Regional Blood Flow Distribution and Left Ventricular Output during Early Neonatal Life: A Quantitative Ultrasonographic Assessment

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ABSTRACT

To examine the serial changes of left ventricular output and regional blood flow distribution during the early neonatal period, we measured blood flow volume in the ascending aorta, middle cerebral artery, celiac artery, superior mesenteric artery, and renal artery in 23 normal term infants at 1, 4–8, 24, and 96 h after birth. The blood flow volume in each vessel was measured by the pulsed Doppler technique. In the middle cerebral artery, celiac artery, and superior mesenteric artery, the blood flow volume at 1 and 4–8 h of age was significantly lower than after 24 h of age. In contrast, renal artery blood flow volume did not change significantly throughout the study period. The reduced organ blood flow volume soon after birth was related to a low diastolic blood flow in the major vessels, and the percent diastolic integral of blood flow velocity in each vessel showed an inverse linear correlation with the diameter of the ductus arteriosus. The left ventricular output 1

h after birth was 365 ± 69 mL/kg/min, which was significantly higher than after 4–8 h of age. Left ventricular output gradually declined to 301 ± 63 mL/kg/min at 4–8 h of age ($p < 0.05$ versus 96 h), 272 ± 48 mL/kg/min at 24 h, and 258 ± 54 mL/kg/min at 96 h. There was a significant positive correlation between left ventricular output and the ductus arteriosus diameter. We concluded that 1) there were significant changes in organ blood flow during the period of ductal closure, 2) the high left ventricular output and reduced regional blood flow at 1 and 4–8 h after birth resulted from diastolic left-to-right shunting through the ductus arteriosus, and 3) left ventricular output and regional organ blood flow were not directly related to each other. Our findings on the changes in regional organ blood flow and left ventricular output may provide a useful basis for interpreting abnormal hemodynamics in the early postnatal period. (*Pediatr Res* 36: 805–810, 1994)

We have shown that left ventricular output increases 2-fold over the fetal level immediately after birth in human neonates (1), which is similar to the data obtained in animal studies (2–5). The regional distribution of the increased left ventricular output and its physiologic role have been mostly studied in newborn lambs (2–7); little is known about the regional blood distribution in human neonates, although it is suggested to be significantly different from that in animals (8). One area of controversy regarding cardiovascular adaptation at birth is the role of the increase in left ventricular output immediately after birth. Previous investigators have suggested based on animal studies that the marked increase in left ventricular output soon after birth is due in part to the increase of

tissue metabolic demands and oxygen consumption (2–4, 7). As a consequence, enhanced regional blood flow should be observed in association with the increase of left ventricular output, but the relationship between regional organ blood flow and left ventricular output has not been clarified yet. In addition, several human studies have suggested that left-to-right shunting through the ductus arteriosus is substantial and influences both left ventricular output and organ blood flow (9–12). Thus, blood flow through the ductus arteriosus may be another factor contributing to the increased left ventricular output soon after birth.

Recently, several studies have demonstrated that the pulsed Doppler technique can be used to examine the pattern of major vessel blood flow and blood flow volume as well as to estimate organ blood flow volume in human neonates (1, 10–15). However, little information is available regarding regional blood distribution and its serial changes during the early neonatal period, because previous studies have not examined these parameters simultaneously or serially. Therefore, we used the two-

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dimensional pulsed Doppler technique to measure left ventricular output, major vessel blood flow volume, and the diameter of the ductus arteriosus simultaneously and longitudinally in normal newborn infants. The purpose of this study was to clarify the changes in the distribution of blood volume in the major peripheral arteries during early neonatal life in an attempt to clarify the relationship between left ventricular output and organ blood volume distribution as well as the influence of the ductus arteriosus on left ventricular output and regional organ blood volume distribution. The findings were expected to have direct clinical relevance in interpreting the cardiovascular adaptations occurring at birth in normal human neonates.

METHODS

Study population. Our study population consisted of 23 normal newborn infants (12 males and 11 females) whose gestational age ranged from 37 to 40 wk (mean: 38 wk) and birth weight ranged from 2363 to 3424 g (mean: 2862 ± 342 g). The gestational age was calculated from the first day of the last menstrual period. All the neonates were normal at birth and were of appropriate size for dates. They all underwent clinical and echocardiographic examination at birth and again before discharge from hospital. These examinations showed no evidence of congenital heart disease or abnormalities of any other organ system.

