Limitations of Expressing Left Ventricular Mass Relative to Height and to Body Surface Area in Children

Bethany J. Foster, MD, MSCE, Tao Gao, MD, Andrew S. Mackie, MD, SM, Babette S. Zemel, PhD, Huma Ali, MD, Robert W. Platt, PhD, and Steven D. Colan, MD, *Montreal, Quebec, Canada; Edmonton, Alberta, Canada; Philadelphia, Pennsylvania; Boston, Massachusetts*

Background: Left ventricular (LV) mass varies in proportion to lean body mass (LBM) but is usually expressed relative to height or body surface area (BSA), each of which functions as a surrogate for LBM. The aims of this study were to characterize the adiposity-related biases associated with each of these scaling variables and to determine the impact of these biases on the diagnosis of LV hypertrophy (LVH) in a group of children at risk for LVH.

Methods: In a retrospective study, LV mass was estimated using M-mode echocardiography in 222 healthy nonoverweight reference children and 112 children "at risk" for LVH (48 healthy overweight children and 64 children with hypertension). LBM was estimated for all children using validated predictive equations and was considered the criterion scaling variable. *Z* scores for LV mass for LBM, LV mass for height, and LV mass for BSA were calculated for each child relative to the reference group. The performance of height-based and BSA-based *Z* scores were compared with that of LBM-based *Z* scores at different levels of adiposity (estimated by the *Z* score for body mass index for age [BMIz]).

Results: Among healthy normotensive children, LV mass–for–height *Z* scores were greater than LV mass–for–LBM *Z* scores at higher values of BMIz and lower than LV mass–for–LBM *Z* scores at lower values of BMIz (R^2 = 0.52, $P < .0001$). LV mass–for–BSA *Z* scores for agreed well with LBM-based *Z* scores at BMIz < 0.7 but were lower than LV mass–for–LBM *Z* scores for at BMIz > 0.7 (R^2 = 0.31, $P < .0001$). Compared with 13% of at-risk children classified as having LVH on the basis of LV mass for LBM > 95th percentile, 30% and 11% had LVH when LV mass was scaled to height and BSA, respectively.

Conclusions: Scaling LV mass to BSA in children results in less misclassification with respect to LVH than does scaling to height. (J Am Soc Echocardiogr 2013;26:410-8.)

Keywords: Left ventricular hypertrophy, Pediatric, Percentile curves, *Z* scores, Indexing, Scaling

Left ventricular (LV) mass is routinely measured during echocardiography in an effort to determine whether LV hypertrophy (LVH) is present. Normally, LV mass should be proportional to body size, so measures of LV mass must be normalized to determine appropriateness relative to body size. This is particularly important in children, among whom variability in body size is large. There has been some controversy regarding the best method of normalizing LV mass,[1-3] and there have been calls to develop a standardized approach.[4] When deciding how best to normalize LV mass for body size, two separate factors must be considered: the normalization method and the most appropriate body-size variable against which to normalize LV mass measurements.[5]

Most prior studies considering the question of how best to normalize LV mass for body size conflated the two issues of normalizing variable and normalizing method.[1,6] Allometric methods (in which LV mass is divided by a body-size variable raised to a power) applied to one scaling variable were compared with ratiometric methods (in which LV mass is simply divided by a body-size variable) applied to another variable, making it impossible to separate the importance of the scaling method from that of the scaling variable. Even when a consistent scaling method was applied, comparisons did not include all the most physiologically relevant scaling variables.[7] The

From the Department of Pediatrics, Montreal Children's Hospital (B.J.F., H.A., R.W.P.), and the Department of Epidemiology, Biostatistics and Occupational Health (B.J.F., T.G., R.W.P.), McGill University, Montreal, Quebec, Canada; the Department of Pediatrics, Stollery Children's Hospital, University of Alberta, Edmonton, Alberta, Canada (A.S.M.); the Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania (B.S.Z.); and the Department of Pediatrics, Boston Children's Hospital Harvard University, Boston, Massachusetts (S.D.C.).

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Reprint requests: Bethany J. Foster, MD, MSCE, Montreal Children's Hospital, 2300 Tupper Street, Montreal, QC H3H 1P3, Canada (E-mail: *beth.foster@muhc.mcgill.ca*).

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Abbreviations
BMIz = Body mass index *Z* score
BSA = Body surface area
LBM = Lean body mass
LMS = Lambda mu sigma
LV = Left ventricular
LVH = Left ventricular hypertrophy
2D = Two-dimensional

question of the most appropriate body-size variable against which to normalize LV mass measurements has not yet been adequately addressed. This issue has become increasingly important as the prevalence of obesity has increased. The most commonly used LV mass scaling variables (height and body surface area [BSA]) may introduce important bias in the setting of overweight or obesity. Several studies concluded that LVH is significantly associated with childhood obesity, without fully accounting for the potential impact of the choice of LV mass scaling variable on diagnosis of LVH.[8,9]

It has been demonstrated repeatedly that LV mass is strongly determined by lean body mass (LBM).[2,5,10-15] LBM explains more of the variability in LV mass than either height or weight alone,[3,11-14] and when LV mass is expressed relative to LBM, sex differences are eliminated.[10] Cardiac output also scales best to LBM.[15] However, LBM is not easily measured in the clinical setting. Therefore, other measures, including height, weight, and BSA,[16,17] have been used as surrogates for LBM. However, these LBM surrogates have important limitations.

