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Progressive anemia of prematurity is associated with a critical increase in cerebral oxygen extraction

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Abstract

Background: Elevated cerebral fractional tissue oxygen extraction (cFTOE) is an adaptation to anemia of prematurity (AOP). cFTOE ≥0.4 is associated with brain injury in infants ≤30 weeks. This longitudinal study sought to investigate the utility of cFTOE in the evaluation of AOP.

Methods: Infants ≤30 weeks estimated gestational age (EGA) underwent weekly hemoglobin, cerebral saturation, and pulse oximetry recordings from the second through 36 weeks post-menstrual age (PMA). Recordings were excluded if they were under 1 hour or if hemoglobin was not measured within 7 days of recording. Mean cFTOE was calculated for each recording. Statistical analysis used linear mixed-effects modeling and receiver operating characteristic analysis.

Results: 144 recordings from 39 infants (mean EGA 27.6 ± 2.2 weeks, BW 1139 ± 286g) were included of whom 39% (15/39) were transfused. The mean recording length was 2.8 ± 1.3 hours. There was a significant negative correlation between hemoglobin and cFTOE ($R = -0.423$, $p=<0.001$). In a multivariate model, adjusting for EGA, PMA, and patent ductus arteriosus treatment the AUC was 0.821. A critical increase in cFTOE occurred at a hemoglobin level of 9.6 g/dL.

Conclusions: AOP is associated with a critical increase in cFTOE that occurs at a significantly higher hemoglobin level than standard clinical thresholds for transfusion.

Keywords

Anemia of prematurity; prematurity; cerebral NIRS; oxygen extraction

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Introduction

Anemia of prematurity (AOP) continues to present a common and significant management challenge in the NICU as demonstrated by the substantial variation in clinical transfusion practices [1-4]. Though transfusions in some populations have decreased, the burden remains high with more than half of preterm infants < 30 weeks estimated gestational age (EGA) and up to 85% of those < 26 weeks EGA receiving packed red blood cell (pRBC) transfusions during their NICU hospitalization [5,6]. Conflicting data on appropriate transfusion thresholds for preterm infants and emerging data on potential sequelae of both severe anemia and transfusion make it difficult for clinicians to decide when to transfuse an individual patient [7-12]. Published randomized trials demonstrate heterogenous results; some studies support a reduction in short-term brain injury and apnea outcomes with liberal transfusion practices [13], others demonstrate no statistically significant difference in neurologic injury or neurodevelopmental outcomes [10,14], and yet others suggest a difference in longer term neurodevelopmental outcomes [9]. Two ongoing studies (Transfusions of Prematures (TOP) NCT01702805, and Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth Weight Infants (ETTNO) NCT01393496) aim to definitively answer this question with adequate statistical power.

Nevertheless, even the existing data are compelling enough to prompt an evaluation into the mechanism which might underlie the link between anemia and brain injury risk. While the brain has a remarkable ability to compensate for fluctuations in the delivery of oxygen by increasing the fraction of oxygen extracted from the blood, this autoregulatory system can be exceeded [15,16]. The central focus of this project was to investigate the impact of anemia of prematurity (AOP) on cerebral tissue hypoxia and compensatory oxygen extraction.

While available data on cerebral compensation for AOP are limited, cross-sectional studies have revealed lower cerebral saturations and higher cerebral oxygen extraction in the setting of anemia and that this pathologic state normalizes with pRBC transfusion [17-20]. Existing studies comparing transfusion thresholds have relied on standard clinical monitoring of vital signs (heart rate, pulse-oximetry) and have not examined compensatory responses to progressive anemia or its impact on end-organ tissue oxygenation. While pulse oximetry provides important information about arterial oxygen saturation, it does not assess oxygen delivery or consumption at the tissue-specific level. In contrast, near-infrared spectroscopy (NIRS) provides a noninvasive measure of regional (cerebral) tissue oxygenation (C-rSO_2) and allows for calculation of cerebral tissue oxygen extraction [21-24].

Prior work by our group demonstrated a strong relationship between hemoglobin and cerebral saturation in transfusion-naïve preterm infants where worsening anemia was associated with a progressive decrease in C-rSO_2. In that study, we demonstrated that a hemoglobin concentration of 9.5g/dL or less results in cerebral desaturation >2 SD below the normative mean [25,26]. This study was limited by a lack of simultaneous pulse-oximetry, which is needed to calculate the cerebral fractional tissue oxygen extraction (cFTOE). Without this information, it is difficult to assess the magnitude of the compensatory response.

