Left Ventricular Diastolic Performance in Neonates

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Background The left ventricular (LV) diastolic performance of infants who were in a stable post-treatment condition in the neonatal intensive care unit was evaluated using echocardiography.

Methods and Results The study group comprised 55 infants (Stable infant group, SI) and the parameters of LV performance were: LV propagation velocity (Vp) by color M-mode Doppler echocardiography (CMD), peak E wave, peak A wave, and the E/A ratio of transmitral flow. In a second set of measurements, a subset of 10 infants (patent ductus arteriosus (PDA) infant group, PI) were evaluated for LV diastolic performance during closure of PDA. The mean Vp in the SI was 27.2±7.3 cm/s and a positive correlation was observed between Vp and gestational age (r=0.477, p=0.0002). In the PI, Vp did not change significantly during closure of the PDA (from 23.3±8.2 cm/s to 27.5±8.4 cm/s); however, the E/Vp ratio decreased significantly with closure (from 3.14±0.83 to 2.12±0.68, p=0.0051).

Conclusion The measurement of Vp by CMD can be considered a parameter for the evaluation of LV diastolic performance, even in the neonatal period. The LV diastolic performance of the infant is maintained from immediately after birth to spontaneous closure of the PDA. (*Circ J* 2005; **69**: 1094–1098)

Key Words: Color M-mode Doppler echocardiography; Diastolic function; Left ventricular diastolic performance; Neonate; Patent ductus arteriosus

It is very important to assess diastolic function in patients with heart diseases in order to evaluate the severity of the disease and to recommend the appropriate therapy! During the neonatal period, particularly, pulsed Doppler measurement of transmitral flow has been widely used for noninvasive assessment of left ventricular (LV) relaxation abnormalities;[2–8] however, it is known that the pulsed Doppler index is affected by many factors, including active relaxation and distensibility of the left ventricle, the pressure gradient between the left ventricle and the atrium, heart rate, and altered loading conditions[9–12] An abnormality of LV relaxation is concealed in some patients because the transmitral flow pattern is normalized by an increased atrioventricular pressure gradient (pseudonormalization)[13–15] Recently, it has become possible to evaluate diastolic function with noninvasive methods using the flow propagation velocity (Vp) measured by color M-mode Doppler echocardiography (CMD). The Vp measured by CMD seems to be free of pseudonormalization and correlates well with the variables of LV diastolic function that are measured invasively[6,17] In the present study, we used echocardiography to measure the serial changes in cardiac function and thus evaluate the LV diastolic performance in the postnatal period.

Methods

Study Population

Study subject were infants admitted to the neonatal intensive care units of Seirei Hamamatsu General Hospital between October 1999 and February 2001. Twins and pa-

tients with congenital heart disease, intrauterine growth retardation, persistent pulmonary hypertension of the newborn, or chromosome anomalies were excluded. All patients were off mechanical ventilation and none was treated with inotropic drugs. Also, patients who had poor systolic performance with LV ejection fraction (LVEF) less than 60% and who were suspected to have pulmonary hypertension by echocardiography were excluded. Final study subjects were 55 infants (Stable infant group, SI) and their characteristics are summarized in Table 1. Primary diagnoses were: transient tachypnea of newborn (24 infants), massive aspiration syndrome (10), normal infants who received a diagnosis the innocent heart murmur or congenital heart disease because of a family history (9), respiratory distress syndrome (7), and initial vomiting (5). The LV diastolic function of a subset of 10 infants was evaluated during closure of patent ductus arteriosus (PDA) using color Doppler echocardiography (PDA infant group, PI). Informed consent was obtained from both parents of each infant on admission.

Echocardiographic Evaluation

Echocardiography measurement was performed while the infants were resting. A complete 2-dimensional echocardiographic examination was performed using a Hewlett-Packard Sonos 2000 with a 5.0 MHz transducer. We mea-

Table 1 Characteristics of the Study Patients (n=55)

	Median	Range	Mean (±SD)
GA (weeks)	37.3	27.4–41.4	36.2±3.6
Birth weight (g)	2,600	999–3,770	2,458±664
M/F	31:24		
Apgar score (5 min)	9.0	7–10	8.5±0.8
Age (days)	4.0	1–30	5.5±5.9
Cesarean sections /normal delivery	18/37		

