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MALLEABILITY OF SKELETAL MUSCLE IN OVERCOMING LIMITATIONS: STRUCTURAL ELEMENTS

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SUMMARY

The quantitative structural composition of skeletal muscle tissue shows a wide range of variability among different species of animals and in any one species among muscles with a different function. Moreover, experimental manipulations such as exercise training or chronic electrical stimulation can dramatically change the ultrastructural appearance of the muscles involved. Both in endurance exercise and in chronic electrical stimulation the volume density of mitochondria can be increased greatly (by more than three-fold in the stimulation experiments). This happens without an apparent change of the internal architecture of the mitochondria, since the surface density of the inner mitochondrial membranes remains constant. In situations where both the mitochondrial volume and the maximal rate of oxygen consumption of the muscle tissue are known, these two variables are found to be linearly related. It can be calculated that the 'maximal' oxygen consumption of a unit volume of mitochondria in muscle is close to 5 ml O_2 min^{-1} cm^{-3} under comparable conditions in man, mouse and a series of African mammals. It is hypothesized that there is a constant volume of oxygen metabolized per unit volume of mitochondria and unit time under limiting conditions in working skeletal muscle tissue. Given the efficiency of muscular energy conversion, this would allow an estimate of the potential for aerobic power production of a muscle from measurement of its volume density of mitochondria.

Muscles allow animals to interact mechanically with their environment. The basic processes concerned with motion as well as the structure of the sliding filaments in muscle cells are found with little modification throughout the animal kingdom (Huxley, 1973). However, the energetic demand imposed on a muscle by the organism may vary greatly depending on the specific function of that muscle. Thus, both the heart and the diaphragm have to deliver high rates of mechanical energy continuously during the whole life-span of an animal, whereas other muscles, such as the gastrocnemius, are only briefly activated every once in a while. The present review analyses the malleability of the structural components of the energetic machinery of

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skeletal muscle cells with regard to the energetic demand placed upon them by the organism.

ENERGETIC MACHINERY

Two metabolic systems can supply energy for muscle contraction. The glycolytic system resides in the sarcoplasm and can deliver ATP at high rates but only for short periods of time (Hochachka, 1985). It is thus not able to fuel sustained mechanical activities. The glycolytic system currently eludes a structural analysis as the relevant enzymes in the sarcoplasm are not bound to specific structures which can be estimated by morphometric methods. However, there is some indication that the capillarity of glycolytic muscles might be related to tissue lactate production (Hudlicka, 1985).

The muscle cell's aerobic system for energy supply mainly consists of mitochondria producing ATP through oxidative phosphorylation. Mitochondria can be well characterized by morphometric methods in terms of their volume density, the surface density of their inner and outer membranes and their distribution within the muscle cells, all of which may be important to mitochondrial energy transduction (Hoppeler *et al.* 1981). The respiratory system of the muscle cell is supported by capillaries running parallel to the muscle fibres. Capillaries are responsible for an adequate supply of oxygen and of substrates as well as for the removal of 'waste' products such as heat.

ENERGY DEMAND

During steady-state contractions the oxygen flow through the respiratory system is set to deliver the oxygen required for energy conversion in the respiratory chain units in the mitochondria which have to rephosphorylate ADP at the same rate as ATP is broken down by both the myosin and the sarcoplasmic transport ATPases. The oxygen flow from the capillaries into the mitochondrial sink can be represented as:

$$\dot{V}_{O_2} = (P_{cap} - P_{mi})_{O_2} \times G(c), \quad (1)$$

where $(P_{cap})_{O_2}$ and $(P_{mi})_{O_2}$ are the capillary and mitochondrial oxygen tensions respectively, while G(c) is the conductance of the muscle cell and of mitochondria for oxygen (Taylor & Weibel, 1981). The conductance G(c) depends heavily on structural properties of the muscle cell such as the volume of mitochondria, the surface of inner mitochondrial membranes and the number of respiratory chain units in these membranes, as well as on the location of mitochondria within the muscle cell. One can assume the rate of O_2 consumption to be closely related to the surface area of inner mitochondrial membranes, since they contain a 'dense' array of respiratory chain units (Racker, 1975; Weibel *et al.* 1981). Direct experimental evidence is lacking at present for this assumption. However, the area of inner mitochondrial