We sought to address this shortcoming in the present study by focusing on the *longitudinal* impact of anemia of prematurity on cFTOE in preterm infants. We hypothesized that preterm infants are able to compensate for mild anemia, but that there is a critical threshold, beyond which pathologic oxygen extraction occurs, increasing the risk for brain injury and that NIRS would provide insight into this loss of compensation. Using simultaneous NIRS and pulse oximetry, we prospectively evaluated the longitudinal impact of increasing anemia on cFTOE in a cohort of preterm infants ≤30 completed weeks EGA from the second week of life through 36 weeks post-menstrual age (PMA).

Methods

Patient selection

In this prospective observational study, preterm infants born at or before 30 weeks completed gestation were recruited in the first 14 days of life from the St. Louis Children's Hospital NICU, a level IV unit serving an urban, suburban, and rural population. Infants were excluded if they had known congenital or chromosomal anomalies or were clinically unstable and not expected to survive the first week of life. Infants with severe IVH (grade III/IV on the Papile scale [27]) were also excluded from the analysis. Prior reports have demonstrated concern that the large pool of deoxygenated blood in the ventricles / parenchyma following severe IVH regionally alters the total hemoglobin and may depress the measured cerebral saturations on the ipsilateral hemisphere as the hemorrhage [28-30]. Additionally, the hemorrhage independently increases fractional oxygen extraction for an extended time period [31], further confounding measurement in these infants.

Informed written consent was obtained from parents for all participants. The study protocol and procedures were reviewed and approved by the Human Subjects Research Protection Office at Washington University.

Sample characteristics

Comprehensive sample characteristics were collected for all infants in the cohort. Antenatal characteristics included mode of delivery, antenatal corticosteroid exposure, delayed cord clamping, and the five-minute Apgar score. Patient characteristics included EGA in completed weeks, birth weight, small for gestational age (SGA) status (defined as birth weight <10th centile), gender, and race/ethnicity. Clinical factors included Clinical Risk Index for Babies II (CRIB-II) score (using the algorithm developed by Parry et al.[32]), IVH, respiratory support type and duration, medication administration, patent ductus arteriosus (PDA) requiring treatment (defined as moderate or large diameter ductus with concurrent left atrial and ventricular enlargement on echocardiogram), hemoglobin measurements, transfusions, and mortality. All hemoglobin values were obtained at clinical provider discretion.

Institutional practices and guidelines

Cerebral NIRS is not part of routine clinical monitoring of preterm infants at our institution. Cranial ultrasound evaluations are performed at least twice in the first ten days, generally on

the third and tenth day of life. All studies are performed through the anterior fontanelle and the mastoid window to identify IVH and cerebellar hemorrhage.

Institutional transfusion guidelines for premature infants recommend pRBC transfusion for hemoglobin ≤10 g/dL in critically-ill infants (defined as invasive mechanical ventilation and/or inotropic support) and for hemoglobin ≤8 g/dL in stable, non-intubated infants. In order to reduce exposure to multiple donors, single units of blood are split into five equal aliquots and are stored until used or expired (6 weeks from split). Transfusions at our institution are generally given via peripheral IV and administered over 2 hours. All transfusions in the study cohort occurred at clinician discretion.

Data collection

Cerebral oximetry data were collected using NIRS via the INVOS 5100C oximeter with the OxyAlert Infant/Neonatal Sensor (Covidien, Mansfield, MA). The device utilizes a two-wavelength (730 and 810 nm) LED-based emitter and two optical detectors located 30 and 40 mm from the emitter, sampled at a rate of 0.2 Hz. The sensor was placed on the left frontoparietal scalp as standard. Weekly cerebral NIRS recordings 6-8 hours in length were conducted from the second week of life through 36 weeks PMA.

Pulse oximetry data (systemic oxygen saturation, SpO_2) were obtained using an adhesive probe place on the infant's hand or foot (Neonatal-Adult SpO_2 sensor, Covidien, Mansfield, MA) and the Nellcor Oximax algorithm integrated into the patient's bedside monitor (Phillips IntelliVue monitor MP70 or MX800, Andover, MA). Time-linked cerebral oximetry and pulse-oximetry data were captured from the infant's monitor using ixTrend software (ixellence, Wildau, Germany).

