CLINICAL STUDY

Early Diastolic Left Ventricular Relaxation in Normal Neonates is Influenced by Ventricular Stiffness and Longitudinal Systolic Function

Yukako Homma,[1] MD, Yasunobu Hayabuchi,[2] MD, Tomomasa Terada,[1] MD, Miki Inoue,[1] MD and Kazuhiro Mori,[1] MD

Summary

Tissue Doppler velocity during early diastole (*e*') is one of the most feasible and reproducible echocardiographic assessments to reflect active relaxation of the left ventricle. Although several reports have described the mechanisms of temporal diastolic dysfunction in the early neonatal period, factors influencing diastolic function have not been determined. The purpose of this study was to elucidate factors significantly influencing *e*' in the early neonatal period.

A total of 179 consecutive normal neonates underwent echocardiographic studies performed at 0 days and 5-10 days after birth. The statistical relationships between *e*' and age, body weight, mean blood pressure, heart rate, shortening fraction of the left ventricle, peak systolic motion velocity (*s*'), early diastolic transmitral flow velocity over annulus velocity, Tei index, and diastolic wall strain (DWS) were analyzed.

Between the 0 days and 5-10-days-after birth groups, significant differences were shown in mean blood pressure, shortening fraction of left ventricle, *e*', and Tei index. Age, body weight, mean blood pressure, *s*', and DWS showed significant correlations with *e*'. In multivariate regression analysis within these parameters, *s*' ($\beta = 0.6119$, $P < 0.0001$) and DWS ($\beta = 0.1216$, $P = 0.0321$) showed positive correlations with *e*'.

Longitudinal systolic motion velocity and ventricular wall stiffness of the left ventricle influence diastolic relaxation in normal neonates. Age, body weight, and circumferential systolic function are not significant factors.

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Key words: Diastolic wall strain, Diastolic function, Myocardial stiffness

Tissue Doppler velocity during early diastole (*e*') is one of the echocardiographic parameters reflecting ventricular relaxation. This feasible and noninvasive assessment can evaluate direct myocardial diastolic function reproducibly. Neonates are known to show temporary diastolic dysfunction soon after birth, but the mechanisms underlying this dysfunction are not clearly identified. In a previous study, the effects of afterload and right ventricular pressure overload due to physiological pulmonary hypertension, maturation, and the number of myocytes was inferred as one factor related to the diastolic function of neonates in the early period.[1-4] Including such factors, significant hemodynamic changes occur during the transition from the fetal to the neonatal environment, and these changes could be presented as characteristic in the neonatal period. Besides these hemodynamic and pathological factors, individual background characteristics such as age, body weight at birth, and systolic function should be considered to have potential relationships with diastolic function. The relationships among these various factors are being considered, but the mechanisms underlying the development and maturation of diastolic function in normal neonates have yet to be clarified. The purpose of this study was thus to investigate the factors influencing *e*', the representative parameter for ventricular relaxation, in the early neonatal period.

Methods

Study patients and echocardiographic measurements: Echocardiography was carried out in 179 normal cases either 0 days after birth ($n = 100$) or 5-10 days after birth ($n = 79$). Clinical characteristics of the two subgroups are shown in Table I. All were healthy subjects born in our hospital with normal blood pressure for the age of the individual. Blood pressure was measured using an automatic blood pressure monitor. None of the subjects showed structural or functional heart diseases. In the 5-10-days-after-birth group, no subjects included patent ductus arteriosus (PDA), whereas PDA was seen in some subjects in

From the [1]Department of Pediatrics, Tokushima Prefectural Central Hospital, Tokushima, Japan and [2]Department of Pediatrics, School of Medicine, University of Tokushima, Tokushima, Japan.

Address for correspondence: Yukako Homma, MD, Department of Pediatrics, Tokushima Prefectural Central Hospital, 1-10-13 Kuramoto-cho, Tokushima City, Tokushima 770-8539, Japan. E-mail: farfalle31@hotmail.co.jp

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Table I. Subject Characteristics and Echocardiographic Measurements

