Interaction Between Body Size and Cardiac Workload
Influence on Left Ventricular Mass During Body Growth and Adulthood

Giovanni de Simone, Richard B. Devereux, Thomas R. Kimball, Gian Francesco Mureddu, Mary J. Roman, Franco Contaldo, Stephen R. Daniels

Abstract—The development of the left ventricle parallels body growth. During infancy, the relation between body size and left ventricular (LV) mass is very close. With advancing age, variability of LV mass in relation to body size markedly increases. To test the hypothesis that the age-related increase in variability of LV mass is due to the progressive impact of hemodynamic stimuli on LV growth, quantitative M-mode echocardiograms were obtained in 766 normal-weight, normotensive individuals over a range of ages from 1 day to 85 years (330 female subjects, 373 subjects younger than 18 years). LV mass was linearly related to height$^{2.7}(r^2=.69).$ Prediction of values of LV mass by body size was more accurate at birth and progressively less precise with increasing age. Stroke work (stroke volume times systolic pressure) was closely related to LV mass ($r^2=.74).$ The explained variance of LV mass increased from 69% in the univariate regression with height$^{2.7}$ to 82% in a multivariate model including height$^{2.7},$ stroke work, and gender. In children and adolescents (younger than 18 years), height$^{2.7}$ was the main determinant of LV mass, whereas during adulthood stroke work and gender were more important predictors of LV mass than height$^{2.7}.$ Thus (1) the influence of body growth on development of LV mass decreases after early infancy because of both the variability of hemodynamic load and the increasing effect of gender; (2) after adolescence, during adulthood, in normotensive, normal-weight individuals, the impact of hemodynamic load and male gender on LV mass is greater than the one of body size; and (3) an appreciable proportion of variability of LV mass remains unexplained with the studied models. This might be due to genotypic variations and/or measurement error. (Hypertension. 1998;31:1077-1082.)

Key Words: age ■ hemodynamics ■ gender ■ ventricular function, left ■ hypertrophy, left ventricular

Body growth influences cardiac development. The close relation between body size and left ventricular (LV) mass$^1$ during childhood and adolescence is the hallmark of this influence. However, in infancy virtually the entire variability of LV mass is explained by body size, whereas with increasing age the ability of body size to precisely predict LV mass decreases. In fact, the difference between the value of observed LV mass and that predicted from body size increases with increasing age (heteroscedastic distribution of residuals).$^2$ This phenomenon might be explained by the progressive hemodynamic load that faces the left ventricle right after birth as the fundamental stimulus for LV muscular development. There is little information on the interaction between change in body size and in cardiac workload induced by body growth in relation to development of LV mass in large normal populations across a wide age span. Accordingly, this study has been designed to investigate the relation between the age-related increase in LV mass and the age-related change in cardiac workload by taking into account the influence of body size during body growth and adulthood in a large study population of normotensive, normal-weight individuals.

Methods

Seven hundred sixty-six normal-weight, normotensive individuals, 1 day to 85 years old, were studied in three centers: 212 men and 138 women from a cohort of employed adults evaluated at the New York Hospital–Cornell Medical Center; 139 boys and 127 girls as part of a population-based epidemiological study at the Children’s Hospital, University of Cincinnati; and 69 boys, 42 girls, 16 men, and 23 women as part of population-based studies at Federico II University of Naples, Italy. Among the 766 subjects, 393 were older than 17 years, and 330 were female (166 children to adolescents and 164 adults). Detailed information on this cohort has been previously reported.$^{1,4}$

