

Such explanations are more difficult at BMR that is determined by the minimal rate of oxygen consumption in all tissues of the body since blood flow is evenly distributed to all organs under these conditions. It is, however, unlikely that BMR is also related to the aerobic capacity of the tissues because the capacity for oxidative metabolism of some if not most cells is certainly higher than their activity at BMR. The liver and the intestine, for example, increase their oxygen consumption upon food uptake but BMR must be measured in the postprandial state. BMR must therefore be determined by other factors, probably of very different nature, for example by the minimal energy needed to maintain cell polarity as well as that needed to maintain blood flow, respiration, and constant body temperature (Bejan, 2000). In view of prevailing notions the question must be asked whether this complex process is primarily and causally related to the design of the vasculature as a fractal network, as proposed in the model of West et al. (1997)—or whether this design is rather the result of integrated adaptation of the dimension of the vascular network to varying needs allowing the redistribution of blood flow to those organ systems that are in greatest need.

Acknowledgements

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Appendix A

The original data for maximal metabolic rate on which the species data in Table 1 of the main paper are based are listed in Table A.1, together with the references where the data are originally reported. $\dot{V}_{O_2}$max is given in ml O_2 STPD per minute, body mass in kg. The data reported are the means of the estimates reported in the reference.

Table A.1
Estimates of $\dot{V}_{O_2}$ max and body mass in mammalian species

Species		n	M_b (kg)	$\dot{V}_{O_2}$ max/M_b (ml/min kg)	$\dot{V}_{O_2}$ max (ml/min)	Reference
Pygmy mice	Baiomys taylori	4	0.0072	261.6	1.883	Seeherman et al. (1981)
European woodmouse	Apodemus sylvaticus	4	0.02	264	5.28	Hoppeler et al. (1984)
C57BL/6J mice	Mus musculus	76	0.021	130	2.73	Kemi et al. (2002)
C57BL/6J mice	Mus musculus	17	0.0218	109	2.3762	Niebauer et al. (1999)
C57BL/6J mice females	Mus musculus	9	0.0212	120	2.544	Maxwell et al. (1998)
C57BL/6J mice males	Mus musculus	72	0.0357	181.0	6.462	Schefer and Talan (1996)
House mouse	Mus domesticus	240	0.021	186.8	3.939	Dohm et al. (2001)
House mouse	Mus domesticus	11	0.0377	139.3	5.251	Swallow et al. (1998)
Deer mice	Peromyscus maniculatus	211	0.0224	220	4.928	Chappell et al. (2003)
Chipmunk	Tamias striatus	2	0.0902	238.2	21.485	Seeherman et al. (1981)
Mole rat	Spalax ehrenbergi	4	0.135	107.5	14.584	Widmer et al. (1997)
White rat	Rattus norvegicus	4	0.140	103.5	14.492	Widmer et al. (1997)
White rat	Rattus norvegicus	3	0.205	96.6	19.803	Seeherman et al. (1981)
Long-Evans rats males	Rattus norvegicus	19	0.317	80.3	25.455	Lambert et al. (1996)
Sprague-Dawley rats males	Rattus norvegicus	20	0.323	88.5	28.585	Gosselin et al. (1997)
Sprague-Dawley rats males	Rattus norvegicus	10	0.247	76.6	18.920	Gonzalez et al. (1998)

Table A.1 (*Continued*)