	Neonates 0 days after birth	Neonates 5-10 days after birth	*P*
n	100	79	
Sex (male, %)	58 (58)	47 (59)	0.8403
Body weight (g)	2611 ± 692 (2474-2749)	2737 ± 652 (2592-2884)	0.2164
Days after birth	0.35 ± 0.27 (0.30-0.40)	6.67 ± 1.90 (6.24-7.10)	< 0.0001*
Gestational age (weeks)	37.13 ± 2.87 (36.56-37.70)	37.95 ± 2.88 (37.30-38.60)	0.0588
Mean blood pressure (mmHg)	44.7 ± 7.9 (43.1-46.3)	51.9 ± 7.9 (50.1-53.7)	< 0.001*
Heart rate (beats/minute)	133.2 ± 14.2 (130.4-136.0)	131.6 ± 14.7 (128.3-134.9)	0.4518
Shortening fraction of left ventricle (%)	33.2 ± 6.8 (31.9-34.6)	38.7 ± 9.1 (36.8-40.8)	< 0.0001*
E/A	1.06 ± 0.34 (0.99-1.12)	1.06 ± 0.22 (1.09-1.11)	0.9584
s'	4.62 ± 0.87 (4.45-4.79)	4.81 ± 0.97 (4.60-5.03)	0.1564
e'	6.06 ± 1.53 (5.76-6.37)	6.69 ± 1.61 (6.30-7.03)	0.0116*
E/*e*'	9.24 ± 2.39 (8.76-9.71)	8.80 ± 2.34 (8.28-9.33)	0.2266
Tei index	0.56 ± 0.17 (0.52-0.59)	0.47 ± 0.13 (0.44-0.50)	0.0002*
DWS	0.28 ± 0.09 (0.26-0.30)	0.34 ± 0.07 (0.32-0.35)	< 0.0001*

Data are expressed as mean ± standard deviation (SD) (95% confidence interval). E indicates early diastolic flow velocity; A, peak atrial early flow velocity; *s*', peak systolic motion velocity; *e*', peak early diastolic motion velocity; and *, significant.

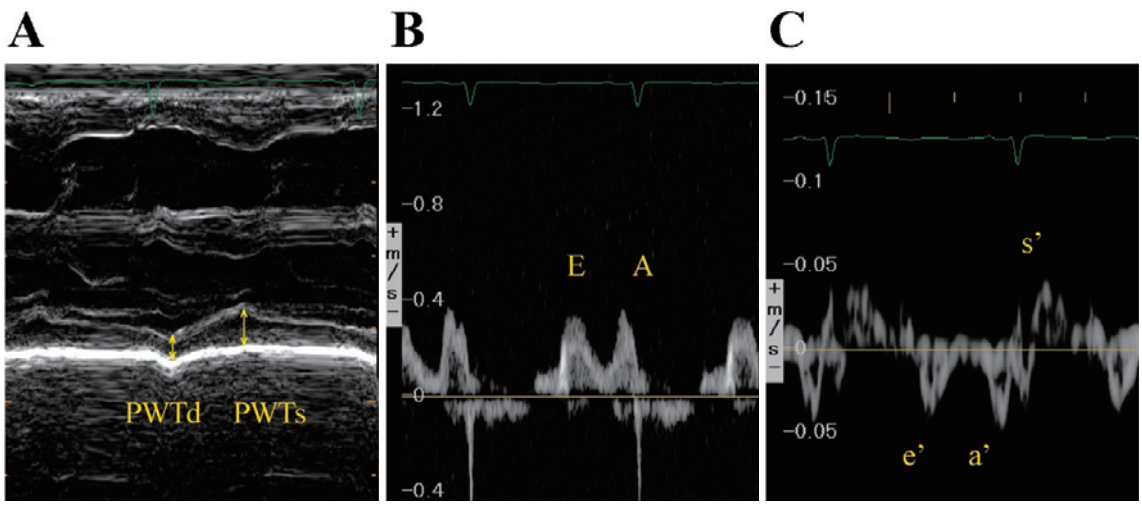

Figure 1. Echocardiographic evaluation of left ventricular diastolic function in a representative 0-day-old neonate. **A:** Diastolic wall strain (DWS) is calculated from M-mode echocardiography using the following formula: DWS = (PWTs - PWTd) / PWTs, where PWTs is posterior wall thickness at end-systole, and PWTd is posterior wall thickness at end-diastole. **B:** E and A waves of transmitral flow. **C:** Tissue Doppler imaging of the lateral left ventricular wall.

the 0-days-after-birth group. Sixty neonates had echocardiography performed on them twice in both the 0-days- and 5-10-days-after-birth groups. On forty neonates it was performed only once in 0 days after birth, and in 19 neonates (who were hospitalized after 1 day of age) it was performed in only 5-10 days after birth. All subjects were breathing spontaneously and were not on inotropic medication.

