Cardiology in the Young (2014), **24**, 685–693
doi:10.1017/S1047951113000954

Original Article

Evaluation of left ventricular volumes in the early neonatal period using three-dimensional echocardiography

Hiroyuki Nagasawa

Department of Neonatology, Gifu Prefectural General Medical Center, Gifu, Japan

Abstract *Background:* Awareness about normal cardiac volumes in the neonatal period is very important for understanding the cardiac function; however, the small cardiac size of neonates makes it difficult to perform invasive examinations. Three-dimensional echocardiography is used to evaluate cardiac volumes in children. However, no studies using this method have examined left ventricular volumes in neonates during the early neonatal period. *Methods:* The study group consisted of 255 normal neonates. Comparisons of the stroke volume calculated according to the velocity–time integral and Pombo method were made. *Results:* The volumes in both end-diastole and end-systole and the stroke volume gradually decreased over time after birth. Participants with continuous a persistent ductus arteriosus flow had higher stroke volumes than those without persistent ductus arteriosus. The average end-diastolic volume per body surface area (m^2) was 30.61 ml/m^2 in boys and 29.80 ml/m^2 in girls, whereas the ventricular end-systolic volume was 12.89 ml/m^2 in boys and 12.80 ml/m^2 in girls among the participants without persistent ductus arteriosus. The average stroke volume was 17.70 ml/m^2 in boys and 17.00 ml/m^2 in girls. Statistically significant gender differences were observed in the end-diastolic volume ($p = 0.0053$), stroke volume ($p < 0.0001$), and ejection fraction ($p = 0.039$). The cardiac index was calculated to be 2.04 L/minute/m^2 in boys and 1.95 L/minute/m^2 in girls, which was significantly lower than that calculated using the velocity–time integral and Pombo method ($p < 0.0001$). *Conclusions:* Significant gender differences in the end-diastolic volume, stroke volume, and ejection fraction at birth were revealed. The cardiac index in the early neonatal period was found to be relatively smaller than what had previously been recognised.

Keywords: Left ventricle; end-diastolic volume; end-systolic volume; stroke volume; normal neonate; gender differences

Received: 3 May 2012; Accepted: 30 June 2013; First published online: 29 July 2013

Awareness about normal cardiac dimensions and volumes is very important for understanding the cardiac function in childhood. Several two-dimensional echocardiographic examinations have been performed to obtain information on the longitudinal development of the left ventricular end-diastolic dimension and left ventricular end-systolic dimension using body height as an index in children and newborns, including premature neonates.[1–4] Linear relationships between height and other dimensions of the heart have been reported in these studies. However, in neonates <1 week of age, the normal dimensions of the left ventricle remain undefined, as physiological pulmonary hypertension exists during the 1st week of life, making the left ventricle appear elliptical on short axis views. The left ventricular end-diastolic volume is altered according to the left ventricular position, as confirmed on echocardiography. The Pombo method is used to calculate left ventricular volumes and ejection fractions because it is a simple method for determining both measurements and calculations. However, this method is not applicable to early neonates because it assumes the presence of a round shape on short axis views. Few studies have estimated left ventricular end-diastolic and

Correspondence to: H. Nagasawa, Department of Neonatology, Gifu Prefectural General Medical Center, 4-6-1 Noisshiki, Gifu, 500-8717, Japan. Tel: 81-58-246-1111; Fax: 81-58-247-3748; E-mail: hironag@ccn2.aitai.ne.jp

end-systolic volumes in normal neonates,[5] as performing invasive examinations is not feasible.

Three-dimensional echocardiography is used to evaluate cardiac volumes in children.[6] This method is performed to assess left ventricular volumes in the early neonatal period.

The objectives of this study were: (1) to assess the normal ranges of left ventricular end-diastolic and end-systolic volumes using body weight and body surface area as indexes, (2) to evaluate volume changes over time after birth and to ascertain the causes, if any, of these changes, (3) to detect any significant gender differences, (4) to compare volume data using the velocity–time integral method and to calculate the results using the Pombo method, and (5) to compare the results with previously reported left ventricular volumes.

Methods

Study participants

Neonates who met all of the following requirements to be "normal" were recruited in this study: (1) a gestational age between 37 weeks 0 days and 41 weeks 6 days, (2) an adequate weight for the gestational age, (3) no foetal distress and an Apgar score of more than 8 points at 5 minutes after birth, (4) no requirements for oxygen supplementation or respiratory or circulatory support, (5) good sucking and urination, (6) no congenital heart disease, normal arterial and mitral valve functions, and no evidence of coronary artery lesions, and (7) blood flow through the oval foramen from left to right on echocardiography.

Only neonates who underwent echocardiographic examinations at Gifu Prefectural General Medical Center were included in this study. The Ethics Committee of Gifu Prefectural General Medical Center approved this study in advance. The aims of the study were explained to the parents or guardians of the neonates and signed permissions were obtained.

