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Blood Flow and Oxygen Uptake in Mammals[1]

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Data on the variation of blood flow and oxygen uptake with weight W are reexamined for mammals at rest. It is concluded that blood flow varies as $W^{0.85}$, while oxygen uptake varies as $W^{0.79}$. The suggestion is made that oxygen uptake for small mammals is often reported with values higher than that given by the above relation, whereas their sleeping consumption is likely appreciably less, i.e., these animals, by their CV and nervous system design, are excitable or "jittery."

In a steady state range of sustainable activity, near universal weight specific blood flow oxygen uptake curves are estimated for mammals of all weights, for the range of states from sleep to peak sustained aerobic activity. It is hoped that these data provide an acceptable experimental data base for study of the design characteristics of tissue perfusion and oxygen transport in the average mammalian microvasculature.

Systems sciences have as one of their chief goals the delineation of design laws, and quantitative biology can be no exception. By design here we mean nature's design as the naturalist seeks it out, or the design relations as sought out by the mechanical engineer. Each discipline asks from what mechanistic reductions the operational properties of a system are expected to emerge. Developing a functioning organism from the emergent character of a genetic code interacting with an environment appears to be a completely different and more difficult problem than having a building erected from a codified set of epigenetic principles carried out by a building crew in a brief construction period. Nevertheless, the programming principle is the same.

This search for design is illustrated in the cardiovascular system. We will examine empirically the basis for the design of the metabolic machinery that determines oxygen uptake, metabolism, and blood flow during work tasks, from rest to peak sustained effort, at steady state conditions of aerobic equilibrium. We present no new data. Instead, we attempt to reconcile data recently made available in a recent FASEB handbook (Altman and Dittmer, 1971; Tables 126, 130, 175) with older summaries in the physiological literature. The composite summary sought is for blood flow and oxygen consumption in mammals; it differs from some earlier descriptive theories that attempt to explain the dependence of blood flow, oxygen consumption, and metabolism on body area. We expect that our more detailed concern with a broad range of empirical findings can bring us to the formulation of a more consistent design hypothesis.

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A prevailing idea (found, for example, in major physiology textbooks) is that resting metabolism (and implicitly blood flow) is proportional to surface area. The basis is the belief that heat transfer considerations, e.g.,

$$M/A = C[T_r - T_s], \tag{1}$$

$$M/A = h[T_s - T_a] + (E/A), \tag{2}$$

where M = metabolism, T_r = deep body ("rectal") temperature, C = tissue conductance, T_s = skin temperature, h = external boundary layer conductance, T_a = (effective) ambient temperature, E = evaporation, dictate the same rest metabolism per unit area for all homeotherms (we restrict ourselves here to mammals, although birds thermoregulate too). Since surface area is proportional to the 2/3rds power of weight ($W^{2/3}$), cardiac output, oxygen uptake, and metabolism should all be proportional to $W^{2/3}$. Kleiber (1947) reported somewhat different results, closer to a proposed $W^{3/4}$ law. For example, Holt *et al.* (1968) report a resting cardiac output nearly proportional to $W^{3/4}$ ($W^{0.785}$); with stroke volume nearly proportional to W ($W^{1.045}$), and heart rate nearly proportional to $W^{-1/4}$ ($W^{-0.255}$). Following Kleiber, Holt *et al.* then assumed that metabolism and oxygen uptake are also proportional to $W^{3/4}$.

However several lines of reasoning suggest that blood flow, metabolism, and oxygen uptake ought to be proportional to W^1. First, the bulk of the body mass consists of tissues not directly involved in thermoregulation. One liver twice the mass of another liver should receive twice the blood flow, consume twice as much oxygen, and release twice as many calories as the other if the work performed is the same per unit mass of tissue. This inference was reached, most plausibly from a modelling study of the geometry, anatomy, and topology of a generalized mammalian arterial system that carried its design features from the aorta down to the local capillary beds (see Altman and Dittmer, Table 144).

Second, in a recent study of thermoregulation (Schindler and Iberall, 1971), it was shown that metabolism, insulation, and heat loss through evaporation are tightly coupled by self-regulatory mechanisms to maintain a near constancy of core temperature. It appears more nearly true that the evaporative mechanism prevents metabolism from overheating the body; whereas metabolism is more nearly regulated to conform to the performance of muscular and other organ tasks. Thus, the thermoengineering design for mammals does not require surface area dependence. As noted above, it would seem more sensible for cardiovascular design to have these variables weight dependent for most organs. Size efficiency in certain homologous organs might make some difference in mammals of greatly different size.

