# Contemporary Reviews in Cardiovascular Medicine

# Does Size Matter?
## Clinical Applications of Scaling Cardiac Size and Function for Body Size

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*Abstract*—Extensive evidence is available that cardiovascular structure and function, along with other biological properties that span the range of organism size and speciation, scale with body size. Although appreciation of such factors is commonplace in pediatrics, cardiovascular measurements in the adult population, with similarly wide variation in body size, are rarely corrected for body size. In this review, we describe the critical role of body size measurements in cardiovascular medicine. Using examples, we illustrate the confounding effects of body size. Current cardiovascular scaling practices are reviewed, as are limitations and alternative relationships between body and cardiovascular dimensions. The experimental evidence, theoretical basis, and clinical application of scaling of various functional parameters are presented. Appropriately scaled parameters aid diagnostic and therapeutic decision making in specific disease states such as hypertrophic cardiomyopathy and congestive heart failure. Large-scale studies in clinical populations are needed to define normative relationships for this purpose. Lack of appropriate consideration of body size in the evaluation of cardiovascular structure and function may adversely affect recognition and treatment of cardiovascular disease states in the adult patient. (*Circulation*. 2008;117:2279-2287.)

**Key Words:** cardiomyopathy ■ hypertrophy ■ body size ■ organ size

*C*linical Vignette No. 1: The patient is a very tall 23-year-old competitive rower with a height of 203 cm and weight of 100 kg referred to the clinic for preparticipation athletic screening. He has never experienced syncope, palpitations, or chest pain during exertion and has no significant past medical history, but he occasionally feels "light-headed" at the end of an exhaustive competitive workout. He has no family history of sudden cardiac death or of premature cardiovascular disease. He is actively training 5 to 6 hours per day, 6 days per week in preparation for the upcoming Olympic Games. The examination is remarkable only for a soft systolic ejection murmur, cardiomegaly, and a third heart sound. An ECG is ordered, which is remarkable for sinus bradycardia, a 15-mV R wave in lead aVL, and R-wave voltage in lead $V_5$ plus S-wave voltage in lead $V_1$ totaling 46 mV. On a follow-up echocardiogram, septal and posterior wall thicknesses of 14.5 mm are observed with a left ventricular (LV) internal dimension in diastole of 53 mm. No significant obstructive LV outflow pattern is present, and wall thickness appears symmetrical. On the basis of current echocardiographic criteria, this patient is in the "gray zone" between physiological and pathological hypertrophy. His nonspecific symptoms and lack of other contributing history add to the ambiguity in diagnosis.

*Clinical Vignette No. 2:* The patient is a 66-year-old woman who has a height of 155 cm and a body mass of 49 kg. She has a history of hyperlipidemia and abdominal aortic aneurysm. She comes to the clinic for her yearly ultrasound follow-up, which shows a maximum aneurysm diameter of 50 mm. She is in a "gray zone" in which neither surgical correction nor watchful waiting is definitively indicated.

Considerable evidence is available that biological processes from metabolic enzyme activity[1] to plant and animal metabolic rates[2–4] to cancer metastasis[5] scale with body size over the entire range of organism size and speciation. Cardiovascular structural and functional variables also scale with body size. Compare, for instance, the blue whale, which has a heart mass of 600 kg and a resting heart rate of 6 bpm, with the smallest mammal, the shrew, which has a heart mass of 12 mg and a resting heart rate of up to 1200 bpm.[6] Despite the clear relationship between body size and cardiovascular dimensions and functional parameters, the practice of scaling cardiovascular measurements is poorly applied in adult clinical cardiology. This contrasts with pediatric medicine, in which measurements are universally indexed to body size. The intuitive idea that body growth implies a greater need for scaling in pediatric medicine is, however, not grounded in evidence. In the National Health and Nutrition Examination Survey (NHANES) 1999 to 2002,[7] the average height of men and women 20 years and older was 175 and 163 cm, respectively. With a standard deviation of 18 cm, 90% of the population would fall within the range 127 to 211 cm.
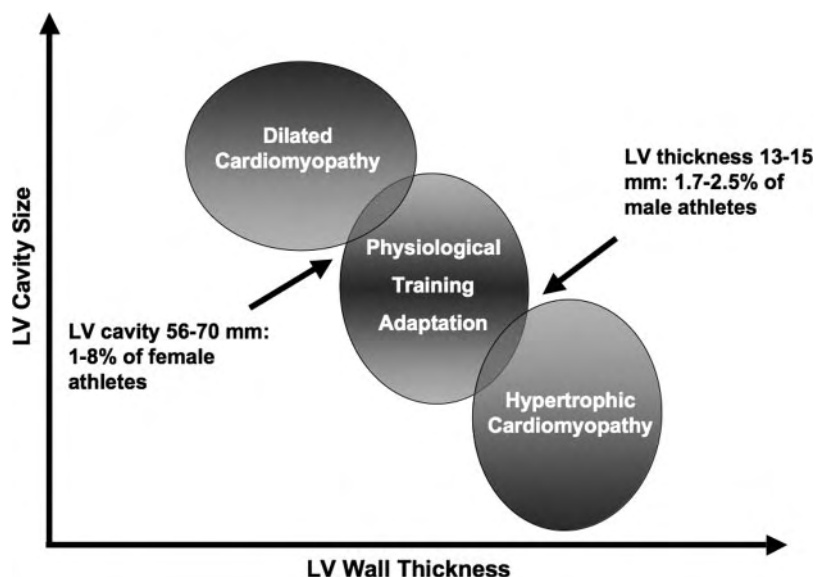
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**Figure 1.** Differential diagnosis of structural adaptations that occur with athletic conditioning.

