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Association of early cerebral oxygen saturation and brain injury in extremely preterm infants

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OBJECTIVE: To assess the association between cerebral saturation ($crSO_2$) using Near-Infrared Spectroscopy (NIRS) and brain injury in extremely preterm infants.

STUDY DESIGN: This retrospective study includes 62 infants (<28 weeks gestation) who underwent continuous NIRS monitoring in the first 5 days after birth. Median $crSO_2$ were compared in 12 h increments between infants with and without germinal matrix/intraventricular hemorrhage (GM/IVH). $crSO_2$ was also compared by IVH severity, onset, and by grade of injury on term equivalent MRI.

RESULTS: After 48 h of life (HOL), infants with GM/IVH had significantly lower $crSO_2$ than those without GM/IVH in analysis adjusted for potential confounding e.g., at 49–60 HOL (69.5 (66.2, 72.8) vs. 74.7 (71.8, 77.6), $p = 0.023$). There were no significant differences in $crSO_2$ by IVH subcategory or injury severity on MRI.

CONCLUSION: Clinical use of NIRS has the potential to identify $crSO_2$ patterns associated with development of GM/IVH.

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INTRODUCTION

The rates of germinal matrix and intraventricular hemorrhage (GM/IVH) in extremely preterm infants (<28 weeks) have not reduced in recent decades, despite improvements in neonatal care, and continue to affect approximately one-third of extremely preterm infants with more severe injury being associated with adverse neurodevelopmental outcomes [1–5]. While the pathogenesis of GM/IVH is multifactorial, a major contributor to development of GM/IVH in extremely preterm infants is cerebral blood flow (CBF) dysregulation. In particular, cerebral pressure passive circulation contributes to decreases, increases, and large fluctuations in CBF in the first few days of life [6–15].

Continuous monitoring of CBF has the potential to guide future preventive and therapeutic strategies for GM/IVH. While near-infrared spectroscopy (NIRS) measures regional cerebral saturation ($crSO_2$), $crSO_2$ may be used as a surrogate for CBF when stable oxygen content and extraction can be reasonably assumed [16]. Although normative values of $crSO_2$ in preterm infants in the first few days of life have been published [17], there are a limited number of studies that have explored the relationship between changes in $crSO_2$ and development of GM/IVH, and these provide conflicting reports on whether relative increases or decreases in $crSO_2$ reflect risk for GM/IVH [14, 18–22]. A few studies have shown increased $crSO_2$ in the first few DOL is associated with GM/IVH [14, 18], while others have found that GM/IVH is associated with decreased $crSO_2$ immediately after birth [19, 20] and within the first few days after birth [21, 23]. In addition to the conflicting prior results, many of these studies have been limited by small sample size and case-control design.

Therefore, the aim of this study was to compare the $crSO_2$ values over the first 5 days of life among extremely preterm infants with and without GM/IVH. In addition, given the known association between brain injury score on term equivalent (TE) MRI and long-term outcomes, we also aimed to explore the relationship between $crSO_2$ patterns and brain injury score on TE MRI.

METHODS

Patients

This is a retrospective cohort study which includes infants born <28 weeks gestational age with NIRS data recorded within the first 108 h of life (HOL). At our institution, beginning January 1st, 2018, all infants born before 28 weeks GA were monitored with NIRS for at least the first 3 days of life as part of the Neonatal Neurocritical Care Program at Brigham and Women's Hospital (BWH) Neonatal Intensive Care Unit, a single tertiary level unit. We included infants <28 weeks gestational age born between January 2018 and August 2020. Institutional review board approval was obtained with a waiver of consent.

Demographic and basic clinical data

Demographic and basic clinical data were extracted from the medical record and Vermont Oxford Network (VON) database, to which the hospital is a contributor. All clinical definitions are concurrent with the VON database definitions. If chorioamnionitis was recorded in either the mother's or the infant's medical record, the infant was identified as having chorioamnionitis. Patent ductus arteriosus (PDA) was defined as left

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to right or bidirectional ductal shunt on Doppler echo, and/or a systolic or continuous murmur, plus at least two of the following: (1) hyperdynamic precordium, (2) bounding pulses, (3) wide pulse pressure, (4) pulmonary vascular congestion, cardiomegaly, or both. Sepsis was defined as having a bacterial pathogen detected in blood and/or cerebrospinal fluid culture. Intubated refers to intubation throughout the entire first 108 HOL.

