SIMILITUDE IN THE CARDIOVASCULAR SYSTEM OF MAMMALS

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Summary

Scaling laws governing the cardiovascular system of mammals are discussed in the present review in a manner emphasizing their experimental basis. Specific attention is given to the well-known experimental laws requiring the rate of oxygen consumption and the heart rate of mammals to vary with body mass raised to the powers 3/4 and −1/4, respectively. This review involves reconsideration and further discussion of the previous work of the writer in which these and other scaling relationships were developed from fundamental considerations. The predicted scaling laws remain unchanged from the earlier work, but alternative assumptions leading to the laws are used so as to provide additional insight. The scaling laws are shown to have their origin in the basic design of the cardiovascular system and in the basic processes involved in its working. Modification of the design assumptions of the system to account for known differences in the relative heart masses of mammals and birds is shown to lead to the scaling laws for rate of oxygen consumption and heart rate of birds.

Key words: allometric relationship, cardiovascular system, similitude, scaling law, mammal, bird, rate of oxygen uptake, heart rate.

Introduction

Similitude, or likeness, in the cardiovascular system of mammals has been discussed previously from an engineering perspective (Dawson, 1991). The approach involved the development of theoretical scaling laws for the system from considerations of the basic physical and mechanical processes involved, and the use of these laws with experimental measurements to demonstrate the similarity in the system for all mammals. Recently, West et al. (West et al., 1997) have considered the subject from the more abstract perspective of hierarchical networks of branching tubes, and Banavar et al. (Banavar et al., 1999) have considered the matter from an even more general perspective of networks.

Theories of the latter kinds may ultimately provide a broad understanding of restraints on the cardiovascular system when viewed as a complex delivery system, but detailed knowledge of how the restraints are implemented by mammals will continue to require study of the system from basic physical considerations. For this reason, and in view of the continuing interest in the subject, it seems worthwhile to reconsider here the development of the scaling laws of the cardiovascular system with particular emphasis on their experimental basis and their implications regarding the basic workings of the system.

Historical perspective

Similitude in the physiological processes of mammals has been a subject of interest in biology for more than 150 years. The rate of heat production of resting mammals and the associated rate of oxygen consumption and cardiac performance have received considerable attention. Early speculations (Sarrus and Remeaux, 1838) on the equality of heat production and heat loss led to the theoretical development of allometric (non-proportional) expressions relating the rates of heat production and oxygen consumption to mammal mass raised to the power 2/3. Measurements on dogs of various sizes (Rubner, 1883) provided apparent confirmation of this simple theory. However, further work in the first half of the twentieth century, with mammals ranging in size from the mouse to the elephant, indicated that the theory and associated allometric relationships were not those that applied best. Kleiber (Kleiber, 1932) and Brody and Procter (Brody and Procter, 1932) found, from experimental measurements, that the rates of heat production and oxygen consumption vary essentially as mammal mass raised to the power 3/4.

Other important measurements of physiological similarity were reported during this period. For example, Clark (Clark, 1927) showed that the heart rate of mammals varies essentially with mammal mass raised to the power −1/4. Woodbury and Hamilton (Woodbury and Hamilton, 1937) and Gregg et al. (Gregg et al., 1937) showed that the systolic and diastolic blood pressures of mammals are independent of mammal size,

and Brody (Brody, 1945) showed that the heart mass and blood volume of mammals vary directly with body mass.

Significant experimental studies of the similarity in mammals continued during the last half of the twentieth century. Schmidt-Nielsen and Larimer (Schmidt-Nielsen and Larimer, 1958), for example, measured the oxygen partial pressure in the blood of mammals and showed decreasing pressure with increasing mammal size. Holt et al. (Holt et al., 1968) examined cardiac output in detail and showed that it varies essentially as body mass raised to the power 3/4, and Gehr et al. (Gehr et al., 1981) studied the respiratory system of mammals and showed that the net capillary volume was proportional to body mass.

Interestingly, the 3/4 power law for rate of oxygen consumption received renewed attention near mid-century when Hemmingsen (Hemmingsen, 1960) reported results indicating that the law applies not only to mammals but also to cold-blooded animals, to unicellular organisms and, perhaps, even to more general forms of life. The rate of oxygen consumption of birds was also discussed in terms of the 3/4 power law (Lasiewski and Dawson, 1967). The emerging implication was that the 3/4 power relationship for rate of oxygen consumption represented something approaching a general rule of biology. However, such an interpretation did not meet with universal acceptance. Prothero (Prothero, 1986), Patterson (Patterson, 1992) and Riisgard (Riisgard, 1998), among others, provided strong evidence countering the claim that the 3/4 power law is a basic feature of biology. Bartels (Bartels, 1982) and Heusner (Heusner, 1991) questioned the fundamental standing of the law for mammals, and Bennett and Harvey (Bennett and Harvey, 1987) questioned its application to birds.

With regard to theoretical developments, the early work of Lambert and Teissier (Lambert and Teissier, 1927) is noteworthy because it attempted to place the subject within the broad framework of dimensional analysis and modeling theory. Predictions from this theory included the results that the rate of oxygen consumption and cardiac output must vary with mammal mass raised to the power 2/3, and that heart rate must vary with mammal mass raised to the power −1/3. The predictions differed somewhat from the developing body of experimental measurements that indicated 3/4 and −1/4 scaling laws for rate of oxygen consumption and heart rate, respectively. However, the theoretical nature of the work allowed it a degree of longevity. The work continued to be regarded into the 1970s, and beyond, as the best available theoretical description of the scaling of the cardiovascular system of mammals (Kenner, 1972).

This was, in large part, the situation that existed some 10 years ago when the present writer first considered the subject (Dawson, 1991). The application of conventional scaling procedures to the cardiovascular system was investigated and shown to be inadequate because of competing scaling laws dictated by the necessary presence in the theory of both the elasticity of the heart muscle and the viscosity of the blood. If viscosity was ignored, contrary to its importance in the system,

the scaling scheme of Lambert and Teissier (1927) resulted, with cardiac output predicted to vary as a 2/3 power law and heart rate as a −1/3 power law. In contrast, if elasticity was neglected rather than viscosity, the resulting scaling rules required the conditions that cardiac output must scale directly with mammal mass and that heart rate must remain unchanged with changing mammal mass.

In this same work, the present writer considered the subject from the more general perspective of non-uniform scaling, i.e. scaling where major descriptive aspects of the system are subject to different geometric scale factors (Dawson, 1991). The analysis started with a simplified representation of the cardiovascular system as a closed system having heart, capillaries and connecting vessels between the two. Elastic effects were restricted to the heart, inertial effects were assumed to be dominant in the connecting vessels and viscous forces were assumed to be dominant in the capillaries, consistent with conditions expected from mechanics. Heart mass and blood volume were assumed to be proportional to mammal body mass. Developments followed systematically as described below.

(a) Details of heart pumping were considered and basic modeling arguments were used to establish the requirement that blood pressure must be independent of mammal mass. Three fundamental relationships were also developed involving the dimensions of the connecting vessels and the dimensions and number of capillaries.

(b) Two additional relationships were introduced, one concerning cell diffusion and the other concerning cardiac contraction. These were combined with the above results to show that the radius and length of the connecting vessels scale with mammal mass raised to the powers 3/8 and 1/4, respectively, and that capillary radius, length and number scale with mammal mass raised to the powers 1/12, 5/24 and 5/8, respectively.

(c) These scaling laws were shown to lead, in turn, to the requirements that rate of oxygen consumption and cardiac output scale with mammal mass raised to the power 3/4 and that heart rate scales with mammal mass raised to the power −1/4.

The first assumption of b, involving cell diffusion, used the conditions of scale-invariant diffusion coefficient and driving force. The second assumption of b, concerning cardiac contraction, involved an experimental power-law relationship connecting contraction speed and cardiac fiber diameter. Small changes in these conditions would, of course, cause small changes in the predicted results. This work is continued in the present review, with further attention to the experimental basis for the description of the system.