All echocardiographic measurements were performed with a commercially available ultrasound machine (HD11 XE system; Philips, Andover, MA) by well-trained pediatricians. All measurements were confirmed by more than two other pediatricians. Standard 2D echocardiographic images (parasternal long-axis view, parasternal short-axis view, and four-chamber view) were recorded for 3-4 cycles. Doppler and tissue Doppler recordings were also performed. Left ventricular (LV) wall thickness and shortening fraction (SF) were measured from the short-axis on M-mode echocardiography. To measure diastolic wall strain (DWS), we used an M-mode cursor that can be positioned perpendicular to the LV posterior wall. DWS was calculated using the following formula: DWS = (PWTs - PWTd) / PWTs, where PWTs is posterior wall thickness at end-systole, and PWTd is posterior wall thickness at end-diastole (Figure 1A). From apical four-chamber view images, we recorded transmitral flow velocity by placing the sample volume at the tip of the mitral leaflet. From peak atrial flow velocity (A) and peak early diastolic flow velocity (E), E/A was determined (Figure 1B). On tissue Doppler echocardiography, peak systolic wall velocity (*s*'), peak early diastolic wall velocity (*e*'), and peak late diastolic wall velocity (*a*') were recorded and E/*e*' was

determined (Figure 1C). Tei index was calculated from tissue Doppler images as follows: Tei index = (*a* - *b*)/*b*, where the *a*-component was measured from the trailing edge of the mitral annular late diastolic wave (*a*') to the leading edge of the subsequent mitral annular early diastolic wave (*e*'), and the *b*-component was measured from the leading edge to the trailing edge of the mitral annular systolic wave (*s*'). For all echocardiographic parameters, the mean values of three heartbeats were used for the analyses.

Intra-observer and inter-observer reproducibilites of *e*' and DWS measurements were assessed by using Bland-Altman analysis in a blinded manner. Data were recorded and assessed at 5-minute intervals by observers 1 and 2 from 12 randomly selected participants. For intra-observer variability, data were analyzed twice. Inter-observer variability was assessed by analyzing data from two separate observers blinded to each other's results.

Statistical analysis: Categorical variables are expressed as absolute values and percentage (%), continuous variables as the mean value ± standard deviation (SD) with 95% confidence interval. The Mann-Whitney *U*-test was used to compare categorical differences between two groups. To evaluate relationships between the continuous variables, simple linear regression analysis was used. Values of $P < 0.05$ were considered statistically significant. A commercially available statistical software package (JMP 12.1.0 for Windows, from SAS, Cary, NC, USA) was used for all analyses. We excluded gestational age from univariate analysis with *e*', since comparing the different ages of neonate at the same gestational age was considered inadequate.

Ethical standards: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients prior to inclusion in the study.

Results

Of the 179 neonates enrolled in this study, 105 (59%) were male, and 74 (41%) were female. No significant differences were seen between body weight and gestational age between the 0 days after birth group and 5-10 days after birth group (2611 ± 692 g versus 2737 ± 652 g, $P = 0.2164$; 37.13 ± 2.87 weeks versus 37.95 ± 2.88 weeks, $P = 0.0588$). Mean blood pressure, SF, *e*', Tei index, and DWS showed significant differences between the two groups. DWS in the 0 days after birth group was lower and ranged more widely than that of the 5-10 days after birth group (0.28 ± 0.09 versus 0.34 ± 0.07, $P < 0.0001$). To investigate which factors influence left ventricular relaxation, we performed univariate analysis with *e*'. Body weight, mean blood pressure, *s*' and DWS showed significant positive correlations with *e*' (Figure 2). In multivariate analysis, *s*' and DWS displayed significant correlations with *e*' (Table II).

The inter- and intra-observer reproducibility obtained from the Bland-Altman plots (bias ± 2 SDs; 95% limit of agreement) of the *e*' during the early neonatal period was 0.008 ± 0.820 cm/sec and 0.100 ± 0.649 cm/sec, respectively. The inter- and intra-observer reproducibility of the DWS was 0.012 ± 0.125 and 0.003 ± 0.108, respectively.

