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Postnatal Left Ventricular Contractility in Very Low Birth Weight Infants

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Abstract. The objective of the study was to evaluate postnatal changes in left ventricular (LV) contractility in very low birth weight (VLBW) infants. An echocardiographic study comparing 18 VLBW infants without significant complications and 16 normal term infants was carried out at the Neonatal Intensive Care Unit in Akita University Medical Hospital, Japan. The echocardiographic examinations were performed within 6 hours of birth and on day 5. We obtained the relations between rate-corrected mean velocity of circumferential fiber shortening (mVcfc) and end-systolic wall stress (ESS), which were calculated from two-dimensional LV short-axis views to compensate for the distorted LV shape, and we compared these relations statistically. In both VLBW and term infants there were inverse linear correlations between mVcfc and ESS for each study period ($p < 0.05$). The regression line of VLBW infants had a lower *y*-intercept and a steeper slope than that of term infants at 6 hours of age but almost corresponded on day 5. It is concluded that the left ventricle of VLBW infants adapts to postnatal hemodynamic alterations with low contractility but operates with a contractile state similar to that of term infants on day 5.

Key words: Left ventricle — Contractility — Very low birth weight

During the fetal-to-neonatal circulatory transition, the various loading changes may place significant hemodynamic stress on the cardiovascular system of very low birth weight (VLBW) infants. Previous Doppler studies have demonstrated, the postnatal changes in left ventricular (LV) pump function in VLBW infants, such as stroke volume and cardiac output [1, 19, 22], but the changes in the LV contractility of VLBW infants are not fully understood. It is well recognized that the left ventricle of premature lambs has less ability to adjust to loading changes than that of mature lambs and that their LV cardiac output is maintained with a near-maximum level of contractility after birth [3, 4, 11, 15]. We have reported similar findings for human preterm infants, as the left ventricle of VLBW infants has less reserve capacity to increase stroke volume in the face of left-to-right ductus arteriosus shunting after birth than that of mature infants [24].

Despite these studies, however, there is little information about the postnatal changes in LV contractility in VLBW infants, which is one of the main determinants of systolic function. The relation between heart rate-corrected velocity of circumferential fiber shortening (mVcfc) and end-systolic meridional wall stress (ESS), as measured by M-mode echocardiography, is known as a sensitive, relatively load-independent index of LV contractility [9]. Additionally, Berdjis et al. [5] have described a compensatory technique with two-dimensional echocardiography that is applicable to neonates with an irregularly shaped left ventricle. The aim of the present study was to investigate LV contractility during the first few hours of life in VLBW infants using the relation between mVcfc and ESS with this compensatory technique and to assess its clinical implications.

Subjects and Method

Subjects

We studied 18 VLBW and 16 term infants, all appropriate for dates, who were born at the Perinatal Care Center in Akita University Medical Hospital. The mean gestational age at birth was 28 and 39 weeks for the VLBW and term infants, respectively; and the mean birth weights were 1015 and 3150 g, respectively. Term infants were born after a normal pregnancy and delivery and had no history of asphyxia. All VLBW infants were admitted to the Neonatal Intensive Care Unit. They had neither severe asphyxia nor clinical signs of shock at birth. They underwent tracheal intubation soon after birth for pulmonary prematurity or apnea; they were then assisted with a pressure-controlled ventilator. Six VLBW infants had clinical and radiologic signs of respiratory distress syndrome, which were not severe and improved following synthetic surfactant replacement therapy. The patient characteristics of the preterm infants are shown in Table 1.

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Table 1. Patient characteristics

Characteristic	VLBW infants	Term infants
Gender (male/female)	9/9	9/7
Gestational age (weeks)	28 (24–32)	39 (37–40)
Birth weight (g)	1015 (470–1357)	3150 (2694–3788)
Apgar score (1 min/5 min)	6/8	9/9
Postnatal age at examinations (hours at first/second examination)	4/131	3/135
Total water intake (ml/kg/day at first/second examination)	40–50/90–110	0/160–180

Values are expressed as the mean (range). Total water intake is expressed as a range.

