Left ventricular preload reserve in preterm infants with patent ductus arteriosus

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Abstract

The left ventricular Frank-Starling response was studied in 15 preterm infants, less than 1500 g birth weight, and in 16 fullterm infants with patent ductus arteriosus. Left ventricular end diastolic volume (LVEDV), stroke volume, and cardiac output were calculated from biplane echocardiographic images with a modified Simpson's rule, and the left ventricular function curve was obtained by standardising with birth weight and body length. In the relationship between LVEDV and stroke volume, the slope of the regression line was significantly milder in preterm than in fullterm infants; however, there was no significant difference in the relationship between LVEDV and cardiac output. The heart rate was significantly higher in preterm than in fullterm infants. Our data indicated that the premature infants had less left ventricular reserve capacity to respond to the increased preload through the left-to-right ductal shunting than the mature ones, and that the high pulse rate made it possible to generate adequate cardiac output in premature infants.

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During the transitional change from fetal to neonatal circulation, the presence of a patent ductus arteriosus (PDA) and a left-to-right ductal shunting adversely affects the cardiopulmonary status of preterm infants as an increase of preload for the left ventricle.^{1,2} Animal research on lambs has shown that the premature lamb has less preload reserve capacity in the left ventricle to respond to volume loading than the mature lamb,³⁻⁶ but this fact has not been fully investigated in human premature neonates. Using echocardiographic techniques, we have studied the Frank-Starling relationship of the left ventricle in preterm (<1500 g birth weight) and full-

term infants with PDA. The purpose of this study was to compare the left ventricular preload reserve capacity of premature infants with that of mature ones, and to investigate the mechanism of cardiovascular adaptation in premature infants with PDA.

Subjects and methods

SUBJECTS

We studied 16 fullterm and 15 preterm infants. The patient characteristics are summarised in table 1. The mean gestational age at birth was 39 weeks in fullterm infants and 29 weeks in preterm infants. The mean birth weight was 3107 g in fullterm infants and 1093 g in preterm infants, and the mean body length was 49.6 and 35.9 cm, respectively. All fullterm infants had a history of normal pregnancy and delivery, and had no symptoms of systemic or cardiovascular diseases on physical examination. All preterm infants were admitted to the neonatal intensive care unit in Akita University Medical Hospital. They had no severe asphyxia (mean Apgar score: 6 at one minute, 8 at five minutes after birth) and clinical signs of shock at birth, and underwent intubation and ventilation with a pressure controlled ventilator. Three preterm infants had clinical signs of respiratory distress syndrome, but improved on synthetic surfactant replacement treatment.

Informed consent was obtained from the parents of each neonate.

PROTOCOL

We performed echocardiographic examinations within six hours after birth: mean time was 3.6 hours in fullterm infants and 3.8 hours in preterm infants. During the examinations, all fullterm infants were in a non-sedated resting state, and the preterm infants were having treatment with intravenous fluid 35-45 ml/kg/day of 10% glucose solution that included 20-40 mg/kg/day of calcium without inotropic agents. To assess whether systemic resistance is constant at the echocardiographic examinations, we measured steady peripheral skin temperature and blood pressure in both fullterm and preterm infants, and additionally the arterial or venous blood pH in preterm infants (table 1). The peripheral skin temperature did not differ significantly between fullterm and preterm infants, but both the systolic and diastolic blood pressures, obtained from a Dinamap 8100 Vital Sign Monitor, were lower in preterm infants than in fullterm ones ($p < 0.05$). The blood samples were obtained from umbilical artery or vein in

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Table 1 Patient characteristics at the echocardiographic examinations; values are mean (range)

	Preterm infants (n=15)	fullterm infants (n=16)
Gestational age (weeks)	29 (24-32)	39 (37-41)
Birth weight (g)	1093 (732-1496)	3107 (2694-3742)
Body length (cm)	35.9 (32.0-40.0)	49.6 (48.0-51.0)
Peripheral skin temperature (°C)	37.0 (36.4-37.7)	36.9 (36.8-37.4)
Blood pressure (mm Hg)		
Systolic*	46 (35-58)	59 (45-74)
Diastolic*	26 (18-36)	34 (26-41)
Blood pH		
Artery (n=8)	7.463 (7.368-7.532)	Not measured
Vein (n=7)	7.377 (7.304-7.512)	Not measured

* $p < 0.05$ compared preterm with fullterm infants by unpaired t test.