Cerebral fractional tissue oxygen extraction (cFTOE) is the ratio of cerebral oxygen consumption to oxygen delivery. It is a composite measure influenced by factors which impair oxygen delivery (hypotension, hypoxia, acidosis, anemia) and oxygen utilization by the brain (from increased cerebral activity [33]). The autoregulatory system of the brain provides a compensatory mechanism which increases oxygen extraction in impaired states (inadequate delivery and/or increased metabolism). In order to define a pathologic or "critical" cFTOE, we utilized normative and outcome data published in the literature. We acknowledge that biologic systems are not truly binary and that the final threshold represents a balance between a practical definition and the evidence in the literature.

Numerous references support the relationship between impaired oxygen delivery from a variety of mechanisms (including anemia, hypotension, and respiratory distress syndrome) and increasing cFTOE [34-37] which is consistent even when using other methodologies for measurement of oxygen extraction such as MRI [38]. Although there are minor variations by gestational age, reference curves of nearly 1000 infants published by Alderliesten et al. suggest a mean cFTOE of 0.32 and that a threshold of 0.40 represents values at least two standard deviations beyond the normative distribution [25]. Increasing FTOE, particularly at levels ≥ 0.4, is also associated with an increased risk of ultrasound-identified brain injury in preterm infants ≤ 30 weeks [19,20,39,40] and adverse neurodevelopment at 2-3 years of age [41].

Recording analysis

Prior to analysis, all recordings were visually evaluated for quality and were eliminated if they were corrupted, of insufficient duration (<1 hour), if a hemoglobin measurement was not obtained within 1 week of the recording, or if a transfusion occurred between hemoglobin measurement and monitoring. The one-hour length threshold for sufficiency of raw data was empirically determined by examining the duration of C-rSO_2 data required to obtain a stabilized mean within 10% of the value for a recording 6-8 hours in length, a methodology utilized by this group in a prior study [26].

After visual quality assessment, recordings underwent three-step error correction for data sufficiency, systemic desaturation, and motion artifact. Error correction was performed by dividing each recording into 60-second epochs. Each epoch was examined for data sufficiency and epochs were discarded if greater than 50% of either the C-rSO_2 or SpO_2 data was missing (e.g. probes not in good contact with skin or removed). Remaining epochs were next examined for systemic desaturation and any 60-second epoch with a mean SpO_2 value <85% was eliminated as desaturation-related changes in arterial and venous contributions to C-rSO_2 make NIRS values unreliable in this setting [42]. Finally, the remaining epochs were examined for motion artifact contamination, which was identified by sudden, non-physiologic changes in the measured SpO_2. Any epoch where the measured SpO_2 had second-to-second variation ≥5% was discarded for motion contamination, as established in a prior study [43]. After error-correction, a mean cFTOE was calculated for each recording along with corrected recording length and error correction rates. Calculation of cFTOE was performed using the standard equation: $FTOE = (SpO_2 - C\text{-}rSO_2)/SpO_2$ [25].

Statistical Approach

The goal of this project was to identify the impact of longitudinally decreasing hemoglobin (with progressive AOP) on the risk of developing critical cerebral oxygen extraction, defined here as a cFTOE ≥0.4. Given the repeated-measures design of the study, a mixed-effects logistic regression model was used. In this model we evaluate the hemoglobin around the time of the NIRS measurement and the resulting cFTOE. This model was adjusted for important confounding fixed effects. These variables, selected from the comprehensive clinical data collected for the project, were included if they were statistically significant in univariate analysis, improved model discrimination, and/or were known determinants of cFTOE such as gestational age at birth and a hemodynamically significant PDA requiring treatment [44,45]. The repeated and randomly sampled nature of the observations are accounted for using the additional fixed effect of PMA at time of recording and a random effect by participant to control for within-subjects correlation.

To determine the hemoglobin threshold where the cFTOE increased beyond 0.4, we computed receiver-operating characteristics (ROC) of hemoglobin values by plotting sensitivity *vs.* 1 – specificity. To identify the hemoglobin value that best correlated with cFTOE ≥0.4, we selected the point with the highest sum of sensitivity and specificity (Youden's *J* statistic) [46]. Differences between ROC curves were assessed using the DeLong method [47].

All statistical tests were two-tailed and considered significant at $p<0.05$. All statistical analysis was performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). Mixed modeling was done using the lme4 package for R. As a similar study has not previously been performed, power was not calculated *a priori* but was rather a convenience sample over a fixed time interval.

