Postnatal hemodynamic changes in very-low-birthweight infants

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1Department of Pediatrics, Women & Infants' Hospital of Rhode Island, Brown University School of Medicine, and 4Rhode Island Hospital, Providence, Rhode Island 02905; 2SUNY Health Science Center, Department of Pediatrics, Children's Medical Center of Brooklyn, Brooklyn, New York 11203; and 3Division of Service and Intervention Research, National Institute of Mental Health, Bethesda, Maryland 20892

Yanowitz, Toby Debra, Alice C. Yao, Karen D. Pettigrew, John C. Werner, William Oh, and Barbara S. Stonestreet Postnatal hemodynamic changes in very-low-birthweight infants. J. Appl. Physiol. 87(1): 370-380, 1999.—The purpose of this study was to characterize postnatal changes in regional Doppler blood flow velocity (BFV) and cardiac function of very-low-birthweight infants and to examine factors that might influence these hemodynamic changes. Mean and end-diastolic BFV of the middle cerebral and superior mesenteric arteries, cardiac output, stroke volume, and fractional shortening were measured in 20 infants birthweight 1,002 ± 173 g, gestational age 28 ± 2 wk) at 6, 30, and 54 h after birth and before and after feedings on days 7 and 14. Postnatal increases in cerebral BFV, mesenteric BFV, and cardiac output were observed that were not associated with changes in blood pressure, hematocrit, pH, arterial Pco2, or oxygen saturation. The postnatal pattern of relative vascular resistance (RVR) differed between the cerebral and mesenteric vasculatures. RVR decreased in the middle cerebral but not the superior mesenteric artery. Physiological patency of the ductus arteriosus did not alter postnatal hemodynamic changes. In response to feeding, mesenteric BFV and stroke volume increased, and mesenteric RVR and heart rate decreased. Postprandial responses were not affected by postnatal age or the age at which feeding was initiated. However, the initiation of enteral nutrition before 3 days of life was associated with higher preprandial mesenteric BFV and lower mesenteric RVR than was later initiation of feeding. We conclude that in very-low-birthweight infants over the first week of life 1) systemic, cerebral, and mesenteric hemodynamics exhibit region-specific changes; 2) asymptomatic ductus arteriosus patency and early feedings do not significantly influence these postnatal hemodynamic changes; and 3) cardiac function adapts to increase local mesenteric BFV in response to feedings.

Doppler blood flow velocity; brain; intestine; patent ductus arteriosus; antenatal steroid; enteral nutrition

INTRAVENTRICULAR HEMORRHAGE, periventricular leukomalacia, and necrotizing enterocolitis are significant morbidities of very-low-birthweight (VLBW) infants. These conditions share in their complex pathogenesis disturbances of regional blood flow. Doppler ultrasound has been used to evaluate hemodynamic abnormalities that may predispose premature infants to these conditions. Fluctuating (32) and low (7) cerebral blood flow velocities (BFVs) have been found in premature infants with respiratory distress syndrome who developed intraventricular hemorrhage. Low mesenteric BFV has been identified (5) in infants at risk for necrotizing enterocolitis. Such Doppler velocity studies have focused predominantly on BFV alterations of isolated organ systems in larger preterm infants with pathological conditions. Limited information is available regarding postnatal hemodynamic changes and the factors that might influence these changes in a homogeneous population of relatively stable premature infants weighing <1,250 g at birth.

VLBW infants are exposed to a variety of prenatal and postnatal factors that might influence their cardiovascular stability. Antenatal steroid treatment, physiological patency of the ductus arteriosus, and the initiation of enteral nutrition are three factors to which stable VLBW infants are commonly exposed and that may modify postnatal hemodynamic responses.

Antenatal glucocorticoids given for the prevention of respiratory distress syndrome (18) reduce the incidence of intraventricular hemorrhage (15, 38), periventricular leukomalacia (15), and necrotizing enterocolitis (3). Infants whose mothers received antenatal steroids have higher blood pressures (15) and less need for blood pressure support (15, 24) than do those whose mothers did not receive steroids. In preterm lambs, antenatal glucocorticoid treatment increases both blood pressure and cardiac output (28). The effect of antenatal steroid therapy on cardiac output and regional hemodynamics in newborn premature infants has not been examined previously.

Physiological patency of the ductus arteriosus does not affect cerebral BFV in healthy full-term infants (2, 20). In contrast, cerebral (19) and mesenteric (39) BFVs decrease significantly when sick premature infants develop symptomatic patent ductus arteriosus. The effects of physiological patency of the ductus arteriosus on the postnatal changes in regional Doppler BFV have not been investigated in stable VLBW infants.

Prandial state is an important determinant of mesenteric blood flow regulation. In full-term (20) and larger preterm infants (21), mesenteric BFV increases after feedings. The initiation of enteral nutrition may also increase preprandial mesenteric BFV (17) and thereby influence mesenteric vascular responses. Local and
systemic responses to feedings and the effect of the preprandial state on postnatal mesenteric Doppler BFV patterns have not been well characterized in VLBW infants.

In this study, we used Doppler BFV measurements in the middle cerebral and superior mesenteric arteries and echocardiographic indexes of cardiovascular func-
tion to examine postnatal hemodynamic changes in VLBW infants over the first 2 wk of life. We hypothe-
sized that 1) cardiac function and Doppler BFV of high (cerebral)- and low (mesenteric)-priority vasculatures in VLBW infants exhibit organ-specific postnatal changes; 2) antenatal steroid administration improves postnatal hemodynamic adaptation of VLBW infants by increasing blood pressure, cardiac output, cardiac contractility, and both cerebral and mesenteric BFVs; 3) closure of an asymptomatic ductus arteriosus does not influence regional hemodynamic changes in VLBW infants; and 4) the initiation of enteral feeding in VLBW infants accelerates postnatal mesenteric BFV changes without affecting systemic hemodynamic indexes.

