Allometric Normalization of Cardiac Measures: Producing Better, but Imperfect, Accuracy

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The purpose of scaling organ dimensions is motivated by the possibility of comparing individuals of different body sizes, a potent determinant of organ size. This is useful in comparative physiology, to understand differences among species, as well as in human pathophysiology, to explore changes induced both by body growth during childhood and by diseases during adulthood and maturity. In human studies, scaling meets the necessity of understanding when a physiologic or pathologic process influences organ development, function, or simply dimension, in the attempt to capture diseased conditions even when not clinically evident.

Human heart size has been a major target for studies of this type. The attempt to normalize left ventricular (LV) mass (LVM) for body size is not merely an academic exercise but has strong clinical implications, because, with the exception of age, LV hypertrophy (LVH) is the most potent (and reversible) marker of cardiovascular risk.[1] The awareness of this power is increasing, and the computation of LVM index is increasingly included in echocardiography reports, despite the technical problems related to correct ultrasound orientation and the identification of interfaces.[2]

All types of anthropometric parameters present substantial limitations, especially when normalizing cardiac structural parameters during childhood.[3,4] Nevertheless, by strong tradition, body surface area (BSA) is the indexing variable most often used to normalize for body size LVM, LV dimensions, and LV volumes in adults. The most popular formula was developed by Du Bois and Du Bois[5] more than a century ago but has never been validated in obesity. BSA has been used ratiometrically to normalize LVM (i.e., assuming that LVM values are linearly proportional to BSA values). Human growth, however, is not isometric (meaning that changes in body size due to growth or other physiologic processes do not lead to proportional changes in organ size), and therefore, that assumption does not fit with physiology.

In addition, on the basis of geometric considerations, a three-dimensional parameter (such as LVM) cannot be a linear function of a two-dimensional measure (such as BSA). This geometric mismatch was nicely represented in a simulation, demonstrating that the power regulating the relation between LVM and BSA is not 1 (linear) but 1.5 (exponential), as would be expected.[6] In other words, to make linear the relation between LVM and BSA, BSA needs to be raised to the power of 1.5, resulting in a cubic function, compatible with the three-dimensionally shaped LVM (i.e., m^2 raised to the power of $1.5 = m^{2\times1.5} = m^3$).

THE BODY WEIGHT ISSUE

Following historical studies,[7] the great comparative physiologist Knut Schmidt-Nielsen spent a substantial part of his life working on scaling,[8] demonstrating that the relations between body size and organ size are in fact allometric (i.e., changes in organ size are not proportional to changes in body size induced by growth or other physiologic processes) and not isometric. This means that they are regulated by power regressions of the type $Y = a \times X^b$, where the coefficient of regression b is the allometric scaling factor Schmidt-Nielsen called the "allometric signal."

The most practical procedure for scaling, therefore, would be to normalize organ size using the allometric signal of body weight (kilograms). This is what has been done for heart weight in a series of 104 mammalian species.[9] As described by Prothero,[9] the allometric regression regulating this relation across the species was the following:

$$\text{Heart weight} = 5.8 \times \text{kg}^{0.98}.$$

As expected, the allometric signal of body weight was very close to 1 (both terms of the equation share a common three-dimensional shape). Because the normal left ventricle represents 40% to 45% of the total weight of the normal heart, this equation indicates that LV weight in a healthy man of 80 kg should be 170 to 190 g.

Taking the opportunity of the large range of body sizes in our laboratory's database, as an example, we tested Prothero's[9] equation in three random subjects with very different body weights. In a normotensive, normal-weight man with a perfect body mass index (Table 1), the equation was accurate in predicting the observed LVM. However, when applied in a class III obese patient, the true LVM was overestimated by 62%. Even more surprising, in a very small girl with anorexia nervosa, the degree of overestimation was even greater (93%).

The reason for this overestimation in conditions of abnormal body size lies in the different body compositions of the three subjects. Both the obese and the anorectic patients have deficits of fat-free mass, relative in the obese patient and absolute in the presence of anorexia. The alteration in body composition explains the impossibility of reliably predicting LVM from weight in individuals who substantially deviate from a "normal" body shape and poses doubts regarding variables derived using weight, such as BSA. And, in fact, the use of normalization to BSA substantially underestimated the prevalence of LVH and the population risk attributable to LVH, when applied in a population with high prevalence of obesity.[10]

Ideally, because the left ventricle is a muscle, LVM should be normalized for fat-free muscle mass. An easily measured surrogate of fat-free mass is body height. In mammals, height (or length) is a measure of the skeletal size, the architecture supporting the muscle mass. The skeleton, therefore, is genetically linked to given amounts of muscle,[11] and skeletal length (or height) is biologically linked to a genetically programmed ("ideal") fat-free body mass.

