Effect of Growth on Variability of Left Ventricular Mass: Assessment of Allometric Signals in Adults and Children and Their Capacity to Predict Cardiovascular Risk

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Objectives. We sought to determine whether growth influences the relation between left ventricular mass and body size and whether use of different body size indexes affects the ability of ventricular mass to predict complications of hypertension.

Background. Allometric (or growth) signals between left ventricular mass and height have recently been reported to improve previous approaches for normalization of ventricular mass for body size.

Methods. Residuals of left ventricular mass–height relations were analyzed in a learning series of 611 normotensive, normal-weight subjects 4 months to 70 years old and, separately, in 383 children (<17 years old) and 228 adults. Ten-year cardiovascular mortality in a test series of 253 hypertensive adults was compared with groups with normal or high baseline left ventricular mass normalized for body weight, height, body surface area and allometric powers of height.

Results. The dispersion of residuals of ventricular mass versus height increased with increasing height or age in children but not in adults, suggesting that the effect of other variables on ventricular growth increases during body growth and stabilizes in adulthood. Therefore, we derived separate allometric signals for adults (predicted ventricular mass = 45.4 × height^{2.13}, r = 0.48) and children (32.3 × height^{2.3}, r = 0.85) (both p < 0.0001). Patients with left ventricular hypertrophy had 3.3 times higher cardiac risk with elevated ventricular mass/height^{2.7} (p < 0.001), 2.6 to 2.7 times higher risk with left ventricular mass indexed for height, height^{2.3} and body surface area (all p < 0.01) and 1.7 times the risk with ventricular mass/weight (p > 0.1).

Conclusions. These results show the following: 1) Variability of left ventricular mass in relation to height increases during human growth; 2) allometric signals of left ventricular mass versus height are lower in adults and children than those obtained across the entire age spectrum; 3) height-based indexes of left ventricular mass at least maintain and may enhance prediction of cardiac risk by hypertensive left ventricular hypertrophy; and 4) the allometric signal derived across the entire spectrum of age appears to be more useful for prediction of cardiovascular risk than that computed in adults.

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predict cardiovascular morbid events in a separate group of adult hypertensive patients.

Methods

Reference patients. The learning group for further analyses of left ventricular mass–body size relations included 611 normal-weight normotensive subjects, 4 months to 70 years old, studied by echocardiography in New York, Naples (Italy) or Cincinnati. This cohort was divided into groups of 383 children, 3 months to 17 years old, from Cincinnati (187 girls, mean ±SD age 9.5 ± 4.7 years; 196 boys, mean age 9.3 ± 4.7 years) and 228 adults, 18 to 70 years old (87 from Naples, 100 from New York, 41 from Cincinnati; 91 women, mean age 36.9 ± 14.6 years; 137 men, mean age 39.4 ± 14.1 years). Detailed characteristics of this reference group and echocardiographic methods have been reported previously (1).

Test patients. The test group consisted of 253 hypertensive patients (166 men, mean age 45 ± 13 years; 87 women, mean age 52 ± 11 years) with a mean clinical follow-up period of 10 years after a baseline evaluation that included echocardiography (3). During follow-up, 40 of 253 patients had a fatal or nonfatal cardiovascular event; major predictors of these events had been reported previously (3) to be age and presence of left ventricular hypertrophy identified using left ventricular mass normalized for body surface area.

Statistical analysis. To test the hypothesis that left ventricular mass–body size relations differ between children and adults, we plotted the distribution of residuals of the regression between left ventricular mass and height\(^{2.7}\) versus height and age. Residuals were standardized (i.e., residuals/square root of mean sum of squares for the error in the regression model) to approximate standard normal deviates. After having determined that the residuals had a different distribution between children and adults, we generated appropriate allometric signals for each group using a nonlinear regression analysis (7). To relate left ventricular mass to prognosis, it was indexed for height\(^{2.7}\) and for height to its allometric power in adults (generated in the present study), as well as for other measures of body size. Upper normal limits were taken from previous studies, or when published partition values were not available, they were calculated as the 97.5 percentile of values of normal adults in the present study (Table 1). The presence of left ventricular hypertrophy was analyzed in relation to the occurrence of cardiovascular events by chi-square statistics and Fisher exact test; the corresponding odds ratio was obtained, and the 95% confidence intervals were calculated using the Cornfield iterative method (8) and plotted for comparison. Odds ratios obtained with each left ventricular mass index partition value were compared with each other by calculating the chi-square statistics (Breslow-Day chi-square) from the summation of the logarithmic transformation of the odds ratios, weighted by the reciprocal of the sampling variances (8).

In the test group K-mean cluster analysis was also performed, using left ventricular mass/height\(^{2.7}\) as an independent variable and the occurrence of cardiovascular events as the grouping variable, to identify the optimal partition value for prognostically adverse levels of indexed left ventricular mass. Because of the potential confounding effect of age, age-adjusted log cumulative hazard functions were also computed using Cox proportional hazard analysis. The Breslow-Gehan log-rank test was used to compare survival curves. The null hypothesis was rejected at two-tailed \(p < 0.05\).

