

Use of allometry in predicting anatomical and physiological parameters of mammals

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Summary

One challenge for veterinarians, animal facilities and research scientists is the making of physiological estimates appropriate to a variety of species for which data are often either completely lacking or are incomplete. Our intent in compiling the data in this paper is to provide the best possible database of normal physiological and anatomical values primarily (though not exclusively) for four common mammalian model species: mouse, rat, dog and man. In order to make those data as accessible and applicable as possible, we have presented the results of this study in the form of body-size dependent allometric equations in which some variable (Y) is expressed as a dependent function of body mass (M) in the power-law equation, $Y = aM^b$. By compiling these data, it is apparent that the resultant equations are quantitatively grouped (with similar slope or 'b' values). These emergent patterns provide insights into body-size dependent 'principles of design' that seem to dictate several aspects of design and function across species among all mammals. In general, the weights of most individual organs scale as a constant fraction of body mass (i.e. the body mass exponent, $b \cong 1.0$). Biological rates (e.g. heart rate, respiratory rate) scale as $b \cong -1/4$. Finally, volume-rates (the product of volume and rate) such as cardiac output, ventilation and oxygen uptake vary as $b \cong 3/4$.

Keywords Scaling; physiological time; laboratory animals; predictions

The number of structural, biochemical and physiological features that all mammals have in common greatly exceeds the number that differentiate them. However, despite these similarities, rarely are primary functions among mammals linear extrapolations of body size. There is a suite of body-size dependent design constraints that dictate many aspects of function among mammals. For example, a 3 g shrew and a 5 metric ton elephant have the same number of bones and muscles and they share identical biochemical pathways, yet the metabolic intensity of the shrew's tissues would be sufficient to cause the elephant's blood to boil. Similarly,

weight-specific (i.e. per unit body weight) drug or metabolite doses must vary greatly between shrews and elephants and the consequences of not recognizing this distinction can be fatal as exemplified by the infamous death of 'Tusko', an Asiatic elephant killed by an accidental overdose calculated without proper consideration of scaling rules (Harwood 1963). By identifying and quantifying the body-size dependent 'rules' of design among mammals, it is our hope that resultant patterns may be useful, to name just a few reasons: (1) in species-to-species extrapolation or interpolation for veterinarians and other animal technicians working with diverse, often poorly understood, species (including endangered species); (2) in the

interpretation of toxicology data; and (3) in interpreting results from studies that may have overlooked these principles.

Allometry—body-size constraints on structure and function

An animal's body size is certainly among the most prominent of all its distinguishing features. Among the mammals, the largest, the 150 ton blue whale is 75 million times the mass of the smallest, the 2 g Etruscan shrew, yet both share the same skeletal architecture, suite of organ systems, biochemical pathways and even temperature of operation. However, what engineers have known for a long time has only slowly gained widespread consideration among biologists: there are trade-offs that must accompany size changes. Scaling-up a bridge, or a mammal, to a size 100 000 times larger requires more than just making bigger parts. For example, changes in size result in shifts in optimal or preferred frequencies of use. These and other size-dependent constraints of design are expressed and best interpreted in the form of allometric equations. *Allometry* (literally 'of another measure') describes the disproportionate changes in shape, size or function that are observed when comparing separate isolated features in animals spanning a range of body sizes. Quantitatively, allometry is usually expressed in the form of power-law equations relating some variable of structure or function (Y) as a dependent function of body mass (M) in the form:

$$Y = a \cdot M^b,$$

where a and b are derived empirically. The exponent b is the slope of the regression line when this equation is plotted on log-log coordinates. The intercept a is the value of Y when $M = 1$.

There are several caveats with using interspecifically-derived allometric equations. First, the data used to derive the equations should span as broad a range of body weights as possible; Calder (1984) recommends at least three orders of magnitude. Second, and related to the above, these kinds of allometric equations are generally

useful *between* rather than *within* species. There is no *a priori* reason to believe that the interspecific relations that we present here should also hold intraspecifically: in fact there are arguments that they should not (see e.g. Feldman & McMahon 1983). Finally, because they are derived using animals often not closely related, they incorporate both measurement error as well as biological variance. As a consequence, these equations are not intended as perfect predictors, although they can function to describe the interspecific standard (or the default value) when actual data are unavailable.

Over the past century hundreds of allometric relationships have been identified among virtually all animal groups. One of the most discussed and still most provocative of these is the relationship between body size and basal metabolic rate among mammals. Pioneering works by Kleiber (1932), Zeuthen (1947), Adolph (1949), and Hill (1950), among others, examined many of the seemingly recurring patterns that have suggested that there may be body-size dependent design constraints operating among the mammals. These constraints, the subject of several books (e.g. Peters 1983, Calder 1984, Schmidt-Nielsen 1984, McMahon & Bonner 1983, Brown & West 2000), are apparent only when several species are examined comparatively; they could not be detected in a single species.

Allometric equations have been successfully applied to pharmacokinetics and risk assessment (e.g. Dedrick & Bishoff 1980, Mordenti 1986, Boxenbaum & D'Souza 1990, Travis *et al.* 1990), and to calculating doses for laboratory animals (Morris 1995). Two workshops on risk assessment, one sponsored by the National Academy of Sciences of the United States (NAS) and the other by the Environmental Protection Agency (USA), both identified a single pressing need to focus research directed toward the development of biologically meaningful models for toxicity risk assessment. For example, Anderson (1987) pointed out in the NAS meeting 'One of the major problems confronting the regulatory agencies today is the extrapolation of ... toxicology data in animals for the assignment of potential risk in the

human population. Both low-dose and species-to-species extrapolation of toxicology data are needed for proper risk assessment of human exposure to chemicals'. The field is now facing a situation in which the toxicity of hundreds of compounds has been carefully characterized, usually to many significant digits in any number of animal species; however the extrapolation of those meticulously collected results is seemingly capricious. There is a recognized need to substitute sound physiological and biochemical understanding in place of arbitrary and potentially dangerous 'safety factors'. However, reliable physiological data must form the essential foundation of all of these models if they are to be relevant.

Similarly, in comparative medicine, research and therapeutics must often proceed without the luxury of a physiological database to assist decision-making. Success depends upon the use of appropriate, informed estimates in applications ranging from estimating appropriate anaesthetic dosage to use of normal physiological rates and processes as diagnostic tools. Zoological veterinarians are often faced with species that are poorly described and hence poorly understood, the physiology of which can often best be predicted from body size relationships.

