Changes in Left Ventricular Diastolic Filling Patterns before and after the Closure of the Ductus Arteriosus in Very-Low-Birth Weight Infants

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Tamura, M., Harada, K., Takahashi, Y., Ito, T., Toyono, M., Ishida, A. and Takada, G. Changes in Left Ventricular Diastolic Filling Patterns before and after the Closure of the Ductus Arteriosus in Very-Low-Birth Weight Infants. Tohoku J. Exp. Med., 1997, 182 (4), 337-346 — To evaluate serial changes in left ventricular diastolic filling patterns in preterm infants, we performed echocardiographic examinations in 18 very-low-birth weight infants and 20 fullterm infants before and after the closure of the ductus arteriosus. In the fullterm infants, the ductal closure induced significant decreases in the peak velocity and flow velocity integral of early diastole, first third filling fraction, and mitral stroke volume. In the preterm infants, by contrast, there were significant increases in the flow velocity integral of early diastole, first third filling fraction, and mitral stroke volume after the ductal closure. No differences following the ductal closure were found in the atrial phase of filling and peak filling rate normalized to stroke volume in either group. When the ductus arteriosus was open, essentially the same left-to-right shunting of the ductus arteriosus was detected in both preterm and fullterm infants, but the Doppler flow patterns of the patent foramen ovale were different: the fullterm infants had a single flow peak mainly during ventricular late systole and early diastole, but the preterm infants had two or three flow peaks with nearly equal amplitudes lasting from ventricular systole to diastole, which resembled the Doppler flow pattern of atrial septal defect. Only a faint Doppler flow signal of the foramen ovale was observed after the ductus arteriosus closed. Our results obtained from the preterms suggest that the left-to-right shunt through the foramen ovale may be one important factor to alter the Doppler transmitral filling patterns during the fetal to neonatal cardiovascular changes. —— ductus arteriosus; preterm infants; Doppler echocardiography; diastolic function © 1997 Tohoku University Medical Press

The transmitral flow velocity patterns by assessing pulsed Doppler echocardiography has been used to evaluate left ventricular diastolic function in many

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patients with cardiac diseases (Demaria et al. 1991; Thomas and Weyman 1991), neonates (Grenaidier et al. 1984; Wilson et al. 1987; Riggs et al. 1989; Harada et al. 1994), and preterm infants (Johnson et al. 1988; Harada et al. 1995a, b, 1996 a, b). Alterations in diastolic performance are well known to occur without impairment of the left ventricular systolic performance (Demaria et al. 1991; Thomas and Weyman 1991). Thus, evaluation of the left ventricular diastolic filling is believed to be important to detect early cardiac dysfunction. Since premature infants are at increased risk of asphyxia, hypoxia, and the left ventricular volume load due to the left-to-right shunt volume through ductus arteriosus after birth (Kitterman et al. 1972; Johnson et al. 1983; Takahashi et al. 1994), the accurate assessment of the left ventricular diastolic function is becoming increasingly important in the management during early neonatal life. However, in normal newborn, diastolic indexes of the left ventricle during early neonatal period can reflect not only the diastolic properties, but also several factors including the left-to-right shunt volume through the ductus arteriosus as reported previously (Wilson et al. 1978; Riggs et al. 1989; Harada et al. 1994). The transmitral flow velocity patterns in preterm infants would be expected to be affected by changes in the circulation during early neonatal period. There is, however, no report on the effects of the ductus arteriosus on the transmitral flow velocity patterns in premature infants. Therefore, we examined the transmitral flow velocity patterns before and after the spontaneous closure of patent ductus arteriosus. The purpose of our study was to demonstrate changes in the left ventricular diastolic filling patterns in preterm infants, and to compare some parameters of the preterm with those of fullterm infants.