Thus, body height is an acceptable surrogate of what should be fat-free mass in normal conditions. Because of the geometric

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Table 1 Examples comparing echocardiographic LVM and value predicted by BW, using the equation from Prothero[9]

Variable	Normal	Obesity	Anorexia nervosa
Sex	Male	Male	Female
Age (y)	39	48	17
Weight (kg)	81	151	34
Height (m)	1.80	1.72	1.58
BMI (kg/m^2)	25	51	14
Blood pressure (mm Hg)	118/64	126/82	92/60
Observed LVM (echocardiography) (g)	188	220	43
Predicted LVM (based on BW) (g)	194	356	83
LVM, difference from observed (g [%])	6 (3)	136 (62)	40 (93)

BMI, Body mass index; *BW*, body weight.

disproportion between height (a linear measure) and LVM (a three-dimensional variable generated by a cubic function), the relation cannot be linear, because LVM should approach a cubic function of height. And, in fact, when examining a very large range of body sizes, encompassing nearly the entire life span (between 3 months and 70 years of age) and maintaining normal proportions between weight and height (i.e., in normal-weight individuals), the allometric signal found to linearize the relation between LVM and height is 2.7, close to 3.[12]

THE AGE ISSUE

The allometric signal of 2.7 for height changes when reducing the age range and confining the analysis to childhood or adulthood. In the Cincinnati children, the allometric signal for height was 3,[13] whereas in adults in the Framingham Heart Study, the allometric signal was 2.0,[14] very close to the allometric signal (2.1) we found in our adult reference subpopulation.[15] More recently, an even lower allometric signal (1.7) was reported in an adult population combining the Multi-Ethnic Study of Atherosclerosis and the Asklepios studies.[16] These disparities suggest that the age range of the reference population is important to generate the allometric signal of height.[4]

During infancy, body size is the most important determinant of heart size. During body growth, other stimuli overlap with changes in body size, and the variance of heart size explained by body size is diluted.[15] From early infancy to puberty, relation of residuals of the regression between LVM and height$^{2.7}$ plotted versus age shows a heteroscedastic distribution (i.e., the scatter about the zero line increases with age), graphically representing the progressive superimposition of stimuli other than body size during body growth.[15]

In contrast, in the range of age comprising 18 to 70 years, this scatter was near constant across the range of age (homoscedastic distribution). Once body development is completed, the variance in LVM consolidates around a number of stimuli that vary from individual to individual and with diseased conditions. Thus, the scaling effect of body size decreases with aging and with the stabilization of body shape in adulthood.[17] This age effect is likely the main reason for the difficulty of scaling heart size and function in neonates and children.[18-20] We postulate that, even for children, consideration of the full age range (i.e., not limited to children and adolescents) might produce a better way to normalize for body size, because the allometric signal incorporates information on changes of the relations between heart dimension and body size with aging.

It is therefore clear that the allometric signal of height changes as a function of age span. The range of the reported allometric signals declines from 3 in children to 1.7 to 2.1 in adults. The question is, What is the best allometric signal to use for the identification of pathologic and harmful changes? In particular, should information on body growth, included in the allometric signal of height obtained over the entire age span (i.e., 2.7), be preferable to that obtained only in adults (1.7–2.1)?

In both the Strong Heart Study and the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale study, the performance of the lower allometric signal of height (2.13) was not significantly better than the allometric signal obtained using the entire age span (2.7), especially when obesity was highly prevalent[10,21]; in either condition, the population risk attributable to LVH was 17%. However, when using lower allometric signals (1.7), performance was clearly reduced,[22] suggesting that even small differences might influence our ability to identify harmful conditions. We are now working to verify these issues in other population-based studies.

THE BODY COMPOSITION ISSUE

In the Strong Heart Study, a population-based study of American Indians with a very high prevalence of obesity, Bella *et al.*[23] found that the magnitude of LVM was closely and independently correlated with fat-free mass but not with adipose mass in both men and women. Their findings provide further evidence that using weight-based measures to normalize heart size in the context of obesity does not fit with physiology. Thus, though the ideal approach might be normalization by lean body mass, this approach might be impractical and does not necessarily resolve the problem of finding a method able to identify obesity-related deviation of cardiovascular geometry from normality, because lean body mass also increases in obesity.[24] Results from studies on "sarcopenic obesity" reinforce this scenario.[25]

Height offers the opportunity of a simple detectable measure, which expresses the genetically programmed amount of muscle mass, which represents about 56% of the body weight in a normal-weight, nonathletic man,[26] allowing detecting the highest proportion of abnormalities related to obesity. Although in longitudinal studies, normalization by the allometric signal of height produces slightly lower hazard ratios than normalization by BSA,[10,27] this method nearly doubles the proportion of obese patients with LVH, resulting in the highest population-attributable risk.[10]

The use of allometric relations has also been extended to normalize LV and left atrial (LA) dimensions. In contrast to what has been reported for LVM, Neilan *et al.*[28] found that body weight, raised to a power close to the cubic root, was the anthropometric measure that best accounted for the explained variance of LA linear dimension. The study was conducted in a large population with an enormous range of body mass indexes (15–86 kg/m^2), including obese subjects, and the allometric power reported for weight well represented the geometric differences among variables. Others found that in an obese population, height was a better normalization for LA dimension than both weight and BSA.[29]

In this issue of *JASE*, Zong *et al.*[30] report their evaluation of a series of obese individuals, in which they generated a number of allometric signals for height, weight, and BSA, to normalize LA and LV dimensions and volumes. In contrast with the findings in the heterogeneous, albeit very large, population of Neilan *et al.*,[28] they found that the

reported allometric signals of height obtained the best normalization of all parameters of chamber dimension they had used.