The study was approved by the Kitasato University Hospital Human Research Committee, and written informed consent was obtained from the mothers of the infants.

Procedure. The initial study was performed at 1 h of age, and thereafter serial ultrasonographic examinations were performed at 4–8, 24, and 96 h after birth using a Hewlett-Packard 77025 A ultrasound system with a 5.0-MHz transducer (Hewlett-Packard Co., Palo Alto, CA). Two-dimensional real-time color flow imaging was used to position the Doppler sample volume in the region of interest for the measurement of blood flow velocity. The pulsed Doppler flow velocity wave form was recorded from the ascending aorta, left middle cerebral artery, celiac artery, superior mesenteric artery, and left renal artery by a single examiner (Y.A.). We sequentially measured only from the left side of the middle cerebral artery and the renal artery to avoid possible influences of anatomical variations, although previous studies have shown velocities did not differ significantly between the right and left sides in normal neonates (14, 16, 17). Doppler studies were performed as rapidly as possible to minimize adverse influences on the neonates and usually took less than 20 min. All examinations were performed while the newborn infants were resting quietly in the supine position. To exclude the possible influence of postprandial changes of intestinal blood volume, studies were not carried out for at least 1 h after feeding. The Doppler flow velocity in the ascending aorta immediately distal to the aortic valve was obtained in the apical long axis view.

For diameter measurement, the ascending aorta was viewed in the long axis, with the M-mode beam perpendicular to the anterior and posterior walls of the artery at the level of aortic valve (1). For measurement of flow in the left middle cerebral artery, the transducer was placed in front of the left ear over the thin temporal window (10, 11, 16, 17), and the sampling volume was placed in the proximal portion of the artery. In the case of the celiac artery and the superior mesenteric artery, the sampling volume was placed in the proximal portion of each vessel using a longitudinal abdominal approach (13). The left renal artery was imaged by placing the transducer in the left dorsolateral area of the flank below the costal arch, and the sampling volume was placed in the proximal portion of the vessel with simultaneous viewing of the abdominal aorta (14). The angle between the estimated direction of blood flow and the Doppler beam was 20° or less in all cases. Care was taken to visualize as much as possible of each of these major peripheral vessels to accurately determine the insonation angle. The diameter of each peripheral vessel was obtained directly from the two-dimensional systolic image showing the maximum diameter, using the color flow images obtained at each examination as a reference.

Data analysis. An average of five beats was used to determine the values reported. Velocity spectra that were not clearly defined or that showed considerable variation in amplitude were not analyzed. The peak systolic velocity and the end-diastolic velocity were determined from the pulsed Doppler velocity wave form for each of the major peripheral arteries. The integral and the percent diastolic integral of the flow velocity wave form and the R-R interval were also determined from the flow velocity tracings and calculation by planimetry. The aortic valve diameter was measured at the level of the annulus in the systolic frame showing the maximum diameter. A pilot study of the serial changes in the diameter of the major peripheral arteries did not show any significant changes during the first 96 h after birth. Therefore, we used the average diameter of the four serial examinations in each subject for calculation of the arterial cross-sectional area. The aortic valve area and the peripheral arterial cross-sectional area were calculated by assuming the valve orifice and the arteries to be circular. Values for each of the following variables were obtained: 1) heart rate (beats/min); 2) stroke volume (mL/kg) = aortic valve area (cm^2) $\times$ a single cardiac cycle flow velocity integral (cm); 3) left ventricular output (mL/kg/min) = stroke volume (mL/kg) $\times$ heart rate (beats/min); 4) peripheral arterial blood flow volume (mL/kg/min) = arterial cross-sectional area (cm^2) $\times$ flow velocity integral (cm) $\times$ heart rate (beats/min); and 5) % diastolic integral = diastolic flow velocity integral/a single cardiac cycle flow velocity integral $\times 100$.

Ductus arteriosus. The inner diameter and the blood flow pattern of the ductus arteriosus were also determined at the time of the other hemodynamic measurements (1, 18, 19). Ductus arteriosus size was determined

from the inner diameter on two-dimensional color echocardiographic images, with the inner diameter being measured at the narrowest portion of the ductal lumen in the parasternal long-axis plane. As reported previously, we judged that the ductus arteriosus was closing when the narrowest diameter was less than 2 mm or nonphasic continuous low velocity flow was recorded upstream from the stenosed portion of the ductus (1, 18). The ductus arteriosus was considered to be closed when a color image and shunt flow were no longer detected.