Methods

Study subjects

We studied 18 very-low-birth weight infants and 20 fullterm infants. The very-low-birth weight infants was defined as birth weight <1500 g. The gestational age at birth ranged from 24 to 32 weeks (mean: 29 weeks) in the preterm, and 37 to 41 weeks (mean: 39 weeks) in the fullterm infants, and the birth weight ranged from 727 to 1403 g (mean: 1119 g), and 2636 to 3934 g (mean: 3149 g), respectively. All the preterm infants were admitted to the Neonatal Intensive Care Unit in the Akita University Medical Hospital. They had neither severe asphyxia (mean Apgar score = 7 at 1 minute, 9 at 5 minutes after birth) nor any clinical signs of shock at birth. None and underwent mechanical ventilation for apnea of prematurity. Although three preterm infants had clinical signs of respiratory distress syndrome, they were improved by synthetic surfactant replacement therapy. Ventilator settings were adjusted to keep transcutaneous blood gases or pulse oximetry within the range of 35–45 torr (Pco2) and 90–98% (O2 saturation). Each one of the fullterm infants had a history of normal pregnancy and delivery, and had no congenital malformation. Informed consent was
obtained from each of the infant’s parents.

Protocol

We serially performed echocardiographic examinations in each case. The initial echocardiogram was obtained when the ductus arteriosus was clearly open, and the second one was obtained after the spontaneous closure of the ductus arteriosus, which was considered to be closed when both the color image and shunt flow were no longer detected. The initial examinations were performed at the mean of 3.8 hours (1–6 hours) after birth in the preterm and 2 hours in the fullterm infants, and those of the second one were taken at 5 days after birth in the both groups. During the examinations, all infants were in a non-sedated resting state. All the preterm infants were under intravenous fluid therapy with 30–50 ml/kg/day of 10% glucose solution including 1–2 mEq/kg/day of calcium and without inotropie agents on the initial examination, and were under 80–100 ml/kg/day water intake by intravenous infusion and tube feeding on the second examination.

Examination technique

Two-dimensional and pulsed Doppler echocardiographic examinations were performed using an Aloka SSD 2200 ultrasonoscope with a 7.5 MHz transducer (Aloka, Tokyo). Initially, two-dimensional color Doppler, and pulsed Doppler echocardiograms were recorded to rule out congenital heart diseases. The patency of the ductus arteriosus was confirmed by the standard parasternal short-axis and suprasternal views. Interatrial shunt was evaluated by the standard subcostal and apical four-chamber views. To record the transmitral flow velocity profile, a standard apical two-chamber view was visualized and the Doppler sample volume was placed at the tip of the mitral valve leaflets within the left ventricular cavity. Minor adjustments in the sample volume position were made to obtain the maximal velocity profile in each subject. No angle corrections were made because the Doppler beam was almost parallel to the presumed flow. All examinations in the fullterm infants were recorded together with their electrocardiogram and respiration curve at a paper speed of 100 mm/sec, and those in the preterm with only the electrocardiogram, since it was too difficult to record their respiration curves. For the analyses of the examinations, we used and averaged five beats of the expiratory phase in the fullterm infants, and ten serial beats irrelevant to respiration in the preterm infants.

Using an off-line computed digitizer (Cardio 500; Kontron Medical System, Echung, Germany), the following Doppler flow indexes were measured from the transmitral flow tracings: the total diastolic flow velocity integral, the flow velocity integral of early diastolic filling and atrial contraction, the flow velocity time integral during the first third of the diastole, the peak velocities of the E wave (peak E wave) and the A wave (peak A wave). The flow velocity integrals of early diastole and atrial contraction were calculated by dropping a vertical line
to the baseline from the intersection of the early and late diastolic waves. Then
the following values were obtained: the ratio of the flow velocity integral of early
diastole to atrial contraction (flow velocity integral of E/A wave), and the ratio
of the peak E wave to peak A wave (peak E/A wave), the ratio of the flow
velocity time integral during the first third of the diastole to the total flow
velocity time (first third filling fraction), peak filling rate normalized to stroke
volume, as peak E wave divided by the total flow velocity time integral during
diastole. The transmitral flow volume was calculated as the product of the total
flow velocity time integral and cross-sectional area of the mitral valve.