Similar to considerations already developed for LVM normalization, also in the case of evaluation of chamber dimensions or volumes, the apparent inconsistency among the different studies may be explained with analysis restrains imposed by the use of a particular range of both age and body size. The peculiarity of the study by Zong *et al.*[30] lies exclusively in the investigators' use of a population of obese subjects to generate allometric signals for BSA and height, to normalize LV and LA chamber dimensions and volumes. The authors, therefore, confined their analysis to the pathologic condition for which most of the allometric approach is suggested.

The results of this study are interesting, because they allow a better understanding of how the allometric signals might change in different conditions of body build and in different populations. Neilan *et al.*[28] studied a large range of body weights, including overweight and obese individuals. The coefficient of variability of body weight in that adult sample was 24%, compared with the fourfold lower variability of height (6%). A better correlation with measures of body weight could be expected in that setting. In Zong *et al.*'s[30] study, the coefficient of variability for body weight was lower (17%) than in Neilan *et al.*'s study, whereas that for height was identical, thus better balancing the variability of the two anthropometric parameters. In these conditions, Zong *et al.* found that allometric signals of height were the best measures to account for body size in obesity, when examining chamber size.

Another important aspect is that the allometric signals found in Zong *et al.*'s[30] study are lower than in that of Neilan *et al.*[28] This is due to the different body compositions of the two population samples (Table 2).

In Neilan *et al.*'s[28] study, the allometric signals are roughly close to what might be geometrically expected, except for height (the allometric signal could be expected to approximate 1). Thus, LA dimension was approximately a square root function of BSA and a cubic root function of weight. The reason for the substantial deviation of the allometric signal of height from what would be expected is unclear but might be related to the selection of individuals with normal LA dimensions (the coefficient of variability was only 13%). In contrast, in Zong *et al.*'s[30] study, the allometric signals are substantially distant from what would be geometrically expected, and this is due to the loss of the normal allometric proportions due to the abnormal body composition in obesity.

According to this scenario, using an allometric signal found in an obese population to identify abnormalities in obesity would be tautological. Identification of obesity-related abnormalities should be performed using distributions of variables in reference normal-weight, normotensive populations.

Table 2 Comparison of allometric signals for anthropometric measures to be used for normalization of LA dimension, in Neilan *et al.*'s[28] large registry including a minority of obese individuals and in Zong *et al.*'s[30] series including only obese subjects

Variable	Allometric signal	
	Neilan *et al.*	Zong *et al.*
Height	0.42	0.20
Body weight	0.26	0.07
BSA	0.45	0.16

CONCLUSIONS

Although limited by the lack of considerations of interactions, the use of any measure of body size might be legitimate depending on the objective of the comparison. If there is a need to explore the effect of stimuli modifying LV geometry (i.e., LVM and/or chamber size), removing the potential effect of obesity, body weight, or BSA might be appropriate, because normalization for weight or any variable including weight tends to offset obesity-related differences.[10,31] But if the goal of the analysis is to highlight (also or only) the effect of obesity, the use of weight or BSA to normalize parameters of heart geometry would be misleading, because this approach would severely underestimate the effect of obesity. In one of our first applications of the allometric criteria in a population of New York employees,[32] the prevalence of LVH was 29% in normal-weight and 33% in obese subjects (P = NS) with BSA normalization. However, using height$^{2.7}$ as a normalization factor, the prevalence of LVH remained stable in normal-weight individuals (30%), but increased to 52% in obese subjects ($P < .001$).

In nonobese subject, the type of anthropometric measure for normalization does not affect the detection of alterations.[21] In contrast, in a population with a large prevalence of obesity, using weight or BSA offsets the effect of obesity, reduces the prevalence of LVH, and might paradoxically increase the prevalence of concentric LV remodeling,[33] which would not make sense from a physiologic perspective.[34] Using weight or BSA in obesity, heart size is also normalized for adipose mass.

Because in obesity, fat-free mass also increases, the possibility of overestimating LVH using height has been pointed out in children.[3] However, we have no evidence to support the assumption that the excess of LVM required to support a supraphysiologic amount of lean body mass is benign.[35] Much needs to be done in this field to refine our ability to compare different body builds and to identify abnormalities related to obesity. Also, aspects of pump performance might be subjected to the same framework, as we have shown by studying stroke volume and cardiac output.[36]

The most relevant problem remains LVM, because of the impact of LVH on prognosis and the very different population-attributable risks that result from different types of normalization.[10,22] We suggest using methods of normalization that maximize population-attributable risk, which is the most important measure of incident disease for programs focused on disease prevention.

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