This study was designed to supplement other studies (e.g. Arms & Travis 1988, Davies & Morris 1993, Brown *et al.* 1997) to expand the size and reliability of the available database of normal physiological values necessary for biological models (e.g. in the field of pharmacokinetics and human risk assessment), as well as for use as reference values when empirical data are unavailable.

Methods

Criteria for data selection

Our intention in producing this report was to utilize available literature sources to compile groupings of representative data, which could be used as species mean values for our four primary species as well as form a database usable for interpolation and extrapolation

among various other mammalian species. We focused our investigation on those species that are most widely used as model species in studies of pharmacokinetics and risk assessment but whenever possible we supplemented those data with that from additional mammalian species.

Our goal was to compile normal values representative of healthy, resting animals. Hence, we were selective, and only those studies in which the animals met specific criteria were included in the final dataset. The criteria included: thermo-neutral ambient temperature, post-absorptive condition of the animals, no apparent manipulation of blood pressure or cardiac output, and internal consistency of the data. For example, most studies are run at room temperature, which is thermo-neutral for rats, dogs and humans. However colder temperatures, especially in mice, result in an increase in metabolism. Likewise, if animals are not post-absorptive, they will have an elevation of metabolism due to the specific dynamic action of digestion. Any study which lacked a normal control (e.g. for blood flow or cardiac output manipulations) was also excluded, as were studies in which total blood flow to the organs accounted for only a fraction of the cardiac output. We also excluded data if there were any reasons to believe that the animals were not in a true resting state; for example, animals that are trained to run on a treadmill will experience a sympathetic nervous system arousal even when standing quietly on the treadmill. In general, we intended to be as selective as possible: if there were a question as to meeting the stated criteria, we excluded the study. The resultant dataset is exclusive rather than inclusive.

Once the literature sources were selected, we compiled species mean values for each of the variables of interest. Even being as selective as possible, the range of values for any given variable frequently spanned a two-fold or greater range of values. Thus we present a major caveat to the reader that there can never be a definitive set of 'correct' physiological values. There are many reasons for the magnitude of variance in the recorded literature values, two of which are foremost. First, there is unavoidable biological

variability; each individual animal will not only vary relative to its conspecifics, but most of the parameters we report here will vary within an individual diurnally, seasonally, ontogenetically, and are a function of temperature, photoperiod, hydration, reproductive and nutritional states, to name a few factors. Ideally these sources of variance should themselves be separately investigated, though this was not the intent of the present study. Thus even if identical measurements are made on the same individual at different times, under the most strictly controlled conditions, different values will probably result (see Delp *et al.* 1991, Brown *et al.* 1997). For that reason, it is not possible for us to further refine the included values to decipher differences attributable to age, sex or strain of animal, though we acknowledge that these factors may be important in setting, for example, oxygen uptake or the distribution of cardiac output.

A second source of variance is introduced because techniques and equipment vary from investigator to investigator. Hence, while heart weight is essentially invariant over time and can be determined with an inexpensive balance, cardiac output is very difficult to measure, can be estimated using one of several different techniques, and may vary up to 20-fold in an individual animal over a period of a few minutes or even seconds! Needless to say the variance in the measurements of heart weight is much lower than that of cardiac output measurements. By being as selective as possible in including data for this study our intent was to minimize the variability attributed to the experimenter or measurement error; if there were no true control animals due to surgical manipulation, reproductive state (e.g. pregnant females), age (e.g. immature individuals), or nutritional irregularities, we excluded those data. Thus we focused primarily (though not exclusively) on recent studies for which the most currently credible techniques were employed. We also relied very heavily on three excellent papers in particular; human reference values, as well as weight-specific organ blood volumes of all species came largely from the two-paper review (Williams & Leggett 1989,

Leggett & Williams 1991). The most complete dataset for rats we found in a paper by Delp *et al.* (1991).

Physiological 'default' values

Because of the variance inherent in these kinds of measurement, we present the following values as the most 'reliable mean values'. They are not intended to substitute for actual measurements, but rather they serve best as 'default values' when the actual measurements are lacking. Thus we present the data in two different forms for that purpose. The first is in the form of species mean values for the four primary species of interest: mouse, rat, dog, and human. Second we combine these mean values with those for other species, when available, to form body-size dependent patterns that may also be used for comparisons among species. To make the data as accessible as possible, we present them in three tables as well as combined into body-size dependent equations. Together these provide 'emergent patterns' which should be sufficiently robust that they could also suffice as 'default values' even if species other than those for which the equations were developed are investigated. By presenting more than species-specific mean values our intent was to provide potential users of these equations with the ability to make a *first approximation* even for novel situations. Because most of the equations that we present suggest patterns that seem to apply to all the mammalian species it is not unreasonable to expect that they may also apply to species that have not as yet been investigated. Again, these and all predicting equations are not intended to substitute for actual measurements, but only to supply defaults when the measurements are unavailable.

Specific data reduction

We have compiled data from diverse literature sources describing several aspects of the normal anatomy and physiology of four primary mammalian species: mouse, rat, dog and human. When available, data from additional species were combined with those from the four key species. These species

include additional members of the Rodentia (hamster and guineapig), Carnivora (domestic cat), and Primates (rhesus monkey), as well as representatives of the Artiodactyla (cattle, goat, sheep and pigs), Perissodactyla (horse) and Lagomorpha (rabbit). Linear regressions were calculated for the combined data from the four primary species as well as a subset of the additional species for each anatomical and physiological parameter. Readers are directed to the specific references for each regression for the complete list of species included. In general, data from additional species were included to extend the range of body sizes wherever possible. In all instances, values are characteristic of normal, resting adult individuals. For humans, if male and female values differed, male values were used, however this distinction was only important in relative amounts of muscle and fat. Separate regression lines are given for these four key species as well as for the combined data of all species, when additional data were available. In all instances, we have expressed these data in the form of power-law equations in which body mass (weight) is the single independent variable.

Because these data come from many sources, individual organ weights were rarely included in the same reference in which, for example, blood flow to the organ was given. Thus, we first calculated mean organ weights for each species from a variety of sources. Next we calculated weight-specific blood flow to each of the organs. When organ blood flows were presented only as a fraction of cardiac output, we used the species' mean cardiac output. Finally, these weight-specific values were re-calculated as absolute values by multiplying by organ (or entire body) weight. As there is no single body weight for these or any other species, we have selected the following weights for the whole-animal manipulations: mouse 25 g; rat 345 g; dog 18 kg; and man 70 kg. Weight-specific values of organ weight, blood volume and blood flow were converted to absolute values using these body weights.

