A Novel Method of Expressing Left Ventricular Mass Relative to Body Size in Children

Bethany J. Foster, MD, MSCE; Andrew S. Mackie, MD, SM; Mark Mitsnefes, MD; Huma Ali; Silvia Mamber, MD; Steven D. Colan, MD

Background—Left ventricular (LV) hypertrophy (LVH) in children is widely defined as a left ventricular mass index (LVMI, g/m²) >95th percentile. However, LVMI increases with decreasing height in young children; thus, the 95th percentile LVMI will depend on the height distribution of the reference population. The objective of this study was to compare the performance of a novel method of expressing LV mass relative to body size (centile curves) with the LVMI method.

Methods and Results—LV mass was estimated by M-mode echocardiography in 440 healthy nonobese reference children (birth to 21 years) and 239 children at risk for LVH; the LVMI was calculated for all children. Three samples of 270 children, each with different height distributions, were drawn from the reference population. A sample-specific 95th percentile LVMI was determined for each reference sample. At-risk children were classified as having LVH or not based on each sample-specific 95th percentile. Four LV mass-for-height centile curves were constructed with the Cole lambda-mu-sigma method and data from each reference sample. At-risk children were each assigned an LV mass-for-height percentile with these curves and were reclassified as having LVH if LV mass-for-height was >95th percentile. The centile method provided a stable estimate of the proportion of at-risk children with LVH regardless of reference group, whereas proportion estimates varied significantly depending on the reference population when the LVMI method was used.

Conclusions—LV mass-for-height centile curves are superior to LVMI as a method of normalizing LV mass to body size in children. (Circulation. 2008;117:2769-2775.)

Key Words: left ventricular hypertrophy • pediatrics • echocardiography • reference standards
preferred. Potential problems with the LVMI have been recognized by others, but no easy-to-use validated alternative has been proposed. The LVMI (g/m^2.7) is easy to calculate, provides a numeric value on a continuous scale, and works reasonably well in adults; these factors likely explain its continued widespread use.

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In children, for whom no particular cutoff has been linked to adverse outcomes, the M-mode–derived LVMI 90th (35.7 g/m^2) and 95th (38.6 g/m^2) percentiles for a single healthy pediatric reference population (192 healthy children 6 to 17 years old) have been proposed as cutoffs to define LVH.2,15 The more conservative, outcome-based adult cutoff of 51 g/m^2 has also been suggested.12,14,17 The 95th percentile cutoff has been broadly applied.5,6,8,28,29 However, although LVMI normalizes LV mass to body size reasonably well in adults, the LVMI increases with decreasing height34 and is therefore a suboptimal method of normalizing LV mass for body size and of defining LVH in children. We hypothesized that the LVMI 95th percentile, and hence the cutoff defining LVH, would depend strongly on the height distribution in the reference group. As a result, a diagnosis of LVH would be influenced by the composition of the reference group.

We propose a novel method of expressing LV mass relative to body size and of defining LVH by use of centile curves. This method is not sensitive to the composition of the reference population and provides a numeric value that reflects LV mass relative to body size on a continuous scale (z score or percentile). The objective of the present study was to compare the performance of the new centile curve method to the LVMI method with respect to the identification of LVH in a group of children at risk for LVH.

Methods

The data for the present study were collected as part of prior research protocols conducted at Children’s Hospital Boston30 (Boston, Mass) and Cincinnati Children’s Hospital Medical Center (Cincinnati, Ohio).10,31,32 Additional data were obtained from studies done for clinical purposes at both Children’s Hospital Boston and The Montreal Children’s Hospital (Montreal, Quebec, Canada). All research protocols were approved by the institutional review boards at the relevant institutions, and all subjects or their guardians gave written informed consent when required.

Reference Subjects

Healthy nonobese (body mass index <95th percentile for age) children (birth to 21 years) were evaluated in the echocardiography laboratory at Children’s Hospital Boston. Reference subjects were free of systemic disease and had structurally normal hearts; none had a family history of hypertrophic cardiomyopathy. All reference subjects were reevaluated 1 year later to verify that they remained free of any identifiable systemic disorder, including hypertension. All had height (wall-mounted stadiometer) or length (length board) measured to the nearest 1 mm and weight measured to the nearest 0.1 kg.