Contrast this with the average height of 3-year-old boys and girls in the same survey (99 and 97 cm, respectively) and compare that with that of 18-year-olds (175 and 163 cm, respectively). Clearly, variation within the adult population is sufficient to justify scaling of cardiovascular parameters.

In the present review, we discuss which cardiovascular structural and functional parameters are currently scaled and how they are scaled. We present the theoretical basis, empirical evidence, and clinical applications of alternative scaling relationships and propose recommendations for incorporation of cardiovascular scaling into adult clinical practice. Lastly, we propose areas for future investigation to extend the clinical utility of cardiovascular scaling.

## Why Scale Cardiovascular Dimensions and Function?

Accurate quantification of cardiovascular dimensions and functional parameters is crucial to distinguishing disease states from normal variants. Technological advancements in imaging, such as cardiac magnetic resonance imaging and echocardiography, have greatly improved measurement accuracy; however, clinical decisions based on these measurements are difficult when overlap is present between the normal and abnormal ranges for cardiovascular morphological and functional variables. Such areas of ambiguity are common in the evaluation of both cardiac and vascular disease, and the influence of body size on cardiovascular structure and function contributes greatly to these ambiguities.

Research into the morphological changes that accompany athletic training has identified a number of different areas of ambiguity between pathological and physiological cardiac states. Recent evidence suggests that preparticipation screening, including echocardiography as a secondary screening tool, reduces risk of sudden death in athletes by nearly 90%.[8] Aside from the financial and practical difficulties inherent in applying such screening programs widely,[9] one of the most important challenges to effective screening strategies in athletes is distinguishing between normal physiological re-

sponses to long-term cardiovascular conditioning and primary pathology. In studies that have quantified the normal range of cardiac morphological responses to training,[10–14] between 1.7% and 2.5% of elite athletes have an LV wall thickness compatible with a diagnosis of hypertrophic cardiomyopathy.[10,12] Similarly, up to 8% of female athletes may develop LV chamber dilation in the "gray area" between dilated cardiomyopathy and physiological adaptation to training.[11] These findings suggest that a significant area of ambiguity exists (Figure 1) in which LV chamber morphology alone cannot distinguish physiological responses to training from cardiomyopathy. The size differences between athletes and nonathletes, who constitute the majority of populations in which normative ranges for cardiac morphology have been defined, contribute to this diagnostic ambiguity. We use the same normal ranges for a National Basketball Association player (the average US National Basketball Association player for the 2006 to 2007 season is 201 cm tall and has a body mass of 101 kg)[15] as we do for the average American (the average American male is 175 cm tall and 87 kg in mass; Figure 2)[16] and for an elderly Chinese woman (the average height of Chinese women is 160 cm).[17] This divergence in body size is only increasing as athlete morphology is continually selected for success.[18]

The stakes of resolving such diagnostic ambiguity are high. Labeling an individual with a diagnosis of hypertrophic cardiomyopathy means life-long abstinence from competitive sport. Furthermore, yearly clinical follow-up, screening of other family members, and, potentially, cardioverter-defibrillator implantation come at high monetary and psychological costs. Consequently, inappropriate diagnosis may lead to severe psychological, societal, and financial consequences for the excluded athlete. False reassurance may also lead to exposure to increased risk of sudden cardiac death. A diagnosis of dilated cardiomyopathy has similar life-altering implications for patients.