Scope of this review

The purpose of the present review is to reconsider in detail the earlier development (Dawson, 1991) of scaling laws for the cardiovascular system of mammals, with emphasis on the experimental basis for the laws and on an increased

understanding of their origin and their application. The basic model used for the cardiovascular system will be the same as employed earlier. However, instead of starting the discussion at the cardiac response level, the starting point will be the condition that blood pressure in mammals is independent of body mass. This is a derived result from the original work and also a widely accepted experimental fact. Its use allows some simplification in the development of the scaling laws.

Starting at this level, three relationships will be developed between the radius and length of the main connecting vessels of the system and the radius, length and number of the capillaries, as in the earlier work (Dawson, 1991). The two additional relationships needed to solve the scaling laws for these variables will, however, be chosen differently from in the original development.

Two cases will be considered. In the first case, the 3/4 power law for the rate of oxygen consumption and the −1/4 power law for heart rate will be employed, and these will be shown to lead to the same vascular scaling laws as found in the earlier work. In the second case, two theoretical relationships involving oxygen utilization and oxygen transfer will be employed as the two additional relationships required. These will also be shown to lead to the same vascular scaling laws as earlier. In addition, this development will be extended to obtain, respectively, the 3/4 and −1/4 scaling laws for the rate of oxygen consumption and heart rate. The alternative developments are intended to provide increased confidence in and understanding of the scaling laws for the system.

The general scheme of the present approach is illustrated in Fig. 1 and contrasted with that of the previous work. The steps and assumptions shown include identification of relationships based on experiment. These involve a cell diffusion law and a cardiac contraction law in the earlier work, the heart rate and oxygen rate laws and an oxygen pressure law in the first case considered here, and the oxygen pressure law in the second case considered here.

Scaling laws for other physiological processes of mammals will also be considered in this review, and additional new laws will be developed. The connection between the scaling laws for mammals and birds will be established, and the role of the 3/4 scaling law for rate of oxygen consumption as an experimental representation, rather than a fundamental law of biology, will be discussed.

The cardiovascular system

The cardiovascular system of mammals consists broadly of the heart, the blood and the blood vessels. In many respects, it is like a mechanical system and, in its simplest engineering form, may be considered as two pumps in series (the left and right sides of the heart) with connecting vessels (the arteries and veins) directing the working substance (the blood) to and from exchange devices (the capillaries) for transfer of products in support of life-sustaining activities.

A simplified representation of the system is shown in Fig. 2. As indicated, the heart consists of four chambers, the left
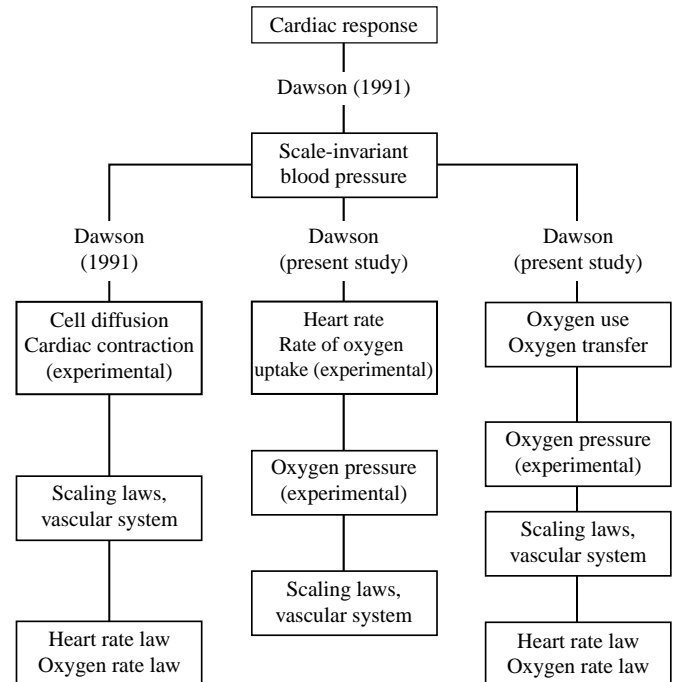

Fig. 1. Scheme of the present approach and comparison with that followed in earlier work.

atrium and left ventricle and the right atrium and right ventricle. The left atrium collects oxygen-enriched blood returning from the lungs, and the left ventricle pumps this blood through systemic arteries to the systemic capillaries of the body for exchange of oxygen and other products. The right atrium collects this blood on return through systemic veins, and the right ventricle pumps this blood through pulmonary arteries to the pulmonary capillaries of the lungs for recharge of oxygen and transfer of gases. Pumping, by contraction, of the left and right ventricles occurs at the same time, so that the blood in the respective sides of the heart is forced simultaneously to the body and lungs.

The essential parts of the cardiovascular system can be seen to be the heart, the blood, the systemic and pulmonary capillaries and the connecting vessels between the left and right sides of the heart and the capillary beds. This idealized system, or model, forms the basis for the development of scaling laws for the system as discussed here. The connecting vessels to and from each side of the heart will be regarded as single macroscopic vessels, and the capillary beds will each be regarded as a parallel array of individual microscopic vessels. Additional properties will be ascribed to the model as indicated by measurements from mammals ranging in size from the mouse to the elephant.

In the idealized model, the characteristic radius and length of the connecting vessel (aorta) are denoted by r_a and L_a, respectively, and the characteristic radius, length and number of the capillary vessels in each capillary bed are denoted by r_c, L_c and n_c, respectively. In addition, the ventricles (pumping chambers) of the heart are regarded as approximately
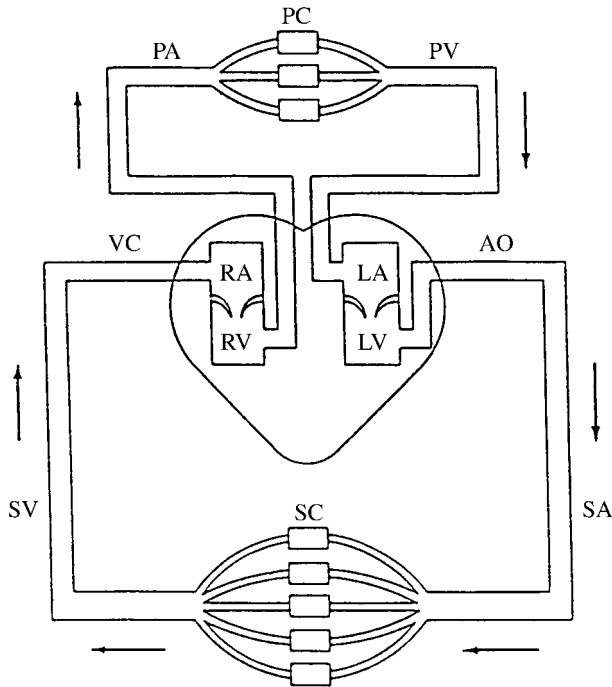
Fig. 2. Illustration of the cardiovascular system of mammals. LA, left atrium; LV, left ventricle; AO, aorta; SA, systemic arteries; SC, systemic capillaries; SV, systemic veins; VC, venae cavae; RA, right atrium; RV, right ventricle; PA, pulmonary arteries; PC, pulmonary capillaries; PV, pulmonary veins.

cylindrical in form, with an average characteristic radius denoted by a, and with an average characteristic length and wall thickness denoted by l and h, respectively. An objective of the present work is to discuss the scaling laws that must apply to these descriptive variables when considering their values for mammals of different sizes. An additional objective is to discuss these results in terms of the actual scaling laws that exist for various physiological processes of mammals and thus contribute to a physical understanding of their origin.

Basic similarity relationships

The total blood volume in mammals is known from extensive measurements to vary directly with their body mass (Brody, 1945). In the model under consideration, this means that the sum of the blood volume in the heart, the connecting vessels and the capillaries must vary directly with mammal mass. If the sum is proportional to body mass, the individual parts can also be expected to be proportional to body mass. Thus, for the dimensions of the ventricles, the connecting vessels and the capillaries, the following volume relationships may be written:

$$a^2 l \propto W, \tag{1a}$$

$$r_a^2 L_a \propto W \tag{1b}$$

and

$$n_c r_c^2 L_c \propto W, \tag{1c}$$

where W denotes mammal mass and where the symbol $\propto$ denotes proportional variation under change in mammal mass.