Protocol

This study was approved by the ethics committee of Akita University School of Medicine, and informed consent was obtained from the parents of each infant. We performed echocardiographic examinations twice in each infant: within 6 hours after birth and on day 5 of life. Before each examination no signs of systemic or cardiovascular diseases were confirmed on physical examinations; and the gender and postnatal time (hours) and total water intake (ml/kg/day) were recorded. The first examinations were performed before the initial feeding of the term infants. In VLBW infants the first feeding was soon after intravenous fluid therapy with 10% glucose solution (35–45 ml/kg/day) including calcium (1–2 mEq/kg/day) without inotropic agents. At the second examinations the term infants underwent breast or bottle feeding, and the VLBW infants had both nasogastric tube feeding and intravenous fluid injection. These patient characteristics are also summarized in Table 1. The VLBW infants were undergoing mechanical ventilation at both the first and the second examination, and both term and VLBW infants were in a nonsedated resting state during examinations.

Echocardiography

Echocardiographic examinations were performed utilizing M-mode, two-dimensional, pulsed-wave Doppler, and a two-dimensional color Doppler method. An Aloka SSD-870 and SSD-2200 ultrasound imaging system equipped with 5.0 and 7.5 MHz transducers (Aloka, Tokyo, Japan) were used. At the first examination, we confirmed no congenital heart disease and checked the patency of the ductus arteriosus by two-dimensional ultrasonography and a two-dimensional color Doppler technique. If the ductus arteriosus was open, we measured its inner diameter as described elsewhere [14].

M-mode echocardiograms were recorded at a paper speed of 100 mm/s. Phonocardiograms, electrocardiograms (ECGs), and axillary pulse tracings were recorded simultaneously; and the peak systolic and diastolic blood pressures were obtained from a Dinamap 8100 Vital Sign Monitor (Criticon, Tampa, FL, USA). The M-mode measurements included end-systolic posterior wall thickness (h) and heart rate. End-systole was defined as the point corresponding to the first component of the second heart sound.

Using two-dimensional echocardiography, an LV short-axis view was imaged at the tips of the mitral valve leaflets from the parasternal position and recorded on 0.5-inch videocassette tape. Then end-diastolic circumference (Ced) and end-systolic circumference (Ces) were measured with a computed digitizer (Cardio 500; Kontron, Germany). LV ejection time (ET) was derived from the pulse trace and was corrected for heart rate (ETc) by dividing it by the square root of the R-R interval. The mVcfc was then calculated as in the report of Berdjis et al. [5]: $\mathrm{mVcfc} = (\mathrm{Ced} - \mathrm{Ces})/(\mathrm{Ced})(\mathrm{ETc})$.

The ESS was calculated by the method of Grossman et al. [13]. The end-systolic pressure (ESP) was measured by assigning the systolic blood pressure to the peak of the trace and the diastolic pressure to the low point of the trace, with subsequent linear interpolation to the level of the dicrotic notch [6]. We used the value of Ces divided by π (Des) instead of Des (LV end-systolic diameter) in order to minimize errors due to distortion of the LV shape [5]. The ESS was calculated as follows: $\mathrm{ESS} = 0.34(\mathrm{Des})(\mathrm{ESP})/\mathrm{h}[1 + (\mathrm{h}/\mathrm{Des})]$.

All echocardiographic measurements were done by two of the authors (Y.T., K.H.), who were unaware of each patient's status. The subsequent echocardiographic measurements were performed according to recommendations of the American Society of Echocardiography [20, 21]. The averaged data from three to five cardiac cycles were used for analysis.

Interobserver and Intraobserver Variability

Interobserver and intraobserver variability were assessed from measurements of the M-mode and two-dimensional echocardiography over five cardiac cycles in five subjects. The variability was determined as the mean percent error, derived as the absolute difference between two observations divided by the mean of the two observations and expressed as a percentage.

Statistical Analysis

We confirmed the normality of the distribution of each parameter. For comparison of data, the paired *t*-test was used, and $p \leqslant 0.05$ was considered to indicate statistical significance. Simple linear regression analysis was used to determine the significance of the correlation between mVcfc and ESS at each study period, and analysis of covariance was also performed to determine the significance of distribution differences between the two study periods or between mVcfc and term infants.