Assessment of LV internal dimensions and filling patterns, the response to deconditioning, family history, and genetic testing have all been proposed as aids to appropriate diagno-
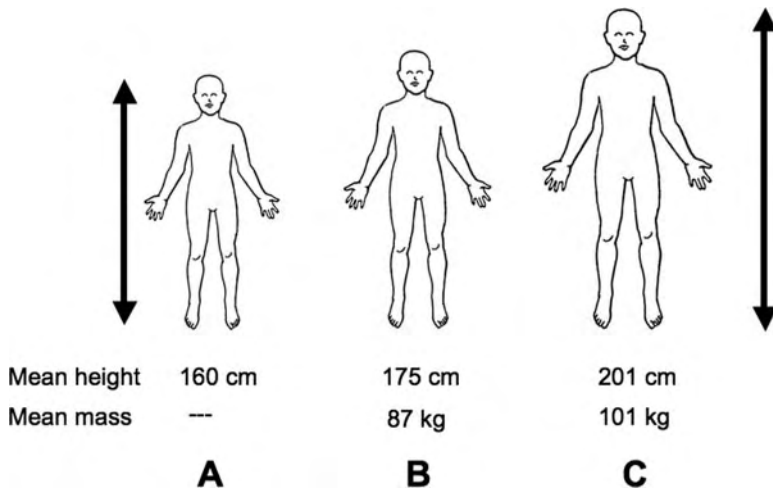
**Figure 2.** Relative size of (A) average Chinese woman in 2001, (B) average 20- to 29-year-old US man according to *NHANES* 1999 to 2002, and (C) NBA player for the 2006 to 2007 competitive season. Data from references 15 to 17.

sis[19]; however, the clinical distinction often remains problematic. A period of detraining may jeopardize an athlete's training status for elite competition, and the expected amount or rate of morphological change with deconditioning in patients with physiological hypertrophy remains uncertain. Genetic testing for 1 of the more than 450 mutations associated with the disease is currently costly, in terms of both initial screening costs and genetic counseling, and is only 70% sensitive.

Areas of ambiguity also exist in the evaluation of vascular structures. Current guidelines for abdominal aortic aneurysms recommend surgical correction at a diameter of 5.5 cm or more and stipulate that aneurysms <4.0 cm do not require intervention. Aneurysms between 4.0 and 5.5 cm, however, fall into a gray area in which surgical correction is neither definitively indicated nor contraindicated. Premature surgical correction unnecessarily exposes patients to high-risk surgical or endovascular procedures, whereas delaying correction of unstable aneurysms puts patients at high risk of rupture and sudden death. The rate of progression of aortic diameter, measurements of wall stress and distensibility,[20,21] coexisting clinical risk factors, and circulating inflammatory and matrix-remodeling biomarkers[22,23] have been associated with rates of aneurysm progression and rupture and may be used to empirically inform this decision-making process. However, the prediction of the probability of aneurysm rupture and subsequent need for preemptive intervention remains difficult and may be aided by appropriate consideration of body size when one evaluates aortic morphology.

## Current Scaling Practices

Despite observations that body size accounts for up to 50% of adult LV dimension variability,[24] scaling of cardiovascular

**Table 1.  Definitions of Scaling Methods Discussed in This Review**

| Scaling Method | Scaling Equation | Relationship |
|---|---|---|
| Ratiometric | Scaled variable=cardiovascular variable/body size variable | Linear |
| Allometric | Scaled variable=cardiovascular variable/(body size variable)$^{scaling\ exponent}$ | Exponential |

structural and functional parameters is currently limited in adult clinical practice. Scaling approaches exclusively use ratiometric relationships, that is, the cardiovascular parameter is simply divided by some measure of body size. The correction is of the form $s=x/y$, where x is the cardiovascular parameter, y is the body size parameter, and s is the scaled cardiovascular parameter (for definitions of the scaling techniques discussed in this review, see Table 1). We have summarized scaling relationships in current use in Table 2. It would not be an exaggeration to say that no cardiac dimensions are routinely scaled in adult clinical practice, but LV mass and LV systolic and diastolic volumes are often scaled via division by body surface area (BSA) in some clinical settings. The use of scaling for functional parameters is more common in clinical practice, with cardiac output and stroke volume routinely scaled to BSA ($L/m^2$) and $\dot{V}o_2$max routinely scaled to body mass ($mL \cdot kg^{-1} \cdot min^{-1}$). In addition, infusions of certain inotropes and vasopressors are commonly dosed on a per-kilogram basis in the intensive care setting.

