Changes in Cardiac Function and Cerebral Blood Flow in Relation to Peri/Intraventricular Hemorrhage in Extremely Preterm Infants

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Objective To investigate whether changes in cardiac function and cerebral blood flow (CBF) precede the occurrence of peri/intraventricular hemorrhage (P/IVH) in extremely preterm infants.

Study design In this prospective observational study, 22 preterm infants (gestational age 25.9 ± 1.2 weeks; range 23-27 weeks) were monitored between 4 and 76 hours after birth. Cardiac function and changes in CBF and P/IVH were assessed by ultrasound every 12 hours. Changes in CBF were also followed by continuous monitoring of cerebral regional oxygen saturation (rSO_2) and by calculating cerebral fractional oxygen extraction.

Results Five patients developed P/IVH (1 patient grade II and 4 patients grade IV). Whereas measures of cardiac function and CBF remained unchanged in neonates without P/IVH, patients with P/IVH tended to have lower left ventricular output and had lower left ventricle stroke volume and cerebral rSO_2 and higher cerebral fractional oxygen extraction during the first 12 hours of the study. By 28 hours, these variables were similar in the 2 groups and myocardial performance index was lower and middle cerebral artery mean flow velocity higher in the P/IVH group. P/IVH was detected after these changes occurred.

Conclusions Cardiac function and CBF remain stable in very preterm neonates who do not develop P/IVH during the first 3 postnatal days. In very preterm neonates developing P/IVH during this period, lower systemic perfusion and CBF followed by an increase in these variables precede the development of P/IVH. Monitoring cardiac function and cerebral rSO_2 may identify infants at higher risk for developing P/IVH before the bleeding occurs. *(J Pediatr 2014;164:264-70)*.

Peri/intraventricular hemorrhage (P/IVH) occurs in about one-third of very preterm infants.[1] In >90% of the cases, P/IVH occurs during the first 3 postnatal days. P/IVH is a major risk factor for death, hydrocephalus, and poor neurodevelopmental outcome.[2,3] Although the etiology is likely multifactorial, hypoperfusion-reperfusion injury has been suggested to play a role. Most studies assessing changes in cerebral blood flow (CBF) in extremely preterm infants found evidence of low CBF during the first postnatal day.[4-6] Moreover, some[7-9] but not all[10,11] studies have found that preterm infants who later develop P/IVH have lower CBF on the first postnatal day than those who do not develop P/IVH later.[7-9] Finally, in all preterm infants, CBF has been shown to significantly increase during the second or third postnatal days followed by a slower rate of increase over the ensuing postnatal weeks.[6]

The underlying causes of the exaggerated low early postnatal CBF occurring in the subset of preterm infants believed to be at higher risk for later development of P/IVH remain to be elucidated. However, it has been speculated that the immaturity of the cardiovascular system and the resultant transient systemic hypoperfusion might play a role.[12] The increased sensitivity of the immature myocardium to afterload and the abrupt increase in systemic vascular resistance (SVR) following the removal of the low-resistance placental circulation upon clamping of the cord can explain, at least in part, the development of myocardial dysfunction and poor cardiac output immediately after delivery. The resultant decrease in systemic perfusion (ie, cardiac output) can, in some patients, lead to cerebral hypoperfusion even if blood pressure remains in the perceived normal range.[12,13]

We hypothesized that extremely preterm infants who later develop P/IVH have lower CBF initially, at least in part, because of their poor cardiac function and that improvements in cardiac function and the resultant increase in CBF precede the development of P/IVH.

CBF	Cerebral blood flow	P/IVH	Peri/intraventricular hemorrhage
CFOE	Cerebral fractional oxygen extraction	PDA	Patent ductus arteriosus
		rSO_2	Regional oxygen saturation
CO_2	Carbon dioxide	RVO	Right ventricular output
LVO	Left ventricular output	SpO_2	Arterial oxygen saturation
MCA	Middle cerebral artery	SVR	Systemic vascular resistance
MCA-MV	MCA mean velocity	US	Ultrasound
MPI	Myocardial performance index	VCF_C	Heart rate-corrected velocity of circumferential fiber shortening
NIRS	Near-infrared spectroscopy		

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Methods

This single center prospective observational study was conducted from January 2009-April 2010 at the Children's Hospital of the University of Oklahoma Health Sciences Center. The Institutional Review Board approved the study. Preterm infants born at ≤27 weeks' gestation with parental consent obtained during the first 4-6 postnatal hours were enrolled. Exclusion criteria included the presence of congenital heart defects and/or multiple congenital anomalies.

After enrollment, a head ultrasound (US) study was performed to rule out the presence of P/IVH at 4-6 hours of age. If no P/IVH was detected, the patient entered the next phase of the study where changes in cardiac function, systemic blood flow, and CBF were monitored for 72 hours.

