Normal Values of Left Atrial Volume in Pediatric Age Group Using a Validated Allometric Model

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Background—Left atrial volume (LAV) increase is an indicator of diastolic dysfunction and a surrogate marker of significant left to right shunts. Normalization of LAV is currently performed by indexing to body surface area^{1} (BSA^{1}). The indexed LAV thus derived does not account for the nonlinear relationship of physiologic variables to BSA and has not been tested for independence to body size. Our objective was to identify a valid allometric model for indexing LAV and use it to develop Z-scores in children.

Methods and Results—LAV was measured in 300 normal subjects by echocardiography using the biplane area length method. LAV/BSA^{1} had a residual relationship to BSA (r=0.52, P<0.0001). The allometric exponent (AE) derived for the entire cohort (1.27) using the least squares regression analysis also failed to eliminate the residual relationship to BSA (r=−0.15, P=0.01). Dividing the cohort in two groups with a BSA cut-off of 1 m^2 provided the best-fit allometric model. The AE for each group was 1.48 and 1.08 for BSA≤1 m^2 and >1 m^2, respectively, and was validated against an independent sample. The mean indexed LAV±SD for BSA≤1 m^2 and >1 m^2 is 31.5±5.5 mL and 26.0±4.2 mL, respectively, and was used to derive Z-scores.

Conclusions—This study demonstrates the fallacy of using "per-BSA^{1} standards" for normalization of LAV in pediatrics. LAV/BSA$^{1.48}$ for children with BSA≤1 m^2 and LAV/BSA$^{1.08}$ for those with BSA>1 m^2 is accurate and can be used to derive Z-scores. **(*Circ Cardiovasc Imaging*. 2012;5:791-796.)**

Key Words: left atrial volume ■ allometry ■ normalization ■ Z-scores ■ children

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Allometry is the study of biological scaling. This term was coined in 1936 by Tessier and Huxler and first used by Tanner for scaling stroke volume and basal metabolic rate, amongst other parameters, in order to adjust for somatic growth.[1] Colan and Sluysmans further proposed and validated the appropriate mathematical scaling for various cardiovascular structures in order to adjust for body size, age, and gender.[2] Derivation and application of allometric scaling to determine normal left atrial volume (LAV) in children has not been systematically evaluated. Our objective was to derive and validate an allometric model that would allow the calculated indexed LAV to be independent of any change in body surface area^{1} (BSA^{1}) and age.

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LA size has been shown to be predictive of cardiovascular health in adults.[3] LAV is the most accurate measure of the true size of the left atrium[4] and a reliable indicator of duration and severity of diastolic dysfunction in both adults and children. Further clinical utility of LAV in children has been proposed in its use as a surrogate marker of magnitude of left to right shunts in patients with ventricular septal defect and patent ductus arteriosus.[5] It has also been shown to be an independent prognostic factor in patients with mitral regurgitation.[6] The American Society of Echocardiography recommends using the biplane area length method for performing LAV measurements by transthoracic echocardiography.[7] The current literature that provides normative LAV data for children and adults has used a linear model of scaling to BSA^{1}.[5,8] In this model, the relationship of LAV (dependent variable, Y) and body size (independent variable, X) takes the form $Y=mX^{1}$ with an assumption that this linear relationship of indexed LAV (Y/X) is size-independent. This assumption does not hold true mathematically and fails to account for the nonlinear relationship between physiologic variables and body size. There has been no study to our knowledge that thoroughly examines the allometric scaling for LAV. We sought to investigate the allometric relationship between LAV and BSA and derive normative data for children (0–18 years).

Methods

Consecutive children ≤18 years of age who had a normal transthoracic echocardiogram between July 2008 and December 2010 were identified. Subjects with abnormal body size (>95th percentile or <5th percentile), unavailable 2-chamber or 4-chamber apical images, and cardiovascular disease were excluded. The presence of patent foramen ovale (<2.0 mm) was considered normal in neonates and was not an exclusion criterion. BSA was estimated using the Haycock method.[9] Permission to review and analyze medical data was granted by the Institutional Review Board.

