Early Cerebral Oxygen Extraction and the Risk of Death or Sonographic Brain Injury in Very Preterm Infants

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Objective To evaluate the relationship between cerebral fractional tissue oxygen extraction (cFTOE), a measure of oxygen delivery–consumption equilibrium, and the risk of early poor outcome in very preterm infants.

Study design Cerebral blood flow, tissue oxygenation index (by near-infrared spectroscopy), and arterial oxygen content were measured, and cerebral oxygen delivery, consumption, and cFTOE were calculated at 3 intervals in the first 72 hours of life in infants ≤30 weeks gestational age (GA). A receiver operating characteristic curve was derived with an a priori defined dichotomized outcome of good or poor, defined as death or sonographic brain injury (grade ≥II intraventricular hemorrhage) by day 7.

Results Seventy-one infants were enrolled, with a mean (SD) GA of 27 (2) weeks. cFTOE demonstrated better discrimination for the study outcome at <24 hours of age than at 48 or 72 hours of age (P = .01). The area under the curve for cFTOE at the initial measurement was no different from that for GA alone (0.87; 95% CI, 0.77-0.95 vs 0.81; 95% CI, 0.69-0.92), but the combined measure of cFTOE and GA had better discrimination (0.96; 95% CI, 0.91-1.0) than either cFTOE (P = .03) or GA (P = .016) alone. A cFTOE of 0.4 had a sensitivity of 82% and specificity of 75% for risk of early poor outcome.

Conclusion Elevated cFTOE values are associated with increased risk of early poor outcome in very preterm infants. Its predictive value is further improved with the addition of GA. *(J Pediatr 2014;164:475-80)*.

Intraventricular hemorrhage (IVH) occurs most frequently in the first hours of life in preterm infants[1,2] and is associated with life-long neurologic impairment.[3] Although IVH is multifactorial, with the most immature newborns at greatest risk, impaired cerebral autoregulation and intrauterine fetal inflammation are associated with brain injury in preterm infants. Importantly, these conditions might not be mutually exclusive, with cerebral hypoxic ischemia representing a common pathophysiological process leading to injury.[4] For extremely preterm infants, the transition to extrauterine life is characterized by low baseline cerebral blood flow (CBF), high oxygen demand, and elevated oxygen extraction.[5,6] Understanding the components of oxygen delivery and the nature of compensation for suboptimal delivery might enable the identification of those infants at greatest risk for early brain injury.

Tissue oxygen extraction is a dynamic variable determined primarily by oxygen consumption in the context of prevailing oxygen delivery. Although cerebral fractional tissue oxygen extraction (cFTOE) has been studied in preterm infants,[7-10] it has not been applied as a surrogate measure of the adequacy of oxygen equilibrium. We hypothesized that high cFTOE in infants would be a marker for restricted oxygen consumption, and consequently would be associated with a risk of significant periventricular/intraventricular hemorrhage (P/IVH) death in preterm infants. Thus, the present study aimed to determine the natural history of cFTOE in the first 72 hours of life and the ability of cFTOE in the first 24 hours of life to identify very preterm infants at risk for early sonographic brain injury or death.

Methods

Preterm infants at ≤30 weeks gestational age (GA) admitted to the newborn intensive care unit of the Women's and Children's Hospital, Adelaide with an arterial catheter inserted for clinical purposes were eligible for this study. Infants with life-threatening congenital abnormalities or congenital heart disease were excluded. The hospital's Research Ethics Committee approved

AUC	Area under the receiver operating characteristic curve	$mCerbVO_2$	Modified cerebral oxygen consumption
CBF	Cerebral blood flow	NIRS	Near-infrared spectroscopy
cFTOE	Cerebral fractional tissue oxygen extraction	P/IVH	Periventricular/intraventricular hemorrhage
GA	Gestational age	PDA	Patent ductus arteriosus
Hb	Hemoglobin	ROC	Receiver operating characteristic
IVH	Intraventricular hemorrhage	RVO	Right ventricular output
$mCerbDO_2$	Modified cerebral oxygen delivery	SaO_2	Arterial oxygen saturation
		TOI	Tissue oxygen index

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the study, with parental consent mandated. Demographic characteristics were recorded from the medical record.

