Monitoring of Cerebrovascular Reactivity for Determination of Optimal Blood Pressure in Preterm Infants

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Objective To define levels of mean arterial blood pressure (MABP) where cerebrovascular reactivity is strongest in preterm infants (ie, optimal MABP, or $MABP_{OPT}$) and correlate deviations from $MABP_{OPT}$ with mortality and intraventricular hemorrhage (IVH).

Study design A total of 60 preterm infants born at median gestational age 26 ± 2 weeks (23 ± 2 to 32 ± 1) with indwelling arterial catheter were studied at a median 34 hours (range 5-228) of age. Tissue oxygenation heart rate (HR) reactivity index, which estimates cerebrovascular reactivity, was calculated as the moving correlation coefficient between slow waves of tissue oxygenation index, measured with near-infrared spectroscopy, and HR. $MABP_{OPT}$ was defined by dividing MABP into 2-mm Hg bins and averaging the tissue oxygenation HR reactivity index within those bins. A measurement of divergence from $MABP_{OPT}$ was calculated as the absolute difference between mean MABP and mean $MABP_{OPT}$.

Results Individual $MABP_{OPT}$ was defined in 81% of the patients. A measurement of divergence from $MABP_{OPT}$ was greater in those patients who died (mean 4.2 mm Hg; 95% CI 3.33-4.96) compared with those who survived (mean 2.1 mm Hg; 95% CI 1.64-2.56), $P = .013$. Patients who had MABP lower than $MABP_{OPT}$ by 4 mm Hg or more had a greater rate of mortality (40%) than those with MABP close to or above $MABP_{OPT}$ (13%), $P = .049$. Patients with MABP greater than $MABP_{OPT}$ by 4 mm Hg had greater IVH scores, $P = .042$.

Conclusions Continuous monitoring of cerebrovascular reactivity allows the determination of $MABP_{OPT}$ in preterm neonates. Significant deviation below $MABP_{OPT}$ was observed in infants who died. Deviation of MABP above optimal level was observed in infants who developed more severe IVH. *(J Pediatr 2015;167:86-91)*.

Disturbances in cerebral perfusion have been implicated in the pathophysiology of hemorrhagic and ischemic brain lesions in preterm newborns.[1] In the healthy adult, cerebral autoregulation is the mechanism that ensures adequate perfusion and oxygenation to the brain, maintaining cerebral blood flow (CBF) relatively constant over a range of cerebral perfusion or arterial blood pressure.[2] Several studies have suggested that cerebral autoregulation is absent in sick preterm infants, predisposing them to cerebral injury and death.[3-7] More recently, it has been suggested that autoregulation fluctuates in the first week of life and that a degree of "pressure passivity" (where changes in arterial blood pressure result in changes in CBF) is associated with intraventricular hemorrhage (IVH).[8]

Strategies for preventing cerebral injury in preterm infants have emphasized the importance of maintaining a "normal blood pressure" to ensure adequate perfusion of the brain. However, the definition of hypotension or hypertension in this population remains uncertain. The current management of hypotension in preterm infants in the first few days of life does not combine quantitative information about organ perfusion.[9] It usually is based on the definition that hypotension is any value of mean arterial blood pressure (MABP) less than 30 mm Hg or less than the gestational age in weeks.[10,11] When these criteria are applied, more than 50% of preterm infants will be classified as hypotensive during the transitional phase, and there is little reliable evidence that treating hypotension according to these thresholds improves organ perfusion or outcome.[12]

ABS	Absolute value of difference between mean MABP from the total monitoring time and mean $MABP_{OPT}$ also from the total time
CBF	Cerebral blood flow
CPP	Cerebral perfusion pressure
CPP_{OPT}	Optimal cerebral perfusion pressure
HR	Heart rate
IVH	Intraventricular hemorrhage
MABP	Mean arterial blood pressure
$MABP_{OPT}$	Optimal mean arterial blood pressure
NIRS	Near-infrared spectroscopy
TOHRx	Tissue oxygenation heart rate reactivity index
TOI	Tissue oxygenation index

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Regulation of CBF must be a crucial mechanism that helps the preterm brain to survive and avoid ischemic injury. Optimizing cerebral perfusion pressure (CPP) according to the strength of cerebral autoregulation is a concept that has been introduced in the context of management of adult patients with traumatic brain injury. On the basis of the determination of cerebral vascular reactivity, the use of a moving correlation coefficient between slow waves of intracranial pressure (measured invasively) and MABP, it is possible to define the level of optimal CPP (CPP_{OPT}) where autoregulation is strongest.[13] Adult patients whose CPP is maintained close to the optimal value seem to have better outcomes compared with those who had values away from the optimal.[14] The same methodology has been validated in adults with the use of near-infrared spectroscopy (NIRS), a noninvasive technique that is used to measure cerebral perfusion, blood volume, and oxygenation.[15] In a population of preterm infants, Gilmore et al[16] used the cerebral oximetry index, a moving correlation coefficient between cerebral oxygenation and MABP measured with NIRS and MABP, to describe the relationship between the strength of autoregulation and MABP.