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Echocardiography

Conventional transthoracic echocardiogram was performed in our echocardiography laboratory by experienced sonographers. Our echocardiography protocol for LA size assessment includes obtaining apical 2-chamber and 4-chamber views with the patient in the left lateral recumbent position. Images were optimized to avoid foreshortening and obtain clear endocardial border delineation. One independent experienced observer (H.K.) performed left atrial measurements, Area 2-chamber, Area 4-chamber, Length 4-chamber, and Length 2-chamber, using a Syngo 9.0 (Siemens, Mountain View, CA) postprocessing system. As per American Society of Echocardiography guidelines, the measurements were performed at end-systole, and LAV was estimated using biplane area length method (Figure 1) using the formula: LAV=0.85×Area 4-chamber×Area 2-chamber/Shortest length (4-chamber or 2-chamber).[7,10]

Statistical Analysis

All data are expressed as mean±SD unless otherwise indicated. The relationship between LAV, BSA, age, and indexing methods was analyzed using Pearson's correlation coefficient. Student's *t*-test was used to examine the mean difference between gender groups. Testing the existing "per BSA" model, identification of the appropriate allometric scale, and validation of the derived allometric model was performed in the following systematic manner:

1. A power analysis to define the number of subjects needed to account for variability in BSA and age was determined (N=300).
2. LAV indexed to BSA^{1} was tested for any residual relationship to BSA.
3. Allometric estimates of indexed LAV were obtained by considering the equation $Y=mX^{b}$. To determine the appropriate AE (b) by which BSA (X) should be raised, a logarithmic transformation of this equation was used: Ln Y=Ln m+b Ln X. The AE was estimated using an ordinary least squares linear regression method.
4. The LAV was indexed using BSA to the power of the derived AE that was then regressed against BSA to assess for residual relationship.
5. In order to correct for the observed residual relationship resulting from the potential error in transthoracic echocardiogram–derived LAV measurements, the entire cohort was further divided into two separate groups using various cut-offs for BSA: 0.9, 1.0, 1.1, and 1.2 m^2. Identification of the allometric model was performed for each group using the above-mentioned methodology.
6. The adequacy of the allometric model for each group was assessed by 1) testing the indexed LAV for residual relationship to BSA and age; 2) the absolute LAV was regressed to BSA^{AE} and the intercept examined for approximation to zero.
7. Normality tests were performed on indexed LAV data for each group using Kolmogorov–Smirnov and Shapiro–Wilk methods.[11]
8. Last, the need for two separate allometric models was postulated to be secondary to underestimation of LAV by transthoracic echocardiogram in subjects with larger BSA. This hypothesis was tested in a small cohort of patients (N=18) that were not subjects of the main study population. Bland–Altman analysis was used to compare LAV estimation using biplane method by transthoracic echocardiogram against cardiac magnetic resonance.[12]
9. Cross-validation of the identified allometric models (separately for BSA≤1.0 and >1.0 m^2) was performed on a validation sample that comprised a separate subset of normal subjects (N=50). This was performed by assessing the correlation of predicted values for Ln(LAV) with the actual values for Ln(LAV) for the validation sample. Predicted values for the validation sample were calculated using the coefficients estimated from the models that were fitted to the study sample.

Interobserver and intraobserver variability was assessed using intraclass correlation coefficient in a subset of 50 subjects.

