



## Normal Percentile Curves for Left Atrial Volume by Echocardiography in Egyptian Healthy Children and Adolescents

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### Abstract

**Background:** Despite the usefulness of echocardiography in evaluating the structure and function of the left atrium (LA), there is a lack of information about the percentiles of LA volume (LAV), and LA volume indexed by body surface area (LAV/BSA) in prospective population-based studies involving healthy children and adolescents in Egypt.

**Methods:** In 100 individuals who did not have any cardiovascular risk factors and were aged between 0 and 18 years old, echocardiographic studies were conducted. Stepwise multiple linear regression analysis was used to create BSA-specific reference values for LAV and LAV/BSA.

**Results:** After conducting covariate analysis (i.e., adjusting for age and body surface area), it was necessary to determine specific BSA-specific percentiles. The BSA-specific percentile values (<5<sup>th</sup>, 5<sup>th</sup>-25<sup>th</sup>, 25<sup>th</sup>-50<sup>th</sup>, 50<sup>th</sup>-75<sup>th</sup>, 75<sup>th</sup>-95<sup>th</sup> & >95<sup>th</sup> percentile) for LAV were reported.

**Conclusion.** Data given in this work may have practical implications as it would contribute to early diagnosis of altered LA dimensions in children and adolescents.

**Keywords:** children; adolescents; echocardiography; left atrial volume; percentiles

### Introduction:

In recent years, there has been increasing interest in the significance of left atrial (LA) volumes (LAV) and function as predictors of cardiac outcomes and as parameters for follow-up.

The different phases of LA function are crucial for ventricular physiology, supporting proper filling and performance of the left ventricle. The ventricles and cardiac valves affect left atrial geometry and functional capacity, and diseases related to them can result in left atrial remodeling and enlargement.

The LA reservoir function depends on the relaxation and compliance of the atrium, as well as on the left ventricular (LV) systolic function. The conduit function is influenced by LA compliance, LA, LV relaxation, and early filling. Both the contractility of the LA and the diastolic compliance of the LV are factors that determine the contractile function [1].

The size and function of the left atrium have been shown in studies of adults to be an indicator of diastolic dysfunction [2,3]. Moreover, it has been established as a significant prognostic indicator in adults with heart failure, ischemic heart disease and atrial fibrillation [4-6].

It is important to assess the size of the left atrium (LA) in children for various conditions such as mitral regurgitation [7]. Taggart et al. [8] and Sakata et al. [9] have shown that in patients with ventricular septal defect and patent ductus arteriosus, who have a left-to-right shunt resulting in a left ventricular (LV) volume overload, enlarged LA volumes can be identified. In children with hypertrophic cardiomyopathy, LA volumes were enlarged, indicating a possible indicator of elevated LV end-diastolic pressure and diastolic dysfunction [8,10].

LA size, initially assessed using M-mode2 and subsequently with two-dimensional echocardiography (2DE), making it one of the earliest non-invasive methods for assessing cardiac dimensions [11,12]. LA dimensions and volumes in children were initially described by Hiraishi et al [13], who reported that LA volumes (LAVOL) measured using echocardiography are highly correlated with invasively obtained data.

Several methods and techniques can be used to noninvasively assess LA structure and function, such as Tissue Doppler, M-mode, speckle tracking, 2DE, magneticresonance, and three-dimensional echocardiography [14,15]. Each of these approaches has its advantages and constraints [16,17].The use of 2DE for evaluating cardiac structures is the preferred method for initially assessing cardiac structure and function, even with advancements in cardiovascular imaging technology. This is due to its combination of accuracy, accessibility, safety, and flexibility [18].2DE continues to be essential for evaluating, diagnosis, and making decisions about congenital or acquired heart disease in children [8,16].The American Society of Echocardiography (ASE) suggests utilizing the biplane area length method for conducting left atrial volume (LAV) measurements using transthoracic echocardiography. [19].

