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Cerebral oxygenation in preterm infants at high altitude: a prospective pilot cohort study

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Abstract:

Introduction:

Near-infrared spectroscopy (NIRS) is a non-invasive technique for measuring regional oxygen saturation. Because preterm infants are susceptible to brain injury secondary to immaturity of the central nervous system (CNS) and cerebral vasculature, there has been significant interest in using cerebral NIRS monitoring to predict and/or decrease the risk of brain injury.

Methods:

Preterm infants born at <32 weeks' gestational age at high altitude were monitored with cerebral near-infrared spectroscopy (NIRS) throughout the first 96 postnatal hours. Regional cerebral oxygen saturation (rcSO2) and cerebral fractional tissue oxygen extraction (cFOTE) were measured. Additionally, we evaluated for possible correlations between cerebral oxygenation and fraction of inspired oxygen (FiO2) received.

Results:

20 infants were studied, with a mean birth weight of 1124 grams and gestational age of 28 5/7 weeks. Median rcSO2 was 73.5% on day of birth, 75.0% at 24-48hrs of age, and 73.0% at 48-72hrs and 72-96hrs of age. Median cFTOE was 23.8% on day of birth, 18.8% at 24-48hrs of age, 21.5% at 48-72hrs of age, and 23.6% at 72-96hrs of age. These patterns of rcSO2 and cFTOE and the median values for rcSO2 are consistent with those obtained in the largest sample of preterm infants reported to date at sea level. FiO2 correlated positively with cerebral oxygen saturation ($r=0.23$, $p<0.001$ for rcSO2) and inversely with cerebral oxygen extraction ($r=-0.25$, $p<0.001$ for cFTOE).

Conclusion:

Cerebral oxygenation at high altitude appears to be similar to that at low altitude in preterm infants in the first 4 postnatal days. Cerebral oxygenation appears to be influenced by FiO2 received.

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Introduction:

Near-infrared spectroscopy (NIRS) is a non-invasive technique for measuring regional oxygen saturation. A sensor applied to the skin measures oxygen saturation at a depth of 1-2cm.[1,2] Regional oxygen saturation (rcSO2), as measured by NIRS, reflects mainly venous oxygen saturation. When compared to contemporaneous peripheral arterial oxygen saturation (SpO2), rcSO2 can provide a measure of regional oxygen utilization, expressed as fractional tissue oxygen extraction (FTOE): (SpO2 – rSO2) / SpO2.[3]

Because preterm infants are susceptible to brain injury secondary to immaturity of the central nervous system (CNS) and cerebral vasculature, there has been significant interest in using cerebral NIRS monitoring to predict and/or decrease the risk of injury. Studies have shown that low regional cerebral oxygen saturation and/or fluctuations in cerebral oxygenation are associated with higher risk of periventricular and intraventricular hemorrhage (PIVH), adverse neurodevelopmental outcomes, and death.[4-7] Multiple trials have assessed the impact of guiding clinical management with cerebral NIRS monitoring on short-term outcomes of cerebral

hypoxia, death, and severe brain injury[8-10]; however, data on long-term neurodevelopment are still pending.[11]

While reference values for rcSO2 have been reported from birth through 8 weeks of age in preterm infants[12-24], it is unknown whether these values can be applied to neonates born at high altitude locations, as data have been obtained primarily at sea level. Peripheral arterial oxygen saturation has previously been shown to be lower in well preterm and term neonates born at high altitude compared to those born at sea level.[25-28] Furthermore, rcSO2 and cerebral fractional tissue oxygen extraction (cFTOE) were recently found to be lower in term neonates born at high altitude compared to those born at low altitude.[29]

In the present study we measured rcSO2 and cFTOE using neonatal sensors during the first 96 postnatal hours in preterm infants born at <32 weeks of gestation in a high-altitude location to obtain normative data. Additionally, we evaluated for possible correlations between cerebral oxygenation and fraction of inspired oxygen (FiO2) received.

Methods:

This study was approved by the University of New Mexico Health Sciences Center Institutional Review Board (IRB) prior to enrollment of participating infants (#20-382).

Participants

Participants in this observational study were recruited prospectively from the level-IV Neonatal Intensive Care Unit (NICU) at the University of New Mexico Hospital (altitude 5150 feet / 1570 meters above sea level) from August 2021 to December 2022 Written parental consent was obtained for all participants. Eligible participants were <32 weeks' gestational age at the time of delivery, and <24 hours of age. Infants were not eligible for participation if they had a known cardiac anomaly or other anomaly that could impair perfusion and blood flow, were born after placental abruption, or had concern for extreme blood loss immediately after birth.