Results

LAV was measured in 300 consecutive subjects who met the inclusion criteria and had optimal images to make precise measurements. The mean age and BSA of the subjects was 6.8 years (range 0–18) and 0.9 m^2 (range 0.17–2.3), respectively. Forty-two percent of subjects were female. The mean absolute LAV for the whole group was 24.8±4.6 mL. As expected, we found a strong correlation between LAV and BSA (r=0.96, P<0.0001); however, the indexed LAV using BSA^{1} had a strong residual relationship with BSA (Figure 2; r=0.52, P<0.0001). Using the least squares regression analysis, the AE derived for the whole group was 1.27. When $LAV/BSA^{1.27}$ was regressed against BSA, there still was a negative residual relationship (Figure 3; r=–0.15, P=0.01). In order to correct for the residual relationship, the entire cohort was divided into two sub-groups, such that each group had a normal distribution, and the derived AE for each group met all the validation criteria for a true allometric model. A cut-off value of BSA=1 m^2 gave the best results when tested for validity of the allometric model. The AE derived for BSA≤1 and >1 m^2 was 1.48 and 1.08, respectively. These models had a good fit when tested in the cross-validation sample of 50 separate subjects who met the inclusion criteria. The indexed LAV using the derived AE for each group did not show any significant residual relationship to BSA (Figures 4 and 5) and age. The intercept of absolute LAV versus $BSA^{1.48}$ was 0.6 and $BSA^{1.08}$ was 0.4.

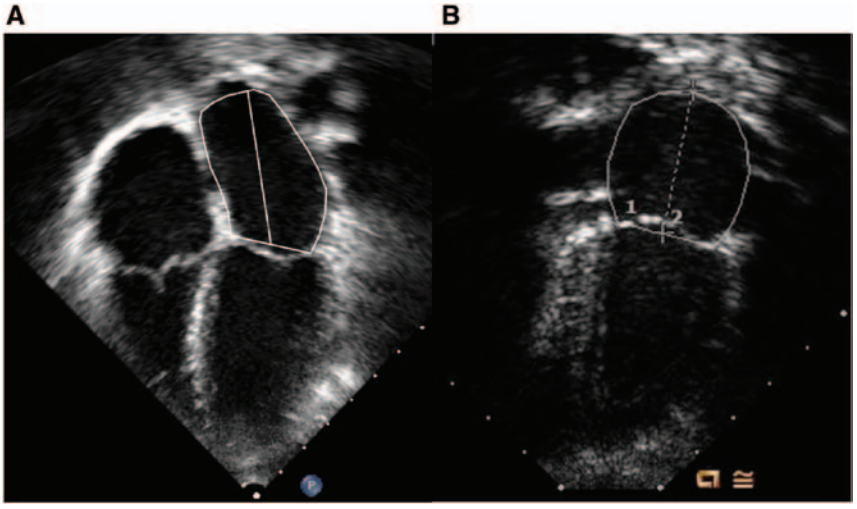


Figure 1. (**A**) Standard apical 4-chamber view end-systolic frame. Imaging plane and settings were adjusted to avoid foreshortening and clearly define the endocardial border. The area (A4C) was obtained by tracing the endocardial border, excluding the pulmonary vein entrance. (**B**) Orthogonal apical 2-chamber end-systolic frame. The area (A2C) was obtained by tracing the endocardial border, excluding the pulmonary vein entrance and LA appendage. The A4C, A2C, and shortest length used in the calculation.

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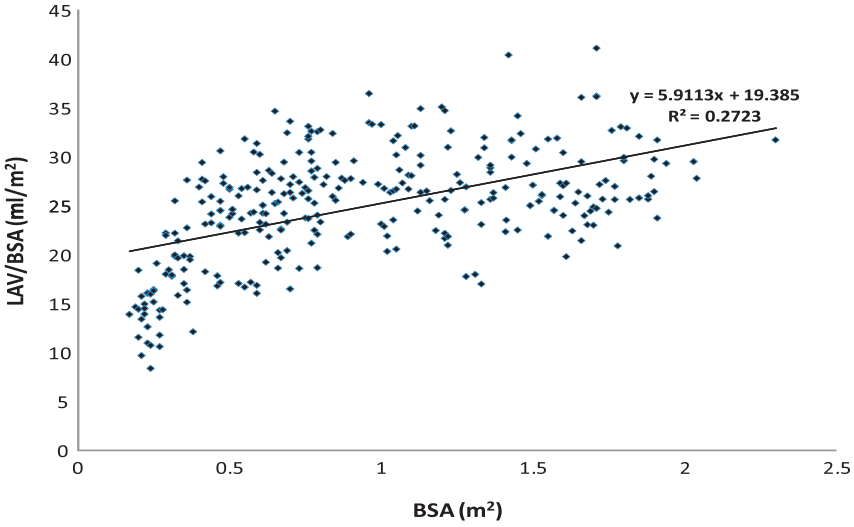