BSA is estimated from height and weight using predictive equations. BSA depends strongly on weight and thus has been criticized as a scaling variable for LV mass, particularly among obese individuals.[6] Because adipose tissue makes up a greater proportion of the weight in obese than in nonobese individuals, there is concern that scaling LV mass to BSA may result in underestimation of relative LV mass among overweight subjects. This theory is based on the observation that compared with lean tissue, fat is less metabolically active and therefore creates less cardiac demand.[11]

In recognition of this potential problem, height has been advocated as a more appropriate variable against which to normalize LV mass.[6,18] However, height alone may be a suboptimal surrogate for LBM. There is considerable variability in LBM among individuals of the same height. Importantly, an overweight individual will have not just a higher fat mass but a higher LBM than a normal-weight individual of equal height.[14,19,20] As a result, expressing LV mass relative to height may result in overestimation of the relative LV mass among overweight individuals.

We hypothesized that expressing LV mass relative to height would result in increasing overestimation of relative LV mass with increasing adiposity and that expressing LV mass relative to BSA would result in increasing underestimation of relative LV mass with increasing adiposity. We sought to characterize the adiposity-related biases associated with using each of height and BSA as scaling variables for LV mass and to compare the performance of each scaling variable with that of LBM with respect to the ability of each to identify LVH in a group of children at risk for LVH; LBM was considered a "reference standard" scaling variable. To increase the accessibility of LBM as a potential scaling variable, we developed and validated predictive equations to estimate LBM from easily measured variables; details of the development of these equations are published elsewhere.[21] We applied the same normalizing method to each scaling variable to ensure that observed differences were due to scaling variable and not to method.

METHODS

This was a retrospective study, conducted using echocardiograms of children seen for clinical evaluation in the echocardiography laboratories at Boston Children's Hospital and Montreal Children's Hospital. Only children free of congenital lesions were included in this study.

Healthy Normotensive Subjects

Healthy, nonoverweight children (body mass index for age < 85th percentile[22]; $n = 222$; age range, 5–21 years) and otherwise healthy overweight children ($n = 48$) were all evaluated in Boston. These subjects were included in a prior research study conducted at Boston Children's Hospital[23] (the protocol was approved by the institutional review board, and all subjects or their guardians gave written informed consent when required). All subjects were free of systemic disease; none had a family history of cardiomyopathy. All subjects were reevaluated 1 year later to verify that they remained free of any identifiable systemic disorder, including hypertension. The 222 nonoverweight children formed the reference group used to generate the reference centile curves. Overweight subjects were not included in the reference group, because of concern that overweight may be a risk factor for LVH, even in the absence of hypertension.[8,9] Race was not recorded.

Subjects "at Risk" for LVH

A group of 112 children considered to be "at risk" for LVH was assembled by combining the 48 healthy overweight children from Boston with 64 hypertensive children studied at Montreal Children's Hospital. To identify hypertensive children, we reviewed the medical records of all children evaluated in the Montreal Children's Hospital Division of Nephrology between July 1999 and June 2006 and identified all those assessed for hypertension; all children assessed for hypertension for whom cardiac echocardiography was done, and who were free of congenital lesions, were included. Race was not recorded.

Figure 1 illustrates the composition of each of the reference, healthy overweight, healthy normotensive, and "at risk for LVH" groups.

Echocardiography

Echocardiography was performed using commercially available cardiac ultrasound scanners and recorded on videocassettes. Each study was reviewed by a single pediatric cardiologist at each site for the purposes of this study. We measured septal, free wall, and LV ventricular chamber dimensions at end-diastole, where end-diastole is defined as maximum dimension. M-mode echocardiograms were recorded from parasternal short-axis views using the tissue-blood interface (inner edge to inner edge), and values were calculated as the average of three successive heartbeats. At the Boston site, the LV surface of the ventricular septum and the endocardial and epicardial borders of the LV posterior wall were hand digitized with a computer-based digitizing station using custom software. LV septal, free wall, and chamber dimensions were calculated from the digitized borders as continuous variables throughout the cardiac cycle. In Montreal, electronic calipers were used for all measurements. LV mass was estimated using the Devereux equation.[24] We used M-mode rather than two-dimensional (2D) images because this is the method used most frequently in quantitative echocardiographic research in children.[8,9,16,17,25]

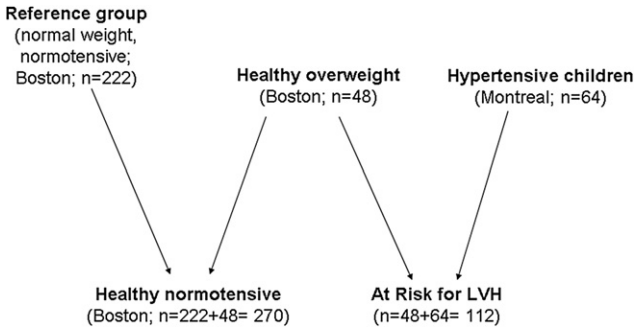

Figure 1 Normal-weight, normotensive, healthy children formed the reference group and were combined with 48 otherwise healthy, normotensive, overweight children to form the healthy normotensive group. In addition, a group at risk for LVH was assembled by combining the 48 healthy normotensive overweight children with a group of 64 hypertensive children.

Anthropometrics

Height was measured to the nearest 1 mm and weight to the nearest 0.1 kg in all participants. Body mass index was expressed as a *Z* score relative to age and sex (BMIz); BMIz values were calculated using the growth curves of the Centers for Disease Control and Prevention, National Centers for Health Statistics.[26] BSA was calculated using the Mosteller equation (BSA = $\sqrt{}$[(height × weight)/3,600]).[27] LBM was estimated for all participants using validated sex-specific predictive equations.[21] The predictive equations were developed using LBM as measured by dual energy x-ray absorptiometry in 437 healthy girls and 399 healthy boys aged 5 to 21 years. The equations were validated in two independent samples and shown to predict LBM within 5% of measured LBM, with no evidence of bias by age or level of adiposity. Equations were developed both including and excluding race. The equations excluding race were used in the present study. The equation for male subjects was ln(LBM) = −2.8990 + 0.8064 × ln(height) + 0.5674 × ln(weight) + 0.0000185 weight^2 − 0.0153 × BMIz^2 + 0.0132 × age. The equation for female subjects was ln(LBM) = −3.8345 + 0.954 × ln(height) + 0.6515 × ln(weight) − 0.0102 × BMIz^2.