Species		*n*	M_b (kg)	$\dot{V}_{O_2}$ max/M_b (ml/min kg)	$\dot{V}_{O_2}$ max (ml/min)	Reference
Wistar rats males	Rattus norvegicus	6	0.287	67.7	19.429	Tanaka et al. (1997)
Wistar rats females	Rattus norvegicus	16	0.302	89.3	26.968	McClelland et al. (1999)
Wistar rats males	Rattus norvegicus	10	0.309	83	25.647	Niederhoffer et al. (2000)
Wistar rats males	Rattus norvegicus	15	0.373	77.4	28.870	Abdelmalki et al. (1996)
Dwarf mongoose	Helogale pervula	2	0.43	126.6	54.438	Mathieu et al. (1981)
Guinea pig	Cavia porcellus	5	0.584	55.8	32.587	Turner et al. (1995)
Rat kangaroos	Bettongia penicillata	2	1.10	177	194.7	Seeherman et al. (1981)
Banded mongoose	Mungos mungo	1	1.14	114	129.96	Mathieu et al. (1981)
Genet cat	Genetta tigrina	2	1.38	106.2	146.55	Mathieu et al. (1981)
Spring hares	Pedetes capensis	2	3.00	97.2	291.6	Seeherman et al. (1981)
Agouti	Agouti paca	1	3.22	102	328.44	Hoppeler and Fluck (2002)
Suni	Nesotragus moschatus	2	3.3	96.3	317.79	Mathieu et al. (1981)
Dik-dik	Madoqua kirkii	2	4.2	54.3	228.06	Mathieu et al. (1981)
Fox	Alopex lagopus	3	4.4	217.2	955.68	Longworth et al. (1989)
Fox	Alopex lagopus	2	4.61	182.1	839.4	Weibel et al. (1983)
Grant's gazelle	Gazella granti	1	10.1	53.4	539.34	Mathieu et al. (1981)
Coyote	Canis latrans	2	12.4	184.1	2283.3	Weibel et al. (1983)
Pigs	Sus scrofa	2	18.5	93.6	1731.6	Seeherman et al. (1981)
African goat	Capra hircus	2	20.9	51.9	1084.71	Mathieu et al. (1981)
Goat	Capra hircus	3	21	66	1386	Vock et al. (1996)
Goat	Capra hircus	3	26	53.8	1399.32	Hoppeler et al. (1987)
African sheep	Ovis aries	2	21.8	46.5	1013.7	Mathieu et al. (1981)
Dog	Canis familiaris	3	21.0	158.4	3326.4	Seeherman et al. (1981)
Dog	Canis familiaris	3	23.7	145.8	3455.46	Vock et al. (1996)
Dog	Canis familiaris	2	25.3	157.9	3993.9	Weibel et al. (1983)
Dog 87	Canis familiaris	3	28	136.8	3830.4	Hoppeler et al. (1987)
Wolf	Canis lupus	2	27.5	156.5	4310.4	Weibel et al. (1983)
Pronghorn	Antilocapra americana	1	28.4	297	8434.8	Lindstedt et al. (1991)
Lion	Panthera leo	2	30.0	60	1800	Seeherman et al. (1981)
Wildebeest	Connochaetes taurinus	1	102	43.8	4467.6	Mathieu et al. (1981)
Waterbuck	Kobus defassa	2	109.8	47.1	5171.5	Mathieu et al. (1981)
Calf	Bos taurus	3	141	36.6	5160.6	Hoppeler et al. (1987)
Pony	Equus caballus	3	171	88.8	15184.8	Hoppeler et al. (1987)
Zebu cattle	Bos indicus	4	192.5	29.4	5659.5	Mathieu et al. (1981)
Eland	Taurotragus oryx	1	240	36	8640	Mathieu et al. (1981)
Steer	Bos taurus	3	475	51	24225	Kayar et al. (1989)
Horse	Equus caballlus	13	421	117	49257	Tyler et al. (1996)
Horse	Equus caballlus	6	425	117	49725	Jose-Cunilleras et al. (2002)
Horse	Equus caballlus	7	436	142	61912	Lacombe et al. (2001)
Horse	Equus caballlus	6	445	117.3	52198.5	McKeever and Malinowski (1997)
Horse	Equus caballlus	3	446	136.2	60745.2	Kayar et al. (1989)
Horse	Equus caballlus	5	547	113.7	62193.9	Kindig et al. (2001)

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