The necessary number of neonates was determined according to the report by Cohen[7] showing that more than 88 participants each are needed to compare groups with a type one error of 0.05 in two-sided tests and a type two error of 0.75 when the absolute difference divided by the standard deviation is presumed to be 0.4.

Study group

The study group consisted of 255 consecutive Japanese neonates – 128 boys and 127 girls. The participant characteristics are shown in Table 1. No significant weight loss was observed between the boys (5.2% and 2.3% (mean and standard deviation)) and the girls (5.6% and 2.4%). The adequate body weight criterion was determined based on a statistical analysis of children performed in Japan in 2008.

Table 1. Characteristics of the 255 neonatal participants undergoing three-dimensional echocardiographic examinations.

	Range	Mean
No. of participants	255	
Sex	Boy 128 (50.2%)	
Gestational age (days)	259–292	272
Birth weight (g)	2255–3885	2967
Birth height (cm)	43.3–52.8	48.0
Age at examination (hours)	2.1–167.1	68.3
Weight at examination (g)	2145–3825	2820
Height at examination (cm)	42.3–52.6	48.0
BSA at examination (m^2)	0.153–0.224	0.185
PDA flow (number of participants)	**Boy**	**Girl**
With	29	26
Without	99	101

BSA = body surface area; PDA = persistent ductus arteriosus

Data acquisition

The three-dimensional echocardiographic studies were performed in an apical four-chamber view with a 7–2 MHz iE33 transducer (Philips Electronics, Bothell, Washington, United States of America) over four cycles during natural sleep. The datasets were post-processed offline using a software program supplied by Philips Medical – the Cardiac 3D Quantification Advanced software program, which is a Q-LAB application (Philips Ultrasound). The 3D Quantification Advanced has the diagnostic power of 3D full-volume imaging based on its ability to provide semiautomated analyses of left ventricular volumes using all voxels in order to generate a full three-dimensional endocardial border. Endocardial markers were placed manually on either side of the mitral annulus in two orthogonal views and at the apex; the semiautomated endocardial border detection software program then traced the endocardium and calculated the volume automatically. The endocardial detection accuracy was assessed and optimised manually (Fig 1).

The maximum and minimum values of the sequenced data were classified as the end-diastolic and end-systolic volumes, respectively. The final values were obtained from the average of more than three examinations in every neonate.

Conventional two-dimensional echocardiographic examinations with a 12–4 MHz iE33 transducer were performed immediately after three-dimensional echocardiography. The left ventricular end-diastolic dimension, the left ventricular end-systolic dimen-

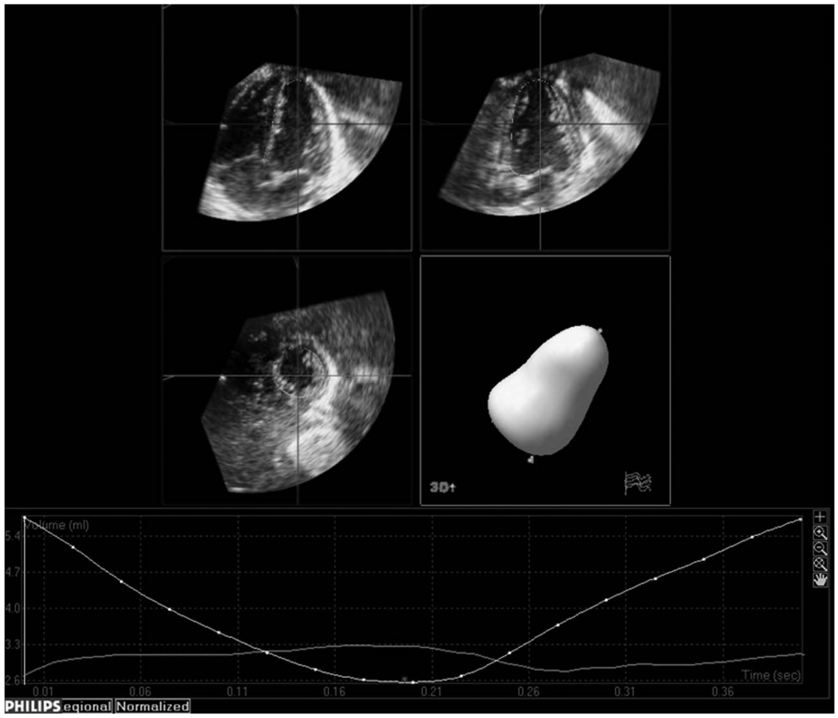

Figure 1.
Representative images of a participant, including an initialised boundary in three planes and a reconstructed three-dimensional cast.