Results

Patient characteristics

This study included 39 infants with mean ± SD EGA of 27.6 ± 2.1 weeks and mean ± SD birth weight of 1139 ± 286 grams. Of the included infants, 12 (31%) had grade I-II IVH. During monitoring, 15% (6/39) had a measured hemoglobin ≤8 g/dL and 69% (27/39) had a measured hemoglobin ≤10 g/dL with a median hemoglobin of 9.9 g/dL (range 7.1-17.0 g/dL). During hospitalization, 15/39 (39%) infants received a pRBC transfusion. Full cohort characteristics are listed in Table 1.

Data quality

A total of 214 C-rSO_2 recordings were obtained from the 39 infants included in our study. 144 recordings (67%) were included in the final analysis. The remaining 70 recordings were excluded due to missing/corrupted data (n=24), insufficient raw recording length (n=8), or absence of a hemoglobin measurement within 7 days (n=38). The mean raw recording length was 4.6 ± 1.0 hours with a mean data rejection rate of 40%. Of the identified errors, 34% were due to systemic desaturation, 34% were due to the NIRS probe not being in contact with the skin, and 32% were due to motion artifact detected in the pulse oximetry data. After error correction, the mean recording length was 2.8 ± 1.3 hours. The mean interval between recording and hemoglobin measurement was 2.3 ± 1.5 days (Figure 1).

Statistical Analysis

Unadjusted linear regression revealed a moderate statistically significant negative correlation between hemoglobin and cFTOE ($r = -0.423$, $p<0.001$). A scatter plot of hemoglobin and cFTOE in the cohort is illustrated in Figure 2. Unadjusted ROC analysis demonstrated moderate discrimination (AUC 0.708, $p<0.001$) with a threshold hemoglobin of 9.6 g/dL for critically increased cerebral oxygen extraction (cFTOE ≥0.4) with a sensitivity of 66% and a specificity of 67%. Density plots demonstrating the distribution of measured hemoglobin around the time of recording, divided into groups for those with a mean cFTOE <0.4 and ≥0.4 are illustrated in Figure 3.

The final mixed-effect model included fixed effects of EGA, hemoglobin around the time of recording, presence of a hemodynamically significant PDA requiring treatment, and PMA at time of recording. The model also included a random effect by participant. After adjustment for all fixed and random effects, hemoglobin remained a significant predictor of a critically increased cFTOE ($p=0.02$). Full characteristics of the mixed model are listed in Table 2.

ROC analysis adjusting for EGA, PMA, and PDA treatment status demonstrated good discrimination (AUC 0.821, $p<0.001$). Both the unadjusted and adjusted ROC curves are

illustrated in Figure 4. The adjusted ROC curve performed significantly better than the unadjusted ($p<0.001$). The model is not affected by history of transfusion, with similar performance when the two groups of infants are compared (never transfused AUC = 0.805, transfused AUC = 0.809).

Pre- and post-transfusion NIRS recordings were available for nine of the fifteen transfused infants. The mean cFTOE before transfusion was 0.44 which improved to 0.35 after transfusion, a ΔcFTOE of 0.09. This finding is comparable to other published studies [48,49].

Discussion

This study demonstrates an association between worsening anemia and increased cerebral oxygen extraction in preterm infants ≤30 weeks. The identified threshold for critical cerebral oxygen extraction in preterm infants is approximately 9.6 g/dL, which is consistent with the threshold we previously identified for critical cerebral desaturation is non-transfused preterm infants [26]. We defined cFTOE ≥ 0.4 as *critical* since this threshold has been associated with an increased risk of brain injury in premature infants [19-21]. This result is consistent with existing cross-sectional studies which have demonstrated lower C-rSO2 and higher cFTOE in anemic preterm infants [18,21,26,50]. It is additionally supported by a 2010 cross-sectional study by van Hoften et al. of 33 preterm infants which found a pre-transfusion hemoglobin ≤9.7 g/dL was associated with an increased incidence of cFTOE ≥0.4 [49]. Using cFTOE rather than C-rSO_2, we were able to identify a threshold that was significant in preterm infants regardless of their transfusion status making it a more generalizable metric than C-rSO_2 for identifying compromised cerebral oxygenation.