Figure 2. Scatter plot of LAV/BSA[1] vs BSA. If the indexed LAV is independent of BSA, the trend line of the indexed LAV against BSA should be parallel to the X-axis, or r^2 should approach a zero value. In this figure, one can observe that LAV/BSA[1] increases as BSA increases, thereby demonstrating a positive residual relationship with linear indexing (r^2=0.27).

The indexed LAV, thus, derived for each group met the criteria for being normally distributed. The mean indexed LAV±SD was 31.5±5.5 mL for BSA≤1 m^2 and 26.0±4.2 mL for BSA>1 m^2. Z-scores were derived using the mean indexed LAV and SD for each group (Figure 6A and 6B). There was no significant difference in LAV/BSA[1.48] between male and female subjects (mean, 31.5±3.5 mL/$m^{2.96}$ versus 31±3.0 mL/$m^{2.96}$; *P*=NS) in smaller subjects (BSA≤1 m^2). This was also true in larger subjects (BSA>1 m^2) with mean indexed LAV of 26.8±3.5 mL/$m^{2.16}$ for males and 25.4±3.0 ml/$m^{2.16}$ (*P*=NS) for females. The comparison of absolute LAV measurement between two-dimensional transthoracic echocardiography (2D-TTE) and cardiac magnetic resonance showed a mean difference of 0.16 mL and excellent limits of agreement (−4.1 to +4.2 mL) in 8 subjects with BSA≤1 m^2. In contrast, there was consistent underestimation of the LAV measurement by 2D-TTE when compared with CMR (mean difference of −26 mL with limits of agreement of −8 to −46 mL) for subjects with BSA>1 m^2 (n=10). Intraclass correlation coefficients for interobserver and intraobserver comparison of LAV measurement were 0.995 and 0.965, respectively.

Discussion

The objective of this study was to examine the relationship between LAV and BSA in order to derive and validate an allometric model that can be used to develop normalized LAV data in the pediatric population. We found that: 1) the conventional technique of indexing LAV using the "per BSA" method fails to eliminate the residual relationship of indexed LAV to body size (BSA) (Figure 2) and age; 2) identification of one allometric model using an AE of 1.27, and its utilization for normalization of LAV across all body sizes, continues to have a negative residual relationship to BSA (Figure 3), and this relationship is contrary to the expected increase in LAV with physiologic increase in cardiac output and stroke volume with an increase in body size[1]; 3) dividing the entire cohort by BSA above and below 1.0 m^2 and indexing LAV using the identified allometric model (AE of 1.48 and 1.08) for each group successfully eliminates the residual relationship to body size, age, and gender (Figures 4 and 5).

The relative growth of cardiac structures in relation to somatic growth is important, and this relationship is known as cardiovascular allometry.[2,13] Identification of a correct allometric relationship and model for cardiovascular structure measurements is critical to its interpretation and clinical application. Multiple authors have advocated the use of an allometric model to identify a true indexing method of a physiologically dependent variable.[2] The goal of this previously published science and methodology is to calculate an indexed physiologic parameter that is independent of age and variability in body size and additionally should minimize any nonconstant variance (heteroscedasticity).[2,14]