sion, that is, the short dimensions, and the distance between the apex and the mitral orifice at end-diastole and end-systole, that is, the long dimensions, were measured. The Pombo method involves the following steps: the left ventricular volumes are calculated from the ventricular dimensions using the volume formula of a prolate ellipse, expressed as $V = \pi/6 \times D^2L$, where D is the shorter diameter and L is the longer diameter. If the longer diameter is assumed to be twice the length of the shorter diameter, the formula is further simplified to $V = \pi/3 \times D^3$. This formula assumes the algebraic cancellation of the factor $\pi/3$. The cube of the end-diastolic dimension is used as an estimation of the end-diastolic volume and the end-systolic dimension is used as an estimation of the end-systolic volume.[8] In this study, the aortic flow velocity was measured from the suprasternal notch view using the pulsed Doppler technique and a region of interest was located just above the Valsalva sinus of the aorta, where the aortic diameter was measured. The measurement convention of the aortic diameter from one leading edge to another was used. The diameter was measured at least four times and the mean value was used as the aortic diameter. Care was taken to minimise the angle of insonation. No angle correction was performed. Velocity time–integrals were obtained manually by tracing the area under the Doppler recordings using the built-in electrical program of iE33. The aortic diameter was measured in the parasternal view with electronic callipers. The stroke volume was calculated as the product of the aortic cross-section area and the velocity–time integral using the two-dimensional M-mode technique. The cardiac output was calculated as the product of the stroke volume and the actual heart rate measurement.

All measurements were obtained by two observers H.N. and J.M. The inter-observer error was 3.7%. The intra-observer errors were 2.8% and 3.2%, respectively, calculated based on data obtained from 30 participants undergoing three measurements each. The examination time after birth was determined randomly. A three-dimensional echocardiographic examination was performed once in each neonate during the early neonatal period.

Clinical information on these participants was collected from inpatient records. Body height in the prone position and weight were measured at the time of echocardiography. The body surface area was calculated according to the formulas given by Haycock et al[9] and DuBois and DuBois.[10]

Statistical analyses

The F-test and Student's t-test were used to determine whether the sample variance and mean values of two categories were statistically equivalent. The Sheffé

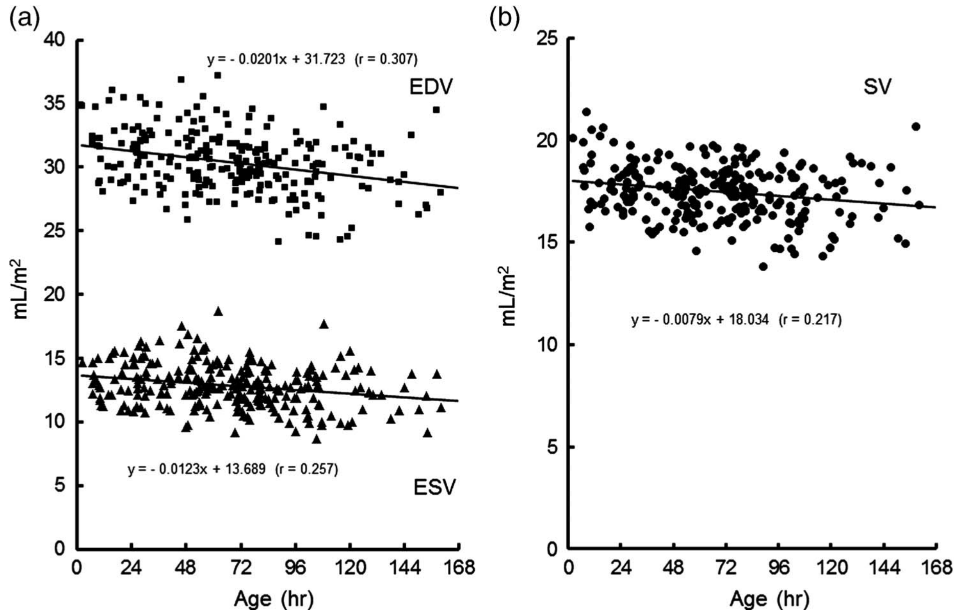

Figure 2.
Relationships between the left ventricular end-diastolic volume, end-systolic volume and stroke volume divided by body weight and time after birth in 255 participants. EDV, left ventricular end-diastolic volume (square); ESV, left ventricular end-systolic volume (triangle); SV, stroke volume (circle).

method was used to compare the mean values of three or more categories. A level of $p < 0.05$ was considered statistically significant.

Results

Body surface area data calculated by the formulas reported by Haycock et al and by DuBois and DuBois are indicated by adding H and D at the end of the results, respectively.

