Cerebral Oxygenation and Autoregulation in Preterm Infants (Early NIRS Study)

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Objective To determine if decreased cerebral oxygenation or altered cerebral autoregulation as measured by near-infrared spectroscopy (NIRS) in the first 96 postnatal hours is associated with an increased risk of death or severe neuroradiographic abnormalities in very preterm infants.

Study design The Early NIRS prospective, multicenter study enrolled very preterm infants with a birth weight of <1250 g from 6 tertiary neonatal intensive care units. Mean arterial blood pressure and cerebral oxygen saturation (Csat) were continuously monitored using a neonatal sensor until 96 hours of age. Moving window correlations between Csat and mean arterial blood pressure determined time periods with altered cerebral autoregulation, and percentiles of correlation were compared between infants with and without the adverse outcome of mortality or severe neuroradiographic abnormalities by early cranial ultrasound.

Results Of 103 subjects with mean gestational age of 26 weeks, 21 (20%) died or had severe neuroradiographic abnormalities. Infants with adverse outcomes had a lower mean Csat (67 ± 9%) compared with those without adverse outcomes (72 ± 7%; P = .02). A Csat of <50% was identified as a cut-point for identifying infants with adverse outcome (area under the curve, 0.76). Infants with adverse outcomes were more likely to have significant positive or negative correlations between Csat and mean arterial blood pressure, indicating impaired cerebral autoregulation (P = .006).

Conclusions Early NIRS monitoring may detect periods of lower cerebral oxygenation and altered cerebral autoregulation, identifying preterm infants at risk for mortality or neuroradiographic injury. An improved understanding of the relationship between altered hemodynamics and cerebral oxygenation may inform future strategies to prevent brain injury. *(J Pediatr 2020;227:94-100)*.

Very preterm infants are at high risk for early hemodynamic instability due to poor modulation of vascular tone, variable responses to agitation, sepsis, development of a hemodynamically significant patent ductus arteriosus, and other factors. Moreover, preterm infants are at risk for altered cerebral autoregulation with increased periods of cerebral pressure passivity, potentially leading to the development of intraventricular hemorrhage (IVH) or white matter injury. Hypotension itself may not lead to cerebral ischemia,[1] and it remains unclear if disturbances in systemic blood pressure also result in compromised end-organ perfusion, specifically perfusion to the brain.

Near-infrared spectroscopy (NIRS) is a noninvasive technology for continuous bedside monitoring of regional tissue oxygen saturation. A sensor placed on the forehead of a very preterm infant measures the underlying cerebral tissue oxygen saturation (Csat). Although an absolute value of Csat associated with tissue damage has not been standardized, in piglets and patients undergoing cardiac surgery, Csat values of <40% were associated with neurologic injury and dysfunction.[2-6] Analysis of a large, single-center cohort of preterm infants found a Csat of <55% was associated with severe IVH and unfavorable cognitive outcome at 24 months using an adult NIRS sensor.[7] However, a multicenter study of very preterm infants using a standardized NIRS device with a neonatal sensor to establish abnormally low Csat measures has not yet been conducted.

Csat	Cerebral tissue oxygen saturation
IVH	Intraventricular hemorrhage
MAP	Mean arterial blood pressure
NIRS	Near-infrared spectroscopy
PVL	Periventricular leukomalacia
ROC	Receiver operating characteristic
SGA	Small for gestational age
SNAPPE-II	Score for Neonatal Acute Physiology Perinatal Extension II
SpO_2	Peripheral capillary oxygen saturation

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Investigator initiated and funded by Medtronic with loan of equipment including INVOS 5100C and Vital Sync devices during the study period. The funding source had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation or decision to submit the manuscript. Medtronic did review and approve the manuscript. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.08.036

When used as a surrogate for cerebral blood flow, Csat as measured by NIRS can be correlated with mean arterial blood pressure (MAP) to assess autoregulation of cerebral blood flow.[8-12] Specifically, concordance between MAP and Csat indicates a pressure passive cerebral circulation and presumed loss of autoregulation.[11,13] Analyses of these measurements using time-domain, frequency-domain, or nonstationary methods demonstrate that cerebral blood flow is frequently pressure passive with loss of autoregulation in extremely premature infants.[11,14-16] Small, single-center studies have reported an association between impaired cerebral autoregulation and an increased risk of mortality, severe IVH, and periventricular leukomalacia (PVL).[12,17-20]

In this prospective multicenter study of very preterm infants, we hypothesized that decreased Csat measures and impaired cerebral autoregulation in the first 96 postnatal hours would be associated with increased mortality and a higher incidence of severe neuroradiographic abnormalities.