In order to indicate the strength of the resultant relations, whenever possible we have added three statistics. First, when we used three or more independent sources of

data to derive a single species mean value, two times the standard error of the mean ($2 \times \text{SEM}$) is plotted on the graph and given in the table. Additionally, linear regression equations for 'all' species include the 95% confidence intervals of the plotted line. Finally, the coefficient of determination (r^2) of each line is given. This coefficient, which varies between 0 and 1.0, is a measure of the variance in Y that is attributable to the variance in X . If r^2 is equal to 1.0 the correlation is a perfect one, if it is 0, there is no correlation.

Results

Organ weights, blood flows, and whole animal metabolic functions are presented as mean values ($\pm 2 \times \text{SEM}$) for the four key species (Table 1). These values have also been used to generate regression equations that can serve as predictive equations for all of these weights, flows and physiological functions (Table 2). For example, when whole animal resting oxygen uptake is regressed against body weight, the resultant log-log relationship demonstrates that metabolism varies as $\cong 3/4$ power of body size ($b \cong 3/4$) for these and seven additional species, ranging in body size from a 4 g shrew to a 4000 kg elephant (Fig 1). In all the figures, log-log regressions are presented in which the four key species (mouse, rat, dog and man) appear as filled circles and any additional species as hollow circles. Because metabolism must be supported by the uptake and delivery of oxygen, it is not surprising that cardiac output (Fig 2) and ventilation (Fig 3) also vary with a similar body size scaling, but with intercepts that are respectively 18 and 38 times greater. Two key volumes involved in supporting oxygen uptake, heart weight (Fig 4) and total blood volume (Fig 5) vary linearly with body size ($b \cong 1.0$). In all the figures the 95% confidence intervals for all species are shown as dotted lines. Error bars representing two times the standard error of the mean are shown only for the four key species; if the mean value was composed of fewer than three values then no error bars are provided.

Table 1 Reference values of organ weights, blood flows and selected physiological measures for the mouse, rat, dog, and human

	Units	Mouse	Rat	Dog	Human	References
Organ weights						
Brain	g/kg	24.70 (-)	6.90 (0.73)	5.47 (0.71)	20.80 (1.11)	18, 24, 69, 72, 77, 83, 92
Fat	g/kg	-	49.86 (-)	-	200.20 (3.36)	24, 65, 75, 100
GI	g/kg	42.21 (-)	25.48 (-)	31.94 (-)	18.9 (2.9)	24, 35, 58, 77, 89, 91
Heart	g/kg	5.61 (0.96)	3.74 (0.52)	8.12 (0.62)	4.82 (0.32)	3, 8, 18, 22, 24, 41, 46, 50, 51, 58, 61, 64, 72, 77, 83, 89, 92
Kidneys	g/kg	14.37 (4.43)	9.88 (1.34)	5.00 (1.00)	4.24 (0.21)	18, 22, 24, 50, 51, 58, 72, 77, 82, 83, 85, 89, 90, 94
Liver	g/kg	45.68 (7.86)	38.90 (4.02)	33.67 (8.71)	24.24 (0.80)	9, 17, 18, 22, 24, 28, 50, 51, 58, 72, 89, 90
Lung	g/kg	14.48 (-)	5.62 (1.20)	13.33 (4.97)	8.47 (3.89)	7, 18, 50, 51, 68, 72, 77, 83, 86, 89, 90
Muscle	g/kg	364.00 (-)	353.50 (-)	440.00 (-)	397.17 (11.59)	3, 54, 76, 77
Skeleton*	g/kg	53.30 (-)	62.90 (-)	206.00 (-)	180.70 (-)	3, 54, 76, 77
Skin	g/kg	186.40 (-)	170.99 (-)	91.20 (-)	50.13 (11.50)	14, 16, 24, 51, 58, 62, 77, 89, 90
Blood flows						
Adrenal	(ml)/(100g · min)	-	542.5 (2322.2)	228.21 (83.67)	-	10, 24, 29, 50, 58, 63, 64, 77, 78
Brain	(ml)/(100g · min)	75.50 (-)	113.95 (24.96)	48.26 (12.85)	42.14 (2.39)	8, 21, 24, 27, 34, 35, 42, 57, 66, 69, 70, 71, 72, 78, 83, 84, 93, 95
Fat	(ml)/(100g · min)	-	27.13 (11.43)	16.15 (-)	2.25 (0.56)	8, 24, 44, 78, 88
Heart	(ml)/(100g · min)	662.90 (-)	475.30 (59.43)	100.38 (22.98)	63.46 (83.41)	8, 13, 24, 31, 41, 42, 46, 61, 63, 64, 66, 70, 72, 77, 78, 84, 92, 95, 96, 98, 100
Renal	(ml)/(100g · min)	571.19 (57.30)	468.20 (70.40)	405.60 (56.60)	306.60 (3.50)	1, 6, 8, 20, 24, 36, 43, 53, 55, 61, 63, 64, 66, 67, 70, 72, 73, 78, 83, 84, 95, 98, 100, 101
Liver (hepatic)	(ml)/(100g · min)	43.40 (-)	19.42 (5.96)	26.30 (12.70)	17.84 (2.57)	8, 13, 24, 50, 60, 61, 64, 66, 70, 72, 78, 83, 84, 86, 95, 100