Third, we should note that homeothermic birds and mammals evolved from poikilotherms whose vascular system never needed to contend with this thermoregulatory problem. Hence, there is no reason for poikilotherms blood flow or oxygen consumption to be surface area dependent. It is more plausible, following the idea of Homer Smith, to assert the axiom that the living system is highly rate regulatory in its own primitive processes and that more complex characteristics emerge while still incorporating such preexisting primitive processes, rather than replacing them. Thus, one might expect that the algorithms of thermoregulation operate by facing the demands of vascular beds whose local processes operate with a weight dependent base. One can imagine that with further evolution, modification of these algorithms require removing some fraction of the blood flow (e.g., skin) from local control and committing it to thermoregulation so that other tissues can look after themselves. The skin is a substantial organ, and its blood flow is not negligible. Any blood flow obligated to thermoregulation will indeed be surface area dependent, and we therefore predict that blood flow, oxygen consumption, and metabolism for the whole organism should be proportional to some function of W greater than $W^{2/3}$ but less than W^1. For all practical purposes, the value of the exponent may be expected to lie between 0.75 and 0.90.

We first need to know how precisely we can expect to determine the exponent. A large whale (120,000 kg) weighs 4×10^7 as much as a small shrew (3 gm). If one takes data on blood flow per unit weight and oxygen uptake per unit weight from the shrew, and then predicts the value of these variables in the whale (or vice versa), an indeterminacy of 0.15 in the exponent for W (e.g., the difference between a $W^{0.75}$ and a $W^{0.90}$ dependence) can produce an error of a factor of 14 for either of these two variables. (Namely, $(4 \times 10^7)^{0.15} = 14$.) It appears likely that the experimental uncertainties of measuring blood flow or oxygen uptake for mammals of any particular weight range are no greater than a factor of 2, rather than a factor of 14. An uncertainty of a factor of 2 would correspond to an uncertainty in the value of the exponent of about 0.04, so that we cannot and do not expect to discover the exponent of W with greater accuracy than 0.04.

Finally, before proceeding to the data, we note that the ratio of blood flow to oxygen uptake determines the $A - V$ difference at "rest". Because of the common blood carrier (hemoglobin) with its limited saturation range (approximately 20 vol %, except for deepwater diving mammals, where it may be as much as 30 vol %), there is at most only a limited difference in extraction possible. (A factor of 2 or 3 between small animals and large animals. For example, the $A - V$ difference for humans at "rest" is about 4 (supine posture) to 6 (standing) vol %, and similar for large animals (Altman and Dittmer); there is a possible $A - V$ difference in shrews at "rest" of 13 vol % (Bloch *et al.* (1971)). Because of these differences in oxygen extraction, an analysis of the sort we propose would lead to a different value in the expression relating blood flow to weight than it would in the expression relating oxygen uptake to weight; a difference in the value of the exponent of as much as 0.05 or 0.06 may be expected. Even if all data for oxygen extraction and blood flow were taken on the same animals, there is the additional uncertainty due to scatter. Holt *et al.* suggest that the value of the exponents for the two expressions may differ by 0.035.

We proceed now to analyze data from Tables 126, 130, and 175 from Altman and Dittmer and data from Holt *et al.* All of these data are plotted in Fig. 1. In Table 126, Patterson (13 references) infers that cardiac output is proportional to W. However, the data are for moderately large animals—dogs to bears. The data from Table 126 are represented in Fig. 1 by a box that encompasses the range of Patterson's data. Data for a similar range of animals taken from Holt *et al.* give lower values for cardiac output than the Patterson data. As Holt *et al.* state, their " . . . results showing cardiac output to be a function of ($W^{0.75}$) are in contrast to