Methods

This multicenter, prospective observational study investigated NIRS monitoring of Csat and cerebral autoregulation at 6 tertiary-care neonatal intensive care units with previous NIRS monitoring experience. Eligibility criteria included birth weight of ≤1250 g, age <24 hours, and the presence of an indwelling arterial line at the time of enrollment. Exclusion criteria were major congenital or chromosomal anomalies, withholding of full intensive care support, or skin integrity insufficient to allow placement of a NIRS sensor as deemed by a clinician. Each participating center received approval from their respective institutional review boards to conduct this study. Informed parental consent was obtained before enrollment, either prenatally or postnatally. Medtronic (Minneapolis, Minnesota) provided support for the study with loan of NIRS equipment and approved the manuscript before submission.

After enrollment, a NIRS neonatal sensor was applied to the infant's right or left forehead for continuous monitoring of cerebral saturation with the INVOS 5100C (Medtronic). Clinicians were blinded to Csat measures by obscuring the monitor with a shield. NIRS sensors were kept in place until 96 hours of age, but were assessed on a daily basis to evaluate surrounding skin integrity and replaced as necessary. NIRS data, in addition to continuous patient data including blood pressure from an indwelling arterial catheter and systemic oxygen saturation, were acquired at a sampling rate of 1/30 Hz until 96 hours of age or earlier if arterial access became unavailable. All data were collected and time-synchronized using a Vital Sync bedside device (Medtronic). Data were downloaded to media for secure electronic transfer and subsequent processing by a central analyst.

Patient demographic and outcome variables were collected from the electronic medical record. Positive or negative moving window correlations with 30-minute overlap between Csat and MAP were computed. Sensitivity analyses did not find significant differences between windows varying from 15 to 60 minutes. Periods with significant missing data (>20%), clinically relevant artifacts (eg, calibration of arterial line), or a >50% difference between adjacent measures (eg, nonphysiologic immediate change in MAP from 50 mm Hg down to 24 mm Hg) were removed. Blood gas arterial partial pressure of carbon dioxide ($paCO_2$) levels and peripheral capillary oxygen saturation (SpO_2) levels were collected for possible confounding effects on cerebral blood flow. Perinatal data including birth weight, gestational age, sex, time of blood transfusions, use of pressors, and Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE-II)[21] were used. Echocardiograms were not routinely available in all infants to assess for hemodynamic significance of a patent ductus arteriosus.

Outcomes

The primary composite adverse outcome was mortality before hospital discharge and severe neuroradiographic abnormalities in the first 10 postnatal days. Severe neuroradiographic abnormalities were defined as grade 3 or 4 IVH (by the Papile classification[22]) or PVL as suggested by echodensity on cranial ultrasound examination. This time period was chosen given the known increased clinical risk for IVH in the first week of life, as well as the increased risk of impaired autoregulation and hemodynamic instability in this same time period, with all centers requiring cranial ultrasound screening in the first 7-10 days.[11,23]

A sample size of approximately 100 infants was estimated a priori to detect a 5% difference in NIRS measures for infants with morbidity-free survival compared with those with adverse outcomes assuming a 10% incidence of the primary outcome and SD of 5% in Csat measures, with 80% power at the 0.05 level of significance. Similar effect size was expected for the correlation coefficient between MAP and Csat.