NIRS data

$crSO_2$ was monitored by an INVOS 5100 C Cerebral/Somatic Oximeter (Medtronic, USA) using neonatal sensors applied according to a locally developed Clinical Practice Guideline. This guideline includes continuous NIRS monitoring of all preterm infants <28 weeks GA for at least the first 3 days of life (https://www.brighamandwomens.org/assets/BWH/pediatric-newborn-medicine/pdfs/nirs-cpg.pdf) for clinical purposes. Using the algorithms included in these guidelines, the clinician utilizes $crSO_2$ data to assess cerebral oxygen delivery and/or extraction. For example, a patient with significantly decreased $crSO_2$ relative to baseline or absolute $crSO_2 < 60\%$ is evaluated for anemia, hypoxia, hypotension, chest hyperinflation, and hypocarbia and is treated accordingly. One sensor was placed on the frontoparietal side of the infant's head and alternated between right and left sides every 4–6 h (https://www.brighamandwomens.org/assets/BWH/pediatric-newborn-medicine/pdfs/nirs-appendix.pdf). These left and right-sided measurements were treated equally in our analysis. Measurements were performed at a sampling rate of 0.03 Hz.

Since the NIRS data were analyzed retrospectively from data collected clinically, we used analytic methodologies to clean the data and remove potential artifacts. Raw $crSO_2$ data were cleaned using MATLAB (ver. R2019b, Mathworks, Inc., Natick, MA) with the following rules in place: (1) to remove sporadic data points and step changes that likely represent detachment of the sensing probe in the last few hours of recording, we rejected a data period at the end of the measurement if it had >50% of points missing within 2 h from the last data point, and in the last 2 h of valid data we rejected the data following an abrupt change (defined as >1.5 times the interquartile range or the signal mean, identified using MATLAB's *isoutlier* or *ischange* functions, respectively); (2) to remove unreliable data points during the measurements, we rejected data if there were more than 90% of missing points in a non-overlapping 1 h sliding window. We also excluded data points >2.5 standard deviations from the mean using a 1 h sliding window, extreme $crSO_2$ values (defined as ≤25% and ≥95%), and all data within 3 min before and after the extreme values. The rejected data points were replaced with NaN (Not a number in MATLAB, which serves as a 'void' place holder). The final signal was summarized by calculating the median of the $crSO_2$ values, excluding the rejected data points, in each hourly time bin from birth, using the *retime* function in MATLAB. Subjects with a total measurement of <1 h within the first 108 HOL were excluded from the analysis. The signal cleaning of NIRS data resulted in an average rejection rate of 5.4 ± 7.9% in all subjects. (Supplemental Explanation of Data Cleaning and Supplemental Table 1). The number of infants with $crSO_2$ data available in first 108 HOL by hour and by 12 h interval is demonstrated in Supplemental Fig. 1A, B.

Cranial ultrasound

Cranial ultrasonography (cUS) was performed by either the GE LOGIQ™ E9 or the GE LOGIQ™ E10, using both the S4-10 baby head ultrasound transducer and the L9 linear probe. The cUS protocol routinely acquires six coronal images (anterior to posterior), coronal clips (frontal through parietal-temporal), eight sagittal images (including midline, right and left parasagittal, occipital horn view from posterior fontanelle), sagittal clips, and axial view of posterior fossa from the mastoid region. cUS was performed based on a local Clinical Practice Guideline (https://www.brighamandwomens.org/assets/BWH/pediatric-newborn-medicine/pdfs/hus-cpg.pdf), which recommends a cUS at one day, 3 days, 1 week and 1 month after birth. An additional cUS at 36 weeks postmenstrual age is obtained if TE magnetic resonance imaging (MRI) is not performed. Clinical cUS reports were used for study analysis. We classified the grade of GM/IVH as the most severe GM/IVH detected on cUS. The cohort was separated into GM/IVH and no GM/IVH. Those with GM/IVH were classified as mild (grade I (germinal matrix hemorrhage) or II) and severe (grade III or IV (periventricular hemorrhagic infarction)) [24]. GM/IVH was also classified into early GM/IVH if the hemorrhage was detected on cUS within the first 36 HOL, and late GM/IVH if there was a cUS performed within 36 HOL that did not show hemorrhage, with a subsequent cUS after the first 36 HOL showing hemorrhage.