membrane per unit volume of mitochondria, although difficult to estimate stereologically in absolute terms (Fig. 1), only varies between 20 and 40 $m^2 cm^{-3}$ (Fig. 2). This parameter is not dependent on body mass (Hoppeler *et al.* 1981; Mathieu *et al.* 1981), nor does it change significantly with training (Hoppeler *et al.* 1973; Davies, Packer & Brooks, 1981). Consequently, while the surface density of inner mitochondrial membranes may vary by as much as two-fold in some cases, for most purposes the mitochondrial volume gives an adequate estimate of a muscle cell's potential for oxygen metabolism. It can thus be hypothesized that changes in cellular energy demand should be reflected by changes in this easily determined morphometric descriptor of the respiratory system of muscle tissue.

MALLEABILITY: TESTING BY VARYING ENERGY DEMAND

The highest steady-state energy demand situation an animal can satisfy is assessed by its maximal oxygen uptake capacity ($\dot{V}_{O_2}max$). Under these conditions most of the oxygen taken up by an animal is consumed by its working muscles (Mathieu *et al.* 1981). In order to appreciate the importance of structural variables on the cellular

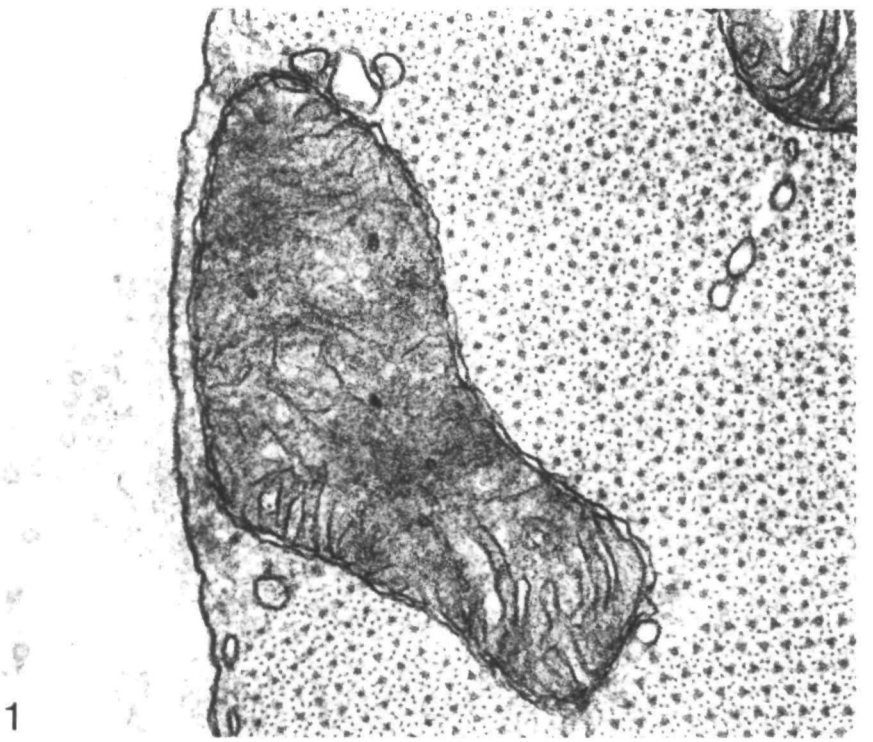

Fig. 1. Subsarcolemmal mitochondrion in a cross-section of a portion of a muscle fibre in dik-dik semitendinosus. Due to tangential sectioning and section thickness large parts of the inner mitochondrial membrane system appear fuzzy. This seriously hinders obtaining stereological estimates of the surface area of these membranes. Magnification, ×87000.

conductance of oxygen G(c), we have related changes in morphometric estimates of structural determinants of oxygen flow in the muscle cell to experimentally induced changes in maximal steady state oxygen flow rate through the respiratory system (Weibel *et al.* 1981).