Statistical Analysis

Generating LV Mass Centile Curves and Z Scores. To avoid the previously demonstrated limitations of allometric[16] and ratiometric[2,28] scaling, we used the lambda mu sigma (LMS) method[29,30] to generate centile curves, as previously described (LMS Chartmaker Pro; Harlow Healthcare, South Shields, United Kingdom).[16] The LMS method is a technique used to generate percentile curves expressing one variable (in this case LV mass) relative to another (in this case height, BSA, or LBM); the LMS method accounts for the nonlinearity, heteroscedasticity, and skew of anatomic data in growing children. This method generates values for L, M, and S corresponding to each level of the scaling variable; the appropriate L, M, and S values are then used to calculate the *Z* score. LMS was the method used to generate both the Centers for Disease Control and Prevention growth curves[31] and the World Health Organization growth curves.[32] The *Z* scores generated using the LMS method are completely independent from the chosen body-size variable.

Three sets of smoothed LV mass reference centile curves were constructed using data from the reference group. In the first set, LV mass was expressed relative to height; separate curves were generated for male and female subjects. The second set of sex-specific curves scaled LV mass to BSA. In the third set, LV mass was expressed relative to LBM. Consistent with prior work,[3,10,12] the relation between LV mass and LBM was independent of sex in our population. Therefore, a single set of curves of LV mass for LBM was generated. Given the wealth of literature demonstrating that LV mass depends most strongly on LBM[5,10-15] and the consistently expressed opinion that LBM represents the ideal LV mass scaling variable,[2,5,17] we considered LV mass–for–LBM *Z* scores to be the reference method to determine the appropriateness of LV mass for body size.

A *Z* score was calculated for each reference and at-risk child for each of the three scaling variables using the following equation[29]: *Z* score = [(LV mass/M)^L − 1]/(L × S). Figure 2 confirms that LV mass *Z* scores had no residual relationship with the chosen scaling variable. The *Z* score is the difference, in standard deviation units, between an individual's LV mass and the mean for healthy reference children of the same height, BSA, or LBM.

Characterizing the Errors Associated with Height-Based and BSA-Based LV Mass Scaling. On the basis of the assumption that LBM is the best available scaling variable, the agreement between the "reference" LV mass–for–LBM *Z* scores and each of the LV mass–for–height and LV mass–for–BSA *Z* scores was assessed among the entire group of healthy children using linear regression and Bland-Altman plots.[33,34]

Characterizing Adiposity-Related Biases. The relationships between BMIz and each of LV mass–for–LBM, LV mass–for–height, and LV mass–for–BSA *Z* scores were evaluated among the healthy normotensive children to screen for adiposity-related differential bias. These relations were investigated using plots of the data and linear regression. Adiposity-related differential bias was further characterized by plotting the difference between each subject's LV mass–for–LBM *Z* score and his or her LV mass–for–height *Z* score against BMIz; the correlation between the difference in *Z* scores and BMIz was determined by regression. The same approach was used to investigate biases associated with BSA-based scaling.

Determining the Impact of Adiposity-Related Biases on LVH Diagnosis. Next, children in the at-risk group were classified as having LVH, or not, by the criterion method: LV mass–for–LBM. The same children were reclassified two more times, once on the basis of LV mass–for–height *Z* score and again on the basis of LV mass–for–BSA *Z* score. A *Z* score > +1.64 (95th percentile) defined LVH in each case. Two-by-two contingency tables were used to describe the classification of subjects as having LVH or not on the basis of LV mass–for–height or LV mass–for–BSA *Z* scores compared with classification on the basis of LV mass–for–LBM *Z* score. A scaling variable that is a good surrogate for LBM should classify subjects as having LVH, or not, similarly to their classification when LBM is used as the scaling variable. The proportion of subjects discordant in classification was calculated, with 95% confidence intervals.

Analyses were performed using Stata version 10.0 (StataCorp LP, College Station, TX), and LMS Chartmaker Pro.

RESULTS

Subject Characteristics

The characteristics of the reference group, the healthy normotensive group, and the at-risk group are presented in Table 1.