Discussion

This study found that *e*' was independently associated with *s*' and DWS, but not with age, body weight, or SF. The representative parameter *e*' describes ventricular relaxation, which can be directly measured. This feasible assessment is also valuable for its reproducibility. E, A, E/A, and E/*e*' are known as other Doppler indices for evaluating left ventricular diastolic function.[5,6] However, E, A, and E/A need careful interpretation, since these show a 'pseudonormal or restrictive filling pattern' in advanced diastolic dysfunction. E and A are combined in one component in increased heart rate, which is likely to occur in neonates. E/*e*' is known to reflect filling pressure, and increased E/*e*' correlates with increasing filling pressure, which infers the presence of increased stiffness.[7] Also, it should be noted that E/*e*' is load-dependent and does not reflect a specific influence on direct passive myocardial stiffness,[8] whereas *e*' reflects the relaxation and diastolic function of the myocardium itself. This study aimed to investigate the alteration of early diastolic function associated with myocardial maturation and hemodynamic changes in the left ventricle in normal neonates.

From multivariate analysis, *e*' showed significant correlations with *s*' and DWS. First, when we focused our interest on the correlation between *e*' and *s*', we noticed that SF, the circumferential velocity parameter, did not show a significant correlation with *e*', but *s*', the longitudinal velocity parameter, did. Infants and children have much smaller velocities than adults, and systolic or diastolic myocardial velocities gradually increase depending on age.[9-11] In addition, as velocities increase with child growth, longitudinal systolic velocities show inexplicably larger increases than radial velocities.[12,13] Superior longitudinal velocity growth may be the reason for the more significant correlation with diastolic function than with radial systolic function. Significant differences in mean blood pressure, shortening fraction of left ventricle, *e*', and Tei index between 0 days and 5-10-days-after-birth groups showed relevant alterations according to age, which were influenced by this growth.

Longitudinal systolic function shows variety according to the location in the heart, and has been considered to be related to the spatial distribution of myocardial longitudinal fibers.[14-16] Since *s*' exerted a significant influence on *e*', *e*' may also have a relationship with longitudinal systolic fibers. The growth and maturation of these fibers may likely alter within ages, so reasonable locations for echocardiographic measurements need to be further examined.

Second, we mentioned the correlation between *e*' and DWS. DWS is based on the linear elastic theory, and its evaluation was advocated by Takeda, *et al*.[17] This noninvasive assessment offers a marker for evaluating LV wall distensibility in the presence of preserved ejection fraction.[18] Suzue, *et al*. described normal values in pediatric populations and the correlation between DWS and mitral

