

## 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<sup>2.7</sup> 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 morbidity 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<sup>2.7</sup> 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 =  $45.4 \times \text{height}^{2.13}$ ,  $r = 0.48$ ) and children ( $32.3 \times \text{height}^{2.3}$ ,  $r = 0.85$ ) (both  $p < 0.0001$ ). Patients with left ventricular hypertrophy had 3.3 times higher cardiac risk with elevated left ventricular mass/height<sup>2.7</sup> ( $p < 0.001$ ), 2.6 to 2.7 times higher risk with left ventricular mass indexed for height, height<sup>2.13</sup> 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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The relations between left ventricular mass and height or body surface area are not linear, but are regulated by allometric (or growth) functions from which exponents (also called allometric signals) may be derived that linearize left ventricular mass–body size relations (1,2). On the basis of findings in normal-weight normotensive subjects from infancy through the seventh decade, we proposed height<sup>2.7</sup> as the most appropriate measure of body size to normalize left ventricular mass. To our knowledge, there is no information about whether left ventric-

ular mass normalized by this approach can predict cardiovascular complications of arterial hypertension as well as or better than has been previously reported for left ventricular mass normalized for body surface area or height to the first power (3-6). Because the proportionality between left ventricular mass and height<sup>2.7</sup> was derived from subjects two thirds of whom were children or adolescents, whereas the risk of cardiovascular morbidity and mortality in hypertension only becomes appreciable in adults, especially those of middle or older age, it would be desirable to understand whether the allometric signal obtained in the whole population sample (and containing growth information) detects clinically important left ventricular hypertrophy in adults. Accordingly, we analyzed further the relations between left ventricular mass and body size separately in children and adult members of our reference group to identify the allometric relation between left ventricular mass and height in adults. Additional analyses compared the impact of using traditional versus allometric-based criteria to index left ventricular mass for body size on the ability to

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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 [ $\pm$ SD] age  $9.5 \pm 4.7$  years; 196 boys, mean age  $9.3 \pm 4.7$  years) and 228 adults, 18 to 70 years old (87 from Naples, 100 from New York, 41 from Cincinnati; 91 women, mean age  $36.9 \pm 14.6$  years; 137 men, mean age  $39.4 \pm 14.1$  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  $45 \pm 13$  years; 87 women, mean age  $52 \pm 11$  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<sup>2.7</sup> 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<sup>2.7</sup> 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 were 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<sup>2.7</sup> as an independent variable and the occurrence of cardiovascular events as the grouping

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

	Source	Partition Values
Unified criteria		
LV mass/body surface area (g/m <sup>2</sup> )	Reference 2	125
LV mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	Present study	51
LV mass/height <sup>2.13</sup> (g/m <sup>2.13</sup> )	Present study	66
Gender-specific criteria		
LV mass/body surface area (g/m <sup>2</sup> )	Present study	
Men		117
Women		104
LV mass/height (g/m)	Present study	
Men		126
Women		105
LV mass/weight (g/kg)	Present study	
Men		3.1
Women		3.0
LV mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	Present study	
Men		50
Women		47
LV mass/height <sup>2.13</sup> (g/m <sup>2.13</sup> )	Present study	
Men		68
Women		61

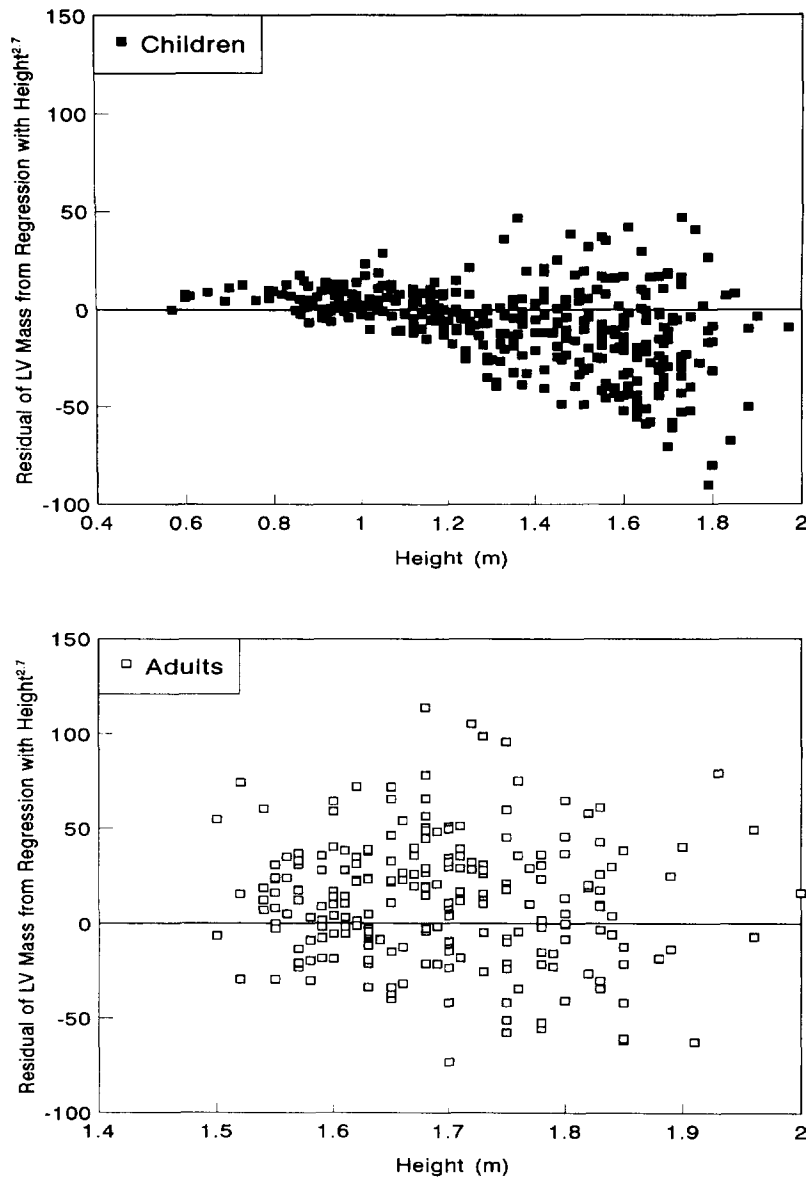
LV = left ventricular.