## Are We Scaling Correctly?

Despite the exclusive use of such ratiometric scaling approaches in clinical practice, theoretical arguments and empirical evidence indicate that indiscriminate use of ratiometric scaling approaches is at best problematic and at worst dangerous. Ratiometric scaling approaches rely on a linear

**Table 2.  Currently Used Anthropomorphic Scaling Relationships for Cardiovascular Variables**

| Cardiovascular Variable | Anthropomorphic Variable | Scaling Method | Scaled Variable |
|---|---|---|---|
| LV end-systolic volume | BSA | Ratiometric | LVESVI |
| LV end-diastolic volume | BSA | Ratiometric | LVEDVI |
| LV mass | BSA | Ratiometric | LV mass index |
| Stroke volume | BSA | Ratiometric | Stroke volume index |
| Cardiac output | BSA | Ratiometric | Cardiac index |
| $\dot{V}o_2$max | Body mass | Ratiometric | $\dot{V}o_2$max index |

LVEDVI indicates LV end-diastolic volume index; LVESVI, LV end-systolic volume index.

relationship between the cardiovascular variable and the body size variable. The relationship is simply not this straightforward in many cases. In addition, mathematical assumptions about the relationship between the correlation and the coefficients of variation for body size and the cardiovascular variable of interest have been shown to be grossly violated in empirical studies.[25,26] A third theoretical argument against indiscriminate use of ratiometric approaches in cardiovascular scaling is drawn from the theory of similarity, which states that relative geometries determine in part the relationships between body size variables.[27] For instance, the LV mass index, which scales a 3-dimensional variable (LV mass) to a 2-dimensional variable (BSA) via simple division, is incompatible with the geometric relationship between the 2 variables. Because ventricular mass is related to the major dimension (ie, radius, ventricular wall thickness, and internal dimensions) raised to the third power, and BSA is related to the body major dimension raised to the second power, LV mass should be proportional to $[BSA]^{3/2}$. This hypothesis has been supported by empirically derived scaling relationships that are dimensionally consistent. These dimensionally consistent relationships contrast to linear regression analysis (analogous mathematically to the ratiometric approach), which yields unphysiological relationships between these 2 variables, such that subjects with zero mass are predicted to have negative LV mass.[26] Furthermore, from an empirical standpoint, appropriate normalization of cardiovascular variables to body size should produce body size–independent scaled cardiovascular variables; however, many cardiovascular variables that have been scaled by ratiometric methods have been shown to correlate with body size. These considerations form the basis for evaluation of alternative scaling techniques.

Allometric scaling approaches divide the cardiovascular variable of interest by a body size variable raised to a scalar exponent. The allometric body size correction is thus given by $s = x/y^b$, where b is defined as the allometric scaling exponent. Body size corrections of this form (1) do not make any assumptions about the variance and correlation between anthropomorphic parameters and cardiovascular parameters, (2) allow for relationships between body size and cardiovascular variables that accommodate different relative geometries, and (3) have been shown empirically to eliminate the effects of body size on cardiovascular structure and function. We will thus focus on allometric scaling as a more appropriate scaling alternative than ratiometric methods.