METHODS

This study was approved by the Institutional Review Board of Women & Infants’ Hospital of Rhode Island.

Subject enrollment. Over an 18-mo recruitment period, 114 infants were screened for participation by using the inclusion criteria of birthweight between 750 and 1,250 g and admis-
sion to the neonatal intensive care unit by 6 h of age. Exclusion criteria included the following: maternal chorioam-
ionitis (n = 20), preeclampsia or pregnancy-induced hyper-
tension (n = 17), intrauterine growth restriction (n = 15), twin-twin transfusion or in utero demise of a twin (n = 6), congenital anomalies [tracheoesophageal fistula (n = 1), renal agenesis (n = 1), chromosomal translocation with cerebral dysgenesis (n = 1), and septo-optic dysplasia (n = 1)], congenital heart disease (n = 1), hydrops fetalis (n = 1), hydranencephaly (n = 2), seizures (n = 1), respiratory failure [pH < 7.0, arterial Pco2 (PaCO2) > 70 mmHg, arterial Pao2 (PaO2) < 40 mmHg] or death before 6 h (n = 4), and investiga-
tor unavailability (n = 21). Informed consent was obtained from the parents of the remaining 22 infants. Two enrolled infants were subsequently excluded for respiratory failure after pulmonary hemorrhage (n = 1) and aortic thrombosis (n = 1).

Study protocol. This is a prospective, sequential study of postnatal regional cardiovascular changes in VLBW infants and the effects of antenatal steroid administration, asymptom-
atic patency of the ductus arteriosus, and the early introduc-
tion of enteral nutrition on these hemodynamic changes. In this report, “regional” refers to the cerebral and the mesen-
 teric vasculatures. Postnatal hemodynamic changes in car-
diac function and regional BFV were examined over the first 2 wk of life at the following intervals: 6, 30, and 54 h (6–54 h, n = 20) and days 7 (n = 20) and 14 (n = 15) after birth. The BFV and cardiac function values obtained at 6, 30, and 54 h for 18 of the 20 study infants in the present investigation have been reported previously as the baseline values (before indomethacin) in our earlier investigation (48). The values on days 7 and 14 have not been reported previously. Fewer infants were examined on day 14 because of retrotransport to level II facilities (n = 3) and study participation in a preliminary version of this protocol that required evaluation on day 28 rather day 14 (n = 2).

Clinical management was directed by nursery personnel not involved in the study. Mode of ventilation, ventilator settings, use of invasive blood pressure monitoring, and volume of fluid administered were not altered for study purposes. However, nursery guidelines suggest placing in-
fants on continuous positive airway pressure for clinical evidence of decreasing lung compliance and/or mild hypoxia (PaO2 < 50 Torr in an inspired O2 fraction (FIO2) of > 0.30) and instituting mechanical ventilation in the presence of moderate-to-severe hypoxia (PaO2 < 50 Torr in an FIO2 of > 0.50) and/or respiratory acidosis (pH > 7.30). Permissive hypercapnia (pH > 7.25) is allowed during the weaning phase from the ventila-
tor. Surfactant is administered to intubated infants with radiographic evidence of type I respiratory distress syn-
drome. Sixty-five percent of the study infants received surfac-
tant dosing as follows: one dose, n = 2; two doses, n = 6; three doses, n = 3; four doses, n = 2.

Ventilator settings, pH, blood-gas values (Corning 170 pH/blood-gas analyzer; Essex, UK), hematocrit values (Ab)

diagnostics Celldyn 1600; Abbott Park, IL), and weight (Scale-Tronix 4800, Wheaton, IL) were recorded at the be-

inning of each study. Blood pressure, heart rate, respiratory rate, and pulse-oximeter saturation (Ohmeda Biox 3700, Louisville, CO) were recorded before, at the midpoint, and after all studies. Because not all infants had indwelling arterial catheters, oxygen saturation, and upper extremity oscil-
ometric blood pressure (Dynamap, Critikon, Tampa, FL) were used for statistical analyses. Analysis of infants with intra-arterial catheters confirmed a previous report (31) that oscilometric mean blood pressure correlates well with intra-
arterial catheter mean blood pressure (r = 0.94, n = 14; P < 0.001).

Physiological ductus arteriosus patency was identified when an open ductus arteriosus was observed on the study echocardiograph and a symptomatic patent ductus was not sus-
pected by the physicians caring for the infant. The status of the ductus arteriosus by echocardiography was not re-
vealed to the caregivers. Symptomatic patent ductus arterio-

sus was diagnosed independently by the physicians caring for the infant if two or more of the following clinical signs were exhibited: widened pulse pressure, bounding peripheral arte-

rional pulses, tachycardia, hyperactive precordium, presence of a new murmur, worsening respiratory status, and cardio-
megaly/pulmonary edema on chest radiograph. The diagnosis was confirmed by a pediatric cardiologist.