Magnetic resonance imaging (MRI)

All TE MRI scans were performed on a 3-T Siemens scanner (Siemens, Erlangen, Germany). The standard clinical imaging protocol includes sagittal motion-corrected magnetization prepared rapid gradient echo T1-weighted images, axial turbo spin echo T1-weighted images, axial turbo spin echo T2-weighted images, and coronal turbo spin echo T2- weighted images. Diffusion-weighted imaging used multidirectional diffusion-weighted measurements. The pattern and severity of brain injury on the TE MRI were assessed via the Kidokoro scoring system, a validated scoring system for evaluating cerebral white matter (WM), cortical gray matter, basal ganglia and thalami, and cerebellum abnormalities. The measurements were corrected for postmenstrual age, and a global brain abnormality score was calculated as the sum of the regional total scores and classified as normal (total score of 0–3), mild (total score of 4–7), moderate (total score of 8–11), or severe (total score of 12 or more) [25].

Statistical analyses

Descriptive statistics of key demographic and clinical characteristics were calculated overall and by IVH status. Differences by IVH status were assessed using chi-square (exact for tests of small sample size, $n < 5$) or Wilcoxon rank sum, as appropriate. The median $crSO_2$ at each hour was calculated for each infant (see section *NIRS Data* above). Using these values, we calculated the median $crSO_2$ in each of nine 12 h intervals from the first to 108th HOL. The association between presence of IVH and $crSO_2$ values over time was modeled using linear mixed regression to take into account repeated measures within subjects nested within intrafamilial clusters (twins). The fixed-effects model included terms for IVH status and time (categorical) as well as their interaction. Models were adjusted for potential confounding by GA at birth, birth weight *z* score, and baseline hematocrit, base deficit, and pCO_2. Baseline values of these latter three factors were measured as the mean value from the first 12 HOL. Trajectories of $crSO_2$ over time for each group (GM/IVH vs. no IVH) were generated using the least square means and 95% confidence intervals for each group at each time point estimated from the analytic models. Similar trajectories were created for subgroups of IVH (severity (mild and severe) and time of onset (early (<36 HOL) and late (≥36 HOL))) as well as for total Kidokoro brain injury score severity categories. Due to reduced sample sizes among subgroup analyses, we focused our results on models unadjusted for potential confounding. Because these analyses were exploratory, we did not adjust for multiple comparisons.

For the earliest 12 h block where we identified a significant difference in $crSO_2$ by IVH status, we generated a receiver operating characteristic (ROC) curve to assess the accuracy of GM/IVH prediction using $crSO_2$. We used an unadjusted model and identified the cutpoint that optimized the Youden index. Based on this ROC curve and the optimal cutpoint, we calculated the diagnostic metrics (area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). All analyses were run using SAS v9.4 Software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographic and clinical results

During the study period, 65 extremely preterm infants (<28 weeks GA) were eligible for inclusion with NIRS data collected during the first 108 HOL. Of these 65, three infants were excluded due to <1 h of NIRS measurements recorded. Thus, 62 infants were included in our cohort. There were 28 (45.2%) infants who developed GM/IVH and 34 (54.8%) who did not. Demographic and clinical data by GM/IVH status are presented in Table 1. Compared with infants with no GM/IVH, those who developed GM/IVH were of younger GA ($p = 0.018$), had lower baseline HCT ($p = 0.0351$), were more likely to be intubated ($p = 0.0025$), and had higher rates of complications such as sepsis ($p = 0.0334$) and retinopathy of prematurity (ROP) ($p = 0.0139$). Among the infants with GM/IVH, 14 (50.0%) had mild GM/IVH (4 grade I and 10 grade II) and 14 (50.0%) had severe GM/IVH (3 grade III and 11 grade IV). The median hours (IQR) of life until first detection of hemorrhage did not differ significantly between the mild (36.8 h (17.7–91.0)) and severe (42.0 h (18.7–65.4)) groups ($p = 0.9795$).

Among the 28 infants who developed GM/IVH, both early and late cUS was available for 24 (85.7%) infants. Of these, 11 (45.8%)

Table 1. Demographic and clinical data of the study cohort ($n = 62$).

