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Articles

Stroke Volume and Cardiac Output in Normotensive Children and Adults

Assessment of Relations With Body Size and Impact of Overweight

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Abstract

Background Relations between organs and body size are not linear but rather follow allometric (growth) relations characterized by their powers (exponents).

Methods and Results Stroke volume (SV) by M-mode echocardiography was related to height, weight, body surface area (BSA), and ideal BSA (derived from ideal body weight for given height) in 970 normotensive individuals (1 day to 85 years old; 426 <18 years old; 204 overweight to obese; 426 female). In normal-weight children, adults, and the entire population, SV was related by allometric relations to BSA (power=0.82 to 1.19), body weight (power=0.57 to 0.71), and height (power=1.45 to 2.04) (all $P<.0001$). Relations of cardiac output to measures of body size had lower allometric powers than those for SV in the entire population (0.41 for body weight, 0.62 for BSA, and 1.16 for height). In overweight adults, observed SVs were 17% greater than predicted for ideal BSA, a difference that was approximated by normalization of SV for height to age-specific allometric powers. Similarly, observed cardiac output was 19% greater than predicted for ideal BSA, a difference that was accurately detected by use of cardiac output/height to age-specific allometric powers but not of BSA to the first power.

Conclusions Indexations of SV and cardiac output for BSA are pertinent when the effect of obesity needs to be removed, because these indexations obscure the impact of obesity. To detect the effect of obesity on LV pump function, normalization of SV and cardiac output for ideal BSA or for height to its age-specific allometric power should be practiced.

Key Words:
growth
obesity
echocardiography
ventricles
cardiac output

Normalization of biological variables for measures of body size needs to take into account that relations between body size and the dimensions or functions of organs are often nonlinear.[1] These relations can be linearized only by taking into account the appropriate power of the allometric (growth) relation between the organ and body size.[2,3] Left ventricular (LV) mass is related to body height (a one-dimensional measure) by an allometric power close to 3, the power regulating relations between one-dimensional (height) and three-dimensional (LV mass) shapes.[2,4] LV mass has also been found to be related to body surface area and body weight by allometric powers that reflect the expected geometric proportions (≈1.5 and 1).[2,3] Normalization of LV mass for height to powers between 2.5 and 2.7 improves the detection of LV hypertrophy in obese normotensive or hypertensive subjects,[5,6] and height$^{2.7}$ has been shown in a large epidemiological study to separate the effects on LV mass of body growth and obesity.[7] Use of height$^{2.7}$ to normalize LV mass has also been shown to improve prediction of cardiovascular events in a population sample of clinical hypertensive patients compared with more traditional indexes of LV mass.[8]

Like LV mass, stroke volume and cardiac output are usually indexed for body surface area to assess LV pump function independently of the effect of body size. Consistent with observations about use of body surface area to normalize LV mass,[2,4,5,6,7,8,9] this approach does not take into account the modification of body composition[10] caused by obesity, in which metabolically active lean body mass increases less than the adipose

mass.[10] However, whether or not indexing stroke volume and cardiac output for body surface area accurately identifies the effect of obesity on LV pump function has not been directly investigated in large population samples, although there is reason to suspect that this indexing might mask rather than highlight the effect of obesity.[11] [12] There is no information about the physiological relations between stroke volume or cardiac output and different measures of body size in humans across a broad range of ages. Accordingly, this study was undertaken to identify the relation of stroke volume and cardiac output to measures of body size and to assess the physiological impact that different types of normalization may have on clinical and epidemiological studies.

Methods

Participants

The study population was composed of 970 newly studied normotensive individuals, 1 day to 85 years old, recruited as normal volunteers (69 adults from Naples, Italy) or from hospital- or worksite-based epidemiological programs (469 adults from New York, NY; 303 children, adolescents, and young adults from Cincinnati, Ohio) or from an epidemiological survey at a school site (129 children from Naples, Italy). Among the 970 subjects, 544 were >17 years old, 204 were overweight to obese, and 426 were female (197 of 426 children/adolescents and 229 of 544 adults). Further characteristics of this population sample will be shown in the “Results” section.