We have exploited two experimental models in which the chronic energy demand of muscle tissue appeared as a variable.

(a) Endurance exercise and chronic electrical stimulation both lead to metabolic adaptations in muscle cells which allow them to sustain aerobically situations of higher energy demand over prolonged periods of time.

(b) Small and large animals offer another possibility to compare muscle tissue which greatly differs in its scope of aerobically covering its energy demand, as small animals have to be able to generate ATP at rates several-fold higher than large animals (Weibel *et al.* 1981).

MITOCHONDRIA AND BODY SIZE

Taylor *et al.* (1981) found that the $\dot{V}_{O_2}max$ of a variety of mammals, from pygmy mice (20 g) to elands (240 kg), scales as body mass to the power 0·809 ($\dot{V}_{O_2}max = 1{\cdot}92M_b^{0{\cdot}809}$, $r = 0{\cdot}987$). The slope of this relationship is not significantly different

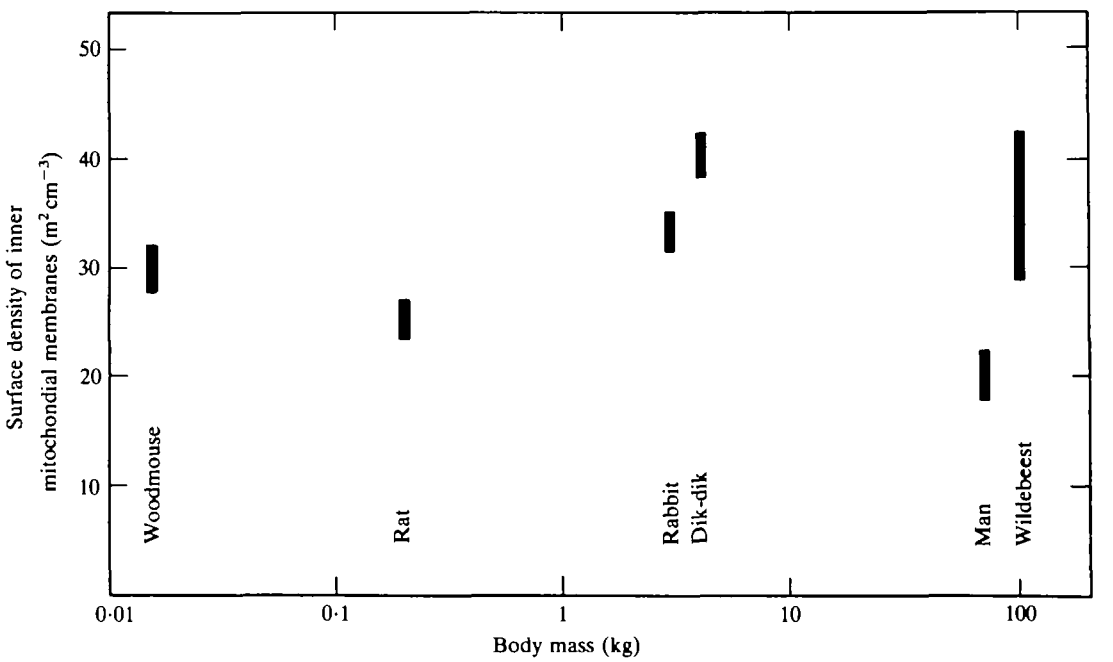

Fig. 2. Range of surface density of inner mitochondrial membranes in several mammalian species of different body masses. It can be seen that although surface density may vary by as much as two-fold, it is not size dependent (woodmouse from Hoppeler *et al.* 1984; rat from Buser *et al.* 1982; rabbit, unpublished data; dik-dik and wildebeest from Hoppeler *et al.* 1981; man from Hoppeler *et al.* 1973).