	No GM/ IVH ($n = 34$)	GM/ IVH ($n = 28$)	p value
GA (weeks)	26.1 (25.3–27.1)	25.1 (24.1–26.1)	0.0180[a]
Birth weight (g)	805 (690–930)	697.5 (582.5–858.5)	0.1431
Multiple Births	11 (32.4)	6 (21.4)	0.3373
Sex (male)	14 (41.2)	18 (64.3)	0.0700
Chorioamnionitis	3 (8.8)	6 (21.4)	0.2773
Cesarean section	30 (88.2)	20 (71.4)	0.1165
Apgar 1 min	4.0 (3.0–6.0)	3.0 (1.5–5.0)	0.0641
Apgar 5 min	7.0 (6.0–8.0)	6.0 (4.0–7.5)	0.1414
Chest compressions in DR	3 (8.8)	3 (10.7)	1.0000
Baseline Base deficit (mEq/L)	2.5 (1.4–4.4)	3.5 (1.8–5.6)	0.2211
Baseline pCO_2 (mmHg)	48.8 (43.2–53.7)	50.2 (43.1–55.3)	0.5812
Baseline Hematocrit (%)	44.4 (39.0–47.8)	40.0 (35.8–45.3)	0.0351[a]
Intubated	10 (29.4)	19 (67.9)	0.0025[a]
PDA	24 (70.6)	20 (71.4)	0.9422
Sepsis	2 (5.9)	8 (28.6)	0.0334[a]
ROP[b]	19/32 (59.4)	20/22 (90.9)	0.0139[a]
Death	1 (2.9)	4 (14.3)	0.1658
HOL until first detection of hemorrhage	N/A	41.2 (18.7–66.2)	0.9795
HOL NIRS measurements began	9.5 (5–19)	7 (4.5–18.5)	0.6099
HOL NIRS measurements ended	80.5 (73–100)	78 (67.5–126.5)	0.9211
Median duration (hours) of measurement	68 (54–89)	70 (48–109)	0.5714

Categorical and binary data presented as n (%), continuous data as medians (Interquartile range (IQR)).
Differences among categories were assessed using chi-square (exact for tests of small sample size, $n < 5$), Wilcoxon rank sum.
GA gestational age, *DR* delivery room, *PDA* Patent Ductus Arteriosus, *ROP* Retinopathy of Prematurity.
[a]p value < 0.05.
[b]Not all subjects had data on ROP status. In the Table we have specified the denominator for this variable to provide the total number of subjects on which our percentages are based.

had early GM/IVH (I ($n = 2$), II ($n = 4$), III ($n = 0$), IV ($n = 5$), and 13 (54.2%) had late GM/IVH (I ($n = 2$), II ($n = 4$), III ($n = 3$), IV ($n = 4$)). The median age in hours (IQR) at detection of GM/IVH in the early group was 18.1 (14.4–23.6), compared with 94.7 (60.6–156) in the late group ($p < 0.0001$). Of note, five infants received a diagnosis of GM/IVH after the 108 h evaluated in this study.

NIRS measurements

NIRS monitoring began at a median (IQR) eight (5–19) h old and ended at 79.5 (72–107) h old, with a median duration of 69 h (52–93). Time to start and duration of NIRS monitoring did not differ based on IVH status (Table 1).

$crSO_2$ comparison between no IVH and IVH

Based on estimates from the unadjusted linear mixed model, the $crSO_2$ trajectory for the GM/IVH group exhibited a steady decrease after 36 h while that for the no GM/IVH group was relatively stable over time. Infants with GM/IVH had significantly lower $crSO_2$ values than those with no GM/IVH after 36 HOL (Fig. 1). When the model was adjusted for potential confounding, there was attenuation of the difference between groups as compared with the adjusted model, but the $crSO_2$ trajectories still exhibited significantly lower levels among the GM/IVH infants compared with the no GM/IVH infants after 48 h (Fig. 2).

Receiver operating characteristic (ROC) curve

We generated an ROC curve to assess the accuracy of GM/IVH prediction between 37 and 48 h using $crSO_2$ (Supplemental Fig. 2). The area under the ROC curve (AUC) was 0.7141 (95% CI: 0.5710, 0.8571, $p = 0.0037$) indicating that the model has a 71.41% chance to distinguish infants by GM/IVH status and that the estimate is significantly better than by chance (50%) alone. A $crSO_2$ cutoff at 73% optimized the Youden index and the distance to the (0,1) point. This cutoff further gave the highest correct classification rate, 70% (along with the cutoff at 71.5%). The diagnostic metrics at the 73% threshold were as follows: sensitivity: 75%, specificity: 66%, PPV: 64.5%, and NPV: 76%.