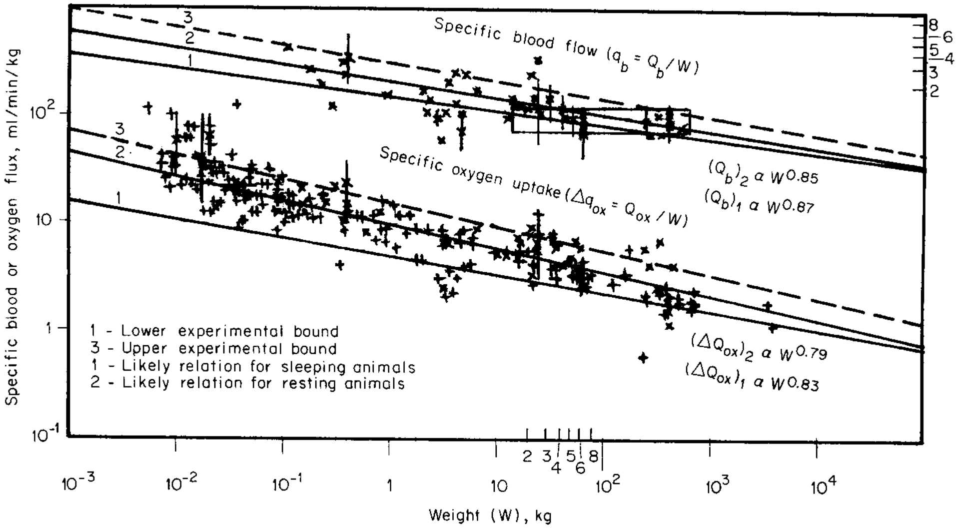

FIG. 1. Variation of weight specific blood flow (q_b) and oxygen uptake (Δq_{ox}) for resting mammals. (Data source: Respiration and Circulation Handbook, FASEB, 1971.)

the results reported by Patterson *et al.* . . . over a range of mammals extending from the dog to the giraffe, cardiac output was directly related to ($W^{1.0}$). The reason for this difference in results is not clear . . . since most of the animals in that study were unanesthetized, it may be that the animals were not in the basal state."

On the other hand, most of the animals in the Holt *et al.* study were anesthetized. Also the two measuring techniques were different. It may be noted that the two sets of data agree for smaller animals. In our assessment, there is no apparent reason for selecting one set of data over the other.

Table 130 presents data on oxygen consumption and cardiac output over a considerably broader range of mammalian size (64 references). Table 175 presents data on oxygen consumption in mammals (103 references). Table 175 suggests a $W^{0.73}$ law. In Fig. 1 the oxygen uptake in blood flow data from Table 130 are plotted using the symbol x; and the oxygen uptake data from Table 175 by the symbol +. The relative experimental issues of cardiac output and oxygen uptake must be treated as if they were independent. The oxygen consumption data seems steeper than the cardiac output data. However, the cardiac output data is more limited. Similar slopes to fit the two sets of data could be achieved only if the Patterson data at the extremes of weight were completely rejected in favor of the Holt *et al.* data.

The blood flow data contain considerable uncertainty. As an example, an important question is whether a 400 kg horse has a resting cardiac output nearer 40 liters/min (Patterson's, i.e., 100 ml/min/kg) or nearer 20 liters/min (Holt's, i.e., 50 ml/min/kg).

With these various uncertainties in mind, the best resolution of the cardiac output data we can provide is to fit the average "rest" blood flow by the expression

$$Q_b = 0.20\ W^{0.85},$$

with Q_b in liters/min and W in kg. This is to be compared with Patterson's $W^{1.0}$, a previous estimate of $W^{0.9}$ (Bloch *et al.*), Holt's estimate of $W^{0.785}$, and an estimate of powers between $W^{0.83}$ and $W^{0.88}$ from Table 130 alone. A provisional estimate of the uncertainty is

$$Q_b = 0.20\,(\pm 15\%)\ W^{0.85 \pm 0.02}.$$

Accepting the proportionality of heart rate to $W^{-1/4}$, resting stroke volume would then vary as $W^{1.10}$ rather than as W (Holt *et al.*). The best fit for the oxygen uptake (or metabolism) data of Fig. 1 appears to be

$$\Delta Q_{\text{ox}} = 10\,(\pm 20\%)\ W^{0.79 \pm .02},$$

with ΔQ_{ox} in ml/min and W in kg.

This is to be compared with a previous estimate of $W^{0.9}$ (Bloch *et al.*), Kleiber's $W^{0.75}$, or $W^{0.73}$ in Table 175 (Altman and Dittmer).

On the basis of these two relations, the following $A - V$ differences would be computed:

W (kg)	$A - V$ diff. (vol %)
.005	7
1	5
10^3	$3\frac{1}{2}$
10^5	$2\frac{1}{2}$

These values are "reasonable", but not necessarily an optimal fit to measured data on $A - V$ differences. Any deviation from optimality represents the penalty paid for providing the best independent fit of blood flow and oxygen uptake, while still minimizing the nonparallelism of the data as plotted in Fig. 1. It was found necessary to have to accept a divergence of the exponent for weight dependence of 0.06. Much greater divergence would yield clearly unreasonable values for the $A - V$ differences.