from the slope for resting oxygen consumption *versus* body mass which scales close to $M_b^{0.75}$ (Kleiber, 1932). Thus $\dot{V}_{O_2}max$ is consistently about 10 times resting oxygen consumption. The slope of 0·8 for the allometric relationship of $\dot{V}_{O_2}max$ *versus* M_b indicates that a mouse consumes some 10 times more oxygen per unit body mass than a cow when both are running at $\dot{V}_{O_2}max$. We expected mitochondria to be similarly more abundant in mouse than in cow skeletal muscles. In fact the total volume of mitochondria (V_{mt}) was found to scale close to $M_b^{0.8}$ in vastus medialis, semitendinosus and diaphragm of a series of African mammals spanning more than three orders of magnitude of body size (Mathieu *et al.* 1981). The main conclusion of the latter study was that there is a constant (body mass independent) relationship between the maximal rate of aerobic power production in animals and the absolute volume of mitochondria in their muscles. These morphometric results are supported by a study of the scaling of oxidative and glycolytic enzymes in mammals; the scaling factors for oxidation enzymes are similar to those for mitochondrial volumes (Emmett & Hochachka, 1981), while glycolytic enzymes were found to scale as $M_b^{1.15}$. This indicates that as animals increase in size, they are endowed with a decreasing scope for aerobic metabolism but with an increasing scope for anaerobic metabolism.

If we examine the scaling of mitochondrial volumes more closely (Mathieu *et al.* 1981) it becomes apparent that while the absolute volumes of mitochondria of the three muscles analysed scaled with nearly identical exponents (i.e. 0·799–0·817), the fractional volumes of mitochondria, $V_v(mt,f)$, varied considerably among the different muscles (−0·055 to −0·231; Fig. 3). As the absolute volume of mitochondria was obtained as:

$$V_{mt} = V_v(mt,f) \times V_{mu}, \quad (2)$$

where V_{mu} is the muscle volume, this means that the volumes of some muscles do not scale linearly to body mass ($M_b^{1.0}$). While some muscles scale with an exponent less than one, others must scale with an exponent greater than one, since the total skeletal muscle mass is consistently near 45% of the total body mass in all mammals irrespective of size (Munro, 1969). For instance, the volume of the diaphragm scales as $M_b^{0.865}$ while the volume density of mitochondria in diaphragm scales as $M_b^{-0.055}$. This indicates that the diaphragm is a much smaller fraction of the body mass in large animals than in small ones while the fractional volume of mitochondria decreases only slightly with increasing body size. Perhaps the different scaling of muscle volume and volume density of mitochondria in some muscles might be related to the specific (size-dependent) use of a particular muscle or muscle group. Note that the slope of the allometric regression of the volume density of mitochondria to body size of the remaining three skeletal muscles (semitendinosus, vastus medialis, longissimus dorsi) is not significantly different from the slope of the regression of weight specific $\dot{V}_{O_2}max$ to body mass (Fig. 3). Such a relationship is to be expected if indeed the rate of cross-bridge cycling between actin and the myosin heads were to set the energetic cost of muscular contraction in direct proportion to the intrinsic rate of muscle shortening (Hoppeler, Lindstedt & Mathieu, 1980; Heglund, Fedak, Taylor & Cavagna, 1982).

MITOCHONDRIA AND ACTIVITY

$\dot{V}_{O_2}$max is not only different among animals of different body size, it can also be changed in animals of one particular size class by increasing physical activity. In man, $\dot{V}_{O_2}$max may vary as much as two-fold between sedentary subjects and extremely well trained endurance athletes such as bicyclists, marathon runners or cross-country skiers (Saltin & Gollnick, 1983). Changes in mitochondrial variables associated with training-induced changes in $\dot{V}_{O_2}$max have been studied mostly by estimating activities of marker enzymes of aerobic metabolism during training and also during recovery from training. The relative changes in the activities of the most important enzymes of aerobic metabolism invariably exceed the relative changes in $\dot{V}_{O_2}$max induced by endurance exercise. This topic has been reviewed extensively (Gollnick & Saltin, 1982; Saltin & Gollnick, 1983; Holloszy & Coyle, 1984). Although the changes in structural variables of the mitochondrial compartment have not been documented as well as the biochemical changes, it is commonly assumed that it is the quantity of mitochondria that changes in proportion to the activities of often studied enzymes of the Krebs-cycle such as citrate synthase and succinate dehydrogenase (Hoppeler *et al.* 1973; Davies *et al.* 1981; Saltin & Gollnick, 1983).

