Normal reference ranges for cardiac valve cross-sectional areas in preterm infants

Lulu Abushaban[1], Mariappa Thinakar Vel[2], Jebaraj Rathinasamy[2], Prem N Sharma[3]

[1]Department of Pediatric Cardiology, Chest Diseases Hospital, Ministry of Health, Faculty of Medicine, Kuwait University, [2]Department of Pediatric Cardiology, Chest Diseases Hospital, Ministry of Health, [3]Department of Biostatistics, Faculty of Medicine, Kuwait University, Kuwait

ABSTRACT

Objective : To establish normal reference ranges for cardiac valve cross-sectional areas (CSAs) in preterm infants and their correlation with gestational age, body weight, and chronological age.

Materials and Methods : In a prospective study, 268 preterm babies fulfilling the criteria for inclusion were examined. Echocardiograms were performed to measure aortic, pulmonary, mitral, and tricuspid valve CSAs on 0–6 day (s) of life and at weekly intervals until they reached 36 weeks. Gestational age was divided into three groups, 24–27, 28–31, and 32–35 weeks, and body weight was divided into five groups, ≤999, 1000–1499, 1500–1999, 2000–2499, and ≥2500 g. Overall group differences were compared for each period of life: 0–6 days and 1–2, 3–4, and ≥5 weeks.

Results : The mean gestational age was 29.8 (±2.38 standard deviation [SD]) weeks, ranging between 24 and 35 weeks, and the mean body weight was 1479 (±413 SD) g, ranging between 588 and 3380 g. All cardiac valve CSAs correlated well with body weight. A significant gradual increase was observed in all valve CSAs with body weight during each period of life. Overall, a progressive and significant increase in all valve CSAs was observed during the first 9 weeks of life.

Conclusions : Cardiac valve CSAs were found to be significantly correlated with body weight. The study also provides reference data, which can be used as a normal reference tool for valve CSAs in preterm infants against gestational age, body weight, and chronological age.

Keywords : Body weight, chronological age, gestational age, preterm infant babies, reference ranges, valve cross-sectional area

INTRODUCTION

Echocardiography has been practiced as a primary mode of investigation to evaluate the anatomy and function of the heart for the past 60 years;[1,2] however, few studies have described the hearts of normal premature neonates. Preterm hearts differ significantly from term neonate hearts, and there is gradual transition to a mature neonate heart. This study evaluates the anatomic and physiologic characteristics of premature baby hearts and the changes that occur during the early postnatal period. As more preterm babies survive due to improvements in critical care, an increasing number of preterm infants require at least one echocardiogram during the 1st month of life; thus, it is vital that adequate reference values are available. Valve stenosis is a common heart disorder and

Access this article online

Quick Response Code:

Website: www.annalspc.com

DOI: 10.4103/apc.APC_76_17

How to cite this article: Abushaban L, Vel MT, Rathinasamy J, Sharma PN. Normal reference ranges for cardiac valve cross-sectional areas in preterm infants. Ann Pediatr Card 2018;11:17-27.

Address for correspondence: Prof. Lulu Abushaban, Consultant Pediatric Cardiologist, Chest Diseases Hospital, Professor in Pediatric Cardiology, Kuwait. University, Kuwait. E-mail: lulu@hsc.edu.kw

an important cause of cardiovascular morbidity and mortality. Echocardiography has become the key tool for the diagnosis and evaluation of valve disease and is the primary noninvasive imaging method for valve stenosis assessment. Clinical decision-making is based on an echocardiographic assessment of the severity of valve stenosis; therefore, it is essential that reference values are available. Unfortunately, there are as yet no universally accepted normal values. Few studies in the literature have examined premature baby hearts.[3,4] Our aim was to establish these normal values based on a study involving a large number of healthy premature babies. The main objectives of this study, therefore, are to establish normal reference values during the first 9 weeks of life and determine whether these valve cross-sectional areas (CSAs) are correlated with variables, including gestational age, body weight, and chronological age.

MATERIALS AND METHODS

Patients

In this prospective study, 400 premature babies under 36 weeks of gestation, who were admitted to neonatal units between January 2008 and December 2010, were consecutively recruited and studied. The babies were from a mixed population (most were Arabic, and the remainder were from other Asian nations). Of these premature babies, only 268 [Table 1] fulfilled the criteria for inclusion in the study. The inclusion criteria were as follows:

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

We excluded sick preterm babies and those with major congenital anomalies (either cardiac or noncardiac anomalies).

Ethical approval was obtained from the ethical committees of both the Ministry of Health, Kuwait, and the Faculty of Medicine, Kuwait University. The study was funded by a grant from the Kuwait Foundation for the Advancement of Sciences (KFAS). The parents were informed that the baby would be enrolled in an observational study rather than a therapeutic trial. Prior written consent was also obtained from the parents.

Methods

Before the study, the pediatric cardiologist responsible for conducting the echocardiograms was trained and observed by two senior pediatric cardiologists using pretest echocardiograms for external validity and generalization. Interpersonal variability was evaluated, and once no significant variability in the readings was found, that doctor was assigned to conduct the study. For generalization, two different senior pediatric cardiologists also supervised these interpretations. The assigned cardiologist was not directly involved in the patients' care. Echocardiographic studies were performed using a Siemens Cypress Scanner equipped with a 7.5 MHz probe. The equipment used was standardized and certified by a biomedical engineer from the Ministry of Health.