Definition of Normal Blood Pressure and Body Size

Blood pressure was measured by mercury sphygmomanometers and cuffs of appropriate size by well-trained technicians or physicians. In adults, blood pressure <140/90 mm Hg as the average of three determinations on at least two clinical examinations was considered normal. In children ≥1 year old, blood pressure was measured by mercury sphygmomanometers and cuffs of appropriate size (at least three measurements in three examinations in American children and in a single school-site measurement in Italian children). Normal blood pressure was defined according to criteria presented by Rosner et al,[13] based on 95th percentile of a sex-, age-, and height-specific normal distribution. Children <1 year old were assumed to have normal blood pressure when systolic and diastolic blood pressures were <101/55 mm Hg, the 95th percentile of blood pressure values in 1-year-old boys at the 25th percentile of height.[13]

Anthropometric measurements were taken in Naples and in New York with beam balances and attached stadiometers. In Cincinnati, for children <1 year old, an electronic scale (Health/O/Meter) was used for measurement of weight, and length was measured with measuring tapes with the subject in the supine position, whereas for the older children and adolescents, a regular beam-balance scale and stadiometer were used. Adults were defined as overweight to obese when their body mass index was higher than the sex-specific partition values from the 1985 NIH Consensus Conference.[14] Children and adolescents >3 to 12 years old were considered overweight to obese when the observed value of body mass index was greater than the sum of age+13 for boys and age+14 for girls.[15] Children <3 years old were considered normal weight.

To provide reference standards for predicted normal stroke volumes and cardiac outputs, ideal body surface area was calculated in all individuals >17 years old from observed height and the ideal body weight for that weight taken from the 1980 tables of the Metropolitan Life Insurance Company,[16] already shown in a previous publication from this laboratory.[2] In normal-weight adults, body surface area calculated from ideal body weight from these tables (1.73±0.16 m^2) was virtually identical to the value generated from observed values of body weight (1.74±0.22 m^2, *P*=NS).

Procedures

Informed consent was obtained from all adult volunteers and from parents of children under protocols approved by the institutional review boards for research in human subjects and, in Italy, also after formal approval by the director of the public school in which echocardiograms were performed. Two-dimensionally targeted M-mode echocardiograms were performed as previously described[17] with the subjects in a partial left decubitus position, during morning hours, with commercially available echocardiographs. In adults and children >5 years old, tracings were recorded with subjects in held expiration. All tracings were recorded on strip-chart paper at 50 mm/s, coded, and interpreted blindly by two investigators. 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 at the onset of the ECG Q wave, according to the American Society of Echocardiography.[18] Segmental wall motion abnormalities were excluded by two-dimensional echocardiographic recording in multiple standard projections.

LV end-diastolic and end-systolic volumes were calculated with the Teichholz correction of the cube formula.[19] LV chamber volumes and stroke volume determined by this approach have been shown to correlate well with invasive and with two-dimensional and Doppler-echocardiographic volume measurements in a variety of populations with symmetrical LV wall motion.[19] [20] [21] [22] Data about reproducibility of M-mode echocardiograms in each laboratory have been reported separately.[23] [24] [25]

Statistical Analysis

Because of demographic differences between Italian and American age-matched participants, primary variables were adjusted for a "center effect" by 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 age range (6 to 11 years), Italian adults were combined with New York adults in the same age range (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 use of the linear coefficient of regression (b). Thus, the adjusted variable (adjV) was $adjV=V-b(x-\mu)$, 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. Descriptive statistics are presented by χ^2 and frequency distribution. The Shapiro-Wilks test of normality has been used to test the normality of the distribution of continuous variables. As in analyses of LV mass in a previous study,[2] relations of stroke volume or cardiac output to measures of body size were assessed by nonlinear regression analysis to identify the allometric power (exponent)[2 26] of the relations, by means of equations of the following type: dependent variable=a×measure of body size^b, where a is a regression coefficient reflecting the quantitative relation between variables and b is the power of the measure of body size that produces the best fit of the data.