Lung	(ml)/(100g · min)	-	102.80 (24.08)	83.65 (39.20)	24.64 (15.61)	24, 28, 50, 63, 66, 72, 77, 78, 83, 86, 95, 100
Muscle	(ml)/(100g · min)	23.59 (-)	23.70 (17.76)	6.46 (1.92)	2.73 (0.33)	1, 8, 20, 24, 26, 50, 63, 64, 73, 77, 78, 79, 92, 95, 100
Skeleton	(ml)/(100g · min)	-	23.50 (-)	10.90 (3.08)	2.85 (0.90)	24, 39, 60, 87, 88
Skin	(ml)/(100g · min)	18.49 (-)	14.11 (-)	9.10 (2.76)	8.59 (1.29)	26, 50, 60, 61, 70, 77, 100
Splanchnic	(ml)/(100g · min)	192.00 (31.80)	162.10 (19.85)	76.20 (16.24)	59.76 (7.17)	13, 23, 24, 38, 66, 72, 82, 83, 92, 95, 99
Other measures						
Oxygen uptake	(ml)/(kg · min)	25.68 (1.81)	19.84 (1.73)	6.45 (1.70)	4.25 (0.78)	2, 4, 5, 11, 12, 15, 20, 29, 30, 31, 32, 37, 38, 42, 45, 46, 56, 61, 74, 81, 95, 98
Ventilation	(ml)/(kg · min)	1555.2 (282.3)	654.4 (190.6)	318.6 (103.8)	114.0 (19.9)	19, 25, 32, 35, 37, 40, 44, 47, 49, 50, 56, 59, 79, 97
Cardiac output	(ml)/(kg · min)	479.4 (8.76)	290.9 (50.3)	131.9 (22.0)	84.0 (12.4)	24, 28, 32, 35, 37, 48, 50, 52, 61, 63, 66, 72, 77, 78, 80, 82, 83, 84, 86
Lung volume	ml/kg	34.52 (-)	37.19 (5.29)	63.86 (2.05)	58.66 (-)	33
DLO ₂	(ml)/(kg · min · torr)	2.28 (-)	1.80 (-)	2.77 (0.01)	1.50 (-)	33
Blood volume	ml/kg	77.80 (-)	54.87 (19.13)	90.56 (5.20)	77.61 (3.88)	3

*Dry weight

Mass of individual body organs, blood flows and selected whole animal metabolic functions are presented as body mass specific values for the four primary species of interest: mouse, rat, dog, and human. In all instances, table values are the means calculated for that species with two times the standard error of the mean in parenthesis. Data from ¹Ackermann and Veress (1980), ²Adolph (1949), ³Altman and Dittmer (1961), ⁴Altman and Dittmer (1971), ⁵Åstrand et al. (1964), ⁶Badr et al. (1988), ⁷Bennett and Tenney (1982), ⁸Bergo et al. (1989), ⁹Boxenbaum (1980), ¹⁰Breslow et al. (1989), ¹¹Bulow et al. (1987), ¹²Bulow et al. (1988), ¹³Carmichael et al. (1988), ¹⁴Caster et al. (1956), ¹⁵Chiu (1974), ¹⁶Clarys et al. (1984), ¹⁷Coniglio et al. (1979), ¹⁸Crile and Quiring (1940), ¹⁹Crossfill and Weddicombe (1961), ²⁰Dascombe et al. (1989), ²¹De Ley et al. (1987), ²²De Marte and Enesco (1986), ²³Dedrick et al. (1973), ²⁴Delp et al. (1991), ²⁵Diamond and O'Donnell (1977), ²⁶Diana and Kaiser (1970), ²⁷Dimagel et al. (1989), ²⁸Ericsson (1972), ²⁹Faraci et al. (1989), ³⁰Flamm et al. (1990), ³¹Franzen et al. (1988), ³²Frostel et al. (1983), ³³Kern and Engerman (1991), ³⁴Gehr et al. (1981), ³⁵Gjedde et al. (1980), ³⁶Gjedde and Gjedde (1980), ³⁷Green et al. (1990), ³⁸Greenway and Stark (1971), ³⁹Guoping et al. (1989), ⁴⁰Guyton (1947), ⁴¹Hachamovitch et al. (1989), ⁴²Halperin et al. (1986), ⁴³Heller and Horacek (1990), ⁴⁴Herd et al. (1968), ⁴⁵Heusner (1991), ⁴⁶Hintze et al. (1975), ⁴⁷Holloway and Heath (1984), ⁴⁸Holt et al. (1968), ⁴⁹Hussain and Roussos (1985), ⁵⁰In-Nami et al. (1974), ⁵¹Jansky and Hart (1968), ⁵²Johnson and Miller (1968), ⁵³Kalkskog et al. (1988), ⁵⁴Kayser and Heusner (1964), ⁵⁵Kern and Engerman (1991), ⁵⁶Lai et al. (1981), ⁵⁷Law and Ferguson (1987), ⁵⁸Leggett and Williams (1991), ⁵⁹Leong et al. (1964), ⁶⁰Liard (1986), ⁶¹Liard (1988), ⁶²Lindstedt and Calder (1981), ⁶³Lipshitz et al. (1986), ⁶⁴Lucking et al. (1989), ⁶⁵Madsen and Malchow-Moller (1983), ⁶⁶Malik et al. (1976), ⁶⁷Michalkiewicz et al. (1989), ⁶⁸Moffatt et al. (1982), ⁶⁹Morii et al. (1986), ⁷⁰Musch et al. (1987), ⁷¹Nakai et al. (1989), ⁷²Nishiyama et al. (1976), ⁷³Norjawaara et al. (1977), ⁷⁴Olson and Dempsey (1978), ⁷⁵Pitts and Bullard (1968), ⁷⁶Prange et al. (1979), ⁷⁷Quillen and Reid (1988), ⁷⁸Riseberg et al. (1987), ⁷⁹Robertson et al. (1977), ⁸⁰Rochester and Pradel-Guena (1973), ⁸¹Saitin (1988), ⁸²Sarin et al. (1990), ⁸³Sasaki and Wagner (1971), ⁸⁴Schrock et al. (1990), ⁸⁵Selwyn (1986), ⁸⁶Seymour et al. (1987), ⁸⁷Shim et al. (1967), ⁸⁸Simkin et al. (1990), ⁸⁹Snyder et al. (1974), ⁹⁰Spector (1956), ⁹¹Stahl (1967), ⁹²Tabrizchi et al. (1989), ⁹³Takei et al. (1982), ⁹⁴Tidgren et al. (1990), ⁹⁵Tsuchiya et al. (1990), ⁹⁶Tuma et al. (1986), ⁹⁷Vinegar et al. (1979), ⁹⁸Von Ritter et al. (1988), ⁹⁹Wetterlin et al. (1977), ¹⁰⁰Williams and Leggett (1989), ¹⁰¹Woods et al. (1986)

Table 2 Linear regression equations for each parameter presented in Table 1 for mouse, rat, dog and human (four species equations) as well as other species where available