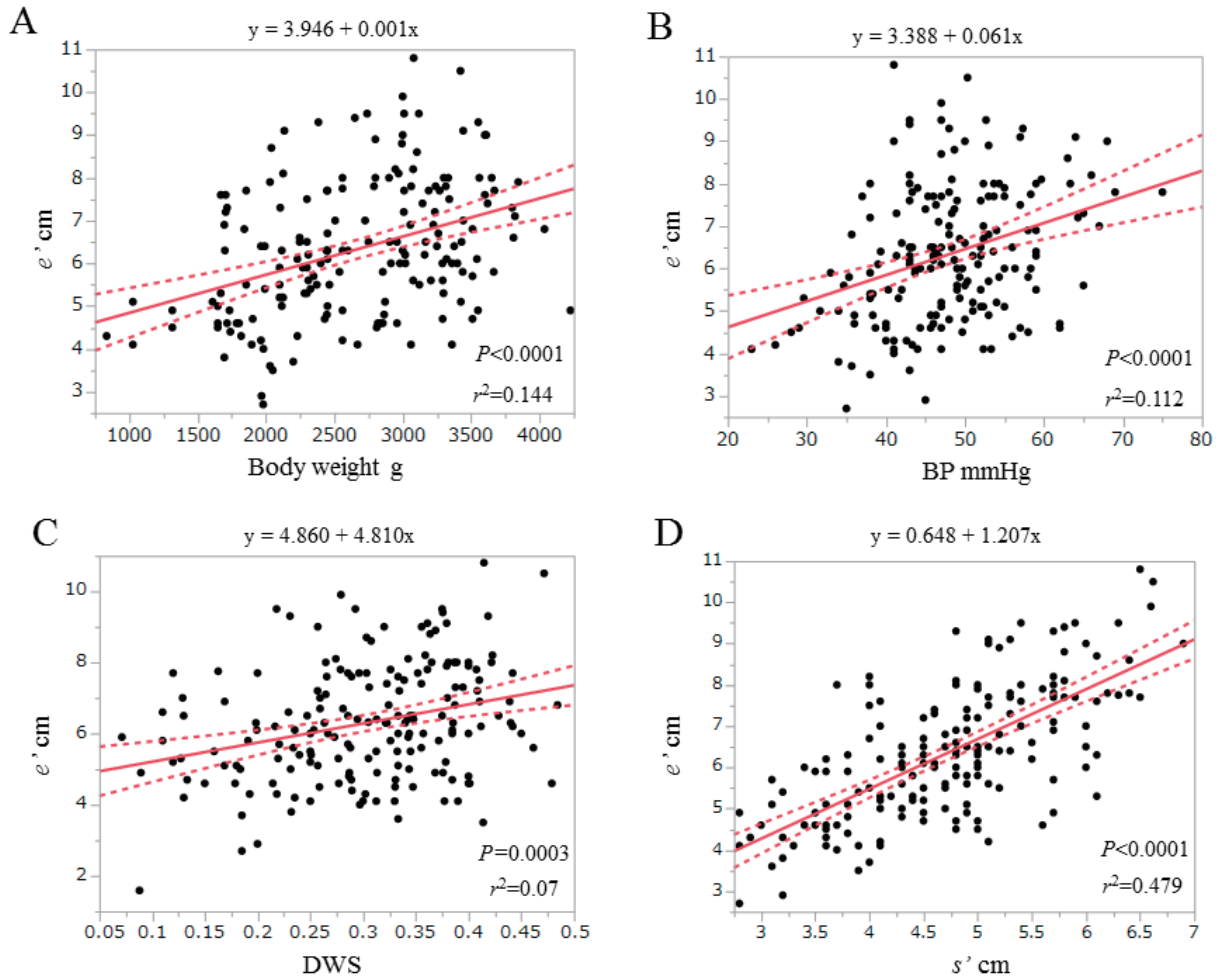

Figure 2. Relationship between *e'* and body weight (**A**), mean blood pressure (**B**), diastolic wall strain (DWS) (**C**), and *s'* (**D**) in the left ventricle. Linear regression lines with 95% confidence interval are indicated with dotted lines.

Table II. Results of Univariate and Multiple Regression Analysis for Variables between *e'*

	Univariate analysis		Multivariate analysis		
	r^2	*P*	β	95%CI	*P*
Body weight (kg)	0.144	< 0.0001*	0.08918	-0.0001 to 0.0004	0.1363
Days after birth	0.035	0.0125*	0.0783	-0.0170 to 0.0906	0.1790
Mean blood pressure (mmHg)	0.112	< 0.0001*	0.0734	-0.0084 to 0.0353	0.2275
s'	0.479	< 0.0001*	0.6119	0.8677 to 1.2676	< 0.0001*
DWS	0.070	0.0003*	0.1216	0.1901 to 4.2128	0.0321*
Shortening fraction of left ventricle (%)	0.018	0.0764	-	-	-
Heart rate (beats/minute)	0.003	0.4577	-	-	-

s' indicates peak systolic motion velocity; DWS, diastolic wall strain; β, standardized partial regression coefficient; and *, significant.

annular tissue Doppler velocity during early diastole (*e'*).[2] The effects of afterload after birth, growth of the LV wall, and other various factors are thought to be possible reasons for such changes.[17,19] The correlation between DWS and *e'* in our study indicates that ventricular stiffness exerts a significant influence on maturation and improvement of active relaxation in the left ventricle. The neonatal myocardium shows a relatively high amount of collagen in relation to myocytes and a large content of type I related to type III collagen, resulting in a more rigid, less compliant heart in the neonate than in older infants.[13] Pathological studies have shown that the ratio of type I to type III collagen gradually decreased during development.[20] In addition, myocytes are smaller, show a disordered arrangement, and contain fewer myofibrils and mitochondria during the neonatal period. Opitz, *et al.* and

Lahmers, *et al*. described the correlations between titin isoform and increasing stiffness of the myocardium with age.[1,3] The maturation and number of myocytes as well as the characteristics of collagen may be possible reasons for the significant influence of DWS on relaxation of the ventricle.

The implications of left ventricular wall movement of neonates soon after birth, and also comparisons of cardiac catheterization data concerning systolic and diastolic functions with echocardiographic measurements in neonates need to be considered in future studies.

Study limitations: Several limitations must be considered with regard to this study. First, we only investigated neonates 0 days after birth and 5-10 days after birth. The possibility of changes between 1 and 4 days after birth that were not detected in this study cannot be denied. However, it is not appropriate to perform daily echocardiographic examination on healthy babies. Since we performed the evaluation within our regular clinical practice, only limited data can be available for this study. Second, PDA was present in some neonates at 0 days after birth. In the presence of PDA, preload was increased, resulting in different preloads between subgroups. In addition, right ventricular pressure and pulmonary pressure also differed.