One generally-held view with regard to the disparate adaptation of $\dot{V}_{O_2}$max and the oxidative capacity of muscle is that mitochondrial adaptations are mostly related to the

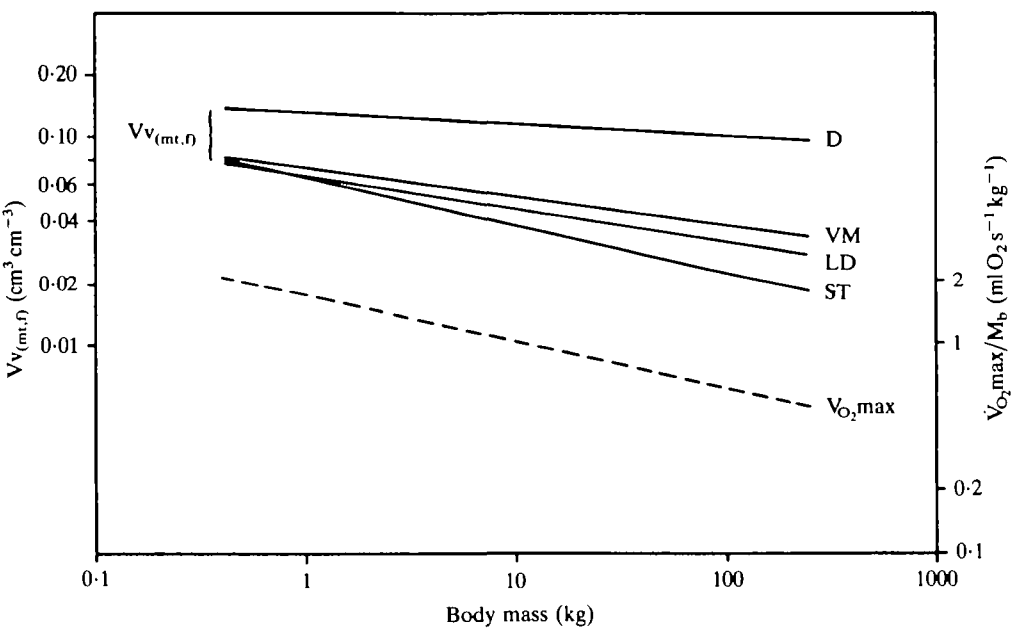

Fig. 3. Regressions of the logarithms of the volume densities of mitochondria, V_v(mt,f) *versus* the logarithms of the body masses (M_b) in diaphragm (D), vastus medialis (VM), longissimus dorsi (LD) and semitendinosus (ST) for a series of African mammals (from Mathieu *et al.* 1981). The regression line of log$\dot{V}_{O_2}$max/M_b *versus* logM_b is added for comparison (dashed line). Note that the slopes for VM, LD and ST *versus* M_b are not significantly different from the slope of $\dot{V}_{O_2}$max/M_b *versus* M_b.

ability of trained subjects to perform strenuous exercises over prolonged periods of time (Gollnick & Saltin, 1982; Holloszy & Coyle, 1984). A causal relationship between the elevation of $\dot{V}_{O_2}$max and the activity of oxidative enzymes in skeletal muscle of man in training is refuted on the grounds that these enzyme activities are found to change out of proportion to $\dot{V}_{O_2}$max (Gollnick & Saltin, 1982). The relationship between central and peripheral determinants of aerobic work performance, and their role, are currently debated. The disproportionate changes in central and peripheral factors of aerobic work performance may not be contradictory, as commonly held, but may well be explained by an inter-related adaptation of the whole cascade of conductances (or resistances) to oxygen flow across the respiratory system of mammals during increased use, as presented elsewhere in this issue (Di Prampero, 1985). By modelling the respiratory system as a cascade of resistances in series, Di Prampero (1985) claims that for two-legged exercise 75 % of $\dot{V}_{O_2}$max is set by oxygen transport. Hence under these conditions, small changes in $\dot{V}_{O_2}$max would require large changes in tissue oxidative capacity in selectively trained muscle groups.