Consideration should also be given to the most appropriate body size parameter for normalization of cardiovascular variables. Because the cardiovascular system has evolved for efficient distribution of metabolic substrates (in particular, oxygen) to tissues with great potential for use of such substrates, the most appropriate scaling might be found in normalizing the circulatory supply (cardiovascular system) to the metabolically active tissue. Current scaling methods normalize cardiovascular parameters to BSA and total body mass. These anthropomorphic variables quantify both tissue that has great metabolic potential, such as muscle, and tissue with relatively little metabolic potential, such as adipose tissue and extravascular fluid volumes. The contribution of such tissues to BSA and total body mass is particularly large in patients in whom accurate scaling of cardiovascular function is most important. For example, extracellular fluid constitutes 30% to 33% of body weight in patients with congestive heart failure, whereas extracellular water constitutes only 22% to 26% of body weight in healthy men and women.[28] Similarly, adipose tissue constitutes >35% of total body mass in obese patients but may constitute 7% or less of total body mass in elite athletes. These theoretical considerations have been supported by empirical evidence that body composition has significant effects on the accuracy of relationships between body mass and surface area and parameters of cardiac structure[29,30] and function.[31] It is also noteworthy that the most widely used method for calculation of BSA, the Dubois and Dubois regression, is an empirically derived formula that was developed via study of only 9 cadaveric subjects more than 90 years ago.[32] It is therefore unsurprising that significant error in estimation has been observed in up to 15% of patients in more contemporary and diverse subject populations.[33] It may be intuitive to conclude that height is a useful scaling parameter because it is not altered by large volumes of adipose tissue or extravascular fluid; however, fat free mass (FFM) may vary greatly for individuals of similar height, and body size has been shown to interact significantly with cardiovascular variables that were scaled to height.[26] From an empirical and theoretical standpoint, scaling of cardiovascular parameters to tissue mass with high metabolic potential (ie, FFM or lean body mass) is more appropriate than scaling to body size parameters that may not accurately quantify tissue with high metabolic potential.

## Evidence for Allometric Scaling of Cardiovascular Structure

A significant body of empirical evidence supports more general approaches such as allometric scaling for normalization of cardiovascular structural parameters to body size. Allometric scaling of cardiovascular structures with organism size has been observed in both intraspecies[34] and interspecies[35] studies. The majority of human scaling research to date has been performed in athletic populations; however, empirical data on scaling relationships in populations of healthy untrained subjects are also available.

We have summarized empirical evidence for scaling of cardiovascular size parameters in humans in Table 3. These studies generally support dimensionally consistent allometric relationships between cardiovascular structure and FFM, but the relationships between total body mass and BSA and cardiovascular structure are less consistent. Gutgesell and Rembold[38] studied the relationship between cardiac dimensions and BSA in 7 theoretical "subjects" spanning human age ranges whose cardiac dimensions and body dimensions were modeled by values derived from several large studies of normal subjects. The authors found that linear cardiac dimensions (LV, aortic, and pulmonary artery diameter) were proportional to BSA raised to the power of 0.5 and that ratiometric scaling systematically underestimated linear dimensions for small subjects and overestimated linear dimensions for large subjects. Similarly, they found that the relationship between BSA and LV volume was better mod-

**Table 3.    Empirical Evidence for Allometric Scaling Relationships Between Body Size and Cardiovascular Structure in Humans**

| Cardiovascular Variable | Anthropomorphic Variable | Allometric Exponent | Study Population | Reference No. |
|---|---|---|---|---|
| LVIDd | Body mass | 0.24 | 11 Male weightlifters and 45 male sedentary controls | 29 |
|  | BSA | 0.46 |  |  |
|  |  |  | … | … |
| LVIDd | Body mass | 0.25 | 464 Male and female elite junior athletes | 26 |
| LV mass | Height | 2.7 | 611 Pooled normotensive subjects | 36 |
|  | Body mass | 1 |  |  |
|  | BSA | 1.5 |  |  |
| LV mass | Body mass | 0.93 | 11 Male weightlifters and 45 male sedentary controls | 29 |
|  | BSA | 1.67 |  |  |
| LV mass | Body mass | 0.93 | 464 Male and female elite junior athletes | 26 |
|  | BSA | 1.44 |  |  |
| LV mass | Body mass | 0.78 | 142 Healthy, untrained males and females | 37 |
|  | FFM | 1.07 |  |  |

LVIDd indicates LV internal dimension at diastole.