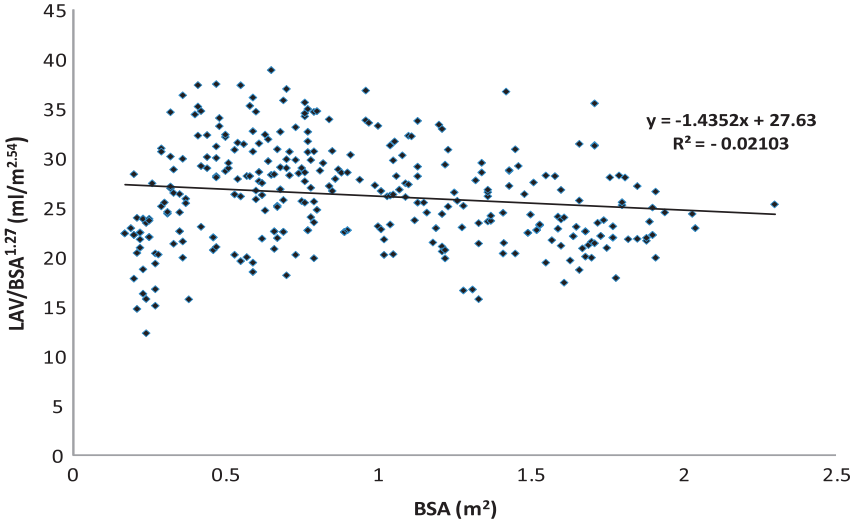


Figure 3. Scatter plot of LAV/BSA[1.27] vs BSA. The trend line of indexed LAV using BSA[1.27] vs BSA demonstrates a negative correlation (r^2=0.02), and it can be appreciated that there is a decrease in indexed LAV with an increase in body size. This negative residual relationship was noted with nonlinear indexing for the entire cohort.

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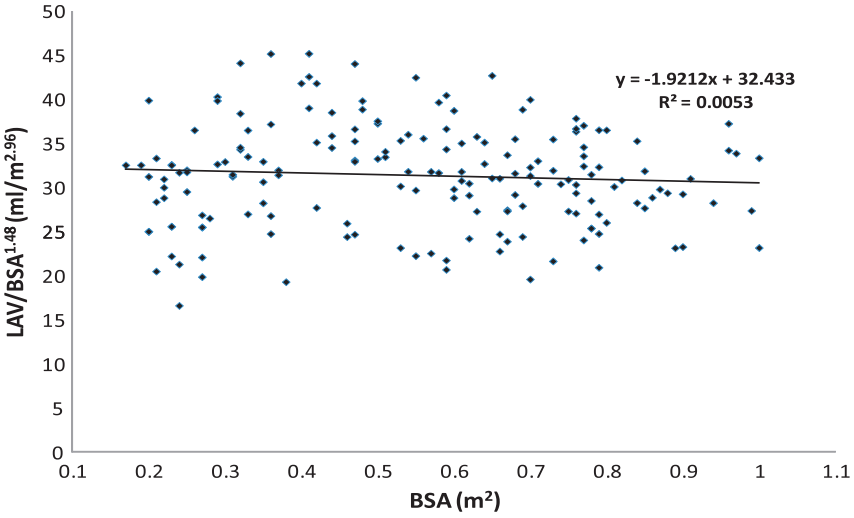


Figure 4. Scatter plot of LAV/BSA$^{1.48}$ vs BSA for subjects with BSA≤1 m^2. The trend line is almost parallel to the X-axis with r^2 approaching zero. There is no significant residual relationship to BSA (r^2=0.005).

LA size assessment is used to diagnose and prognosticate diastolic dysfunction and is used as an outcome measure for risk stratification in heart failure, cardiomyopathy,[15] shunt,[5] and regurgitant lesions.[6] The current recommendation for LA size measurement advocates the derivation of LAV using biplane area length method.[7] It is also recommended to index LAV to BSA[1] to account for the effects of body size.[7] Multiple studies have used this linear model of indexing to provide normative data in both adults and children.[5,16,17] The indexed LAV thus derived has not been tested for independence from body size. Furthermore, this relationship does not account for the nonlinear relationship of the physiologic variables to body size. This continued reliance on "per BSA standard" despite the lack of validity prompted us to look at the residual relationship of indexed LAV (LAV/BSA)[1] to BSA. We observed a significant positive residual relationship between LAV/BSA[1] and BSA (Figure 2) in our study population of 300 normal children. This finding suggests that the conventional assumption of linearity of indexed LAV and body size may be flawed, and such a relationship should be expressed using a nonlinear allometric model.