In 2010, guidelines were published by the ASE that detailed Quantification Methods for the Performance of a Pediatric Echocardiogram. [20] The guidelines for quantifying cardiac chambers using echocardiography in adults were revised in 2015 [21].

The current guidelines have set standard measurements for the left atrium, but they do not provide much guidance on interpreting these measurements during puberty and adolescence. It's essential to recognize that as the body grows and develops, there may be changes in the structure and function of the left atrium (LA). Therefore, the normal or reference values for LA size may differ based on a person's age, gender, and body surface area (BSA) [8, 18].

There is limited data available on the relationship between left atrium (LA) size and the characteristics of Egyptian children and adolescents. Before creating percentile curves for left atrial volume (LAV) in this age group, it is important to determine whether there are variations in atrial size related to body surface area (BSA).

The main goal of this research was to determine the percentiles for Left Atrial Volume (LAV) and LAV indexed to Body Surface Area (LAV/BSA) by analyzing information gathered from 2D and M-

mode echocardiography in a group of healthy children and adolescents who had not been exposed to cardiovascular risk factors (CRFs) from the Egyptian population.

## Methods

This research is a component of a project that commenced in 2010 in Egypt. It aims to investigate cardiovascular disease and chronic renal failure in a population-based study. The Ethics Committee of the National Research Centre (NRC) approved the study protocol, and it was carried out in compliance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. Participants or legal guardians of children or adolescents always provided written informed consent before their involvement.

Between January 2014 and July 2017, 100 healthy children without symptoms, aged 18 or younger, who had a normal transthoracic echocardiogram, were eligible for participation. These children were collected from the Echocardiographic clinic of the Center of Excellence of NRC (CENRC). Each subject underwent a clinical interview, cardiovascular examination, and anthropometric assessment. Normotensive participants were enrolled, excluding those with a history of hyperlipidemia, diabetes, and cardiovascular, renal, or pulmonary disease.

The study did not include participants with abnormal body size (>95th percentile or <5th percentile), those who were unable to provide 2-chamber or 4-chamber apical images, or individuals with cardiovascular disease. In neonates, a patent foramen ovale<2.0 mmwas considered a normal finding and was not a reason for exclusion. BSA was calculated using the Haycock method [22]. (Table 1).

## Echocardiography

Subjects were instructed to avoid vigorous physical activity and consumption of caffeine-containing beverages for at least three hours prior to the examination. Conventional transthoracic echocardiogram (ultrasound machine Vivid 3 pro Dimension, General Electric Healthcare Company, Norway) using Doppler transducers and 3 and 7 MHz combined imaging)was carried out in our echocardiography laboratory by an experienced sonographer. During evaluations, the subject was placed in a quiet environment with a constant temperature of  $22 \pm 1^{\circ}\text{C}$ , they were positioned lying on their left side. Following a minimum of 10 minutes of comfortable rest While maintaining normal breathing, images were taken from parasternal long and short cardiac axes, as well as from apical four-, five-, and two-chamber long-axis perspectives. We follow a specific echocardiography protocol for evaluating the size of the left atrium (LA). This involves acquiring apical 2-chamber and 4-chamber views while the patient is in the left lateral decubitus position. The images were enhanced to prevent foreshortening and to ensure clear delineation of the inner border of the heart. One experienced independent observer (H.K.) conducted measurements of the left atrium, as well as the Area 2-chamber, Length 2-chamber, Area 4-chamber, and Length 4-chamber by using a Syngo 9.0 (Siemens, Mountain View, CA) postprocessing system. According to ASE recommendations, the measurements were conducted during end-systole, and LAV was

determined using biplane area length method (Figure 1) with the equation:  $LAV=0.85 \times \text{Area 4-chamber} \times \text{Area 2-chamber} / \text{Shortest length (4-chamber or 2-chamber)}$  [19, 23].

### Statistical analysis

Data was analyzed and managed with version 27 of the Statistical Package for Social Sciences (SPSS). Numerical data was summarized using means, standard deviations, medians, ranges, and percentiles. Categorical data was presented as percentages and numbers, and frequency was calculated using both numbers and percentages. We used the Kolmogorov-Smirnov test and Shapiro-Wilk test to evaluate the normality of numerical data."