Subjects at Risk for LVH

Children at risk for LVH were evaluated at 2 other centers. Eighty-five children with hypertension were studied in the echocardiography laboratory at the Montreal Children’s Hospital. At Cincinnati Children’s Hospital Medical Center, 84 children with chronic renal insufficiency, 33 children undergoing dialysis, and 49 children who had kidney transplants were studied. Height or length was measured to the nearest 1 mm and weight to the nearest 0.1 kg in all at-risk children.

Echocardiograms

Echocardiograms were performed on commercially available cardiac ultrasound scanners according to the guidelines of the American Society of Echocardiography.33 Studies were recorded on VHS videotape. All studies were reviewed by a single pediatric cardiologist at each of the sites. Studies performed for clinical purposes were reexamined for the purposes of the present study. 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 microcomputer-based digitizing station with custom software. LV internal diameter, septal thickness, and posterior wall thickness were calculated from the digitized borders as continuous variables throughout the cardiac cycle. End diastole was defined as the time of maximum LV dimension. End-diastolic dimensions and wall thicknesses were calculated as the average of 3 consecutive cardiac cycles.34 At the Cincinnati and Montreal sites, electronic calipers were used to measure interventricular septal thickness, LV posterior wall thickness, and LV dimension at end diastole from M-mode images. Measurements were repeated over 3 consecutive cardiac cycles and averaged. LV mass was estimated by the Devereux equation,35 and the LVMI was calculated for all children. We used M-mode rather than 2D images for 2 reasons. First, this remains the most commonly used method in clinical practice. Second, the allometrically scaled LVMI (g/m^2) was originally derived with M-mode measurements. Because we compared our new method to the LVMI method, we thought it was best to use the same measurement technique. However, regardless of the technique used to obtain the estimate of LV mass, the issue of how best to normalize LV mass to body size remains the central question.

Statistical Analysis

Analyses were performed with Stata 8.2 (College Station, Tex) and LMS Chartmaker Pro (Institute for Child Health, London, United Kingdom).

Evaluating the LVMI

A measure that is adequately normalized for body size should have no residual correlation with body size.24,26 Hence, if LVMI is an acceptable means of normalizing LV mass for body size, the LVMI distribution (and LVMI 95th percentile) should be constant across a broad range of body sizes among healthy children; the height distribution of the reference population should not influence the LVMI distribution. To determine the impact of varying the height distribution of the reference population on the LVMI distribution, we drew 3 samples of 270 children each from the reference group and determined the 95th percentile for LVMI in each reference sample and for the entire reference group (n=440). The reference samples were selected to each have a different height distribution; the sex distribution was held constant. Samples of 270 allowed substantial differences in height distribution between the reference samples while maintaining a reasonable sample size. Reference sample 1 contained all reference children ≥120 cm tall and a random sample of those <120 cm (a distribution heavily skewed toward taller children but including some smaller children). Reference sample 2 was limited to children >100 cm tall (a distribution similar to sample 1 but limited to taller children only). Reference sample 3 included all children <120 cm and a random sample of taller children (a distribution heavily skewed toward smaller children but including some taller children).