The identified hemoglobin threshold for critically increased cFTOE is significantly greater that that used in existing randomized control trials, such as the PINT trial where thresholds levels for the majority of infants ≥15 days were 8.5g/dL or less [1]. One possible reason for the PINT study's equivocal short-term outcomes may be that the selected thresholds were below the level where critical cerebral oxygen extraction occurs. As cerebral oxygenation was not considered in that study, infants in both groups may have experienced anemia that overwhelmed their cerebral compensatory mechanisms and potentially caused injury without meeting study criteria for transfusion thus preventing a distinction in outcomes between groups.

Although we have identified a hemoglobin threshold below which there is a significantly increased risk of critical cerebral oxygen extraction, the intent is not to provide a new threshold for transfusion. Instead, this study argues that cerebral oxygenation should be an important component of the overall decision to transfuse and should be used in conjunction with clinical and laboratory findings. Cerebral oximetry, and cFTOE in particular, offers a means to assess the often silent loss of compensation to anemia in an infant who may otherwise lack standard signs of physiologic decompensation such as tachycardia, apnea, and respiratory distress. NIRS monitoring could be crucial in helping clinicians determine if an individual patient is experiencing cerebral tissue hypoxia and therefore an elevated risk of brain injury from their anemia that would prompt transfusion [22-24]. Use of cFTOE could

individualize transfusion thresholds to patient physiology and provide guidance in a current area of clinical ambiguity. That the group threshold identified in this study is above current clinical practice merely suggests that this compromise will likely be found at less severe degrees of anemia than might be anticipated in the current clinical paradigm.

This study has a few limitations. First, this was an observational study that relied on clinically obtained hemoglobin data with elimination of recordings that lacked a hemoglobin measurement within 7 days. During even the most acute phases of anemia of prematurity (the first six weeks), the hemoglobin is estimated to drop by no more than approximately 1g/dL/week [51,52]. The overwhelming majority of recordings were made within 72 hours of the most recent hemoglobin measurement, and most of those were within 48 hours; differences in hemoglobin between such short intervals is within the margin of error of most commercial analyzers (approximately 0.25-0.5 g/dL) [53]. Aggressive error correction was used to eliminate segments of data where C-rSO_2 or pulse oximetry were unreliable such as probe displacement, systemic desaturation (SpO_2 <85%), or motion artifact to ensure recorded results were not contaminated by errors. Although we were not able to control for other determinants of cFTOE (hypercapnia, sedation, and hypotension), the recordings were made after the first week of life and the majority (94%) occurred in extubated infants minimizing the risk of these confounding factors. Finally, infants with severe IVH were eliminated to ensure that cFTOE alterations seen in the population truly represented globally compromised physiology rather than local pathology. Further study is needed as to the reliability and norms of C-rSO_2 and cFTOE in infants with severe IVH.

Future directions for this work will include longitudinal measures of hemoglobin and cerebral tissue hypoxia burden using NIRS in preterm infants and correlations with short term outcomes using MRI-based assessment of brain injury at term-equivalent age and long-term follow-up of neurodevelopmental outcomes. This will allow for a more rigorous evaluation of the link between anemia, cerebral hypoxia, and brain injury in this population and provide further validation for the use of NIRS in the assessment of the anemic preterm infant.

In conclusion, cerebral fractional tissue oxygen extraction as measurement by NIRS presents a valuable means for identifying compromised cerebral oxygenation in this population of hemodynamically stable, preterm infants with anemia of prematurity. Decreasing hemoglobin was associated with a progressive increase in cFTOE in all infants regardless of their transfusion status with a hemoglobin threshold for critical cerebral oxygen extraction (cFTOE ≥0.4) of 9.6 g/dL.

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Highlights

- Cerebral fractional tissue oxygen extraction (cFTOE), derived from regional cerebral saturations measured using near-infrared spectroscopy (NIRS) and pulse oximetry, is a marker of regional tissue oxygen delivery and metabolic activity.
- Elevated cFTOE is a known adaptation to anemia, but values ≥0.4 are associated with brain injury in preterm infants.
- Current clinical threshold hemoglobin levels for pRBC transfusions in anemia of prematurity are population based and not based on individual patient physiology.
- This study identified the threshold for critical oxygen extraction (cFTOE ≥0.4) as 9.6 g/dL in stable preterm infants ≤ 30 weeks with anemia of prematurity, significantly higher than current standard clinical thresholds for transfusion (<8 g/dL).
- Longitudinal evaluation of premature infants with anemia of prematurity using concurrent hemoglobin levels and cerebral NIRS may help define patient specific transfusion thresholds of hemoglobin in preterm infants.