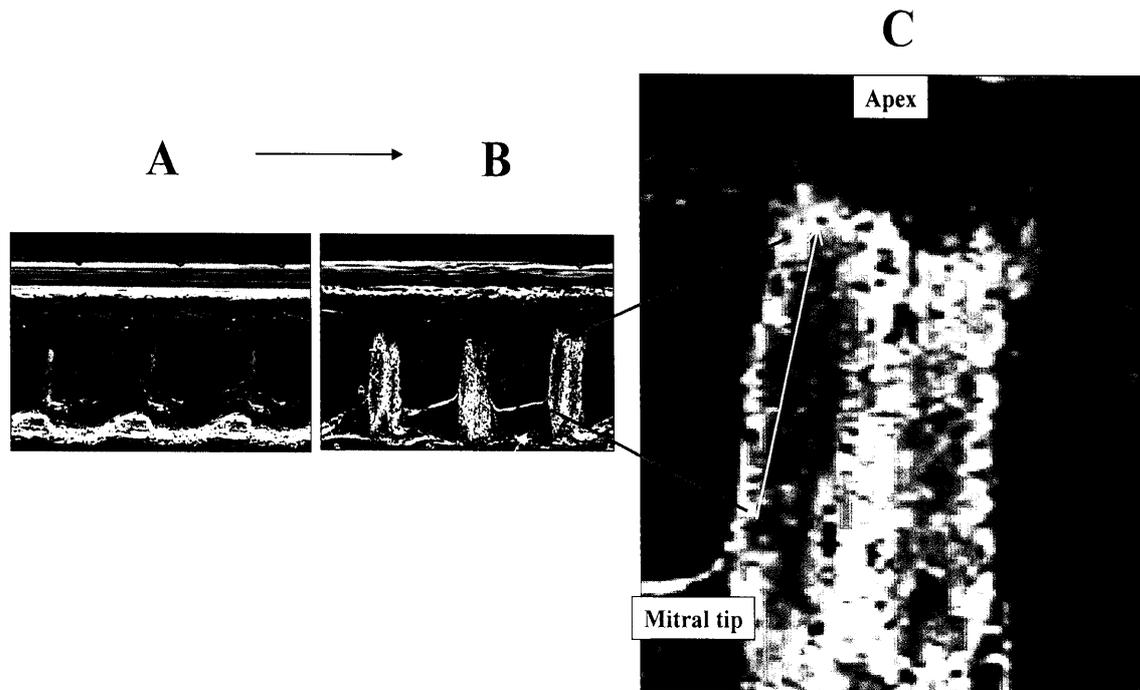GA, gestational age; SD, standard deviation.

C

A ⟶ B

Fig 1.   Color M-mode Doppler image of left ventricular filling flow in early diastole in the apical long-axis view. (A,B) The aliasing velocities are limited color Doppler filter at 55 cm/s and 31 cm/s, respectively, in the same cardiac cycle. (C) The slope of the white line of arrow drawn from the mitral tip to the apex was defined as the rate of propagation velocity of left ventricle![6]

sured Vp, peak E wave, peak A wave, E/A ratio, LVEF, LV diastolic dimension (LVDd), LV systolic dimension (LVDs), peak S wave, peak D wave, S/D ratio of transpulmonary venous flow, and heart rate (HR, beats/min). The Doppler sample volume was set at an axial length of 2 mm with a wall filter setting of 200–400 Hz. The transmitral flow velocity was recorded from the apical 4-chamber or apical long-axis view with the pulsed wave Doppler sample volume positioned at the tips of the mitral leaflets during diastole. The pulmonary venous flow was recorded from the apical 4-chamber view with the sample volume positioned at the orifice of the right upper pulmonary vein. The transducer beam was set as close to the Doppler beam as possible at an angle of 20° in selected planes. No angle correction of the Doppler signal was made. LVEF, LVDd, and LVDs were obtained by M-mode echocardiography; Vp was measured by CMD.

Color M-Mode Doppler Imaging

We determined LV filling in early diastole by CMD in the apical long-axis view. To measure the distance/time ratio, the ultrasound beam was directed from the apex of the heart toward the center of the mitral orifice as parallel to the filling flow as possible using the baseline shift technique (Fig 1, Takatsuji et al[16]) between the mitral tip from the apex region. As a preliminary study, we measured the Vp a total of 939 times in 345 infants. In the present study, Vp could be evaluated 773 times (82.3%), but not in the other 166 times (17.7%) because of the fusion of the transmitral flow wave when the neonates had tachycardia >170 beats/min, or for other reasons, which made it impossible to obtain the apical long-axis view. Doppler echocardiograms were recorded with a sweep speed of 100 mm/s. We could measure Vp by changing the color Doppler filter setting from 12 cm/s to 31 cm/s. All measurements were performed by 1 examiner and 3–5 different cardiac cycles