Normal left ventricular end-diastolic and end-systolic volumes in all participants

The average end-diastolic volumes were 30.33 (2.32; standard deviation) ml/m^2 (H) and 32.26 (2.52) ml/m^2 (D). The average end-systolic volumes were 12.85 (1.71) ml/m^2 (H) and 13.67 (1.83) ml/m^2 (D). The stroke volumes and ejection fraction were estimated to be 17.48 (1.28) ml/m^2 (H) and 18.59 (1.40) ml/m^2 (D) and 0.577 (0.034), respectively. The cardiac indexes were calculated to be 2.04 (0.30) L/minute/m^2 (H) and 2.17 (0.32) L/minute/m^2 (D). However, as the blood flow changes dramatically in the early neonatal period, more concise evaluations are needed, especially with respect to the effects of persistent ductus arteriosus, physiological pulmonary hypertension, and so forth.

Volume changes over time after birth: the influence of persistent ductus arteriosus

Changes in the end-diastolic and end-systolic volumes of the left ventricle over time are shown in Figure 2a, whereas those in the stroke volume are shown in Figure 2b. The volumes were seen to gradually decrease over time.

To determine the cause of this phenomenon, the participants were divided into two groups: the ductus group, which had a ductus arteriosus flow with persistent ductus arteriosus (n = 55, 29 boys and 26 girls), and the non-ductus group, which had no ductus arteriosus flow and no persistent ductus arteriosus (n = 200, 99 boys and 101 girls), based on the findings of conventional colour Doppler echocardiography. The results are shown in Figure 3 and Table 2. Very minor volume changes over time were observed in the non-ductus group (slope: −0.0029). There were no significant differences in the end-diastolic volumes, end-systolic volumes, stroke volumes, or ejection fractions according to the F-test. There were significant differences between the ductus group and the non-ductus group, respectively, in terms of the end-diastolic volume, (31.05 (2.51) ml/m^2 (H)) and (30.19 (2.27) (H)) ($p < 0.042$); stroke volume, (18.32 (1.32) ml/m^2 (H)) and (17.35 (1.24) (H)) ($p < 0.0001$); and ejection fraction (0.585 (0.034)) and (0.576 (0.033)) ($p = 0.040$). However, there were no significant differences in the end-systolic volume ($p = 0.243$). It is presumable that the ductus arteriosus flow is attributable to increases in the stroke volume, the primary cause of the aforementioned gradual volume decreases.

There was a significant difference in the end-diastolic volume between the ductus group and

https://doi.org/10.1017/S1047951113000954 Published online by Cambridge University Press

the non-ductus group (p = 0.042(H), 0.017(D)) when indexed to body surface area, although there were no significant differences when it was indexed to body weight (p = 0.401; Tables 2 and 4).

The average end-diastolic and end-systolic volumes of the participants without a ductus arteriosus flow were 30.19 (2.27) ml/minute/m^2 (H) and 12.85 (1.68) L/minute/m^2 (H), respectively. The stroke volume and ejection fraction were estimated to be 17.35 (1.24) ml/minute/m^2 (H) and 0.576 (0.033), respectively.

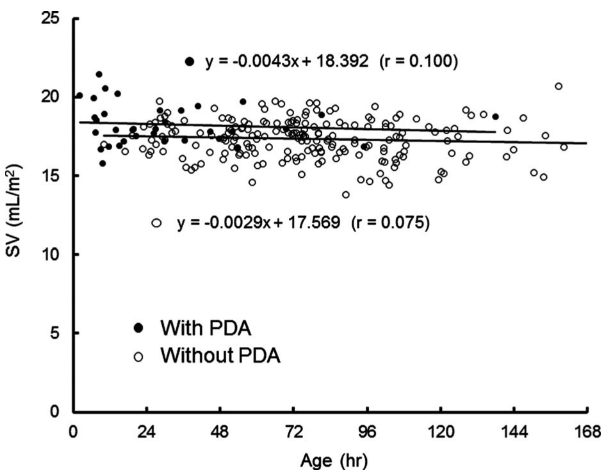

Figure 3.
Stroke volumes of the participants with and without a persistent ductus arteriosus flow. Each volume is represented by closed and open circles, respectively. There were no stroke volume changes in the participants without a ductus arteriosus flow. PDA, persistent ductus arteriosus.

Comparison of stroke volume between genders

A comparison of the stroke volume of the participants without persistent ductus arteriosus was made between the 99 boys and the 101 girls included in this study. The results are shown in Figure 4 and Table 3. No significant differences in variance were observed in any item according to the F-test. There were significant gender differences in terms of the end-diastolic volume (30.61 (2.22) ml/m^2 (H), boys) (29.80 (2.26) ml/m^2 (H), girls) (p = 0.0053); stroke volume (17.70 (1.10) ml/m^2 (H), boys) (17.00 (1.27) ml/m^2 (H), girls) (p <0.0001); and ejection fraction (0.580 (0.032), boys) (0.572 (0.033), girls) (p = 0.039). However, the end-systolic volume did not differ significantly between the genders (12.89 (1.72) ml/m^2 (H), in boys and 12.80 (1.65) ml/m^2 (H) in girls) (p = 0.343). These results indicate the gender differences to be primarily attributable to the end-diastolic volume.