Enrolled infants received indomethacin for the prevention of intraventricular hemorrhage (23). Because indomethacin prophylaxis reduces cerebral and mesenteric BFVs (48), the first Doppler ultrasound examination was completed before indomethacin was administered. Subsequent Doppler studies were begun 30 min before the next indomethacin dose was scheduled, or 23.5 h after the previous 0.1 mg/kg dose had been administered. Because the BFV reductions after indo-

methacin treatment for symptomatic patent ductus arterio-
sus are reported to last no more than 3 h (41) and the BFV reductions are less with prophylactic indomethacin (48), the prophylactic administration of preventive indomethacin could conceivably affect the results of Doppler BFV measurements. Therefore, all Doppler examinations were performed 30 min before and after a single intravenous feeding. Infants who were not fed on these days had the baseline study performed.

The time to initiation of enteral feedings, the type of milk offered, and the volume of feedings administered were deter-
mained by caregivers not involved in the study. To evaluate the influence of feeding on preprandial mesenteric BFVs, infants were divided into “early” and “late” groups, determined by whether they began feeding on/before (early, n = 8) or after

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(late, \( n = 12 \)) day 3 of life. To evaluate the changes in mesenteric and systemic hemodynamics after feeding, infants who fed on both days 7 and 14 (\( n = 10 \)) were analyzed. These infants received 59 ± 14 (SE) ml/kg of milk on day 7 and 102 ± 14 ml/kg of milk on day 14 of life.

After the National Institute of Child Health and Human Development consensus conference on the effects of corticosteroids for fetal maturation (47), >80% of VLBW infants at Women & Infants' Hospital received antenatal steroids. Because we considered it unethical to withhold this proven beneficial therapy in a randomized controlled trial, infants were enrolled into three groups on the basis of maternal steroid treatment: “none,” i.e., infants born to untreated mothers (\( n = 6 \)); “partial,” i.e., infants whose mothers received one dose of antenatal steroid (\( n = 4 \)); and “full,” i.e., those whose mothers received two or more doses of antenatal steroid (\( n = 10 \)). The three groups were statistically analyzed for homogeneity. Because no differences were found among groups for any hemodynamic measure, the groups were combined and hemodynamic changes of the entire cohort were studied.

Doppler methodology. Infants were studied in a supine and quiet state, with their heads turned to the right. Temperature was maintained by servo control (Ohmed 5000 Infant Warmer, Columbia, MD). The ultrasound gel was prewarmed to near body temperature (Parker Laboratories Thermasonic Gel Warmer, Orange, NJ). Phototherapy lights were discontinued 45 min before each study and remained off for a total of 1.5 h. Phototherapy has been shown to attenuate mesenteric vascular responses to enteral feedings (49), although it does not appear to affect baseline superior mesenteric artery (49) or anterior cerebral artery (1) BFV. Peripheral blood flow returns to baseline 30 min after phototherapy is discontinued (26). Thus 45 min was selected as a reasonable interval over which the potential effects of phototherapy on regional BFV would be attenuated without discontinuing this necessary treatment for a prolonged period of time.

The Doppler examinations were performed in the following order: 1) left middle cerebral artery BFV, 2) superior mesenteric artery BFV, 3) right ventricular cardiac output, 4) left ventricular shortening fraction, and 5) ductus arteriosus patency. All Doppler studies were performed on a Hewlett-Packard Sonos 500 (\( n = 11 \)) or 2,000 (\( n = 9 \)) echocardiogram (Andover, MA) by a single investigator (T. D. Yanowitz). The transducer used was a 7.5 mHz for tissue imaging and 5.0 mHz for Doppler recordings. Color flow mapping was used to identify arteries, and pulsed-wave Doppler was applied to measure regional BFVs. The transducer was placed perpendicular to the pterion of the temporal bone for the middle cerebral artery and in the midepigastrium for the superior mesenteric artery (20). Angle correction was used on occasion for the superior mesenteric artery with angles ranging from 0 to 30°. Mean and end-diastolic BFV measurements were made from the screen during the Doppler study by averaging values from three consecutive waves. Mean BFV was used as a qualitative measure of the direction of change in blood flow. We have previously demonstrated that BFV correlates linearly with cerebral blood flow measured by radionuclide-labeled microspheres (11). Similarly, we used end-diastolic BFV because end-diastolic mesenteric BFV has been shown to correlate with mesenteric blood flow (22). Relative vascular resistance (RVR), calculated as mean arterial blood pressure divided by mean BFV (20, 48), was used as a qualitative measure of the direction of change in vascular resistance.

Right ventricular cardiac output was measured from the left parasternal short-axis view (40). The volume was sampled in the middle of the pulmonary artery outflow tract at the level of the pulmonary valve leaflet insertions. Velocity waveforms were considered optimal when the leaflet signal was visible on both sides of the waveform, and the characteristic sound of the pulmonary Doppler signal was loudest. The internal diameter of the pulmonary annulus was measured when pulmonary valve leaflet separation was maximal. Stroke volume was calculated as BFV × vessel cross-sectional area. Cardiac output (ml·min⁻¹·kg⁻¹) was calculated from an average of three cycles as \((\text{stroke volume} \times \text{heart rate}) / \text{present weight}\). The transducer was then angled slightly toward the apex for M-mode determination of left ventricular fractional shortening. Last, patency of the ductus arteriosus was determined by color flow mapping and confirmed by continuous-wave Doppler.

All studies were recorded, and a random sample was reviewed by a second investigator (J. C. Werner), who was not aware of the order of the studies. Regression analysis revealed an excellent correlation between the two investigators (T. D. Yanowitz and J. C. Werner: \( r = 0.92, n = 20; P < 0.001 \)). The intraobserver variability (T. D. Yanowitz) was 4.5% for mean cerebral BFV, 6.6% for end-diastolic cerebral BFV, and 8.0% for cardiac output.