$crSO_2$ comparison between subgroups of IVH

In linear mixed models both unadjusted (Supplemental Fig. 3) and adjusted (not shown) for potential confounding, there were no significant differences between median $crSO_2$ levels among infants with mild GM/IVH compared to those with severe GM/IVH. The trajectories of the two IVH groups exhibited a decrease in $crSO_2$ values over time after 36 ho compared to the no IVH group. However, there was overlap between the mild and severe IVH trajectories and a consistent difference in $crSO_2$ between them was not evident.

In models unadjusted (Fig. 3) and adjusted (not shown) for potential confounding, comparing early GM/IVH and late GM/IVH, $crSO_2$ values among early GM/IVH infants were higher than those among late GM/IVH infants in the initial 24 h of life (e.g., between 13 and 24 HOL, 76.4% (early) vs. 69.5% (late), $p = 0.066$). This trend was also observed when the model was adjusted for potential confounding ($p = 0.094$).

Term equivalent brain abnormalities

MRI data for Kidokoro scorings were available for 44 (77.2%) of the 57 surviving infants among the original 62. Median (IQR) of the global brain abnormality score in our cohort was in the normal

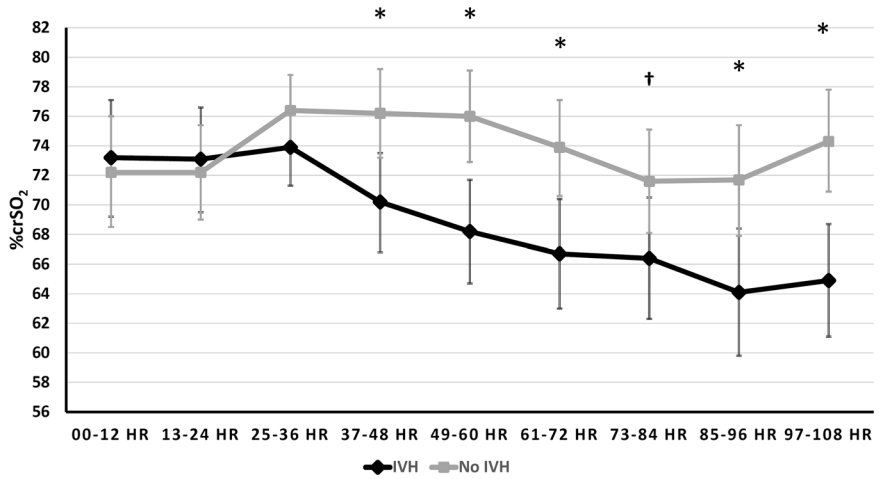


Fig. 1 Trajectories of %crSO$_2$ (least square means and 95% CIs) over time by IVH status. Repeated measures analysis with intrafamilial clustering among subjects using linear mixed models unadjusted for potential confounding. *$p < 0.05$; Least square means (95% CI): 37–48 h (IVH 70.2 (66.8,73.5), no IVH 76.2 (73.2, 79.2), $p = 0.0094$); 49–60 h (IVH 68.2 (64.7, 71.7); no IVH 76 (72.9, 79.1), $p = 0.0015$); 61–72 h (IVH 66.7 (63,70.4); no IVH 73.9 (70.6,77.1), $p = 0.0053$); 85–96 h (IVH 64.1 (59.8, 68.4), no IVH 71.7 (67.9,75.4), $p = 0.0097$); 97–108 h (IVH 64.9 (61.1, 68.7), no IVH 74.3 (70.9, 77.8), $p = 0.0005$). $^{\dagger}p < 0.1$; Least square means (95% CI): 73–84 h (IVH 66.4 (62.3,70.5), no IVH 71.6 (68.1,75.1), $p = 0.0603$).

(scores 0–3)-to-mild (scores 4–7) range (3 (1–6)). The majority of MRIs (28 (63.6%)) were categorized as normal, while the rest had abnormalities categorized as mild in eight (18.2%) infants, moderate in four (9.1%), and severe in four (9.1%). There were no significant differences in crSO$_2$ levels by Kidokoro severity category (normal, mild, moderate, severe) using linear mixed models unadjusted (Supplemental Fig. 4) or adjusted (not shown) for potential confounding overall or within any single time interval.

DISCUSSION

In a contemporary cohort of extremely preterm newborns utilizing NIRS for clinical brain monitoring, exploratory analysis showed that infants with no GM/IVH had relatively stable crSO$_2$ in the first 108 h after birth, while those who developed GM/IVH showed a decline in their crSO$_2$ after the second day of life.