Instrument

An INVOS cerebral / somatic oximeter monitor (INVOS model 5100C; Medtronic, Minneapolis, MN, USA) with a neonatal sensor (INVOS Cerebral/Somatic Oximetry Infant-Neonatal Sensor; Medtronic, Minneapolis, MN, USA) was used to measure regional cerebral oxygen saturation (rcSO2).

Data Collection and Processing

As soon as possible after delivery, a Mepitel One contact layer (Molnlycke; Goteborg, Sweden) was affixed directly to the skin on the right frontoparietal area, and the neonatal sensor (INVOS Cerebral/Somatic Oximetry Infant-Neonatal Sensor; Medtronic, Minneapolis, MN, USA) was placed on top. rcSO2 was recorded once per minute from time of sensor placement until infant reached 96 hours of age. Null values for rcSO2 were excluded, all other values for rcSO2 obtained through 96 hours of age were included for analysis. Standard physiologic measures, including peripheral oxygen saturation (SpO2), heart rate, mean arterial blood pressure via indwelling catheter (or oscillometric cuff if no indwelling catheter was present) were recorded with an Intellivue patient monitor (Philips Medizin Systeme, Boeblingen, Germany) and placed in the medical record per routine unit documentation. Time and date on the NIRS monitor were synchronized with the patient monitor at the time of NIRS monitor placement. Upon completion of NIRS monitoring, standard physiologic measures as above and fraction of inspired oxygen (FiO2) administered throughout the duration of NIRS monitoring were obtained from participant's medical record.

At time of enrollment, perinatal history and demographic data were collected from the medical record. At time of discharge or death, information on the neonatal course and outcomes were collected, including: type and length of respiratory support received, presence and grade of intraventricular hemorrhage according to the classification of Papile, et al.[30], diagnosis of necrotizing enterocolitis (Bell's stage IIa[31] or higher), other medical complications, and length of stay.

Statistical Analysis

The cerebral regional oxygen saturation data were averaged for each infant across the study period and by post-natal day. We conducted a prospectively planned sub-analysis of the enrolled infants based on sex and gestational age (GA). Specifically, the infants were divided into the following GA groups: Group 1:

23 to ≤26 weeks' gestation; Group 2: >26 weeks' gestation to ≤29 weeks' gestation; Group 3: >29 weeks' gestation to 31 6/7 weeks' gestation. We tested for significant differences between sexes and among the three age groups. Birthweight and per infant mean heart rate across the observation period were summarized as mean and standard deviation. The relative cerebral fractional tissue oxygen extraction (cFTOE) was calculated using the following equation: (SpO2 – rcSOs)/SpO2. NIRS parameters (rcSO2 and cFTOE) were summarized as median and interquartile ranges.

We conducted Levene's and Shapiro-Wilk tests to confirm homogeneity of variances and normality for continuous variables, then compared age groups via one-way ANOVA followed by a post-hoc Dunn's test for significant results and compared the sexes using t-tests. We analyzed NIRS parameters using Mann-Whitney U and Kruskal-Wallis tests. Spearman's rank correlation coefficient was used to assess the pairwise associations among rcSO2, SpO2, cFTOE, heart rate, FiO2, birthweight, and gestational age. All analyses were done in R, version 4.1.1 (R Core Team, 2021).[32] We adjusted the p-values for multiplicity using the Benjamini-Hochberg method.

Results:

During the enrollment period, 63 infants were born at <32 weeks of gestation, of whom 21 were consented for the study and 20 had NIRS monitoring conducted (see Figure 1). The mean gestational age was 28 5/7 weeks and mean birth weight was 1124 grams. Demographic and clinical outcome data are shown in Table 1. All but one of the participants were on positive pressure respiratory support throughout the NIRS monitoring period, including mechanical ventilation, non-invasive positive pressure ventilation (NIPPV), and/or continuous positive airway pressure (CPAP). FiO2 ranged from 0.21 to 1.0 with a median of 0.25 (IQR 0.1). Median heart rate was 152 beats per minute (IQR 17) and median mean arterial blood pressure was 33 mmHg (IQR 9). Monitoring was started between 1-21 hours, with a median start time of 6 hours (interquartile range, IQR, 11.5hrs) and ended at 96 hours in all but one participant. Equipment failure led to cessation of monitoring at 82 hours of age for that participant.