Each baby was examined as follows: in the supine position, the studied parameters were measured using the following views: (1) The left ventricular outflow tract (LVOT) diameter was measured in the parasternal long-axis view in midsystole from the White–Black interface of the septal endocardium to the anterior mitral leaflet, parallel to the aortic valve plane, and within 0.5 cm of the valve orifice. (2) The LVOT velocity was measured from the apical approach either in an apical long-axis view or an anteriorly angulated four-chamber view. Using pulsed Doppler, the sample volume (SV), with a length (or gate) of 3–5 mm, was positioned on the LV side of the aortic valve, immediately proximal to the region of flow acceleration into the jet. An optimal signal shows a smooth velocity curve with a narrow velocity range at each time point. Maximum velocity was measured. Velocity time integral (VTI) was measured by tracing the modal velocity (in the outer border of the dense signal) for use in the continuity equation or in the calculation of stroke volume. (3) The aortic valve velocity of VTI was measured using the apical approach in either an apical long-axis view or an anteriorly angulated four-chamber view. Using continuous Doppler, with an adjusted baseline for the velocity signal to fill the vertical scale, the maximum velocity at the maximum of the dense velocity curve was recorded, and VTI was traced from the outer edge of the dense signal curve. (4) The pulmonary valve velocity of VTI was measured from the parasternal short-axis view using continuous-wave Doppler. (5) The aortic annulus was measured from the parasternal long-axis view. (6) The pulmonary annulus was measured from the parasternal short-axis view. (7) The mitral valve annulus lateral dimension was measured from the apical four-chamber view. (8) The tricuspid annulus lateral dimension was measured from the apical four-chamber view. (9) The mitral valve velocity of VTI was measured from the apical four-chamber view using pulse-wave Doppler. Finally, (10) the tricuspid valve velocity of VTI was measured from the apical

four-chamber view using pulse-wave Doppler. All measurements were performed following the American Society of Echocardiography recommendations[5] as adapted by Silverman[6] for premature babies and the recently published recommendations for quantification methods used during the performance of pediatric echocardiography by the Pediatric Council of the American Society of Echocardiography.[7] According to the latest recommendations of the American Society of Echocardiography, aortic and pulmonary valve annular diameters are best measured with magnification in the parasternal long- and short-axis views, respectively, from the inner edge of the proximal valve insertion hinge point within the arterial root to the inner edge of the opposite hinge point in midsystole[7]. Babies were examined within the first 6 days of life and at weekly intervals until they reached term (36 weeks).

The examinations were recorded on video, and all data were stored in DICOM format and analyzed at the end. Before the study was undertaken, the pediatric cardiologist responsible for conducting the echocardiograms was trained and observed by two senior pediatric cardiologists using pretest echocardiograms for external validity and generalization. Interobserver and intraobserver variability were evaluated using repeated-measures analyses of variance in fifty subjects, and when no significant variability was found in the readings, the doctor was assigned to conduct the study. All interpretations were made by the assigned pediatric cardiologist who recorded the images and were observed by two senior pediatric cardiologists. The interpreter was blinded to the age, sex, and previous/succeeding data of the patient at the time of image analysis. Standard parameters were measured by the interpreter, and the parameters were calculated using computer software that was included with the echocardiography instrument. In rare situations, when the readings recorded by the computer were found inconsistent, the measurements were repeated on the same day to check their accuracy. Two pediatric cardiologists who were blinded to the serial values of that particular baby validated the measurement. Adequate time was spent by the three pediatric cardiologists to obtain accurate values and avoid errors as much as possible.

Some very premature babies became unfit after 1 or 2 echocardiograms and were excluded. A few babies (9 babies) were re-included as they recovered rapidly after a brief period of illness.

Statistical analysis

The data were analyzed using the computer software package "Statistical Package for the Social Sciences," version 21.0 (IBM Corp., Armonk, NY, USA). The CSA of each valve was calculated based on the continuity principle using the stroke volume method. Valve CSAs were calculated using the computer software included with the echocardiography machine after entering the required parameters for each valve. The normal distribution assumption for valve CSA variables and for weight and gestational age was verified using the Kolmogorov–Smirnov test. Descriptive statistics are presented as the means and standard deviations (SDs), medians, ranges, and interquartiles (IQs) because all variables did not meet the assumption of data normality. The IQ range is the difference between the first quartile (25th percentile) and the third quartile (75th percentile) of an ordered range of data and contains the middle 50% of the distribution; IQ is therefore unaffected by extreme values. For practical purposes and easy understanding, the babies were grouped as follows: Gestational age was grouped into 4-week periods. Body weight was grouped in 500 g ranging to render the tables easier to understand and ensure the accuracy of the values. Since the number of preterm babies with body weights of >2500 g was much lower, these babies were grouped together. Gestational age was divided into three age groups (24–27, 28–31, and 32–35 weeks), and body weight was divided into five groups (<1000; 1000–1499; 1500–1999; 2000–2499; and >2500 g). In most of the neonatal units, echocardiograms are routinely performed once in the 1st week and are usually repeated at 1–2-week intervals. Therefore, to reduce the number of tables and render them easier to understand, chronological age was divided into periods of 2 weeks. Since the number of preterm babies with a chronological age of >5 weeks was very low, these comprised one group. Therefore, valve CSAs were compared between the age groups 0–6 days and 1–2, 3–4, and ≥5 weeks using ANOVA or the nonparametric Kruskal–Wallis test. Spearman's rho was applied to determine whether the two variables were correlated. A two-tailed $P < 0.05$ was considered statistically significant [Tables 1 and 2].

RESULTS

Among the 400 recruited preterm babies, 268 who fulfilled the inclusion criteria were studied and examined at weekly intervals until the age of 36 weeks; in all, 418 echocardiograms were conducted during the study period. The general characteristics of the babies are presented in Table 1. There was a slight female predominance (male:female = 1:1.13). The mean gestational age was 29.8 (±2.38 SD) weeks, ranging between 24 and 35 weeks, and the mean body weight was 1479 (±413 SD) g, ranging between 588 and 3380 g.

Regarding the overall spectrum of valve CSAs in preterm babies, three reference ranges are presented. Reference ranges with means ± SD, ranges, and IQ values for aortic, pulmonary, mitral, and tricuspid valve CSAs at various periods of life according to gestational age and

body weight are presented in Tables 3-10. Although body surface area (BSA) is very useful for indexing the valve CSAs because body length was not routinely measured and could not be accurately measured in this group of preterm infants, it was felt that for routine practical purposes, gestational age and body weight would facilitate the derivation of normal values against chronological age without indexing. Overall, the CSA of the pulmonary valve was found to be greater than those of the aortic and tricuspid valves, which were in turn greater than those of the mitral valve.

At the first scan (0–6 days of life), the CSAs of all valves were well correlated with both body weight and gestational age ($P < 0.001$). In the subsequent weeks, valve CSAs were well correlated with body weight. Tricuspid, aortic, and pulmonary valve CSAs were well correlated with gestational age ($P < 0.01$) only for the age group of 1–2 weeks [Table 4], and mitral and aortic valve CSAs were well correlated with gestational age ($P < 0.01$) only for the age group of 3–4 weeks; all valve CSAs were not well correlated with gestational age after 5 weeks of age.