We recently described tissue oxygenation heart rate reactivity index (TOHRx) as an index of cerebral vascular reactivity, which is the correlation coefficient between slow waves of heart rate (HR) and tissue oxygenation index (TOI) measured with NIRS. Low correlation between HR and TOI suggests active stabilization of CBF, independent of variable cardiac output, ie, intact autoregulation. High correlation, however, suggests poor autoregulation of CBF.[17] We hypothesized that by using NIRS we could define the levels of MABP where cerebrovascular reactivity is strongest in preterm infants optimal MABP ($MABP_{OPT}$). Furthermore, we correlated the deviations from optimal blood pressure with outcome of IVH and mortality in a limited group of prospectively investigated preterm infants.

Methods

This prospective observational study was conducted from September 2010 to February 2013 at The Rosie Hospital, Cambridge, UK. The study was authorized by The Research and Development Department of Cambridge University Hospitals NHS Foundation Trust and approved by The East of England Research Ethics Committee. All infants were studied following signed informed parental consent.

Preterm infants born at ≤32 weeks' gestational age, with birth weight <1500 g, who had indwelling arterial catheters inserted for clinical reasons were eligible. Infants born with major malformations were excluded. The median (range) age of the 60 preterm infants the beginning of the study was 34 hours (5-228 hours), and the median time of recorded data was 2 hours (1-24 hours) (**Table**).

Table. Characteristics of enrolled infants

Variables	Total (n = 60)
Gestational age, wk	26 ± 2 (23 ± 2 to 32 ± 1)
Birth weight, g	845 (445-1440)
Sex, male:female	1.4:1
CRIB II	11 (4-17)
IVH	27 (45%)
Inotrope medication	31 (51%)
Mortality	11 (18%)

CRIB II, Clinical Risk Index for Babies II.
Gestational age, birth weight, and CRIB II values are presented as median (range). Remaining variables are presented as frequency.

A NIRS sensor from a NIRO200NX near-infrared spectrophotometer (Hamamatsu Photonics, KK, Hamamatsu, Japan) was placed on one side of the temporoparietal area of the infant's head. The NIRO200NX uses 3 light-emitting diodes with wavelengths of 735, 810, and 850 nm, respectively, and 2 detecting photodiodes to measure light attenuation at different distances from the source. The TOI is measured by the use of spatially resolved spectroscopy and reflects the mean tissue oxygen saturation mostly influenced by the hemoglobin saturation in the venous compartment.[3,18-20] Assuming constant cerebral metabolic rate for oxygen, changes in TOI will follow changes in CBF, according to the Fick Principle. A probe holder was used to fix the light source at 3 cm away from the receiver diodes and adhesive paper secured the sensor to the infant's skin. A light-proof cover was also used. If the study duration was longer than 8 hours, the sensor was changed to the opposite temporoparietal side of the infant's head to avoid skin marks. This change allowed us to average the data from both sides.

Continuous measurements of MABP, peripheral oxygen saturation, and HR were recorded simultaneously from the neonatal intensive care monitors (Marquette Solar 8000; GE Healthcare, Milwaukee, Wisconsin). All signals were collected and stored using ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK).[21]

Clinical data within the study period were collected from the medical notes. Clinical decision-making was at the sole discretion of the attending neonatal consultant and included the management of blood pressure, which according to the unit protocol included the use of inotropes (dopamine/dobutamine) at 5 μg/kg/min if the arterial blood pressure values were persistently less than the gestational age in weeks. Cranial ultrasonography scans were performed by the clinical team at days 1, 2, 3, 7, and every 2-3 weeks until corrected gestational age at term. IVH was defined according to Papile et al[22] and the greatest grade of hemorrhage during the admission period was used for analysis.

Data Analyses

Data recorded on ICM+ was retrospectively analyzed, using the same software, after artifacts were identified and removed. Most of the artifacts were the result of umbilical arterial line sampling, infants being handled, or movements.

TOHRx, was calculated from a moving correlation coefficient, using 5-minute time windows between 10-second average values of TOI and HR.[17] The 5-minute window for