Statistical Analyses

Analyses included Student t test, χ^2, or Wilcoxon test to compare demographic and perinatal variables between groups. Adjusted linear regression models examined the relationship between mean Csat and the primary outcome of severe neuroradiographic abnormalities or in-hospital mortality. Unadjusted receiver operating characteristic (ROC) curves were generated and cut-off values to maximize sensitivity and specificity of Csat to predict adverse outcome were chosen. Secondary analyses examined the association between additional NIRS measures including cerebral fractional tissue oxygen extraction (calculated as SpO_2 – Csat/SpO_2) and low Csat indices (based on published data from neonatal and animal studies) and relation to adverse outcomes.[2,6,24] The correlation coefficients between Csat and MAP within 30-minute sliding windows were calculated for each infant. Percentiles of the distribution of the correlation coefficients were extracted. Multiple linear regression was used to compare percentiles of

correlation between Csat and MAP for infants with and without the adverse outcome after adjusting for center, gestational age, sex, and SNAPPE-II score. All analyses were conducted using R environment (version 3.5.3, The R Foundation, Vienna, Austria).

Results

Of 385 eligible infants, 111 were enrolled from participating centers over a 3-year period. Eight subjects had significant missing MAP or Csat data preventing further analysis, leaving a total of 103 subjects (**Figure 1**; available at www.jpeds.com). The median age at initiation of NIRS monitoring was 15 hours (IQR, 8-21 hours), with a median monitoring duration of 101 hours (IQR, 40-159 hours). Absence of artifact or missing data permitted calculation of correlation coefficients for 80% of the sliding time windows on average. Twenty-one infants (20%) had the primary adverse outcome of death before hospital discharge (n = 11 [11%]) or severe neuroradiographic abnormalities in the first 10 days of life (n = 14 [14%]). Four of the infants who died also had severe IVH (mean age of diagnosis on day 1 [range, 1-2 days] and mean age of death, 9 days). Other causes of death and postnatal age at death included necrotizing enterocolitis or bowel perforation (n = 3; days 2, 8, and 29), late onset sepsis (n = 1; day 29), cardiac tamponade (n = 1; day 14), disseminated herpes simplex virus (n = 1; day 8), and severe pulmonary interstitial emphysema (n = 1; day 20). The mean age at death was 13 days (range, 2-29 days). Neuroradiographic abnormalities included grade IV IVH (n = 10), grade III IVH (n = 2), and echodensities concerning for PVL (n = 2). The mean age at detection of abnormalities was 10 days (range, 0-77 days). Severe IVH was diagnosed by age 72 hours in 10 infants (83%) and by age 7 days in all infants. Head ultrasound abnormalities for the 2 infants with PVL were not noted until 7 and 77 days. The mean gestational age of all subjects was $26^{4/7} \pm 2^{0/7}$ weeks and mean birth weight 823 ± 217 g. Demographic data and perinatal variables are presented in the **Table**. Infants with adverse outcomes had higher median SNAPPE-II scores than those who did not (53 vs 37; $P = .01$), indicating greater severity of clinical illness after birth.

Comparison of NIRS and autoregulation measures are also shown in the **Table**. The mean Csat but not MAP was significantly lower in infants with adverse outcomes compared with those without adverse outcomes. Infants with adverse outcomes spent a higher percentage of time with Csat of <65%, <55%, and <50% (**Table**). A Csat of <40% occurred infrequently in the study population and was similar between the groups. A ROC curve was generated and demonstrated a cut-point for Csat of <50% for identifying infants with adverse outcome with an AUC of 0.76 (**Figure 2**). If the Csat was <50% for ≥1% of the monitoring period (Csat <50% for ≥29 minutes over a 48-hour monitoring period), the sensitivity was 52% and specificity was 87% for an adverse outcome. The positive predictive value was 50% and the negative predictive value 87.7%. There was no difference in cerebral fractional tissue oxygen extraction between groups (28 ± 14% vs 22 ± 9%; $P = .1$). In a subanalysis, there was no significant relationship between Csat and mortality, including specific cause of death or timing of death. Median Csat in infants who died was 64% (IQR, 62%-70%) compared with a median Csat of 71% in survivors (IQR, 66%-77%; $P = .14$).