MITOCHONDRIA AND OXYGEN CONSUMPTION

Is it possible that there is a constant and predictable relationship between the volume of skeletal muscle mitochondria and tissue oxygen consumption under limiting conditions? A direct link between mitochondrial volumes and oxygen consumption could be established if both of these variables could be determined in identical compartments. An experimental model which allows one to estimate both variables is the isolated, autoperfused cat gracilis and soleus muscle preparation (Bockmann, McKenzie & Ferguson, 1980). By using this model we have calculated oxygen consumption from blood flow obtained by a photoelectric drop-counter inserted in the outflow of surgically isolated muscles and from arteriovenous oxygen content differences estimated by using a Lex-O_2-Con oxygen analyser (Hoppeler, Hudlicka & Uhlmann, 1982). Peak oxygen consumption of the muscles was reached at stimulation frequencies of 6–10 Hz. Volume densities of mitochondria were estimated in muscle samples prepared for electron microscopy by standard stereological procedures. We found peak oxygen consumption to be higher by as much as three-fold in the oxidative soleus as compared to the glycolytic gracilis muscles. Similarly, values for peak oxygen consumption that were three-fold higher than in controls were obtained in gracilis muscles electrically stimulated over periods of up to 28 days. In all muscles analysed, peak oxygen consumption was found to be linearly related to volume density of mitochondria ($\dot{V}_{O_2}\text{max} = 2{\cdot}06 + 115V_v(\text{mt,f})$; $r = 0{\cdot}778$; $N = 21$). Peak oxygen consumption per unit volume of mitochondria can hence be calculated as $1{\cdot}4\ \text{ml}\ O_2\ \text{min}^{-1}\ \text{cm}^{-3}$ (Hoppeler *et al.* 1982). The highest value for mitochondrial oxygen consumption ($2{\cdot}2\ \text{ml}\ O_2\ \text{min}^{-1}\ \text{cm}^{-3}$) was found in a gracilis muscle electrically stimulated for 28 days.

Apart from the autoperfused single muscle preparation in the cat, there are a few more studies in several animal species in which one can at least approximate 'maximal' oxygen consumption of a unit volume of skeletal muscle mitochondria (Table 1).

(1) In man, Saltin (1985) elegantly demonstrated the maximal oxygen consumption of the functionally isolated extensor muscle group of the knee joint to be 30–36 ml O_2 min^{-1} 100 g^{-1} of muscle tissue. By assuming the mitochondrial volume density of all extensor muscles to be similar to that of vastus lateralis (approx. 5 % of the fibre volume in untrained subjects; Hoppeler *et al.* 1973) the mitochondrial oxygen consumption can be calculated as 5 ml O_2 min^{-1} cm^{-3}.

(2) In the mouse, a novel sampling technique has made it possible to determine the total skeletal muscle mitochondrial volume (Hoppeler *et al.* 1984). We were thus able to measure maximal running and cold exposure oxygen consumption, as well as whole body skeletal muscle mitochondrial volumes in the same animals (European woodmice). Mitochondrial oxygen consumption under both conditions was found to be 4·9 ml O_2 min^{-1} cm^{-3}. This value indicates a lower limit of mitochondrial oxygen consumption in this species as (a) not the whole muscle mass is activated simultaneously in running and (b) not all the oxygen taken up by the body is used by the skeletal muscles.

(3) In a series of African mammals, Mathieu *et al.* (1981) have demonstrated a strong and constant relationship between the mitochondrial volume of individual muscles and whole animal $\dot{V}_{O_2}max$. As mammals are all nearly 45 % muscle (Munro, 1969) it must then hold that the total volume of all skeletal muscle mitochondria likewise scales parallel to $\dot{V}_{O_2}max$. By assuming the mean volume density of the leg muscles to be representative for the volume density of muscle mitochondria of the whole body (Hoppeler *et al.* 1984), we can calculate a lower limit for mitochondrial oxygen consumption at $\dot{V}_{O_2}max$ for the series of African mammals to be 5·3 ml O_2 min^{-1} cm^{-3}.