The data indexed to body weight are shown for reference in Figure 4.

Comparison of the stroke volume of the left ventricle measured using three-dimensional echocardiography and the velocity–time integral and Pombo methods

The results are shown in Figure 5. The stroke volume obtained with the velocity–time integral

Table 2. Left ventricular volumes measured using three-dimensional echocardiography in normal neonates with and without a ductus arteriosus flow.

	EDV (ml/m^2)	ESV (ml/m^2)	SV (ml/m^2)	CI (L/minute/m^2)
BSA was calculated using the formula given by Haycock et al[9]				
With PDA	31.05 (2.51)§	12.73 (1.79)	18.32 (1.32)*	2.196 (0.314)†
Without PDA	30.19 (2.27)§	12.85 (1.68)	17.35 (1.24)*	1.995 (0.293)†
§p = 0.042; *p < 0.00001; †p = .0002				

	EDV (ml/m^2)	ESV (ml/m^2)	SV (ml/m^2)	CI (L/minute/m^2)
BSA was calculated using the formula given by DuBois and DuBois[10]				
With PDA	32.92 (2.75)§§	13.67 (1.88)	19.25 (1.52)**	2.288 (0.324)††
Without PDA	32.09 (2.46)§§	13.65 (1.80)	18.44 (1.33)**	2.120 (0.301)††
§§p = 0.017; **p = 0.0001; ††p = 0.002				

	EF
With PDA	**0.585 (0.034)§§§**
Without PDA	0.576 (0.033)§§§

CI = cardiac index; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume;
PDA = persistent ductus arteriosus; SV = stroke volume
Values within parentheses represent SD values
Significant differences were found in EDV, SV, CI, and EF
§§§p = 0.040

https://doi.org/10.1017/S1047951113000954 Published online by Cambridge University Press

Table 3. Left ventricular volumes measured using three-dimensional echocardiography in normal neonates without persistent ductus arteriosus according to gender.

	EDV (ml/m^2)	ESV (ml/m^2)	SV (ml/m^2)	EF
BSA was calculated using the formula given by Haycock et al[9]				
Boy	30.61 (2.22)*	12.89 (1.72)	17.70 (1.10)†	0.580 (0.032)§
Girl	29.80 (2.26)*	12.80 (1.65)	17.00 (1.27)†	0.572 (0.033)§

*p = 0.0053; †p < 0.0001; §p = 0.039

	EDV (ml/m^2)	ESV (ml/m^2)	SV (ml/m^2)
BSA was calculated using the formula given by DuBois and DuBois[10]			
Boy	32.50 (2.44)**	13.69 (1.86)	18.81 (1.52)††
Girl	31.70 (2.44)**	13.61(1.75)	18.09 (1.39)††

**p = 0.010; ††p = 0.0001

CI [$L/minute/m^2$]	Haycock	DuBois
Boy	2.04 (0.32)***	2.17 (0.34)†††
Girl	1.95 (0.23)***	2.08 (0.25)†††

CI = cardiac index; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume;
PDA = persistent ductus arteriosus; SV = stroke volume
Values within parentheses represent SD values
Significant gender differences were found in EDV, SV, EF, and CI
***p = 0.013; †††p = 0.017

Table 4. Left ventricular volumes measured using three-dimensional echocardiography in normal neonates without persistent ductus arteriosus when indexed to body weight (kg)

	EDV (ml/kg)	ESV (ml/kg)	SV (ml/kg)	CO/BW (ml/minute/kg)
With PDA	2.125 (0.168)	0.883 (0.126)	1.242 (0.079)*	147.5 (19.1)†
Without PDA	2.119 (0.154)	0.901 (0.117)	1.217 (0.083)*	140.1 (20.8)†

*p = 0.027; †p = 0.010

	EDV (ml/kg)	ESV (ml/kg)	SV (ml/kg)	EF
Boy	2.136 (0.146)**	0.900 (0.114)	1.236 (0.079)†	0.580 (0.032)§
Girl	2.102 (0.160)**	0.903 (0.120)	1.199 (0.084)†	0.572 (0.033)§

**p = 0.048; †p = 0.0006; §p = 0.039

CO/BW	(ml/minute/kg)
Boy	143 (23)***
Girl	138 (17)***

BW = body weight; CO = cardiac output; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; PDA = persistent ductus arteriosus; SV = stroke volume
Values within parentheses represent SD values
***p = 0.045

method was highest at 27.69 (95% confidence interval, 27.10–28.29) ml/m^2 (H), followed by 19.91 (19.42–20.39) ml/m^2 (H), with the Pombo method and at 17.48 (17.32–17.64) ml/m^2 (H) on three-dimensional echocardiography. There were significant differences in the values obtained with these methods ($p < 0.0001$).