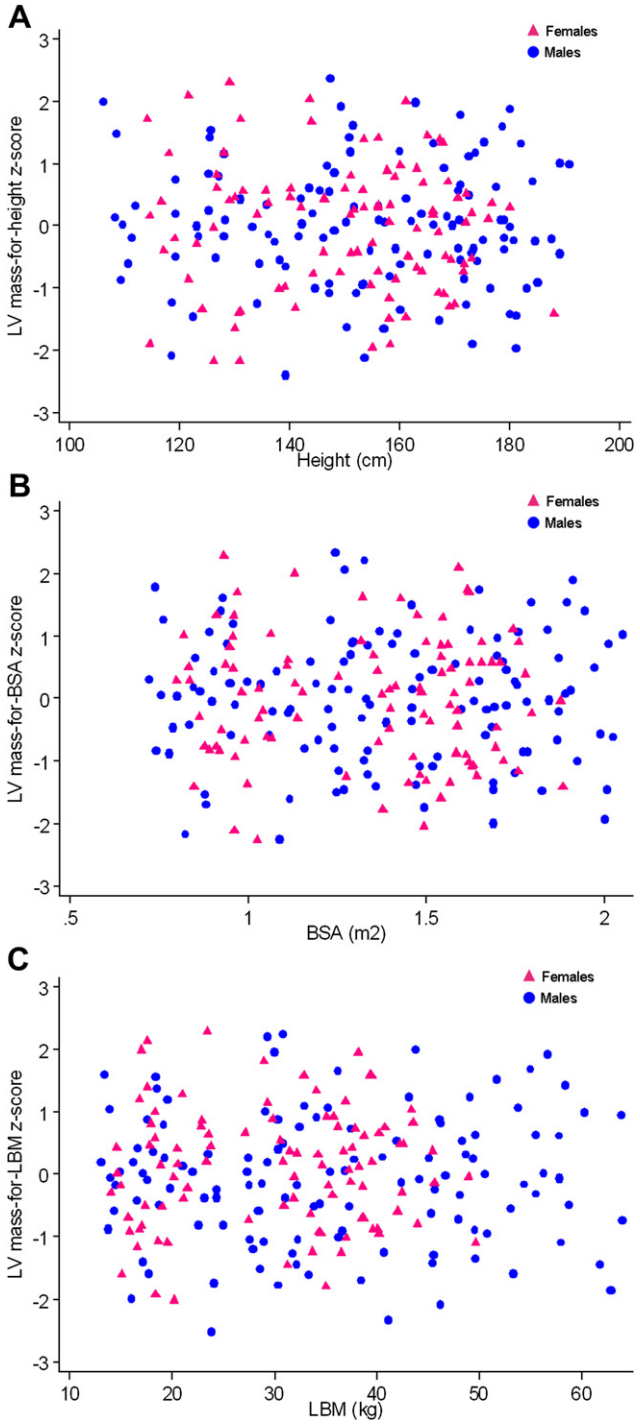

Figure 2 There was no residual relationship between Z scores for LV mass–for–height **(A)**, LV mass–for–BSA **(B)**, or LV mass–for–LBM **(C)** and their respective scaling variables.

LV Mass Scaled to LBM

Among all 270 healthy, normotensive children (222 reference and 48 healthy overweight children), there was no relationship between LV mass–for–LBM Z score and adiposity, as estimated by BMIz ($R^2 = 0.00001$, $P = .93$; slope = −0.0054; 95% confidence interval, −0.13 to 0.12).

LV Mass Scaled to Height or BSA

Excellent agreement between LV mass–for–height or LV mass–for–BSA and LV mass–for–LBM Z scores would be indicated by a strong correlation (high R^2 value), a regression line with a slope and an intercept not significantly different from 1 and 0, respectively, a small root mean square error, a small mean difference between LBM-based and height-based Z scores with tight 95% limits of agreement, and no evidence of differential bias. Table 2 summarizes the agreement between LV mass–for–LBM Z scores and each of LV mass–for–height and LV mass–for–BSA Z scores. Among healthy normotensive children, LV mass–for–BSA Z scores agreed more closely with LV mass–for–LBM Z scores than did height-based Z scores. Both height-based and BSA-based Z scores were strongly correlated with LV mass–for–LBM Z scores. However, the slope of the regression of LV mass–for–height with LV mass–for–LBM was significantly different from 1, and the root mean square error was quite large at 0.45. The slope of the regression line with LV mass–for–BSA was not significantly different from 1, and the root mean square error was smaller (0.23). In addition, the 95% limits of agreement between LV mass–for–LBM and LV mass–for–height Z scores were wide (−1.00 to 0.82) compared with those for LV mass for BSA (−0.42 to 0.55). Neither height-based nor BSA-based Z scores showed evidence of differential bias (Figure 3).

LV mass–for–height Z score was significantly positively correlated with BMIz ($R^2 = 0.10$, $P < .0001$; slope = 0.35; 95% confidence interval, 0.23–0.48) among healthy, normotensive children. Furthermore, the difference between LV mass–for–LBM Z score and LV mass–for–height Z score was significantly inversely correlated with BMIz ($P < .0001$; Figure 4a), indicating that scaling LV mass to height results in increasing overestimation of relative LV mass at higher BMIz and increasing underestimation of relative LV mass at lower BMIz. Importantly, the relationship between BMIz and LV mass–for–height Z scores was evident across the entire range of BMIz, including in thin and normal-weight children.

Although LV mass–for–BSA Z score was not correlated with BMIz ($R^2 = 0.0098$, $P = .10$), there was evidence of differential bias by adiposity, as illustrated in Figure 4b. When BMIz was <0.7, the difference between LV mass–for–LBM and LV mass–for–BSA Z scores had no apparent relationship with BMIz ($P = .70$). However, at BMIz > 0.7 (approximately the 75th percentile), the Z-score difference was significantly positively correlated with BMIz ($P < .0001$), indicating increasing underestimation of relative LV mass with higher BMIz.

Impact of the Choice of Scaling Variable on LVH Diagnosis

The impact of the adiposity-related differential biases associated with using height and BSA as LV mass scaling variables on the diagnosis of LVH among "at risk" children is highlighted in Table 3.