Patients without P/IVH on the initial head US were monitored by echocardiography and vascular Doppler to assess cardiovascular function and changes in CBF, respectively, every 12 hours. In addition, cerebral regional oxygen saturation (rSO_2) and pre-ductal arterial oxygen saturation (SpO_2) were continuously monitored for 72 hours using near-infrared spectroscopy (NIRS) and pulse oximetry, respectively. Whenever an indwelling arterial catheter was present, blood pressure was also monitored continuously using a pressure transducer. Otherwise, blood pressure was measured via the noninvasive oscillometric method at the time of the echocardiographic measurements and according to the standards of clinical care as this method is considered to be reliable.[14] Finally, to document the timing of the occurrence of P/IVH, head US studies were also performed every 12 hours immediately after completion of the hemodynamic studies.

We also collected additional data during routine clinical care, such as blood gases and hemoglobin concentration. Accordingly, these tests were often performed at times different from the hemodynamic studies. Furthermore, clinical guidelines called for allowing moderate permissive hypercarbia with carbon dioxide (CO_2) values up to the 60 mm Hg range.

Standardized sagittal and coronal images were recorded by one of the investigators (S.N.) and reviewed by one of the authors (F.R.), a pediatric radiologist, who was blinded to the patients' clinical characteristics and hemodynamic findings.

One of the authors (S.N.) with expertise in echocardiography performed and analyzed the studies using a SONOS 7500 echocardiography machine (Philips, Andover, Massachusetts). Each echocardiographic exam included the following measurements, assessments, and calculations: shortening fraction and heart rate-corrected velocity of circumferential fiber shortening (VCF_C) (2 load-dependent measures of myocardial contractility); stress-velocity index (a mainly load-independent measure of myocardial contractility); left ventricular output (LVO); right ventricular output (RVO); assessment of the ductus arteriosus; myocardial performance index ([MPI]; a measure of global myocardial function); end-diastolic left ventricular diameter (a surrogate for preload); left ventricular wall stress (a measure of afterload); and SVR. The measurements were performed off-line and in batches blinded to the head US results and clinical characteristics of the subjects. All measurements shown are the average of the findings of three consecutive heart cycles.

Shortening fraction and stress-velocity index (the relation between VCF_C and wall stress) were measured by M-mode.[15] Stress-velocity index was calculated as a z-score based on published normative data.[16,17] Diameter of aortic and pulmonary valve annulus was used for calculation of LVO and RVO, respectively.[18] The diameter of the ductus arteriosus was measured using color flow mapping, and all diameters >1.5 mm were considered hemodynamically significant.[19] The MPI was calculated using pulse wave Doppler.[20] Because MPI is inversely related to myocardial function, an increase in the index indicates a deterioration of global myocardial function. SVR was calculated using the formula: SVR = (mean blood pressure − right atrial pressure)/LVO. As we did not measure right atrial pressure, we estimated it to be at 4 mm Hg[21] and used this value to calculate the SVR.

Doppler interrogation of middle cerebral artery (MCA) was carried out by placing the transducer over the temple with an angle of insonation of <10°. We used MCA mean velocity (MCA-MV) as a surrogate for CBF.[22-24]

Cerebral rSO_2 was continuously measured by NIRS (INVOS, Covidien [previously Somanetics], Mansfield, Massachusetts). The INVOS sensor measures the oxy-hemoglobin as a percentage of total hemoglobin in the tissue and is referred to as rSO_2.[25]

The neonatal NIRS cerebral sensor was placed on the skin of the forehead. Cerebral rSO_2 was measured continuously for 72 hours starting at 4-6 hours after birth. Because most (~75%) of blood in the tissue is in the venous system, cerebral rSO_2 primarily reflects venous oxygen saturation. Therefore, cerebral fractional oxygen extraction (CFOE) can be calculated as $(SpO_2 - rSO_2)/SpO_2$.[26] Assuming there are no significant changes in the metabolic rate, SpO_2, hemoglobin concentration, and the relative contribution of venous and arterial blood to the tissue interrogated, changes in rSO_2 and CFOE reflect changes in CBF. As for CFOE, it is inversely related to CBF because in order to maintain tissue oxygen delivery to meet cellular oxygen demand, CFOE increases when CBF decreases. Data on cerebral rSO_2, SpO_2, heart rate, and blood pressure were collected and downloaded every 30-60 seconds using the Vitalsync data acquisition system (Covidien [previously Somanetics]) and averaged for the 12-hour study periods (see below).

Statistical Analyses

Data were assessed for normality and analyzed using parametric and non-parametric statistical methods, as appropriate. Comparisons of rSO_2 and CFOE between the P/IVH and no-P/IVH groups were made at each 12-hour interval and at the suspected time of P/IVH detection using Student *t* test or the Wilcoxon–Mann–Whitney test, as appropriate. We assessed the statistical significance of changes of serial measurements using ANOVA with Bonferroni correction. We also assessed the differences in the pattern of changes