The determinations of interobserver and intraobserver variabilities of the
Doppler echocardiographic measurements were described in our previous report
(Harada et al. 1994).

Statistical analysis

All data are expressed as the mean ± s.d. Within-group comparisons (the

![Doppler echocardiograms](image)

Fig. 1. Doppler echocardiograms obtained before and after the closure of the
ductus arteriosus from the preterm and fullterm infants. Notice that the
serial changes in the left ventricular diastolic filling patterns are quite
different between the two groups. Before, before ductal closure; After, after
the ductal closure; EFVI, flow velocity time integral of E wave; AFVI, flow
velocity time integral of A wave.
indexes of serial changes both in the preterm and fullterm infants) were made by Student's paired two-tailed $t$-test. Values of $p$ less than 0.05 were considered statistically significant.

**Results**

*Left ventricular diastolic filling patterns*

Doppler echocardiograms obtained before and after the closure of the ductus arteriosus from the preterm and full term infants were shown in Fig. 1. The results are summarized in Table 1. In the fullterm infants, the ductal closure induced significant decreases in the total flow velocity time integral, flow velocity time integral of early diastole, and first third filling fraction without significant change in the flow velocity time integral during atrial contraction, causing a significant decrease in the flow velocity time integral of E/A wave. There was a significant decrease in the peak E wave after the closure, but no significant changes in the peak A wave, peak E/A wave, or peak filling rate normalized to stroke volume were observed. Heart rate did not show any significant difference between the two observations. The mitral stroke volume decreased significantly after the ductal closure.

In the preterm infants, by contrast, there were significant increases in the total flow velocity time integral during diastole, flow velocity time integral of early diastole, and first third filling fraction without a significant change in the

| Table 1. Changes of the left ventricular filling in the preterm and fullterm infants |
|-----------------------------------|------------------|------------------|------------------|------------------|
|                                  | Preterm          | Fullterm         |
|                                  | PDA (+)          | PDA (-)          | PDA (+)          | PDA (-)          |
| Heart rate (beats/min)           | 147±13*          | 136±11           | 125±10           | 124±11           |
| Total flow velocity time integral during diastole (cm) | 3.87±1.02*       | 4.85±1.11        | 8.02±1.10        | 6.91±1.21        |
| Flow velocity time integral of early diastole (cm) | 1.81±0.76*       | 2.62±0.74        | 4.97±0.87†       | 4.05±0.93        |
| Flow velocity time integral during atrial contraction (cm) | 2.06±0.46        | 2.23±0.50        | 3.04±0.58        | 2.86±0.49        |
| Flow velocity time integral of E/A wave | 0.90±0.36*       | 1.19±0.28        | 1.70±0.42†       | 1.45±0.36        |
| First third filling fraction      | 0.31±0.09*       | 0.40±0.10        | 0.41±0.07†       | 0.50±0.08        |
| Peak filling rate normalized to stroke volume (/sec) | 7.54±1.56        | 6.94±1.13        | 7.62±1.19        | 7.41±0.86        |
| Peak velocity of E wave (cm/sec) | 29.3±10.6        | 33.6±9.2         | 60.9±9.3†        | 50.5±6.2         |
| Peak velocity of A wave (cm/sec) | 34.2±10.4        | 34.9±7.1         | 46.2±5.3         | 43.2±6.3         |
| Peak velocity of E/A wave        | 0.86±0.17        | 0.96±0.17        | 1.28±0.26†       | 1.18±0.15        |
| Mitral stroke volume (ml)        | 1.61±0.03*       | 2.22±0.04        | 6.40±0.05†       | 5.03±0.04        |