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 height<sup>2.7</sup> about the zero line 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 height<sup>2.7</sup> increased until about age 18 and became stable after that age. There was a tendency toward a higher proportion of positive than negative residuals in middle-aged and older subjects (Fig. 2); this tendency was absent in adults when residuals were plotted against height (Fig. 1). Thus, the distribution of ventricular mass-height<sup>2.7</sup> residuals was heteroscedastic compared with that for age (i.e., increased with age) in younger subjects but was more nearly homoscedastic (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



**Figure 1.** Relation of residual (g) of the regression between left ventricular (LV) mass and height<sup>2.7</sup> ( $r = 0.84$ ) plotted versus height in 383 children 4 months to 17 years old (**top**) and adults (**bottom**). The dispersion about the zero line increased with height in children.

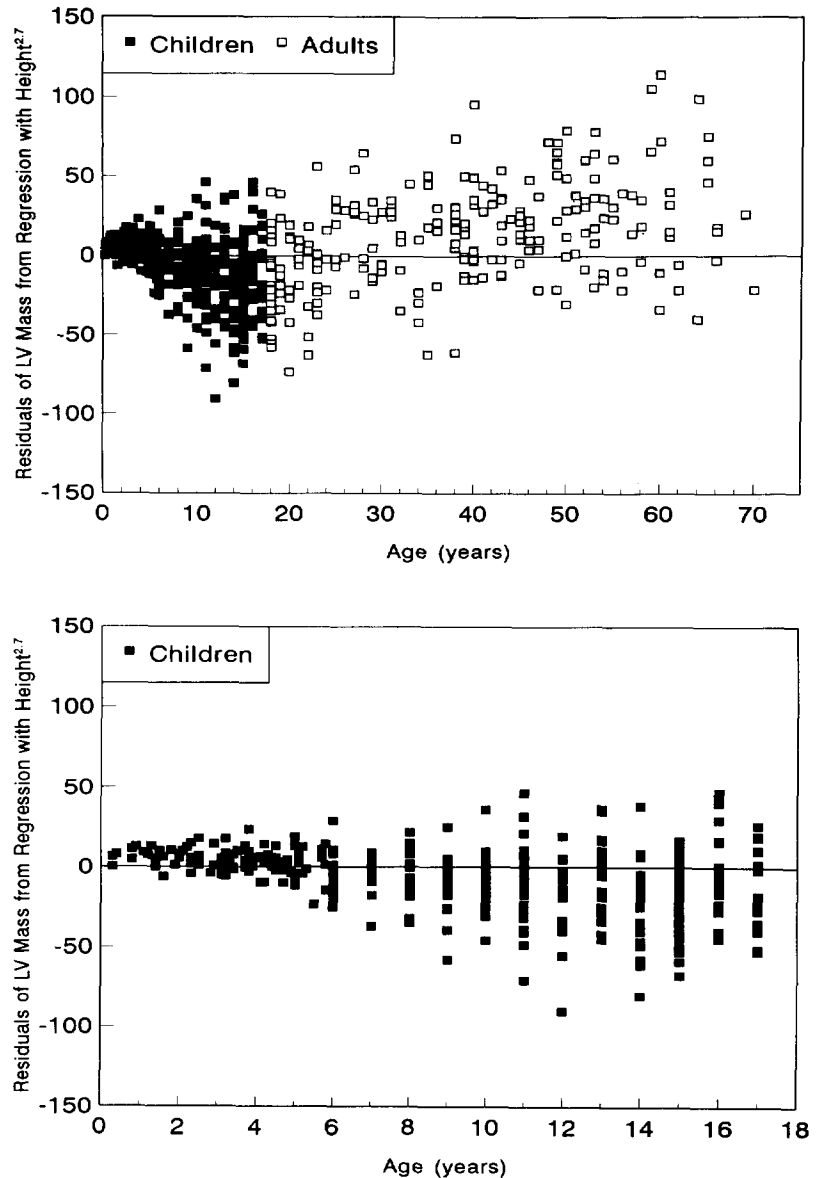
allometric equations were calculated for children and adults. The allometric equations were: Left ventricular mass =  $45.4 \times \text{Height}^{2.13}$  ( $r = 0.48$ ,  $p < 0.0001$ ) in adults and Left ventricular mass =  $32.3 \times \text{Height}^{2.3}$  ( $r = 0.85$ ,  $p < 0.0001$ ) in children.