The first relationship requires that ventricular volumes be proportional to mammal mass, the second requires that the volume of the connecting vessels be proportional to mammal mass, and the third requires that the net volume of the capillaries be proportional to mammal mass.

Measurements (Holt et al., 1968) for the end-diastolic volumes of the left and right ventricles of mammals ranging in size from rat to cow provide direct experimental support for the proportional relationship for ventricular volume (relationship 1a). Also, measurements reported by Gehr et al. (Gehr et al., 1981) for the net volume of pulmonary capillaries for a similar range of mammals provide direct support for the proportional relationship for total capillary volume (relationship 1c). And measurements reported by Clark (Clark, 1927) for the aortic cross-sectional flow area, when combined with typical measurements reported by Noordergraaf et al. (Noordergraaf et al., 1979) for aortic length, provide support over a wide range of mammal sizes for the proportional relationship for the connecting vessels (relationship 1b).

Scaling laws for heart dimensions

In addition to blood mass, it is also well established that the empty heart mass of mammals varies directly with mammal mass (Brody, 1945). The same is true for the ventricles (Holt et al., 1968). Thus, assuming the same cardiac tissue mass per unit volume for all mammals, the mass relationship for the ventricles is $a^2 h + alh \propto W$, where the first term is proportional to the mass of the ends and the second to the mass of the lateral portion. As with relationships 1a–c, each of the two products in this last relationship can be considered proportional to mammal mass. The resulting two relationships, together with equation 1a, then require the following scaling relationships for the dimensions of the ventricles:

$$a \propto W^{1/3}, \tag{2a}$$

$$l \propto W^{1/3} \tag{2b}$$

and

$$h \propto W^{1/3}. \tag{2c}$$

Measurements providing experimental support for the second of these relationships, involving ventricular length l, have been given by Clark (Clark, 1927) for the lengths of the left ventricle of mammals ranging in size from the mouse to the horse. This result, together with the known validity of relationship 1a in the form $a^2 \propto W/l$, establishes the validity of relationship 2a for ventricular radius a. The fact that ventricular mass is proportional to mammal mass then finally confirms the validity of relationship 2c for ventricular thickness h. In particular, the foregoing mass relationship on which relationships 2a–c are based may be written as $h \propto W/(a^2 + al)$. With a and l varying as mammal mass raised to the power 1/3, h must also vary in this manner.

Scaling relationships from blood flow

The derivation of the scaling laws for the dimensions of the

blood vessels presents more of a problem than that for the heart ventricles. Relationships 1b,c provide two connections between the five vascular variables r_a, L_a, r_c, L_c and n_c. Three additional relationships are therefore needed to define the scaling laws for these variables. To assist in identifying these relationships, the mechanics of ventricular pumping and blood flow can be examined. For simplicity in this regard, only blood flow from the left side of the heart will be considered. Similar considerations will apply to the right side.

The underlying principle to be employed here is that the maximum blood pressure due to the pumping of the blood out of the ventricles must be the same for all mammals. This is a similarity requirement of mammals that can be established from general considerations of heart elasticity and cardiovascular response (Dawson, 1991), but may also be regarded as a fundamental experimental fact on the basis of previous measurements (Woodbury and Hamilton, 1937; Gregg et al., 1937; among others).

Stroke volume

Consider first the radial contraction of the left heart ventricle during its pumping cycle. Let U_m denote the maximum inward movement of the walls of the ventricle. The maximum volume of blood B_m squeezed into the connecting vessel may then be represented by the proportional relationship:

$$B_m \propto a l U_m \left(1 - \frac{1}{2} \frac{U_m}{a}\right). \qquad (3)$$

The volume B_m denotes the stroke volume of the ventricle and has been shown by measurement (Holt et al., 1968) to vary directly with mammal mass. Thus, in view of relationships 2a–c, the displacement U_m must, like a, l and h, vary with mammal mass raised to the power 1/3. Relationship 3 can then be written as the simpler expression $B_m \propto a l U_m$.

Resistance to blood flow

The blood volume pumped into the connecting vessel by the ventricle must, of course, force the blood already in the vessel and in the capillaries to move forward. If there were no resistance to the blood movement, this displacement would take place with no increase in the blood pressure in the ventricle. Such, however, is not the case. The blood flow is resisted by inertial force in the connecting vessel, where viscous resistance is negligible, and by viscous force in the capillaries, where inertial resistance is negligible. Each of these forces causes a pressure increase in the blood. For the maximum pressure to be the same for all mammals, the maximum pressure from each force must be independent of mammal mass.

The maximum pressure P_I from the inertial resistance of blood flow in the connecting vessel is related in a proportional sense to the density of the blood ρ and its maximum acceleration A_m in the connecting vessel through the product $\rho L_a A_m$. The acceleration is also related in a proportional sense to the maximum displacement U_m of the ventricle through the ratio $a l \omega^2 U_m / r_a^2$, where ω denotes cyclic heart rate. This ratio

follows directly from the condition that blood flow out of the ventricle must equal blood flow in the connecting vessel. The following relationship may thus be written for the blood pressure from inertial resistance:

$$P_I \propto \frac{\rho l a^2 L_a \omega^2 U_m}{a r_a^2} . \qquad (4)$$

Now, the blood density ρ is the same for all mammals, the product $a^2 l$ is proportional to mammal mass and the ratio U_m/a is independent of mammal mass. Hence, on using the relationship 1b and requiring P_I to be independent of mammal mass, this last relationship is found to provide the simple scaling law:

$$L_a \propto \omega^{-1}, \qquad (5)$$

which requires, on considering different mammal sizes, that the length of the connecting vessels vary inversely with heart rate.

Interestingly, the validity of this last relationship was implicitly confirmed in an earlier independent work (Noordergraaf et al., 1979), in which wavelengths associated with the pressure pulses in the aorta during heart beats were shown to be proportional to aortic length. Such wavelengths are inversely proportional to heart rate and, hence, the aortic length was implicitly shown to vary inversely with heart rate, as in relationship 5.

Attention may next be directed towards the viscous resistance to blood flow in the capillaries. This resistance is well-known in fluid mechanics and is representable by Poiseuille's Law. The resulting maximum pressure P_V in the blood may be expressed in proportional terms as the ratio $\mu L_c V_m / r_c^2$, where μ denotes the viscosity of the blood and V_m denotes the maximum velocity of the blood through each of the capillaries. In a manner similar to that used for blood acceleration in connection with relationship 5, the velocity may be related in proportional terms to the maximum displacement of the ventricle by the ratio $a l \omega U_m / n_c r_c^2$. The pressure may then be expressed as:

$$P_V \propto \frac{\mu l a^2 L_c \omega U_m}{a n_c r_c^4} . \qquad (6)$$

The blood viscosity μ is the same for all mammals. Also, the product $l a^2$ is proportional to mammal mass and the ratio U_m/a is independent of mammal mass, as noted above. On using relationships 1 and 5, this last relationship thus provides, for P_V independent of mammal mass, the scaling relationship:

$$r_c^2 n_c^{2/3} \propto r_a^{2/3} W^{1/3} . \qquad (7)$$

It can be seen from the above that relationships 1b,c and 7 provide three relationships between the five variables r_a, L_a, r_c, L_c and n_c of the system. Two additional relationships are thus still needed for determination of the scaling laws of each. Once these are known, relationship 5 can be used to determine the scaling law for heart rate.

