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Cerebral Blood Flow Velocities in Hypotensive Extremely Low Birth Weight Infants and Normotensive Infants

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Abstract

Objective—To determine if hypotensive extremely low birth weight (ELBW) infants have similar cerebral hemodynamics when compared with normotensive controls. We hypothesized that hypotensive and normotensive ELBW infants have similar cerebral blood flow (CBF) velocity.

Study design—In this case–control study, CBF velocity (using Doppler ultrasound), PCO₂, and mean arterial blood pressure (MABP) were continuously monitored twice daily prior to intensive care procedures. If an infant became hypotensive (MABP $\leq$ gestational age in weeks), additional monitoring was performed for 10–20 minutes, prior to treatment with dopamine. Thirty ELBW infants were enrolled (637 ± 140 g, 24.2 ± 1.1 weeks); 15 were hypotensive and 15 were gestational age/birth weight-matched normotensive controls. CBF velocity was compared using the Mann-Whitney U test.

Results—The groups did not differ significantly in gestational age, birth weight, race, sex, PCO₂, Apgar scores, or occurrence of severe intraventricular hemorrhage. There was no difference in mean CBF velocity ($P = .934$) in hypotensive infants (MABP: 23 [20–24.9] mm Hg) compared with normotensive infants (MABP: 32.6 [27.5–35.7] mm Hg).

Conclusion—Despite being hypotensive, ELBW infants (prior to treatment), had similar CBF velocity compared with normotensive controls. Based on these results, hypotension may not indicate decreased CBF.

Keywords

hypotension; blood pressure; cerebral blood flow velocity; cerebral perfusion; infant: extremely low birth weight

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In premature newborns undergoing neonatal intensive care, hypotension and its treatment are common and have been associated with adverse outcomes including intraventricular hemorrhage (IVH), neurodevelopmental disability, hearing loss, and death.¹⁻⁴ Extremely low birth weight (ELBW, birth weight ≤ 1000 g) infants represent an especially vulnerable group, where the reported prevalence of treated hypotension is $\sim 40\%$.^{1, 5} Controversies surround the threshold value for mean arterial blood pressure (MABP) used to define hypotension (MABP in mm Hg $<$ gestational age in weeks,⁶ $< 10^{\text{th}}$ percentile for gestational and postnatal age from published norms,² or < 30 mm Hg^{7, 8}) as well as the various treatment strategies^{3, 9, 10} (volume boluses,^{11, 12} vasopressors such as dopamine,¹³ and/or hydrocortisone). There is wide variation among centers in the prevalence of vasopressor use for the treatment of hypotension.³ Despite the theoretical benefit of increasing BP into a normotensive range, no convincing evidence demonstrates that normalizing BP improves mortality and neurological morbidity in hypotensive premature infants¹¹—in fact treatment may be associated with development of IVH.^{12, 14}

Hypotension is treated with the intent of improving perfusion to organs, especially the brain,¹⁵ but it is unclear whether cerebral blood flow (CBF) is lower in hypotensive premature infants, in the absence of hypovolemia or sepsis, than in their normotensive counterparts. Previous investigations evaluating the relationship between BP level and cerebral perfusion produced discrepant results.^{8, 16, 17} Two of these studies concluded that CBF was not different in hypotensive and normotensive premature infants ($n = 30$, $n = 16$),^{16, 17} and another study of ELBW infants reported that CBF was lower in hypotensive (before treatment) than normotensive ELBW infants ($n = 17$).⁸ Because it is unclear from these previous studies^{8, 16, 17} whether hypotensive infants have reduced baseline CBF, the purpose of this case-control study was to compare baseline CBF velocity in hypotensive ELBW infants (before any treatment for hypotension) to normotensive infants (gestational age- and birth weight-matched controls) who never received treatment for hypotension.

METHODS

The study was approved by the University of Arkansas for Medical Sciences Institutional Review Board. Infants were enrolled after written informed consent from their parents.

Study Population

All infants enrolled in this case-control trial were part of a larger study examining development of cerebral autoregulation in premature infants.¹⁸⁻²⁰ Infants born at the University of Arkansas for Medical Sciences were eligible for this study if they required mechanical ventilation for respiratory distress syndrome and had an umbilical artery catheter placed during newborn stabilization. Infants with major congenital anomalies, obvious hypovolemia, early-onset sepsis, or air leaks and infants who received fluid boluses or vasopressors (before study procedures) were excluded. Routine intensive care procedures were left to the discretion of the attending neonatologists.

