

# Normal reference ranges for the left ventricular mass and left ventricular mass index in preterm infants

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## ABSTRACT

- Objective** : The objective of this study is to establish normal reference ranges for the left ventricular mass (LVM) and LVM index (LVMI) in preterm infants according to the body surface area (BSA) and assess their correlation with body weight and gestational age.
- Subjects and Methods** : In a prospective study, 268 preterm babies who fulfilled the criteria for inclusion were examined. Echocardiograms were performed to measure the LVM and LVMI on 0–6 day (s) of life and at weekly intervals until the babies reached 36 weeks. The preterm infants were divided into six groups according to their BSA: 0.07–0.08 m<sup>2</sup>, 0.09–0.10 m<sup>2</sup>, 0.11–0.12 m<sup>2</sup>, 0.13–0.14 m<sup>2</sup>, 0.15–0.16 m<sup>2</sup>, and 0.17–0.19 m<sup>2</sup>.
- Results** : The mean gestational age was 29.8 (±2.38 standard deviation [SD]) weeks, ranging from 24 to 35 weeks. The mean body weight was 1479 (±413 SD) g, ranging from 588 to 3380 g, and the mean BSA was 0.13 m<sup>2</sup>, ranging from 0.07 to 0.19 m<sup>2</sup>. The LVM correlated well with the gestational age, body weight, and BSA. The LVMI correlated well with body weight and BSA. Reference ranges with the mean ± SD, range, and interquartile range were calculated for the LVM and LVMI according to the BSA. A significant gradual increase was observed in a LVM with increasing BSA. Overall, a progressive and significant increase in the LVM was observed during the first 9 weeks of life.
- Conclusion** : The LVM and LVMI exhibited a significant correlation with the BSA and body weight. This study provides reference data that can be used as a normal reference tool for the LVM and LVMI for preterm infants based on the BSA.
- Keywords** : Body surface area, left ventricular mass, left ventricular mass index, preterm infants, reference ranges

## INTRODUCTION

For the past 60 years, echocardiography has been practiced as the primary mode of investigation to evaluate the anatomy and function of the heart.<sup>[1,2]</sup> However, few studies have described a normal premature neonate's heart. Preterm hearts differ significantly from a term

neonate's heart, and there is a gradual transition to a mature neonate heart. This study aimed to evaluate the anatomic and physiologic characteristics of the premature infant's heart and the changes that occur during the early postnatal period. As more preterm infants survive due

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to improved critical care services, an increasing number of preterm infants require at least one echocardiogram during the 1<sup>st</sup> month of life. Thus, it is vital to have adequate reference values. Left ventricular mass (LVM) is an important clinical measure given its association with left ventricular hypertrophy and its significance as a strong independent risk factor for cardiovascular disease and mortality. The diagnosis of an enlarged or hypertrophied heart has an important effect on the treatment of children with congenital or acquired heart disease.<sup>[3]</sup> M-mode echocardiography makes it possible to assess the LVM by measuring cardiac dimensions and wall thicknesses.<sup>[4]</sup> Unfortunately, there are currently no universally accepted normal values for this age group. Few studies in the literature involve the hearts of premature infants.<sup>[5,6]</sup> The aim of this study was to establish these normal values using a large number of healthy premature babies. The main objective of the study was to establish these normal reference values during the first 9 weeks of life and determine whether these values correlate with other variables, such as the body surface area (BSA), body weight, and chronological age.

## MATERIALS AND METHODS

### Patients

In this prospective study, 400 premature infants <36 weeks of gestation admitted to the neonatal units between January 2008 and December 2010 were consecutively recruited and studied. The babies were from mixed populations. A majority was Arabic, and the remainder was from other Asian nations. Of these infants, 268 premature babies [Table 1] fulfilled the following inclusion criteria:

- Infants with normal hearts (infants with small patent foramen ovale or small patent ductus arteriosus were not excluded)
- Healthy preterm infants with no evidence of sepsis, renal failure, and other comorbidities
- Absence of other major congenital anomalies or syndromes
- Absence of gestational diabetes in the maternal history
- Preterm infants on low ventilator settings (when infant did not require high-frequency ventilation or unusually high rates and pressures) or nonventilated preterm infants.