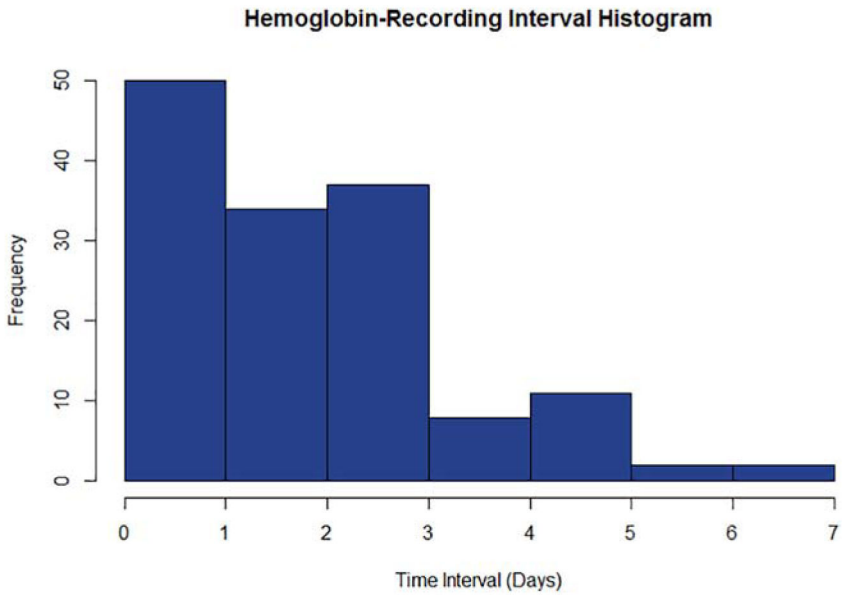

Figure 1.
Histogram illustrating the latency between hemoglobin measurement and cerebral NIRS recording in days.

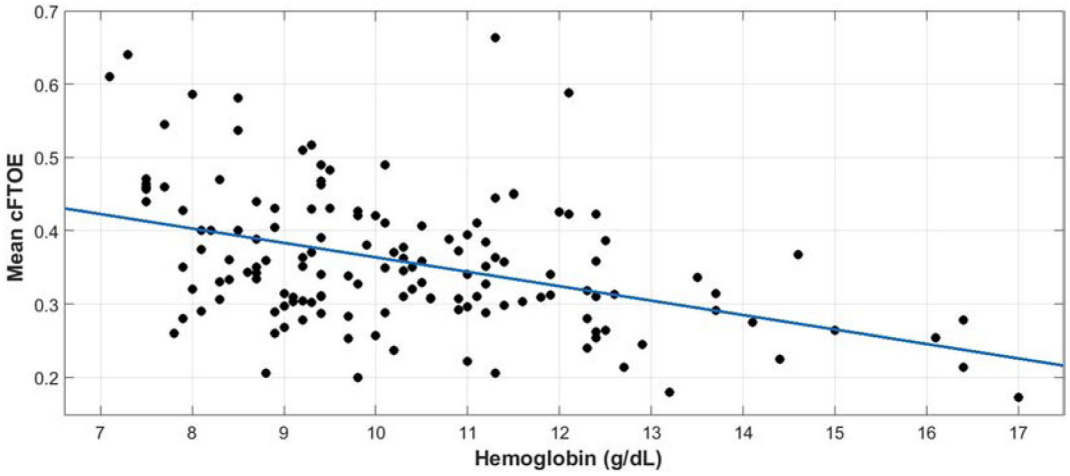

Figure 2.
Scatter plot illustrating the population-level correlation between hemoglobin and cFTOE.