A case example of a subject with normal outcome (**Figure 3**, A) shows an approximately normal distribution of correlation coefficients centered around zero, indicating no correlation between Csat and MAP, or essentially intact cerebral autoregulation. In contrast, case example of a subject with adverse outcome (**Figure 3**, B) has observations skewed to ≥0.5, indicating MAP and Csat more likely to be highly correlated, and representing impairment in autoregulation. Additional analyses found infants with adverse outcomes were likely to have more negative correlations between Csat and MAP, and a greater variability of correlations between Csat and MAP measured by the difference between the 95th and 5th percentiles of the correlation coefficients (**Table** and **Figure 4**). The groups did not differ with respect to other variables affecting cerebral oxygenation including degree of anemia, hypocarbia, time with SpO_2 of <85%, hypotension, or hypoglycemia. Given the potential for a different mechanism of injury in infants with PVL compared with IVH, analyses were repeated after removal of these 2 cases, but no differences were found.

Discussion

Early continuous cerebral NIRS monitoring in these very preterm infants revealed an association between lower cerebral saturation measures and the primary adverse outcome of death before hospital discharge or severe neuroradiographic brain injury. Other investigators have similarly established an association between abnormally low Csat and IVH.[7,25-28] In the largest single-center cohort published to date, Alderliesten et al found that a regional oxygen saturation of <55% was significantly associated with severe IVH with an OR of 1.017 (95% CI, 1.007-1.026) per single percent of time <55% and that 20% of time spent with regional oxygen saturation of <55% in the first postnatal 72 hours was also associated with death or unfavorable cognitive outcome at 24 months with an OR of 1.4 (95% CI, 1.1-1.7).[7] This lower threshold was established from the authors' previous population-based reference data in 439 preterm infants born at <32 weeks of gestation using the lowest 10th percentile of cerebral saturation values in the first 3 postnatal days.[24] The 55% low Csat threshold was further used for a targeted NIRS interventional study (SafeBoosC trial), which suggested that targeted NIRS monitoring could reduce the

burden of cerebral hypoxia.[29] However, these studies were undertaken using the small adult NIRS sensor. Extrapolation to threshold values for a neonatal sensor was done with a subset of 16 patients.[30] An approximate 10% difference to account for a neonatal sensor would set the lower threshold of Csat to be 65%. In contrast, our ROC analysis determined a lower Csat threshold of 50% to be most associated with adverse outcomes, although thresholds of 55% and 65% were also significantly different between those with and without adverse outcome, similar to the findings by Alderliesten et al using cognitive outcomes).[7] Our study population was more premature (mean gestational age, 26.6 weeks vs 28.5 weeks) and may have been more heterogeneous due to the participation of diverse centers and these factors may account for the differences in our study results. In addition, we obtained data from neonatal sensors compared with the extrapolated values used by Alderliesten, and this factor may contribute to the observed differences. Instead of population-based reference values from available NIRS data, our study focused on outcomes and identified a Csat level of 50% as a low threshold associated with death and neuroradiographic evidence of brain injury. Despite this finding, the clinical relevance of this threshold must be considered because the positive predictive value was 50% and the median percent time spent below the threshold was 1.5% (IQR, 0.4%-7.7%) in infants with adverse outcomes. Longer term neurodevelopmental outcomes were also not available for this cohort but may have implicated a different Csat threshold. We caution the need for any threshold to be evaluated in a randomized clinical trial setting before use in clinical practice.

In a subanalysis, death was not associated with Csat. However, causes of death were heterogeneous. Of note, 4 infants who died with severe IVH were diagnosed at 1-2 days of age, potentially reflecting the effects of early cerebral hypoxia. Early cerebral hypoxia may have paralleled a process of gut hypoxia, which could have contributed to the development of necrotizing enterocolitis and bowel perforation in the 3 infants who later died of these complications of prematurity. The remaining infants died at later time periods (days 8-29) of cardiac tamponade, late-onset sepsis, pulmonary interstitial emphysema, or disseminated herpes simplex virus and were unlikely to have been affected at the time of death by their cerebral saturations in the first 96 hours of life.

We found statistically significant correlations between Csat and MAP, indicating impaired cerebral autoregulation in those with adverse outcomes. Other investigators using time-domain based methods to assess for impaired autoregulation have noted similar findings: 80% of preterm infants with severe IVH or PVL showed correlations of >0.5.[12,20] Both positive and negative correlations were associated with abnormal neurodevelopmental outcomes in a cerebral autoregulation study in asphyxiated newborns.[31] Frequency-domain based or nonstationary methods for determining impaired cerebral autoregulation have yielded similar results in other single center studies with pressure passive cerebral blood flow being associated with IVH.[14,16,18,19,32,33] Other investigators have not found a significant association between impaired cerebral autoregulation and mortality or severe neuroradiographic brain injury.[11,15,34] Differences may be attributable to method of analysis, patient population, or other confounders. However, our study population is the largest to date suggesting impaired cerebral autoregulation in the first few days of life is associated with mortality or early brain injury and supports the critical need to maintain stable cerebral flood flow in the transitioning preterm infant.