Statistical analysis. Postnatal changes in all variables were analyzed by repeated-measures ANOVA with one repeated factor, followed by the Bonferroni corrected paired t-test. Repeated-measures ANOVA with two repeated factors was used to analyze the effects of antenatal steroids on these postnatal hemodynamic changes, to compare the patterns of change for the cerebral and mesenteric circulations, to determine the influence of ductus arteriosus patency on hemodynamic changes, and to analyze the response to feedings. Correlational analyses were used to calculate inter- and intrainvestigator reliability and to relate Doppler hemodynamic values to mean arterial blood pressure, weight, and gestation. Missing values were estimated by using the average percent change from the remaining babies in each group. All values are expressed as means ± SE unless otherwise indicated, and \( P < 0.05 \) is considered statistically significant.

RESULTS

Infant characteristics are shown in Table 1. The physiological and respiratory variables in Table 2 indi-

Table 1. Characteristics of study infants

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<table>
<thead>
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<tr>
<td>n</td>
<td>20</td>
</tr>
<tr>
<td>Birthweight, g</td>
<td>1,002 ± 173</td>
</tr>
<tr>
<td>Gestation, wk</td>
<td>28 ± 2</td>
</tr>
<tr>
<td>Gender, no. male</td>
<td>12</td>
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<tr>
<td>Race, no. Caucasian</td>
<td>13</td>
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<tr>
<td>RDS, a</td>
<td>65</td>
</tr>
<tr>
<td>Symptomatic PDA, b</td>
<td>1</td>
</tr>
<tr>
<td>IVH, c</td>
<td>3</td>
</tr>
<tr>
<td>PVL, a</td>
<td>0</td>
</tr>
<tr>
<td>NEC, c</td>
<td>1</td>
</tr>
<tr>
<td>Mortality, c</td>
<td>1</td>
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Birthweight and gestation values are means ± SD; n, no. of infants.

RDS, radiographic evidence of type I respiratory distress syndrome, requiring exogenous surfactant administration. b PDA, symptomatic patent ductus arteriosus requiring treatment with indomethacin on days 10–12. c IVH, unilateral intraventricular hemorrhage of Papile (29) grade I–II (\( n = 2 \)) and IV (\( n = 1 \)). c PVL, periventricular echolucencies seen on cranial sonogram at 1 mo of age. c NEC, necrotizing enterocolitis of Bel status II or greater, at 10 days of age. c Infant died of Candida sepsis at 18 days of life.
cate that the infants were stable and required minimal supplemental oxygen. No infant required vasopressor support.

Changes in middle cerebral artery BFV. As shown in Fig. 1A, mean and end-diastolic cerebral BFVs increased (ANOVA: time, \( P < 0.05 \)) 96 and 300%, respectively, from 6 h to 14 days of life. The majority of the change in mean cerebral BFV and all of the change in end-diastolic cerebral BFV occurred over the first 54 h. However, the increase in mean cerebral BFV from 54 h to 14 days remained significant. Changes in mean and end-diastolic cerebral BFVs over time did not correlate with changes in blood pressure, pH, \( \text{PaCO}_2 \), oxygen saturation, or hematocrit. Closure of the ductus arteriosus did not account for the increases in cerebral BFV.

Changes in superior mesenteric artery BFV. Mean mesenteric BFV increased 160% (Fig. 1B; ANOVA: time, \( P < 0.05 \)) over the 14 days, with proportional increases between successive studies. The 46% increase in end-diastolic mesenteric BFV (Fig. 1B) from 6 to 54 h was not significant. Changes in mean mesenteric BFV did not correlate with changes in blood pressure, cardiac output, oxygen saturation, hematocrit, or closure of the ductus arteriosus.

Changes in cardiac and systemic hemodynamics. Right ventricular cardiac output increased significantly over the first 14 days of life (Fig. 1C; ANOVA: time, \( P < 0.05 \)). Right ventricular cardiac output did not correlate with ductus arteriosus patency, birthweight, or gestational age. Blood pressure (Fig. 1D), heart rate, and stroke volume increased (Table 2, ANOVA: time, \( P < 0.05 \)) over the 14 days, whereas left ventricular fractional shortening did not change.

Comparison of cerebral and mesenteric Doppler velocity patterns. Cerebral RVR decreased (Fig. 2; ANOVA: interactions, \( P < 0.05 \)) over the 2-wk study period, whereas mesenteric RVR did not change. The difference in the postnatal RVR patterns between the cerebral and the mesenteric vasculatures was significant (ANOVA: interactions, \( P < 0.05 \)).