Height-Based Scaling. Compared with the 13% of at-risk children (14 of 112) classified as having LVH using LBM-based scaling, 30% (34 of 112) had LVH when LV mass was scaled to height. In this overweight population, 20% of children (22 of 112) were misclassified with respect to LVH when height-based scaling was used, with a false-positive rate of 21% (21 of 98) and a false-negative rate of 7% (one of 14). As expected, when at-risk children were separated into normal-weight ($n = 30$) and overweight ($n = 82$) groups, substantially more misclassification was observed among the overweight than among the normal-weight children. Height-based scaling resulted in 26% misclassification (21 of 82) among overweight children, all but

Table 1 Subject characteristics

Variable	Reference group (*n* = 222)		Healthy normotensive (*n* = 270)	At-risk group (*n* = 112)
	Male (*n* = 123)	Female (*n* = 99)		
Male			152 (56.3%)	70 (62.5%)
Age (y)	13.2 (9.7 to 15.7)	12.9 (9.4 to 15.8)	12.7 (9.0 to 15.4)	12.6 (9.1 to 15.5)
Height-for-age *Z* score	0.023 (−0.74 to 0.74)	0.12 (−0.65 to 1.03)	0.13 (−0.63 to 0.97)	0.28 (−0.68 to 1.00)
Corresponding percentile	51 (23 to 77)	55 (26 to 85)	55 (26 to 83)	61 (25 to 84)
BMI-for-age *Z* score	0.012 (−0.57 to 0.62)	0.071 (−0.34 to 0.64)	0.29 (−0.31 to 0.88)	1.41 (0.96 to 1.78)
Corresponding percentile	51 (29 to 73)	53 (37 to 74)	61 (38 to 81)	92 (83 to 96)
Estimated LBM (kg)	33.4 (23.8 to 47.9)	32.3 (20.1 to 38.5)	32.2 (20.9 to 42.0)	35.5 (24.6 to 48.1)
Overweight	0	0	48 (17.8%)	82 (73.2%)

BMI, Body mass index.
Data are expressed as number (percentage) or as median (interquartile range).

Table 2 Comparison of LV mass–for–LBM *Z* scores with each of LV mass–for–height and LV mass–for–BSA *Z* scores

	LV mass–for–height *Z* score vs LV mass–for–LBM *Z* score	LV mass–for–BSA *Z* score vs LV mass–for–LBM *Z* score
Regression results		
R^2	0.81 ($P < .0001$)	0.95 ($P < .0001$)
Root mean square error	0.45	0.23
Slope (95% CI)	0.94 (0.88 to 0.99)	0.99 (0.97 to 1.02)
Intercept (95% CI)	0.10 (0.04 to 0.15)	−0.05 (−0.08 to −0.02)
Agreement		
Mean difference* (95% CI)	−0.097 (−0.15 to −0.04)	0.052 (0.024 to 0.080)
95% limits of agreement	−1.00 to 0.82	−0.42 to 0.55
Differential bias†	No	No
Slope	−0.046 (−0.102 to 0.0095)	−0.022 (−0.050 to 0.0061)
R^2	0.010 ($P = .10$)	0.009 ($P = .10$)

CI, Confidence interval.
*LV mass–for–LBM *Z* score minus LV mass–for–height or LV mass–for–BSA *Z* score.
†Differential bias was determined on the basis of the relation between the *Z*-score difference and the average of LV mass–for–LBM *Z* score and either LV mass–for–height *Z* score or LV mass–for–BSA *Z* score.

one of which were false-positives. In contrast, only one of 30 (3%) normal-weight, at-risk children was misclassified (false-positive).

BSA-Based Scaling. When BSA-based scaling was used, 11% of at-risk children (12 of 112) were classified as having LVH; only 2% (two of 112) were misclassified. There were no false-positives. The false-negative rate was 14% (two of 14). All misclassified individuals were overweight: two of 82 (2%) overweight, at-risk children were inappropriately classified as having no LVH by BSA-based scaling. The false-negative rate among the overweight was 33% (two of six).

LV Mass–for–LBM Reference Values

Table 4 provides the L, M, and S values corresponding to each level of LBM, and Figure 5 illustrates the percentile curves.

DISCUSSION

The presence of LVH has been shown to be a predictor of mortality and of cardiovascular events in adults.[35] However, the usefulness of LVH as a predictor of future adverse outcomes depends on its accurate diagnosis, which depends to a large extent on the appropriate normalization of LV mass for body size. Prior work comparing different LV mass indices demonstrated little difference in the ability of the different indices to predict future morbidity; in fact, indexed LV mass barely outperformed raw LV mass, suggesting that the predictive capacity of LVH was driven primarily by very severe LVH, detectable regardless of the indexing method or scaling variable chosen.[1] If we wish to improve the prognostic value of a diagnosis of LVH, it is critical that both the normalization method and the scaling variable be selected carefully.

No prior study has identified the limitations associated specifically with different scaling variables. Previous work focused mainly on creating an index that removed variability in LV mass due to variability in body size. Among adults, the allometric index LV mass (g)/height$^{2.7}$ succeeded in this regard where LV mass (g)/BSA (m^2) did not. Although LV mass/height$^{2.7}$ is also a popular method of normalizing LV mass in children, it has important limitations. We and others recently demonstrated that LV mass/height$^{2.7}$ does not adequately normalize LV mass for height in children[16,17]; LV mass/height$^{2.7}$ increases with decreasing height below about 140 cm. Therefore, it is not possible to accurately diagnose LVH on the basis of a fixed LV mass/height$^{2.7}$ cutoff across the entire pediatric age range. We previously demonstrated that LV mass can be successfully normalized for body size using the LMS method,[16,30] which returns