Gender-specific partition values (mean  $\pm 1.96 \times \text{SD}$ ) 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<sup>2.7</sup> than left ventricular mass/body surface area, left ventricular mass/height or left ventricular mass/height<sup>2.13</sup>. The latter three were virtually identical in performance to left ventricular mass/body surface area (all odds ratios 2.50 to 2.66).

**Figure 2. Top,** Relation of residuals (in g) of the regression between left ventricular (LV) mass and height<sup>2.7</sup> ( $r = 0.84$ ) plotted versus age in 383 children (closed squares) and 228 adults (open squares). The dispersion about the zero line increased with age in children but was stable in adults. In adults the residuals indicate that observed left ventricular mass tended to exceed that predicted by height<sup>2.7</sup> in middle and older age. **Bottom,** Magnification of the portion of the relation in subjects 4 months to 17 years of age. The heteroscedasticity of the distribution is evident.



To optimize the capacity to discriminate the level of risk using left ventricular mass/height<sup>2.7</sup>, a cluster analysis was performed using occurrence of cardiovascular events as the grouping variable. A gender-independent partition value of 51 g/m<sup>2.7</sup> (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<sup>2.7</sup> 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<sup>2.7</sup> 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<sup>2.7</sup> 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<sup>2.7</sup> 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,

**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

	LVH		No LVH		Odds Ratio (95% CI)	p Value
	No. of Pts	No. (%) of Total Events	No. of Pts	No. (%) of Total Events		
Unified criteria						
LV mass/body surface area	67	18 (27)	186	22 (12)	2.74 (1.36-5.51)	< 0.01
LV mass/height <sup>2.7</sup>	87	25 (29)	166	15 (9)	4.06 (2.01-8.22)	< 0.0001
LV mass/height <sup>2.13</sup>	94	25 (27)	159	15 (9)	3.48 (1.72-7.01)	< 0.001
Gender-specific criteria						
LV mass/body surface area	92	22 (24)	161	18 (11)	2.50 (1.26-4.96)	< 0.01
LV mass/height	108	25 (23)	145	15 (10)	2.61 (1.30-5.24)	< 0.008
LV mass/weight	65	14 (21)	188	26 (14)	1.71 (0.83-5.52)	< 0.17
LV mass/height <sup>2.7</sup>	97	25 (26)	156	15 (10)	3.26 (1.62-6.57)	< 0.001
LV mass/height <sup>2.13</sup>	107	25 (23)	146	15 (10)	2.66 (1.33-5.35)	< 0.008

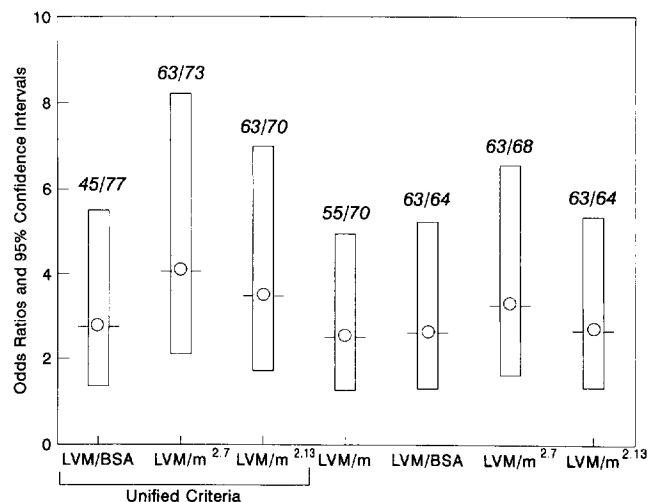
CI = confidence interval; LV = left ventricular; LVH = left ventricular hypertrophy.