Procedures

Informed consent was obtained from all adult volunteers and from parents or guardians of children under protocols approved by the Institutional Review Boards for Research in Human Subjects. Blood pressure was measured with mercury sphygmomanometers and cuffs of appropriate size. In adults, blood pressure below 140/90 mm Hg (three readings in at least two clinical examinations) was considered normal. In American children 1 year of age or older, normal blood pressure was defined according to criteria presented by Rosner et al,$^5$ based on 95th percentile of a gender- and height-specific normal distribution. Children under 1 year of age were assumed to have normal blood pressure when systolic and diastolic blood pressures...
were lower than 101/55 mm Hg, the 95th percentile of blood pressure values in 1-year-old boys at the 25th percentile of height. In Italian children, who have been reported to have higher average blood pressure than children of the same age from other European countries, normal blood pressure was established by the Blood Pressure Tables of the Italian Society of Pediatrics for Italian children. In a subset of 223 of the New York subjects who also underwent 24-hour blood pressure monitoring, the resting systolic pressure used for this study was at least as closely correlated with LV mass as was the awake ambulatory systolic blood pressure (r=.41 and .39, respectively, both P<.0001; P=NS for difference between the two correlation coefficients). Mean awake systolic blood pressure was modestly higher than resting systolic blood pressure, by 5.9 ± 0.9 mm Hg (P<.001 by paired t test).

Body weight and height were measured on the day of echocardiographic examination. Definition of normal weight was based on gender-specific body mass index partition values from the 1985 NIH Consensus Conference for adults. For children and adolescents older than 3 to 12 years of age, the age-based method recommended by Himes and Dietz was used to define normal weight. Children younger than 3 years old were considered normal weight.

Echocardiography
Two-dimensionally targeted M-mode echocardiograms were performed by expert sonographers as previously described with the subjects in a partial left decubitus position and in held expiration, when possible, with commercially available echocardiographs. M-mode tracings were recorded on strip-chart paper at 50 mm/s. In New York, echocardiograms were performed by a single experienced sonographer and read by an experienced investigator (R.B.). In Naples, echocardiograms were performed by a single experienced sonographer and double-read by two experienced investigators (G.F.M. and G. de S.). In Cincinnati, echocardiograms were performed by two experienced sonographers and double-read by two experienced investigators (T.R.K. and S.R.D.). In these centers the two readers’ measurements were averaged. Measurements of interventricular septal thickness, posterior wall thickness, and LV dimensions were taken at or just below the mitral valve tips, by the leading edge-to-leading edge method, according to the American Society of Echocardiography recommendations. Interobserver and intraobserver variability for echocardiographic measurements from the laboratories involved in the present study has been previously reported. Short- and long-term test-retest analyses on various M-mode primary or derived measurements have also been reported from all three laboratories.

LV mass was calculated by adjusted ASE-method and was normalized for height, as previously reported. LV end-diastolic and end-systolic volumes were calculated with the Teichholz constant-volume formula by this method, as recently shown to parallel closely Doppler-derived stroke volume with a mean difference of 2 mL/beat in a large population sample. Blood pressure was recorded at the end of echocardiographic examination, with arm-cuff sphygmomanometer with cuffs of appropriate size for children and infants. Stroke work (SW) was estimated as systolic blood pressure times stroke volume and was normalized for height2.7, as previously reported. Stroke work (SW) was lower (by a mean of 26% ± 5%) but closely correlated (r=.99, P<.0001) with those derived by systolic arterial pressure (SWa=0.14+0.74SW±4); similarly, use of awake systolic blood pressure gave stroke work values that were closely correlated with those obtained by resting systolic pressure (r=.95, P<.0001). Stroke work index was calculated as systolic blood pressure times stroke volume (stroke work/body surface area).

Statistical Analysis
Because Italian children had blood pressure values slightly higher than same-age Americans, analyses have been adjusted for “center effect” by use of the following procedure: primary echocardiographic measurements (end-diastolic and end-systolic LV internal dimension and wall thickness), blood pressure, and heart rate were related as dependent variables to a dichotomous variable representing the center in age-matched groups of subjects. Thus Italian children were combined with Cincinnati children in the same range of age (6 to 11 years) and Italian adults were combined with New York adults in the same range of age (20 to 69 years) and dependent variables were related to the dummy variable indicating the center (1 or 2). The variables considered in this preliminary analysis were therefore adjusted by the linear coefficient of regression (r). Thus the adjusted variable (adjV) was adjV=V−b(x−μ), where V was the observed value of the dependent variable, x was the dummy variable representing the Center, and μ was the average value of the variable representing the centers.