Statistical analysis. Data were expressed as the mean $\pm$ 1 SD. One-way analysis of variance was used to evaluate the differences between sets of measurements obtained from 1 to 96 h after birth. The Doppler echocardiographic variables were plotted against ductus arteriosus diameter, and the respective correlations were determined by regression analysis. Results with a p value < 0.05 were considered to be statistically significant.

RESULTS

The sequential changes in heart rate, stroke volume, and left ventricular output are depicted in Figure 1.

Heart rate. The mean heart rate at 1 h of age was 147 ± 14 beats/min and the heart rate decreased significantly at 4–8 h after birth to 131 ± 12 beats/min. At 24 h of age, the heart rate was 121 ± 12 beats/min, which was significantly lower than at 1 and 4–8 h of age. However, there was no significant changes between 24 and 96 h after birth.

Left ventricular output. The left ventricular output at 1 h after birth was 365 ± 69 mL/min/kg, and it decreased significantly to 301 ± 63 mL/min/kg at 4–8 h of age. Left ventricular output subsequently continued to decline gradually, reaching 272 ± 48 mL/kg/min at 24 h and 258 ± 54 mL/kg/min at 96 h of age. There was a significant decrease between 4–8 and 96 h of age, but there was no significant difference between 4–8 and 24 h after birth or between 24 and 96 h. The alterations in stroke volume were similar to those of left ventricular output. Stroke volume was 2.5 ± 0.4 mL/kg at 1 h of age and decreased significantly to 2.3 ± 0.3 mL/kg at 4–8 h. Subsequently, no significant changes were noted, with the stroke volume being 2.2 ± 0.4 at 24 h of age and 2.2 ± 0.4 mL/kg at 96 h. Left ventricular output showed a significant positive correlation with the ductus arteriosus diameter ($p = 0.0001$, $r = 0.54$) during the first 96 h after birth.

Doppler flow velocity. The serial changes of peak systolic and end-diastolic blood flow velocity and the percent diastolic integral as well as the statistical correlations between these hemodynamic parameters and the ductus arteriosus diameter are shown in Table 1. Peak systolic flow velocities did not change significantly throughout the study period, except in the renal artery. The mean renal artery systolic peak flow velocity was 59.1 ± 17.7 cm/s at 1 h of age, which was significantly higher than at the other times examined. In contrast, the end-diastolic flow velocities of all the peripheral arteries

Figure 1. Serial changes in heart rate (*top*), stroke volume (*middle*), and left ventricular output (*bottom*) during the first 96 h after birth. Data are represented as the mean $\pm$ 1 SD. ★, $p < 0.05$ vs 1 h of age; #, $p < 0.05$ vs 4–8 h of age.

showed a similar pattern of serial alterations. The end-diastolic flow velocities 1 and 4–8 h after birth were significantly lower than those determined after 24 h of age. No negative flow velocity was noted during diastole while the ductus arteriosus remained open. The percent diastolic integral showed similar changes, with the values 1 and 4–8 h after birth being significantly lower than those determined after 24 h of age. There was also a significant increase in the percent diastolic integral at 4–8 h of age when compared with 1 h in all the peripheral arteries, but there were no significant changes from 24 to 96 h after birth. A strong inverse correlation was noted between the the ductus arteriosus diameter and the percent diastolic integral for all the major peripheral arteries examined.

Table 1. Blood flow velocity, percent diastolic integral, and correlations with ductus arteriosus diameter in various arteries during the early neonatal period*