Next, children in the at-risk group were classified as having or not having LVH, defined as LVMI >95th percentile, on the basis of each reference sample–specific 95th percentile LVMI. This was done to highlight the impact of varying the height distribution of the reference population on our ability to accurately classify children as having LVH using the LVMI method. The proportion of at-risk children with LVH (with 95% CIs) was calculated 4 times based on the entire reference group and each of the 3 reference samples. The
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Reference Group</th>
<th>Sample 1 (n=270)</th>
<th>Sample 2 (n=270)</th>
<th>Sample 3 (n=270)</th>
<th>At-Risk Group (n=239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>254 (57.7)</td>
<td>157 (58.2)</td>
<td>157 (58.2)</td>
<td>157 (58.2)</td>
<td>156 (65.3)</td>
</tr>
<tr>
<td>Age, y</td>
<td>7.6 (1.7–13.8)</td>
<td>12.7 (8.6–15.5)</td>
<td>12.3 (8.2–15.4)</td>
<td>2.9 (0.6–7.0)</td>
<td>13.8 (10.5–16.8)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>125.1 (82.9–157.4)</td>
<td>152.6 (130.0–168.0)</td>
<td>151.1 (127.0–167.0)</td>
<td>93.9 (70.0–118.0)</td>
<td>151.0 (137.0–165.0)</td>
</tr>
<tr>
<td>BMI for age percentile</td>
<td>58.7* (35.6–76.8)</td>
<td>56.5 (32.6–76.8)</td>
<td>60.7 (37.7–77.3)</td>
<td>59.6 (35.6–76.6)</td>
<td>71.4 (31.8–93.8)</td>
</tr>
</tbody>
</table>

All values are medians and interquartile ranges unless otherwise indicated.
*Based on the 321 subjects at least 2 years of age.
†Based on the 249 subjects at least 2 years of age.
‡Based on the 151 subjects at least 2 years of age.

The proportion of at-risk children who actually have LVH must be fixed. Therefore, if the LVMI method works well, the proportion classified as having LVH should remain stable even if the composition of the reference group is altered.

Generating and Evaluating LV Mass-for-Height Centiles

Four sets of smoothed LV mass-for-height reference centile curves were constructed by the lambda-mu-sigma (LMS) method and data from each of the reference samples. This is the same technique that was used to construct the National Centers for Health Statistics growth curves (height for age, weight for age, and body mass index for age) with which pediatricians are so familiar. This technique, described in detail by Cole, is able to deal effectively with skewness and heteroscedasticity in the data. Briefly, the method generates a set of 3 curves for each of L, M, and S values that are then used to create centile curves. A z score was calculated for each reference and at-risk child with the following equation: z score = (LV mass/M)^(1/2) / (L × S); the L, M, and S values were determined from the L, M, and S versus height curves described above. A table that includes the L, M, and S values at each height is available in the online-only Data Supplement. The z score is the difference, in SD units, between an individual's LV mass and the mean for healthy reference children of the same height. z Scores were converted into percentiles with normal distribution tables. LVH was defined as LV mass-for-height >95th percentile. The proportion of at-risk children with LVH (with 95% CIs) was also calculated 4 times (this time by the centiles method) based on the reference range of the entire reference group and all 3 reference samples. Those with LVH were classified as having LVH. However, none of those >140 cm tall were classified as having LVH, whereas 8.4% of those <140 cm and a full 15% of healthy children <100 cm were classified as having LVH.

LV Mass-for-Height Centile Curves

LV mass-for-height centile curves describe the distribution of LV mass relative to height among healthy, nonobese children. By definition, the mean LV mass-for-height z score for each reference sample was zero, with an SD of 1.0. At-risk children were plotted on the centile curves and had z scores and corresponding percentiles calculated. Figure 2 shows at-risk children plotted on the curves generated with data from the entire reference group. Those with LV mass above the 95th percentile for height (z score >1.64) were classified as having LVH.

Comparison of LVMI and Centiles Methods

Unlike the LVMI, LV mass-for-height z scores showed no relationship with height (R^2=0.0004, P=0.7) among healthy

Results

Subject Characteristics

Four-hundred forty healthy reference children and 251 children at risk for LVH were included in the study. Of the 251 at-risk children, 239 had a height that was represented within the height range of the entire reference group and all 3 reference samples. Therefore, only these 239 were included in subsequent comparisons; LV mass-for-height percentiles could not be generated for subjects with a height outside the reference range. The characteristics of the entire reference group, each of the 3 reference samples, and the at-risk group are presented in Table 1.