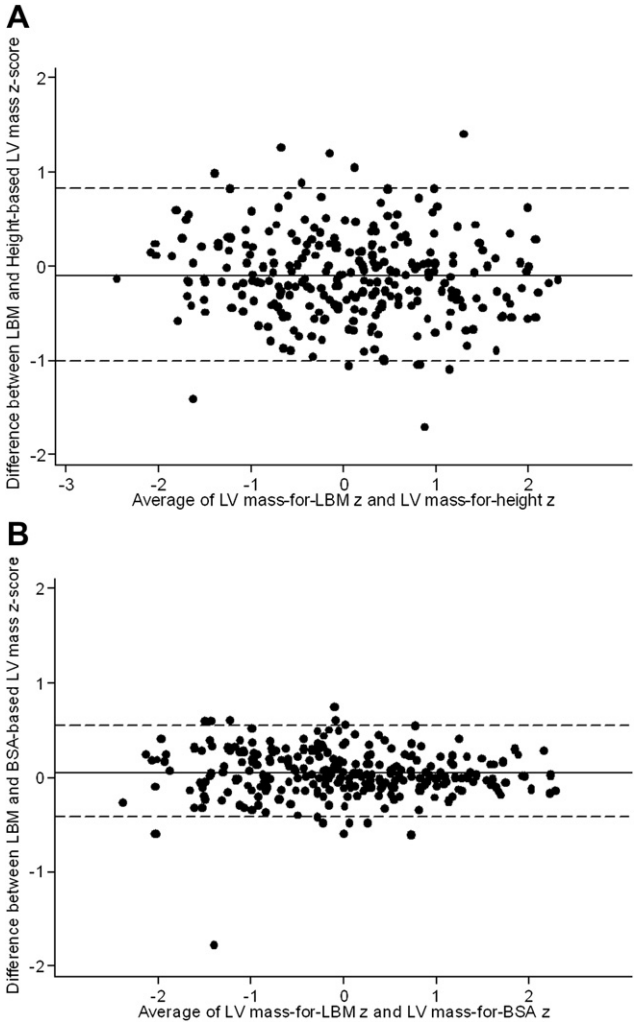

Figure 3 Bland-Altman plots indicating agreement between LV mass–for–LBM *Z* scores and each of **(A)** LV mass–for–height *Z* scores and **(B)** LV mass–for–BSA *Z* scores.

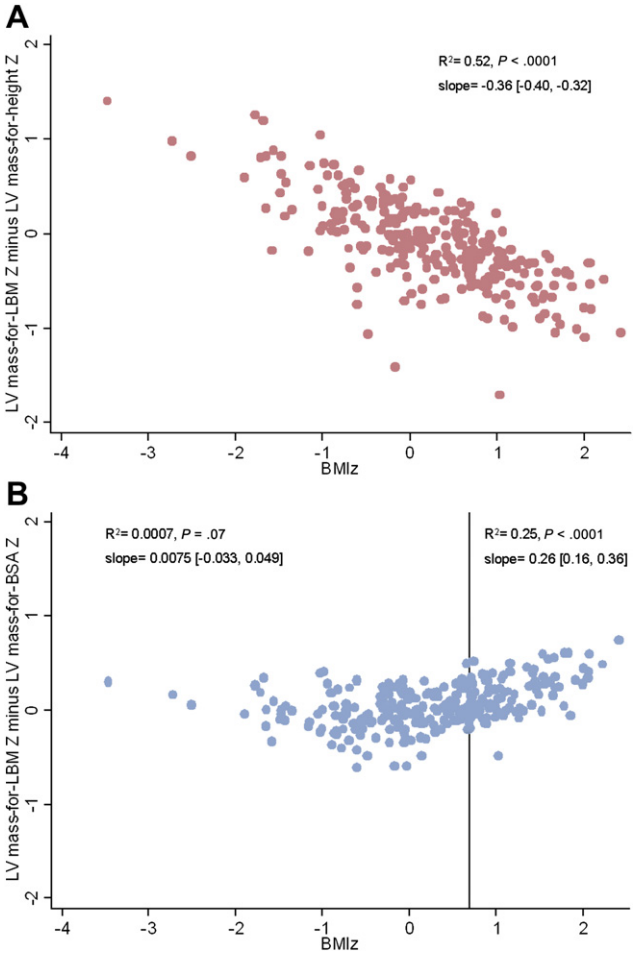

Figure 4 Difference between LV mass–for–LBM and LV mass–for–height *Z* scores **(A)** and between LV mass–for–LBM and LV mass–for–BSA *Z* scores **(B)** plotted against BMIz. These graphs illustrate the adiposity-related differential bias associated with using each of height **(A)** and BSA **(B)** as the scaling variable. Relative LV mass is increasingly overestimated at higher BMIz and increasingly underestimated at lower BMIz when height is used. Relative LV mass is increasingly underestimated at higher BMIz among individuals with BMIz > 0.7 when BSA is used.

an LV mass–for–body size percentile or *Z* score that is completely independent of body size.[16]

Before embarking on a comparison of different LV mass scaling variables, it is critical that a normalization method be selected that truly removes variability in LV mass that is due to variability in the chosen scaling variable and that allows comparison of different scaling variables on the same scale. The LMS method fulfills both these criteria.

We compared each of height and BSA with the criterion scaling variable, LBM. Height has been accepted as a reasonable surrogate for LBM and favored over BSA as a LV mass scaling variable because of reasonable concerns that BSA-based scaling may result in underestimation of relative LV mass in overweight individuals.[6] However, the possibility that scaling LV mass to height may introduce errors of equal or greater importance has not been evaluated. The high degree of variability in LBM at any given height limits the achievable precision of height-based LV mass scaling; the dependence of LBM on adiposity[19] necessarily introduces adiposity-related differential bias. If height were an accurate and unbiased surrogate for LBM, then the difference between LV mass–for–height and LV mass–for–LBM *Z* scores would be small and would have no relationship with adiposity. We have demonstrated that height is a biased surrogate for LBM.