This concern with weight dependence raises some other issues. Before the data under consideration here were published, we assessed the more limited number of measurements previously available (Bloch *et al.*) and concluded that measurements of metabolism and cardiac output were biased overestimates for small animals, particularly at rest. Consider the data of Bartels (discussed in Bloch *et al.*). He presents oxygen uptake data on shrew (10 g) to elephant (3000 kg). The lower values in his data agree quite well with the curve selected in Fig. 1. On the other hand, at the near-10-g level (bat and shrew), he shows uptakes ranging from 25 to 120 ml/min/kg. The large range of these data can lead to a suspicion that small animals may be "jittery" at "rest" (see below). It is more tempting to believe the lower value of 25 ml/min/kg (i.e., 0.25 ml/min for 10-g shrew at "rest") rather than the upper value of 120 (i.e., 1.2 ml/min for 10-g shrew at "rest").

At the upper weight end of Bartels' data, high values are indicated by the whale and porpoise (total aquatic mammals). These are 2 to $2\frac{1}{2}$ times Bartels' indicated curve (which agrees with Fig. 1 at the high end). On the other hand, the dugong and manatee are comparably low. Thus, one could either derive a $W^{0.75}$ or $W^{0.79}$ law from Bartels', with the latter more likely if the high data of small "jittery" animals are neglected.

With regard to blood flow, the curve in Fig. 1 agrees with Bartels' results over the range of 0.1 to 1000 kg. At the upper end, $W = 3000$ kg (elephant), Bartels shows 40 ml/min/kg (120 liters/min), whereas Fig. 1 shows 55 ml/min/kg (165 liters/min). While this is well within the factor of 2 "reliability" hoped for, nevertheless it moves in the direction of the Holt *et al.* data, namely, to perhaps $W^{0.83}$. However, this too is within the estimated range $W^{0.85 \pm .02}$.

One additional reference to be considered is White *et al.* (discussed in Bloch *et al.*). For small mammals (0.2–2 kg) they report cardiac output (on the average) proportional to $W^{0.78}$. The curves in Fig. 1 and theirs are in agreement at 0.1 kg, but they then tend toward the Holt *et al.* relation.

$$Q_b = 0.16\ W^{0.78}(\text{White } et\ al.),$$

$$Q_b = 0.18\ W^{0.78}(\text{Holt } et\ al.).$$

The experimental issue that remains unresolved is the cardiac output of the large animal, e.g., the 400-kg "horse". From Bartels, one estimates 35 liters/min; from Patterson, 40 liters/min; from Holt, 20 liters/min; and White's data extrapolates to near 20 liters/min. (It should be noted that Bartels' interpolation is supported by elephant measurements; Patterson's by giraffe measurements.)

White *et al.* interpret oxygen uptake measurements on small animals as proving that Patterson's W^1 relation for cardiac output is not plausible because it would imply impossibly high $A - V$ oxygen differences (see their Fig. 3). Their collected results can be interpreted differently. It is assumed that the flatness of the oxygen uptake data that they assembled (3-g shrew to 3-kg cat), exhibiting proportionality to $W^{0.5}$, is representative of quite "jittery" animals. Specifically, we believe that an uptake approaching 0.5 ml/min for a 10-g animal at "rest" is too high. For the curve in Fig. 1 a value of about 0.3 ml/min has been selected. Thus the lower border of their data, $W^{0.8}$, is an agreement with the curve selected in Fig. 1.

As a tentative conclusion, an average "rest" curve for oxygen uptake proportional to $W^{0.8}$ for all mammals seems to be the soundest inference. On the other hand, there is an unresolved discrepancy for the more limited cardiac output data. It is either nearly proportional to $W^{0.8}$ or to $W^{0.85}$. Here proportionality to $W^{0.85}$ has been selected as more probable.