Figure 1: Enrollment

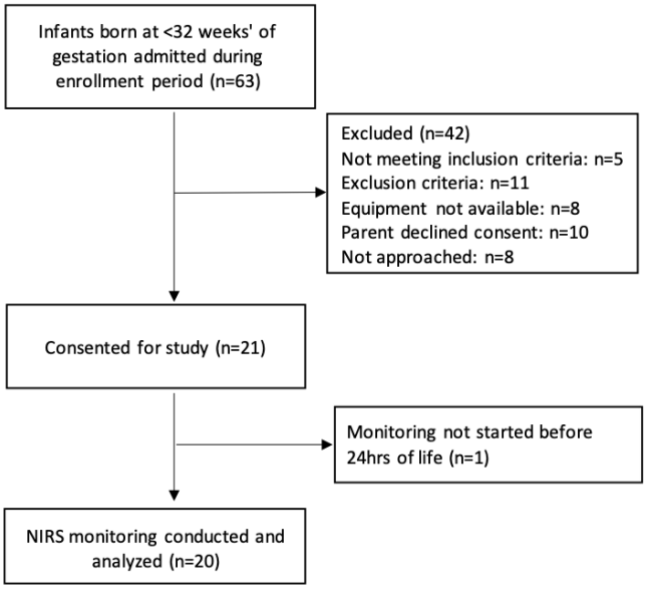

Table 1: Demographics

Demographics	
Gestational Age (wk), mean (SD)	28.5 (2.4)
Birth weight (g), mean (SD)	1124 (376)
SGA, n (%)	1 (5)
Male, n (%)	7 (35)
Vaginal delivery, n (%)	7 (35)
Any prenatal steroids, n (%)	19 (95)
≥2 doses prenatal steroids, n (%)	12 (60)
1-min Apgar score, median (IQR)	4 (2)
5-min Apgar score, median (IQR)	7 (2)
CRIB II score, median (IQR)	8.5 (5.3)
Respiratory support during NIRS monitoring, n (%)	
Mechanical ventilation	10 (50)
NIPPV	5 (25)
CPAP	14 (70)
HFNC	1 (5)
Outcomes, n (%)	
Died	1 (5)
IVH - grade I/II	6 (30)
IVH - grade III/IV	2 (10)
Intraparenchymal hemorrhage	2 (10)
ROP requiring treatment	2 (10)
NEC	2 (10)
Early onset sepsis	0 (0)
Late onset sepsis	3 (15)
PDA treatment received	3 (15)
Length of stay, median (IQR)	77 (47)

wk = weeks, g = grams, SD = standard deviation, n = number, IQR = interquartile range, NIPPV = non-invasive positive pressure ventilation, CPAP = continuous positive airway pressure, HFNC = high flow nasal cannula, IVH = intraventricular hemorrhage, ROP = retinopathy of prematurity, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus

Two other participants had interruptions in their monitoring secondary to equipment failure, lasting 19 hours 48 minutes (from 9hrs 37 minutes to 29hrs 25 minutes) and 15 hours 38 minutes (from 74 hours 38 minutes to 90 hours 16 minutes).

Results for rcSO2 and cFTOE are shown in Table 2. Median rcSO2 and cFTOE did not differ between the days of monitoring (Figures 2 and 3 in supplemental), sexes, or different gestational age groups.

Table 2: Regional oxygen saturation and cerebral fractional tissue oxygen extraction

rcSO2, median (IQR)

	0-96hrs	0-24hrs	24-48hrs	48-72hrs	72-96hrs	p
All participants	73.5 (11)	73.5 (10.5)	75 (10.5)	73 (11)	73 (13)	0.165
Male	75.5 (9)	75 (17)	76 (16)	75 (10)	76 (12)	0.311
Female	73 (15)	72 (16)	74 (12)	73 (15)	71 (14)	
23 to <26 weeks	75.5 (18)	78 (19)	75 (16)	74 (15.5)	68 (20.5)	0.278
26 to <29 weeks	71 (3.5)	71 (2)	72 (7)	71 (3)	71 (9)	
29 to <32 weeks	79 (11)	79 (7)	80 (5)	79 (9)	79 (12)	

cFTOE, median (IQR)

	0-96hrs	0-24hrs	24-48hrs	48-72hrs	72-96hrs	p
All participants	21.9 (11.4)	23.8 (10.1)	18.8 (10.1)	21.5 (10.3)	23.6 (12.0)	0.089
Male	19.7 (8.2)	19.1 (15.7)	18.6 (14.5)	20.9 (9.2)	20.2 (9.6)	0.234
Female	22.8 (14.0)	24.2 (15.1)	18.9 (12.4)	22.0 (16.8)	25.4 (13.1)	
23 to <26 weeks	18.7 (18.4)	15.7 (17.7)	20.5 (15.2)	21.9 (16.5)	28.7 (22.8)	0.448
26 to <29 weeks	24.6 (4.5)	25.3 (1.4)	22.2 (10.6)	23.4 (4.1)	25.4 (6.1)	
29 to <32 weeks	18.6 (11.8)	19.0 (10.4)	17.1 (3.2)	18.8 (8.6)	18.6 (13.0)	

p = p-values are based on assessment of significant different using mixed effects models. rcSO2 = regional cerebral saturation, cFTOE = cerebral fractional tissue oxygen extraction, IQR = interquartile range