We excluded sick preterm infants and those with major cardiac or noncardiac congenital anomalies (sepsis and multi-organ failure – 40, gestational diabetes – 32, cardiac anomalies – 20, high-frequency ventilators – 16, syndromic – 12, and major congenital anomalies – 12).

Ethical approval was obtained from the Ethical Committees of both the Kuwait Ministry of Health and the Faculty of Medicine of Kuwait University. The study

**Table 1: General characteristics of the preterm babies**

Characteristic	Values
Male:female (n)	126:142
Gestational age (weeks)	
Mean±SD	29.8±2.38
Median (range) IQ	30 (24-35) 28-32
Weight (g)	
Mean±SD	1479±413
Median (range) IQ	1460 (588-3380) 1164-1730
Length (cm)	
Mean±SD	40.1±3.56
Median (range) IQ	40 (25-50) 38-42
BSA (m <sup>2</sup> ), mean (range)	0.123 (0.07-0.19)
Echos per baby (minimum-maximum)	1-5
Age (weeks) at study (minimum-maximum)	1 day - 9 weeks

IQ: Interquartile, BSA: Body surface area, SD: Standard deviation

was funded by a grant from the Kuwait Foundation for the Advancement of Sciences (KFAS). The parents were informed that the infants would be enrolled in an observational study and not a therapeutic trial. Prior written consent was also obtained from the parents.

### Methods

Before the study was undertaken, the pediatric cardiologist responsible for conducting the echocardiograms was trained and observed by two senior pediatric cardiologists through the pretest echocardiograms for external validity and generalization. Interpersonal variability was evaluated. Once a lack of significant variability was noted in the readings, the doctor was assigned to conduct the study. Two different senior pediatric cardiologists also supervised these interpretations for generalization. The assigned cardiologist was not directly involved in the patient's care. Echocardiographic studies were performed with a Siemens Cypress scanner using a 7.5 MHz probe. The equipment used was standardized and certified by the Ministry of Health's biomedical engineer.

Each infant was examined as follows. Two-dimensional (2D) and M-mode echocardiographic studies were performed in the supine. The 2D image was used to obtain the optimum position and angulation of the M-mode line. The standard parasternal short-axis view was used. End diastole and end systole were defined as the beginning of the QRS complex in the electrocardiogram and the most thickened phase in the left ventricular posterior wall, respectively. Each thickness was measured according to the American Society of Echocardiography (ASE) recommendations<sup>[7]</sup> as adapted by Silverman<sup>[8]</sup> for premature infants and the recently published guidelines for performance of a pediatric echocardiogram by the pediatric council of the ASE.<sup>[9]</sup> Infants were examined within the first 6 days of life and at weekly intervals until they reached term (36 weeks). The end-diastolic left ventricular internal dimension (LVIDd), end-diastolic left ventricular posterior wall thickness (LVPWd), and

end-diastolic interventricular septum (IVSd) values were determined by echocardiographic examination. Using these values, LVM was calculated based on the formula of Devereux,<sup>[10]</sup> which has been validated for use in children with normal hearts. In the present study, we used Devereux and Reichek “cube” formula:  $1.04 ([IVSd + LVIDd + PWTd]^3 - LVIDd^3) + 0.6 \text{ g}$ .

The examinations were recorded on video, and all data were stored in Dicom format. Before the study was undertaken, the pediatric cardiologist responsible for conducting the echocardiograms was trained and observed by the two senior pediatric cardiologists through the pretest echocardiograms for external validity and generalization. Inter- and intraobserver variabilities were evaluated using repeated measures analysis of variance in 50 individuals. Once no significant variability in the readings was confirmed, the doctor was assigned to conduct the study. All the interpretations were made by an assigned pediatric cardiologist who recorded the images and were observed by two different senior pediatric cardiologists. The interpreter was blinded to the age, sex, and patient’s previous/succeeding data at the time of image analysis. Standard parameters were measured by the interpreter, and the calculated parameters were performed using the computer software, which was part of the echo machine. In rare situations, when the readings recorded by the computer were inconsistent, the readings were repeated on the same day to reassess for accuracy. Two pediatric cardiologists who were blinded to the serial values of a particular infant validated the measurement. Adequate time was spent by the three pediatric cardiologists to obtain accurate values and avoid errors.