Ours is not the first study to conclude that height-based LV mass normalization results in overestimation of the prevalence of LVH among the obese. Kuch *et al.*[3,14] drew similar conclusions in a comparison of different LV mass scaling variables in adults, including fat-free mass, height, and BSA. However, these studies compared not only scaling variables but scaling methods, using allometric scaling for some variables and ratiometric for others. Our approach, using LMS-derived *Z* scores to normalize LV mass, ensured that the differences observed were due only to the choice of scaling variable, not to the normalization method. The use of *Z* scores also allowed us to quantify the magnitude of the errors associated with height-based and BSA-based LV mass scaling and enhanced our ability to show that the adiposity-related bias associated with height-based LV mass scaling is operative across the entire range of adiposity, not just among the obese.

The present study showed that LV mass–for–height *Z* scores were about 1 standard deviation lower than LBM-based *Z* scores at the

Table 3 Classification and misclassification of LVH by scaling variable

Variable	Scaling variable		
	LBM	Height	BSA
All "at risk" (n = 112)			
Proportion with LVH (%)	13 (7–20)	30 (22–40)	11 (6–18)
Proportion misclassified (%)	—	20 (13–28)	2 (0.2–6)
False-positive rate (%)	—	21 (14–31)	0 (0–4)
False-negative rate (%)	—	7 (0.2–34)	14 (2–43)
Overweight subgroup (n = 48 otherwise healthy + n = 34 hypertensive)			
Proportion with LVH (%)	7 (3–15)	30 (21–42)	5 (1–12)
Proportion misclassified (%)	—	26 (17–36)	2 (0.3–9)
False-positive rate (%)	—	26 (17–38)	0 (0–5)
False-negative rate (%)	—	17 (0.4–64)	33 (4–78)
Normal-weight subgroup (n = 30; all hypertensive)			
Proportion with LVH (%)	27 (12–46)	30 (15–49)	27 (12–46)
Proportion misclassified (%)	—	3 (0.08–17)	0 (0–12)
False-positive rate (%)	—	5 (0.1–23)	0 (0–15)
False-negative rate (%)	—	0 (0–37)	0 (0–37)
Hypertensive subgroup (n = 64)			
Proportion with LVH (%)	17 (9–29)	36 (24–49)	16 (8–27)
Proportion misclassified (%)	—	22 (13–34)	2 (0.04–8)
False-positive rate (%)	—	25 (14–38)	0 (0–7)
False-negative rate (%)	—	9 (0.3–41)	9 (0.3–41)

All values are proportions (95% confidence intervals).

lower end of the BMIz range and almost 1 standard deviation higher than LBM-based Z scores at the upper end of the BMIz range. Errors were smaller, but still important, in the middle of the BMIz range. When height was used as the scaling variable, relative LV mass was increasingly overestimated with higher adiposity and increasingly underestimated with increasing thinness.

The errors associated with height-based scaling resulted in misclassification with respect to LVH in almost 20% of at-risk children. All but one of these misclassifications were false-positives, leading to an LVH prevalence when height-based scaling was used that was more than twice that when LBM was used as the scaling variable. The vast majority of misclassifications were false-positives among the overweight. If one were to assess a group of very thin children, most misclassifications would be false-negatives. Given the increasing prevalence of childhood obesity, using a measure of LV mass that results in overdiagnosis of LVH among overweight children may result in many unnecessary costly investigations and interventions and provoke considerable anxiety among patients and families.

As anticipated by prior investigators, BSA-based scaling of LV mass was not free of adiposity-related differential bias. However, BSA proved to be a better surrogate for LBM than did height; there were no misclassifications among normal-weight children, and only 2% of overweight children were misclassified with respect to LVH. However, the false-negative rate among overweight children was disturbingly high, at 33% (though this was based on only six subjects).

We have shown that neither height nor BSA is a perfect surrogate for LBM in the normalization of LV mass for body size. However, although BSA-based LV mass scaling was associated with some underdetection of LVH, height-based scaling resulted in a 10-fold higher rate of LVH misclassification than BSA-based scaling. BSA is appealing as a scaling variable because of the simplicity of its calculation, and it has been demonstrated here to be a reasonable surrogate for LBM among children with body mass indices below the 75th percentile (BMIz $\approx$ 0.7). However, in overweight children, or when a very precise estimate of the relative LV mass is desired, the safest approach is to use the predictive equations to estimate LBM and to express LV mass as a Z score relative to LBM. Expressing LV mass relative to LBM will allow an assessment of the independent impact of excess adiposity on the appropriateness of LV mass.

We acknowledge that this study had some limitations. Ideally, we would have scaled LV mass to measured, rather than predicted, LBM. This would require dual-energy x-ray absorptiometric scans and echocardiography to have been performed in the same population; we did not have such data, and dual-energy x-ray absorptiometric scans are not generally available in clinical practice. Therefore, we used LBM predictive equations that were validated in a population representative of the general American pediatric population.[21] Although the equations may not provide a perfect estimate of LBM, they do provide an unbiased estimate of LBM; in particular, estimates were not biased by adiposity.

Our study did not include children <5 years of age, because the LBM predictive equations were not validated for this younger age group. Therefore, our conclusions cannot be extended to infants and very young children. In addition, we had no information about the race of participants. Accounting for an individual's race may further increase the accuracy of estimates of the appropriateness of LV mass relative to body size. Individuals of African descent have higher LBM for height than individuals of European descent.[36,37]

In addition, this was a retrospective study, using echocardiographic data acquired at two different laboratories. Importantly, all reference children and healthy normotensive overweight children were studied at the same laboratory. The fact that the hypertensive children were studied at a different laboratory does not introduce any bias, because of the design of the study: we compared LV mass expressed relative to height and to BSA with LV mass expressed relative to LBM. In effect, each child was only ever compared with himself or herself; the LV mass measure (expressed relative to one body-size variable) was compared with the same LV mass measure (expressed relative to another body-size variable).