Data are expressed as mean±SD. The 95% confidence interval is also reported for variables derived from echocardiographic measurements. The χ2 statistic was used for categorical variables. Student’s t test was used for simple comparisons of continuous variables. Least squares linear regression was used to assess univariate relations. Distribution of residuals of the relation of LV mass to height in relation to age was assessed by least squares linear regression of their absolute value versus age. Weight estimation was used to determine the extent of impact of increasing age on the precision of prediction of LV mass from body size. With this procedure, data points were weighted by the reciprocal of age to a power determined by a best-fitting iteration in which the program evaluated the log-likelihood function for all powers within a given grid (−2 to 2) to select the power correspondent to the largest log-likelihood.

Stepwise multiple regression analysis was used to study the hemodynamic and demographic predictors of LV mass, with F to enter and F to remove set to P<.05 and to P<.10, respectively. Gender was treated as a dummy variable, by assigning 1 to male subjects and 2 to female subjects. Unstandardized β coefficients (slope) with relative standard error, standardized β coefficients and the value of constant±SE are reported for each model. Statistical significance was set at a two-tailed value of P<.05.

Results
Table 1 shows demographic characteristics in children-adolescents and in adults. Table 1 also shows that males exhibited higher values of LV mass (as both absolute values and normalized for height), stroke volume, stroke index, stroke work, and stroke work index than females (.05<P<.0001) in both age strata, with greater differences during adulthood.

Effect of Age on Relation Between LV Mass and Body Size
LV mass was related to all measures of body size, linearly to body weight (r=1.84) and by allometric signals to body surface area (r=53x1.5) and body height (Fig 1; y=27x1.8; all P<.0001). For consistency with our initial study in a nonoverlapping subject population, height was used as the main measure of body size linearly related to LV mass. Similar to the findings in the previous study-population, residuals of the relation between LV mass and height increased their dispersion with increasing age during infancy, childhood, and early adolescence (heteroscedastic distribution, Fig 2), whereas the dispersion was more homogeneous across the age span during adulthood (homoscedastic distribution, Fig 2).

A weight estimation of LV mass was therefore implemented by using age (ie, a physiologically possible source of heteroscedasticity as shown by Fig 1) as a weight variable. With this procedure, explained variance of LV mass rose to 91% (R2=.91, SEE=6.2 g, P<.0001). The effects on the relation between LV mass and body height of variables other
than body size, able to influence development of LV mass, were therefore examined.

**Interaction Between Body Size, Cardiac Workload, and LV Mass**

Cardiac workload was measured as stroke work. The relations of the two components of stroke work to age were determined. Systolic blood pressure increased by 0.33 mm Hg per year in the age stratum formed by infants, children, and adolescents (n=373, r=.13, P<.0001) and, similarly, by 0.33 mm Hg per year in the wider age range of the adult population (n=393, r=.40, P<.0001). In contrast, stroke volume increased markedly between birth and 17 years (2.7 mL/beat per year, r=.64, P<.0001), whereas it was stable during adulthood (r=−.02, P=NS).

Stroke work increased with age by 4.44 g-m/beat per year in infants, children, and adolescents (P<.0001) and by 0.30 g-m/beat per year in adults (P<.02) (Fig 3).

In the entire study population, LV mass was closely related to systolic blood pressure (r=.56, P<.0001), stroke volume (r=.85, P<.0001), and stroke work (Fig 4, r=.86, P<.0001). Increase in LV mass with increasing stroke work was similar in children and adults (0.87 and 0.82 g/m−g per beat, respectively), as well as in boys and girls (0.96 and 0.74 g/m−g per beat) and men and women (0.70 and 0.63 g/m−g per beat).