The strength of association between normally distributed measurements was assessed using Pearson's correlation coefficients ( $r$  is the correlation coefficient & it ranges from -1 to +1). Comparisons of two groups for numeric variables that are normally distributed were conducted using the Student's t-test. The one-way analysis of variance (ANOVA) is used for comparing more than 2 groups when the variables are normally distributed. On the other hand, the Kruskal-Wallis test is employed for comparing non-normally distributed variables among multiple groups. To determine the individual impact of various factors on (LAV), factors with a significance level below 0.10 were chosen for inclusion in stepwise multilinear regression analysis.

We conducted a multilinear regression to determine the adjusted odds ratio and the extent of the impact of various risk factors in relation to (LVA). We also computed the odds ratio (OR) and 95% Confidence Interval (95% CI); a 95% CI that does not include 1.0 is deemed to be significant.

The intraclass correlation coefficient (ICC) method was employed to evaluate intra-observer reproducibility and inter-observer reliability for the values of 2D LS, RS, and CS. The clinical significance was classified as follows: "excellent," if the ICC was 0.80 or greater; "good," if the ICC was between 0.61 and 0.79; "moderate," if the ICC was between 0.41 and 0.60; and "poor," if the ICC was 0.4 or less. All statistical tests were two-tailed, and a p-value of  $\leq 0.05$  was considered significant.

### Results

In a sample of 100 sequential children meeting the inclusion and having optimal images for accurate measurements, left atrial volume (LAV) was assessed.

The participants had an average age of 9 years (range 0–19) and a body surface area (BSA) of 1 m<sup>2</sup> (ranging from 0.244–1.69). 57% of the participants were female. The mean absolute LAV for the entire group was  $12 \pm 6$  mL, and the mean absolute indexed LAV was  $12 \pm 4.1$  mL (Table 1).

In Table 2, it was observed that there was no notable difference in left atrial volume (LAV) between male and female subjects, (mean,  $12.1 \pm 6$  mL versus  $11.9 \pm 6$  mL;  $P=0.873$ )

The correlation analysis in Table 3 showed demographic, and

anthropometric, potentially associated with LAV. There were significant positive associations between LAV, and age, body weight, and height ( $P<0.001$ ).

As predicted, we observed a significant correlation between LAV and BSA ( $r=0.67$ ,  $P<0.001$ ) (Figure 2). Conversely, there was no significant correlation between indexed LAV and BSA ( $r=0.07$ ,  $P=0.477$ ) (Figure 3).

The percentiles of BSA are shown in Table 4. They ranged from 0.51 at the 5<sup>th</sup> percentile to 1.6 at the 99<sup>th</sup> percentile. The BSA-specific percentile values (<5<sup>th</sup>, 5<sup>th</sup>-25<sup>th</sup>, 25<sup>th</sup>-50<sup>th</sup>, 50<sup>th</sup>-75<sup>th</sup>, 75<sup>th</sup>-95<sup>th</sup> & >95<sup>th</sup> percentile) for LAV were shown in Table 5 and percentile curves were shown in Figure 4. LAV ranged from 5.6 (1.5-7.2) mL at <5<sup>th</sup> percentile to 23 (14.9-28.4) mL at >99<sup>th</sup> percentile. All volumes increased significantly with increasing BSA.

To assess the independent effect of different covariates affecting LAV, factors with significance level less than 0.100 were chosen to enter into stepwise multilinear regression analysis (MLR). Table (5) showed the covariate which was significant in the stepwise MLR.

The impact of each variable is shown by the regression coefficient after controlling the effect of other variables in the model. BSA was the most important predictor for LAV.

### Interobserver and intraobserver reproducibility

Data included in this study represent the average of three consecutive cardiac cycles. LAD and LAV measurements exhibited high intra-observer repeatability. The intraclass correlation coefficients for inter-observer and intra-observer comparison of LAV measurement ranged between 0.81 and 0.9.