Finally, because echocardiography has the limitation that a stationary sample volume is positioned on a moving target, the effect of translation is not eliminated.

Conclusion

This study established a population of healthy neonates, and the resulting observations suggested that longitudinal systolic velocities and ventricular stiffness correlated significantly with relaxation of the ventricles.

Disclosures

Conflicts of interest: None.

References

1. Opitz CA, Leake MC, Makarenko I, Benes V, Linke WA. Developmentally regulated switching of titin size alters myofibrillar stiffness in the perinatal heart. Circ Res 2004; 94: 967-75.
2. Suzue M, Mori K, Inoue M, Hayabuchi Y, Nakagawa R, Kagami S. Developmental changes in the left ventricular diastolic wall strain on M-mode echocardiography. J Echocardiogr 2014; 12: 98-105.
3. Lahmers S, Wu Y, Call DR, Labeit S, Granzier H. Developmental control of titin isoform expression and passive stiffness in fetal and neonatal myocardium. Circ Res 2004; 94: 505-13.
4. Hsu DT, Pearson GD. Heart failure in children: part I: history, etiology, and pathophysiology. Circ Heart Fail 2009; 2: 63-70.
5. Fenk S, Fischer M, Strack C, *et al*. Successful weight reduction improves left ventricular diastolic function and physical performance in severe obesity. Int Heart J 2015; 56: 196-202.
6. Namba T, Masaki N, Matsuo Y, *et al*. Arterial stiffness is significantly associated with left ventricular diastolic dysfunction in patients with cardiovascular disease. Int Heart J 2016; 57: 729-35.
7. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, *et al*. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000; 102: 1788-94.
8. Maurer MS, Spevack D, Burkhoff D, Kronzon I. Diastolic dysfunction: can it be diagnosed by Doppler echocardiography? J Am Coll Cardiol 2004; 44: 1543-9.
9. Hiarada K, Orino T, Yasuoka K, Tamura M, Takada G. Tissue Doppler imaging of left and right ventricles in normal children. Tohoku J Exp Med 2000; 191: 21-9.
10. Mori K, Hayabuchi Y, Kuroda Y, Nii M, Manabe T. Left ventricular wall motion velocities in healthy children measured by pulsed wave Doppler tissue echocardiography: normal values and relation to age and heart rate. J Am Soc Echocardiogr 2000; 13: 1002-11.
11. Eidem BW, McMahon CJ, Cohen RR, *et al*. Impact of cardiac growth on Doppler tissue imaging velocities: a study in healthy children. J Am Soc Echocardiogr 2004; 17: 212-21.
12. Choi SH, Eun LY, Kim NK, Jung JW, Choi JY. Myocardial tissue Doppler velocity in child growth. J Cardiovasc Ultrasound 2016; 24: 40-7.
13. Kozák-Bárány A, Jokinen E, Rantonen T, *et al*. Efficiency of left ventricular diastolic function increases in healthy full-term infants during the first months of life; a prospective follow-up study. Early Hum Dev 2000; 57: 49-59.
14. Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RG. Left ventricle fiber architecture in man. Br Heart J 1981; 45: 248-63.
15. Galiuto L, Ignone G, DeMaria AN. Contraction and relaxation velocities of the normal left ventricle using pulsed-wave Doppler echocardiography. Am J Cardiol 1998; 81: 609-14.
16. Oki T, Tabata T, Mishiro Y, *et al*. Pulsed Doppler tissue imaging of left ventricular systolic and diastolic wall motion velocities to evaluate differences between long and short axes in healthy subjects. J Am Soc Echocardiogr 1999; 12: 308-13.
17. Takeda Y, Sakata Y, Higashimori M, *et al*. Noninvasive assessment of wall distensibility with the evaluation of diastolic epicardial movement. J Card Fail 2009; 15: 68-77.
18. Minamisawa M, Miura T, Motoki H, *et al*. Prognostic impact of diastolic wall strain patients at risk for heart failure. Int Heart J 2017; 58: 250-6.
19. Beinlich CJ, Vitkauskas KJ, Morgan HE. Characterization of ventricular myocytes from the newborn pig heart. J Mol Cell Cardiol 1998; 30: 1263-74.
20. Iwashima S, Seguchi M, Ohzeki T. Left ventricular diastolic performance in neonates. Circ J 2005; 69: 1094-8.