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

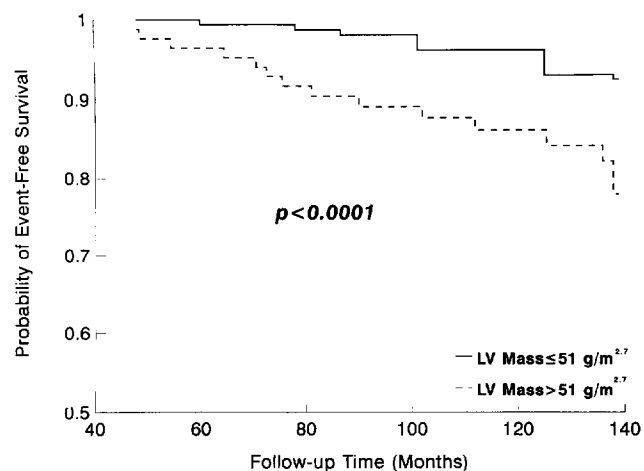
allometric power was indeed extremely close among young children and exhibited increasing scatter through later childhood and adolescence, as shown in Figures 1 and 2. After puberty, factors other than body height that determine the extent of physiologic hypertrophy of left ventricular myocytes are already 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.

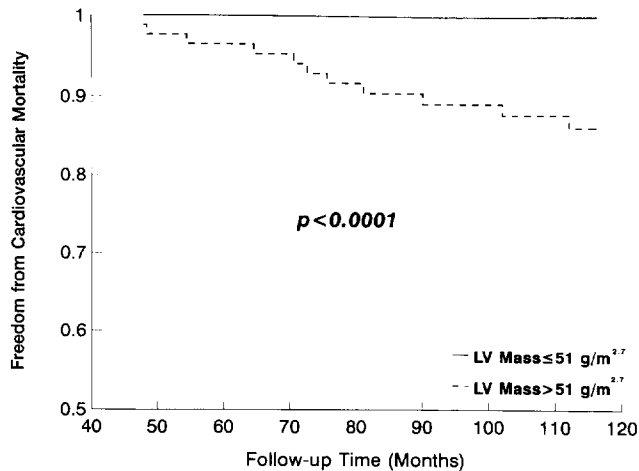
In adults, the observed values of left ventricular mass increased with increasing age (not with increasing height) more than the value predicted by height<sup>2.7</sup>. This trend is most likely due to the effects of both an age-related increase in blood pressure in men and women and changes in hormonal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

**Figure 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.



**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>.





**Figure 5.** Probability of survival free of cardiovascular mortality during follow-up in hypertensive patients with increased or normal left ventricular (LV) mass indexed for body height<sup>2.7</sup>.

predicted for the given height. When children and adults were evaluated separately, slightly lower allometric signals were obtained than had been identified in the whole study sample, because of this difference. The allometric power of 2.13 that we found from the ventricular mass-body height relation in adults closely resembles the finding among apparently normal women and men in the Framingham Study (16) that left ventricular mass was most closely related to height to the 2.0 to 2.1 power, suggesting reasonable stability of this result across populations.

**Relation of ventricular mass indexation to prognosis.** Our second set of analyses, performed in a group of hypertensive patients followed up for 10 years, found that the best predictor of future cardiovascular risk was obtained using partition values for left ventricular mass/height<sup>2.7</sup> to define left ventricular hypertrophy. Although comparison among the different odds ratios did not give statistically significant results, this comparison tests the hypothesis of significant heterogeneity among the 2 × 2 tables, which was unlikely to occur because all the indexes were formed using the same variable, that is, left ventricular mass. Our findings suggests that the growth information contained in the allometric signal obtained from the whole reference group may be useful for identifying prognostically adverse levels of left ventricular hypertrophy. Conversely, the only method of indexing that rendered statistically nonsignificant the predictive value of left ventricular mass was that for body weight, supporting previous suggestions (17,18) that it is undesirable to use an index that would be forgiving of overweight.

A common partition value of 51 g/m<sup>2.7</sup> for both women and men was also identified by discriminant analysis and separated patients with or without a follow-up cardiovascular event even better than gender-specific partition values. This result parallels previous evidence that similar values of left ventricular mass/body surface area or left ventricular mass/height appear to identify high risk status in women and men (2,3). Although the explanation for this finding is uncertain, one possibility is

that initial left ventricular mass is nearly the same in young girls and boys (e.g., 30 ± 9 vs. 32 ± 8 g in subjects <5 years old in the present series) and that a physiologic left ventricular hypertrophy develops in adult men in response to the hormonal cascade occurring in puberty. Carrying this reasoning further, one can hypothesize that women may have more of a hypertrophic 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<sup>2.7</sup> was 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 or 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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