These results are consistent with other studies that have demonstrated that GM/IVH is associated with lower crSO$_2$ immediately after birth [19, 20] and in the first 2–15 DOL [21, 23]. Other authors who extended NIRS monitoring beyond this period have demonstrated a lower crSO$_2$ in babies with GM/IVH up to 68 postnatal days, suggesting that these early deviations in crSO$_2$ may persist for prolonged periods, well beyond the time when the hemorrhage actually occurred [22].

Identifying a cut-off value of crSO$_2$ that represents increased risk for GM/IVH would be of great clinical value. One prior prospective study using crSO$_2$ attempted to identify a risk cutoff for the period immediately after birth among preterm infants <32 weeks. Using an outcome of death or severe IVH in the first 72 h of life, the authors calculated a ROC curve and demonstrated a crSO$_2$ threshold of 66 during the period from seven to 10 min of life, with a sensitivity of 89% and specificity of 81% in predicting poor outcome [19], although the number of infants with the outcome was very small ($n = 4$). In our study, we found a threshold of 73% at 37–48 h to predict GM/IVH, with a sensitivity of 75% and specificity of 66%. This difference in threshold could be explained by the fact that in our study we evaluated any degree of IVH and not severe IVH/death as in the aforementioned study. In addition, caution is necessary when using NIRS absolute values, especially when different devices and sensors are used for measurements. In the prior study, crSO$_2$ was measured via a FORE-SIGHT Elite Absolute Tissue Oximeter by CASMED combined with EEG, so the absolute values may not be directly comparable to ours.

In our study, the severity of GM/IVH did not affect the magnitude of decline in crSO$_2$. This finding is consistent with those from some previous studies with similar sample size to ours [21]. For example, in a case-control study of 34 preterm infants (mean GA 29 weeks) using NIRS for 2 h a day over the first 2 weeks of life, crSO$_2$ was lower and fractional tissue oxygen extraction was higher in infants with GM/IVH throughout the first 15 days of life, regardless of the IVH grade [21]. However, other reports from larger cohorts found a negative correlation between the severity of GM/IVH and crSO$_2$ [22, 26]. It is possible that the sample size of our cohort may have limited our ability to detect small differences in crSO$_2$ between infants with varying severity of GM/IVH.

The mechanism of the association of GM/IVH with low crSO$_2$ is not well defined, and it is unknown whether the association between low crSO$_2$ and GM/IVH is causal. The low saturation very early in life prior to the development of hemorrhage may relate to low cardiac output with a resulting cerebral hypoperfusion leading to GM/IVH. Later in the first few days of life, with declining pulmonary pressure, a hemodynamically significant PDA could be associated with a significant left to right shunt and a cerebral "steal phenomenon," leading to decreased cerebral perfusion [27–29] or fluctuations increasing risk for GM/IVH [30]. Disturbance of cerebrovascular autoregulation is thought to be a key factor in GMH/IVH as impaired autoregulation limits the buffering of fluctuations in systemic blood pressure resulting in cerebral ischemic-reperfusion and hemorrhagic injury [31, 32]. Fluctuating pressure passivity occurs in the majority of very low birth weight infants [10], and increased passivity in this population has been associated with GM/IVH [11, 14, 23]. One prior study using NIRS in the immediate postpartum period among infants born less than 32 weeks GA showed that crSO$_2$ was lower in GM/IVH group [20] despite no differences in systemic oxygen saturation between groups, supporting the premise that clinically significant differences in crSO$_2$ likely represent differences in CBF. In the presence of established GM/IVH, low crSO$_2$ could also be related to impaired autoregulation with an altered brain tissue metabolism in injured tissue leading to increased oxygen extraction [22]. Alternatively, low crSO$_2$ may be due to altered regional blood flow affecting cortical and subcortical regions in the presence of GM/IVH [33]. Finally, low crSO$_2$ could also reflect an associated developing