Table 2 shows that among infants, children, and adolescents, the ratios of stroke work to LV mass was not statistically different in males and females, whereas the values were lower by a mean of 8% in adult men than in women (P<.0001). This result remained statistically significant even after taking into account body surface area.

In the whole study population, the variance of LV mass associated with independent variables increased from the 69% observed for the univariate relation with height to 82% in a multiple regression model including sex (slope=−5.71±1.57, β=−0.06, P<.0001) and stroke work (slope=0.65±0.03, β=0.52, P<.0001) in addition to height (slope=17.05±0.97, β=0.42, P<.0001; constant=−10.85±3.65, multiple R = .90, SEE = 21 g, P<.0001). When systolic blood pressure and stroke volume were added to the regression model, the result did not change: partial r values were .004 for systolic blood pressure and −.03 for stroke volume (both P=NS). Similar results were obtained in a subset of 133 adults who also had Doppler stroke volume measurements: neither resting systolic press-

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**Table 1. Demographics, LV Mass, and Hemodynamic Parameters in Normal Individuals**

<table>
<thead>
<tr>
<th></th>
<th>Boys (n=207)</th>
<th>Girls (n=166)</th>
<th>Men (n=229)</th>
<th>Women (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>9.8±3.4</td>
<td>9.7±3.3</td>
<td>46±12</td>
<td>44±13</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>37±17</td>
<td>35±15†</td>
<td>74±8</td>
<td>61±9§</td>
</tr>
<tr>
<td>Body height, m</td>
<td>1.40±0.23</td>
<td>1.37±0.31†</td>
<td>1.75±0.08</td>
<td>1.62±0.07§</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>106/63±8/9</td>
<td>105/63±9/9</td>
<td>121/75±9/7</td>
<td>114/70±12/8†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>80±14</td>
<td>82±13</td>
<td>66±11</td>
<td>69±11</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>71±32</td>
<td>62±25‡</td>
<td>155±33</td>
<td>111±25§</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>(30–133)</td>
<td>(28–106)</td>
<td>(110–216)</td>
<td>(71–152)</td>
</tr>
<tr>
<td>Stroke volume, mL/beat</td>
<td>48±14</td>
<td>44±14‡</td>
<td>78±16</td>
<td>64±12§</td>
</tr>
<tr>
<td>Stroke index, mL/beat/m²</td>
<td>42±9</td>
<td>39±9*</td>
<td>43±8</td>
<td>40±7§</td>
</tr>
<tr>
<td>Stroke work, g-m/beat</td>
<td>74.12±20.33</td>
<td>67.84±24.28*</td>
<td>136.15±30.38</td>
<td>105.21±25.06§</td>
</tr>
<tr>
<td>Stroke work index, g-m/beat/m²</td>
<td>(37.81–118.21)</td>
<td>(39.41–114.95)</td>
<td>(93.41–194.30)</td>
<td>(63.42–151.29)</td>
</tr>
</tbody>
</table>

LV indicates left ventricular.

95% confidence intervals are shown in parentheses.

*P<.05; †P<.01; ‡P<.005; §P<.0001 for gender difference within age stratum.

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**Figure 1. Relation between left ventricular (LV) mass and height in 373 children and adolescents (□) and 393 adults (●): The allometric signal regulating this relation is 2.8 (r=.834), similar to 2.73 (r=.833, SEE=28.7 g, in the present study-population) previously reported in Reference 1.**
sure nor stroke volume (both $P > .06$) added to the significant association ($P < .0001$) between LV mass and stroke work by the formula used in this study. Weighting for age slightly increased the magnitude of variance of LV mass associated with independent variables (86%) compared with the un-weighted model (82%), indicating that most of the association between age and LV mass in this model appeared to be mediated by age-related increases in stroke work and by the effect of male gender after puberty. In this analysis, 18% of variance of LV mass was not mathematically attributed to demographic or hemodynamic factors.