An increase was noted in the valve CSAs with respect to gestational age although this was not significant in all valves and differed between each age group [Tables 3-6]. All the valve CSAs showed a gradual but significant increase ($P < 0.001$) with respect to body weight in each age group [Tables 7-10]. Overall, a progressive and significant increase for all valve CSAs was observed during the first 9 weeks of life. For example, if one wants to obtain the reference range for a baby with a particular gestational age and determine the body weight for a specific chronological age, one should consult Tables 3-10 accordingly. Tables 3-10 are quite exhaustive and self-explanatory and provide the normal reference ranges of valve CSAs for gestational age and body weight against chronological age as the means ± SD, ranges, and IQ, thus providing multiple options. Graphs [Figures 1-4] show the means ± SD of the valve CSAs in preterm infants against the gestational age and chronological age. Graphs [Figures 5-8] show the means ± SD of the valve CSAs in preterm infants against the body weight and chronological age.

Attempts were made to reduce the number of tables and graphs. To obtain more accurate values and provide an easy ready reference for pediatric cardiologists who routinely conduct echocardiograms, it was decided to reduce the tables to ten self-explanatory tables and eight graphs.

Figure 9 presents the number of echocardiograms performed against body weight and gestational age.

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
Echo's per baby (minimum-maximum)	1-5
Age (weeks) at study (minimum-maximum)	1 day to 9 weeks

IQ: Interquartile, SD: Standard deviation

Table 2: Correlation of valve cross-sectional area with gestational age and body weight

Valve CSA (cm^2)	*r* (*P*)	
	Gestational age (weeks)	Weight (g)
AV CSA	0.302 (<0.001)**	0.656 (<0.001)**
PV CSA	0.195 (<0.001)**	0.563 (<0.001)**
MV CSA	0.289 (<0.001)**	0.638 (<0.001)**
TV CSA	0.324 (<0.001)**	0.676 (<0.001)**

**Correlation significant at 0.001 probability level. CSA: Cross-sectional area, AV: Atrioventricular, PV: Pulmonary valve, MV: Mitral valve, TV: Tricuspid valve

DISCUSSION

We present reference ranges for cardiac valve CSAs based on a complete population of preterm infants. There is a close correlation between body weight for all valve CSAs. All the valve CSAs were well correlated with gestational age ($P < 0.01$) only up to 1 week of age. Normal reference

Table 3: Mean±standard deviation (range) and interquartile values of valve cross-sectional area at 0-6 days of life by gestational age

Gestational age (weeks)	*n*	0-6 days			
		AV-CSA (cm^2)	PV-CSA (cm^2)	MV-CSA (cm^2)	TV-CSA (cm^2)
24-27	6	0.253±0.085[a] (0.17-0.40)[b] 0.185-0.325[c]	0.262±0.103 (0.17-0.44) 0.193-0.357	0.773±0.276 (0.48-1.27) 0.555-0.940	0.867±0.262 (0.47-1.21) 0.680-1.068
28-31	51	0.272±0.062 (0.14-0.41) 0.240-0.320	0.273±0.064 (0.17-0.42) 0.220-0.320	0.895±0.241 (0.49-1.33) 0.690-1.080	1.007±0.221 (0.58-1.54) 0.800-1.190
32-35	78	0.307±0.055 (0.17-0.45) 0.270-0.340	0.311±0.067 (0.20-0.53) 0.260-0.350	1.025±0.204 (0.45-1.35) 0.877-1.200	1.181±0.205 (0.64-1.65) 1.035-1.310
P		0.002	0.004	0.001	<0.001

Kruskal-Wallis test: Great artery diameters versus gestational age. [a]Mean±SD, [b]Range, [c]IQ. CSA: Cross-sectional area, AV: Atrioventricular, IQ: Interquartile, SD: Standard deviation, PV: Pulmonary valve, MV: Mitral valve, TV: Tricuspid valve

Table 4: Mean±standard deviation (range) and interquartile values of valve cross-sectional area at 1-2 weeks of life by gestational age

Gestational age (weeks)	*n*	1-2 weeks			
		AV-CSA (cm²)	PV-CSA (cm²)	MV-CSA (cm²)	TV-CSA (cm²)
24-27	6	0.218±0.033[a] (0.17-0.26)[b] 0.193-0.253[c]	0.203±0.039 (0.15-0.24) 0.158-0.240	0.802±0.184 (0.54-1.09) 0.675-0.925	0.835±0.221 (0.59-1.15) 0.628-1.068
28-31	100	0.281±0.064 (0.15-0.53) 0.240-0.320	0.282±0.065 (0.13-0.48) 0.240-0.320	0.904±0.221 (0.40-1.74) 0.750-1.035	0.994±0.207 (0.48-1.65) 0.822-1.130
32-35	33	0.295±0.051 (0.17-0.37) 0.260-0.340	0.297±0.062 (0.12-0.44) 0.260-0.340	1.020±0.154 (0.79-1.39) 0.890-1.110	1.170±0.154 (0.75-1.45) 1.070-1.310
P		0.019	0.005	0.007	<0.001

[a]Mean±SD, [b]Range, [c]IQ. CSA: Cross-sectional area, AV: Atrioventricular, IQ: Interquartile, SD: Standard deviation, PV: Pulmonary valve, MV: Mitral valve, TV: Tricuspid valve

Table 5: Mean±standard deviation (range) and interquartile values of valve cross-sectional area at 3-4 weeks of life by gestational age

Gestational age (weeks)	*n*	3-4 weeks			
		AV-CSA (cm²)	PV-CSA (cm²)	MV-CSA (cm²)	TV-CSA (cm²)
24-27	19	0.252±0.059[a] (0.16-0.37)[b] 0.200-0.280[c]	0.259±0.074 (0.13-0.42) 0.220-0.300	0.822±0.213 (0.53-1.33) 0.640-1.000	0.959±0.220 (0.58-1.41) 0.790-1.190
28-31	51	0.279±0.048 (0.16-0.38) 0.250-0.310	0.288±0.060 (0.17-0.42) 0.250-0.310	0.965±0.166 (0.66-1.45) 0.830-1.090	1.040±0.153 (0.75-1.41) 0.920-1.150
32-35	3	0.367±0.057 (0.32-0.43) 0.320	0.307±0.023 (0.28-0.32) 0.280	1.327±0.172 (1.19-1.52) 1.190	1.237±0.251 (1.04-1.52) 1.040
P		0.002	0.194	<0.001	0.030