	Units	Four species equations			All species equations			References
		Intercept	Slope	r^2	Intercept	Slope	r^2	
Organ weights								
Brain*	g	8.55	0.785	0.978	8.16	0.716	0.985	7
Fat	g	–	–	–	67.1	1.14	0.913	17
Heart	g	5.28	1.02	0.993	5.68	1.00	0.995	2, 4
Kidneys	g	8.13	0.843	0.999	8.35	0.853	0.998	7, 20
Liver	g	36.1	0.931	0.999	39.4	0.917	0.998	4, 6, 20
Lung	g	9.88	0.986	0.986	9.27	1.00	0.992	4, 5, 7, 20
Muscle	g	383	1.02	0.999	383	1.00	0.999	2, 14, 18
Skeleton	g	94.7	1.18	0.998	93	1.16	0.998	2, 14, 18
Skin	g	121	0.842	0.995	125	0.87	0.996	16, 20
Blood flows								
Adrenal	ml/s	0.016	0.753	0.982				
Brain*	ml/s	0.101	0.704	0.999				
Heart	ml/s	0.224	0.714	0.991				
Renal	ml/s	0.603	0.774	0.999				
Liver (hepatic)	ml/s	0.156	0.856	0.987				
Liver (splanchnic)	ml/s	0.648	0.764	0.994				
Lung	ml/s	0.107	0.889	0.907				
Muscle	ml/s	0.769	0.737	0.984				
Skeleton	ml/s	0.525	0.632	0.971				
Skin	ml/s	0.255	0.741	0.995				
Other measures								
Oxygen uptake	ml/s	0.208	0.766	0.997	0.193	0.725	0.997	1, 3, 10
Ventilation	ml/s	8.72	0.704	0.990	7.72	0.745	0.960	8, 11, 12, 15, 19
Cardiac output	ml/s	3.75	0.786	0.999	3.72	0.750	0.986	9, 13
Lung volume	ml	48.1	1.10	0.996				
DLO ₂	(ml)/(s · torr)	0.046	0.983	0.994				
Blood volume	ml	73	1.02	0.997	71.5	1.01	0.998	2

*Excluding human

Linear regression equations of the form $Y = a \cdot M^b$ in which Y is each of the parameters presented in Table 1, a = the intercept of the regression line when plotted on log-log coordinates, and b is the slope of that regression. The coefficient of determination (r^2) is also presented. Separate equations are given for the four key species and for all species. References for each equation are as in Table 1 for the four species equations and references for additional species are as follows for the all species regressions: ¹Adolph (1949), ²Altman and Dittmer (1961), ³Altman and Dittmer (1971), ⁴Bartels *et al.* (1979), ⁵Bennett and Tenney (1982), ⁶Boxenbaum (1980), ⁷Crile and Quiring (1940), ⁸Crossfill and Weddicombe (1961), ⁹Duda *et al.* (1988), ¹⁰Greenway and Stark (1971), ¹¹Guyton (1947), ¹²Holloway and Heath (1984), ¹³Holt *et al.* (1968), ¹⁴Kayser and Heusner (1964), ¹⁵Leong *et al.* (1964), ¹⁶Lindstedt and Boyce (1985), ¹⁶Lindstedt and Calder (1981), ¹⁷Marringas *et al.* (1986), ¹⁸Prange *et al.* (1979), ¹⁹Schlenker (1984), ²⁰Spector (1956)

Volumes and weights

As is true of heart weight and blood volume, the weights and volumes of most individual organs scale as a constant fraction of body mass ($b \cong 1.0$, Table 2). Thus, skeletal muscle makes up about 39% of body mass in all mammals, total blood volume about 7%, heart mass 0.55% and lung weight nearly 1.0%. However, several organs scale with

an exponent less than one. When $b < 1.0$, the relative weight (fraction of total body mass) is greater in small than large mammals. Because small animals have a much greater surface area relative to their volume than do larger animals, skin weight scales with an exponent of about 0.84. Humans seem to fall below the line for the other species, probably because we have thin skin and no fur. Also scaling with exponents < 1.0

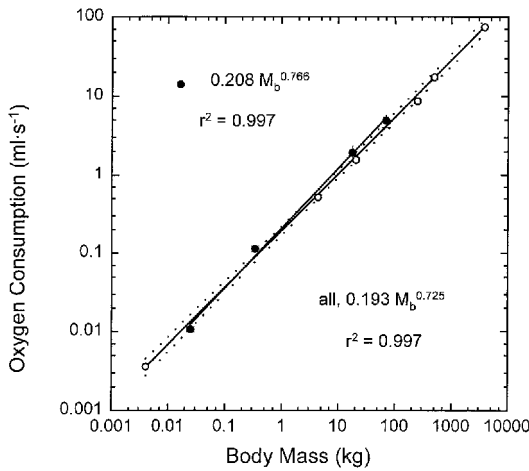


Fig 1 Whole animal oxygen consumption at rest is shown as a function of body mass on a log–log plot in mouse, rat, dog and human (filled circles) and other mammalian species (hollow circles). Dotted lines represent the 95% confidence intervals of the equation including all species. Separate equations (and lines) are given for the four key species and for all species (references for each regression are given in Tables 1 and 2). In both cases, resting oxygen consumption scales as $\cong 3/4$ power of body mass

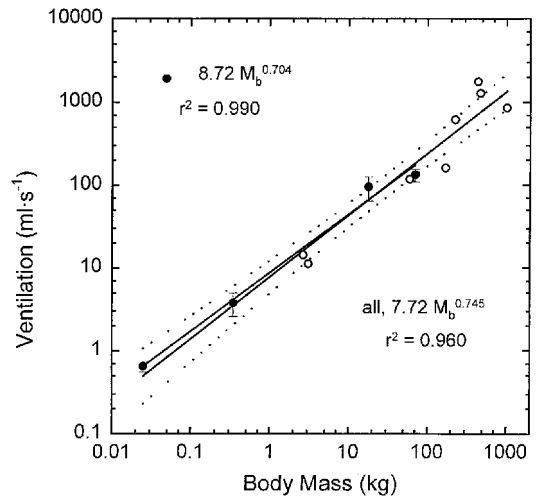


Fig 3 Minute ventilation at rest is shown as a function of body mass on a log–log plot. Symbols and regressions are as in Fig 1. Scaling of minute ventilation is also similar to that of oxygen consumption. In this case the intercept is about 40 times greater, and thus slightly more than two times cardiac output