There is an additional aspect worth discussing, which can be related to results found in Taylor *et al.* (1970). The merit of having proposed near-weight specific parameters is that we can now provide oxygen uptake curves for all activity levels within the range of an aerobic equilibrium. Figure 2 is such a construction. It must be stressed that much of Fig. 2 is speculative. It has been stretched out by using human data, very small bits of peak or intermediate activity data on a few species, and some very crude estimates on the heartbeat range for small animals. (Nominally, it is assumed that heart rate can triple for humans engaged in sustainable activity, i.e., from 60 to 180 beats/min; that the peak aerobic oxygen uptake is about 3 liters/min for a 70-kg man; that heart rate for small animals can likely only double, e.g., from 600 to 1200 beats/min; that very large animals might increase 5–6 fold, e.g., an elephant's heart rate might jump from 10–12 to 60 beats/min). It is assumed that heart rate and cardiac output are proportional, that is, the stroke volume does not change much (discussed in Bloch *et al.*).

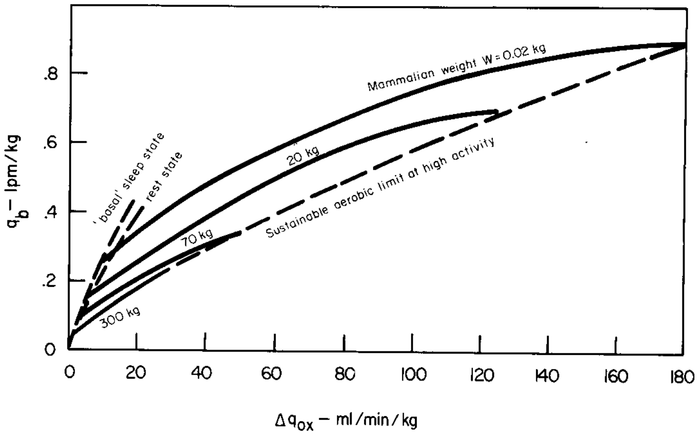

FIG. 2. Variation of weight specific blood flow (q_b) and oxygen uptake (Δq_{ox}) for exercising mammals.

The curves in Fig. 2 have been constructed by using these assumptions, and whatever data could be found in Altman and Dittmer's tables. The curves shown are based on a very limited number of animal species: data from horses (300 kg); dogs (20 kg); mice (0.02 kg); and somewhat more for man (70 kg) are used. Referring now to Fig. 1 in Taylor *et al.*, it is found that the oxygen consumption of animals varies linearly with running velocity. The variation is very steep for small animals. If the exercising data are extrapolated to rest, the results differ from the observed rest data. Table 1 illustrates these data.

Inspection of the data as plotted by Taylor *et al.* suggests that there is a common consumption intersection of all the straight lines at a "negative" velocity intercept. That common intercept is indicated in Table 1. It suggests that there may be a basal metabolism lower than "rest" for small animals. The table also includes the uptake values from the mean curve in Fig. 1 ($W^{0.79}$). One may note that the oxygen uptake is comparable to, but a little lower than, the rest data from Taylor *et al.*

TABLE 1
OXYGEN UPTAKE FOR SMALL ANIMALS (TAYLOR *et al.*)

	Oxygen uptake (ml/min/kg)			
Weight (kg)	Extrapolated to rest	At rest	Negative intercept	The "rest" curve in Fig. 1
0.021	56	38	4	24
0.041	29	25	4	19
0.10	30	19	4	17
0.236	21	19	4	13
0.384	25	17	4	12
2.6	12.5	10	4	8
18.0	11	5.3	4	5

We can now make a final suggestion with regard to the oxygen uptake with weight and activity state. The replot of oxygen uptake data at rest in Fig. 1, taken from data in Table 175, suggests proportionality to $W^{0.78}$ (rather than $W^{0.73}$). Thus it is possible that the argument regarding oxygen uptake may be narrowed to the limits of $W^{0.78}$ and $W^{0.85}$. While this difference might appear trivial, over the weight range of 10^7 to 1, a difference in ratio of $W^{0.1}$ represents an error of $10^{0.7}$, or a five-fold difference. We believe that the "rest" rates of the very small "jittery" animals are overestimated by that amount.

We therefore propose, as a speculation, that both results for oxygen uptake may be consistent under the following conditions: $W^{0.78}$–$W^{0.81}$ holds for resting awake mammals, $W^{0.83}$–$W^{0.85}$ holds for sleeping mammals, and that the two curves diverge from common values for large mammals. An attempt to suggest these dual results was made in Fig. 2 by distinguishing between the basal sleep state and a nominal rest state.

We hope that these arguments will serve to stimulate very careful measurements among the very small mammals (5–100 g) and the very large mammals (5000–100 000 kg) on one hand, and a theoretical pursuit of such systems relations within developmental biology on the other hand.

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