[a]Mean±SD, [b]Range, [c]IQ. CSA: Cross-sectional area, AV: Atrioventricular, IQ: Interquartile, SD: Standard deviation, PV: Pulmonary valve, MV: Mitral valve, TV: Tricuspid valve

Table 6: Mean±standard deviation (range) and interquartile values of valve cross-sectional area at ≥5 weeks of life by gestational age

Gestational age (weeks)	*n*	≥5 weeks			
		AV-CSA (cm²)	PV-CSA (cm²)	MV-CSA (cm²)	TV-CSA (cm²)
24-27	29	0.321±0.095[a] (0.20-0.54)[b] 0.260-0.375[c]	0.332±0.100 (0.16-0.64) 0.260-0.375	1.023±0.312 (0.52-1.79) 0.770-1.190	1.182±0.236 (0.80-1.61) 0.995-1.430
28-31	41	0.292±0.062 (0.18-0.44) 0.250-0.320	0.328±0.081 (0.20-0.53) 0.272-0.370	0.995±0.208 (0.62-1.41) 0.850-1.140	1.088±0.181 (0.72-1.47) 0.940-1.20
32-35	1	0.330	0.230	0.820	1.650
P		0.283	0.539	0.693	0.010

Mann-Whitney test, Gestational age: (24-27) versus (28-31). [a]Mean±SD, [b]Range, [c]IQ. CSA: Cross-sectional area, AV: Atrioventricular, IQ: Interquartile, SD: Standard deviation, PV: Pulmonary valve, MV: Mitral valve, TV: Tricuspid valve

Table 7: Mean±standard deviation (range) and interquartile values of valve cross-sectional area at 0-6 days of life according to body weight

Body weight (g)	*n*	0-6 days			
		AV-CSA (cm²)	PV-CSA (cm²)	MV-CSA (cm²)	TV-CSA (cm²)
588-999	17	0.202±0.038[a] (0.14-0.26)[b] 0.170-0.235[c]	0.216±0.047 (0.17-0.33) 0.175-0.230	0.619±0.084 (0.48-0.77) 0.555-0.685	0.756±0.157 (0.47-1.04) 0.640-0.875
1000-1499	43	0.275±0.037 (0.20-0.35) 0.260-0.300	0.279±0.051 (0.19-0.40) 0.240-0.310	0.933±0.184 (0.45-1.31) 0.820-1.040	1.039±0.157 (0.72-1.43) 0.950-1.130
1500-1999	50	0.306±0.0.050 (0.17-0.40) 0.270-0.343	0.308±0.057 (0.21-0.44) 0.260-0.350	1.013±0.195 (0.53-1.35) 0.900-1.175	1.168±0.194 (0.71-1.61) 1.050-1.290
2000-2499	23	0.346±0.045 (0.24-0.44) 0.320-0.340	0.334±0.068 (0.20-0.49) 0.280-0.360	1.147±0.176 (0.75-1.35) 1.080-1.190	1.310±0.153 (0.99-1.65) 1.190-1.410
2500-3380	2	0.385±0.092 (0.32-0.45) 0.320	0.510±0.028 (0.49-0.53) 0.490	1.290±0.028 (1.27-1.31) 1.270	1.330±0.028 (1.31-1.35) 1.310
P		<0.001	<0.001	<0.001	<0.001

[a]Mean±SD, [b]Range, [c]IQ. CSA: Cross-sectional area, AV: Atrioventricular, IQ: Interquartile, SD: Standard deviation, PV: Pulmonary valve, MV: Mitral valve, TV: Tricuspid valve

ranges are available for adults and children, but very few references have been produced for preterm babies, which is less helpful for modern neonatal units. The available studies include small numbers of very preterm infants and include measurements performed on infants over a wide age range.

Table 8: Mean±standard deviation (range) and interquartile values of valve cross-sectional area at 1-2 weeks of life according to body weight

Body weight (g)	*n*	1-2 weeks			
		AV-CSA (cm²)	PV-CSA (cm²)	MV-CSA (cm²)	TV-CSA (cm²)
588-999	19	0.234±0.064[a] (0.17-0.43)[b] 0.200-0.260[c]	0.220±0.055 (0.13-0.32) 0.160-0.260	0.732±0.187 (0.40-1.33) 0.640-0.800	0.717±0.0.148 (0.48-1.19) 0.720-0.820
1000-1499	65	0.264±0.041 (0.15-0.39) 0.240-0.290	0.272±0.052 (0.16-0.41) 0.230-0.300	0.880±0.177 (0.45-1.27) 0.755-1.010	0.964±0.160 (0.64-1.31) 0.850-1.070
1500-1999	53	0.316±0.060 (0.17-0.53) 0.275-0.355	0.312±0.061 (0.12-0.44) 0.275-0.355	1.032±0.158 (0.79-1.39) 0.870-1.150	1.176±0.156 (0.83-1.65) 1.085-1.300
2000-2499	1	0.350	0.310	1.330	1.430
2500-3380	1	0.430	0.480	1.740	1.560
P		<0.001	<0.001	<0.001	<0.001

ANOVA (excluding last two body weight groups). [a]Mean±SD, [b]Range, [c]IQ. CSA: Cross-sectional area, AV: Atrioventricular, IQ: Interquartile, SD: Standard deviation, PV: Pulmonary valve, MV: Mitral valve, TV: Tricuspid valve

Table 9: Mean±standard deviation (range) and interquartile values of valve cross-sectional area at 3-4 weeks of life according to body weight