Regression analysis was also repeated in separate groups of children and adolescents, and adults. In children and adolescents, height$^{2.7}$ was the main determinant of LV mass (slope = $17.8 \pm 0.98$, $\beta = 0.63$, $P = .0001$), with minor but significant independent contributions of stroke work (slope = $0.36 \pm 0.04$, $\beta = 0.30$, $P < .0001$) and sex (slope = $-3.88 \pm 1.55$, $\beta = -0.07$, $P < .01$; constant = $1.58 \pm 3.47$ g; multiple $R = .87$, SEE = $14.7$ g, $P < .0001$). In contrast, during adulthood, the level of LV mass was most strongly associated with stroke work (slope = $0.64 \pm 0.04$, $\beta = 0.56$, $P < .0001$) and sex (slope = $-18.1 \pm 3.23$, $\beta = -0.24$, $P < .0001$) and less strongly with height$^{2.7}$ (slope = $6.63 \pm 2.48$, $\beta = 0.12$, $P < .001$; constant = $55.37 \pm 13.82$ g; multiple $R = .78$, SEE = $23.2$ g, $P < .0001$).

**Discussion**

Studies of comparative physiology have shown that the fundamental determinant of dimensions, and often functions, of organs is body size, in mammals as well as in other animals. The weight of the human left ventricle follows this rule and has been shown to strictly depend on body size, especially during body growth. The positive influence of body size, however, progressively decreases during body growth until the maturation

| Boys (n=207) | 1.15 $\pm$ 0.36 | 1.13 $\pm$ 0.77 |
| Girls (n=166) | 1.18 $\pm$ 0.38 | 1.18 $\pm$ 0.88 |
| Men (n=229) | 0.89 $\pm$ 0.17* | 0.47 $\pm$ 0.1* |
| Women (n=164) | 0.97 $\pm$ 0.23 | 0.59 $\pm$ 0.15 |

LV indicates left ventricular.

* $P < .0001$ vs women.
of the body is completed. This phenomenon is clearly shown by the heteroscedastic distribution of residuals of the relation between LV mass and body height, plotted with age, as reported in a previous study-population and confirmed in the present nonoverlapping population that extends our previous observations to the neonatal period. The present study also confirms our previous observations that, in contrast, the distribution of residuals of the LV mass–body height relation in adults is homogeneous (heteroscedastic).

The increasing error of prediction of LV mass by a measure of body size (height in this study) with increasing body size (and age) may be due to (1) increasing methodological error with the increasing magnitude of LV mass; (2) unrelated and undetectable biological phenomena; or (3) changes in biological variables other than body size occurring with increasing age. In the present study this third hypothesis has been tested. It was made evident by a weighting procedure that the role of age as a source of heteroscedasticity of residuals of LV mass was associated with a real biological phenomenon that could help to explain the progressively increasing scatter of residuals. Increase in stroke work with age was primarily due to rising mean levels and interindividual variability of arterial pressure in adults and to increasing levels of scatter of both blood pressure and stroke volume in children and adolescents.

Previous studies from this and other laboratories have shown that volume load is an even more important determinant of increase in LV mass than blood pressure, even when the latter is measured by ambulatory monitoring. Of note, the statistically independent association of higher Doppler-derived stroke volume with LV mass has been presumed to be mediated by stimulation of LV growth by an increase in end-diastolic LV wall stress. The evidence that LV concentric remodeling is associated with very high peripheral resistance and low stroke volume suggests that the interaction between the two hemodynamic components (volume and pressure) is crucial for increasing LV mass. Accordingly, stroke work represents an approximate measure of this interaction. Stroke work rises quickly after birth and on average reaches a maximum level at the time of complete body maturation, when both stroke volume and blood pressure are stabilized. During adulthood, aging is only weakly associated with further increase in stroke work in normotensive individuals. As expected from the above considerations, the relation of LV mass with stroke work was strong and, in multivariate analysis, completely excluded arterial pressure and stroke volume from the regression model.