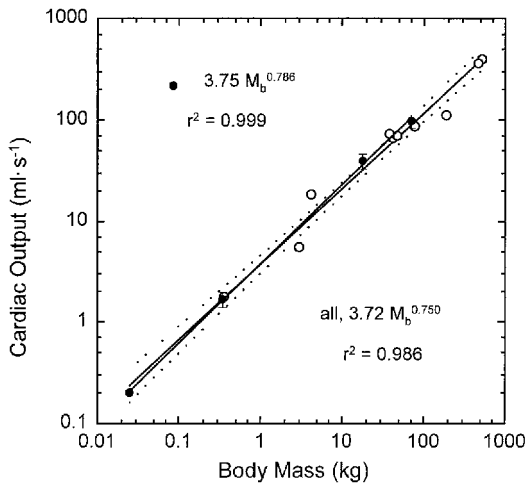


Fig 2 Cardiac output at rest is shown as a function of body mass on a log–log plot. Symbols and regressions are as in Fig 1. Scaling of cardiac output is similar to that of oxygen consumption, but with an intercept about 18 times greater

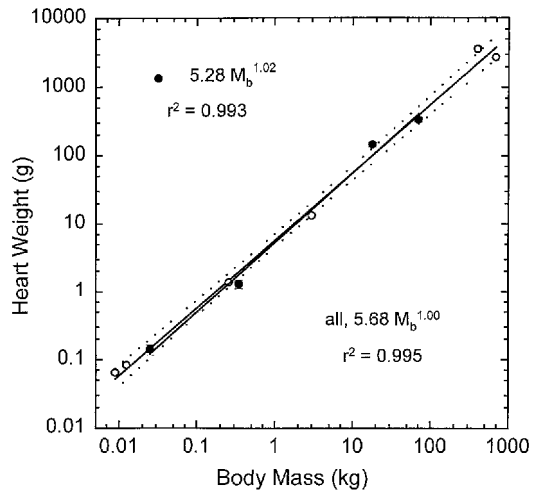


Fig 4 Heart mass is shown as a function of body mass on a log–log plot. Symbols and regressions are as in Fig 1. Heart mass scales as $\cong 1$ st power of body mass, thus the heart consists of a near constant 0.55% of body mass

are the organs responsible for biochemical and neurological ‘control’, liver ($b = 0.93$), kidneys (0.84) and brain (0.78, excluding man). Perhaps this may be because the

number of cells that are being regulated increases with size, but the number of controlled functions is constant. Conversely, if $b > 1.0$, the relative weight increases with

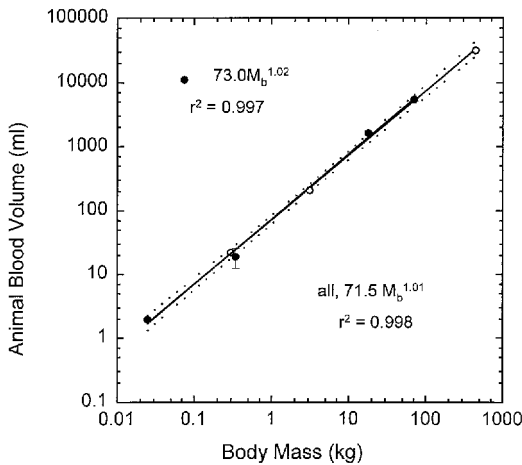


Fig 5 Whole animal blood volume is shown as a function of body mass on a log-log plot. Symbols and regressions are as in Fig 1. Like heart mass, blood volume also scales as $\cong 1$ st power of body mass, thus consisting of about 7% of body mass in all mammals. Note that as cardiac output scales as the $3/4$ power of body mass, the time to circulate the entire blood volume should scale as about the $-1/4$ power of body mass and should thus be shorter in smaller animals

increasing body mass. Because bone strength is proportional to its cross-sectional area, for all vertebrate skeletons to be built with the same structural strength larger animals must have relatively more bone mass. Skeleton mass in the four key species fits on a general mammalian line for which $b = 1.18$. Both skin and bone are large components of body mass; together they comprise about 25% of body mass in all mammals, though the skin is much heavier in small mammals and the skeleton in large ones. Finally, the same pattern is found for the scaling of adipose tissue. Two studies have examined the scaling of adipose tissue mass in mammals: using the data of Pitts and Bullard (1968) we calculated an exponent of 1.14, and Pond (1978) reported an exponent of 1.19. Values from rats and humans (the two species for which we found data) closely fit this predictive relationship. The scaling of fat reserves means that larger animals are able to survive longer periods of fasting, for example, at higher latitudes (Lindstedt & Boyce 1985).

Blood flow of individual organs

The distribution of cardiac output to the individual organs is roughly constant across species; ordinarily the same fraction of cardiac output perfuses each of the organs. Hence, because cardiac output varies as $b \cong 3/4$ so does flow to most of the organs (Table 2). Blood flow to the gastrointestinal (GI) tract, heart, kidneys, skin and skeletal muscle all scale nearly in proportion to $b \cong 3/4$ and hence receive equal fractions of cardiac output, independent of body size. Together, the perfusion of these organs accounts for about 70% of total resting cardiac output, distributed as follows (in a 1.0 kg mammal): GI tract (splanchnic flow) 15%; heart 6%; kidneys 16%; skin 8%; and skeletal muscle 27%. In addition, blood flow to adipose tissue of rats and humans is 5% of cardiac output (hence a constant function of metabolism, $0.182M_b^{0.744}$, $n = 2$), despite the considerably larger contribution that fat makes to the weight of humans (17%) than to rats (5%). Additional examples of organ blood flows are listed in Table 2.

Discussion

The goal of this study was to derive allometric equations to characterize the normal physiology and anatomy of four key species used in the development of physiologically-based pharmacokinetic models. While the resultant set of equations is still far from complete, it is sufficient to suggest several design principles.

General observations and patterns

The four selected species (mouse, rat, dog, human) seem to be fairly typical of mammalian species in general. Thus, the equations we derived for these animals alone are in most instances very similar to the equations we derived for the larger datasets including several additional species. The most notable exception relates to the scaling of brain mass (and brain blood flow) of man. Further, these equations are in excellent agreement with equations from other sources formulated for mammals in general. Examples of the latter are listed in Table 3.