**Table 1:** General characteristics of the studied group

	n=100 (%)
<b>Sex</b>	
Female	57 (57)
Male	43 (43)
	<b>Mean <math>\pm</math>SD</b>
<b>Age (Years)</b>	9 $\pm$ 4
<b>Weight (kg)</b>	29.6 $\pm$ 13.6
<b>Height (cm)</b>	125 $\pm$ 23
<b>LAV (ML)</b>	12 $\pm$ 6
<b>Indexed LAV</b>	12 $\pm$ 4.1
<b>BSA (m2)</b>	1 $\pm$ 0.3

BSA=Body surface area, LAV=Left atrial volume, SD: Standard deviation

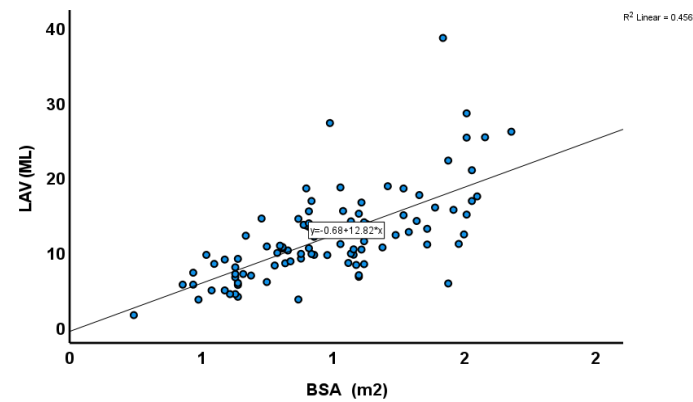
**Table 2:** LAV & indexed LAV in male and female group

	Female	Male	
	Mean $\pm$ SD	Mean $\pm$ SD	P value
<b>LAV (ML)</b>	11.9 $\pm$ 6	12.1 $\pm$ 6	0.873
<b>Indexed LAV</b>	11.6 $\pm$ 4.1	12.6 $\pm$ 4.1	0.243

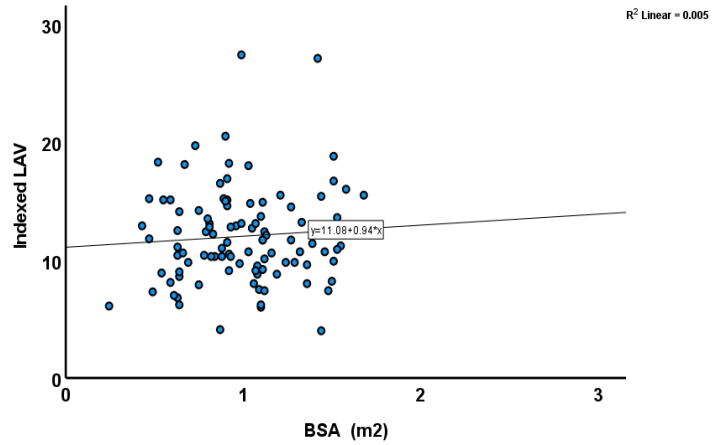
**Table 3:** Correlation between LAV& indexed LAV with different factors in the studied group

Factors	LAV		Indexed LAV	
	r	P value	r	P value
Age	0.52	<0.001		
Weight	0.64	<0.001	-0.03	0.741
Height	0.66	<0.001	0.06	0.585
BSA	0.67	<0.001	0.11	0.273
			0.07	0.477

BSA= Body surface area, LAV=Left atrial volume, r = correlation coefficient (from -1 to +1),p-value<0.05 was considered significant



**Figure 2:** Scatter plot diagram representing correlation between BSA&LAV (r =0.456r=0.67, p<0.001)



**Figure 3:** Scatter plot diagram representing the correlation between BSA& indexed LAV. The trend line on the graph is nearly horizontal and close to the X-axis, and the correlation coefficient r 2 approaches zero. This indicates that there is almost no significant relationship to BSA (r 2 =0.005, r= 0.07, p=0.477).