LV Mass Index

As illustrated in Figure 1, a strong relationship existed between LVMI and height (R^2=0.7, P<0.00001) among healthy reference children. The dependence of LVMI on height was strong for children <140 cm tall (R^2=0.6, P<0.00001). However, among those ≥140 cm tall, no significant relationship was found between LVMI and height (R^2=0.001, P=0.7), which suggests that the LVMI works reasonably well in those >140 cm. This has been observed in prior studies.16

The LVMI 95th percentile for the entire reference group was 82.1 g/m^2. When this was used as a cutoff to define LVH, then, as expected, 5% of the healthy reference group was classified as having LVH. However, none of those >140 cm tall were classified as having LVH, whereas 8.4% of those <140 cm and a full 15% of healthy children <100 cm were classified as having LVH.
The impact of the errors generated by the failure of the LVMI method to adequately normalize for body size are highlighted in Table 2, which indicates the median and 95th percentile LVMI and the median LV mass-for-height $z$ score and corresponding centile for the entire reference group and each reference sample. In the last 2 rows of Table 2, the proportion of at-risk children with LVH, defined as LVMI greater than each reference sample–specific 95th percentile, was compared with the proportion of at-risk children with LVH, defined as LV mass-for-height greater than each reference sample–specific 95th percentile. The LV mass-for-height centile method provided a stable estimate of the proportion of at-risk children with LVH regardless of reference group: All CIs were overlapping. In contrast, proportion estimates varied widely and significantly depending on the composition of the reference population when the LVMI method was used. Although the height distributions in reference samples 1 and 2 were very similar, the LVMI 95th percentiles for each of these samples (and consequently, the proportion of at-risk children classified as having LVH compared with each of these samples) differed dramatically. This highlights the important impact of even small variations in height distribution of the reference population on performance of the LVMI method.

The LVMI-based proportion estimate determined with the 95th percentile cutoff for reference sample 2 was closest to the proportion estimates obtained by the centiles method. This is logical, because the height distribution of at-risk children (median 151.0 cm, range 100.0 to 185.3 cm) was most similar to that of children in reference sample 2 (median 151.1 cm, range: 97.9 to 191.0 cm).

All comparisons were repeated with sex-specific LVMI 95th percentile cutoffs and sex-specific centile curves (data not shown). The same flaws with the LVMI method were revealed.

Discussion

The ability to accurately measure LV mass relative to body size and to correctly diagnose LVH is important both for clinical care and for cardiovascular health research. Prior publications have proposed the LVMI as a means of expressing LV mass relative to body size, with values exceeding specific LVMI cutoffs indicating LVH in children. However, because LVMI increases with decreasing body size, no one cutoff value derived from a single reference population can be uniformly applied to all children; this would result in overdiagnosis of LVH among small children and potentially in underdiagnosis of LVH among larger children (if the reference population included a substantial number of small children). We have demonstrated that the 95th percentile LVMI for healthy children depends heavily on the height distribution in the healthy group. As a result, the proportion of at-risk children classified as having LVH did not differ significantly when the composition of the reference population was altered. Clearly, the proportion of at-risk children who actually have LVH is fixed and should not depend on the makeup of the reference population.

We propose LV mass-for-height centiles, generated by the LMS method, as a superior means of normalizing LV mass for body size. The advantage of this method over the LVMI method is that it provides a measure of LV mass expressed relative to body size that has the same meaning regardless of the size of the child. When the 95th percentile LV mass-for-height was used as the threshold to define LVH, the proportion of at-risk children classified as having LVH did not differ significantly when the composition of the reference population was altered. Slight variations in the centile-based proportion estimates reflect instability of the centile curves at the lower and upper ends of the height range with relatively small reference samples ($n=270$). The LV mass-for-height 95th percentile was chosen as the cutoff for LVH rather arbitrarily. The 97th percentile might also be a logical cutoff because it corresponded to an LVMI $>51 \text{ g/m}^2$ among reference subjects $>140 \text{ cm}$ tall, which is the LVMI cutoff associated with adverse outcomes among hypertensive adults.\(^\text{17}\)
Table 2. Comparison of Centiles Method and LVMI Method