Cases included all hypotensive ELBW infants who were enrolled in a pilot study to examine cerebral hemodynamics in hypotensive infants (born between January 2006 and May 2007). Hypotension was defined as MABP (in mm Hg) $\leq$ gestational age (in weeks)⁶ for ≥ 30 minutes, during the first 2 days of life. Control infants were normotensive (never required fluid boluses, vasopressors or hydrocortisone for hypotension) and were matched with case infants for gestational age (within 1 week) and birth weight (within 100 g). The process for selecting control infants was blinded to baseline CBF velocity and all neonatal outcomes.

Study Design

In the larger study, we continuously monitored infants' BPs, PaCO₂ and/or transcutaneous CO₂, and CBF velocities for approximately 1 hour before (baseline) and during surfactant administration and tracheal suctioning twice daily during the first 3 days of life, then once daily during days of life 4–7.^{18–20} On the first day of life, enrolled infants were usually monitored at approximately 6 hours of age (corresponding to the second surfactant dose) and between 12 and 18 hours of age, during a tracheal suctioning session. Between January 2006 and May 2007, if an enrolled ELBW infant became hypotensive at any time (including the middle of the night) of any day (including weekends) an investigator or research assistant initiated additional continuous monitoring of BP, PaCO₂ and/or transcutaneous CO₂, and CBF velocity, beginning with a 10–20-minute baseline period before dopamine treatment and continuing throughout dopamine infusion until optimal MABP was reached (>15% above gestational age in weeks),²¹ for a total of 2–3 hours.

Monitoring Equipment

Continuous BP monitoring was performed with an umbilical arterial catheter (Diametrics, St. Paul, MN; or Argyle/Tyco Healthcare/Kendall, Mansfield, MA) attached to a BP transducer (Transpac IV, Abbott Critical Care Systems, North Chicago, IL). The transducer was connected to a cardio-respiratory monitor (Spacelabs, Redmond, WA) and calibrated.

Continuous blood gas monitoring was performed with a Neotrend-L (Diametrics Medical Ltd) fiber-optic sensor placed in the umbilical arterial catheter. The continuous blood gas monitor became unavailable; subsequently, transcutaneous PCO₂ (MicroGas 7650 *rapid*, Radiometer, Westlake, Ohio) was used for continuous monitoring. Briefly, the skin on either side of the chest was prepped with a small amount of Aquaphor Emollient Ointment (Beiersdorf, Norwalk, CT). A double-sided adhesive ring of tape was applied to the skin, and one drop of an electrolyte solution (Radiometer) was placed into the center of the adhesive ring. The probe was then affixed to the adhesive ring, which resulted in reproducible PCO₂ readings with minimal to no skin irritation. After 5 minutes of continuous monitoring (by either system), an arterial blood gas measurement was obtained from the umbilical arterial catheter. The Neotrend-L and/or transcutaneous blood gas monitor was then calibrated with the PaCO₂ laboratory result (the change was rarely >3 mm Hg).

CBF velocity in the right middle cerebral artery was continuously monitored using transcranial Doppler ultrasound (Nicolet Biomedical Pioneer, Madison, WI). A lightweight 2-MHz pulsed-wave button transducer was placed transtemporally, anterior to the ear and above the zygomatic arch, and held in place by an appropriately sized crocheted hat (courtesy of the Arkansas Homemakers Extension Council). A depth of 16–22 mm was used to study the M1 portion of the middle cerebral artery.^{18–20} A 100-Hz low-pass filter was used to dampen “noise” from the vessel wall. To obtain reliable CBF velocity measurements, the transducer was placed with the minimum angle of insonation, accomplished when the highest intensity acoustic signal was perceived and the highest intensity Doppler spectrum was visualized.²² The ultrasound intensity was 5–21 mW/cm². CBF velocity tracings were consistent for more than 1 hour, with minimal to no drift in signal intensity.

Analog signals from the BP monitor (112 Hz), blood gas monitor (1 Hz) or transcutaneous CO₂ monitor (1 Hz), and transcranial Doppler (100 Hz) were simultaneously collected with a data acquisition system (PowerLab 8 channel, ADInstruments, Mountain View, CA). Cyclic waveform analyses were performed on the BP data to calculate MABP (average amplitude of the BP waveform over one cycle) and systolic and diastolic BPs (maximum and minimum values of the BP cycle, respectively). Digital output from the blood gas monitor was converted

to an analog signal by a digital-to-analog converter. Fast Fourier analysis was performed on the CBF velocity signal to determine the systolic, diastolic, and mean CBF velocities.