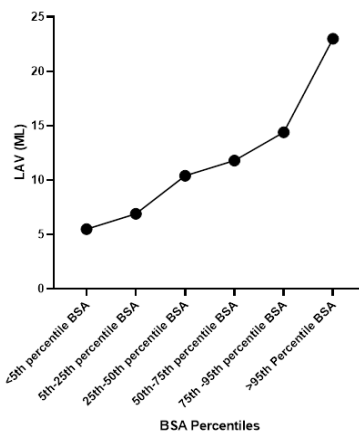
**Table 4:** Percentiles of BSA in the studied group

	Perce ntile 5 <sup>th</sup>	Percentile 25 <sup>th</sup>	Per cent ile 50 <sup>th</sup>	Percentil e 75 <sup>th</sup>	Perce ntile 95 <sup>th</sup>	Perce ntile 99 <sup>th</sup>
BSA (m2)	0.51	0.77	0.97	1.2	1.5	1.6

BSA=Body surface area

**Table 5.** The BSA-specific percentiles values for LAV

	BSA percentiles						P value
	<5th percentile BSA	5th-25 percentile BSA	25th-50 percentile BSA	50th-75th percentile BSA	75th -95th percentile BSA	>95th Percentile BSA	
	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)	
LAV (ML)	5.6 (1.5-7.2)	6.9 (3.9-14.4)	10.4 (3.6-18.4)	11.8 (6.6-27.1)	14.4 (5.7-38.5)	23 (14.9-28.4)	<0.001
Indexed LAV	11.8 (6.1-15.2)	10.5 (6.2-19.7)	12.8 (4.1-20.5)	10.6 (6-27.4)	10.7 (4-27.1)	14.6 (9.9-18.8)	0.142



**Figure 4:** Percentile curves for LAV

**Table 5:** stepwise multi linear regression analysis

Factors	B	SE	95.0% CI for B	P value
BSA	12.7	1.5	9.8-15.7	<0.001

BSA=Body surface area, Standard error, B: regression coefficient, P value <0.05 is considered significant

## Discussion

This study is the first attempt in Egypt to establish LAV percentiles in healthy children, and adolescents through a prospective population-based study.

The results are obtained from a large cohort of healthy children in Egypt, which consists of a diverse sample of children ranging from 0 to 19 years old. Having these reference values and percentile for 2DE could be highly beneficial for the longitudinal and the cross-sectional evaluation and follow-up of pediatric patients. It could also aid clinicians to more effectively identify LA dysfunction and monitor disease progression.

The study aimed to explore the correlation between left atrial volume (LAV) and body surface area (BSA) in order to derive and validate BSA-based percentiles. These percentiles are useful for creating standardized LAV data in pediatric population.

The presence of these reference values and percentiles for 2DE could be crucial in assessing and monitoring pediatric patients, enable clinicians to more effectively recognize left atrial dysfunction and the disease progression. In our study of 100 healthy children, we did not find any significant correlation between indexed LAV and BSA.

It is crucial to regularly measure the size of the left atrium in pediatric patients with mitral valve disease and left ventricular pathology. Utilizing 2D echocardiography, the determination of the left atrium size has been associated with adverse hemodynamics and an unfavorable prognosis in children with ventricular septal defects, patent ductus arteriosus, and cardiomyopathy.

[8,10,23,24]. The current recommendation for measuring LA size suggests using the biplane area length method to derive LAV. It is also recommended to index LAV to BSA to account for body size [19]. LAV has been recommended over linear dimensions due to its higher accuracy and stronger association with adverse outcomes in adults [26]. There are several methods available for calculating LA volume using 2D data, but there is significant variation in clinical practice [27].

Bhatla et al [25] conducted a study involving 300 children and adolescents and created an allometric model to analyze LAV/BSA. The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) both suggested a unified cutoff value for LAV/BSA normality (34 mL/m<sup>2</sup>) in individuals  $\geq$  16 years old, irrespective of gender [21]. Utilizing this cutoff value might lead to a misdiagnosis of LA enlargement. It has been shown that both ethnicity [28] and genetic factors [29] play a role in explaining the variability in LA dimensions.