Table 2   Clinical and Echocardiographic Characteristics

	n	Median	Range	Mean (±SD)
Vp (cm/s)	55	26.8	12.2–44.1	27.2±7.3
E wave (cm/s)	55	53.0	32.0–80.0	53.7±13.6
A wave (cm/s)	55	47.0	29.0–70.0	47.7±8.5
E/A ratio	55	1.12	0.76–2.11	1.14±0.25
S wave (cm/s)	55	36.0	21.0–82.0	38.2±11.4
D wave (cm/s)	55	38.0	20.0–101.0	40.9±13.6
S/D ratio	55	1.00	0.42–1.27	0.97±0.20
LVDd (mm)	55	16.8	11.2–21.6	16.5±2.3
LVDs (mm)	55	10.9	7.4–14.5	10.8±1.6
LVEF (%)	55	72.0	60–83	71.2±6.5
HR (beats/min)	55	122.4	89–160	124.2±15.2

SD, standard deviation; Vp, left ventricular propagation velocity; E wave, peak early transmitral Doppler flow velocity; A wave, peak atrial transmitral Doppler flow velocity; E/A ratio, early/atrial transmitral Doppler flow velocity; S wave, peak systolic wave of transpulmonary venous flow; D wave, peak diastolic pulmonary venous flow; S/D ratio, S wave/D wave of transpulmonary venous flow; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; HR, heart rate.

were analyzed. The mean values of the measurements were used for each parameter.

Reproducibility of Measurements

To test the intra- and interobserver variability, Vp was measured for 10 infants who were randomly selected and measurements were obtained by 2 independent observers, and by 1 observer on 2 different occasions.

Statistical Analysis

Results are expressed as mean values ± standard deviation. Univariate and multivariate regression analyses were performed by the least square methods to asses the relationship between Vp and various factors. Comparison of the parameters between PDA open and closed used Wilcoxon's

Table 3 Univariate Correlates of Vp

	All infants (n=55)		Pre-term infants (n=25)	
	r	p value	r	p value
GA (weeks)	0.477	*0.0002	0.563	*0.0084
Weight (g)	0.447	*0.0005	0.598	*0.0040
HR	−0.477	*0.0008	−0.674	*0.0005
E wave	0.378	*0.0041	0.607	*0.0032
A wave	0.233	NS	0.226	NS
E/A ratio	0.230	NS	0.491	*0.0117
S wave	0.133	NS	−0.147	NS
D wave	0.105	NS	0.056	NS
S/D ratio	−0.073	NS	−0.200	NS
LVDd (mm)	0.370	*0.0052	0.457	*0.0206
LVDs (mm)	0.298	*0.0269	0.214	NS
LVEF (%)	0.084	NS	0.356	NS

Vp, left ventricular propagation velocity; Pre-term infant, gestational age <37 weeks; GA, gestational age; HR, heart rate; E wave, peak early transmitral Doppler flow velocity; A wave, peak atrial transmitral Doppler flow velocity; NS, not significant; E/A ratio, early/atrial transmitral Doppler flow velocity; S wave, peak systolic wave of transpulmonary venous flow; D wave, peak diastolic pulmonary venous flow; S/D ratio, S wave/D wave of transpulmonary venous flow; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; *Significant.

Table 4 Influence of Doppler Flow Velocity Parameters and Heart Rate

	PDA open	PDA closed	p value
Vp (cm/s)	23.3±8.2	27.5±8.4	NS
E wave (cm/s)	67.6±10.0	54.7±12.6	*0.0208
A wave (cm/s)	61.1±11.7	50.9±6.8	NS
E/A ratio	1.14±0.27	1.08±0.21	NS
E/Vp ratio	3.14±0.83	2.12±0.68	*0.0051
S wave (cm/s)	59.4±18.5	42.2±11.8	*0.0069
D wave (cm/s)	60.2±16.6	41.8±8.5	*0.0108
S/D ratio	0.99±0.11	1.02±0.24	NS
LVEF (%)	71.0±7.9	73.7±6.6	NS
HR (beats/min)	135.0±14.3	123.0±12.9	0.0218

Abbreviations see Table 3. PDA, patent ductus arteriosus.

rank sum test. The intra-observer reliability was determined using the intraclass correlation coefficient (ICC). Intra-observer variability was based on a one-way analysis of variance (ANOVA) and interobserver reliability was based on two-way ANOVA. For all statistics, a p-value <0.05 was considered statistically significant. Data were analyzed using the statistical software program StatView for Windows, version 5.0 (SAS Inc, Cary, NC, USA).