<table>
<thead>
<tr>
<th>Reference Group</th>
<th>Entire</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI median, g/m²</td>
<td>41.9</td>
<td>36.2</td>
<td>36.1</td>
<td>50.8</td>
</tr>
<tr>
<td>LVMI 95th percentile, g/m²</td>
<td>82.1</td>
<td>59.3</td>
<td>51.8</td>
<td>91.8</td>
</tr>
<tr>
<td>LV mass-for-height z score median (interquartile range)</td>
<td>0.01 (−0.68–0.60)</td>
<td>0.01 (−0.73–0.65)</td>
<td>0.01 (−0.70–0.62)</td>
<td>0.003 (−0.69–0.62)</td>
</tr>
<tr>
<td>LV mass-for-height percentile median (interquartile range)</td>
<td>50.6 (24.7–72.7)</td>
<td>50.7 (23.2–74.2)</td>
<td>50.7 (24.3–73.3)</td>
<td>50.1 (24.4–73.3)</td>
</tr>
<tr>
<td>Percentage of at-risk children with LVH defined as LVMI &gt;95th percentile (95% CI)</td>
<td>0.4 (0–1.2)</td>
<td>4.2 (1.6–6.7)</td>
<td>15.0 (10.8–20.1)</td>
<td>0 (—)</td>
</tr>
<tr>
<td>Percentage of at-risk children with LVH defined as LV mass-for-height &gt;95th percentile (95% CI)</td>
<td>17.2 (12.3–22.0)</td>
<td>19.2 (14.2–24.3)</td>
<td>20.0 (15.0–25.2)</td>
<td>16.3 (11.6–21.0)</td>
</tr>
</tbody>
</table>

The percentage of at-risk children with LVH defined as LVMI greater than each reference sample–specific 95th percentile (row 5) is compared to the percentage of at-risk children with LVH defined as LV mass-for-height greater than each reference sample–specific 95th percentile (row 6). Percentage estimates varied significantly depending on the composition of the reference population when the LVMI method was used. In contrast, the LV mass-for-height centile method provided a stable estimate of the proportion of at-risk children with LVH regardless of reference group.

A further advantage of the centiles method is that the z scores generated by this method facilitate interpretation of the magnitude of abnormalities; the score indicates how many SDs an individual’s LV mass is above or below the average for children of the same height. This method will not only classify LV mass as normal or elevated more accurately than the LVMI, but it will capture important changes in LV mass relative to body size over time in the growing child, changes that may be missed by the LVMI. An LVMI that remains stable as a child grows may actually reflect progressive LVH. The centiles method will improve interpretability of changes in LV mass during clinical follow-up and in longitudinal research studies. Effectively, the centiles method will increase the “signal-to-noise ratio” for the LV mass measure by reducing the “noise.” This is particularly important for pediatric studies, in which the sample size is often small.

Further improvements to our ability to accurately characterize disturbances in LV mass relative to body size may be possible with the use of sex-specific definitions for LVH. When height is used as the body size variable, it serves as an easily measured surrogate for lean body mass, with which LV mass correlates more closely. Because males have a greater lean mass for height than females, it follows that LV mass relative to height will be greater in males than females. Recognizing this, prior studies have proposed sex-specific 95th percentile LVMI cutoffs: 39.4 g/m² for boys and 36.9 g/m² for girls. Thresholds for LVMI that are not sex-specific have the potential to overdiagnose LVH in boys and underdiagnose LVH in girls. Sex-specific LVMI cutoffs are clearly superior to non–sex-specific cutoffs; however, the major disadvantage of the LVMI remains that normal LVMI varies with body size. Sex-specific LV mass-for-height centile curves may be preferred. For simplicity, we have presented a non–sex-specific comparison of the LVMI method with the LV mass-for-height centile method. The results of comparisons that used sex-specific LVMI cutoffs and sex-specific centile curves revealed the same flaws with the LVMI method.