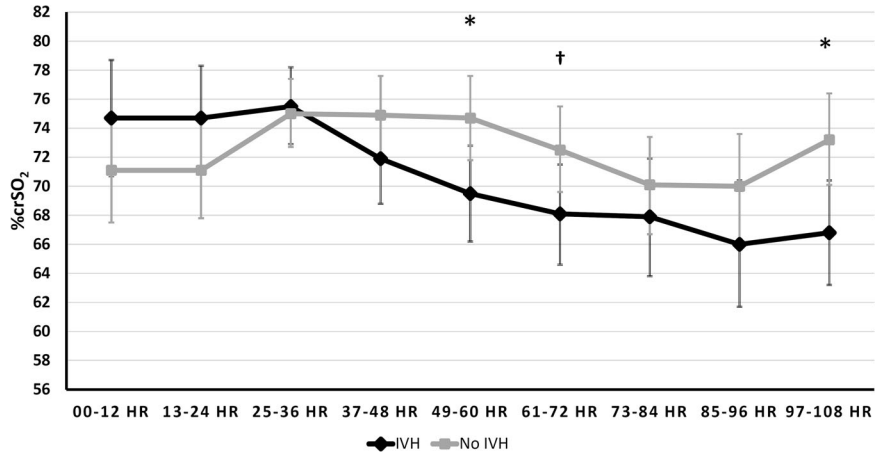


Fig. 2 Trajectories of %crSO$_2$ (least square means and 95% CIs) over time by IVH status. Repeated measures analysis with intrafamilial clustering among subjects using linear mixed models adjusted for potential confounding by gestational age at birth, birth weight *z* score & baseline hematocrit, base deficit and pCO2. *$p < 0.05$; Least square means (95% CI): 49–60 h (IVH 69.5 (66.2, 72.8); no IVH 74.7 (71.8, 77.6), $p = 0.0232$); 97–108 h (IVH 66.8 (63.2, 70.4), no IVH 73.2 (70.1, 76.4), $p = 0.0104$). †$p < 0.1$; Least square means (95% CI): 61–72 h (IVH 68.1 (64.6,71.5), no IVH 72.5 (69.6,75.5), $p = 0.0584$).

anemia, although we controlled for baseline hematocrit in our study.

Although we did not capture a clear sequence of an initial hypoperfusion followed by reperfusion, crSO$_2$ values for early GM/IVH tended to be higher than for late (and no) GM/IVH in the first 24 HOL, particularly between 13 and 24 h ($p = 0.066$). This finding among those who developed early GM/IVH is similar to results reported from previous studies which demonstrated an increase in crSO$_2$ prior to development of hemorrhage [14, 15, 34]. In one prospective study, newborns who developed severe GM/IVH after 12 HOL had higher crSO$_2$ *preceding* the development of GM/IVH when compared to matched controls without IVH (cUS was done on admission and then daily) [14]. This finding was also reported in a small, well-designed prospective observational study of infants with no IVH who had cardiac function, CBF and IVH status monitored every 12 h for 72 h beginning within 4–6 HOL. Although this study only had five infants with GM/IVH, it observed a hypoperfusion-reperfusion pattern before development of GM/IVH. While infants without IVH had stable myocardial function and cerebral perfusion, those who developed GM/IVH had low initial stroke volume and lower crSO$_2$ followed by improved systemic and cerebral perfusion before development of GM/IVH [15]. Similarly, a recent study using daily cUS and echocardiogram showed that although infants with GM/IVH had overall lower crSO$_2$, a temporary rise in crSO$_2$ was noted between the 12 and 36 h preceding GM/IVH detection. That study also showed that those with IVH had increased pressure passive circulation using the heart rate reactivity index, but there was no change in left ventricular output [34]. In our study, a trend of increased crSO$_2$ was only observed in the early group, but not the late group. An explanation for this difference could be that the late group developed GM/IVH over a longer time period, making it difficult to detect a clear trend in crSO$_2$. This late IVH group includes five patients who were diagnosed with GM/IVH after 108 HOL, which goes beyond the time of NIRS monitoring. In addition, this difference in trends could point to a difference in pathogenesis of GM/IVH that happens early (with more pronounced impact of hemodynamic changes) vs. late (with more impact from other comorbid factors e.g., sepsis, etc.).

We also analyzed the TE MRIs of study patients. Although low crSO$_2$ was associated with WM injury in a previous study [22], in our study, we did not identify a relationship between crSO$_2$ and total brain abnormality score. Although the Kidokoro score reflects WM injury as well as other causes of altered brain growth which are common in this population, these causes may not be related to NIRS measurements in the first few days of life.

A key feature of crSO$_2$ is that it is not only a marker of perfusion, but also of oxygen delivery and extraction. Low crSO$_2$ is associated with short and long-term adverse outcomes [35, 36]. Whether low crSO$_2$ is a marker for GM/IVH or if it is a modifiable risk factor is not fully understood. Other authors have shown that although established practice algorithms could reduce the burden of cerebral hypoxia immediately after birth [37] and in the first few DOL [38], no improvement was noted in imaging, EEG, or biomarkers of brain injury [39, 40]. We await the results of ongoing trials to determine if correcting for cerebral hypoxia immediately after birth [41] or in the first few DOL [42] can prevent or reduce the occurrence of GM/IVH and improve neurologic outcomes.