A comprehensive review of 36 studies involving 30,607 children and adolescents underscored the importance of establishing race-specific reference ranges for left cardiac chamber dimensions and the standardization of echocardiographic methods to derive the reference ranges [18].

In the EchoNoRMAL collaboration study, the potential variations in reference values for standard echocardiography measurements based on age, sex, and ethnicity were recently evaluated. The study involved 22,404 participants from Asia, Europe, Australia, and the United States [30]. Quantile regressions were utilized to identify the upper reference value (URV) and lower reference value (LRV) for each measurement at the 95th and 5th percentiles, respectively. These percentiles were determined based on age, gender, and ethnicity.

The study revealed the following findings: 1) European and American Black individuals at 30 years old have higher upper reference values (URVs) for LA diameter, while South Asian and African subjects have lower URVs; 2) URVs for LAV were also found to be higher for Europeans compared to East Asians, with less pronounced differences among women; 3) Even after indexation by BSA or height, differences in the URVs for LA diameter and volume persisted in men; 4) Significant age-related changes in LA diameter's URVs were observed for European, African, and American Black men, and varied for women based on the method of measurement; 5) Age-related changes in LAV were not significant, except for European women.

The findings mentioned support the idea that the links between individuals' characteristics and LA dimensions are not straightforward and may differ based on the group being examined. In this respect, our research characterizes the determinants of LA dimensions, providing unique and additional information collected from children and adolescents in Egypt.

Various demographic and anthropometric factors have been recognized as determinants of LA dimensions. There is ongoing debate regarding the role of aging in this context [31].

In this context, our findings are consistent with the information presented by Taggart et al [8] regarding individuals aged 0 to 18 years. The authors did not establish reference values, but data (scatterplots) they shared enabled us to verify that LAV/BSA values increase with age in children and adolescents. The authors found that changes in left atrial volume (LAV) during childhood are associated with periods of somatic growth, which is consistent with the reported changes in other cardiac parameters.

Nistri et al [31] discovered a positive correlation between age and LAV/BSA. Additionally, following a thorough regression analysis, age was determined to be as an explanatory variable for LAV. However, it's worth noting that the association between LA size and

aging is not universally accepted, and conflicting data exists.

Some studies have suggested that the age-related increase in LAV may be attributed to concurrent age-related changes in LV diastolic physiology (i.e., LA size increase could be an expression of pathological conditions rather than of normal aging) [32].

ASE and EACVI have suggested using a single cutoff point for LAV/BSA normality for individuals aged 16 and above, indicating that LA volumes remain constant with age [21]. According to Díaz A et al [27], a thorough interpretation of LA diameter, LAV, and LAV/BSA data obtained from 2DE studies in children, adolescents, and young adults necessitates the consideration of age- and sex-specific percentiles. 3D echocardiography reliably measured pediatric left atrial volume (LAV) and phasic function indices. These reference values for pediatric patients can be used to assess the left atrium using 3D echocardiography and aid in identifying left atrial dysfunction and follow-up of patients with congenital heart diseases and various cardiac pathologies [1,33]. Šileikienė et al [34] found that obesity might have an adverse impact on atrial and ventricular function, as measured by 2D speckle tracking echocardiography. Even apparently healthy obese children might experience subclinical myocardial dysfunction.

## Conclusion

To summarize, BSA-specific percentile curves for atrial dimensions were established using information gathered from healthy children, adolescents, and young adults.

The information presented in this study could be useful for evaluating LA size in children and adolescents, it could also help in monitoring changes in left atrial dimensions during the stages of growth from childhood to early adulthood and could be beneficial in the early detection of altered LA dimensions. Further research is scheduled to compare left atrial volumes, as determined by 3DE, in healthy children with these reference values.

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## Competing Interest

Authors declare that no competing interest

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