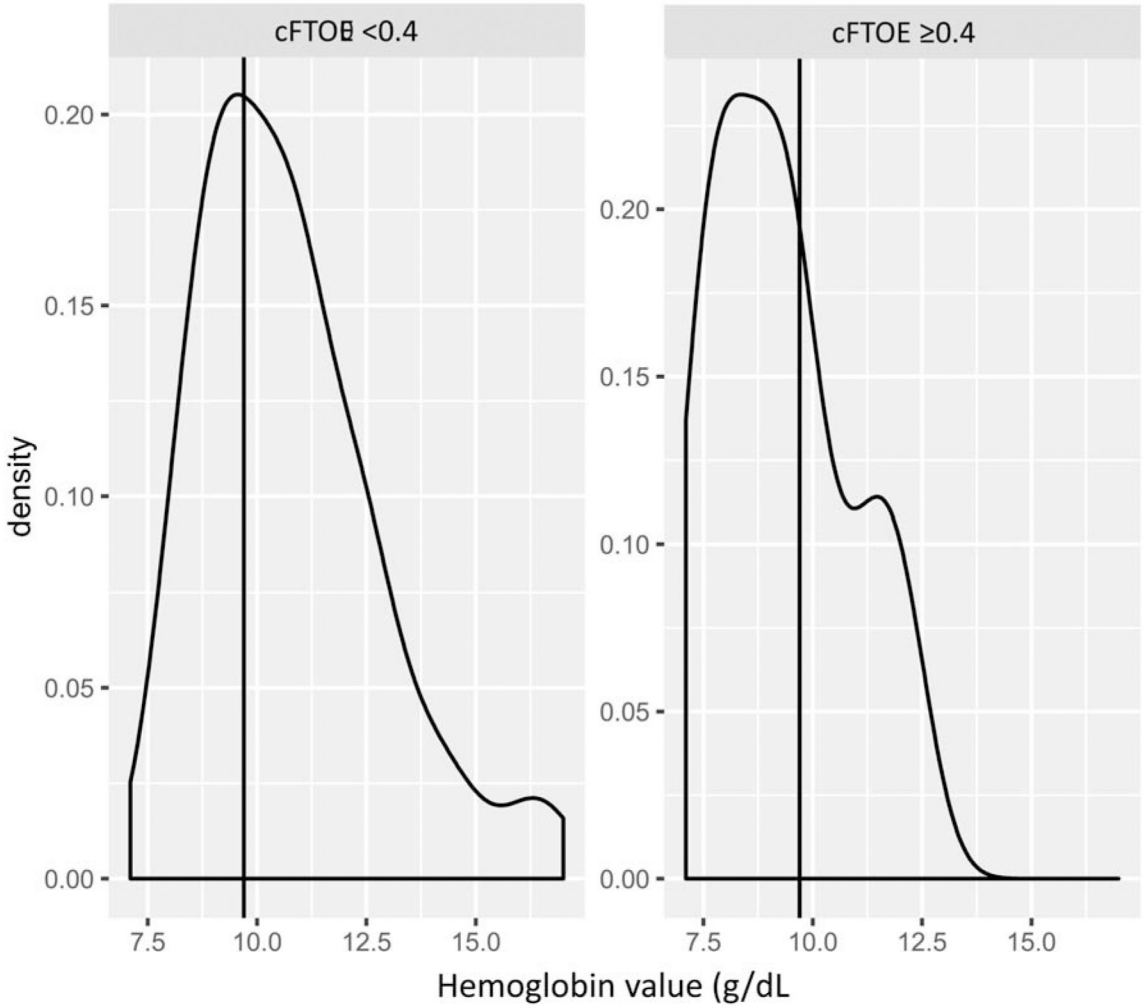

Figure 3.
Plots illustrating the normalized densities of hemoglobin values amongst recordings with cFTOE <0.4 (left) and cFTOE ≥0.4 (right).