The close linear relation with a near-zero intercept between stroke work and LV mass confirms the appropriateness of normalizing stroke work for the first power of LV mass, a ratio used in the past as an index of LV performance. Application of this procedure in our population study allowed us to clarify that stroke work per unit of LV mass was higher in females than in males, a difference that attained statistical significance during adulthood. Therefore, for comparable LV mass, adult women develop more cardiac work at rest than men, suggesting better resting LV performance, consistent with previous findings from these and other laboratories.

In regression analysis a substantial part of the variance of LV mass that remained statistically unexplained could be due to both intrinsic error of measurements, and, perhaps mainly, undetectable (in this study) genetic or environmental influences. The extent of technical error can be suggested to be at least 9%, which is the difference between the variance of LV mass that is expected to be explained by the weighting procedure (91%) and that actually explained in multivariate model including body size, gender, and cardiac load (82%).

**Age-Related Changes of Correlates of LV Mass**

After birth, a rapid and progressive increase in cardiac workload occurs because of both a mild increase in blood pressure and a more marked and progressive increase in stroke volume. Therefore, the two basic hemodynamic stimuli for development of LV mass, volume, and pressure, begin to progressively affect initially tight correlation between body and cardiac size during growth and maturation. In our study population stroke work, as a simple summary measure of LV workload increases markedly during childhood and adolescence and adds substantially to the variance of LV mass. However, in the younger age group body growth remains the main determinant of LV mass. Until puberty, male gender has a minor though statistically significant impact.

During adulthood, when there is little further increase in weight, the influence of changes in body size is minimal in this normal-weight normotensive population, whereas the variability of stroke work becomes the overwhelming correlate of LV mass. As expected, the effect of male gender on the variability of LV mass becomes more important after puberty.

**Limitations**

The cuff systolic blood pressure has been used in this study as a surrogate for mean LV systolic pressure to calculate stroke work. Mean LV systolic pressure is lower than the peak pressure measured at the arm, and this difference increases with increasing arterial stiffness. In addition, stroke volume measured by M-mode echocardiogram may be affected by imprecision of measurements. However, in an epidemiological study, M-mode stroke volume was as closely related to Doppler stroke volume (mean difference = 1.6 ± 5.0 mL/beat) as closely as the latter has been to invasive stroke volume determination in validation studies.

Stroke volume does not completely determine the LV filling volume that contributes to LV end-diastolic stress because of the variable volume remaining after the previous systole and the potential impact of valvular regurgitation. However, the exclusion of individuals with valvular regurgitation eliminates one source of confounding in the present study. Furthermore, a supplemental regression analysis showed that Doppler stroke volume remained a highly significant (P < .0001) correlate of LV mass in New York subjects after end-systolic volume was taken into account.

Finally, LV mass represents a relatively stable geometric adaptation to cardiac workload that varies over time. A measurement of cardiac workload at rest at a single point in time cannot completely reflect chronic LV load. However, the relatively modest paired difference between awake am-
Conclusions

This study demonstrated that the influence of body growth on the level of LV mass decreases after early infancy because of both the variability of hemodynamic load and the increasing effect of gender. After adolescence, in normotensive, normal-weight individuals, the impacts of hemodynamic load and male gender on LV mass are greater than that of body size. A regression model including a measure of body size, a measure of cardiac workload, and gender can explain up to 82% of the variability of LV mass in a population ranging in age from early infancy to late adulthood. The reported regression equation derived from normal subjects can provide a tool for estimating the adequacy of LV hypertrophic response in a number of diseases affecting cardiac loading conditions.

Acknowledgments

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References


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