(A) Relationship between the LVEDV/BW and the stroke volume/BW in the preterm and fullterm infants with PDA; (B) that between the LVEDV/BL and the stroke volume/BL; (C) that between the LVEDV/BW and the cardiac output/BW; and (D) that between the LVEDV/BL and the cardiac output/BL.

preterm infants, and blood pH was measured using an AVL947 blood gas analyser. The mean values of arterial or venous blood pH were 7.463 and 7.377, respectively, and they did not apparently differ from those of fullterm infants described previously.⁷

ECHOCARDIOGRAPHY

We performed echocardiographic examinations by two dimensional pulsed Doppler and two dimensional colour Doppler. An Aloka SSD-870 ultrasound imaging system equipped with a 5.0 MHz pencil type transducer was used. Initially, we confirmed the absence of congenital heart disease and the patency of the ductus arteriosus with the left-to-right high velocity jet stream by these two methods. All the subsequent echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography,⁸ and the averaged data from 3–5 cardiac cycles were used for analysis.

The standard apical two and four chamber views were used for analysis of left ventricular volume. Using an off-line computed digitiser (Cardio 500, Kontron Medical System), we calculated left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV) by a modified Simpson's rule method; in addition, heart rates were obtained simultaneously. To compare the values of preterm infants with those of fullterm ones, the

LVEDV and LVESV measurements were divided by birth weight (BW) and body length (BL) in each infant. Then the following variables were obtained: (1) LVEDV/BW (ml/kg); (2) LVEDV/BL (ml/cm); (3) stroke volume/BW (ml/kg) = $[\text{LVEDV} - \text{LVESV}] / \text{BW}$; (4) stroke volume/BL (ml/cm) = $[\text{LVEDV} - \text{LVESV}] / \text{BL}$; (5) cardiac output/BW (ml/min/kg) = $\text{heart rate} \times [\text{LVEDV} - \text{LVESV}] / \text{BW}$; (6) cardiac output/BL (ml/min/cm) = $\text{heart rate} \times [\text{LVEDV} - \text{LVESV}] / \text{BL}$; (7) ejection fraction = $\text{LVEDV} - \text{LVESV} / \text{LVEDV}$. Finally, we obtained the relationships between LVEDV and stroke volume and that between LVEDV and cardiac output, which were standardised with birth weight and body length.

INTEROBSERVER AND INTRA-OBSERVER VARIABILITY

Interobserver and intraobserver variability were assessed for the left ventricular volume calculations over five cardiac cycles in five randomly selected subjects. The variability was determined as a mean per cent error, derived as the absolute difference between two observations divided by the mean of the two observations and expressed in per cent.

STATISTICAL ANALYSIS

The normality of the distribution of each parameter was initially confirmed. To standardise the measurements with birth weight

and body length, we confirmed the close relationship between birth weight and LVEDV, stroke volume, and cardiac output, as well as that between body length and those parameters, in both fullterm and preterm infants. A simple linear regression analysis was used to determine the significance of the correlation between LVEDV and stroke volume, and that between LVEDV and cardiac output. An analysis of covariance was used to determine the significance of the distribution difference between preterm and fullterm infants. For comparison of data, the unpaired *t* test was used, and $p \leq 0.05$ was considered to indicate statistical significance. All values were expressed as the mean (SD).

Results

ECHOCARDIOGRAPHIC DATA AND CHANGE OF HEART RATE
The findings are summarised in table 2. The LVEDV, stroke volume, and cardiac output were significantly lower in preterm infants as expected. The ejection fraction was also significantly lower in preterm infants than in fullterm ones; however, the heart rate was significantly higher in preterm infants.

RELATIONSHIP BETWEEN LVEDV AND STROKE VOLUME AND BETWEEN LVEDV AND CARDIAC OUTPUT
The relationships are shown in the figure. There was a linear correlation between the LVEDV/BW and the stroke volume/BW in both preterm and fullterm infants (figure A); preterm infants: (stroke volume/BW)=0.35 (LVEDV/BW)+0.12, $r=0.87$, $p<0.001$; fullterm infants: (stroke volume/BW)=0.67 (LVEDV/BW)-0.11, $r=0.88$, $p<0.001$. Similarly, there was a linear correlation between the LVEDV/BL and the stroke volume/BL (figure B); preterm infants: (stroke volume/BL)=0.42(LVEDV/BL)+0.01, $r=0.91$, $p<0.001$; fullterm infants: (stroke volume/BL)=0.72 (LVEDV/BL)-0.01, $r=0.94$, $p<0.001$. In comparison between preterm and fullterm infants, the distribution of values was significantly different in both relationships by analysis of covariance; in addition, the slope of the regression line was significantly milder in preterm infants than in fullterm ones.