Table 3 Previously published regression equations for physiological parameters

	Units	Literature equations			References
		Intercept	Slope	r^2	
Organ weights					
Brain	g	15.4	0.76	–	1
Brain	g	10.9	0.76	–	15
Fat	g	75	1.19	0.97	17
Heart	g	5.75	0.98	–	1
Heart	g	4.34	1.00	–	9
Heart	g	5.80	0.98	0.98	25
Kidney	g	7.52	0.85	–	1
Kidney	g	7.32	0.85	0.98	5
Kidney	g	7.10	0.85	–	21
Liver	g	33.4	0.87	–	1
Liver	g	37.0	0.85	0.994	4
Liver	g	35.4	0.87	0.988	20
Lung	g	11.6	0.99	–	1
Lung	g	7.72	1.03	0.992	3
Lung	g	11.3	0.99	0.92	25
Skeleton	g	93.0	1.14	–	11
Skeleton	g	61.0	1.09	0.984	18
Skin	g	139	0.94	0.986	16
Blood flows					
Liver (Total)	ml/s	0.923	0.89	0.986	4
Liver (Total)	ml/s	0.841	0.91	0.990	20
Renal	ml/s	0.593	0.82	0.997	21
Renal	ml/s	0.363	0.77	–	6
Renal	ml/s	0.37	0.80	–	1
Renal	ml/s	0.583	0.81	0.980	8
Other measures					
Blood volume	ml	75.6	0.99	0.99	19
Blood volume	ml	55.0	0.99	–	24
Blood volume	ml	65.6	1.02	0.99	25
Cardiac output	ml/s	2.76	0.79	–	9
Cardiac output	ml/s	3.11	0.81	0.96	25
DLO ₂	(ml)/(s · torr)	0.037	0.99	0.994	7
DLO ₂	(ml)/(s · torr)	0.108	0.96	–	10
GFR	ml/s	0.099	0.77	–	1
GFR	ml/s	0.089	0.72	0.98	6
GFR	ml/s	0.065	0.79	0.98	8
Lung volume	ml	46.0	1.06	0.994	7
Lung volume	ml	53.5	1.06	0.96	25
Oxygen uptake	ml/s	0.188	0.75	–	12
Oxygen uptake	ml/s	0.152	0.73	0.96	13
Oxygen uptake	ml/s	0.193	0.76	0.96	25
Ventilation	ml/s	4.50	0.71	–	1
Ventilation	ml/s	5.57	0.76	–	24
Ventilation	ml/s	6.31	0.80	0.96	25
Times and rates					
Lifespan	Years	11.6	0.20	0.59	22
Gestation period	Days	66.3	0.26	0.72	23
Blood circulation time	s	21	0.21	0.96	25
Plasma clearance, inulin	s	391	0.27	0.96	6, 25

(Table 3 continued)

Ventilatory rate	s^{-1}	0.89	-0.26	0.83	25
Heart rate (rest)	s^{-1}	4.02	-0.25	0.77	25
Heart rate (max)	s^{-1}	6.50	-0.15	0.86	2, 26
Muscle shortening rate	s^{-1}	2.93	-0.23	-	14

Regression equations taken from the literature. As in Table 2, regression equations have the form $Y = a \cdot M^b$ in which Y is each of the parameters presented in Table 1, a = the intercept of the regression line when plotted on log-log coordinates, and b is the slope of that regression. The correlation coefficient (r^2) is also presented when available. References for each equation are as follows: ¹Adolph (1949), ²Baudinette (1978), ³Bennett and Tenney (1982), ⁴Boxenbaum (1980), ⁵Brody (1945), ⁶Edwards (1975), ⁷Gehr *et al.* (1981), ⁸Holt and Rhode (1976), ⁹Holt *et al.* (1968), ¹⁰Jones and Longworth (1992), ¹¹Kayser and Heusner (1964), ¹²Kleiber (1932), ¹³Lechner (1978), ¹⁴Lindstedt *et al.* (1985), ¹⁵Martin (1981), ¹⁶Pace *et al.* (1979), ¹⁷Pond (1978), ¹⁸Prange *et al.* (1979), ¹⁹Prothero (1980), ²⁰Prothero (1982), ²¹Prothero (1984), ²²Sacher (1959), ²³Sacher and Staffeldt (1974), ²⁴Schmidt-Nielsen (1977), ²⁵Stahl (1967), ²⁶Taylor *et al.* (1988)

Much of the observed allometry can be explained by what seem to be scaling laws. These have been described previously by category: biophysical constraints, volumes, control organs and frequencies or biological times (for full description see Calder 1984). These categories and their respective scaling may be briefly summarized as follows.

The nearly complementary 0.8 scaling of skin mass and 1.2 scaling of skeletal mass may both be explained by simple *biophysics* that describe size-dependent changes in surface-to-volume and relative skeletal strength. These together comprise nearly 25% of the body mass of all mammals. In general all *volumes* or capacities scale linearly with body mass ($b \cong 1.0$). In addition to the organ masses listed above (Table 2, Fig 4), lung volume, blood volume and pulmonary diffusing capacity also fit this apparent rule (Table 2, Fig 5). While the number of cells increases with increasing body mass, the number of functions controlled does not. Hence, the size of the *control* organs: brain, kidneys and liver, are all relatively larger in small than large mammals. Together these organs account for 20% of the mass of small mammals and less than 5% of that of large mammals. The difference in scaling seems to be accounted for by the mass of body fat, which varies roughly as $b \cong 1.2$.

Finally, there are many time-dependent functions that impact upon animals. Whether these are physiological times spanning milliseconds (e.g. time to peak tension in a contracting muscle) or ecological times lasting years (e.g. population doubling times), 'biological times' vary as a consistent and

predictable function of body size, $b \cong 0.25$ (Table 3). Thus, while life span in a shrew may be 4 years and in an elephant 100 years, the ratio of these and all other times are constant; *all* times are proportionately shorter in shrews than elephants. As rates are the reciprocal of time (1/time), biological rates (heart rate, respiratory rate) vary as the inverse of times, such that $b \cong -0.25$ (Lindstedt & Calder 1981, Mordenti 1986, Lindstedt & Thomas 1994). Consequently, biological rates are consistently and proportionately higher in the smallest mammals. Cardiac and respiratory cycles, drug half-lives, muscle contraction times, protein turnover rates, times of growth to maturity and even longevity are all among the biological times that scale with body mass exponents of nearly 1/4 (Lindstedt & Calder 1981). Because these diverse biological times are quantitatively so similar, it has been suggested that all these rates are coupled to a common physiological clock. While the quantitative support for such a clock is relatively new, the concept of 'physiological time' was introduced over half a century ago by Brody (1945). Hill (1950) refined the concept by suggesting that within an organism physiological time may be as dependable as is chronological time. His speculation was that all physiological events are likely entrained to the same body-size dependent clock. He ended this most intriguing discourse by suggesting that 10 s to a large animal may be physiologically equivalent to one second in a small one, implying that they differ only in pace of life, not in absolute number of life's events.