Allometric equations were generated by an iterative computer technique seeking to estimate the unknown parameters (a and b) in a way that the sum over all the observations of the squared differences between the observed and predicted values of the dependent variable was minimized, producing the highest possible R^2. A best fitting procedure was used to study the relation of stroke volume to age.[27]

Two-way hierarchical ANOVA was used to detect the impact of sex and overweight on stroke volume and cardiac output[2] : with this method, the interaction between sex and body mass index was adjusted for both variables and the effect of body mass index was adjusted for sex, whereas that of sex was not adjusted for any other effects. Adults and children/adolescents were considered separately in these analyses.

Stepwise multiple regression analysis was used to study the independent effect of variables found to be significant predictors of LV chamber dimension in univariate analyses. F to enter and F to remove were set to $P<.05$ and to $P<.10$, respectively. Sex was treated as a dummy variable by assigning 1 to females and 2 to males. Stability of the estimates of regression coefficients was assessed with collinearity diagnostics.[27] A two-tailed value of $P\leq.05$ was used to reject the null hypothesis.

Results

Table 1⇓ shows the range of demographic and clinical variables in the reference group of 766 normotensive, normal-weight subjects. Table 2⇓ shows that Italian children were more obese than their American peers ($P<.02$) and had significantly higher systolic and diastolic blood pressures (both $P<.0001$). LV dimensions were also higher than in the American children ($P<.0001$). The American adults were >10 years older than the Italian adults and had a lower prevalence of obesity, lower heart rate, and lower LV end-systolic dimension (all $P<.0001$).

Table 1.

Characteristics of Normotensive, Normal-Weight Subjects by Sex and Age

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Table 2.

Characteristics of American and Italian Participants in the Same Age Ranges

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Nonlinear regression analysis of relations of both stroke volume and cardiac output to measures of body size has been performed in those age-comparable, country-specific groups of participants to exclude potential bias due to center adjustment. Similar allometric powers were found in American and Italian children (eg, between stroke volume and height, 1.19 and 1.15, respectively, both $P<.0001$, P=NS for the difference between exponents; between cardiac output and height, 0.81 and 0.91, both $P<.002$, P=NS for the difference between exponents). American and Italian adults also had statistically indistinguishable allometric powers of the relations under study. Thus, the following analyses are presented for the entire study population after adjustment for center effect.

Relation of Stroke Volume to Age

In children and adolescents, stroke volume increased with age, with the highest correlations achieved by power regressions in both girls (stroke volume=22.2×age$^{0.30}$, r=.69, P<.0001) and boys (stroke volume=20.85×age$^{0.36}$, r=.68, P<.0001). In adult men, stroke volume decreased minimally with age (r=−.14, P<.04), whereas it tended to increase in women (r=.12, P=.2). When boys and girls were pooled, the equation was similar to those obtained in separate series of boys and girls (stroke volume=21.88×age$^{0.32}$, SEE=6 mL/beat, r=.68, P<.0001). The following analyses determine the extent to which this power relation was due to body growth.

Relation of Stroke Volume to Body Size

In the entire population, stroke volume was closely related to body weight, body surface area, and height (Fig 1⇓, top) by allometric (power) equations (Table 3⇓, upper section, left columns, all P<.0001). The correlations were closer but the allometric powers were lower in children and adolescents up to 17 years old than in adults (Table 3⇓, middle and lower sections, left columns).

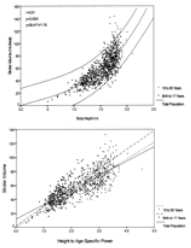

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Figure 1.