### Table 2. Hematocrit, and respiratory and cardiovascular physiology

<table>
<thead>
<tr>
<th>Time After Birth</th>
<th>6 h</th>
<th>30 h</th>
<th>54 h</th>
<th>7 days</th>
<th>14 days</th>
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<tr>
<td>Hematocrit,* %</td>
<td>43 ± 1</td>
<td>42 ± 1</td>
<td>41 ± 1</td>
<td>42 ± 1</td>
<td>38 ± 1†</td>
</tr>
<tr>
<td>Intubated, no.</td>
<td>18</td>
<td>13</td>
<td>11</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>MAP, cmH2O</td>
<td>7.0 ± 0.1</td>
<td>5.8 ± 0.2</td>
<td>5.8 ± 0.3</td>
<td>4.9 ± 0.6</td>
<td>6.2 ± 1.5</td>
</tr>
<tr>
<td>( \text{FiO}_2 ), %</td>
<td>34 ± 1</td>
<td>25 ± 1</td>
<td>23 ± 1</td>
<td>23 ± 1</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>( \text{SaO}_2 ), %</td>
<td>94 ± 1</td>
<td>93 ± 1</td>
<td>93 ± 1</td>
<td>94 ± 1</td>
<td>94 ± 1</td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>7.34 ± 0.01</td>
<td>7.36 ± 0.01</td>
</tr>
<tr>
<td>( \text{PaCO}_2 ), Torr</td>
<td>39 ± 1</td>
<td>39 ± 1</td>
<td>38 ± 1</td>
<td>43 ± 1</td>
<td>44 ± 1</td>
</tr>
<tr>
<td>HR,* beats/min</td>
<td>151 ± 1</td>
<td>147 ± 1</td>
<td>161 ± 1†</td>
<td>161 ± 1†</td>
<td>166 ± 1†</td>
</tr>
<tr>
<td>Stroke volume,* ml</td>
<td>1.9 ± 0.1</td>
<td>2.7 ± 0.1†</td>
<td>2.5 ± 0.1†</td>
<td>2.8 ± 0.1†</td>
<td>3.0 ± 0.1†</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>34 ± 1</td>
<td>32 ± 1</td>
<td>32 ± 1</td>
<td>32 ± 1</td>
<td>34 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAP, mean airway pressure in intubated infants; \( \text{FiO}_2 \), inspired \( \text{O}_2 \) fraction; \( \text{SaO}_2 \), arterial \( \text{O}_2 \) saturation; \( \text{PaCO}_2 \), arterial \( \text{PCO}_2 \); HR, heart rate. *ANOVA: time, \( P < 0.05 \) indicates a change over time. †Bonferroni correction, \( P < 0.05 \) vs. 6 h.

Fig. 1. Changes in cerebral and mesenteric blood flow velocities (BFVs; A and B, respectively), cardiac output (CO; C, D), and blood pressure (BP; D), \( n = 20 \) infants unless otherwise noted in parenthesis. Cerebral mean (■) and end-diastolic (○) BFVs (A), mesenteric mean BFV (■; B), CO, and BP increased significantly over the first 2 wk of life (*ANOVA: time, \( P < 0.05 \); †Bonferroni correction, \( P < 0.05 \) vs. 6 h). Changes in cerebral BFV, CO, and BP were significant by 54 h, whereas increase in mean mesenteric BFV was not significant until 7 days. End-diastolic mesenteric BFV (●; B) did not change.
Effect of antenatal steroids on regional hemodynamics. Infant characteristics (Table 1) and baseline physiological variables (Table 2) did not differ among steroid-treatment groups. Mean and end-diastolic cerebral BFVs, mean and end-diastolic mesenteric BFV, cerebral RVR, mesenteric RVR, mean arterial blood pressure, right ventricular cardiac output, left ventricular fractional shortening, stroke volume, and heart rate were similar with respect to both absolute values and patterns of change among the steroid nontreated, partially treated, and fully treated groups [ANOVA, not significant (NS)]. To confirm that the analysis over the entire 2-wk period did not obscure a difference shortly after birth, the 6-h time point was analyzed separately. This analysis confirmed that there were no differences among the three groups for any of the above variables.

Status of the ductus arteriosus in infants. The number of infants who had an echocardiographically patent ductus arteriosus was 19 at 6 h, 8 at 30 h, 6 at 54 h, and none on days 7 and 14 of life. No infant had a symptomatic patent ductus arteriosus on any study day. One infant had symptomatic reopening of the ductus arteriosus at 10 days of life despite initial echocardiographic closure before 30 h of life. She was treated with indomethacin, and her ductus arteriosus was closed echocardiographically before the 14-day study.

The six infants with persistent echocardiographic ductal patency at 54 h did not differ in gestational age, birthweight, weight loss from birth, antenatal steroid treatment (Table 3), blood pressure, or cardiac function from the 14 infants whose ductus arteriosus had closed by 54 h. However, PaCO₂ was higher (Table 3; P < 0.05) in the infants with an echocardiographically patent ductus arteriosus at 54 h, and more infants with an open ductus remained ventilated for respiratory insufficiency at this time (Table 3; P < 0.05). Despite subsequent spontaneous closure of the ductus arteriosus, these infants were ventilated longer (Table 3; P < 0.001) and required more prolonged supplemental oxygen (Table 3; P < 0.01) than did infants whose ductus had closed before 54 h.

Effects of physiological ductus arteriosus patency on cerebral BFV. At 6 h, one infant with an echocardiographically patent ductus arteriosus had retrograde diastolic cerebral BFV, and five infants with open ductus arteriosus had undetectable end-diastolic cerebral BFV. Because most infants (19 of 20) had a physiologically patent ductus arteriosus at 6 h, the effect of an open ductus on cerebral hemodynamics could not be evaluated at this time.

At 30 h, no infant had retrograde and only one infant had absent end-diastolic cerebral BFV. Mean and end-diastolic cerebral BFVs were similar for infants with open (n = 8) and closed (n = 12) ductus arteriosus at 30 h. However, infants with physiological patency of the ductus arteriosus had lower mean arterial blood pressure (31 ± 3 vs. 41 ± 7 mmHg; P < 0.05) and cerebral RVR (2.0 ± 0.5 vs. 2.8 ± 0.3 mmHg·cm⁻¹·s⁻¹; P < 0.05) than did infants whose ductus arteriosus had closed. At 54 h, mean and end-diastolic cerebral BFVs were higher (Table 3; P < 0.05) in the open-ductus group, whereas cerebral RVR was similar between groups.