Body weight (g)	*n*	3-4 weeks			
		AV-CSA (cm²)	PV-CSA (cm²)	MV-CSA (cm²)	TV-CSA (cm²)
588-999	11	0.225±0.060[a] (0.16-0.38)[b] 0.200-0.260[c]	0.210±0.069 (0.13-0.38) 0.170-0.230	0.723±0.138 (0.53-0.90) 0.590-0.870	0.845±0.0.178 (0.58-1.21) 0.720-0.900
1000-1499	36	0.264±0.040 (0.16-0.33) 0.243-0.290	0.277±0.042 (0.17-0.35) 0.253-0.310	0.899±0.148 (0.62-1.15) 0.790-1.020	0.980±0.0.123 (0.75-1.27) 0.900-1.075
1500-1999	23	0.311±0.050 (0.22-0.43) 0.270-0.350	0.310±0.062 (0.17-0.42) 0.280-0.350	1.097±0.153 (0.83-1.52) 0.990-1.190	1.169±0.156 (0.88-1.52) 1.080-1.270
2000-2499	3	0.333±0.035 (0.30-0.37) 0.300	0.367±0.042 (0.32-0.40) 0.320	1.093±0.0.401 (0.66-1.45) 0.660	1.173±0.155 (1.02-1.33) 1.020
2500-3380		-	-	-	-
P		<0.001	<0.001	<0.001	<0.001

[a]Mean±SD, [b]Range, [c]IQ. CSA: Cross-sectional area, AV: Atrioventricular, IQ: Interquartile, SD: Standard deviation, PV: Pulmonary valve, MV: Mitral valve, TV: Tricuspid valve

Table 10: Mean±standard deviation (range) and interquartile values of valve cross-sectional area at ≥5 weeks of life according to body weight

Body weight (g)	*n*	≥5 weeks			
		AV-CSA (cm²)	PV-CSA (cm²)	MV-CSA (cm²)	TV-CSA (cm²)
588-999		-	-	-	-
1000-1499	33	0.277±0.066[a] (0.20-0.47)[b] 0.225-0.290[c]	0.296±0.077 (0.16-0.50) 0.255-0.325	0.859±0.182 (0.52-1.25) 0.720-0.980	1.054±0.205 (0.72-1.65) 0.925-1.110
1500-1999	25	0.296±0.050 (0.18-0.43) 0.270-0.320	0.340±0.078 (0.24-0.53) 0.285-0.370	1.022±0.167 (0.75-1.35) 0.900-1.140	1.128±0.190 (0.85-1.56) 0.970-1.200
2000-2499	10	0.364±0.076 (0.26-0.49) 0.298-0.428	0.371±0.0.115 (0.20-0.64) 0.310-0.420	1.263±0.172 (0.92-1.47) 1.165-1.415	1.335±0.113 (1.15-1.52) 1.265-1.410
2500-3380	3	0.473±0.099 (0.36-0.54) 0.360	0.440±0.056 (0.38-0.49) 0.380	1.583±0.261 (1.29-1.79) 1.290	1.397±0.258 (1.11-1.61) 1.110
P		<0.001	0.006	<0.001	<0.001

[a]Mean±SD, [b]Range, [c]IQ. CSA: Cross-sectional area, AV: Atrioventricular, PV: Pulmonary valve, MV: Mitral valve, TV: Tricuspid valve, IQ: Interquartile, SD: Standard deviation

There are many ways to calculate the CSA of valves, including planimetry, continuity equation, Gorlin equation, Hakki equation, and Agarwal–Opkara–Bao equation. Valve areas can be estimated using Doppler echocardiography based on the application of the continuity principle.

In our study, we used the continuity principle and the stroke volume method to calculate the valve CSAs. Using this principle, it is theoretically possible to determine any valve area, native, or prosthetic. The continuity principle is based on the principle of the conservation of mass, which simply states "what goes in must come out." Two methods can be used to calculate the area of a narrowed orifice using the continuity principle in echocardiography: (1) the stroke volume method and (2) the proximal isovelocity surface area method. The stroke volume method is based on the calculation of volumetric flow using the CSA and VTI rather than the CSA and peak velocity. This is because flow within the heart is pulsatile; thus, the VTI rather than peak velocity is used.

The continuity principle as implemented in the stroke volume method[8] is most commonly used for calculating

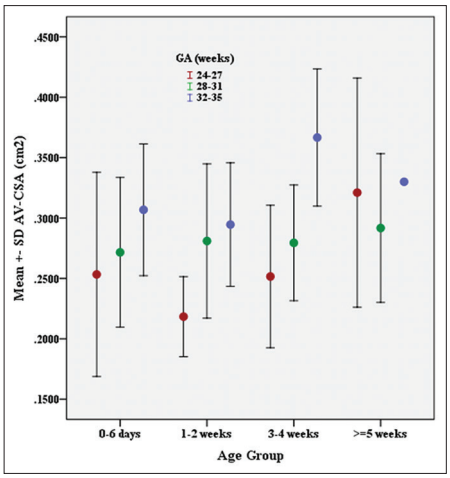

Figure 1: Means ± standard deviation for aortic valve cross sectional area (cm²) for gestational age (weeks) against chronological age

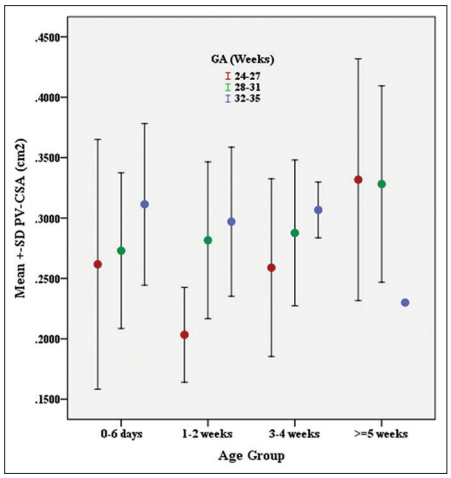

Figure 2: Means ± standard deviation for pulmonary valve cross sectional area (cm²) for gestational age (weeks) against chronological age