There was also a linear correlation between the LVEDV/BW and the cardiac output/BW in both preterm and fullterm infants (figure C); preterm infants: (cardiac output/BW)=47.0 (LVEDV/BW)+26.2, $r=0.81$, $p<0.001$; full-

term infants: (cardiac output/BW)=82.4 (LVEDV/BW)-12.6, $r=0.76$, $p<0.001$, as well as the relationship between the LVEDV/BL and the cardiac output/BL (figure D); preterm infants: (cardiac output/BL)=0.42 (LVEDV/BL)+0.01, $r=0.91$, $p<0.001$; fullterm infants: (cardiac output/BL)=0.72 (LVEDV/BL)-0.01, $r=0.94$, $p<0.001$. In comparison between preterm and fullterm infants, in contrast to the relationship between the LVEDV and the stroke volume, there was no significant difference in the distribution and the slope of the regression line.

INTEROBSERVER AND INTRAOBSERVER VARIABILITY
The coefficient of variation for interobserver and intraobserver variability for the left ventricular volume calculations was 0.3-7.6% and 0.2-6.1%, respectively.

Discussion
The present study showed that premature infants had less reserve capacity in the left ventricle to respond to the increased preload through the left-to-right ductus arteriosus shunting than the mature ones; however, the increased heart rate in the premature infants compensated for their low left ventricular stroke volume and made it possible to generate the adequate left ventricular output.

The previous Doppler echocardiographic studies well demonstrated the left-to-right ductus arteriosus shunting and its effect as an increase of left ventricular preload.^{9 10} As the index of this increased preload, we divided LVEDV by both birth weight and body length instead of body surface area usually used in older children, because it is difficult to measure accurately the body surface area of premature infants, especially those less than 1500 g at birth. A previous investigator divided the volumetric measurements of preterm infants by birth weight for adjustment,⁹ while another described that adjustment only with body weight may be misleading.¹¹ Thus we divided LVEDV and other measurements not only by birth weight but also by body length to confirm the conclusion. In the present study we calculated LVEDV by the biplane Simpson's rule geometric method, because it is more accurate to estimate neonatal left ventricular volume with distortion due to the relatively high right ventricular pressure after birth^{12 13} than an area/length or M mode determined volume calculation method. As far as we know, there are few reports estimating LVEDV in human premature and mature neonates by a biplane echocardiographic images with a modified Simpson's rule.

In the relationship between the LVEDV and the stroke volume, the slope of the regression line was significantly milder in preterm than in fullterm infants (figure A, B), and the left ventricular ejection fraction was also significantly lower in preterm than in fullterm infants. These findings, indicating that premature infants had less capacity to generate adequate

Table 2 Echocardiographic results and the change of heart rate; values are mean (SD)

	Preterm infants (n=15)	Fullterm infants (n=16)
LVEDV (ml)	1.40 (0.36)*	3.79 (0.65)
Stroke volume (ml)	0.62 (0.17)*	2.22 (0.50)
Cardiac output (ml/min)	94.7 (24.4)*	274.1 (64.3)
Ejection fraction	0.45 (0.05)*	0.58 (0.05)
Heart rate (/min)	152 (11)*	123 (14)

* $p<0.001$.

left ventricular stroke volume in proportion to the quantity of the left-to-right ductal shunting than the mature infants, were consistent with the previous reports of the Frank-Starling relationships on fetal and neonatal lambs.¹⁴⁻¹⁶ We could not observe the 'plateau limb' of the Frank-Starling curve as reported in animal research.¹⁴⁻¹⁶ This may be because of the difference between the artificial and natural volume loading. In contrast to the relationship between LVEDV and stroke volume, there was no significant difference between preterm and fullterm infants in the relationship between LVEDV and cardiac output, indicating that the high pulse rate compensated for the low left ventricular stroke volume in the premature infants.

It is necessary to assess the afterload, in addition to the preload, to investigate left ventricular contractile state in preterm and fullterm infants. We have measured the steady peripheral skin temperature, blood pH, and blood pressure, which mainly influence systemic resistance. There seemed to be no apparent difference in the steady peripheral skin temperature and blood pH between preterm and fullterm infants, however, the blood pressure in the preterm infants was significantly lower than that in the fullterm ones. In animal research on preterm lambs Clyman *et al* hypothesised that the reduced left ventricular afterload plays an important part to increase its stroke volume when challenged with PDA.⁶ In the present study the preterm infants with PDA showed less capacity to generate stroke volume even under the lower blood pressure.

We have confirmed that a high pulse rate is necessary for the cardiovascular adaptation in premature infants with PDA, and that a careless use of plasma volume expander or bradycardia may result in the failure of maintaining adequate left ventricular output in the premature infants. This study has

hopefully provided useful basic data concerning the left ventricular contractile state in premature and mature infants with PDA.

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