Effects of physiological ductus arteriosus patency on mesenteric BFV. No infant had retrograde mesenteric diastolic BFV at any time. One infant had absent end-diastolic mesenteric BFV at 6 h. End-diastolic mesenteric BFV was antegrade in all infants after 6 h. Mean mesenteric BFV, end-diastolic mesenteric BFV, and mesenteric RVR were not different for infants with an open vs. a closed ductus arteriosus at any time.

Effects of physiological ductus arteriosus patency on cardiac function. Right ventricular cardiac output, stroke volume, and left ventricular fractional shortening did not differ at any time in infants with open vs. closed ductus arteriosus. At 30 h, infants with an echocardiographically open ductus arteriosus had lower
mean arterial blood pressure than did those whose ductus arteriosus had closed.

Regional hemodynamic responses to feedings. Mean (Fig. 3A) and end-diastolic (Fig. 3B) mesenteric BFV increased and mesenteric RVR (Fig. 3C) decreased (ANOVA, P < 0.05) after feedings. Heart rate decreased (Fig. 3D; ANOVA, P < 0.05), whereas stroke volume increased (Fig. 3E; ANOVA, P < 0.05) after feedings. The increase in cardiac output was not statistically significant (Fig. 3F; ANOVA, P = 0.05). Left ventricular fractional shortening, blood pressure, oxygen saturation, mean and end-diastolic cerebral BFV, and cerebral RVR did not change after feedings. Although the volume of feeding received differed between day 7 and day 14 (P < 0.05), mesenteric and systemic hemodynamic responses were similar on the 2 study days. The magnitude of the mesenteric response did not correlate with the volume of feeding received.

Effect of early vs. late initiation of feedings. Infants who were fed early had higher preprandial mean and end-diastolic mesenteric BFVs and lower preprandial mesenteric RVR than did those who were fed late at all study time points (Fig. 4; ANOVA: main effect, P < 0.05). However, the mesenteric vascular response to feedings was identical (ANOVA: interactions, NS; data not shown) for infants in the early- and late-fed groups. The early fed infants were of higher birthweight (1,146 ± 85 vs. 937 ± 156 g; P = 0.005) than were those fed later. There were no differences in gestational age, blood pressure, cardiac output, heart rate, arterial oxygen saturation, pH, PaCO₂, hematocrit, or cerebral BFV (ANOVA: main effect, NS) to indicate that the early-fed babies were otherwise healthier than the late-fed infants.

Regional BFVs in infants who developed intraventricular hemorrhage or necrotizing enterocolitis. The two infants with Papile (29) grade I–II intraventricular hemorrhage had mean and end-diastolic cerebral BFVs, cardiac outputs, and blood pressures at all times that did not differ significantly from the group mean. One infant was diagnosed with a grade IV intraventricular hemorrhage at 3 h of life. His mean and end-diastolic cerebral BFV at 6 and 30 h were not different from the group mean. However, concurrent with the development of systemic arterial hypertension, his 54-h mean and end-diastolic cerebral BFVs were >2 SDs above the group mean. When examined at 7 days, his blood pressure and cerebral BFV were again indistinguishable from the group as a whole.

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**Fig. 3.** Hemodynamic response to feedings. n = 10 Infants. bpm, Beats/min. Mean (A) and end-diastolic (ED; B) mesenteric BFV increased (*ANOVA: main effect, P < 0.05) and mesenteric RVR (C) decreased (*ANOVA: main effect, P < 0.05) from before (open bars) to after (solid bars) feeding on both day 7 and day 14 of life. Heart rate (HR; D) and stroke volume (E) increased (*ANOVA: main effect, P < 0.05) from before (open bars) to after (solid bars) feeding on both day 7 and day 14 of life. Increase in CO (F) was not significant (ANOVA: main effect, P = 0.05).
One infant developed necrotizing enterocolitis at 10 days of life. His mean mesenteric BFV at 6, 30, and 54 h was indistinguishable from that of infants who did not develop necrotizing enterocolitis. Although this infant's preprandial mean mesenteric BFV on day 7 (20.3 cm/s) was lower than that of all other infants (38.8 ± 14 cm/s), the 83% increase in mean mesenteric BFV he demonstrated in response to feeding did not differ from the 60% increase of the group as a whole.

**DISCUSSION**

The overall goal of our study was to characterize the postnatal changes in cerebral and mesenteric BFVs and cardiac function of stable VLBW infants over the first 2 wk of life. VLBW infants are commonly exposed to endogenous and exogenous factors that might influence postnatal hemodynamic adaptation. The three factors investigated in this study were exposure to antenatal glucocorticoids, physiological patency of the ductus arteriosus, and the initiation of enteral feeding. We intentionally excluded infants born to mothers with either preeclampsia (10) or clinical chorioamnionitis (8) because such infants may have elevated endogenous cortisol concentrations that might affect the interpretation of maternally administered antenatal steroids. We also excluded growth restricted infants because they may have abnormal Doppler BFVs (16). The major findings in our study were 1) cardiac function and regional Doppler BFVs of the VLBW infant demonstrate region-specific postnatal increases; 2) antenatal steroid administration does not appear to alter echocardiographic indexes of postnatal cardiac function or Doppler BFV patterns in relatively stable VLBW infants; 3) physiological patency of the ductus arteriosus does not significantly affect postnatal regional hemodynamic changes in VLBW infants; and 4) VLBW infants respond to feedings by adapting cardiac function to increase local mesenteric BFV.