Small for gestational age (SGA) infants comprised only a small percentage of our study population (n = 17 [16.5%]); however, SGA status has previously been shown to affect cerebral saturation and cerebral autoregulation measures.[35,36]

Table. Demographics, perinatal characteristics, NIRS, and autoregulation measures*

Variables	Infants with adverse outcome (n = 21)	Infants without adverse outcome (n = 82)	*P* value
Demographics and perinatal characteristics			
Gestational age (weeks)	26.2 ± 1.7	26.7 ± 1.8	.26
Birth weight (g)	775 ± 217	836 ± 216	.27
Male	13 (62%)	39 (48%)	.33
SGA	2 (10%)	15 (18%)	.51
5-minute APGAR	7 (6-8)	7 (5-8)	.19
SNAPPE-II score†	53 (38-61)	37 (24-55)	.01
NIRS and autoregulation measures			
Hours monitored	121 (59-130)	100 (63-130)	.53
Csat (%)†	66.6 ± 9.4	72.2 ± 7.4	.02
MAP (mm Hg)	38 ± 5	40 ± 8	.13
% time with Csat <65%†	36.1 (20.3-58.5)	12.7 (2.6-52.3)	.02
% time with Csat <55%†	6.5 (0.9-16)	0.6 (0.1-2.8)	.03
% time with Csat <50%†	1.5 (0.4-7.7)	0.1 (0.01-0.6)	.0003
% time with Csat <40%	0.09 (0.03-0.44)	0.0 (0.0-0.05)	.24
5th percentile of correlations between Csat and MAP†	−0.61 ± 0.13	−0.52 ± 0.15	.04
95th percentile of correlations between Csat and MAP	0.65 ± 0.12	0.61 ± 0.14	.47
5th to 95th percentile range of correlations between Csat and MAP†	1.26 ± 0.19	1.14 ± 0.15	.006

*Unless otherwise indicated, values are presented as mean ± SD, number (%), or median (IQR).
†$P < .05$.

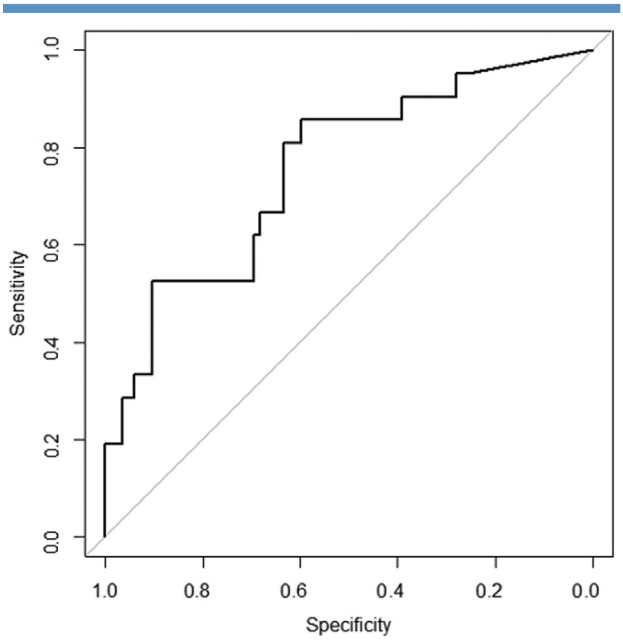

Figure 2. ROC curve for cerebral saturation <50% identifies infants with adverse outcome with an area under the curve of 0.76.

Although not statistically significant, more SGA infants were in the nonadverse outcome group. We were unable to detect a significant difference in mean Csat or correlation data for the SGA infants compared with the appropriate for gestational age infants in our study, although sample size limits this comparison. Other investigators have demonstrated SGA infants to have higher Csat levels with brain-sparing effects of continued high oxygen delivery, but more frequently impaired cerebrovascular autoregulation compared with appropriate for gestational age infants.[35,36] It remains unclear to what extent cerebral saturation and autoregulation impact outcomes in the SGA population.