(4) In birds, Pennycuick & Rezende (1984) analysed the sustained power requirements of flight muscles by means of a simplified model of muscle function in which they also measured the volume density of mitochondria in sparrow and quail pectoralis muscle. They proposed that the specific power output of flight muscles required 1 ml of mitochondria to sustain a mechanical power output of 1–2 W.

Table 1. *Rate of oxygen consumption per unit volume of mitochondria at $\dot{V}_{O_2}max$ for various species and muscles*

Species	Body mass (kg)	Muscles	Mitochondrial oxygen consumption at $\dot{V}_{O_2}max$ (ml O_2 min^{-1} cm^{-3})
Cat[1]	2–4	gracilis, soleus	1–2·2
Man[2]	75	knee extensors	4·5–5·5
Woodmouse[3]	0·02	whole body skeletal muscles	4·9
African mammals[4]	0·4–214	semitendinosus, vastus medialis, longissimus dorsi	5·3
Sparrow, quail[5]	0·02, 0·1	pectoralis	3–6

Rates calculated from data reported in the literature: [1] Hoppeler, Hudlicka & Uhlmann (1982); [2] Saltin (1985); [3] Hoppeler *et al.* (1984); [4] Mathieu *et al.* (1981); [5] Pennycuick & Rezende (1984).

Converting Watts into units of oxygen consumption this would indicate that mitochondrial oxygen consumption would minimally have to be 3–6 ml O_2 min^{-1} cm^{-3}.

In summary, we have several lines of evidence which suggest that there is a rather constant volume of oxygen metabolized under limiting conditions of $\dot{V}_{O_2}max$ per unit volume of skeletal muscle mitochondria. This holds despite a more than five-fold difference in weight specific $\dot{V}_{O_2}max$ among the species analysed (not including birds). This might support Pennycuick & Rezende's (1984) hypothesis that the potential for aerobic power production of skeletal muscles can be characterized by estimating their volume density of mitochondria. Such a prediction critically depends on the composition of the mitochondria and the efficiency of the muscular energy conversion being constant or known for one set of experiments.

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REFERENCES

Bockmann, E. L., McKenzie, J. E. & Ferguson, J. L. (1980). Resting blood flow and oxygen consumption in soleus and gracilis muscles of cat. *Am. J. Physiol.* **239**, H516–H524.

Buser, K. S., Kopp, B., Gehr, P., Weibel, E. R. & Hoppeler, H. (1982). Effect of cold environment on skeletal muscle mitochondria in growing rats. *Cell Tissue Res.* **225**, 427–436.

Davies, K. J. A., Packer, L. & Brooks, G. A. (1981). Biochemical adaptation of mitochondria, muscle, and whole-animal respiration to endurance training. *Archs. Biochem. Biophys.* **209**, 539–554.

Di Prampero, P. E. (1985). Metabolic and circulatory limitations to $\dot{V}_{O_2}max$ at the whole animal level. *J. exp. Biol.* **115**, 319–331.

Emmett, B. & Hochachka, P. W. (1981). Scaling of oxidative and glycolytic enzymes in mammals. *Respir. Physiol.* **45**, 261–272.

Gollnick, P. D. & Saltin, B. (1982). Significance of skeletal muscle oxidative enzyme enhancement with endurance training. *Clin. Physiol.* **2**, 1–12.

Heglund, N. C., Fedak, M. A., Taylor, C. R. & Cavagna, C. A. (1982). Energetics and mechanics of terrestrial locomotion. IV. Total mechanical energy changes as a function of speed and body size in birds and mammals. *J. exp. Biol.* **97**, 57–66.

Hochachka, P. W. (1985). Fuels and pathways as designed systems for support of muscle work. *J. exp. Biol.* **115**, 149–164.

Holloszy, J. O. & Coyle, E. F. (1984). Adaptations of skeletal muscles to endurance exercise and their metabolic consequences. *J. appl. Physiol.* **56**, 831–838.

Hoppeler, H., Hudlicka, O. & Uhlmann, E. (1982). The relationship of maximal oxygen consumption and volume density of mitochondria in different cat muscles. *J. Physiol., Lond.* **338**, 56–57P.