Results

The clinical and echocardiographic characteristics of the 55 study patients are summarized in Table 2. Mean Vp in SI was 27.2±7.3 cm/s. Univariate correlates of Vp are shown in Table 3. In SI, a positive correlation was observed between gestational age (GA) and Vp (r=0.477, p=0.0002), weight (r=0.447, p=0.0008), E wave (r=0.378, p=0.0041), LVDd (r=0.370, p=0.0052), LVDs (r=0.298, p=0.0269). In

the SI, a negative correlation was observed between Vp and HR (r=−0.477, p=0.0008). Little improvement was noted in these correlations when Vp was incorporated in the multivariate analyses. In the univariate analysis of Vp in 25 preterm SI infants who were born at GA less than 37 weeks, a positive correlation was also observed between Vp and GA (r=0.563, p=0.0028), weight (r=0.598, p=0.0012), E wave (r=0.607, p=0.0010), LVDd (r=0.457, p=0.0206), and E/A ratio (r=0.491, p=0.0117). A negative correlation was observed between Vp and HR (r=−0.674, p=0.0001). Little improvement was noted in these correlations when Vp was incorporated in the multivariate analyses. The correlation between Vp and GA is shown in Fig 2. In pre-term SI infants (GA <37 weeks), the correlation between Vp and GA was significant (Fig 2; Vp=1.452×GA −23.461, r=0.563, p=0.0028); however, in term SI infants (Fig 2) it was not significant. In term SI infants (GA >37 weeks), the correlations between Vp and GA, HR, E wave, E/A ratio, LVDd, and other parameters were not significant.

In PI, the influence of diastolic LV performance with spontaneous closure of the PDA is shown in Table 4. The time of spontaneous closure of the PDA ranged from 1 to 6 days (mean 3±2 days) after birth. The Vp in the PI did not change, even though the pulmonary venous flow decreased significantly during closure of the PDA. The E waves in the PI decreased significantly with closure (from 67.6±10.0 to 54.7±12.6, p=0.0208), but the E/A ratio in the PI did not differ significantly. The E/Vp ratio in the PI decreased signifi-

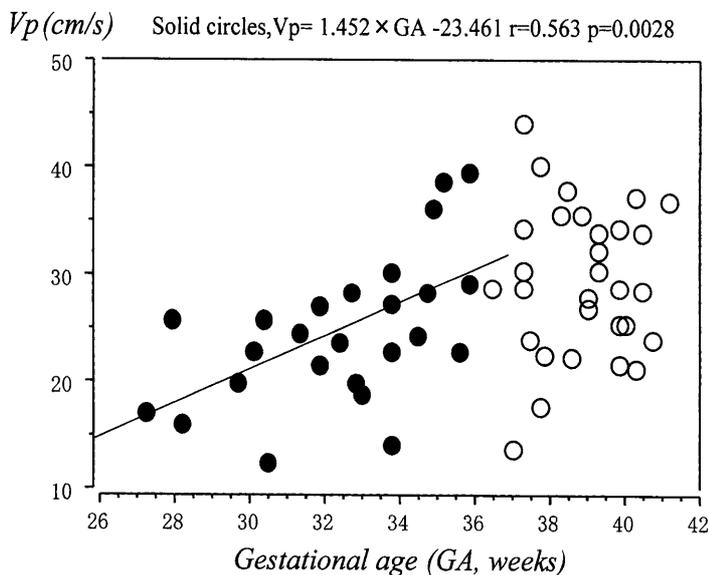Vp (cm/s)   Solid circles, Vp= 1.452 × GA -23.461 r=0.563 p=0.0028

Fig 2. Linear regression between left ventricle propagation velocity and gestational age. In preterm infants, the correlation was significant (solid circles, Vp=1.452×GA−23.461, r=0.563, p=0.0028), but not in term infants (open circles).

cantly with closure (from 3.14±0.83 to 2.12±0.68, p=0.0051) and the HR in the PI also decreased significantly with closure (from 135.0±14.3 beats/min to 123.0±12.9 beats/min, p=0.0218).

Reproducibility

The intra- and interobserver variations were within an acceptable range (intra-observer reliability: ICC=0.82, standard error of the mean (SEM)=6.09, interobserver reliability: ICC=0.91, SEM=7.933).