No gender differences in stroke volume were found with either the velocity–time integral method ($p = 0.225$) or the Pombo method ($p = 0.070$).

https://doi.org/10.1017/S1047951113000954 Published online by Cambridge University Press

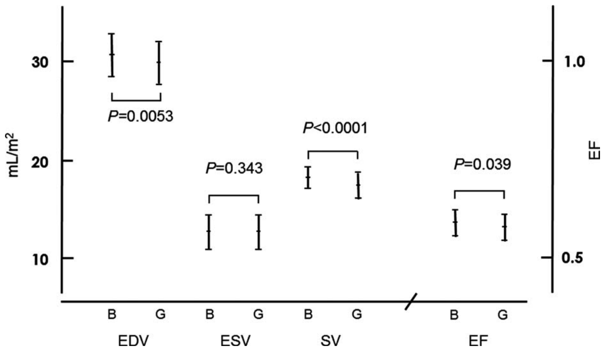

Figure 4.

Left ventricular end-diastolic, end-systolic, and stroke volumes divided by body surface area in the participants without persistent ductus arteriosus according to gender. Each bar shows the mean and 95% confidential interval. There was a significant gender difference in the stroke volume. B, boy; EDV, left ventricular end-diastolic volume; ESV, left ventricular end-systolic volume; G, girl; SV, stroke volume.

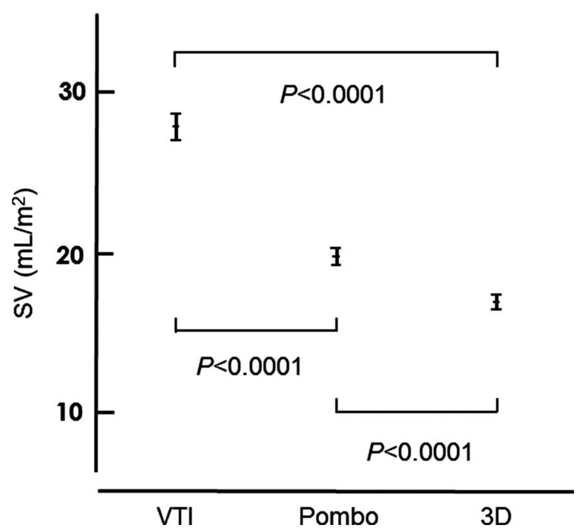

Figure 5.

Comparisons among left ventricular stroke volumes measured using 3D echocardiography and the velocity–time integral and Pombo methods. Each bar shows the mean and 95% confidential interval. There were significant differences in the values obtained with these three methods. SV, stroke volume; VTI, velocity–time integral; 3D, three-dimensional echocardiography.

Discussion

Approaches to evaluating the left ventricular volume include biplane angiocardiography, the Fick method, dye dilution techniques, the velocity–time integral method, and the Pombo method. However, it is not possible to evaluate normal neonatal left ventricular volumes using invasive methods. The three-dimensional echocardiography modality has been used in children to evaluate morphological structures and estimate the volumes of heart chambers.[6] However, the use of three-dimensional echocardiography is limited in neonates, partially because the probes are too large and heavy for application in neonates and because the small size of the neonatal heart makes it impractical to obtain clear and accurate images. Advances in three-dimensional echocardiography apparatuses have allowed the application of three-dimensional echocardiographic examinations in neonates. However, there are no reports of neonatal left ventricular volume assessments using this modality. The present report is therefore the first to evaluate left ventricular volume assessments in the early neonatal period. A comparison was made among the results obtained with three-dimensional echocardiography and those obtained using the velocity–time integral and Pombo methods.

Influence of persistent ductus arteriosus on the stroke volume

The end-diastolic and end-systolic volumes changed over time after birth, whereas there were no apparent volume changes in the neonates examined more than 72 hours after birth. This can be attributed to the presence of a ductus arteriosus flow. The stroke volumes of the participants with and without a ductus arteriosus flow were compared. The stroke volumes of those with a ductus arteriosus flow were 2.9% higher than those of the participants without a ductus arteriosus flow. In those without a ductus arteriosus flow, the stroke volume demonstrated only a minor change in slope through the early neonatal period. These observations prompted the speculation that a ductus arteriosus flow contributes to a higher stroke volume in neonates with a ductus arteriosus flow.

It is not unexpected for the stroke volume to be higher in participants with a ductus arteriosus flow than in those without it. However, it was quite interesting to observe that the increased stroke volume was attributable not to an increased end-diastolic volume, but rather to a decreased end-systolic volume. This may have been because of lower end-systolic pressures in the participants with a continuous persistent ductus arteriosus flow than in those without it, although no direct evidence explaining this phenomenon was found.