The Early NIRS study evaluated continuous NIRS monitoring data for time-domain analysis of cerebral autoregulation. The study was limited by data resolution without the availability of continuous wave-form data for more sophisticated analyses such as transfer gain function analyses. Owing to limitations of the 1/30 Hz sampling rate, correlations at a higher frequency may not have been adequately captured, potentially underestimating the true degree of impaired autoregulation. Real-time autoregulation indices and the relation to the exact timing or grade of IVH are not precisely known. Impaired autoregulation may also have antenatal origins that were not explored, with risk factors including abnormal umbilical artery Doppler indices.[37] In the adult neurocritical care population, individualized autoregulation curves have further been used to develop MAP targets.[38,39] In addition, low cerebral saturation measures and impaired autoregulation were associated only with early inpatient mortality and short-term neuroradiographic abnormalities, because longer term neurodevelopmental outcomes are not available from the cohort. A central ultrasound reader was not used. Further

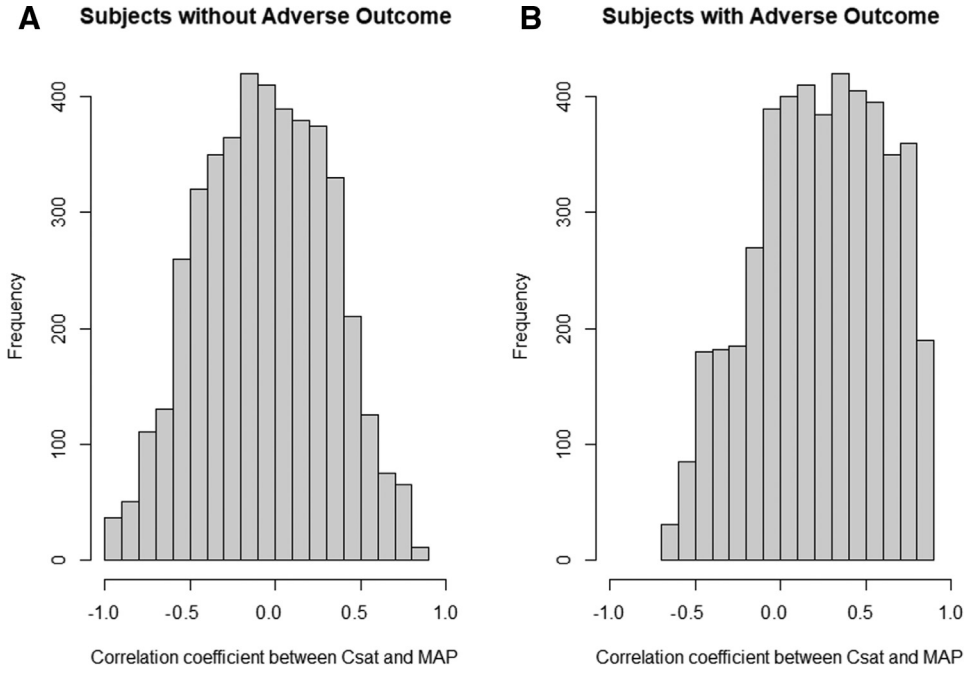

Figure 3. **A,** Case example of subject without adverse outcome demonstrates relatively normal distribution of correlations between cerebral saturation and MAP centered around zero, indicating intact cerebral autoregulation. **B,** Case example of subject with adverse outcome demonstrates positively skewed distribution of correlations between cerebral saturation and MAP, representing impairment of cerebral autoregulation.