Antenatal steroids administered for pulmonary maturation enhance maturation of many organ systems (27). The protection against intraventricular hemorrhage (15, 38) and necrotizing enterocolitis (3) afforded by antenatal steroid administration may result from accelerated cellular development in the brain and intestine. On the other hand, it is tempting to invoke the improved blood pressure (15, 24) and cardiac output (28) observed after antenatal steroid administration as the mechanism of protection because both intraventricular hemorrhage and necrotizing enterocolitis may be associated with disturbances in organ perfusion. We hypothesized that postnatal changes in Doppler BFV and cardiac function would differ between infants whose mothers did and did not receive antenatal glucocorticoids. We were unable to prove this hypothesis in our population of stable VLBW infants. We found no difference in early cerebral, mesenteric, and systemic vascular indexes or the postnatal changes in Doppler hemodynamic measures among infants born to mothers who received no, partial, or full antenatal steroid treatment. By excluding infants with symptomatic patent ductus arteriosus and infants born to mothers with either preeclampsia or clinical chorioamnionitis, we have selected a population of infants with relatively normal blood pressure and cardiac function. The ability of antenatal steroids to elevate blood pressure may be greatest in infants with abnormally low blood pressure. Similarly, antenatal steroids may improve cardiac output in premature infants with poor cardiac function as a result of hypoxia or sepsis. Therefore, our findings in stable VLBW infants do not exclude a potentially beneficial effect of antenatal steroid administration in infants with compromised cardiovascular status.

Mean and end-diastolic cerebral BFVs and mean mesenteric BFV increased over the first 2 wk of life in our VLBW infants. Cerebral RVR decreased, whereas
mesenteric RVR did not change. Regional differences might result from differences in local vascular responses to endogenous variables such as blood pressure, hematocrit, cardiac function, and patency of the ductus arteriosus, as well as exogenous influences such as the initiation of enteral nutrition. However, we could find no association between these systemic factors and the cerebral and mesenteric Doppler BFV patterns.

Mean arterial blood pressure increased over the first 2 wk of life in our infants. Nevertheless, we found no correlation between changes in mean arterial blood pressure and either cerebral or mesenteric BFV when mean arterial blood pressure was within the normal range reported for VLBW infants (12, 13). These long-term increases may represent independent developmental changes in each region and must be differentiated from the short-term effects of blood pressure on regional BFV. Because preterm lambs (30) and babies (42) have a narrow range of cerebral blood flow autoregulation compared with older subjects, relatively small but abrupt changes in blood pressure may result in pressure-passive changes in cerebral blood flow. The marked increase in cerebral BFV in our infant who developed arterial hypertension is consistent with a pressure-passive change in cerebral BFV that was confined to the period of hypertension.

Anemia is associated with increased cerebral blood flow if arterial oxygen content is decreased (14). The hematocrit values decreased over the first 2 wk of life in our infants, but the change was not statistically significant until day 14 and did not correlate with the increase in cerebral BFV. It should be emphasized that the largest increase in cerebral BFV occurred in the first 54 h when the hematocrit had not changed.

Improvements in cardiac function could also account for the increases in regional BFV. We used shortening fraction to assess left ventricular function. Our values for left ventricular shortening fraction confirm the finding (9) that shortening fraction is >30% in healthy VLBW infants. In addition, we now report that shortening fraction does not change over the first 2 wk of life in this population. Because left ventricular cardiac output does not increase (46) and left ventricular shortening fraction stays constant, changes in left ventricular function cannot explain the increases in regional BFV that occur in VLBW infants over the first 2 wk of life.

We measured right rather than left ventricular cardiac output because it should be affected less by physiological shunting through the ductus arteriosus and has, in fact, been shown to be highly correlated with left ventricular output in preterm infants without symptomatic patent ductus arteriosus (45). Right ventricular cardiac output and stroke volume increased over the first 2 wk of life in our VLBW infants. The increase in cardiac output and stroke volume was not influenced by changes in blood pressure, hematocrit, or ductus arteriosus patency. Although not measured in this study, decreases in right-to-left atrial shunting and/or tricuspid regurgitation after birth could potentially explain the increase in right ventricular cardiac output. Premature infants have high initial pulmonary artery pressure (37) in the presence of respiratory distress syndrome and may have early right-to-left atrial shunting. As pulmonary vascular resistance decreases, pulmonary blood flow and left atrial return may increase, reducing atrial right-to-left shunting and tricuspid valve regurgitation so that right ventricular stroke volume and consequently cardiac output increase.

The timing of ductus arteriosus closure did not appear to influence the increases in cerebral and mesenteric BFV in our infants. However, closure of the ductus arteriosus is an integral component of postnatal cardiovascular adaptation in stable VLBW infants. The cerebral Doppler BFV results of our infants with physiological patency of the ductus arteriosus were able to exhibit both cerebral blood flow autoregulation and cerebrovascular responsiveness to $P_{aCO_2}$. At 30 h of life, mean arterial blood pressure was lower in infants with an echocardiographically open, compared with closed, ductus arteriosus. Nevertheless, infants with physiological patency of the ductus arteriosus were able to maintain cerebral BFV by reducing cerebral RVR sufficiently. Thus these VLBW infants appeared to exhibit cerebrovascular autoregulation. At 54 h, our infants with persistent physiological patency of the ductus arteriosus had significantly higher mean and end-diastolic cerebral BFVs than did infants whose ductus arteriosus had closed. In contrast, sick premature infants with symptomatic patent ductus arteriosus have been reported to exhibit significant decreases in cerebral BFV (19). The higher cerebral BFV in our infants can be explained by the higher $P_{aCO_2}$ in these infants at 54 h of age. This finding is consistent with previous work (33) demonstrating that VLBW infants exhibit cerebrovascular reactivity to small changes in arterial carbon dioxide tension. Therefore, in association with physiological ductal patency, our stable VLBW infants appeared to exhibit evidence of both cerebrovascular autoregulation and chemosensitivity to increased $P_{aCO_2}$.