Table 2. Echocardiographic data and blood pressures

Parameter	VLBW infants		Term infants	
	<6 Hours	Day 5	<6 Hours	Day 5
Heart rate (bpm)	154 ± 11*,**	136 ± 13	124 ± 15	130 ± 14
Ejection time (s)	0.16 ± 0.01*,**	0.17 ± 0.01***	0.21 ± 0.02****	0.19 ± 0.01
Ded (cm)	1.38 ± 0.19**	1.34 ± 0.26***	2.00 ± 0.14	2.00 ± 0.15
Des (cm)	1.09 ± 0.25**	0.99 ± 0.26***	1.48 ± 0.17	1.51 ± 0.16
h (cm)	0.28 ± 0.06**	0.26 ± 0.04***	0.35 ± 0.05	0.37 ± 0.04
mVcfc (circ/s)	0.79 ± 0.15*,**	1.01 ± 0.18	0.89 ± 0.15	0.90 ± 0.17
Blood pressure (mmHg)				
Systolic	45 ± 7**	53 ± 7***	58 ± 7****	71 ± 7
Diastolic	27 ± 6**	32 ± 6***	33 ± 4****	42 ± 5
End-systolic pressure (mmHg)	38.5 ± 6.2**	47.2 ± 5.5***	49.0 ± 8.2****	61.8 ± 7.0
ESS (g/cm^2)	43.2 ± 7.2**	50.4 ± 8.7***	56.7 ± 11.6****	67.8 ± 16.7

The values are expressed as the mean ± 1 SD.
Ded, value of LV end-diastolic circumference divided by π, Des, value of LV end-systolic circumference divided by π: h, end-systolic posterior wall thickness; mVcfc, mean velocity of circumferential fiber shortening; ESS, end-systolic wall stress.
* $p < 0.05$, <6 hours versus day 5 in VLBW infants.
** $p < 0.05$, VLBW infants versus term infants at <6 hours.
*** $p < 0.05$, <6 hours versus day 5 in term infants.
**** $p < 0.05$, VLBW infants versus term ones on day 5.

Results

Echocardiographic Data and Blood Pressures

At the first examinations, the ductus arteriosus was open in all VLBW and term infants with left-to-right dominant shunt, and the mean diameters were 1.6 and 3.1 mm, respectively. Other measurements are summarized in Table 2. In VLBW infants the heart rate was significantly higher at 6 hours of age than on day 5, but there was no such difference in term infants. In VLBW infants the ejection time was significantly shorter at 6 hours than on day 5, probably because of the high heart rate; in contrast, it was significantly longer at 6 hours in term infants. As anticipated, due to the large difference in body size, the calculated end-diastolic and systolic diameters and the posterior wall thickness were significantly larger in term infants than in VLBW infants. In VLBW infants the mVcfc was significantly lower at 6 hours than on day 5, but no such difference was found in term infants. In a comparison between VLBW and term infants, the mVcfc of VLBW infants was significantly lower than that of infants term at 6 hours of age, but there was no difference on day 5. The systolic and diastolic blood pressures, end-systolic pressure, and ESS showed similar changes: they were significantly lower at 6 hours of age than on day 5 in both VLBW and term infants; and those of VLBW infants were significantly lower than those of term infants for each study period.

Relation Between mVcfc and ESS

There were significant inverse and linear relations between mVcfc and ESS for each study period; their regression equations are summarized in Table 3. Six hours after birth the regression line of VLBW infants had a lower *y*-intercept with a steeper slope than that of the term infants (Fig. 1A), but they almost corresponded on day 5 (Fig. 1B). In VLBW infants the regression line at 6 hours of age had a steeper slope than that on day 5 (Fig. 1C); a similar but small change was observed in term infants. (Fig. 1D). Analysis of covariance showed no statistical difference between the examinations.

Interobserver and Intraobserver Variability

Interobserver variabilities were 2.9 ± 1.8% (range 0.3–6.3%) and 4.4 ± 3.0% (range 1.2–8.3%) for M-mode and two-dimensional measurements, respectively. Intraobserver variabilities were 2.8 ± 1.8% (range 0.2–6.1%) and 3.3 ± 1.7% (range 0.2–7.8%), respectively.

Discussion

The present data demonstrate that, despite the fact that the VLBW infants enrolled in this study had no severe complications, such as severe asphyxia or shock, their LV contractility was significantly lower 6 hours after birth than on day 5, whereas no such difference was found in term infants. During the fetal-to-neonatal circulatory transition, the left ventricle of VLBW infants may adapt successfully to the various postnatal hemodynamic alterations with low contractility.