Gender differences

There was also a significant difference in stroke volume between boys and girls in the early neonatal period. This indicates a significant gender difference in the internal dimension of the left ventricle starting from the beginning of human life.

It has previously been reported that there is a significant gender difference in the left ventricular end-diastolic volume measured using conventional two-dimensional echocardiography in children and infants with body heights of more than 75 cm[1] and that there are no significant differences in the left ventricular end-diastolic volume between boy and girl neonates and in infants <75 cm in height.[3] The results of this study do not support the former conclusion that there are no gender differences. The gender difference in end-diastolic volumes observed in this study was 0.034 ml, which is 1.60% of the mean end-diastolic volume in boys. This was converted to a 0.54% difference in the left ventricular end-diastolic dimension when using two-dimensional echocardiography. This result was acquired using the following calculations: the end-diastolic volumes in boys and girls and the gender difference in the left ventricular end-diastolic volume were expressed as Vm (ml), Vf (ml), and ΔDd (%), respectively. $(Vm - Vf)/Vm = 0.0160$ and $Vf/Vm = 1 - 0.0160$ if the end-diastolic volume is proportionate to left ventricular end-diastolic volume^3. The latter formula can be changed to $(1 - \Delta Dd/100)^3 = 1 - 0.0160$, that is, $\Delta Dd = 0.54\%$. For example, if the left ventricular end-diastolic volume is 18.33 mm – a mean left ventricular end-diastolic dimension of 48.0 cm height = the average height of the participants in this study – the gender difference is only 0.10 mm.[3] It was expected that three-dimensional echocardiography alone would have the capacity to identify the gender difference in left ventricular end-diastolic volumes at birth because ascertaining extremely small differences is quite difficult and even impossible using two-dimensional echocardiography. The gender difference at a height of 75 cm was estimated to be 0.15 mm according to the regression equations shown in earlier reports.[1,3] These observations suggest that the gender difference in the left ventricular end-diastolic volume continues to increase throughout the infantile period. It can readily be imagined that the gender difference persists throughout human life, that is, from the stage of human cardiac development through adulthood.[1–4] It was speculated that the gender disparity in exercise capacity could be attributable to this dimensional difference, at least in terms of the circulatory capacity. The cardiac indexes were 2.04 (0.32) L/minute/m^2 (H) and 2.17 (0.34) L/minute/m^2 (D) in boys and 1.95 (0.23) L/minute/m^2 (H) and 2.08 (0.25) L/minute/m^2 (D) in girls (Table 3).

Evaluation of the differences in left ventricular volumes measured using three-dimensional echocardiography and the velocity time integral and Pombo methods

The region of intensity is usually placed at the centre of the vessels when measuring the velocity–time integrals. The flow velocity in the peripheral area of the vessel is always lower than that observed in the centre. According to the Hagen–Poiseuille law, the average velocity within the vessel is two-thirds of the maximum velocity. In addition, the direction of the pulsed wave and the flow of blood are not always parallel. If the angle is estimated to be ~20°, the true velocity time integral is 2/3/cos (20°) = 0.70 of the time of the original velocity–time integral. The stroke volume was calculated to be 19.10 mL/m^2 on using the velocity–time integral method.

When applying the Pombo method, there are two points to consider. First, the calculation in this method is a rough approximation. For example, the major dimension is usually less than twice the left ventricular end-diastolic volume – it was estimated to be ~1.72 times the actual left ventricular end-diastolic volume. Second, this method assumes that the anteroposterior and lateral lengths of the minor dimension are equal. These lengths are usually not equal in the early neonatal period at end-diastole. In general, a tendency to overestimate the end-diastolic volume and underestimate the end-systolic volume is observed, as the fraction shortening of the major dimension (=0.161 [0.153–0.169, 95% confidence interval]) is significantly smaller than that of the minor dimension (=0.332 [0.326–0.338]). The true stroke volume is seen to be lower than that reported by Pombo et al.

It is assumed that the value of the ejection fraction measured on three-dimensional echocardiography (0.58) corresponds better to the clinical impression compared with that obtained with the Pombo method (0.70).

The stroke volume estimated on three-dimensional echocardiography is considered to be more accurate and sensitive than that obtained with the other two methods.