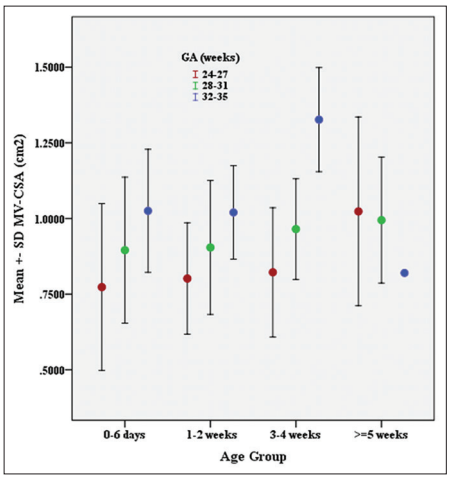

Figure 3: Means ± standard deviation for mitral valve cross sectional area (cm²) for gestational age (weeks) against chronological age

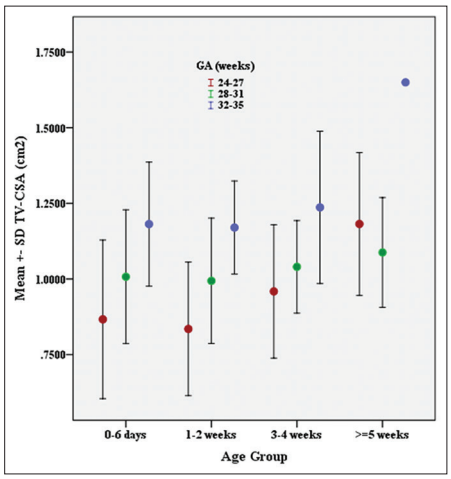

Figure 4: Means ± standard deviation for tricuspid valve cross sectional area (cm²) for gestational age (weeks) against chronological age

the stenotic aortic valve area (AVA). Using this principle, it is assumed that the stroke volume through the stenotic aortic valve is equal to the stroke volume proximal to the stenotic valve (that is, the stroke volume within the LVOT).

Stroke volume is the product of the integrated velocity over time (VTI) and the CSA. LVOT CSA is determined by measuring the diameter of the LVOT during systole. The CSA is then calculated by squaring the diameter and multiplying this value by 0.785. Therefore, any error in the measurement of the diameter is magnified. Suboptimal imaging and excessive calcification of the LVOT annulus further affect the accuracy of this measurement.

Several studies[9-12] have demonstrated that AVA can be determined accurately by Doppler echocardiography based on the equation of continuity, which shows the validity of the equation of continuity as applied to the heart. This method might also be applicable to mitral stenosis.[13]

Furthermore, because the flow duration through the LVOT and across the aortic valve is the same, the AVA can also be derived by substituting the peak velocities obtained from the LVOT and across the aortic valve for the VTI. In very large or very small patients, indexing the AVA to the BSA may assist in determining the severity of aortic stenosis.

Cardiac catheterization and Doppler echocardiography are the standard methods used to measure AVA for the purpose of assessing the severity of aortic stenosis.[14] Although some investigators have found a good agreement between these methods, others have reported important discrepancies.[15-18] In the latter studies, catheter AVA was usually found to be higher than the Doppler AVA.

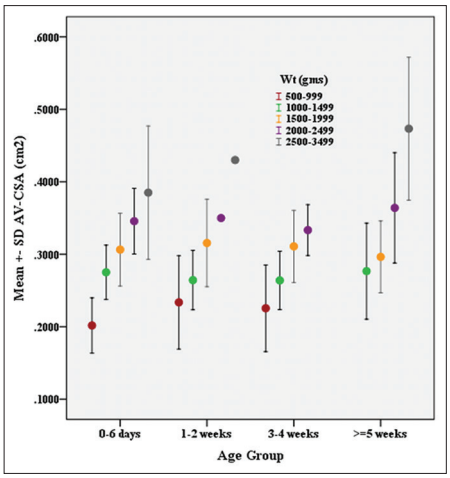

Figure 5: Means ± standard deviation for aortic valve cross sectional area (cm²) for body weight (g) against chronological age

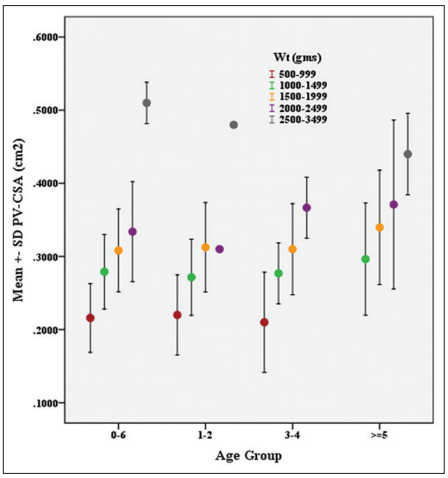

Figure 6: Means ± standard deviation for pulmonary valve cross sectional area (cm²) for body weight (g) against chronological age

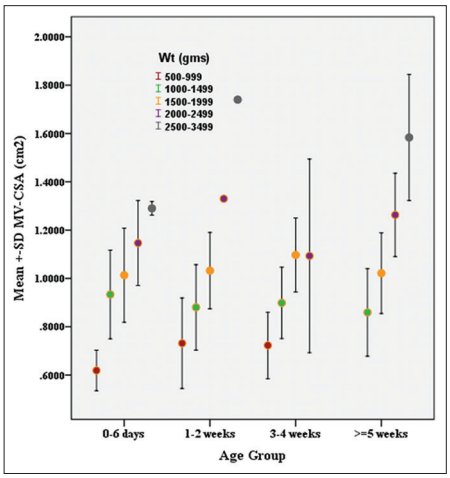

Figure 7: Means ± standard deviation for mitral valve cross sectional area (cm²) for body weight (g) against chronological age

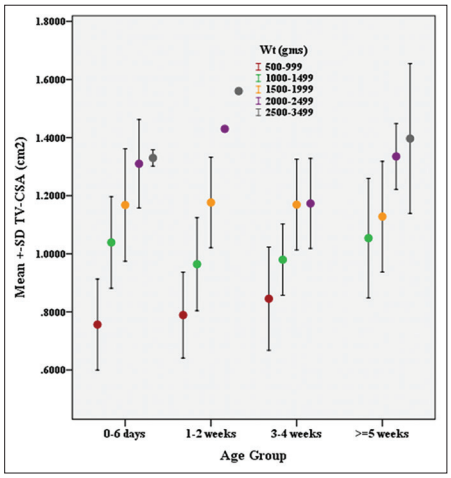

Figure 8: Means ± standard deviation for tricuspid valve cross sectional area (cm²) for body weight (g) against chronological age

The mitral, tricuspid, and pulmonary valve areas (native or prosthetic) can also be determined by application of the continuity principle. As discussed above, calculation of the valve area by this method requires measuring the stroke volume proximal to the stenotic/prosthetic valve. However, it is not always easy to measure the stroke volume proximal to the mitral, tricuspid, or pulmonary valves (this is especially true for the atrioventricular [AV] valves). Fortunately, measurement of stroke volume through the LVOT is relatively easy, and providing that the stroke volume through the AV/pulmonary valve and the LVOT are equal, the stroke volume of the LVOT can be substituted for the stroke volume proximal to the AV/pulmonary valve.