To our knowledge, this is the first study that explores derivation of an allometric model for indexing LAV. The AE identified for the entire cohort using the above-mentioned methodology was 1.27. Indexing of LAV using BSA$^{1.27}$ demonstrated a significant negative residual relationship to body size (Figure 3). This finding of a negative relationship of LAV to BSA is contrary to the expected positive physiologic relationship between cardiac measurement and somatic growth. We hypothesized that this difference could be due to an acoustic window limitation leading to an error in either accurate delineation of left atrial endocardial border due to poor resolution in the far field or foreshortening of the left atrium in its long axis, which then results in underestimation of LAV for larger subjects. This hypothesis is supported by published data in adults that have demonstrated a significant underestimation of LAV using transthoracic echocardiogram as compared with the 3D-derived volume by multidetector computed tomography.[18] Whitlock et al have also reported a significant underestimation of 2D-TTE-derived LAV estimation using similar methodology (biplane area length method) by transthoracic echocardiogram when compared with cardiac magnetic resonance.[19] This discrepancy has been proposed to be due to the foreshortening of the LA and limited spatial resolution at this level due to the significant distance of the left atrial roof from the transducer.

The indexing of LAV using BSA$^{1.27}$ failed to meet the validation criteria (see criteria below). In order to correct for the

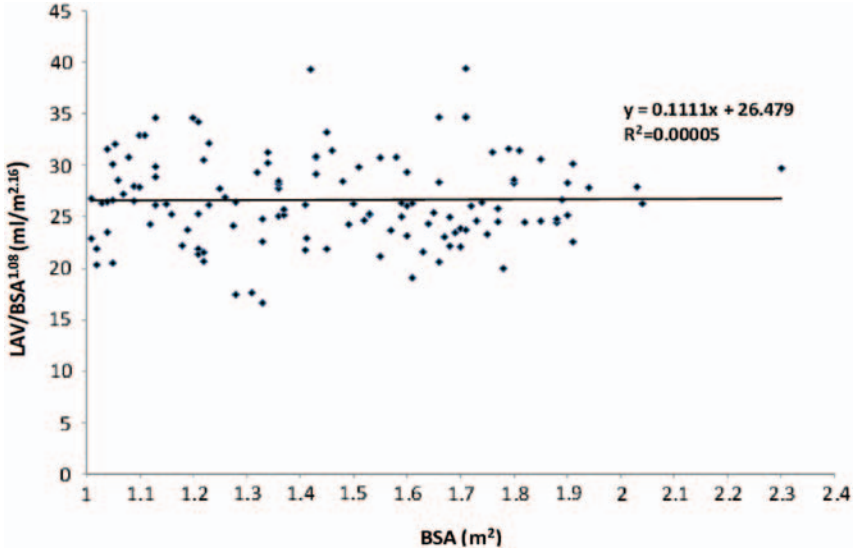


Figure 5. Scatter plot of LAV/BSA$^{1.08}$ vs BSA for subjects with BSA>1 m^2. The trend line is almost parallel to the X-axis with r^2 approaching zero. There is no significant residual relationship to BSA (r^2=0.0005).