It is well known that there is an inverse and linear correlation between mVcfc and ESS, not only in adults

Table 3. Relation between mVcfc and ESS

Time of measurement	Regression line for mVcfc	*r*
VLBW		
<6 Hours	1.28 - 0.0110 × ESS	0.55
Day 5	1.25 - 0.0053 × ESS	0.47
Term		
<6 Hours	1.30 - 0.0070 × ESS	0.55
Day 5	1.26 - 0.0052 × ESS	0.52

See Table 2 for abbreviations.

but in children and healthy term infants [10, 16, 18]. Studies have shown that a similar relation exists in low birth weight infants at a few weeks of age [17, 23]. In addition to these findings, our data show that an inverse and linear correlation between mVcfc and ESS also exists a few hours after birth in VLBW infants. Furthermore, it was noteworthy that the slope of the regression line in VLBW infants was steeper at 6 hours of age than on day 5 (Fig. 1C). Kimball et al. [18] demonstrated the age dependency of this relation, as younger infants have a steeper slope and a higher *y*-intercept of the regression line; they suggested that LV pump function may be highly dependent on afterload in young infants. Similarly, Igarashi et al. [16, 17] compared these relations in low birth weight and term infants at a few weeks of age and revealed that the slope of the regression line was steeper in low birth weight infants than in those born at term. To our knowledge, there is little information about LV contractility in VLBW infants and their response to afterload, especially a few hours after birth. In the present study, the steeper slope of the regression line at 6 hours (Fig. 1C) suggested that the left ventricle in VLBW infants was more sensitive to an increase in afterload a few hours after birth than on day 5. In animal studies Baylen et al. [2] found that the left ventricle of preterm lambs has the ability to handle increasing afterload immediately after birth, but our clinical data suggest that the LV contractility of VLBW infants may deteriorate easily in the face of an acute and inappropriate increase in afterload a few hours after birth.

Previous echocardiographic studies of mVcfc and ESS have demonstrated the characteristic LV contractile state in low birth weight infants, as their left ventricle is operated by enhanced contractility under low afterload condition [17, 23]. These studies were performed at a few weeks of age, however, and it is a matter of controversy whether such a characteristic contractile state exists when the infant is only a few hours old. In the present study, despite a significantly lower ESS value in VLBW infants at 6 hours of age compared with that on day 5, the value of mVcfc at 6 hours was not high but significantly low (Table 2), which does not represent the characteristic contractile state of ''high contractility under low afterload'' previously shown in infants a few weeks after birth. This difference was also clearly shown in the relation between mVcfc and ESS: the regression line at 6 hours had a lower intercept and a steeper slope than that on day 5 (Fig. 1C). Therefore it is likely that the left ventricle of VLBW infants may be operated by a different contractile state a few hours after birth compared with that on day 5. In this study, it remained unclear why LV contractility was significantly low only in VLBW infants soon after birth. Studies on premature lambs have demonstrated that their left ventricle has a reduced ability to respond to increased preload and afterload because of the immaturity of the myocardium [3, 4, 11, 15]. We therefore can only speculate that, during the fetal-to-neonatal circulatory transition various hemodynamic stresses on premature myocardium may contribute to the low LV contractility of VLBW infants during the first few hours after birth.

In the previous study, using two-dimensional echocardiography and the biplanar Simpson's rule method, we measured the LV volume and ejection fraction of VLBW and term infants during patency of the ductus arteriosus after birth; that study showed that the ejection fraction was significantly lower in VLBW infants than in term infants [24]. However, the reason for and the background of this difference remained unclear in that study, because the ejection fraction is dependent on contractility and loading conditions. As the relation between mVcfc and ESS utilized in this study is known as a relatively load-independent index of contractility [9], we consider that the low LV contractility of VLBW infants a few hours after birth that was observed in this study may be one of the reasons for the low ejection fraction found in the previous study.

It was interesting that the relation between mVcfc and ESS in VLBW infants was almost equal to that of term infants on day 5 (Fig. 1B). Although many studies have evaluated the contractile state of the premature left ventricle during the transitional circulation [3, 4, 8], there is little information about it just after the transition, which is clinically important in VLBW infants. In the present study, there was no apparent difference in the relation of mVcfc and ESS in VLBW and term infants on day 5, which indicated that VLBW infants may be capable of maintaining sufficient LV contractility within a few days after birth if they have no significant hemodynamic stress.