There were no significant correlations between cerebral oxygenation parameters (rcSO2 and cFTOE) and FiO2, SpO2, or heart rate among the whole population. Significant negative correlations between FiO2 and birth weight ($r=-0.78$, $p<0.001$) and gestational age ($r=-0.82$, $p<0.001$) were noted. Analysis for correlation between FiO2 and cerebral oxygenation parameters within individuals showed a significant positive correlation with rcSO2 ($r=0.23$, $p<0.001$) and negative correlation with cFTOE ($r=-0.25$, $p<0.001$).

Discussion:

Use of normative values for cerebral oxygenation in preterm infants is complicated by multiple factors. Available data differ between machines and type of sensor (adult vs. neonatal), as well as the gestational age at birth and chronologic age of the infant being monitored.[33,34] Thus, some have argued that only trends should be used, rather than the absolute values.[1,35] On the other hand, clinical trials have been conducted aimed at achieving "normal" absolute values of cerebral oxygenation with use of targeted treatment algorithms for cerebral hypoxia and hyperoxia.[8,10,11]

Regardless of desire to use cerebral oxygenation information for trend comparison or targeted treatment, a framework is needed for differentiating typical from atypical levels of rcSO2. The first several postnatal days in infants born at <32 weeks of gestation are of particular concern, as this is a high-risk period for cerebral injury. While multiple studies have published data from serial cerebral oxygenation measurements in this gestational age group and time period,[16-22] they have been conducted primarily at altitudes near sea level, with the exception of the study by Chock, et al.[22] in which 2 of 19 sites were >4000 feet (~1200 meters). Furthermore, only four of these studies used an INVOS monitor, as used in this study,[18,20-22] and only two obtained data using neonatal sensors.[21,22] One of these was a 2016 study conducted at sea level that reported data from the largest sample of preterm infants to date (n=999). Most of their data were obtained using adult sensors, but a subset of participants underwent simultaneous monitoring with a neonatal sensor and mathematical modelling was then conducted to obtain "neonatal sensor-equivalent" data. In our study, we found similar median values for cerebral oxygen rcSO2 to the "neonatal sensor-equivalent" values, which ranged approximately between 70-80%. Furthermore, we found a similar pattern of change in rcSO2 over time, with an increase in the median value between day of birth and 24-48 hours of age, followed by a subsequent decline; and a similar inverse parabolic pattern for cFTOE over the first several days.

In contrast, the only other study to report cerebral oximetry data in preterm infants born at <32 weeks of gestation obtained with INVOS monitors and neonatal sensors found that rcSO2 significantly decreased over time.[22] Chock et al. collected continuous cerebral oximetry over the first postnatal week and did not find a parabolic change in rcSO2 in the first 72 hours, perhaps because infants were enrolled up to 48hrs and thus had fewer data for the first 2 postnatal days. The median rcSO2 in our population (73.5%, IQR 11) was higher than the mean rcSO2 reported in the Chock study (65 ± 16%). The fact that the Chock study measured rcSO2 through postnatal day 7 and found that rcSO2 significantly decreased over that time may account for some of the difference in the average values between the 2 studies. Similar to both the

Alderliesten[21] and Chock[22] studies, the rcSO2 increased and cFTOE decreased with increasing gestational age.

While we had hypothesized that rcSO2 would be lower in preterm infants at high altitude, our findings of similar rcSO2 values may be due to the use of supplemental oxygen to maintain desired peripheral oxygen saturation levels. Unfortunately, the Alderliesten and Chock studies[21,22] do not report on FiO2 received by participants, so a comparison of this factor is not possible. However, it has been postulated that adjusting FiO2 will affect cerebral oxygenation. The SafeBoosC trials sought to minimize cerebral hyper- and hypoxia as determined by NIRS monitoring and their algorithm for responding to a low rcSO2 includes adjusting FiO2.[36] Arterial oxygen content, with peripheral oxygen saturation being its most common surrogate, has been cited as one of three physiological components that influence rcSO2[37] and in clinical practice, adjustment of FiO2 is commonly used to alter peripheral oxygen saturation.