*p < 0.05, preterm with PDA vs. without PDA; †p < 0.05, fullterm with PDA vs. without PDA.*

PDA, patent ductus arteriosus.
flow velocity time integral during atrial contraction after the ductal closure, causing a significant increase in the flow velocity time integral of E/A wave. The peak E/A wave also showed a significant increase after the ductal closure, but there was no significant change in the peak E wave nor peak A wave. Heart rate increased significantly before the ductal closure. The peak filling rate normalized to stroke volume did not change between before and after the ductal closure. The mitral stroke volume in the pre-ductal closure showed a significant reduction compared with that after the ductal closure.

Ductus arteriosus and foramen ovale

In this study, we evaluated qualitatively, but not quantitatively, the blood flows through the ductus arteriosus and foramen ovale (Fig. 2). At the initial examination, the Doppler flow signal patterns of the ductus arteriosus demonstrated a predominant left-to-right shunting in all infants, which were bidirectional in the majority of the infants and continuous in the others. These Doppler wave-

Fig. 2. The Doppler flow patterns of the ductus arteriosus (PDA) and foramen ovale (PFO) from the preterm and fullterm infants with the ductus arteriosus. The Doppler flow patterns of the ductus arteriosus are essentially the same between the two groups. On the other hand, those of the patent foramen ovale are different between the two. It seems that the waveform of the patent foramen ovale in the preterm infants is similar to that of atrial sepal defect.
forms were essentially the same in the preterm and fullterm infants. On the other hand, the Doppler flow signal patterns of the foramen ovale were different between the two groups. All the fullterm infants had a single flow peak mainly during the ventricular late systole and ending in the early diastole, which was similar to the pattern reported by Shiraishi et al. (1987). In the preterm infants, two or three positive flow peaks with nearly equal amplitude lasting from ventricular systole to diastole were detected in all cases, indicating a relatively large left-to-right shunt through the foramen ovale. Only a faint Doppler flow signal of the foramen ovale was observed at the second examination.

**Discussion**

The transmirtal flow velocity patterns during the transition from the fetal to neonatal circulation are known to be affected by several factors including the left-to-right shunt volume through the ductus arteriosus (Harada et al. 1994). However, previous studies have not evaluated the influence of the patent ductus arteriosus on the transmirtal Doppler flow patterns in preterm infants. To our knowledge, this is the first Doppler echocardiographic examination demonstrating serial changes in very-low-birth weight infants before and after the closure of the ductus arteriosus.

Our present study in the fullterm infants showed that the total flow velocity time integral during diastole, flow velocity time integral of early diastole, and the first third filling fraction were significantly higher under the open ductus arteriosus, which was related to the increase in the left ventricular volume due to the left-to-right shunt through the ductus arteriosus as reported previously (Harada et al. 1994). In contrast to the fullterm infants, these filling indexes in the premature infants with the ductus arteriosus were significantly lower than those after the ductal closure. No differences following ductal closure were found in the atrial phase of filling in either group. The Doppler filling patterns found in the premature infants with the ductus arteriosus suggest a significant shift of the filling to the end of diastole related to the atrial contraction. In the premature infants with the ductus arteriosus, the lower values for the flow velocity time integral of early diastole, first third filling fraction, and the E/A wave without any changes in the A wave may be a consequence of the reduced left ventricular early diastolic relaxation and normal left ventricular filling pressure (Demaria et al. 1991; Thomas and Weyman 1991). However, the peak filling rate normalized to stroke volume, which was reported to be independent of loading conditions (Bowman et al. 1988), showed no significant difference between before and after the ductal closure. Thus, the alteration in the Doppler filling patterns in the premature infants with the ductus arteriosus would not be necessarily due to a lack of myocardial compliance.