Comparison of the volumes estimated in this study and those of former studies

Only a few studies have examined the neonatal stroke volume. Mandelbaum–Isken et al[11] reported the cardiac index to be 167 ml/minute/kg (modal) using the pulsed Doppler method with a sampling point in the ascending aorta. Patel et al[12] obtained a cardiac index of 216 ml/minute/kg (95% confidence interval, 179–253 ml/minute) in healthy neonates using conventional two-dimensional echocardiography of the suprasternal notch. Foran et al[5] estimated the stroke volume of premature infants to be 1.3 ml/kg or 1.6 ml/kg per stroke based on two methods using magnetic resonance imaging. The estimated stroke volume and cardiac index in this study were

1.22 ml/kg and 141 ml/minute/kg or 2.16 L/minute/m^2, respectively, using three-dimensional echocardiography. These values are 6–33% lower than those estimated by the above-mentioned reports. This discrepancy is primarily attributable to the differences in the methods of measuring and calculating the stroke volume and cardiac index. Friedberg et al[13] reported that there are no significant differences in the end-diastolic volume between the values obtained on three-dimensional echocardiography and magnetic resonance imaging, whereas the three-dimensional echocardiographic ejection fraction is significantly smaller (9.3%) than the magnetic resonance imaging ejection fraction in neonates and infants with congenital heart disease. These results indicate that the stroke volume obtained on three-dimensional echocardiography is smaller than that obtained on magnetic resonance imaging. Lytrivi et al[14] reported that the mean left ventricular end-diastolic volume indexed to (body surface area)$^{1.38}$ is 70.4 ml/$m^{2.6}$, which corresponds to 30.79 ml/m^2 in neonates. These data are similar to those reported in this study. The true cardiac index could possibly be lower than that reported using the three-dimensional echocardiographic results obtained in this study. This low cardiac index may contribute to the circulatory system vulnerability that often appears in the early neonatal period.

The significance levels indexed to body surface area were lower than those indexed to body weight in all comparisons. This indicates that body height is much more informative than body weight when indexing.

Conclusion

In this study, the left ventricular volumes in the early neonatal period were measured using three-dimensional echocardiography. The cardiac index for this age is smaller than that previously recognised. Significant gender differences in the end-diastolic volume, stroke volume, and ejection fraction, but not in end-systolic volume, can be seen.

Further observations are warranted to confirm the points shown in this study.

Acknowledgements

The author thanks Junko Miyamoto and Masaki Sawa for their devoted coordination towards this manuscript.

Disclosures

None.

References

1. Nagasawa H, Arakaki Y, Yamada O, Nakajima T, Kamiya T. Longitudinal observations of left ventricular end-diastolic dimension in children using echocardiography. Pediatr Cardiol 1996; 17: 169–174.
2. Mertens L, Istvan S, Marek J, et al. Targeted neonatal echocardiography in the neonatal intensive care unit: practice guidelines and recommendations for training. J Am Soc Echocardiogr 2011; 24: 1057–1078.
3. Nagasawa H. Novel regression equations of left ventricular dimensions in infants less than 1 year of age and premature neonates obtained from echocardiographic examination. Cardiol Young 2010; 20: 526–531.
4. Nagasawa H, Arakaki Y. Identification of gender differences in the thickness of the left ventricular wall by echocardiography in children. Cardiol Young 2002; 12: 37–43.
5. Foran AM, Fitzpatrick JA, Allsop J, et al. Three-tesla cardiac magnetic resonance imaging for preterm infants. Pediatr 2007; 120: 78–83.
6. Acar P, Marx GR, Salibe Z, Sidi D, Kachaner J. Three-dimensional echocardiographic measurement of left ventricular stroke volume in children: comparison with Doppler method. Pediatr Cardiol 2001; 22: 116–120.
7. Cohen J. Statistical Power Analysis for the Behavioral Sciences, 2nd edn, Lawrence Erlbaum Associates, Hillsdale, NJ, 1988: 52–66.
8. Pombo JF, Troy BL, Russell RO. Left ventricular volumes and ejection fraction by echocardiography. Circulation 1971; 43: 480–490.
9. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height–weight formula validated in infants, children, and adults. J Pediatr 1978; 93: 62–66.
10. DuBois D, DuBois EF. Clinical calorimetry. X. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916; 17: 863–871.
11. Mandelbaum-Isken VH, Linderkamp O. Cardiac output by pulsed Doppler in neonates using the apical windows. Pediatr Cardiol 1991; 12: 13–16.
12. Patel N, Dodsworth M, Mills JF. Cardiac output measurement in newborn infants using the ultrasonic cardiac monitor: an assessment of agreement with conventional echocardiography, repeatability and new user experience. Arch Dis Child Fetal Neonatal Ed. 2011; 96: F206–F211.
13. Friedberg MK, Su X, Tworetzky W, Soriano BD, Powell AJ, Marx GR. Validation of 3D echocardiographic assessment of left ventricular volumes, mass, and ejection fraction in neonates and infants with congenital heart disease: a comparison study with cardiac magnetic resonance imaging. Circ Cardiovasc Imaging 2010; 3: 735–742.
14. Lytrivi ID, Bhatla P, Ko HH, et al. Normal value for left ventricular volume in infants and young children by the echocardiographic subxiphoid five-sixth area by length (bullet) method. J Am Soc Echocardiogr 2011; 24: 214–218.