	Time after birth				Correlation with DAD (<i>r</i>)
	1 hr	4–8 h	24 h	96 h	
MCA					
Peak systolic (cm/s)	46 ± 8	49 ± 14	49 ± 8	54 ± 11	0.24
End-diastolic (cm/s)	8 ± 4	8 ± 5	17 ± 5†‡	15 ± 5†‡	0.59
% Diastolic integral	23 ± 6	29 ± 6†	41 ± 5†‡	40 ± 4†‡	0.72
CA					
Peak systolic (cm/s)	75 ± 13	65 ± 17	71 ± 25	71 ± 18	0.07
End-diastolic (cm/s)	8 ± 6	14 ± 6†	25 ± 8†‡	19 ± 6†‡§	0.57
% Diastolic integral	21 ± 7	35 ± 6†	43 ± 4†‡	42 ± 6†‡	0.75
SMA					
Peak systolic (cm/s)	62 ± 16	58 ± 12	57 ± 13	67 ± 17	0.28
End-diastolic (cm/s)	3 ± 3	5 ± 3	13 ± 6†‡	13 ± 5†‡	0.69
% Diastolic integral	17 ± 9	21 ± 6†	33 ± 4†‡	34 ± 5†‡	0.90
RA					
Peak systolic (cm/s)	59 ± 16	50 ± 13†	44 ± 8†‡	47 ± 13†	0.38
End-diastolic (cm/s)	2 ± 4	6 ± 3†	8 ± 2†‡	10 ± 4†‡	0.62
% Diastolic integral	16 ± 6	25 ± 9†	33 ± 5†‡	36 ± 7†‡	0.74

* Values represent the mean ± SD. MCA, middle cerebral artery; CA, celiac artery; SMA, superior mesenteric artery; RA, renal artery; DAD, ductus arteriosus diameter.

† $p < 0.05$ vs 1 h.

‡ $p < 0.05$ vs 4-8 h.

§ $p < 0.05$ vs 24 h.

Regional blood volume. The changes in the blood flow volume of the major peripheral arteries are shown in Figure 2. In the middle cerebral artery, the celiac artery, and the superior mesenteric artery, the serial changes of regional blood flow were similar: there was no significant difference between 1 and 4-8 h after birth, with the mean blood flow volume subsequently showing a significant increase at 24 h of age. Then there was no significant change between 24 and 96 h of age. The arterial blood flow volume at 1 and 4-8 h of age (based on the low percent integral of the diastolic flow velocity) was significantly lower than at 24 and 96 h of age. In contrast, renal artery blood flow volume did not change significantly during the first 96 h after birth.

Figure 2. Bar graph showing the regional blood flow volume distribution during the first 96 h after birth. MCA, middle cerebral artery; CA, celiac artery; SMA, superior mesenteric artery; RA, renal artery. ★, $p < 0.05$ vs 1 h of age; #, $p < 0.05$ vs 4-8 h of age.

Ductus arteriosus diameter and shunt pattern. The inner diameter of the ductus arteriosus was 5.1 ± 0.9 mm at 1 h of age (Fig. 3), and all infants showed a bidirectional shunt pattern in which left-to-right shunting was dominant compared with right-to-left shunting. The ductus arteriosus was still patent in all subjects at 4-8 h of age, although the mean diameter had decreased significantly to 3.3 ± 0.9 mm (Fig. 3). The ductus subsequently closed in 65% (15/23) of the infants at 24 h of age and was closing in the others at this time, with complete closure being noted in all cases by 96 h after birth. A significant inverse linear correlation was found between the ductus arteriosus diameter and the percent diastolic integral for each of the major peripheral arteries studied.

Figure 3. Serial changes in the diameter of the ductus arteriosus (DA) during the first 96 h after birth. DA, ductus arteriosus. ★, $p < 0.05$ vs 1 h of age; #, $p < 0.05$ vs 4-8 h of age; @, $p < 0.05$ vs 24 h of age.

DISCUSSION

We have reported the first observations on the changes of regional blood flow associated with changes of left ventricular output in human neonates. It was somewhat surprising that most of the regional blood flow volumes obtained at 1 and 4–8 h of age were significantly lower than those after 24 h of age, whereas left ventricular output at 1 and 4–8 h was considerably higher than after 24 h. Previous studies have suggested that the increase in left ventricular output partly results from an increase of metabolic demands, because parallel changes of left ventricular output and tissue oxygen consumption have been demonstrated in newborn lambs (2–4, 7). However, a recent study in lambs showed that the increased oxygen consumption at birth is met by enhanced extraction of oxygen from arterial blood and not by an increase in blood flow (6). The authors of this study concluded that the increases in oxygen consumption and left ventricular output at birth are not directly related to one another, which is consistent with our data. Thus, it seems likely that the increase of left ventricular output soon after birth does not reflect an increase in regional organ blood flow.