Some of the very premature babies became unfit after 1 or 2 echocardiograms and were excluded. A few babies were re-included as they recovered rapidly after a brief period of illness.

**Statistical analysis**

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21.0 software (IBM Corp., Armonk, NY, USA). The normal distribution assumption for the LVM and LVM index (LVMI) variables as well as the weight and gestational age was ascertained with Kolmogorov-Smirnov test. The descriptive statistics are presented as the mean and standard deviation (SD), range, and interquartile (IQ), given that some of the variables failed to meet the assumption of data normality. IQ range is the difference between the first quartile (25<sup>th</sup> percentile) and the third quartile (75<sup>th</sup> percentile) of an ordered range of data. The range contains the middle 50% of the distribution and is unaffected by extreme values. The BSA was used as the independent variable in different regression analyses to predict the mean values of LVM and LVMI. The BSA was used to index the LVM.

The BSA in square meters (m<sup>2</sup>) was calculated using the Dubois and Dubois formula.<sup>[11]</sup>

For practical purposes and easy understanding, the babies were divided into six groups according to their BSA: 0.07–0.08 m<sup>2</sup>, 0.09–0.10 m<sup>2</sup>, 0.11–0.12 m<sup>2</sup>, 0.13–0.14 m<sup>2</sup>, 0.15–0.16 m<sup>2</sup>, and 0.17–0.19 m<sup>2</sup>.

The Spearman’s rho was applied to determine any correlation between the two variables. The two-tailed probability value  $P < 0.05$  was considered statistically significant [Table 2]. Measured values were plotted as a scatter plot.

**RESULTS**

Among the 400 infants, a total of 268 preterm infants who fulfilled the inclusion criteria were studied at weekly intervals until they reach 36 weeks of age. A total of 418 echocardiograms were conducted during the study period. The general characteristics of the infants are presented in Table 1. A slight female predominance was noted (M:F = 1:1.13). The mean gestational age was 29.8 (±2.38 SD) weeks, ranging from 24 to 35 weeks. The mean body weight was 1479 (±413 SD) g, ranging from 588 to 3380 g, and the mean BSA was 0.123 m<sup>2</sup>, ranging from 0.07 to 0.19 m<sup>2</sup>.

In view of the overall spectrum relating to the LVM and LVMI in preterm infants, three different reference ranges are presented. Reference ranges with mean ± SD, range, and interquartile values for the LVM and LVMI according to the BSA are presented in Table 3. Our ranges of normal values based on the BSA are similar to the expected values.

Overall, a progressive and significant increase for LVM was observed during the first 9 weeks of life. For example, to observe the reference range for an infant with a particular BSA [Table 3]. Scatter plot graphs [Figures 1 and 2] show the measured values of the LVM and LVMI in preterm infants against the BSA.

To obtain more accurate values and create an easy ready reference for the pediatric cardiologists who routinely conduct echocardiograms, we decided to consolidate our findings into one self-explanatory table and two scatter plot graphs.

**Table 2: Correlation between left ventricular mass and left ventricular mass index with gestational age and body weight**

Variable	r (P)	
	Gestational age (weeks)	Weight (g)
LVM (g)	0.261 (0.001)**	0.701 (0.001)**
LVMI (g)	-0.026 (0.603)	0.267 (0.001)**

\*Correlation significant at 0.05, and \*\*Correlation significant at 0.01 probability level. LVM: Left ventricular mass, LVMI: Left ventricular mass index

## DISCUSSION

We present reference ranges of the LVM and LVMI for a complete population of preterm infants. There is a close correlation between the body weight and BSA and the LVM. From the embryogenesis period, immediately after birth, progressive cardiac development and growth can be observed in newborn and children. In parallel, an increase in LVM occurs during childhood. Normal reference ranges are available for adults and children, but few references have been produced for evaluating preterm infants in modern neonatal units. Available studies include a small number of preterm infants and measurements performed over a wide age range.