Scaling laws for blood vessels – first approach

The two additional similarity relationships needed for establishing the scaling laws for the vascular system may be
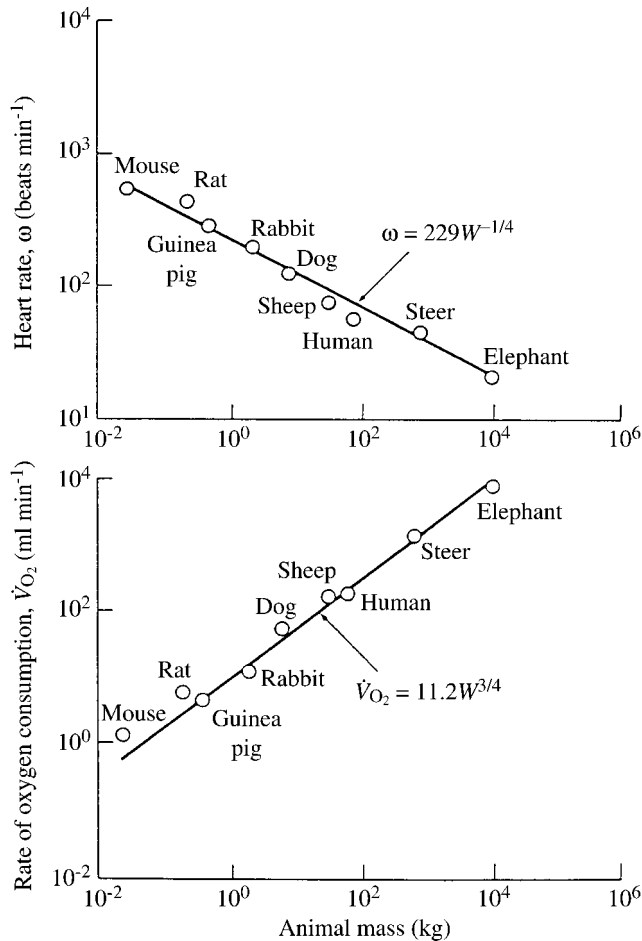
Fig. 3. Variation of heart rate ω and the rate of oxygen consumption $\dot{V}_{O_2}$ with mammal mass W (data from Brody, 1945).

found from general theoretical considerations, or they may come directly from generally accepted experimental relationships. The latter approach will be employed first, followed by a discussion of alternative theoretical relationships.

It is well known from measurement that the heart rate of mammals can be considered to vary approximately with mammal mass raised to the power $-1/4$ and that the rate of oxygen consumption $\dot{V}_{O_2}$ can be considered to vary approximately with mammal mass raised to the power $3/4$. These variations are illustrated in Fig. 3 using some of the original data (Brody, 1945). Here, logarithmic axes are used, so that data of the form $y=AW^n$ plot as a straight line with slope equal to n and with value y at $W=1$ equal to the value A. The solid lines in the plots indicate predictions from the indicated relationships for heart rate and rate of oxygen consumption.

The overall agreement shown in Fig. 3 between measurements and the power-law relationships can be seen to be good. However, the representations must be considered approximate as a result of more recent studies. For example, Bartels (Bartels, 1982) has demonstrated deviations from the 3/4 power law for $\dot{V}_{O_2}$ for very small mammals, and Heusner

(Heusner, 1991) has reported deviations on the basis of detailed statistical analyses of numerous measurements.

In the present work, the 3/4 power law for rate of oxygen consumption and the $-1/4$ power law for heart rate will accordingly be regarded as good average representations of measurements over the size range from mouse to elephant. The following relationships may thus be written as experimental scaling laws describing the workings of the cardiovascular system of mammals:

$$\omega \propto W^{-1/4}, \tag{8a}$$

$$\dot{V}_{O_2} \propto W^{3/4}. \tag{8b}$$

The first of these relationships may be used directly with relationship 5 to establish the scaling law for the length of the connecting vessels, and this may then be used with relationship 1b to establish the scaling law for the radius of these vessels. The results may be expressed as:

$$L_a \propto W^{1/4}, \tag{9a}$$

$$r_a \propto W^{3/8}. \tag{9b}$$

These scaling laws are the same as those derived earlier from alternative considerations (Dawson, 1991). Typical values reported by Noordergraaf et al. (Noordergraaf et al., 1979) for the length of the aorta of mammals provide a scaling exponent of 0.30, in fair agreement with the 1/4 (0.250) exponent of relationship 9a. Detailed measurements (Clark, 1927) of aortic flow area provide an exponent of 0.72, which converts to an exponent of 0.36 for the aortic radius, in good agreement with the 3/8 (0.375) exponent of relationship 9b.

Relationship 8b requires some additional consideration of oxygen utilization before application. Oxygen utilization must equal oxygen transfer from the systemic capillaries and also oxygen transfer to the pulmonary capillaries. Total oxygen transfer rate from, or to, a capillary is governed by the well-known diffusion relationship for gases and is proportional to the product of (i) the difference in average oxygen partial pressure inside and immediately outside the capillary and (ii) the capillary surface area. It is also inversely proportional to capillary wall thickness, i.e. the difference between the outside and inside radii of the capillary. Basic similarity considerations suggest that the inside and outside oxygen pressures are proportional to one another under change of scale. The same is expected for the capillary radii. Using these conditions, the resulting proportional relationship for net oxygen transfer then involves simply the product of the average partial pressure in the capillaries P_o, their number n_c and their length L_c, that is:

$$\dot{V}_{O_2} \propto P_o n_c L_c. \tag{10}$$

In using this last relationship, it is, of course, necessary to know how, if at all, the oxygen partial pressure in the blood varies with mammal size. Fortunately, Schmidt-Nielsen and Larimer (Schmidt-Nielsen and Larimer, 1958) have made extensive measurements of this pressure for a wide range of mammal sizes, and their results have been shown to be in general agreement with the following relationship (Dawson, 1991):
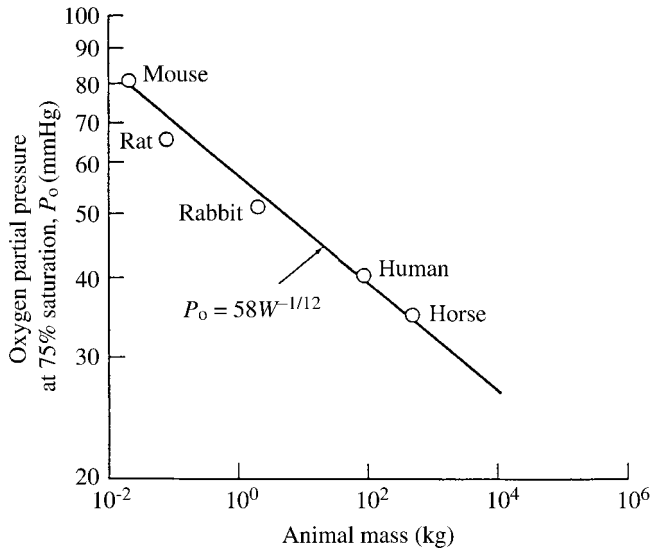
Fig. 4. Variation of oxygen partial pressure P_o in the blood with mammal mass W (data from Schmidt-Nielsen and Larimer, 1958). 1 mmHg=0.133 kPa.

$$P_o \propto W^{-1/12}. \quad (11)$$

The adequacy of the relationship is illustrated in Fig. 4 for typical measurements. More extensive comparisons have been given previously (Dawson, 1991). Using relationships 10 and 11 and relationship 8b, the scaling relationship for the product is accordingly:

$$n_c L_c \propto W^{5/6}. \quad (12)$$

On combining this relationship with relationship 1c, the scaling law for radius may be determined. The scaling law for capillary length L_c and number n_c may then be determined from relationships 7 and 12 with relationship 9b. In this way, the following scaling laws for the capillary vessels are found:

$$r_c \propto W^{1/12}, \quad (13a)$$

$$L_c \propto W^{5/24} \quad (13b)$$

and

$$n_c \propto W^{5/8}. \quad (13c)$$

These scaling laws are identical to those derived earlier using alternative arguments (Dawson, 1991) rather than the experimental laws of relationships 8a,b. Figs 5 and 6 illustrate the general validity of the relationships using data for capillary radius r_c (Fig. 5) and net length $n_c L_c$ (Fig. 6), as determined from measurements (Gehr et al., 1981) of the volume and surface area of the pulmonary capillaries (Dawson, 1991).