Top, Relation of stroke volume (vertical axis) to height (horizontal axis) in 373 normal-weight children/adolescents (open triangles) and 393 adults (solid squares). Relation is curvilinear and is best represented by an allometric (power) equation. Bottom, Relation of stroke volume (vertical axis) to height$^{1.78}$ (horizontal axis) in 373 children/adolescents (open triangles, dotted line) and 393 adults (solid squares, shaded line). Relations became linear with near-zero intercepts.

Table 3.

Allometric Relations of Stroke Volume and Cardiac Output to Measures of Body Size in Normal-Weight Subjects

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Comparing stroke volume with all three measures of body size to the powers generated in age-specific groups resulted in plots that showed normal distribution and wider scatter at greater body size, and age-specific regression equations with near-zero intercepts (illustrated for height in Fig 1⇑, bottom). Similar results were obtained when stroke volume was plotted separately in pooled age groups versus measures of body size to powers generated in the entire study population. The powers obtained in the age-specific groups have been used for the following analyses.

Normalization of stroke volume for the measures of body size to their age-specific appropriate powers minimized the residual relations of the indexed stroke volume to the corresponding first-power measure of body size in each age group (all r<.01, P=NS).

Interrelations Among Heart Rate, LV Chamber Size, and Body Size

Heart rate was negatively related to body weight (y=92.96−0.34x, r=−.51, SEE=12 bpm), body surface area (y=101.64−18.61x, r=−.55, SEE=12 bpm), and height (y=127.94−34.97x, r=−.57, SEE=12 bpm) and less closely (P<.01 versus height) to age (y=83.0−0.32x, r=−.46, SEE=13 bpm).

End-diastolic LV linear dimensions and calculated volumes were negatively related to heart rate both in the entire population sample (r=−.56 and −.53, respectively) and in age-specific groups (r=−.52 and −.49 in children and adolescents, r=−.21 for both relations in adults, all P<.001). In multiple linear regression analysis, larger LV chamber dimensions were independently predicted by slower heart rate (β=−.11, slope=−0.005, P<.0001) after the positive effects of height (β=.71, slope=1.91, P<.0001), male sex (β=.13, slope=0.17, P<.0001), and age (β=.06, slope=0.002, P<.0001) were taken into account (intercept=2.04 cm, multiple R^2=.85, SEE=0.33 cm, P<.0001). Similar results were obtained when the two age strata were examined separately. As a consequence of its negative relation with LV chamber size, heart rate was also negatively related to stroke volume (stroke volume=112.57−0.72×heart rate, r=−.50, SEE=17 mL/beat).

Allometric Relations Between Cardiac Output and Body Size

As expected, cardiac output was related to measures of body size by lower allometric powers than found for stroke volume, reflecting the interaction of the positive relation of stroke volume and the negative one of heart rate to body size. Table 3⇑ (upper section, right columns) shows that the relation of cardiac output to height in the entire population was almost linear (allometric power ≈1), whereas the relations of cardiac output to body weight and body surface area had powers ≪1. As a consequence, cardiac output/body weight showed a strong negative relation with body weight (Fig 2⇓), and cardiac output/body surface area had a moderate negative relation with body surface area (r=−.48, P<.0001). In contrast, only a weak positive relation existed between cardiac output/height and body height (r=.11, P<.002).

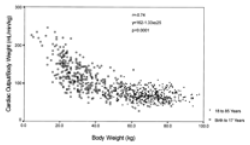

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Figure 2.

Relation of cardiac output/body weight (vertical axis) to body weight (horizontal axis) in 373 children/adolescents (open squares) and 393 adults (solid squares) showing strong negative relation between indexed value of cardiac output and body weight.