Given that an increased LVM has been established as a strong independent risk factor for cardiovascular morbidity (e.g., arrhythmia, congestive heart failure, and myocardial infarction) and mortality, normal LVM

values are also needed for the treatment management and prognostic evaluation.<sup>[12,13]</sup>

Echocardiography offers a reliable, noninvasive, rapidly available, and relatively inexpensive method for estimation of LVM. M-mode echocardiography is used most widely to measure LVM because of its wide availability, moderate expense, and anatomic and prognostic validation.<sup>[14]</sup>

The first and most commonly used echocardiography method of LVM estimation is the linear method, which uses end-diastolic linear measurements of the interventricular septum (IVSd), LV inferolateral wall thickness, and LV internal diameter derived from 2D-guided M-mode or direct 2D echocardiography. This method utilizes the Devereux and Reichek “cube” formula, which assumes a prolate ellipsoid shape of the LV with a ratio of 1:2 minor-to-major axis.<sup>[15]</sup>

There is no agreement in the literature about the anthropometric parameter that presents the best correlation with the echocardiographic measurements. Some studies present a better correlation with the BSA, whereas some studies present a better correlation with weight and others with height.<sup>[16-18]</sup> BSA is the expression of body size with the highest correlation to cardiac dimensions.<sup>[19]</sup>

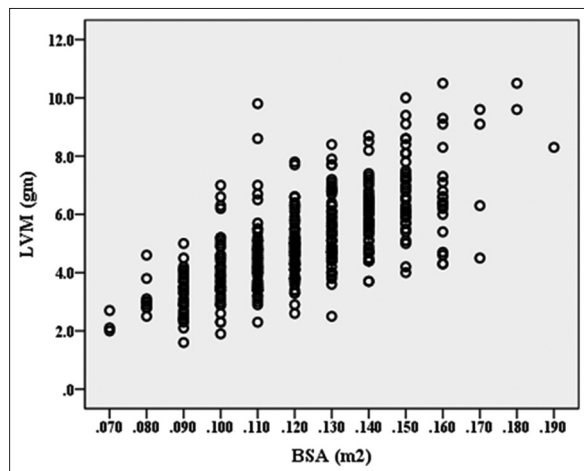
The BSA was the first anthropometric variable used to index the LVM and has demonstrated a stronger statistical correlation with the LVM than height.<sup>[20]</sup> The BSA has been widely adopted by the ASE and the European Association of Cardiovascular Imaging as the preferred method for indexing the LVM.<sup>[21]</sup> Normalization to the BSA is a standard approach in the current era.<sup>[22-25]</sup> However, various formulas to calculate the BSA exist,<sup>[26-29]</sup> and there is no agreement regarding which formula should be used in preterm neonates and infants.<sup>[27,29]</sup>

It was suggested that the number of human cardiac myocytes is determined within the 1<sup>st</sup> year after birth when mitotic activity of cardiocytes appears to cease.

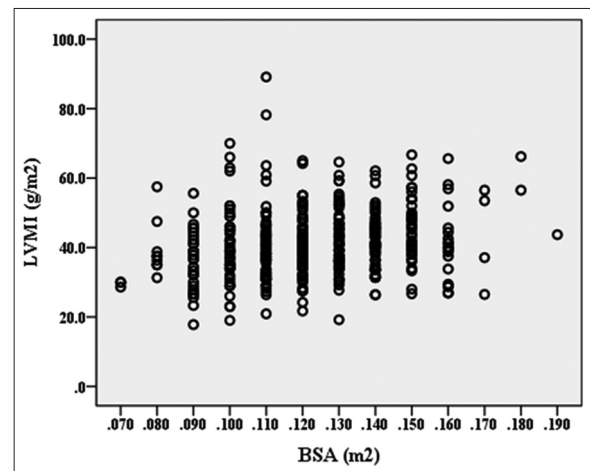
**Table 3: Mean±standard deviation (range) and interquartile values of left ventricular mass and left ventricular mass index according to body surface area groups**