Results

Residual analysis. Figure 1 shows that the scatter of residuals of left ventricular mass versus age (i.e., present study) increased with increasing height (i.e., it was heteroscedastic) in the young subjects; it was stable (i.e., homoscedastic) in the adult subjects. When age was plotted on the x axis, the scatter of residuals of left ventricular mass about the zero line versus age (i.e., stable at different ages) in adults. Log transformation of left ventricular mass in children made the distribution of their residuals versus height homoscedastic.

Age-specific allometric equations and normal limits of indexed left ventricular mass. Because different distributions of residuals in children and adults appeared to be a real biologic phenomenon because of effects of age or growth, separate

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### Table 1. Partition Values for Identification of Left Ventricular Hypertrophy by Left Ventricular Mass Indexed for Various Measures of Body Size

<table>
<thead>
<tr>
<th>Source</th>
<th>Partition Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass/body surface area (g/m²) Reference 2</td>
<td>125</td>
</tr>
<tr>
<td>LV mass/height(^{2.7}) (g/m²(^{2.7})) Present study</td>
<td>51</td>
</tr>
<tr>
<td>LV mass/height(^{2.7}) (g/m²(^{3})) Present study</td>
<td>66</td>
</tr>
<tr>
<td>LV mass/height(^{2.7}) (g/m²(^{3})) Present study</td>
<td>61</td>
</tr>
</tbody>
</table>

LV = left ventricular.
allometric equations were calculated for children and adults. The allometric equations were: Left ventricular mass = 45.4 × Height$^{2.13}$ ($r = 0.48, p < 0.0001$) in adults and Left ventricular mass = 32.3 × Height$^{1.3}$ ($r = 0.85, p < 0.0001$) in children.

Gender-specific partition values (mean ± 1.96 × SD) for left ventricular mass indexed for height to the allometric powers obtained from the whole study group (i.e., 2.7) and that detected separately in adults (i.e., 2.13) and for other measures of body size are presented in Table 1. As in an earlier report from our laboratory (9), we assessed the performances of both gender-specific partition values and unified criteria applicable to detection of left ventricular hypertrophy in both genders.

**Assessment of ability to predict cardiovascular events (Table 2).** Table 2 shows the odds ratios, their 95% confidence intervals and Fisher exact tests of significance for the proportion of patients with a cardiovascular morbid event with or without left ventricular hypertrophy on the basis of different indexes of left ventricular mass. During follow-up, left ventricular mass indexed for body surface area or for height consistently demonstrated that a higher proportion of patients with left ventricular hypertrophy (23% to 29%) had a subsequent cardiovascular event than those without hypertrophy (9% to 12%). Left ventricular hypertrophy assessed using partition values for left ventricular mass/body weight did not significantly predict cardiovascular events. Of all indexes examined, identification of the proportion of patients who had a morbid event with or without baseline left ventricular hypertrophy was slightly better with height-based than body surface area indexes (Fig. 3). Among gender-specific criteria, a higher odds ratio was obtained using left ventricular mass/height$^{2.7}$ than left ventricular mass/body surface area, left ventricular mass/height or left ventricular mass/height$^{2.13}$. The latter three were virtually identical in performance to left ventricular mass/body surface area (all odds ratios 2.50 to 2.66).
To optimize the capacity to discriminate the level of risk using left ventricular mass/height$^{2.7}$, a cluster analysis was performed using occurrence of cardiovascular events as the grouping variable. A gender-independent partition value of 51 g/m$^{2.7}$ (representing the 97.5th percentile of normal distribution) was found to produce the best prediction. When this partition value was used, patients with left ventricular hypertrophy had a 4.1-fold greater risk of cardiovascular morbidity than hypertensive patients without left ventricular hypertrophy, greater than the 2.7-fold increased risk detected using our previous left ventricular mass/body surface area partition value (Table 2). Use of left ventricular mass/height$^{2.7}$ identified a larger number of patients with left ventricular hypertrophy with at least as high a proportion who had a morbid event than did left ventricular mass/body surface area (25 [29%] of 87 vs. 18 [27%] of 67), whereas the group with normal left ventricular mass by the new left ventricular mass/height$^{2.7}$ criterion was at lower risk (15 [9%] of 166 vs. 22 [12%] of 22, odds ratio 0.74 [95% confidence interval 0.37 to 1.0, $p = 0.05$]). Sensitivity of height-based methods was always >60%; using the unified criteria height$^{2.7}$ also maintained moderate specificity (Fig. 3). Comparison of the different odds ratios performed by adapting the Cornfield method (8) showed no heterogeneity among these separate estimates.

Life-table analyses showed that left ventricular mass >51 g/m$^{2.7}$ strongly predicted both event-free survival (Fig. 4) and freedom from cardiovascular mortality (Fig. 5) after adjustment for the strong effect of age.