The data for the capillary radius show considerable scatter, but the trend is in agreement with that expected from relationship 13a. A best-fit equation to the data provides a scaling exponent of 0.079, in good agreement with the 1/12 (0.083) exponent of relationship 13a. The data for the net capillary length is likewise in good agreement with the prediction from relationships 13a–c. A best-fit to these data
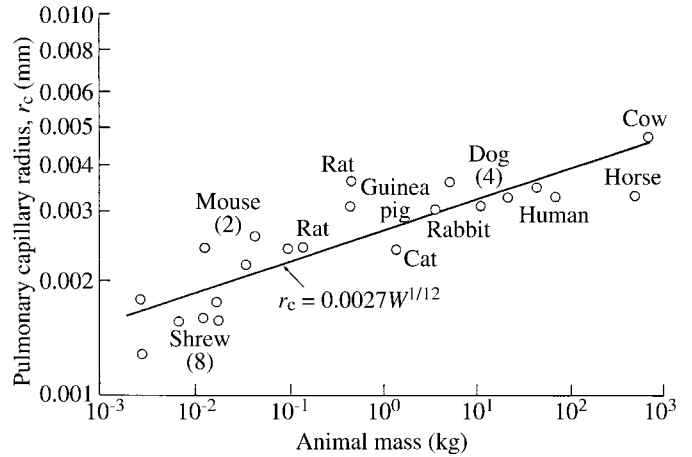

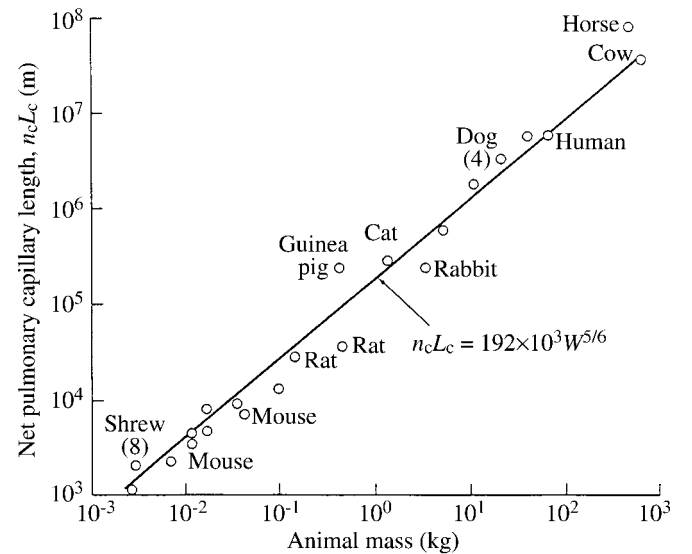Fig. 5. Variation of pulmonary capillary radius r_c with mammal mass W (data from Gehr et al., 1981).

Fig. 6. Variation of net length of the pulmonary capillaries $n_c L_c$, where n_c is capillary number and L_c is capillary length, with mammal mass W (data from Gehr et al., 1981).

provides an exponent of 0.85, in good agreement with the exponent of 5/6 (0.833) given by relationships 13b,c.

Scaling laws for physiological processes

The scaling laws of relationships 9 and 13 for the vascular system provide a basis for the scaling laws of various physiological processes of mammals. In particular, by starting with these relationships and reversing the foregoing arguments, the scaling laws for blood pressure, heart rate and the rate of oxygen consumption can readily be established. The origin of these well-known laws is thus seen to rest in the underlying scaling laws for the vascular system. Additional scaling relationships also follow from this description, as described below.

Cardiac output

In addition to the basic geometric scaling relationships for blood vessels, the scaling law for cardiac output can be brought within the framework of the description simply by noting that it is determined by considering the product of stroke volume and heart rate as represented by relationships 3 and 8a. The result is that cardiac output must, like the rate of oxygen consumption, scale with mammal mass raised to the power 3/4. This law is in agreement with measured values (Holt et al., 1968).

Urine output and nephra number

The scaling law for urine output of mammals may also be brought within the framework of the present description. The governing relationship is analogous to that of relationship 10 for oxygen transfer rate, except that the driving force is the scale-independent blood pressure rather than the scale-dependent oxygen partial pressure. Thus, the scaling law for urine output is that for the product $n_c L_c$, and this is proportional to mammal mass raised to the power 5/6. Analysis (Adolph, 1949) of various experimental measurements indicated a scaling exponent of 0.82, in good agreement with the 5/6 (0.833) exponent expected here.

The scaling law for the variation in the number of fundamental renal units in the kidneys of mammals, the nephron units and the nephra numbers, may also be considered with the present theory. These units consist of a set of capillaries through which fluid is extracted and partially reabsorbed to rid the body of waste water. Thus, considering nephron architecture to be similar among mammals, with the same number of capillaries in all such units, the number of nephrons, for example, can be expected to scale directly as the number of capillaries of the present theory, i.e. as mammal mass raised to the power 5/8 (0.625). Interestingly, this is, in fact, the case. Measurements and countings (Kunkel, 1930) at Johns Hopkins, many years ago, provided nephra numbers for mammals ranging in size from the mouse to the ox; and Adolph (Adolph, 1949) later showed these to be described by a best-fit power law involving mammal mass raised to the power 0.62.

The agreement between the present theory and the measurements of urine output and nephra number is important not only in general terms but also because it provides specific support for scaling relationships 13 for the systemic side of the circulation. The results presented in Figs 5 and 6 provided this experimental support for the pulmonary side of the circulation. The indications are, therefore, that relationships 13 apply to the capillaries of the body in general, as expected from the theoretical development.

The average body cell

In a further study of scaling laws for physiological processes, attention may be directed to the small amount of average body tissue, or average body cell, serviced by a single capillary. The mass of this tissue is evidently proportional to the ratio W/n_c, and, since mass is proportional to volume, its characteristic length dimension l_s is determined by the relationship:

$$l_s \propto (W/n_c)^{1/3}, \qquad (14)$$

i.e. as mammal mass raised to the power 1/8.

In addition, since mammal mass and heart mass are proportional under change of scale, the characteristic length defined by relationship 14 is the same as that for heart tissue. Thus, average body tissue and heart tissue may be considered to be the same for the present purposes. The diameter of a cardiac muscle fiber, for example, should therefore scale with mammal mass in the manner of relationship 14. No measurements presently exist to test this prediction, but the scaling law indicates that a factor of more than 4 should be found between such measurements for the mouse and the elephant.

Because of the similarity between average body tissue and heart tissue, the cyclic rate of operation of average body tissue may also be considered equal to that of cardiac tissue, i.e. equal to the heart rate ω. Using this condition, the oxygen utilized by the small amount of average body tissues per unit volume in a cycle of operation may thus be expressed in the form:

$$\frac{\dot{V}_{O_2}}{n_c \omega l_s^3} \propto \frac{P_s l_s}{\omega l_s^3}, \qquad (15)$$

where P_s denotes the oxygen partial pressure immediately exterior to the tissue in the interstitial fluid. On using the previously described scaling laws for $\dot{V}_{O_2}$, n_c, ω and l_s, it can easily be seen that the left-hand side of this relationship is independent of mammal size, as may be expected from physical considerations. The right-hand side of the relationship must then also have this property. It can accordingly be seen from the scaling laws for l_s and ω that the partial pressure P_s must be independent of mammal size. This is in contrast with the partial pressure in the blood, which varies with mammal mass in the manner of relationship 11, but is consistent with general diffusion processes in tissues.