eled by allometric scaling in a dimensionally consistent manner than by ratiometric scaling.[38] In a cohort of 464 junior athletes, the relationships between LV and left atrial dimensions and body mass and BSA were observed to be dimensionally consistent: The authors found that LV mass scaled allometrically to body mass and BSA with scaling exponents not significantly different from 1 and 1.5, respectively. Other LV dimensions were similarly dimensionally consistent. Importantly, these allometric relationships were independent of body size, whereas LV dimensions scaled by ratiometric methods to BSA were not.[26] It is noteworthy that this study used regression constrained to pass through the origin, which yields a high coefficient of determination ($R^2$) compared with methods that are not constrained as such. Similarly, in a study of 142 healthy untrained adult subjects, LV mass scaled ratiometrically with FFM; however, in contrast to the findings in the athletic population, these authors found that LV mass scaled allometrically with body mass with a scaling exponent of 0.8. These scaled LV mass indices were independent of FFM and body mass, whereas LV mass scaled ratiometrically to body mass was not.[37] A pooled cohort of 611 normotensive subjects spanning an age range from infancy to late maturity, however, demonstrated dimensionally consistent relationships between LV mass and all anthropomorphic parameters considered, including body mass.[36] These apparent disparities may result from different age ranges in the studied subjects and from differences in methodology used to determine the relationship between anthropometry and cardiac dimensions. Direct comparisons of scaling relationships with total body mass in athletic and nonathletic populations have yielded similarly varied results. In 1 series, dimensionally consistent scaled cardiac parameters were not different between sedentary subjects and subjects engaged in isometric sports,[29] which indicates that scaling relationships between body mass and LV structures were similar between these 2 groups. Similarly, in a study of 30 endurance-trained adult athletes and 28 untrained adult control subjects, neither LV mass nor LV end-diastolic dimension, scaled in a dimensionally consistent manner to FFM and height, differed significantly between athletes and control subjects.[39] However, these differences persisted in adult athletes engaged in dynamic sports in another study,[40] which indicates that differences in scaling relationships may persist between athletic and sedentary populations.

Allometric scaling has also contributed to the debate about intrinsic differences in cardiovascular dimensions between males and females. Because of the significant size difference between adult men and women, appropriate normalization to body size may minimize gender differences in cardiac size. Although cardiac dimensions generally are larger in men than in women when scaled ratiometrically to body size, evidence exists that allometric scaling minimizes these differences. Gender differences were completely abolished in some studies when cardiac dimensions were scaled allometrically[26,40] but persisted, albeit at reduced magnitude, in other studies.[37,41]

Vascular scaling research has primarily been constrained to interspecies studies, in which vessel diameter and total cross-sectional area scale allometrically in theoretically and empirically derived relationships to mammal mass.[35,42] In these studies, aortic diameter scales with body mass with an allometric exponent of $\approx$0.4,[42–44] whereas capillary density appears to be relatively invariant with regard to body size.[42,45,46] Blood volume appears to scale ratiometrically with body mass,[42,47,48] which provides a rationale for scaling intravenous infusions to this variable. There has been little empirical research to date, however, to quantify allometric scaling properties of vascular structure over the range of body sizes in humans. It remains to be seen whether these relationships are consistent in humans, in whom the range of body mass encompasses a wider range of body compositions than in other mammals. It may be acceptable, however, to extend these allometric relationships to relationships between vessel dimensions and FFM.

**Table 4. Empirical Evidence for Allometric Scaling Relationships Between Body Size and Cardiovascular Function in Humans**

| Cardiovascular Variable | Anthropomorphic Variable | Allometric Exponent | Study Population | Reference No. |
|---|---|---|---|---|
| $\dot{V}_{O_2}$ | FFM | 0.72 Maximum | 24 Adult and 21 youth male elite soccer players | 49 |
| | | 0.60 Submaximal | | |
| $\dot{V}_{O_2}$max | Body mass | 0.91 Males | 75 Male and 49 female young distance runners | 50 |
| | | 0.85 Females | | |
| $\dot{V}_{O_2}$max | FFM | 0.91 Males | 126 Maturing children | 51 |
| | | 0.87 Females | | |
| $\dot{V}_{O_2}$max | Body mass | 0.61 | 94 Females | 31 |
| | Lean body mass | 1.04 | | |
| Q at rest | Height | 1.16 | 970 Normotensive subjects 1 to 85 y old | 52 |
| | Body mass | 0.41 | | |
| | BSA | 0.62 | | |
| SV at rest | Height | 1.78 | 970 Normotensive subjects 1 to 85 y old | 52 |
| | Body mass | 0.62 | | |
| | BSA | 0.93 | | |
| Q at 60% of $\dot{V}_{O_2}$max | Body mass | 0.35 | 337 Men and 422 women: HERITAGE cohort | 53 |
| | FFM | 0.46 | | |
| | BSA | 0.93 | | |
| SV at 60% of $\dot{V}_{O_2}$max | Body mass | 0.49 | 337 Men and 422 women: HERITAGE cohort | 53 |
| | FFM | 0.81 | | |
| | BSA | 0.71 | | |
| Qmax | Body mass | 0.55 | 24 Premenarchal girls | 54 |
| | BSA | 1.08 | | |
| SVmax | Body mass | 0.59 | 24 Premenarchal girls | 54 |
| | BSA | 1.05 | | |

Q indicates cardiac output; Qmax, maximal cardiac output; HERITAGE, Health, Risk Factors, Exercise Training, and Genetics family study; and SV, stroke volume.