The reasons for the decreased early diastolic filling patterns in the premature infants with the ductus arteriosus are unclear. Possible explanations can be
proposed to explain the Doppler filling abnormalities in the premature infants with the ductus arteriosus. First, left ventricular systolic function in the premature infants with the ductus arteriosus might be reduced compared with those after the ductal closure. Although we did not evaluate the left ventricular systolic function in this study, our recent study demonstrated that the left ventricular contractility in premature infants with the ductus arteriosus (within 6 hours of life) showed no significant differences from that after ductal closure (day 5) (Takahashi et al. 1995). Therefore, it appears unlikely that depressed left ventricular systolic function played a role altering the Doppler filling patterns in our premature infants. Second, in this study, the heart rate was significantly higher in the preterm infants with the ductus arteriosus than that with the ductal closure. In the normal fullterm infants without the ductus arteriosus, the increased heart rate caused a significant reduction in the flow velocity time integral of E wave, the first third filling fraction, and the total flow velocity time integral (Harada et al. 1995b), which may be related with the decrease in the mitral stroke volume as seen in our present study. Thus, the altered early diastolic filling patterns in the premature infants with the ductus arteriosus may be due to the changes in the heart rate. Finally, in our present study, the Doppler flow signal patterns through the foramen ovale were different between in the premature and fullterm infants as reported previously (Evans and Lyer 1994); the waveform in the preterm infants was similar to that in a previously reported Doppler echocardiographic study of atrial septal defect (Minagoe et al. 1985). Size of the functional foramen ovale in relation to the inferior vena cava was reported to decrease from 54% in a group of preterm babies to 39% at term (Patten et al. 1929). At term the foramen ovale is structurally and functionally ready for the postnatal need to separate the pulmonary and systemic circulation (Hannu et al. 1989). These observations reported previously may support the Doppler findings in this study. Mori et al. (1989) referred to left ventricular diastolic filling patterns in the children with atrial septal defect and demonstrated a tendency of the peak E to decrease and a significant decrease in the peak E/A wave. On the basis of their observation, in our premature infants, a large left-to-right shunt at atrial level may leads to the decreased mitral stroke volume even if widely patent ductus arteriosus was present as seen in this study. Therefore, continuity of these hemodynamics in the premature infants may cause respiratory failure due to pulmonary overcirculation. In the present study, the increased heart rate in the premature infants with ductus arteriosus may be one factor compensating for the low mitral stroke volume and to maintain adequate cardiac output, implying that bradycardia must be avoided.

Study limitation

Many factors must be considered in evaluating Doppler-derived data. By necessity, all the preterm infants were receiving positive pressure ventilation
during the study. Appleton et al. (1987) showed that there were no differences in the diastolic variables between the groups of preterm infants with and without ventilatory support. Therefore, we believe that the results of this study reflected the difference between the preterm and fullterm infants. This study is lack of any quantitative assessment of shunt volume through the ductus arteriosus and foramen ovale or of pulmonary venous flow both of which would influence diastolic filling and might differ between the groups in the early observations. Since the Doppler waveforms were essentially the same between the two groups and showed a predominance in the left-to-right shunting, the shunt flow volume through the ductus arteriosus might be similar. In this study, there is certainly a qualitative difference in the left to right atrial shunt between the two groups of infants with the open ductus arteriosus. However, the physiological meaning are unknown. The changes in flow patterns through the foramen ovale during early neonatal life in premature infants may possibly be attributed to alterations in either the pulmonary vascular resistance or the right ventricular performance both of which were not assessed in this study.

Conclusions

Serial changes in the left ventricular diastolic filling pattern during early neonatal period are quite different between preterm and fullterm infants. This fact might reflect a different adjustment to the change in circulation between preterm and fullterm infants. In contrast to fullterm infants, the left-to-right shunt volume through the foramen ovale in premature infants seems to be one important factor to alter Doppler transmitral filling patterns in early neonatal period. This study hopefully provides useful basic data for the assessment of the left ventricular diastolic filling in premature infants during the fetal to neonatal cardiovascular changes.

References