We used LV mass as measured by M-mode rather than 2D echocardiography because the majority of prior quantitative echocardiographic studies in children used M-mode imaging.[8,9,16,17,25] We would anticipate that findings would be similar if 2D images were used to estimate LV mass. M-mode and 2D measures are highly correlated.[38] Furthermore, these findings are driven more by the relationships between LBM and each of height and BSA than the method used to estimate LV mass. Nevertheless, it would be useful to confirm these findings using 2D images.

We have included the centile curves and tables of the L, M, and S values needed to calculate LV mass–for–LBM Z scores for illustrative purposes and for the use of other investigators. However, it is not our intention that these serve as definitive reference data. As pointed out in our prior study,[16] and noted by others,[39] our reference children tended to have higher LV masses relative to height than those in some other published groups.[10,40] The reasons for this difference are not clear but may include differences in measurement methods or differences in body composition between groups.

Our findings highlight the limitations of height and BSA as LV mass scaling variables in children aged >4 years. These limitations are likely also applicable to adults; however, separate studies are needed to

Table 4 LMS table for LV mass relative to predicted LBM

LBM (kg)	L	M	S	LBM (kg)	L	M	S	LBM (kg)	L	M	S
13	−1.26735	53.32952	0.150987	31	−0.61895	103.5205	0.170021	49	0.244128	163.0017	0.186919
14	−1.23064	55.74982	0.152452	32	−0.57443	106.5352	0.170452	50	0.28822	166.8401	0.188905
15	−1.19394	58.20771	0.153914	33	−0.52811	109.5625	0.170855	51	0.332525	170.7342	0.191006
16	−1.1573	60.75559	0.155361	34	−0.48031	112.6174	0.171252	52	0.377297	174.6656	0.193208
17	−1.1207	63.40502	0.15677	35	−0.43139	115.7098	0.171666	53	0.422721	178.6151	0.195497
18	−1.08418	66.09552	0.158124	36	−0.38168	118.8321	0.172123	54	0.468936	182.5686	0.197861
19	−1.04806	68.77439	0.159417	37	−0.33141	121.9733	0.172643	55	0.516091	186.5069	0.20029
20	−1.01262	71.44731	0.160656	38	−0.28078	125.131	0.173244	56	0.564341	190.412	0.202775
21	−0.97796	74.13548	0.161842	39	−0.23001	128.3078	0.173934	57	0.61378	194.2742	0.205308
22	−0.94395	76.8418	0.162976	40	−0.17932	131.5179	0.174718	58	0.664378	198.0914	0.207881
23	−0.91039	79.57587	0.164054	41	−0.12906	134.7794	0.175601	59	0.71596	201.8685	0.210487
24	−0.87711	82.35598	0.165062	42	−0.0796	138.1031	0.176588	60	0.768316	205.6116	0.213119
25	−0.84387	85.22161	0.165991	43	−0.0311	141.4798	0.177692	61	0.821197	209.3281	0.21577
26	−0.81019	88.17646	0.166846	44	0.0167	144.8964	0.178916	62	0.874396	213.0285	0.218431
27	−0.77556	91.2037	0.167629	45	0.0638	148.3622	0.180261	63	0.927727	216.7232	0.221095
28	−0.73949	94.28593	0.168342	46	0.110015	151.9016	0.181733	64	0.979186	220.2878	0.223666
29	−0.70153	97.39776	0.16898	47	0.155327	155.5248	0.183331				
30	−0.66135	100.4839	0.169537	48	0.199928	159.2272	0.185059				

LV mass–for–LBM *Z* scores are calculated for an individual by finding the L, M, and S values that correspond to the individual's LBM and using them in the following equation, where $LVmass_{obs}$ is the individual's LV mass in grams: *Z* score = $[(LVmass_{obs}/M)^{L}-1]/(L \times S)$.

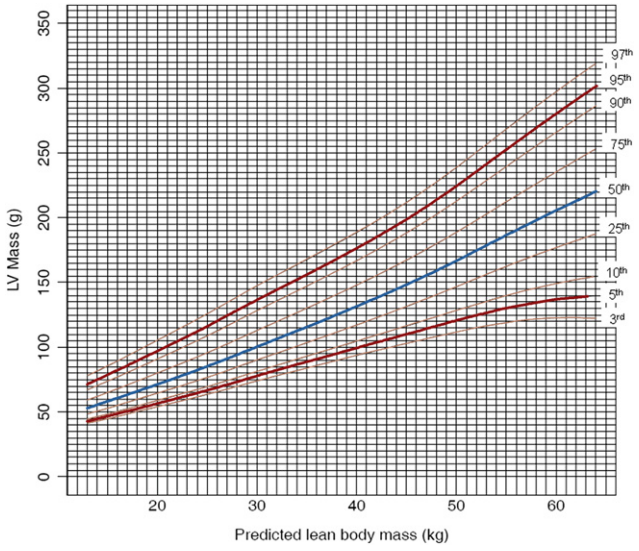

Figure 5 Reference percentile curves for LV mass relative to predicted LBM for children and adolescents between 5 and 21 years of age.

address this question in adults. Overall, BSA appears to perform better than height as a scaling variable for LV mass. However, LBM is likely the best scaling variable and may be estimated reasonably accurately in children aged 5 to 21 years. Only by scaling LV mass to LBM will we be able to determine the impact of obesity on heart size. Further larger studies are needed to generate robust reference centile curves for LV mass relative to LBM.

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