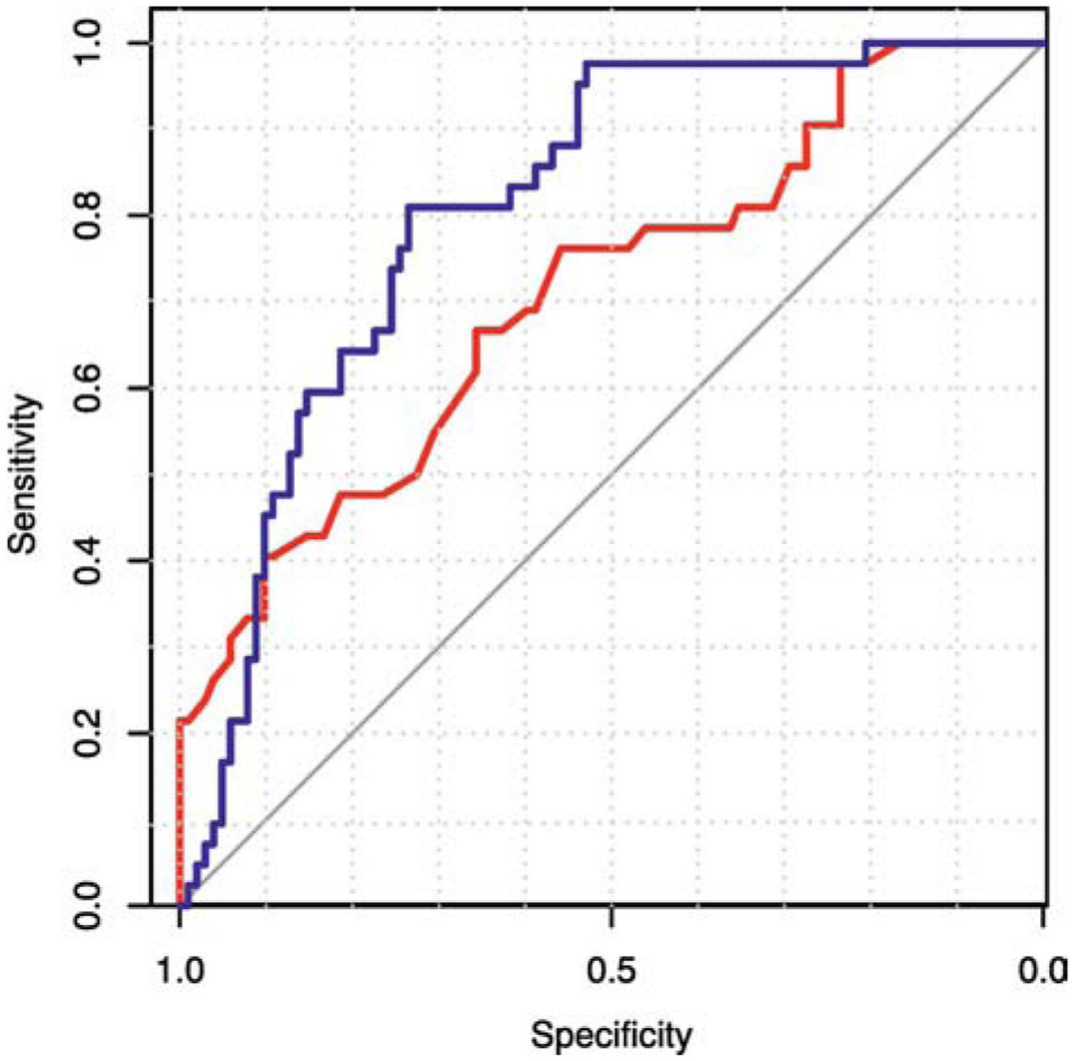

Figure 4.

ROC curves for cFTOE by total hemoglobin (red) and by total hemoglobin adjusting for EGA, PMA, and PDA treatment status (blue) for critically increased oxygen extraction (cFTOE ≥0.4, $p<0.001$ for both).

Table 1.

Cohort Clinical Characteristics

	n=39
EGA, mean ± SD	27.6 ± 2.1 weeks
BW, mean ± SD	1139 ± 286 g
Male sex, n (%)	12 (31%)
Race, n (%)	
African-American	15 (39%)
Caucasian	24 (61%)
Antenatal steroids, n (%)	
Any	25 (64%)
Complete	20 (51%)
Cesarean delivery, n (%)	28 (72%)
Delayed cord clamping, n (%)	11 (29%)
5 minute Apgar, median (range)	6 (1-9)
CRIB-II score, median (range)	9 (3-15)
Small for gestational age[1]**, n (%)**	2 (5%)
Anemia during monitoring, n (%)	
Hemoglobin ≤8 g/dL	6 (15%)
Hemoglobin ≤10 g/dL	27 (69%)
Transfused, n (%)	15 (39%)
Intraventricular hemorrhage, n (%)	12 (31%)
Inotropic medications, n (%)	2 (5%)
PDA treatment, n (%)	5 (13%)
Necrotizing enterocolitis, n (%)	1 (3%)
Bronchopulmonary dysplasia, n (%)	17 (46%)
Mortality, n (%)	1 (3%)

[1]Defined as BW <10th percentile.

Table 2.

Statistical characteristics of the mixed-model

Variable	β-coefficient	z-value	p-value
Hemoglobin	−0.77	−1.49	0.13
EGA	−1.02	−2.25	0.02 *
PMA	−0.21	−1.36	0.17
PDA treatment	3.12	1.36	0.17

Model = Critical_FTOE ~ EGA + Hgb + PMA + PDA_tx + (1 | StudyID), AIC = 110.6,

'*' denotes significance at $p<0.05$.