Data Collection and Definitions

For each infant in this study, time and date of birth, birth weight, gestational age, race, sex, Apgar scores at 1 and 5 minutes, presence of severe (grade III–IV) IVH, survival to hospital discharge, and postnatal age at the time of physiological monitoring was obtained from our research database. Gestational age was estimated based on obstetrical criteria (e.g., last menstrual period, ultrasound confirmation) and neonatal criteria; the neonatal estimate was used if the two estimates differed by >2 weeks. Severe IVH was determined using the staging criteria of Papile et al,²³ based on any cranial ultrasound during the hospitalization.

Statistical Analyses

Baseline values (median) for MABP, PCO₂, systolic CBF velocity, diastolic CBF velocity, and mean CBF velocity were determined from approximately 10–20 minutes of continuous monitoring that preceded treatment with dopamine (cases) or surfactant administration and tracheal suctioning.

Demographic and clinical characteristics of hypotensive and normotensive subjects were compared using appropriate statistical tests (*t* test, Mann-Whitney U test, median test, χ^2 , and Fisher exact test). Results are expressed as percentage, mean $\pm$ SD, or median (IQR [interquartile range]), as appropriate.

RESULTS

Thirty ELBW infants were enrolled; 15 in the hypotensive group and 15 in the normotensive group.⁶ The groups did not differ in birth weight, gestational age, race, sex, postnatal age (at the time of the study), 1- and 5-minute Apgar scores, and severe IVH occurrence (Table I). The hypotensive group had more deaths than the normotensive group ($P = .053$). There were no differences in arterial pH (first arterial blood gas after placement of an umbilical arterial catheter) between hypotensive and normotensive infants. Umbilical arterial pH was not available for most infants.

An infant was selected for inclusion in the hypotensive group when the MABP (in mm Hg) was lower than the gestational age (in weeks)⁶ for ≥ 30 minutes, so this group had a clear difference in MABP from that of the normotensive group. Concomitant measurements of baseline CBF velocity revealed no difference (Figure) in mean CBF velocity between hypotensive and normotensive infants matched for gestational age and birth weight. Similarly, PCO₂, systolic CBF velocity, and diastolic CBF velocity did not differ between the two groups (Table II).

DISCUSSION

Using a case–control study we demonstrated that hypotensive ELBW infants (prior to dopamine treatment) have baseline CBF velocities similar to normotensive control ELBW infants. Thus, the results of this study suggest that blood flow to the brain is not impaired in hypotensive ELBW infants, questioning the common rationale for treating hypotension—to ensure perfusion to the brain. Controversy and uncertainty surround the threshold MABP used to define hypotension and instigate treatment. We used the most conservative definition of hypotension⁶ to provide convincing evidence that MABP is a poor surrogate of adequate CBF. This result is consistent with previous studies demonstrating that BP is also poorly correlated with systemic blood flow.^{24, 25}

Our study was prompted by the inconsistent results of the previous studies examining the relationship between MABP and cerebral hemodynamics in premature infants.^{8, 16, 17} Our findings were consistent with those of two of the studies^{16,17}—hypotensive and normotensive premature infants do not differ in cerebral hemodynamics. Both of these studies, however, used heterogeneous study populations with wide ranges of birth weights (531–2100 g¹⁶ and 540–2100 g¹⁷) and gestational ages (24–34 weeks¹⁶ and 24–32 weeks¹⁷). Further, one of these two studies¹⁷ performed multiple measurements of CBF on individual infants (including some measurements in the “hypotensive” group when they were normotensive), included significant differences in postnatal age at the time of study between the hypotensive (13 hours) and normotensive infants (43 hours), and delivered volume expansion or vasopressor support to many of the infants during the study.¹⁷ Finally, our results are inconsistent with those of the remaining study⁸ that observed that hypotensive ELBW infants had lower CBF reactivity than normotensive ELBW infants; however, this study included only 5 normotensive and 12 hypotensive infants, and infants of the hypotensive group were more immature (25.7 ± 0.4 vs 27.4 ± 0.9 weeks) and weighed less at birth (748 ± 63 vs 832 ± 101 g) than those of the normotensive group. Our study demonstrates similar CBF velocities in a homogeneous group of hypotensive and normotensive ELBW infants matched for birth weight and gestational age.