This last result can be used to infer the scaling relationship for the spacing between a capillary and the tissue mass (or average body cell) serviced by it. Assuming, in particular, that the oxygen partial pressure decreases linearly from its value in the capillary to zero at the center of the tissue mass, the expression for the oxygen pressure at distance D from the capillary is $P_o - P_o D/d_s$, where P_o denotes, as above, the partial pressure in the capillary and d_s denotes the spacing between the capillary and tissue-mass center. The distance from capillary to the outside surface of the tissue mass is $d_s - l_s$. Substituting this for D in the above expression, the value of the oxygen pressure P_s, at the surface is found to be $P_o l_s/d_s$. For this to be independent of mammal size, it is therefore necessary, from the scaling relationships for P_o and l_s, that the spacing d_s vary with mammal size raised to the power 1/24. No measurements exist for this spacing at the present time. However, the scaling law should be that for the spacing between capillary and cardiac muscle fiber in mammals. The spacing for the elephant, for example, should be approximately 1.6 times that for the mouse.

Of course, variation in spacing between capillary and tissue mass for the purposes of oxygen diffusion would presumably leave unchanged other diffusion processes that are associated with life-sustaining activities of the tissue mass.

Cardiac contraction

The scaling law of relationship 14 for the characteristic length of an average body cell allows investigation of the fundamental processes involved in heart contraction. In particular, contraction occurs as a result of the propagation of an action potential over the length of the heart. The net time for propagation must be proportional to heart length and inversely proportional to propagation speed. This time must also be proportional to the time between heart beats for different mammals, i.e. the reciprocal of heart rate ω. The appropriate relationship is $\omega \propto C/l$, where C denotes propagation speed and l denotes ventricular length.

Now, the propagation speed C is known from measurements on nerve fibers to vary with the diameter of the fiber carrying the signal. The relationship is generally assumed to be a power law with an exponent in the range 0.5–1.0 (Jack et al., 1975). With b denoting the value of the exponent, and the fiber diameter identified with the characteristic cell length of relationship 14, the proportional relationship for the process may therefore be written as $\omega \propto l_s^b l^{-1}$. Using the scaling relationships from the present theory, it can readily be seen that the exponent b must have the value 2/3. The cardiac contraction speed is thus predicted to vary with cardiac fiber diameter according to a 2/3 power law. No experimental measurements presently exist to confirm this result. Since, according to the present theory and relationship 14, cardiac fiber diameter varies with mammal mass raised to the power 1/8, the contraction speed in the heart muscle of an elephant can be expected to be approximately 2.6 times faster than that in the mouse.

Scaling laws for blood vessels – second approach

The two empirical relationships 8a,b describing scaling laws for heart rate and the rate of oxygen consumption may be replaced by theoretical relationships for the purposes of deriving these scaling laws from basic concepts, as well as those for the vascular system. As indicated above, earlier theoretical work of this kind relied on fundamental considerations of cell diffusion and cardiac contraction (Dawson, 1991). The present discussion involves consideration of the oxygen consumption of tissue serviced by a capillary and consideration of oxygen transfer to the tissue. The two assumptions are based on the previous discussion of average body cell and can be expressed as follows.

(a) The oxygen utilization of an average body cell per volume in a cycle of operation is the same for all mammals, i.e. $P_s l_s / \omega l_s^3 \propto W^0$.

(b) The oxygen transferred to an average body cell per volume in a cycle of operation is the same for all mammals, i.e. $P_o L_c / \omega l_s^3 \propto W^0$.

The additional assumptions to be used here may be summarized as follows.

(c) Relationships 1b,c, requiring blood volumes in the connecting vessels and capillaries to be proportional to mammal mass.

(d) Relationship 5, requiring blood pressure in the connecting vessel to be independent of mammal size.

(e) Relationship 7, requiring blood pressure in the capillaries to be independent of mammal mass.

(f) The condition that the partial pressure of oxygen P_s at the surface and within the interior of an average body cell is independent of mammal mass.

(g) The condition that the partial pressure of oxygen in the blood varies with mammal mass raised to the power $-1/12$.

(h) Net rate of oxygen consumption is determined by the product of oxygen partial pressure in the blood, the number of capillaries and their length.

The internal consistency of each of these assumptions can be verified using the foregoing solution for the scaling laws of the vascular system and the experimental laws for heart rate and the rate of oxygen consumption. The objective here is to show that these assumptions can be used alone to derive the scaling laws for the system.

Assumptions a and f for oxygen utilization provide the general relationship $\omega l_s^2 \propto W^0$. Using relationship 5 of assumption d expressing heart rate in terms of vessel length and relationship 14 defining l_s in terms of capillary number, this relationship may be written as:

$$n_c^{2/3} \propto L_a^{-1} W^{2/3}, \qquad (16)$$

which provides the first of the two theoretical relationships required.

Assumptions b and g for oxygen transfer, relationship 5 of assumption d relating ω to L_a, and relationship 14 defining l_s in terms of n_c, provide the relationship $W^{-1/12} L_c \propto L_a^{-1} W / n_c$. Using relationship 1c of assumption c for capillary volume, this result may also be written as:

$$r_c^2 \propto L_a W^{-1/12}, \qquad (17)$$

which provides the second of the theoretical relationships required.

On using these last two relationships with relationships 1b,c of assumption c, and relationship 7 of assumption e, the full set of five scaling relationships for the vascular system can now be determined without the use of the empirical relationships for heart rate and the rate of oxygen consumption.

In particular, by substituting relationships 16 and 17 into relationship 7, the scaling law for r_a can be obtained. Relationship 1b then provides the scaling law for L_a. The scaling law for r_c may next be determined from relationship 17 and that for n_c from relationship 16. Finally, the scaling law for L_c can be determined from relationship 1c. These laws, so found, are, in fact, identical to those already determined here and in the earlier work of the writer (Dawson, 1991), namely the two relationships 9 governing the scaling of the length and radius of the connecting vessels and the three relationships 13

governing the scaling of the radius, length and number of the capillary vessels.

Heart rate and rate of oxygen consumption

With the above results, it can be seen that the scaling law for the heart rate is now determined theoretically from relationship 5 of assumption d to be the well-known $-1/4$ law. The scaling law for the rate of oxygen consumption is now also determined theoretically from assumption g and relationship 10 of assumption h be the well-known 3/4 law.

These last results are significant in that they demonstrate that the origin of the 3/4 law for the rate of oxygen consumption rests in the basic design and operation of the cardiovascular system. The only direct experimental relationship used in the derivation is that of assumption g, relating oxygen partial pressure in the blood to mammal mass. If this relationship were changed slightly, as might be permitted by the measurements, a slight deviation from the predicted 3/4 power law would result. For example, if the $-1/12$ relationship were assumed instead to be a -0.09 relationship, the scaling law for the rate of oxygen consumption would become a 0.73 law rather than the 3/4 power law. This indicates, of course, that the 3/4 power law predicted in the present work is a convenient representation and not a fundamental feature of the theory, consistent with the work of Bartels (Bartels, 1982) and Heusner (Heusner, 1991), where deviations from the 3/4 power law were determined from statistical study of measurements.

In connection with the above remarks, it is interesting to note also that, if the oxygen pressure in the blood were assumed to be independent of mammal size, the theory would then require that heart rate be the same for all mammals and that the rate of oxygen consumption should vary directly with mammal mass. Capillary radius and length would also be required to be independent of mammal size. Such results are, of course, inconsistent with measurements and illustrate again the sensitivity of the performance of the system to its components and to physiological processes.

Restraints on the system when viewed as a delivery system (as in the recent theories, e.g. West et al., 1997; Banavar et al., 1999) may ultimately provide reasons for the design of the cardiovascular system being as it is. However, before that possibility can be assessed, such descriptions need to be generalized to allow variation of capillary dimensions with mammal mass. At present, existing theories assume scale-invariant capillary dimensions.

Previous work of the writer

It is worthwhile in this review, and here in particular, to note the details of the two assumptions used in place of a and b in the original work of the writer (Dawson, 1991). As noted above, these involve consideration of cell diffusion and cardiac contraction. Cell diffusion referred not only to oxygen diffusion but to any of the life-sustaining diffusion activities of an average body cell. With scale-invariant diffusion coefficient and driving force envisioned, the resulting

relationship involved the heart rate ω and the characteristic length l_s of an average body cell in the form $\omega l_s^2 \propto W^0$, as is also the case here for oxygen diffusion with assumptions a and f above. Cardiac contraction was considered in terms of ventricular length l and the propagation speed of contraction. The resulting relationship, as discussed above, involved heart rate and cell length in the form $\omega \propto l_s^{2/3} l^{-1}$, where the exponent 2/3 in this relationship was chosen to be consistent with experimental measurements. With these two relationships used in place of assumptions a and b above, the scaling laws for the vascular system and rate of oxygen consumption described here can also be established.