Hoppeler, H., Lindstedt, S. L. & Mathieu, O. (1980). Scaling structural parameters of oxygen consumption against $\dot{V}_{O_2}max$ and body mass. In *Exercise Bioenergetics and Gas Exchange*, (eds P. Cerretelli & B.J. Whipp), pp. 129–135. Amsterdam: Elsevier/North-Holland.

Hoppeler, H., Lindstedt, S. L., Uhlmann, E., Niesel, A., Cruz-Orive, L. M. & Weibel, E. R. (1984). Oxygen consumption and the composition of skeletal muscle tissue after training and inactivation in the European woodmouse (*Apodemus sylvaticus*). *J. comp. Physiol.* **155B**, 51–61.

Hoppeler, H., Lüthi, P., Claassen, H., Weibel, E. R. & Howald, H. (1973). The ultrastructure of the normal human skeletal muscle. A morphometric analysis on untrained men, women, and well-trained orienteers. *Pflügers Arch. ges. Physiol.* **344**, 217–232.

Hoppeler, H., Mathieu, O., Krauer, R., Claassen, H., Armstrong, R. B. & Weibel, E. R. (1981). Design of the mammalian respiratory system. VI. Distribution of mitochondria and capillaries in various muscles. *Respir. Physiol.* **44**, 87–111.

HUDLICKA, O. (1985). Development and adaptability of microvasculature in skeletal muscle. *J. exp. Biol.* **115**, 215–228.

HUXLEY, H. E. (1973). Muscular contraction and cell motility. *Nature, Lond.* **243**, 445–449.

KLEIBER, M. (1932). Body size and metabolism. *Hilgardia.* **6**, 315–353.

MATHIEU, O., KRAUER, R., HOPPELER, H., GEHR, P., LINDSTEDT, S. L., ALEXANDER, R. MCN., TAYLOR, C. R. & WEIBEL, E. R. (1981). Design of the mammalian respiratory system. VII. Scaling mitochondrial volume in skeletal muscle to body mass. *Respir. Physiol.* **44**, 113–128.

MUNRO, H. N. (1969). Evolution of protein metabolism in mammals. In *Mammalian Protein Metabolism*, (ed. H. N. Munro), pp. 133–182. New York: Academic Press.

PENNYCUICK, C. J. & REZENDE, M. A. (1984). The specific power output of aerobic muscle, related to the power density of mitochondria. *J. exp. Biol.* **108**, 377–392.

RACKER, E. (1975). Inner mitochondrial membranes: basic and applied aspects. In *Cell Membranes. Biochemistry, Cell Biology and Pathology*, (eds G. Weissmann & R. Claiborne), pp. 135–141. New York: HP Publishing Company.

SALTIN, B. (1985). Malleability of the system in overcoming limitations: functional elements. *J. exp. Biol.* **115**, 345–354.

SALTIN, B. & GOLLNICK, P. D. (1983). Skeletal muscle adaptability: significance for metabolism and performance. In *Handbook of Physiology. Skeletal Muscle*, (eds L. D. Peachy, R. H. Adrian & S. R. Geiger), pp. 555–631. Baltimore: Williams & Wilkins.

TAYLOR, C. R., MALOIY, G. M. O., WEIBEL, E. R., LANGMAN, V. A., KAMAU, J. M. Z., SEEHERMAN, M. J. & HEGLUND, N. C. (1981). Design of the mammalian respiratory system. III. Scaling maximum aerobic capacity to body mass: wild and domestic mammals. *Respir. Physiol.* **44**, 25–37.

TAYLOR, C. R. & WEIBEL, E. R. (1981). Design of the mammalian respiratory system. I. Problem and strategy. *Respir. Physiol.* **44**, 1–10.

WEIBEL, E. R., TAYLOR, R. C., GEHR, P., HOPPELER, H., MATHIEU, O. & MALOIY, G. M. O. (1981). Design of the mammalian respiratory system. IX. Functional and structural limits for oxygen flow. *Respir. Physiol.* **44**, 151–164.