Scaling of metabolism, the Kleiber equation

A final size-dependent relation can be derived from the empirical patterns listed above. If volumes scale linearly and times as $1/4$, then expressions of volume divided by time must scale as $M^1 \div M^{1/4} = M^{3/4}$. One of the most studied of all volume rates has been oxygen consumption ($\text{mlO}_2 \cdot \text{s}^{-1}$).

The $3/4$ scaling of oxygen uptake reported here (Fig 1), was first described in a now classic paper by Max Kleiber in the relatively obscure agriculture journal, *Hilgardia* in 1932, and reconfirmed multiple times since then. Although this relationship has been strengthened considerably over the past 60 years by the addition of data from literally hundreds of species, this $3/4$ relation is still occasionally challenged (e.g. Heusner 1991). As standard metabolism is set in proportion to $M^{3/4}$, those structures and functions responsible for the uptake, delivery and utilization of oxygen are also constrained to vary with nearly identical body mass exponents. Thus, cardiac output and minute volume both scale as $b \approx 3/4$ (Figs 2 and 3), which suggests two consequences. First, all mammals extract about the same amount of oxygen from the air they are ventilating at rest. For each litre of air ventilated, ≈ 30 ml of oxygen (3% of the air ventilated) is consumed. Second, the extraction of oxygen from the blood is likewise constant: for each 18 ml of blood leaving the heart, one millilitre of oxygen is delivered to the tissues. These observations suggest that fundamental mammalian mechanisms of oxygen uptake and delivery are size-independent.

Pulmonary and cardiac allometry

Lung volume and pulmonary diffusing capacity scale linearly with body mass (Tables 2 and 3). Thus since metabolic rates scale as body mass to the $3/4$ power, per unit volume (or diffusing capacity) small mammals move much more oxygen through their pulmonary structures than do large ones, an apparent 'paradox' (Weibel *et al.* 1981). However, small mammals need less structure because they are able to use that structure with a higher frequency (breathing rates scale as body mass

to the $-1/4$ power, Table 3; Lindstedt 1984). Similarly, because the heart mass scales linearly, the weight-specific work of the heart is higher in small mammals. It is not surprising that myocardial blood flow varies in proportion to myocardial work (cardiac output) rather than to heart mass (Table 2).

Renal allometry

At rest, the kidneys receive the highest blood flow per unit mass of all the organs. Although the weight of the kidneys scales such that their relative size in a mouse is three times that in humans (Tables 1 and 2), the kidneys of all four species receive roughly the same proportion of cardiac output (18%). A roughly constant fraction of the blood flow to the kidneys is filtered through the glomeruli (14% of renal blood flow or 2.5% of cardiac output).

Liver allometry

The liver receives blood from two sources: the hepatic artery and the portal vein. Portal blood flow scales with an exponent roughly equal to that of whole animal metabolism, a finding we find consistent with the task of the liver. However, the arterial blood flow scales with a slightly higher exponent, closer to liver weight, suggesting that in larger animals the liver has a higher weight-specific metabolic rate than in smaller animals. Also, the ratio of portal to hepatic blood flow ranges from nearly six times that of the arterial flow in mice to nearly 3 times arterial flow in man, and is expected to be less than double in an elephant (Table 2).

Organ transit times and size-dependent kinetics

Organ perfusion rates can be combined with total organ blood volumes (from Brown *et al.* 1997) to calculate blood flow transit times (volume \div flow = time). For example, as the pulmonary blood volume scales as $b = 1.0$ and cardiac output as $b = 0.75$, pulmonary transit time must scale as $b = 0.25$. This time scaling has definite consequences on the kinetics of oxygen uptake in the lung, though likely only during exercise when cardiac output is highest (Lindstedt 1984). Although

the perfusion and flow rates differ slightly organ by organ, in general organ transit times are consistently faster in small mammals, thus the metabolic tasks of those organs must be accomplished more rapidly.

Adaptive deviations

The allometric relationships presented above are representative of the majority of eutherian species. However, the caveat must be made that some species will deviate from the predictions made using 'typical' mammals. Even in these cases, the allometric relationships may have predictive utility. For example, the whole animal metabolic rates deviate from the allometric predictions in both sloths and pronghorn antelope. Although initial estimates of metabolic rate using body size predictions would be erroneous, applying a correction factor to further rate processes based upon knowledge of the deviation observed in the metabolic rate is strikingly accurate. Metabolic rate in sloths is about 40–50% that predicted from body mass (McNab 1985). Similarly, cardiac output is about 35% that predicted (Cabral *et al.* 1980), ventilation is about 40% that predicted (Hill & Tenney 1974) and cardiac mass is also about 45% that predicted. In the pronghorn antelope, $\dot{V}O_{2\max}$ is about 5 × that predicted, while structural and functional measures responsible for oxygen uptake, delivery and utilization are similarly increased (Lindstedt *et al.* 1991). While the equations reported here are all derived from eutherian mammals, we anticipate that equations derived for metatherian physiological processes would similarly deviate, in that the slopes of those equations would be similar to those of eutherian mammals but with altered intercepts. Relationships between body mass and anatomical volumes in metatherians would likely be similar to those of eutherian mammals, due to constraints imposed by the same biophysical principles as described for eutherians; however these relationships remain to be described.

Conclusions

We present reference values for selected anatomical and physiological values for

humans and three common laboratory species: mouse, rat and dog. These values are representative for these species but do not represent a single 'true' value for each parameter, but rather can serve as default values when direct measurement is not possible. Of potentially greater utility, these data are presented as allometric relationships that demonstrate the predictability of physiological parameters from body size alone. These relationships allow the modeller to develop general forms for physiological time courses in cross-species comparisons. Further, predictions can be made for physiological processes in species for which data are either lacking or the collection of new data is not plausible (e.g. many rare species).

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