For example, the mitral valve area can be calculated based on the stroke volume through the LVOT and the VTI across the mitral valve. This calculation assumes that the stroke volume through the mitral valve is equal to the stroke volume within the LVOT. The easiest and least variable place to measure cardiac output is at the LVOT. The LVOT diameter changes very little through systole and diastole and is assumed to be constant, and the LVOT is assumed to be approximately circular.

In theory, the continuity equation should provide a robust method for determining the effective valve area as the stroke volume divided by the tricuspid inflow VTI, as recorded using pulse-wave Doppler.[19] The main limitation of the method is the need to obtain an accurate measurement of the inflow volume passing through the tricuspid valve. In the absence of significant tricuspid regurgitation (TR), one can use the SV obtained from either the LVOT or right ventricular outflow.

In 1991, Gutgesell *et al.*[20] performed two-dimensional and Doppler echocardiography in seventy subjects who were aged from 1 day to 16 years to determine aortic and pulmonary valve areas in normal children and adolescents. Valve areas were determined based on the continuity equation using echo-determined ventricular outflow tract diameters and Doppler-determined flow

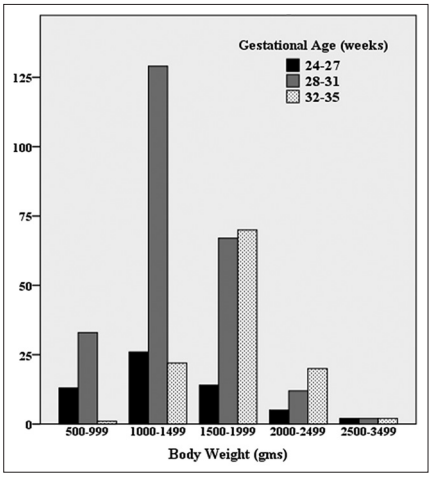

Figure 9: Number of echocardiograms for preterm babies by body weight and gestational age

velocities from the outflow tracts and corresponding great arteries. The authors found that outflow tract diameters were linearly related to the square root of BSA, flow velocities were unrelated to body size, and valve areas were linearly related to BSA.

In 1994, Singh *et al.*[21] determined mitral and tricuspid valve orifice areas in 78 healthy subjects with ages ranging between 2 months and 50 years using a combined echo-Doppler approach to establish normal values and their relationship with BSA. The authors found that mitral valve orifice areas measured using direct planimetry and based on the continuity equation were similar. Tricuspid valve orifice areas based on the continuity equation were closely correlated with mitral valve orifice area.

To ensure appropriate positioning of the pulsed-wave SV within the LVOT, the SV is placed through the aortic valve and is then slowly stepped back toward the LVOT. When the signal displays a laminar profile with minimal spectral broadening and a closing click, the SV is in the correct position.

When accurate measurement of the LVOT diameter is not possible, the degree of aortic valve stenosis can also be determined by calculating the dimensionless severity index (DSI). The DSI (or velocity ratio) is simply the ratio of the LVOT VTI (or peak velocity) to the aortic valve VTI (or peak velocity).

Determination of the valve area by the continuity equation requires that the stroke volumes through the region proximal to the stenosis and through the stenotic orifice are equal. Therefore, differential flow, caused by processes such as valvular regurgitation or intracardiac shunt flow, may invalidate the calculation of the valve area based on the continuity equation.

There are some limitations of using the continuity equation in the stroke volume method. Assumptions of volumetric flow calculations and calculation of the valve area based on the continuity equation are based on the determination of the stroke volume. Stroke volume calculations are, in turn, based on a simple hydraulic formula that determines the volumetric flow through a cylindrical tube under steady flow conditions. To apply this concept to the heart, certain assumptions regarding flow properties and conditions are made. These assumptions include the following: (1) The flow occurs in a rigid and circular tube; (2) velocity is uniform across the vessel; (3) the derived CSA is circular; (4) the CSA remains constant throughout the period of flow; and (5) the SV remains in a constant position throughout the period of flow. However, blood vessels are elastic and, therefore, change throughout the duration of flow within the cardiac cycle. In addition, annular diameters may change throughout the period of flow, and while the LVOT and right ventricular outflow tracts assume a circular configuration, the same may not be said for the AV valves, which assume a more elliptical shape.

Regarding the limitations of continuity equation valve area, the clinical measurement variability for continuity equation valve area depends on the variability in each of the three measurements, including variability in acquiring the data and variability in measuring the recorded data. When LVOT diameter is squared for the calculation of CSA, it becomes the greatest potential source of error in the continuity equation. When transthoracic images are not adequate for the measurement of LVOT diameter, transesophageal echo measurement is recommended in cases where this information is needed for clinical decision-making.

Another limitation is that the continuity equation measures the effective valve area - the area of the flow stream as it passes through the valve rather than the anatomic valve area. The effective valve area is smaller than the anatomic valve area due to contraction of the flow stream in the orifice as determined by the contraction and discharge coefficients for a given orifice geometry.[22]

Our study involved 268 premature babies (the largest number of babies studied thus far). All babies were healthy, and any baby who became sick during the study was excluded. This study reports serial measurements of all cardiac valve CSAs during the first 9 weeks of life in a selected population of preterm infants with a body weight of 588–3380 g and a gestational age of between 24 and 35 weeks. Measurements of all valve CSAs showed a significant correlation with body weight. There were progressive and significant increases in valve CSAs over time.