## Evidence for Allometric Scaling of Cardiovascular Function

Evidence is also available that allometric relationships between body size and cardiovascular functional variables minimize the confounding effects of body size more effectively than ratiometric scaling methods, particularly in obese patients. We have summarized the evidence for allometric scaling of cardiovascular function in Table 4. In a cohort of 970 normotensive children and adults, normal-weight men and women had resting stroke volumes that were related to BSA with an allometric scaling exponent not significantly different from 1. However, in overweight and obese subjects, these indexed values systematically underestimated stroke volume. The derived relationship between resting cardiac output and BSA in this population was allometric with a scaling exponent of 0.62 and was independent of body size. In contrast, the ratiometrically scaled cardiac index was negatively correlated with BSA.[52] These findings suggest that the current use of the stroke volume index may be appropriate in normal-weight populations but not in overweight or obese patients, in whom the adequacy of stroke volume for a given patient size is underestimated. The currently used cardiac index similarly underestimates the adequacy of cardiac output for larger patients regardless of body composition.

Cardiovascular functional parameters during both submaximal and maximal exercise appear to scale ratiometrically with body size. Allometric scaling of submaximal exercise cardiac output and stroke volume produced size-independent measures of cardiac output and stroke volume and normalized submaximal cardiac output and stroke volume between sexes in the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study cohort, whereas ratiometric methods did not.[53] In premenarchal girls, allometric scaling of $\dot{V}_{O_2}$max eliminated the effects of body size, whereas ratiometric scaling methods did not.[54] Similarly, in athletes, the associations between body size and allometrically scaled $\dot{V}_{O_2}$max were minimal in cross-sectional[49] and longitudinal[50,51] studies, whereas significant correlations between body size and unscaled $\dot{V}_{O_2}$max were observed.

Similar scaling laws appear to govern the time scale of cardiac function. Mammalian heart rate is thought to vary with mass to the power of $-1/4$,[35,43] whereas empirical evidence shows that the PR interval scales allometrically with mass raised to the power of 1/4 in mammals.[55] These "quarter law" relationships are the basis for allometric scaling theory, and although these relationships have been well defined in interspecies scaling studies, the relationships between time scales of cardiac function and anthropometry remain to be elucidated in humans.

Many parameters of cardiovascular function are affected by a complex interplay of factors, some of which may be only indirectly related to body size. For example, whereas heart rate appears to be directly affected by body size, inotropy, preload, and afterload are only indirectly, if at all, dependent on body size. This fact may be at the origin of many of the controversial findings in different subject populations in which 1 or many of these factors may dominantly influence parameters of cardiovascular function.

## Theoretical Basis of Allometric Scaling

The cardiovascular system has evolved for effective distribution of metabolic substrates to tissue with high metabolic potential. Therefore, the leading theories for the physiological basis of allometric scaling relationships appeal to maximization of efficient metabolic substrate distribution. Scaling of efficient transportation networks and energy transduction have been proposed as principal determinants of the scaling properties of biological structure and function.[42,56] In particular, efficient transport of oxygen has been proposed as the primary determinant of efficient vascular network formation.[57,58] Fractal scaling theory, which is based on the concept of structural self-similarity on defined size and time scales, has been used to derive characteristics of maximally efficient energy transportation networks. A discussion of the derivation of these characteristics is beyond the scope of the present review, but the origins of this theory are well described by West and Brown.[59] These theoretically derived network characteristics describe body size–dependent limitations on metabolic rate that correspond to empirical findings and demonstrate that basal metabolic rate is proportional to body mass raised to the power of 0.75.[3,4,60] Maximum metabolic rate also scales allometrically with body size, but faster than basal metabolic rate, such that maximum metabolic rate is proportional to body mass raised to the power of 0.9.[57,61] Some investigators have gone as far as to argue that these fractal scaling components of biological structures are the "fourth dimension" of life.[62]