The limitations of this study include the retrospective nature of the data collected. The objective nature of the exposure variable (crSO$_2$), however, limits potential bias related to the retrospective design. To further mitigate these effects, we adjusted for possible confounding due to key demographic and clinical differences between groups. Although a hemodynamically significant PDA could affect crSO$_2$ values, we did not add PDA as a confounder due to absence of consistent echocardiography findings in first few days of life. It is a strength of our study that these data were collected clinically, which demonstrates that clinical NIRS data were of adequate quality to detect differences between infants with or without IVH, highlighting the potential clinical utility of the NIRS device. Another limitation is that there was no cUS performed on admission. In most cases, there were only two cUS available in the first four DOL and nearly 50% of these with GM/IVH developed it prior to the first cUS. This infrequent imaging does not allow for an accurate estimation as to the timing of GM/IVH development. In the absence of accurate timing of IVH, a cause-effect relationship between the onset of IVH and the crSO$_2$ changes described in the study cannot be presumed. In addition, since simultaneous systemic oxygen saturation data were unavailable, we were unable to calculate oxygen extraction. Furthermore, there was no long-term developmental follow-up of the study population. However, it is known that the degree of GMH/IVH impacts neurodevelopmental outcomes.

In summary, infants with GM/IVH exhibit divergent crSO$_2$ trajectories in the first few DOL when compared to infants without hemorrhage. In those with GM/IVH, crSO$_2$ levels decline after the second DOL, whereas infants without hemorrhage have

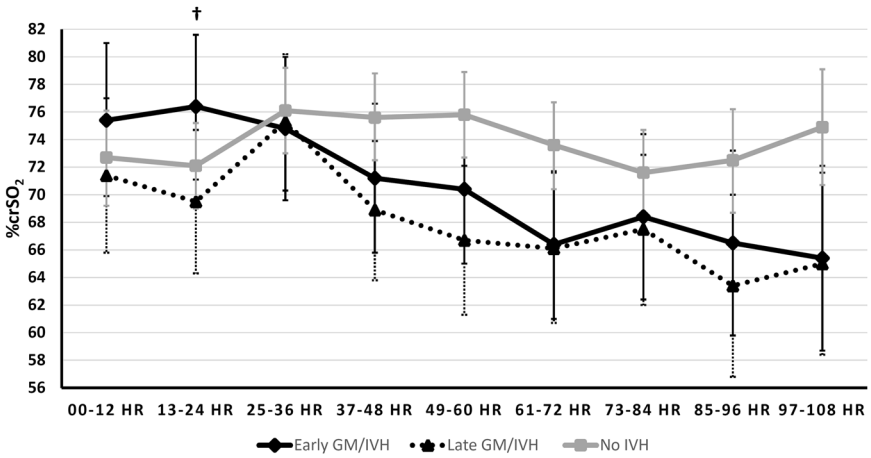


Fig. 3 Trajectories of $crSO_2$ (least square means and 95% CIs) over time by Early/Late/No IVH status. Repeated measures analysis with intrafamilial clustering among subjects using linear mixed models unadjusted for potential confounding. $^{\dagger}p < 0.1$; Least square means (95% CI): 13–24 h (Early GM/IVH 76.4 (71.1,81.6), Late GM/ IVH 69.5 (64.3,74.7), $p = 0.0660$).

stable $crSO_2$ levels. Thus, non-invasive monitoring of $crSO_2$ using NIRS may provide a useful bedside tool to monitor interventions aimed at prevention of GM/ IVH.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

MED conceptualized and designed the study, drafted the initial paper, and reviewed and revised the paper. CM participated in research data acquisition, helped to draft the initial paper, and reviewed and revised the paper. JS assisted in data processing, helped to draft the initial paper, and reviewed and revised the paper. SC performed the statistical analyses, helped to draft the initial paper, and reviewed and revised the paper. SL, EH, and TS participated in research data acquisition and reviewed and revised the paper. KB, MAF, and JV provided guidance around the study design, and reviewed and revised the paper. TI helped to conceptualize and design the study and reviewed and revised the paper. All authors approved the final paper as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

MEl-D discloses he is the PI of an investigator-initiated research funded by Medtronic and served once on an advisory board for Radiometer but these are not related to this work. Other authors declare that they have no competing interests.

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