**Discussion**

Ventricular mass body size relations at different ages. The present study showed that variability of left ventricular mass among subjects of a given body height increases during growth,
VARIABILITY OF LEFT VENTRICULAR MASS

Table 2. Proportion of Patients With or Without Left Ventricular Hypertrophy, Identified by Left Ventricular Mass Normalized for Different Measures of Body Size, Who Had a Cardiovascular Event During Follow-Up

<table>
<thead>
<tr>
<th>Unified criteria</th>
<th>LVH</th>
<th>No LVH</th>
<th>Odds Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Events</td>
<td>No. (%)</td>
<td>Total Events</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>LV mass/body surface area</td>
<td>67 (18)</td>
<td>186 (22)</td>
<td>2.74 (1.36-5.51)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>LV mass/height&lt;sup&gt;2.7&lt;/sup&gt;</td>
<td>87 (25)</td>
<td>166 (15)</td>
<td>4.06 (2.01-8.22)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LV mass/height&lt;sup&gt;2.13&lt;/sup&gt;</td>
<td>94 (25)</td>
<td>159 (15)</td>
<td>3.48 (1.72-7.01)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Gender-specific criteria

| LV mass/body surface area | 92 (22)       | 161 (18)       | 2.50 (1.26-4.96)    | < 0.01  |
| LV mass/height           | 108 (25)      | 145 (15)       | 2.61 (1.30-5.24)    | < 0.008 |
| LV mass/weight           | 65 (14)       | 188 (26)       | 1.71 (0.83-3.52)    | < 0.17  |
| LV mass/height<sup>2.7</sup> | 97 (25)      | 156 (15)       | 3.26 (1.62-6.57)    | < 0.001 |
| LV mass/height<sup>2.13</sup> | 107 (25)    | 146 (15)       | 2.66 (1.33-5.35)    | < 0.008 |

CI = confidence interval; LV = left ventricular; LVH = left ventricular hypertrophy.

reaching a relatively stable level after puberty. Left ventricular weight in infancy is mostly determined by the number of cardiac myocytes, which reach their maximal number during the first year (10). After the first year, continued left ventricular growth depends on the increasing size of the myocytes (i.e., physiologic hypertrophy). During growth, many factors influence this physiologic process (e.g., body size changes, blood pressure, circulatory volume load, genetic factors, salt intake, blood viscosity) (11–14). These factors contribute to the phenotypic determination of myocardial growth over time and produce increasing variability of left ventricular mass in relation to its initial determination by infant body size. The relation between left ventricular mass and body height to its

Figure 3. Risk of follow-up cardiovascular morbid events using normal distribution-based partition values of left ventricular mass (LVM) indexed by various measures of body size. The risk is represented by odds ratios (circles) and the respective 95% confidence intervals (bars). Numbers above the bars are sensitivity/specificity for each method. Unified left ventricular mass/height<sup>2.7</sup> produces the highest odds ratio and the best sensitivity/specificity ratio. BSA = body surface area.

allometric power was indeed extremely close among young children and exhibited increasing scatter through later childhood and adolescence, as shown in Figures 1 and 2. After puberty, factors other than body height that determine the extent of physiologic hypertrophy of left ventricular myocytes are already operating, and the variability of left ventricular mass to body size does not increase appreciably among apparently normal adults into early old age. Thus, the different distribution of residuals in children and adults represents a biologic phenomenon indicating that the accuracy of prediction of left ventricular mass by height decreases with maturation.

In adults, the observed values of left ventricular mass increased with increasing age (not with increasing height) more than the value predicted by height<sup>2.7</sup>. This trend is most likely due to the effects of both an age-related increase in blood pressure in men and women and changes in hormonal status in women (15) on the level of left ventricular mass that would be

Figure 4. Probability of event-free survival during follow-up in hypertensive patients with increased or normal left ventricular (LV) mass indexed for body height<sup>2.7</sup>.
the explanation for this finding is uncertain, one possibility is to identify high risk status in women and men (2,3). Although mass/body surface area or left ventricular mass/height appear better than gender-specific partition values. This result parasite patients with or without follow-up cardiovascular event even further, one can hypothesize that women may have more of a hypertropic reserve than men before their left ventricular mass reaches values associated with an adverse prognosis. This in turn could contribute to relative cardiovascular protection in women. However, the unified partition value for left ventricular mass/height is identified retrospectively and must be related to prognosis prospectively in a different population sample.

Conclusions. 1) Analysis of residuals of the allometric or growth relation between left ventricular mass and height reveals a different relation for children versus adults between variability of left ventricular mass around the allometric or growth relation between it and height and either age of height. 2) Allometric signals for left ventricular mass in relation to height in separate groups of children and adults are lower than those obtained across the entire age spectrum. 3) Height-based methods of indexing left ventricular mass maintain or possibly enhance the prediction of cardiac risk by left ventricular hypertrophy in arterial hypertension. 4) The allometric signal derived from normal subjects across the entire spectrum of age may predict cardiovascular risk even better than the allometric signal computed only for adults.

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References
3. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in men and women with essential hypertension. Ann Intern Med 1991;114:345–52.