A variation of the exponent 2/3 for l_s in the above relationship for cardiac contraction will, of course, lead to a deviation from the predicted 3/4 law for the rate of oxygen consumption. This was noted in the original work, such that if the exponent 2/3 were changed to 1/2, the predicted law for the rate of oxygen consumption would become a 0.73 power law rather than the 3/4 power law.

It is also of interest to note, from the earlier work, the observation that the general diffusion relationship in the form $\omega \propto l_s^{-2}$ provides an explanation as to how heart rate increases with decreasing mammal size. With $l_s \propto W^{1/8}$, as in this work, the heart rate is predicted to follow a $-1/4$ law, as required from measurement. Moreover, the smaller the mammal, the smaller the cell – and hence the faster the diffusion process and the resulting heart rate.

Similarity of birds – a brief study

The fact that birds have a four-chambered heart and a closed circulatory system similar to that of mammals suggests the advisability of examining the application of the present theory to birds. Early work (Brody and Procter, 1932) indicated that resting rate of oxygen consumption of birds varied essentially as a 2/3 power relationship with body mass, in contrast with the essentially 3/4 power relationship found by them for mammals. Lasiewski and Dawson (Lasiewski and Dawson, 1967) divided birds into two size groups (passerine and non-passerine species) and showed that the rate of oxygen consumption of each group was proportional essentially to body mass to the power 3/4, but with different proportional coefficients. A 2/3 power law was, however, indicated when both groups were considered together. More recently, Bennett and Harvey (Bennett and Harvey, 1987), using a larger database and more detailed methods of analysis, argued persuasively that no such natural division exists between species of birds and that a 2/3 power relationship for the rate of oxygen consumption provides the appropriate description.

If birds followed the 3/4 power law for oxygen consumption (as indicated by Lasiewski and Dawson, 1967), the workings and similarity of their cardiovascular system would be the same as described by the present theory for mammals. However, if they follow the 2/3 power law (as indicated by the work of Bennett and Harvey, 1987), then some modification is required. Taking the latter position, a clue for the modification

can be found in the work of Calder (Calder, 1968) and Lasiewski and Calder (Lasiewski and Calder, 1971) in which the heart mass W_h and heart rate ω_b of birds were shown to scale according to the relationships:

$$W_h \propto W^{0.91}, \tag{18a}$$

$$\omega_b \propto W^{-0.23}. \tag{18b}$$

Thus, unlike mammals, heart mass is not proportional to body mass, and the heart rate does not follow the $-1/4$ power law described above for mammals.

A reconsideration of the various parts of the present theory will show that heart mass could equally well be substituted for body mass in the various descriptions without loss of meaning. For example, the condition that blood volume is proportional to body mass could also have been stated relative to heart mass. Of course, with mammals, no significant differences would result because of the proportional relationship between heart mass and body mass. If there were a difference, the use of heart mass could be argued to be the more correct reference mass. This is the case with birds, and the argument for replacing body mass with heart mass is indeed persuasive on the basis of the heart-rate law of relationship 18b. In particular, replacing body mass with heart mass W_h in the relationship $\omega \propto W^{-1/4}$ and using relationship 18a for birds, the heart rate is predicted to vary as body mass raised to the power -0.23. This is in precise agreement with the measured relationship, relationship 18b.

Applying the rule to other quantities in the theory, it is easily found that, for birds, the rate of oxygen consumption and cardiac output are predicted to scale with body mass to the power 0.68, i.e. essentially to the power 2/3 (as indicated in the work of Bennett and Harvey, 1987). The radius and length of connecting vessels should now scale with body mass raised to the powers 0.34 and 0.23, respectively; and the capillary radius, length and number should scale with body mass raised to the powers 0.076, 0.23 and 0.57, respectively. Also, the term 'average body cell' in the previous discussion should be replaced with 'average cardiac cell'. Interestingly, the oxygen partial pressure is now predicted to scale with body mass raised to the power -0.076. It is also reassuring to note that the 2/3 exponent associated with contraction propagation and cardiac fiber diameter, as considered above, remains unchanged in this modification.

Discussion

The scaling laws governing the cardiovascular system of mammals have been derived here in a manner emphasizing the experimental basis for the laws. A simple model of the cardiovascular system has been used, consisting of the heart, the capillaries and connecting vessels between the two. The fundamental assumptions used in the first part of the work may be summarized as follows: (i) blood volume is proportional to mammal mass; (ii) heart mass is proportional to mammal mass; (iii) blood pressure is independent of mammal size; (iv) stroke volume is proportional to mammal mass; and (v) oxygen partial pressure in the blood varies as mammal mass raised to the power $-1/12$.

As a consequence of assumption i and the simplified model of the cardiovascular system, the blood volumes in the heart, the capillaries and the connecting vessels are all required to be proportional to mammal mass. As a consequence of assumptions i and ii, all linear dimensions of the ventricles of the heart are required to scale with mammal mass raised to the power 1/3. As a consequence of assumption iii, the blood pressure in the connecting vessels and in the capillaries are both required to be independent of mammal mass.

Three scaling relationships are also provided from assumptions i and iii for the characteristic radius and length of connecting vessels and the characteristic radius, length and number of capillaries. Two additional relationships are therefore needed to complete the solution for the scaling laws for the characteristic dimensions of the vascular system. These two additional relationships are first assumed in the present review to be the well-known experimental relationships requiring heart rate and rate of oxygen consumption to scale with mammal mass raised to the powers $-1/4$ and 3/4, respectively. The resulting five relationships, together with assumption v, are then shown to yield scaling laws for the vascular system requiring that the radius and length of connecting vessels (main arteries) vary with mammal mass raised to the powers 3/8 and 1/4, respectively, and that the radius, length and number of capillary vessels vary with mammal mass raised to the powers 1/12, 5/24 and 5/8, respectively.

These laws are the same as those derived earlier by the writer in a different manner (Dawson, 1991). In that work, consideration of the mechanics of heart pumping and ventricular contraction led to predictions for blood pressure and stroke volume identical to those in assumptions iii and iv, above. Also, in place of assumptions concerning heart rate and rate of oxygen consumption, two conditions were originally assumed for cell diffusion and cardiac contraction, as discussed above.

To provide further insight into the physical origin of the scaling laws for the vascular system, and for the heart rate and rate of oxygen consumption, two additional relationships have been presented here concerning oxygen consumption by the small mass of average body tissue (or average body cell) serviced by a capillary and the oxygen transfer by a capillary. Additional assumptions used in this part of the work are that oxygen transferred and used, per average body cell in a heart cycle, are both independent of mammal size, and that the partial pressure of oxygen in body tissue is independent of mammal size. The associated two relationships, specifically relationships 16 and 17, have been used in place of the experimental scaling laws for heart rate and rate of oxygen consumption to derive again the same scaling laws for the vascular system as found from the use of the experimental laws. The laws for heart rate and rate of oxygen consumption also follow from this development.

The theory described in the present review for mammals has been extended here to include the cardiovascular response of birds. Differences in the scaling relationships of heart rate and

Table 1. *Predicted scaling laws for mammals for variable* y *and mammal mass* W *in the form* y ∝ Wᵃ

Variable	Symbol	Exponent a
Ventricular length	l	1/3
Aortic radius	r_a	3/8
Aortic length	L_a	1/4
Capillary radius	r_c	1/12
Capillary length	L_c	5/24
Capillary number	n_c	5/8
Heart rate	ω	−1/4
Rate of oxygen uptake	$\dot{V}_{O_2}$	3/4
Cardiac output	–	3/4
Urine output	–	5/6
Nephra number	–	5/8
Cardiac action potential propagation velocity	C	1/12
Oxygen pressure	P_o	−1/12

Additional scaling laws are noted in the text. The last relationship for oxygen partial pressure in the blood is experimental, although it can be considered as one of the relationships required for the theory.

the rate of oxygen consumption are shown to be attributable directly to the non-proportional relationship between heart mass and body mass for birds. The basic theory remains unchanged.