Discussion

Accurate and comprehensive assessment of ventricular diastolic function is becoming increasingly important in the treatment of pediatric patients with cardiac conditions, particularly as outcomes continue to improve in neonatal congenital heart disease. Noninvasive evaluation of LV diastolic performance can facilitate the clinical assessment and management of neonates with birth asphyxia, hypotensive shock, persistent pulmonary hypertension of the newborn, and assisted ventilation in the neonatal intensive care units.

Measurement of Vp in the left ventricle by CMD was first reported by Jacobs et al[18] who showed that the measurement was free of pseudonormalization and correlated well with the invasively measured variables of LV relaxation.[16,17,19–23] Vp is a very useful parameter in the evaluation of diastolic performance and is reduced in a variety of disease states affecting LV diastolic function, including dilated cardiomyopathy, hypertension, aortic stenosis, and atrial fibrillation.[24,25]

In the present study, we determined LV diastolic performance using echocardiography. In the neonates we evaluated, mean Vp was 27.2±7.3 cm/s, which is lower than the mean Vp reported for normal adult controls[16] (Vp=74.3± 17.4 cm/s) and child controls[22] (54.63±14 cm/s). It has been reported that the E wave was lower in pre-term infants than in term infants,[2] and in the present study we observed a positive correlation between Vp and the E wave. Pathological studies have shown that the ratio of type I to type III collagen is very high in the hearts of neonates, followed by a gradual decrease in the ratio during development,[26] so we speculate that the premature myocardium is more rigid and less compliant and therefore, the force generated by the myocardium of premature infants may be very weak. Thus, not only the peak early velocity of transmitral flow, but also the propagation velocity from the LV inflow to apex may be insufficient for LV diastolic function.

We observed a positive correlation between Vp and GA, weight, and LVDd; in the pre-term infants there was a stronger correlation between Vp and GA, weight and LVDd. The change in Vp was related to maturational changes with increasing gestation. Previous studies have addressed the cardiac diastolic function of the neonatal period[2–8] and maturational changes in both systolic and diastolic properties have been suggested to occur in human infants and young children.[27,28] Even in the neonatal period, Vp by CMD can be considered an appropriate parameter for the evaluation of LV diastolic performance.

Vp did not change, even though pulmonary venous flow decreased significantly. A decrease in pulmonary venous flow occurs immediately after birth,[29] and reflects a sudden increase in pulmonary circulatory volume with additional left to right shunting through the PDA. Also, E/Vp decreases with closure of the PDA. It has been reported that the E/Vp ratio is most reliable when measured over all indices of LV filling pressure.[7,22,23,25] Measurement of Vp is a method that may be less load-sensitive and more quantitative than mitral inflow Doppler assessment. We suggest that a decrease in pulmonary venous flow and E/Vp leads to an increase in the LV filling pressure because of a left to right shunt through the PDA after birth; thus, the LV diastolic function of the infant is maintained from immediately after birth until spontaneous closure of the PDA.

We observed a negative correlation between Vp and HR. In the postnatal period, physiologic changes in HR can cause significant alteration in transmitral Doppler flow velocity patterns.[2] An increase in HR is a limiting factor in the assessment of diastolic performance; however, Vp has been reported as independent of HR in cats.[30] If the LV stiffness is constant, then reduced pulmonary capillary wedge pressure would occur at a faster HR. However, in adult studies, Vp has been found to be sensitive to changes in HR.[31] The relationship between Vp and HR is complex; therefore, when alterations in HR are present, it is necessary to carefully evaluate the diastolic performance measured using CMD.

Study Limitations

The number of patients studied was small. Although there were a few normal neonates in the study, we included as many near normal neonate as possible. It was not possible to determine when the LV diastolic performance matured because we could not perform a longer follow-up, particularly of the pre-term infants. Vp can be measured by several methods and an optimal method has not yet been established, so there may be differences in the Vp or E/Vp values measured by different systems. We used the modified baseline shift method proposed by Takatsuji et al[16] who defined the first aliasing limit as 70% of maximal velocity. We considered it appropriate, as in their method, to use a color Doppler filter setting from 12 cm/s to 31 cm/s, because this setting was about 70% of the E wave velocity. However, the validity of this approach could not be ascertained. Further studies are necessary in order to establish a generally accepted method of Vp measurement.

We conclude that it is possible to evaluate the diastolic performance in the neonatal period using CMD. However, when using this method, it is prudent to estimate the diastolic performance when altered loading conditions prevail, such as with a PDA, which can lead to increased pulmonary circulation immediately after birth.

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