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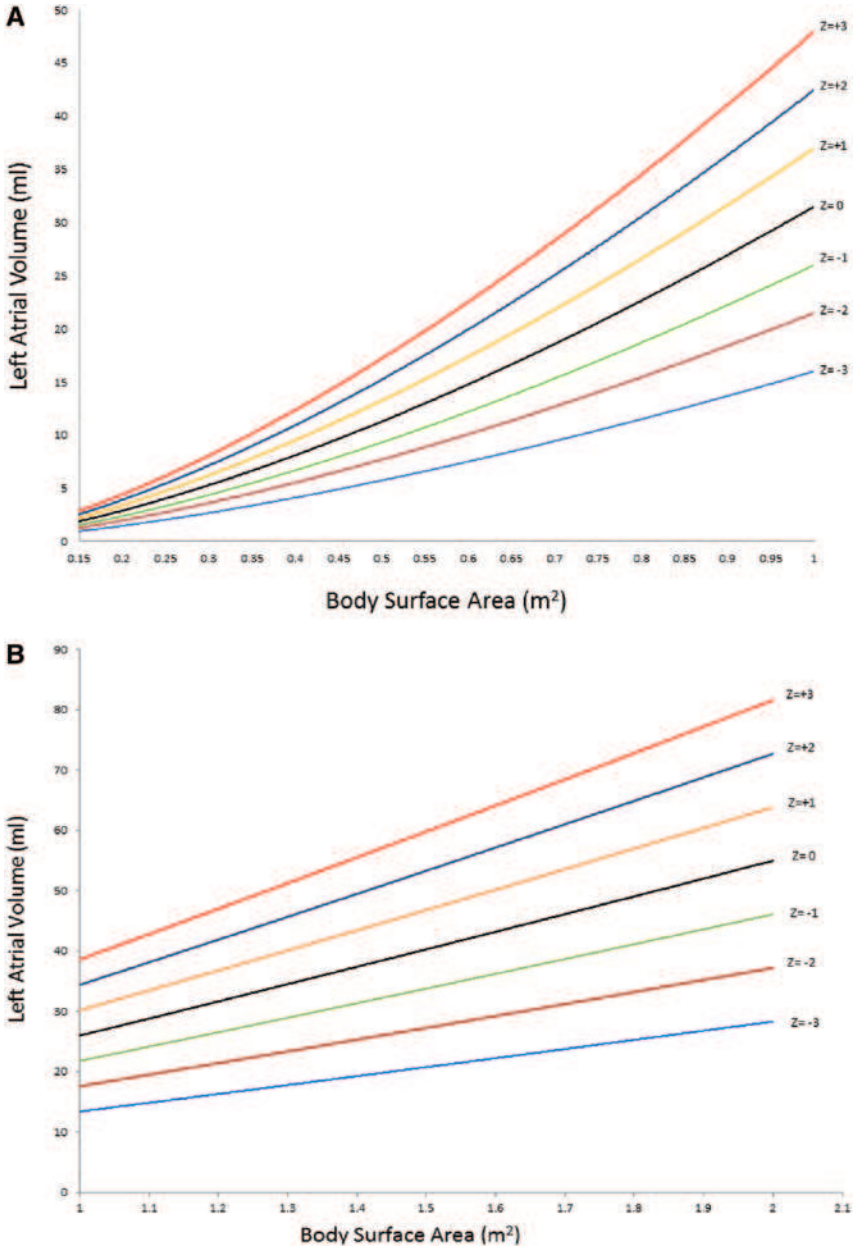


Figure 6. (**A**) Regression lines for Z-scores between –3.0 and +3.0 for nonindexed LAV by BSA for subjects with BSA≤1 m^2 using the mean value of 31.5±5.5 mL/$m^{2.96}$. (**B**) Regression lines for Z-scores between –3.0 and +3.0 for nonindexed LAV by BSA for subjects with BSA>1 m^2 using the mean value of 26.0±4.2 mL/$m^{2.16}$.