In separate age strata, allometric powers for cardiac output differed between children/adolescents and adults. Similar to findings with stroke volume, the allometric powers were lower in children and adolescents up to 17 years old than in adults (Table 3⇑, middle and lower sections), because the rate of changes in cardiac output with increasing body size, as indicated by the powers of the allometric relations, was about half as high in adults as in children. This difference was approximately the same for all three measures of body size. In adults, the exponent for body surface area was close to 1 (1.15), whereas in children and adolescents it was close to the square root of body surface area (0.53). In adults, the allometric powers of the relation between cardiac output and the three measures of body size were virtually identical to the corresponding powers detected in relations with stroke volume, whereas they differed substantially in children (Table 3⇑, right columns). As with stroke volume, normalization of cardiac output for the measures of body size to their age-specific appropriate exponents minimized the residual relations of the indexed cardiac output to the corresponding first-power measure of body size in each age group (all r<.01, P=NS).

Sex Differences in Allometric Relations of Stroke Volume and Cardiac Output to Measures of Body Size

When examined in separate sexes, the allometric signals for stroke volume were slightly lower than in the pooled population but quite similar in males and in females for height (1.74 and 1.76, respectively), body surface area (0.90 and 0.94), and body weight (0.60 and 0.62). Similar results were obtained for cardiac output: allometric signals were 1.10 and 1.17 for height, 0.58 and 0.64 for body surface area, and 0.39 and 0.43 for body weight in males and females, respectively.

Sex was an independent but weak predictor of stroke volume after measures of body size to their age-specific allometric power were taken into account. The contribution of male sex to the change in R^2 was ≤.01 and did not attain statistical significance in adults when body surface area to the 1.19 power was used in the multiple regression model. An independent contribution of sex to the level of cardiac output was not detectable in children, regardless of which measure of body size to the appropriate age-specific allometric power was used. In adults, male sex influenced the magnitude of cardiac output (change in R^2=.01, β=.13, P<.02) only when height$^{1.83}$ was used in multiple regression analysis, whereas no effect was detected when body surface area or body weight was used.

Effect of Obesity on Stroke Volume and Cardiac Output

Overweight or obesity (highest body mass index=50.5 kg/m^2) was detected in 204 individuals in this population sample (21%): 22 boys (9.3±4.3 years old), 31 girls (9.1±4.0 years old), 86 men (45.8±10.3 years old), and 65 women (44.9±14.2 years old).

Ideal body surface area was used with the age-specific allometric regression equations shown in Table 2⇑, lower section, to predict values of ideal stroke volume. Normal-weight adults exhibited values of observed stroke volume (72.2±16.0 mL/beat) that were slightly higher than the values predicted from ideal body surface area using the age-specific allometric equation (69.2±6.8 mL/beat, 4% difference, P<.001).

In contrast, observed stroke volume in the 151 overweight adults was 17% greater than the stroke volume predicted by ideal body surface area with the age-specific allometric equations (Table 4⇓, upper section, P<.0001). Table 4⇓ (upper section) shows that in overweight adults, stroke volume was 14% higher than predicted by height to its age-specific (2.04) allometric power. Stroke volume was correctly predicted by observed body surface area, but the other measures of body size failed to detect the expected increase or even predicted a reduced stroke volume in overweight subjects (Table 4⇓,

upper section). Very similar results were obtained for cardiac output (Table 4⇓, lower section).

Table 4.

Comparison Between Observed Stroke Volume or Cardiac Output and Values Predicted by Measures of Body Size in 151 Normotensive Overweight to Obese Adults

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Discussion

Consistent with results obtained from studies of relations between LV mass and body size in previous population samples of normotensive, normal-weight subjects over a broad range of ages,[2 5 6 7 8 9] in the present study stroke volume and cardiac output have been shown to be nonlinearly related to measures of body size. The allometric signals found for these measures of pump function are lower than those generated between measures of body size and LV mass. It is of note that the allometric signal for stroke volume in relation to body surface area in the present study is lower than that derived by Gutgesell and Rembold in a theoretical study.[3] In that study, body surface area was related to LV volume by a power of 1.5, which is the power resulting from comparison of a cube and a square function (ie, 3/2). This theoretical prediction has been shown to be approximately correct for LV mass in previous population studies[2 6 7] and was also confirmed in the new population sample used for the present study (LV mass=53×body surface area$^{1.5}$). The allometric relation with stroke volume, however, had a much lower exponent, suggesting that pump function increases less than LV mass in relation to body growth. This may be because LV mass is also influenced by pressure-related increases in LV wall thickness with advancing age in addition to the effect of body growth on LV cavity size and stroke volume.