In conclusion, we observed the successful adaptation of the left ventricle in VLBW infants to the various postnatal hemodynamic alterations. It should be noted, however, that this successful LV adaptation was supported by low and unstable contractility during the first few hours of life. Therefore we speculate that if VLBW infants have any complications, such as perinatal asphyxia or shock, they may be at risk for diminished contractility as noted in previous reports [7, 12]. Addi-

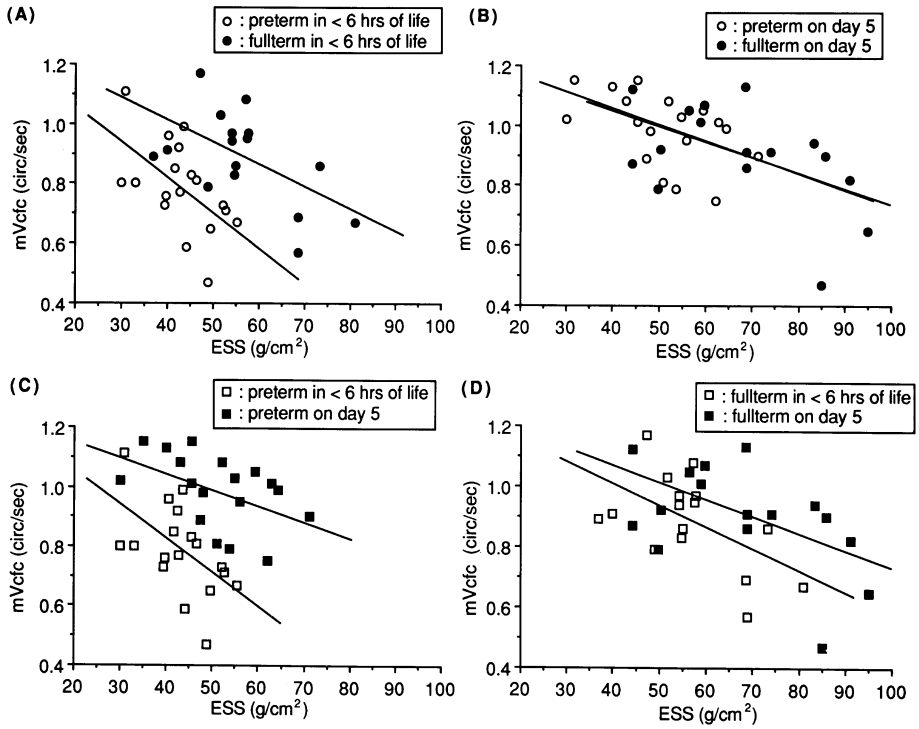

Fig. 1. Relation between mVcfc and ESS. **(A)** VLBW infants versus term infants at <6 hours of age. **(B)** VLBW infants versus term infants on day 5. **(C)** VLBW infants: <6 hours of age versus day 5. **(D)** Term infants: <6 hours of age versus day 5.

tional studies may be necessary to establish if any cardiotonic agent can improve LV contractility of such VLBW infants during the first few hours of life. Several potential limitations on measurements, such as the influences of mechanical ventilation and synthetic surfactant replacement therapy, need to be considered, but we believe this study provides important information relevant to postnatal clinical care in VLBW infants.

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Radical Modes of Therapy!

In a 125 page book titled *Congenital Cardiac Disease* [1], printed in 1915, Maude E. Abbot explores various congenital heart diseases accompanied by pathological illustrations of some cardiac defects. Treatment of congenital heart diseases was presented in a little over one page, the essence of such therapy was outlined in the following paragraph:

> "A carefully regulated life, a plentiful supply of light, fresh air, and warmth, the maintenance of an equal body temperature, the avoidance of mental agitation and of undue physical exertion, rest and quiet forms of exercise, where this last is permitted by the condition of the patient, are all essential"

Surgical repair of cardiac diseases was not performed in the early years of this century; however, it was a concept in its infancy. Dr. Abbot addresses this issue in the previously mentioned reference [1]:

> "Operative interference in patent ductus areteriosus in the form of ligation of the duct, was suggested by Murro (Ann. Surg. 1907 xlvi, 335) on the ground that a probable diagnosis is now possible and that the vessel lies in an accessible structure. The fact that distinctive signs occur only after pulmonary dilation has taken place and a certain adjustment of the vessel to the new order of the circulation has set in, would make one hesitate to resort to so radical a measure, which might introduce a new faction of disturbance".

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