There are some limitations to this study. First, we used continuous Doppler ultrasound measurements of CBF velocity instead of more direct measures of CBF. CBF velocity correlates with CBF in infants²⁶ and neonatal animals^{27, 28} and correlates with near-infrared spectroscopy measures of CBF in infants²⁹ and neonatal animals.³⁰ Further, CBF velocity and near-infrared spectroscopy measures of cerebral hemodynamics show similar relative changes during development³¹ and after medication administration.³² Therefore, CBF velocity using Doppler ultrasound is a reliable measure of CBF. Moreover, the Doppler method is clinically advantageous for the fragile population of ELBW infants because it is noninvasive; easily performed at the bedside; provides real-time continuous information; and does not require radioactive materials, patient manipulations, or alterations of oxygen concentrations. A second potential problem is our somewhat small sample size ($n = 30$); however, this compares with the largest previous study¹⁶ on this topic. A final limitation is that we did not evaluate effects of hypotension on perfusion to other organs, such as the kidneys or heart. These issues will be important for future studies, but we focused on the brain because disturbances of CBF velocity have been associated with brain injuries in premature infants.³³ It is also plausible that hypotension itself may be a manifestation of a preceding insult. However, we were unable to confirm this given the similarity of Apgar scores and arterial pH between hypotensive and normotensive infants.

Although not a primary focus of this study, it is important to comment on our observations that more hypotensive ELBW infants died ($P = .053$) and developed severe IVH and/or died ($P = .141$) than normotensive control infants; all hypotensive infants received dopamine treatment after this baseline study session, as is routinely administered for such infants at our institution. Although not statistically significant, these observations are consistent with previous studies reporting an association between hypotension and increased morbidity and mortality in premature infants.^{1, 2} On the surface, this observation seems to support the need to treat hypotension in ELBW infants; however, it is possible that the higher mortality results from the dopamine treatment,³⁴ rather than the hypotension itself. Ongoing studies at our institution are investigating a possible mechanism to explain how dopamine therapy may be associated with increased development of brain injury and mortality.

We conclude that CBF velocity in a homogeneous group of the smallest and most premature infants is similar in hypotensive (prior to treatment for hypotension) and matched normotensive control ELBW infants. Thus, low MABP by itself may be a poor indicator of decreased CBF and should not be used alone to determine whether to initiate therapy for hypotension in ELBW

infants. If a primary goal of treating hypotension is to ensure blood flow to the brain, and this is already maintained prior to any treatment, then ELBW infants may be placed at risk by unwarranted therapies that have not been well studied in this population.

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ABBREVIATIONS

ELBW

Extremely low birth weight

BP	Blood pressure
CBF	Cerebral blood flow
MABP	Mean arterial blood pressure
IVH	intraventricular hemorrhage

Figure.
Mean Cerebral Blood Flow Velocity for Hypotensive and Normotensive ELBW Infants. The horizontal lines indicate the median values.

Table I

Infant characteristics

Characteristic	Hypotensive (n = 15)	Normotensive (n = 15)	P
Birth weight* (g)	625 ± 174	650 ± 100	.637
Gestational age (weeks) [†]	24 (23–24.8)	24 (24–24.8)	.740
Black (n)	5	3	.682
Female (n)	8	8	.714
Postnatal age at study (hours) [†]	6 (4.1–8.3)	7 (6–14.5)	.176
Apgar, 1 minute [†]	3 (2–4)	2 (1–4)	.343
Apgar, 5 minutes [†]	5 (4–6)	7 (5.3–7)	.107
First arterial pH*	7.26 ± .16	7.24 ± .13	.719
Time to arterial pH* (minutes)	37 ± 11	39 ± 18	.695
Severe IVH (n)	5	2	.390
Death (n)	8	2	.053
Severe IVH and/or death (n)	9	4	.141

* Mean ± SD

[†] Median (IQR)

Table II

Physiological data at baseline

	Hypotensive	Normotensive	<i>P</i>
PCO ₂ * (mmHg)	48.9 ± 12.1	42.7 ± 6.8	.102
MABP † (mmHg)	23 (20–24.9)	32.6 (27.5–35.7)	<.001
CBF velocity (cm/sec) †			
Systolic	17.3 (13.1–22.1)	14.7 (13.6–18.1)	.481
Diastolic	5.0 (3.8–6)	5.6 (5–6.6)	.089
Mean	10.0 (7.8–12.3)	9.6 (9.1–11.6)	.934

Baseline values determined before dopamine treatment (hypotensive infants) or surfactant administration and tracheal suctioning (normotensive infants).

* Mean ± SD

† Median (IQR)