How Should Stroke Volume and Cardiac Output Be Normalized for Body Size in Normal-Weight Individuals?

Manipulation of the three measures of body size with their allometric powers linearized comparably all their relations with stroke volume or cardiac output, allowing them to be indexed by division of their values by the corresponding value of body size raised to the appropriate allometric power.

Allometric relations between body size and either stroke volume or cardiac output in children/adolescents were very similar to those detected in the entire study population, whereas they differed in the adult subset (Table 3⇑). In adults, the allometric powers for both stroke volume and cardiac output were very similar in relation to all three measures of body size, suggesting a minor influence of heart rate on the variability of cardiac output and stroke volume in relation to body size. In children and adolescents, in contrast, allometric signals for stroke volume were higher than for cardiac output, suggesting that both stroke volume and cardiac output are best normalized for body size by use of different allometric powers for children/adolescents or adults. Thus, whereas the traditional indexation of stroke volume and cardiac output for the first power of body surface area appears to be acceptable in adults, because the allometric powers detected were close to unity (1.19 and 1.15), the same indexation in children introduces a significant error, because the power detected by allometric regression is $\ll 1$, especially for cardiac output. Accordingly, if used in children, body surface area needs to be raised to the appropriate power, which, for cardiac output, is approximately its square root function.

Normalization for body surface area, however, can be used when in comparisons of the effects of cardiac diseases or treatments, the impact of obesity in the study population needs to be removed. To study the effect of obesity or to take into account the effect of obesity in comparative or interventional studies, the use of body surface area as the measure of body size to normalize stroke volume and cardiac output should be strongly discouraged.

Effect of Obesity on Stroke Volume and Cardiac Output

As is well known from previous studies,[28 29 30] obese children and adults of both sexes had higher stroke volumes than otherwise comparable normal-weight individuals. This effect was magnified for cardiac output because of the relative increase of heart rate in obese subjects, a known consequence of obesity-related alterations of autonomic tone.[31] As with observations reported for LV mass,[2] those differences were reduced, eliminated, or even reversed when stroke volume and cardiac output were normalized for body weight or body surface area, whereas they were confirmed when body height to its age-specific allometric powers was used to generate stroke and cardiac indices.

The utility of body height to appropriate allometric powers as the most effective measure of body size for normalization of variables closely related to the metabolic demand, such as LV mass and stroke volume, is most likely a consequence of the close relations between height and lean body mass.[32] Because fat mass, a tissue with a low metabolic demand,[33] increases more than lean body mass in obesity,[10 29] normalization of stroke volume or cardiac output for measures of body size that are strongly influenced by the increase in body

fat (such as body weight or body surface area) is misleading. The influence of body fat on LV mass has recently been shown to be extremely low in comparison to the influence of either lean body mass in a population sample of normotensive children[34] or of fat-free mass in middle-aged to elderly American Indians.[35]

Conclusions

In normal-weight, normotensive individuals over the age range from early infancy into the ninth decade, the rate of changes in stroke volume and cardiac output with increasing body size was lower in children than in adults (lower allometric powers). Body surface area to the first power or to allometric powers ≈1 is an appropriate way to normalize both stroke volume and cardiac output for body size in normal-weight adults, whereas body surface area needs to be raised to its appropriate (approximately square root) power in children and adolescents. Indexation for body surface area is also pertinent when the effect of obesity needs to be removed by the normalization, because it obscures the impact of obesity. To detect the effect of obesity on LV pump function, use of body surface area should be discouraged and normalization of stroke volume and cardiac output for ideal body surface area or for height to its age-specific allometric power should be practiced.

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