BSA (m <sup>2</sup> )	n	LVM (g)	LVMI (g <sup>2</sup> )
0.07-0.08	12	2.94±0.70 <sup>a</sup> (2.0-4.6) <sup>b</sup> 2.55-3.08 <sup>c</sup>	37.08±8.22 <sup>a</sup> (28.6-57.5) <sup>p</sup> 30.33-38.48 <sup>c</sup>
0.09-0.10	75	3.71±1.06 (1.6-7.0) 2.90-4.20	38.54±10.41 (17.8-70.0) 32.00-45.00
0.11-0.12	144	4.65±1.12 (2.3-9.8) 3.90-5.10	40.27±9.69 (20.9-89.1) 33.75-43.60
0.13-0.14	125	5.61±1.13 (2.5-8.7) 4.70-6.35	41.77±8.26 (19.2-64.6) 36.20-46.65
0.15-0.16	55	6.78±1.51 (4.0-10.5) 5.90-7.80	44.27±9.98 (26.7-66.7) 38.00-51.90
0.17-0.19	7	8.27±2.13 (4.5-10.5) 6.30-9.60	48.57±13.56 (26.5-66.2) 37.10-56.50

<sup>a</sup>Mean±SD, <sup>b</sup>Range, <sup>c</sup>IQ. LVM: Left ventricular mass, LVMI: Left ventricular mass index, BSA: Body surface area, SD: Standard deviation, IQ: Interquartile



**Figure 1: The relationship between the left ventricular mass and body surface area**



**Figure 2: The relationship between the left ventricular mass index and body surface area**



Thus, subsequent increases in the LVM reflect cellular enlargement (hypertrophy).<sup>[17]</sup> According to studies in normal adults, the LVM is larger in men compared with women.<sup>[12,30]</sup> Normal reference values of the LVM indexed to the BSA using 2D guided M-mode echocardiography are 49–115 g/m<sup>2</sup> for men and 43–95 g/m<sup>2</sup> for women.<sup>[21]</sup>

In 2011, Kervancioglu *et al.*<sup>[31]</sup> evaluated 208 children (143 males and 65 females) aged 1 day to 14 years who had no cardiovascular disease. The LVIDD, LVPWd, and IVSd values were determined by M-mode echocardiographic examination. The LVM was calculated using these values. The LVM and its components presented a good correlation with the age, weight, height, and BSA.

The present study involved 268 premature infants (the largest in number to date). All infants were healthy, and any infant who became sick during the study was excluded. This study reports serial measurements of LVM during the first 9 weeks of life in a selected population of preterm infants with a body weight of 588–3380 g and between 24 and 35 weeks of gestational age.

Measurements of the LVM exhibited a significant correlation with body weight and BSA. A progressive and significant increase in the LVM was noted over time.

The present study provides accurate reference ranges, as the data were collected from a large number of preterm infants. The results established according to the BSA in this study contribute to the determination of the lower and upper limits of the LVM obtained by echocardiography in normal preterm infants.

We hope that these data will be accepted by neonatal units as normal reference ranges of the preterm LVM. These data will be useful as a ready reference for pediatric cardiologists who routinely perform echocardiograms in preterm infants. These self-explanatory tables will provide normal reference ranges of the LVM based on the BSA presented as the mean  $\pm$  SD, range, and interquartile values as multiple options for reference values.

### Strengths and limitations

Our study has several strengths. First, we evaluated important echocardiographic parameters in a large group of preterm infants for whom the available normal reference values were limited or even absent. Second, we prospectively enrolled the largest population of healthy preterm infants studied to date. Third, all reported measurements in the database represent only those performed with excellent visualization and no ambiguity. A minor limitation of our study is the fact that we used the Dubois and Dubois formula to calculate the BSA; however, it occasionally underestimates BSA.<sup>[28,29,32]</sup> This difference is negligible in very low body weight and length.

## CONCLUSION

Significant correlations are noted between the body weight and BSA and the LVM. A progressive and significant increase in the LVM was observed during the first 9 weeks of life. The values presented can be used as a normal reference tool for the LVM for preterm infants based on the BSA.

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### Conflicts of interest

There are no conflicts of interest.

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