Our study provides accurate reference ranges because the data were collected from a large number of preterm babies. We hope that these data will be accepted by

neonatal units as normal reference ranges for preterm great artery diameters. These data will be useful as a ready reference for pediatric cardiologists who routinely perform echocardiograms in preterm babies. The self-explanatory tables provide normal reference ranges for all valve CSAs for babies of various gestational ages and for body weight against chronological age; multiple data options are provided, including means ± SD, ranges, and IQs. The self-explanatory graphs provide valve CSAs against gestational age and body weight for chronological age.

Our study has several strengths. First, we evaluated important echocardiographic parameters in large group of preterm infants for whom nomograms were limited or even absent. Second, we prospectively enrolled the largest population of healthy preterm infants studied so far. Third, all reported measurements in the database represent only measurements performed with excellent visualization and no ambiguity. Fourth, the computer-generated values for valve CSAs were randomly cross-checked against those obtained using manual methods. Fifth, until now, no reports on normal valve CSAs in preterm infants have been available. Minor limitations of our study are that we used the continuity equation to calculate valve CSAs, which sometimes alters due to changes in hemodynamics. The continuity equation method might be more complicated for clinical use, and we did not correlate the results obtained using this method with those obtained using other methods.

CONCLUSIONS

Body weight is significantly correlated with all cardiac valve CSAs. All valve CSAs were well correlated with gestational age ($P < 0.01$) only up to 1 week of age. A progressive and significant increase of all valve CSAs was observed during the first 9 weeks of life. The values presented can be used as a normal reference tool for all valve CSAs in preterm infants against body weight, gestational age, and chronological age.

Acknowledgment

We would like to acknowledge Dr. Niran Al Naqeeb and Dr. Majda Sabri, Neonatologists, for facilitating access to preterm babies.

Financial support and sponsorship

This study was funded by a grant from the KFAS (Grant number: 2003-1302-05).

Conflicts of interest

There are no conflicts of interests.

REFERENCES

1. Edler I, Hertz CH. The use ultrasonic reflectoscope for the continuous recording of movements of heart walls. Kungl Fysiogr Sallsk I Lund Forhandl 1954;24:5.
2. Solinger R, Elbl F, Minhas K. Echocardiography in the normal neonate. Circulation1973;47:108-18.
3. Abushaban L, Vel MT, Rathinasamy J, Sharma PN. Normal reference ranges for left ventricular dimensions in preterm infants. Ann PediatrCardiol2014;7:180-6.
4. Abushaban L, Vel MT, Rathinasamy J, Sharma PN. Normal reference ranges for cardiac valve annulus in preterm infants. PediatrCardiol2016;37:112-9.
5. Henry WL, DeMaria A, Gramiak R, King DL, Kisslo JA, Popp RL, *et al.* Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. Circulation1980;62:212-7.
6. Silverman N. Quantitative methods to enhance morphological information using M-mode Doppler and cross sectional ultrasound. In: Silverman N, editor. PaediatricEchocardiography. 1st ed., Vol. 1. London: Williams and Wilkins; 1993.p. 35-6.
7. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, *et al.* Guidelines and standards for performance of a pediatric echocardiogram: A report from the Task Force of the Pediatric Council of the American Society of Echocardiography. J Am SocEchocardiogr2006;19:1413-30.
8. Bednarz JE, Krauss D, Lang RM. An echocardiographic approach to the assessment of aortic stenosis. J Am SocEchocardiogr1996;9:286-94.
9. Hatle L, Brubakk A, Tromsdal A, Angelsen B. Noninvasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. Br Heart J1978;40:131-40.
10. Holen J, Aaslid R, Landmark K, Simonsen S. Determination of pressure gradient in mitral stenosis with a non-invasive ultrasound Doppler technique. Acta Med Scand1976;199:455-60.
11. Holen J, Simonsen S. Determination of pressure gradient in mitral stenosis with Doppler echocardiography. Br Heart J1979;41:529-35.
12. Herman MV, Cohn PF, Gorlin R. Resistance to blood flow by stenotic valves: Calculation of orifice area. In: Grossman W, editor. Cardiac Catheterization and Angiography. 2nd ed.Philadelphia, Lea and Febiger; 1980. p. 124.
13. Robson DJ, Flaxman JC. Measurement of the end-diastolic pressure gradient and mitral valve area in mitral stenosis by Doppler ultrasound. Eur Heart J1984;5:660-7.
14. Garcia D, Kadem L. What do you mean by aortic valve area: Geometric orifice area, effective orifice area, or gorlin area? J Heart Valve Dis2006;15:601-8.
15. Oh JK, Taliercio CP, Holmes DR Jr., Reeder GS, Bailey KR, Seward JB, *et al.* Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: Prospective Doppler-catheterization correlation in 100 patients. J Am CollCardiol1988;11:1227-34.
16. Garcia D, Dumesnil JG, Durand LG, Kadem L, Pibarot P. Discrepancies between catheter and Doppler estimates of valve effective orifice area can be predicted from the pressure recovery phenomenon: Practical implications

with regard to quantification of aortic stenosis severity. J Am CollCardiol2003;41:435-42.

17. Levine RA, Schwammenthal E. Stenosis is in the eye of the observer: Impact of pressure recovery on assessing aortic valve area. J Am CollCardiol2003;41:443-5.
18. Danielsen R, Nordrehaug JE, Vik-Mo H. Factors affecting Doppler echocardiographic valve area assessment in aortic stenosis. Am J Cardiol1989;63:1107-11.
19. Karp K, Teien D, Eriksson P. Doppler echocardiographic assessment of the valve area in patients with atrioventricular valve stenosis by application of the continuity equation. J Intern Med1989;225:261-6.
20. Gutgesell HP, French M. Echocardiographic determination of aortic and pulmonary valve areas in subjects with normal hearts. Am J Cardiol1991;68:773-6.
21. Singh B, Mohan JC. Atrioventricular valve orifice areas in normal subjects: Determination by cross-sectional and Doppler echocardiography. Int J Cardiol1994;44:85-91.
22. Gilon D, Cape EG, Handschumacher MD, Song JK, Solheim J, VanAuker M, *et al.* Effect of three-dimensional valve shape on the hemodynamics of aortic stenosis: Three-dimensional echocardiographic stereolithography and patient studies. J Am CollCardiol2002;40:1479-86.