Table 1 provides a summary of various scaling laws for mammals from the present theory. Additional scaling laws are noted in the text. All invite further experimental investigation. In connection with the scaling laws in Table 1, it may be noted that the scaling variation of capillary radius with mammal mass is not very pronounced and that, without the aid of the theory, the scatter in measurements, such as shown in Fig. 5, could lead to the incorrect conclusion that capillary radius does not vary with mammal size. A similar situation may also exist with the red blood cells, whose radius might be expected to be correlated with mammal mass in the same way as capillary radius. The lack of observed correlationship of such measurements (as reported by Schmidt-Nielsen, 1984, and others) may therefore be due simply to scatter in measurements and the small variations that actually exist. Other factors such as cell flexibility may also enter and minimize the correlationship. In any case, arguments for scale-invariant capillary radius based on the scale-invariant dimensions of red blood cells, as sometimes made, are not persuasive in view of the present work and the results shown in Fig. 5.

Concluding remarks

On the basis of the present review, and the earlier work of the writer, it may be concluded that the well-known similitude in the cardiovascular system of mammals has its origin in the basic design of the system and in the basic physiological processes involved in its workings. Ordinary dimensional analysis and modeling theory are unable to reveal the laws describing this similarity because of the implicit assumption of uniform scaling. The use of extended theory for non-uniform scaling of the system does not suffer from this limitation, and the results, as discussed here, provide a degree of understanding not otherwise available.

The non-uniform scaling theory leads to the conclusion that the rate of oxygen consumption and heart rate scale with mammal mass raised to the powers 3/4 and −1/4, respectively. As discussed here, these are theoretical results, based in part on representations of measurements of cardiovascular processes. Slight variations in the representations will lead to slight variations in predicted results. The strict 3/4 power law for the rate of oxygen consumption cannot therefore be viewed as fundamental to the theory, but rather simply as a convenient form representing measurements and the working of the system. What appears fundamental is the design of the system and the basic physiological processes involved.

The fact, discussed here, that the rate of oxygen consumption of birds can be considered to follow a 2/3 scaling law rather than the 3/4 scaling law for mammals suggests further that the 3/4 scaling law is not a fundamental feature of biology. It is also significant that the 2/3 scaling law for birds can be obtained from the similarity laws of mammals by replacing the proportional relationship between heart mass and body mass for mammals with the non-proportional relationship identified for birds.

The present review has attempted to provide some additional understanding and insight into the basic similarity existing in the cardiovascular system of mammals. Why the design of the system is as it is has not been addressed and remains an intriguing question in biology.

References

Adolph, E. F. (1949). Quantitative relations in the physiological constitution of mammals. *Science* **109**, 579–585.

Banavar, J. R., Maritan, A. and Rinaldo, A. (1999). Size and form in efficient transportation networks. *Nature* **399**, 130–132.

Bartels, H. (1982). Metabolic rate of mammals equals the 0.75 power of their body weight. *Exp. Biol. Med.* **7**, 1–11.

Bennett, P. M. and Harvey, P. H. (1987). Active and resting metabolism in birds – allometry, phylogeny and ecology. *J. Zool., Lond.* **213**, 327–363.

Brody, S. (1945). *Bioenergetics and Growth, with Special Reference to the Efficiency Complex in Domestic Animals.* New York: Reinhold Publishing.

Brody, S. and Procter, R. C. (1932). Relation between basal metabolism and mature body weight in different species of mammals and birds. *Univ. Missouri Agr. Exp. Station Res. Bull.* **166**, 89–102.

Calder, W. A. (1968). Respiratory and heart rates of birds at rest. *Condor* **70**, 359–365.

Clark, A. J. (1927). *Comparative Physiology of the Heart.* Cambridge: Cambridge University Press.

Dawson, T. H. (1991). *Engineering Design of the Cardiovascular System of Mammals.* Englewood Cliffs, NJ: Prentice Hall Biophysics and Bioengineering Series.

Gehr, P., Mwangi, D. K., Ammann, A., Maloig, G. M. D., Taylor, C. R. and Weibel, E. R. (1981). Design of the mammalian respiratory system. V. Scaling morphometric pulmonary diffusing capacity to body mass: wild and domestic mammals. *Respir. Physiol.* **44**, 61–86.

Gregg, D. E., Eckstein, R. W. and Fineberg, M. H. (1937). Pressure pulses and blood pressure values in unanesthetized dogs. *Am. J. Physiol.* **118**, 399–410.

Hemmingsen, A. M. (1960). Energy metabolism as related to body size and respiratory surfaces and its evolution. *Rep. Steno. Mem. Hosp. (Copenhagen)* **9**, 1–110.

Heusner, A. A. (1991). Size and power in mammals. *J. Exp. Biol.* **160**, 25–54.

Holt, J. P., Rhode, E. A. and Kines, H. (1968). Ventricular volumes and body weight in mammals. *Am. J. Physiol.* **215**, 704–715.

Jack, J. J. B., Noble, D. and Tsien, R. W. (1975). *Electric Current Flow in Excitable Cells.* Oxford: Clarendon Press.

Kenner, T. (1972). Flow and pressure in the arteries. In *Biomechanics – Its Foundations and Objectives* (ed. Y. C. Fung, N. Perrone, M. Anliker), pp. 381–434. Englewood Cliffs, NJ: Prentice Hall.

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

Kunkel, P. A., Jr (1930). The number and size of the glomeruli in the kidney of several mammals. *Bull. Johns Hopkins Hosp.* **47**, 285–291.

Lambert, R. and Teissier, G. (1927). Theorie de la similitude biologique. *Ann. Physiol.* **3**, 212–246.

Lasiewski, R. C. and Calder, C. A., Jr (1971). A preliminary allometric analysis of respiratory variables in resting birds. *Respir. Physiol.* **11**, 152–166.

Lasiewski, R. C. and Dawson, W. R. (1967). A re-examination of the relation between standard metabolic rate and body weight in birds. *Condor* **69**, 13–23.

Noordergraaf, A., Li, J. K. J. and Campbell, K. B. (1979). Mammalian hemodynamics: a new similarity principle. *J. Theor. Biol.* **79**, 485–489.

Patterson, M. R. (1992). A mass-transfer explanation of metabolic scaling relations in some aquatic invertebrates and algae. *Science* **255**, 1421–1423 (see also **256**, 722).

Prothero, J. (1986). Scaling of standard energy-metabolism in unicellular organisms – a reanalysis. *Comp. Biochem. Physiol.* **83**A, 243–248.

Riisgard, H. U. (1998). No foundation of a '3/4 power scaling law' for respiration in biology. *Ecol. Lett.* **1**, 71–73.

Rubner, M. (1883). Ueber den Einfluss der Korpergrosse auf Stoff und Kraftwechsel. *Z. Biol.* **19**, 535–562.

Sarrus, F. and Rameaux, J. (1838). Rapport sur un memoire addresse a l'Academie royale de Medecine. *Bull. Acad. R. Med., Paris* **3**, 1094–1100.

Schmidt-Nielsen, K. (1984). *Scaling: Why is Animal Size So Important?* Cambridge: Cambridge University Press.

Schmidt-Nielsen, K. and Larimer, J. L. (1958). Oxygen dissociation curves of mammalian blood in relation to body size. *Am. J. Physiol.* **195**, 424–428.

West, G. B., Brown, J. H. and Enquist, B. J. (1997). A general model for the origin of allometric scaling laws in biology. *Science* **276**, 122–126.

Woodbury, R. A. and Hamilton, W. F. (1937). Blood pressure studies in small animals. *Am. J. Physiol.* **119**, 663–674.