Studies have reported conflicting results in this regard, finding that adjusting FiO2 increased,[38] decreased,[39] or had no effect[40] on cerebral oxygenation. None of these studies specifically examined correlations between FiO2 and cerebral oxygenation. In our study, we found that FiO2 had a highly significant positive correlation with rcSO2 and negative correlation with cFTOE ($p < 0.001$ for both). This has physiologic plausibility, as one would expect cerebral venous oxygen saturation to increase and brain oxygen utilization to decrease with increased oxygen delivery.

In prior studies documenting decreased peripheral oxygen saturation in term and preterm infants at high altitude, those on supplemental oxygen were excluded.[25-28] In the study that found lower rcSO2 and cFTOE in term infants born at high altitude, NIRS monitoring was conducted only in infants without respiratory support.[29] Further studies are needed to elucidate the effects of FiO2 on cerebral oxygenation, particularly at high altitude locations.

The strengths of this study include the enrollment of preterm infants at a high-altitude location, use of continuous cerebral oxygenation monitoring, use of a neonatal sensor to obtain data on cFTOE, and inclusion of analysis of correlations between FiO2 and cerebral oxygenation parameters. To our knowledge, there are no previously published studies on cerebral oxygenation values in preterm infants at high altitude. There are limited published data on normative values for cFTOE using neonatal sensors. Finally, several studies have examined interactions between FiO2 and cerebral oxygen, but statistical analyses of correlations were not conducted. The limitations of our study include our small sample size, interruptions in monitoring in some participants, and a delay in initiation of monitoring after birth or resuscitation.

Conclusion:

We found that preterm infants who were born at <32 weeks of gestation at high altitude and received respiratory support to maintain targeted oxygen saturations had cerebral oxygenation similar to infants born at lower altitudes. This may be due, at least in part, to the use of supplemental oxygen to maintain normal peripheral oxygen saturation, but further study is needed on the effect of supplemental oxygen and respiratory support on cerebral oxygenation. More data are also needed on normative values for cFTOE using neonatal sensors, to evaluate for any potential effect of altitude on this measurement.

Author Contributions:

All authors contributed equally to the conception and design, acquisition of data, or analysis, interpretation of data, manuscript preparation and review.

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Potential Conflicts of Interest Disclosures:

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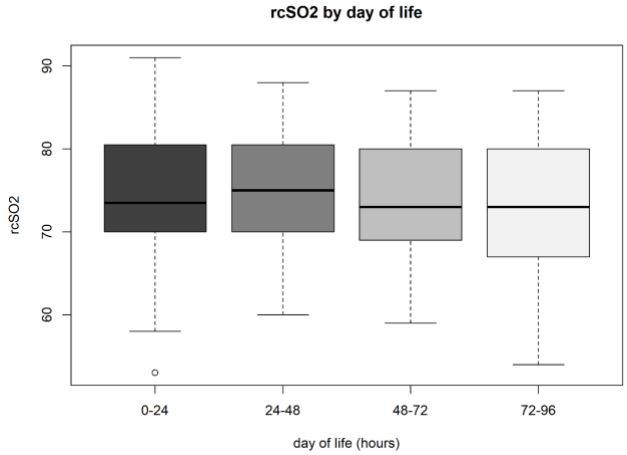
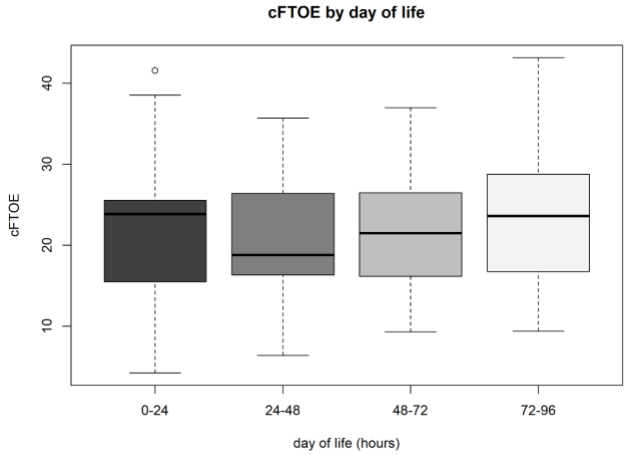
Supplemental:

Figure 2: rcSO2 by day of life



Median regional cerebral oxygen saturation $rcSO_2$ by day of life

Figure 3: cFTOE by day of life



Median cerebral fractional tissue oxygen extraction (cFTOE) by day of life