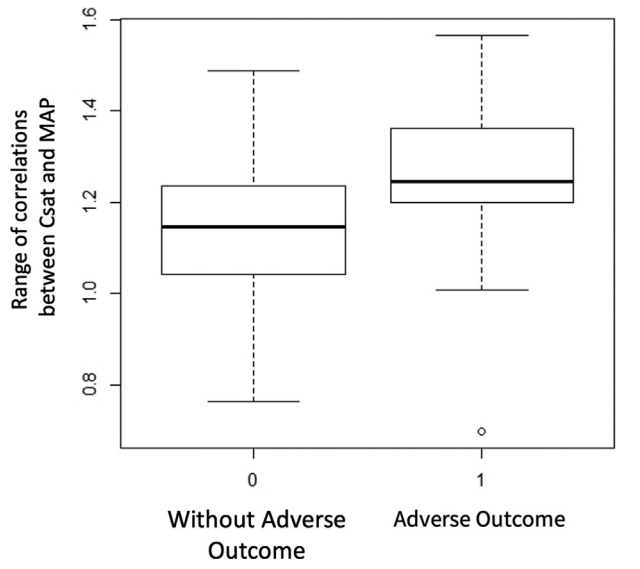

Figure 4. Correlations between cerebral oxygen saturation and MAP in infants with and without adverse outcomes. The 5th to 95th percentile range of correlations was 1.26 ± 0.19 in infants with adverse outcomes compared with 1.14 ± 0.15 in those without adverse outcomes (P = .006).

research is needed but our data suggest that targeting cerebral saturations at a minimum of >50% and avoiding hemodynamic alterations with ensuing impaired cerebral autoregulation may be strategies to reduce death and IVH in preterm infants. Notably, a Csat threshold of >50% may be necessary to avoid other detrimental neurodevelopmental outcomes because rigorous trials have not yet investigated the longer term effects of early cerebral hypoxia on cognitive and motor outcomes. The duration of cerebral hypoxia at various thresholds also needs further investigation. The clinician should keep in mind that a Csat threshold of >50% and favorable outcomes are only associations and do not imply causation as the positive predictive value was only 50% for this threshold, and findings may have been affected by other potential confounders. We emphasize that future designations of clinically relevant thresholds for Csat should occur in the context of a large, randomized clinical trial. ■

We thank the Early NIRS Study research coordinators who participated in data collection for this study including Diana Vasil, Patty Luzader, Jacqueline McCool, Allison Spenner, Tara McNair, Elaine Romano, Alexander Hwang, and Lucy Schoen. We also thank Jessica Gronsbell and Peiyi Kan for their assistance with data processing.

acknowledgments: We would like to acknowledge Medtronic, USA for loan of equipment.

Submitted for publication Jan 26, 2020; last revision received Aug 6, 2020; accepted Aug 13, 2020.

Data Statement

Data sharing statement available at www.jpeds.com.

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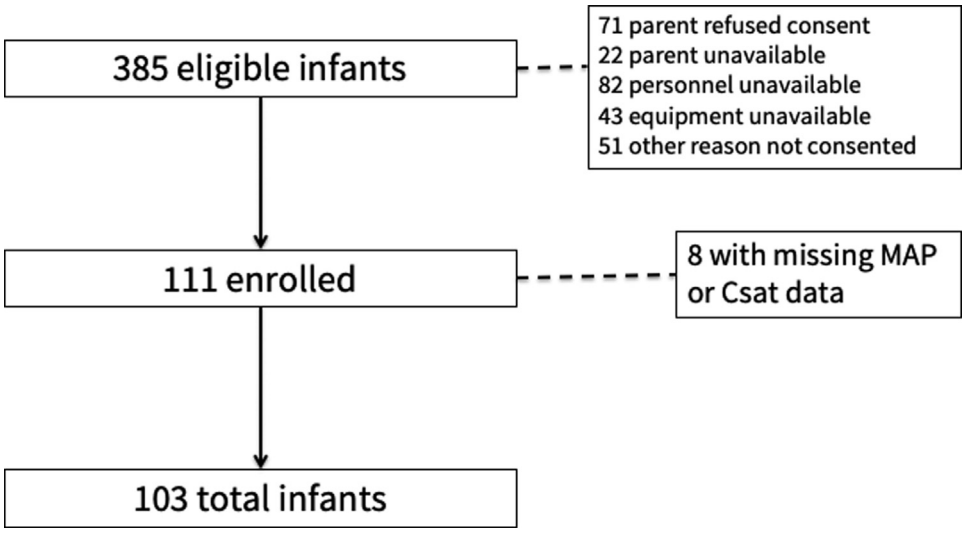

Figure 1. Flow diagram of patient population.