Another possible explanation for the increase of left ventricular output is left-to-right shunting through the ductus arteriosus combined with left ventricular compensation for the loss of systemic flow supplied by the right ventricle *in utero*, because, in the latter, systemic blood flow is supplied from both right and left ventricles in the fetus but only from left ventricle in the newborn (8). We assessed the pattern of shunting through the ductus arteriosus in all our subjects while the ductus was patent, but our data were not suitable for direct quantification of ductal blood flow volume because the ductus is not necessarily cylindrical in shape (19, 20). Indirect estimation of ductal flow volume from pre- and postductal aortic flow has demonstrated that left-to-right shunting averages more than 60 mL/kg/min shortly after birth (9). A significant decrease in left ventricular output associated with ductal closure occurred by 24 h of age in the present study, and there was a significant positive correlation between left ventricular output and the diameter of the ductus arteriosus. These data suggest that the increase of left ventricular output immediately after birth is largely related to left-to-right shunting through the ductus arteriosus. However, the left ventricular output after 24 h of age was still substantially higher than the output in a normal term fetus just before parturition, inasmuch as our previous study demonstrated that fetal left ventricular output was 170 mL/kg/min using the same Doppler echocardiographic technique (1). This increment compared with the fetal level may be explained by left ventricular compensation for the loss of blood supplied by the right ventricle during fetal life.

This study showed that the reduced regional organ blood flow immediately after birth was related to reduced blood flow during diastole and was associated with ductal patency. Diastolic blood flow increased significantly in

association with ductal closure after 24 h of age, with a good inverse correlation being noted between the percent diastolic integral of organ blood flow and the ductus arteriosus diameter. In previous studies, a patent ductus arteriosus with left-to-right shunting has been shown to influence diastolic blood flow in the brain as well as the abdominal organs (9–12). Diastolic or continuous reverse flow from the systemic to the pulmonary circulation was always seen in the ductus arteriosus as long as it remained patent in the present study. These previous studies and our study suggest that ductal patency may directly affect regional organ blood flow by the diversion of blood via left-to-right shunting. Consequently, the significant reduction of regional blood flow in the first few hours of life may lead to a reduced organ perfusion pressure. Autoregulatory systems that influence the distribution of blood may act to maintain a certain organ perfusion pressure during ductal closure, because there were significant changes in the blood flow of most organs during this period but no changes were demonstrated in renal blood flow. It is of interest that the reduced organ blood flow was not altered by the significant decrease in ductus diameter between 1 and 4–8 h after birth, although the major artery diastolic flow velocities showed significant changes. However, no sequential information is available even in animals regarding changes in blood flow distribution after ductal closure. Further investigation is necessary to clarify the autoregulatory mechanisms controlling organ blood flow.

Ultrasonographic measurements of peripheral arterial blood flow volume are derived as the product of the Doppler blood flow velocity integral, the cross-sectional area of the vessel, and the heart rate. The most important factors influencing the accuracy of such measurements are estimation of the vessel diameter for the determination of cross-sectional area and the insonation angle between the pulsed Doppler beam and the artery (21). Although the diameter remains fairly constant in the proximal portions of the arteries where we determined the diameter data, even small errors in the measured diameter may have a large effect on the calculated blood flow volume (16). A pilot study of peripheral arterial diameter showed no significant changes during the first 96 h after birth, so we assumed that the diameters of arteries we studied remained constant throughout the experiment and used the average diameter of four serial examinations to minimize errors caused by the measurement of small neonatal arteries. Angle correction may lead to overestimation of the peak velocity, so the values determined will be most accurate when the insonation angle is kept small. Maintaining a small angle was not difficult in the present study, but it proved relatively difficult to keep the vessel visible long enough to accurately determine the insonation angle, especially in the renal artery. Therefore, care was taken to monitor peripheral arterial blood flow for as long as possible to ensure that the insonation angle was correct. As a result, our angle-corrected maximal velocity in the renal artery was similar to and slightly

lower than the values reported previously in human neonates (14).

In summary, this study examined the serial changes in regional blood flow and left ventricular output during early neonatal period. Our results indicated that a low organ blood flow volume immediately after birth was related to left-to-right shunting through the ductus arteriosus. The increase of left ventricular output soon after birth was not for the enhancement of organ blood flow, but was for maintaining the perfusion pressure in the face of left-to-right shunting through the ductus arteriosus. The decrease in left ventricular output during the first 24 h of life also seemed to be directly related to ductal closure, which led to the enhancement of regional organ blood flow. These findings may provide a useful basis for the interpretation of cardiovascular adaptations at birth and the circulatory abnormalities associated with birth-related events.

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