The genetic origins of anthropomorphic relationships also merit discussion. Total lean body mass has been shown to be a highly heritable trait that is independent of other body size parameters, with 65% of variability attributable to independent genetic effects of quantitative trait loci in 1 series.[63] The relationship between lean body mass and skeletal length has been shown to have genetic origins in providing a "uniform safety factor" for skeletal failure in organisms of different body masses.[64] The consistent and strong relationship between height and FFM (but a weaker relationship between height and weight) has been used as evidence to provide a framework for height-normalized indexes.[65] This approach has some prognostic merit, as was shown by de Simone et al,[66] who demonstrated the superiority of height-indexed LV mass measurements over BSA-indexed LV mass measurements. These findings may suggest that height may be the preferred index for cardiovascular measurements when FFM cannot be determined.

## Practical Aspects of Anthropomorphic Measurements

Practical aspects relating to the clinical use of allometric scaling remain to be addressed. Scaling to FFM requires an accurate assessment of body composition. Dual-energy x-ray absorptiometry (DEXA), isotope dilution, and hydrodensitometry are the current "gold standards" for measurement of body composition; however, their routine use in clinical practice is impractical. Devices such as bioelectrical impedance analysis and skinfold calipers may be viable alternatives for determining body composition.

## Conclusions

In this review, we have described current ratiometric methods for scaling cardiovascular parameters to body size and their theoretical and evidential limitations. In light of the shortcomings of ratiometric scaling methods, we have described the theoretical basis and evidence for allometric scaling as an alternative scaling method.

We propose that cardiovascular parameters allometrically scaled to FFM or, if practical constraints make determination of FFM unwieldy, height in a dimensionally consistent manner may better indicate the normalcy of cardiovascular size and function for a given patient size. Similarly, we propose that cardiovascular functional parameters scaled allometrically to FFM or height according to empirically derived relationships will reduce the confounding effects of body size and improve clinical management. Clinical investigations should be performed to define normative ranges of these indexed values for clinicians' reference. The prognostic applications of these indexed values should then be evaluated for incorporation into clinical decision-making algorithms that depend on precise assessment of cardiovascular structure and function. Reliance on parameters ratiometrically scaled to BSA for clinical decision making should be discouraged. In all cases, but particularly when differences in body mass or BSA may not reflect differences in tissue mass with high metabolic potential (such as in obese patients), unscaled parameters should be considered alongside scaled parameters.

Scaling is routine in pediatric practice, yet adult size variation is equivalent to that of the pediatric population. The time is quite right for a reassessment of our current practice of normalization of cardiovascular variables to body size in adult clinical practice.

### Clinical Vignette No. 1

Bioelectric impedance is used to measure the patient's body fat percentage, which is determined to be 7%. LV wall thickness is normalized to FFM, yielding a normalized value of:

$$14.5 \text{ mm}/(100-7 \text{ kg})^{1/3} = 3.20 \text{ mm}/(\text{kg}^{1/3})$$

Given the currently accepted upper limit of normal for LV wall thickness of 13 mm, as well as the mean FFM calculated from skinfold thicknesses for the 1999 to 2002 NHANES population (data for US male citizens 20 to 29 years of age) of 26.2%, this falls below the estimated upper limit for the scaled LV thickness of 3.26 mm/(kg$^{1/3}$). The patient is

reassured that his cardiac dimensions may fall within the normal range for his size. In accordance with current guidelines, the patient is prescribed a 6-week period without athletic training, after which a follow-up echocardiogram demonstrates septal and posterior wall thicknesses of 11.5 mm. He is told that his increased wall thickness is due to intense endurance athletic conditioning, and he is allowed to resume training.

## Clinical Vignette No. 2

Given the patient's mass of 49 kg, her normalized aortic diameter is 50 mm/(49 kg$^{0.4}$)=10.54 mm/(kg$^{0.4}$). Given that surgical abdominal aortic aneurysm correction is indicated for patients with aortic diameters of >55 mm and a mean body mass from NHANES 1999 to 2002 for people 60 to 69 years of age of 76.4 kg, the estimated normalized diameter at which surgery is indicated is 9.71 mm/(kg$^{0.4}$). Together, the patient and surgeon decide that surgical repair of the abdominal aortic aneurysm is indicated.

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