The 95th percentile LVMI in the reference group in the present study was much higher than previously published 95th percentile values. This reflects in large part the composition of the present reference population. Forty-five percent of the reference children in the present study were <6 years old, and 31% were <3 years old; 60% were <140 cm tall. The published 95th percentile LVMI of 38.615 and 38.06 g/m² were derived in populations in which the youngest subjects were 6 and 3 years old, respectively. However, even among reference children >10 years of age in the present study (in whom LVMI did not depend on height), the median and 95th percentile LVMI were 35.2 and 51.8 g/m², respectively, which was higher than in some prior studies but reasonably close to other studies. It appears that the estimated LV masses of reference children in the present study are higher relative to height than in some previously published groups. The reasons for this are not clear. It may reflect differences in sex or race distribution between the present reference population and prior healthy populations. Healthy blacks tend to have higher LV mass for height than Americans of European ancestry; if a greater proportion of the present reference children were black than in prior studies, this may explain the higher LVMI observed in the present study population. Unfortunately, race data were not available for the present study. A higher degree of adiposity in the present reference children than in prior studies may also have contributed to the higher LVMI. Although obese children were excluded, the body mass index-for-age percentile distribution for the present reference children was skewed toward higher values (Table 1). Higher adiposity has been recognized to be associated with higher LV mass. Finally, minor variations in both echocardiographic and height measurement techniques may also have had an influence on LVMI, but this should not have resulted in systematic differences.

The goal of the present study was not to develop definitive LV mass-for-height reference centile curves but rather to expose the flaws of the LVMI and to propose an alternative, superior method of expressing LV mass relative to body size in children. Regardless of whether the reference group in the present study does or does not reflect the “true” typical distribution of LV mass relative to height against which all other populations can be compared, the conclusions of this study are unaffected. We have demonstrated the dependence...
of LVMI on height in children and the resulting failure of a single LVMI cutoff to accurately identify LVH among children across a wide age range. Furthermore, we have proposed a new method of expressing LV mass relative to body size and demonstrated its consistent performance with respect to diagnosis of LVH across a broad range of body sizes.

Additional studies of large numbers of children may be required to create definitive reference centiles. Sex- and race-specific reference centiles would be ideal. Once created, these could easily be included in echocardiography software, which would allow automated generation of an LV mass-for-height z score and percentile for each child undergoing echocardiography. Uniform measurement methodology will be critical for meaningful application of reference standards.

Future studies aimed at further refining our ability to accurately diagnose LVH in children are also warranted. The physiological basis for normalizing LV mass to height alone is not particularly strong. LV mass, like cardiac output, is determined primarily by the demands of metabolically active tissues, or lean body mass.15,39,40 Although height correlates very well with lean body mass, the correlation is by no means perfect. Consideration should be given to the inclusion of additional easily measured body size variables, such as weight, in regression models used to normalize LV mass for body size. The combination of height and weight may provide a better surrogate for lean body mass than height alone, which could result in a superior prediction of expected LV mass. This approach differs from normalization for body surface area; although body surface area equations include both height and weight, the particular combination of height and weight is lost once the surface area calculation is done. Future work will address methods of expressing LV mass relative to both height and weight, as well as the physiological validity of such methods.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The diagnosis of left ventricular hypertrophy (LVH) in children and adolescents has important implications. Among hypertensive youth, for example, the presence of LVH may influence the decision to start or adjust antihypertensive therapy. The presence of LVH in children with aortic stenosis or other left-sided obstructive lesions may be an important factor in recommending intervention. It is therefore important that criteria for the diagnosis of LVH be valid and reliable. The left ventricular mass index (LVMI), expressed as $g/m^2$, has been gaining popularity as a method of normalizing left ventricular mass to body size in children. Fixed LVMI cutoffs, applicable to all children, have been proposed to define LVH and have been widely applied in prior pediatric studies. The present study examines the potential limitations of the LVMI in children. We demonstrate that the LVMI increases with decreasing height in healthy children $< 140$ cm tall and show that a fixed LVMI cutoff for LVH cannot be meaningfully applied to all children. We propose a new method of normalizing left ventricular mass for body size using centile curves and validate this method across a broad range of body sizes. The new method will allow accurate diagnosis of LVH in children of all sizes.
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