Enrolled infants were nursed in double-walled incubators in a neutral thermal range. Oxygen saturation (85%-95%) and pCO_2 (45-55 mmHg) were maintained within a target range. Study measurements were obtained even with the infant quiet and in the supine position and avoided for 2 hours after clinical interventions known to alter cerebral oxygen kinetics, including administration of surfactant,[11] indomethacin/ibuprofen,[12] or caffeine.[13] Measurements were obtained as soon as possible within 24 hours of birth, and again at 48 (6) and 72 (6) hours. Early poor outcome was defined as death or IVH grade ≥ 2[14] by transcranial sonography up to day 7 of life. Sonographers and clinicians were blinded to cFTOE measurements. Physiological stability at delivery was assessed using the Clinical Risk Index for Babies II.[15]

Cerebral Oxygen Delivery and Consumption

The tissue oxygen index (TOI) was measured by near-infrared spectroscopy (NIRS) (NIRO-200; Hamamatsu Photonics, Hamamatsu City, Japan). The sensor was placed on the right frontotemporal region, and data were captured at 1-second intervals. A continuous 20-minute period was recorded. From this, a 10-minute epoch of stable data was averaged for determination of TOI and used in the oxygen kinetic equations as a surrogate for cerebral venous oxygen saturation.

Serial pulsed-wave Doppler ultrasound measurement of the internal carotid artery was performed by a single operator (K.B.) using an 8-MHz linear phased-array transducer (Philips iE33 Ultrasound System; Philips Healthcare, Andover, Massachusetts). The internal carotid artery was visualized at the base of the skull below the level of the sella, and the cross-sectional area of the internal carotid artery was measured. A pulse Doppler flow waveform was measured at an angle of insonation <15 degrees.[16] Peak systolic, end-diastolic, and mean flow velocities were determined from the average of 5 sequential waves, and total internal carotid blood flow was calculated.

Cardiac Function

Left ventricular output, right ventricular output (RVO), patent ductus arteriosus (PDA) (including flow direction), and size of the foramen ovale were determined by functional echocardiography at each of the 3 time points. A hemodynamically significant PDA was defined as >1.4 mm in diameter with bidirectional or left-to-right shunting.

Other Measurements

At the end of each NIRS study, an arterial blood sample was obtained for measurement of hemoglobin (Hb) concentration and blood gas variables (co-oximetry, 128 wavelengths; ABL 725 spectrophotometer; Radiometer, Copenhagen, Denmark). Heart rate, invasive mean blood pressure, inspired oxygen concentration, mean airway pressure, temperature, and concurrent therapies were recorded at each measurement interval. Hospital sonographers performed transcranial ultrasonography at prespecified intervals (days 1, 2, 3, and 7) using standardized views according to unit practice. IVH was classified according to Papille et al.[14]

Calculations

cFTOE (%) was calculated using the formula

$$\text{cFTOE} = [(\text{SaO}_2 - \text{TOI})/\text{SaO}_2],$$

where SaO_2 is co-oximetry–derived arterial oxygen saturation and TOI is used in place of cerebral venous oxygen saturation. Modified cerebral oxygen delivery ($mCerbDO_2$, mL/kg/min) was calculated using the formula

$$\text{mCerbDO}_2 = (\text{CBF} \times ((1.39 \times \text{Hb} \times \text{Hbsat}/100) + (0.003 \times \text{PaO}_2))),$$

where total internal carotid flow (mL/kg/min) is a surrogate for CBF, Hb is Hb concentration (g/dL), and Hbsat is Hb saturation (%). Modified cerebral oxygen consumption ($mCerbVO_2$, mL/kg/min) was calculated according to the Fick principle,

$$\text{mCerbVO}_2 = (\text{CBF} \times \text{C(a} - \text{v)O}_2),$$

where CaO_2 is arterial oxygen content and CvO_2 is venous oxygen content (mL/100 mL blood). The formula was simplified to CBF × (SaO_2 − TOI), assuming that arterial and venous Hb concentrations were identical and dissolved oxygen level was insignificant.

Statistical Analyses

Differences between the dichotomized groups were assessed using independent-samples t tests for continuous variables displaying normal distribution and the Wilcoxon rank-sum test for variables not normally distributed. Differences in frequencies for categorical variables were tested using the χ^2 test or Fisher exact test. Mixed models were used to examine changes over time and the association between continuous variables and early poor outcome. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated for early poor outcome for various predictors, and differences among the AUCs were tested. Finally, after review of ROC curves for both GA and cFOTE, post hoc logistic regression was performed, combining the 2 variables to derive another ROC curve. All analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina) and Stata 12 (StataCorp, College Station, Texas).

Results

Compared with the 58 surviving, noninjured infants, the 13 infants with early poor outcome were born at a significantly lower GA ($P < .001$) and were more likely to have received mechanical ventilation during the first 24 hours of life ($P = .004$) (Table I). However, there was no difference in the proportion requiring inotropic support for hypotension ($P = .23$) or the proportion diagnosed with hemodynamically significant PDA ($P = .07$). Furthermore, there was no observed effect of GA or