error, we divided the entire cohort into two separate groups based on BSA cut-off value of 0.9, 1.0, 1.1, and 1.2. Multiple allometric models were then derived and tested for each group using the above-mentioned methodology. BSA of 1.0 m^2 yielded two best-fit allometric models for indexing of LAV. Moreover, this cut-off value also provided the best trade-off for model fit, as assessed by R-squared and Akaike information criterion between the model for the smaller and the larger children. Specifically, although increasing the cut-off from 1.0 to 1.1 would have slightly improved (raised) the R-squared for smaller children by 0.3%, it would have done so at the expense of worsening (lowering) the R-squared for larger children by 9.3%. Lowering the cut-off from 1.0 to 0.9 had no appreciable effect on fit (R-squared changed by less than 1% for both smaller and larger children). Furthermore, the slopes demarcated at the cut point of 1.0 had a statistically significant difference. For the subjects with BSA≤1.0 m^2, the slope was 1.48 with a 95% confidence interval of (1.42, 1.55); whereas for those with BSA>1.0 m^2, the slope was 1.08 with a 95% confidence interval of (0.94, 1.22). The 95% confidence intervals were not overlapping, and the slopes were significantly different.

A cut-off value of BSA less than or equal to 1 m^2 yielded an AE of 1.48 and met all the criteria of a valid allometric model. The validation criteria met included: 1) the indexed LAV showed no significant residual relationship to BSA (Figure 4); 2) the intercept of LAV to $BSA^{1.48}$ for this group was not significantly different from zero (0.6 mL); 3) there was minimal heteroscedasticity observed by visual inspection (Figure 4). The allometric model identified for subjects with BSA>1 m^2 (AE=1.08) also met all the above validation criteria, rendering an intercept of LAV to $BSA^{1.08}$ near zero (0.4 mL).

The AE identified for smaller subjects is close to the previously published expected AE for cardiovascular volume (1.4–1.5).[2,20] In contrast, the AE identified for larger subjects (1.08) is closer to the traditionally used scaling factor of 1 and

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significantly lower than the expected theoretically derived AE for cardiovascular volume. Poor 2D-TTE acoustic windows affect the accuracy of cardiac measurements in larger subjects. The accuracy of LAV measurements in smaller subjects (BSA≤1 m^2) and the use of 1.48 as AE enables the derivation of normative data and Z-scores. However, for larger subjects (BSA>1 m^2), the expected technical error in LAV measurements by echocardiography should warrant caution in the use of this AE towards derivation of Z-scores.

Limitations

The main limitations of this study are as follows: 1) retrospective design; 2) use of small number of subjects for comparative CMR measurements; and 3) potential variability in the error of measurements could influence the derivation of allometric model for larger subjects.

Conclusion

LAV has become an important measure of disease severity and outcomes. An appropriate indexing method to normalize for somatic growth is important. Although a simple linear regression model describes the relationship between LAV and BSA, it cannot be used to derive normalized values in children. Indexing LAV to $BSA^{1.48}$ for BSA≤1 m^2 should be used to normalize LAV and develop Z-scores in children. Indexing LAV to $BSA^{1.08}$ provides the best-fit allometric model for larger subjects with BSA>1 m^2. Although in this population, the use of such a model should be used with caution because of the potential of making nonconstant error in LAV measurements.

Disclosures

None.

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CLINICAL PERSPECTIVE

Left atrial size is an important diagnostic and prognostic measure of severity of disease and outcomes. Normal standards for left atrial size in children are not yet established. Current standardization methods have not been validated and if used clinically will categorize children with normal left atrial size in the abnormal category. Allometric scaling allows for accurate correction of chamber size for changes in body size (body surface area [BSA]), age, and sex. We have used this science to derive validated allometric models for the left atrial volume (LAV). In our study, we derived and validated an allometric model for children with BSA ≤1 m^2 and >1 m^2. The allometric models were further validated in a prospective cohort of children with structurally normal hearts and BSA. Indexing chamber volumes using BSA to the exponent of 1 is physiologically incorrect, and this has been published previously for left ventricular volumes. Results of our analysis show that z scores for indexed LAV should be based on indexing $LAV/BSA^{1.48}$ and $LAV/BSA^{1.08}$ in children with BSA ≤1 m^2 and >1 m^2, respectively. Using the validated allometric model will allow for accurate diagnosis of left atrial enlargement that will be independent of patients' body size, age, and sex. The z-score graphs provided will allow for referencing and allocation of z scores for measured LAV.

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