Symptomatic patent ductus arteriosus is a well-recognized risk factor for bronchopulmonary dysplasia (36). Our study is the first to demonstrate that asymptomatic ductus arteriosus within the previously defined physiological range (0–4 days) (35) is also associated with greater ventilatory and oxygen requirements. Antenatal steroid administration (43) and lower fluid intakes (4) result in earlier ductus arteriosus closure and less bronchopulmonary dysplasia. Our infants with echocardiographically patent ductus arteriosus at 54 h were equally distributed among steroid treatment groups and had similar gestational age, birthweight, and weight loss from birth as did infants whose ductus arteriosus had closed. Because positive-pressure ventilation is an independent risk factor for delayed ductal closure (34), it may be that the ductus arteriosus patency is prolonged in infants with more immature pulmonary status irrespective of gestational age, birthweight, postnatal diuresis, and antenatal steroid therapy.
Our finding that physiological ductus arteriosus patency does not affect postnatal changes in mesenteric BFV in VLBW infants is important because it is contrary to findings in larger preterm (21) and term (20) infants. In these larger infants, there was an early (from 2 to 24 h) rise in mean and end-diastolic mesenteric BFVs that was attributed to early closure of the ductus arteriosus (20, 21) and the early initiation of enteral nutrition (6, 20, 21). The increase in mean mesenteric BFV in our VLBW infants began early, was significant by day 7, continued through day 14, and did not correlate with ductus arteriosus closure. The introduction of early enteral nutrition to our infants did not appear to influence this pattern. Although infants who were fed early (before 54 h) had higher mean and end-diastolic mesenteric BFVs than did infants who were fed later, the two groups demonstrated similar patterns of change in the preprandial mean mesenteric BFV. In addition, the differences in preprandial mesenteric BFV between the early- and late-fed infants were evident by the 6 h study, before any infant had been fed.

Therefore, the higher mesenteric BFV in the infants who were fed early may indicate a preexisting favorable gastrointestinal state rather than a beneficial effect of the early enteral nutrition. There were no physiological differences between the groups to suggest that early-fed infants were otherwise healthier. The infants who were fed early were of similar gestational age but were of higher birthweight than the infants who were fed later. Therefore, the higher mesenteric BFV in this group may also be attributed to a potentially greater intestinal mass.

The postprandial increases in mean and end-diastolic mesenteric BFVs in our VLBW infants were similar to those observed in term (17, 20) and larger preterm (21) infants. The postprandial response did not differ between the early- and late-fed groups or between days 7 and 14, suggesting that the response is independent of the duration of exposure to enteral feedings. This finding has been reported previously for full-term (20) and larger premature (21) infants examined between 3 and 7 days after birth. In addition, the magnitude of the mesenteric response was not influenced by the volume of the feeding that our VLBW infants received. Our findings are similar to those in premature infants at 33–35 wk of gestation in whom the volume of feeding had no effect on the magnitude of the mesenteric vascular response (21).

Feeding may be associated with systemic hemodynamic changes to meet the increased mesenteric metabolic demand. When mesenteric BFV increases after bottle feeding in full-term infants, cardiac output and blood pressure are not affected (20). In contrast, when larger preterm infants are nipple fed, cardiac output increases but mean arterial blood pressure decreases (21). In our VLBW infants, the increase in stroke volume in response to enteral feedings was sufficient to offset the decrease in heart rate such that arterial blood pressure was maintained. It is important to point out that cerebral BFV was not compromised during this systemic hemodynamic adaptation to feedings, confirming findings in larger premature infants (21). Because our infants were gavage fed, we cannot comment on the effect nipple feedings might have on systemic and regional hemodynamics in VLBW infants.

The infant who developed necrotizing enterocolitis had mesenteric BFV and cardiac output values that were indistinguishable from the population mean on the first 3 days of life. On day 7 his baseline mesenteric BFV was very low, but the postprandial response was similar to that of the other infants. Low baseline mesenteric BFV has been previously reported in infants at risk for developing necrotizing enterocolitis (5). Further work is required to determine whether the normal postprandial mesenteric BFV increase in infants with low baseline BFV provides adequate oxygen delivery to meet the increased metabolic demand of feedings (25).

We conclude that, over the first 2 wk of life, VLBW infants demonstrate significant increases in cerebral BFV, mesenteric BFV, and cardiac output that cannot be attributed to closure of the ductus arteriosus alone. Cerebral RVR decreases more than does mesenteric RVR over this interval. Administration of antenatal steroids does not appear to alter this adaptive response. In response to feeding, mesenteric BFV and stroke volume increase, and mesenteric RVR and heart rate decrease. Early enteral feedings are associated with increased preprandial mesenteric BFV, but the timing of initiation of enteral nutrition does not appear to influence the postnatal pattern of change in mesenteric BFV or the postprandial mesenteric response. We speculate that differences in BFV patterns of the cerebral and mesenteric circulations are the result of differences in the local regulation of vascular control in response to regional metabolic demands. We further speculate that the protective effect of antenatal steroids on the brain and gut is the result of microvascular and cellular maturation rather than large vessel control of regional circulation.

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REFERENCES


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