

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 (cFTOE) 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 injury⁸⁻¹⁰; 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 infants¹²⁻²⁴, 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 IIa³¹ 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: $(SpO_2 - rcSO_2)/SpO_2$. 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

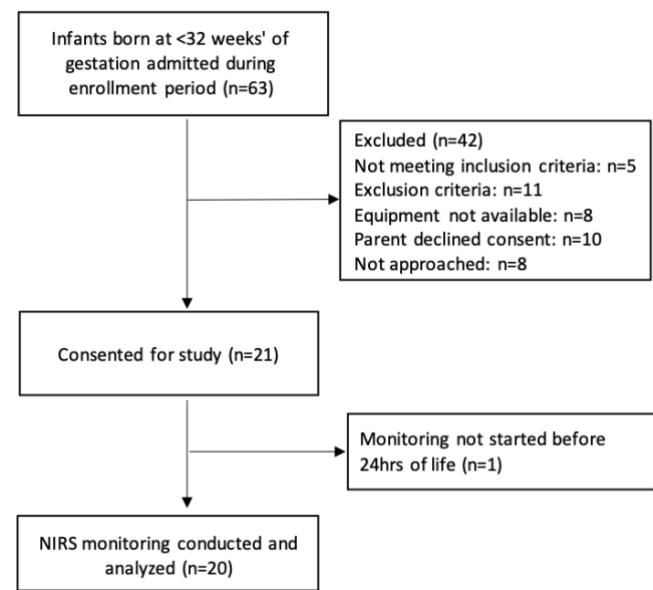


Table 1: Demographics

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

	rcSO ₂ , median (IQR)					p
	0-96hrs	0-24hrs	24-48hrs	48-72hrs	72-96hrs	
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)					p
	0-96hrs	0-24hrs	24-48hrs	48-72hrs	72-96hrs	
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

Alderliesten²¹ and Chock²² 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 rcSO₂³⁷ 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 effect⁴⁰ 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:

The authors disclose that there were no conflicts of interest or financial support in the development of this project. All data is authentic and accurate.

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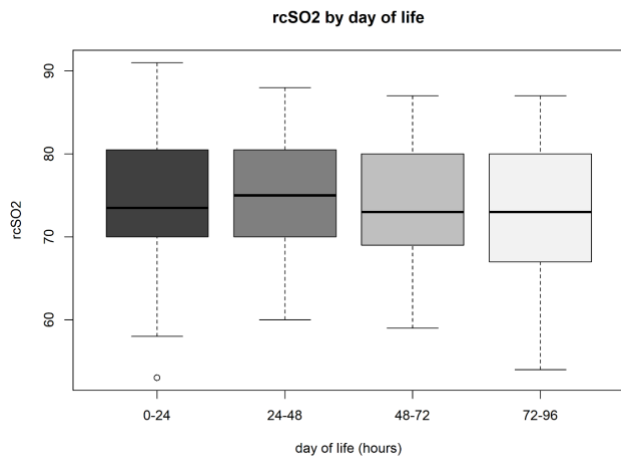
References:

1. Sood BG, McLaughlin K, Cortez J. Near-infrared spectroscopy: applications in neonates. *Semin Fetal Neonatal Med.* 2015 Jun;20(3):164-72. doi: 10.1016/j.siny.2015.03.008. Epub 2015 Apr 29.
2. Dix LM, van Bel F, Lemmers PM. Monitoring Cerebral Oxygenation in Neonates: An Update. *Front Pediatr.* 2017 Mar 14;5:46. doi: 10.3389/fped.2017.00046. Erratum in: *Front Pediatr.* 2017 Jul 21;5:160. doi: 10.3389/fped.2017.00160.
3. Pavlek LR, Mueller C, Jebbia MR, et al. Near-Infrared Spectroscopy in Extremely Preterm Infants. *Front Pediatr.* 2021 Jan 21;8:624113. doi: 10.3389/fped.2020.624113.
4. Chock VY, Kwon SH, Ambalavanan N, et al. Cerebral Oxygenation and Autoregulation in Preterm Infants (Early NIRS Study). *J Pediatr.* 2020 Dec;227:94-100.e1. doi: 10.1016/j.jpeds.2020.08.036. Epub 2020 Aug 17.
5. Alderliesten T, van Bel F, van der Aa NE, et al. Low Cerebral Oxygenation in Preterm Infants Is Associated with Adverse Neurodevelopmental Outcome. *J Pediatr.* 2019 Apr;207:109-116.e2. doi: 10.1016/j.jpeds.2018.11.038. Epub 2018 Dec 18.
6. Katheria AC, Stout J, Morales AL, et al. Association between early cerebral oxygenation and neurodevelopmental impairment or death in premature infants. *J Perinatol.* 2021 Apr;41(4):743-748. doi: 10.1038/s41372-021-00942-w. Epub 2021 Feb 15.
7. Alderliesten T, Lemmers PM, Smarius JJ, et al. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. *J Pediatr.* 2013 Apr;162(4):698-704.e2. doi: 10.1016/j.jpeds.2012.09.038. Epub 2012 Nov 6.
8. Hyttel-Sorensen S, Pellicer A, Alderliesten T, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ.* 2015 Jan 5;350:g7635. doi: 10.1136/bmj.g7635.
9. Dempsey EM, Barrington KJ, Marlow N, et al.; HIP consortium. Hypotension in Preterm Infants (HIP) randomised trial. *Arch Dis Child Fetal Neonatal Ed.* 2021 Jul;106(4):398-403. doi: 10.1136/archdischild-2020-320241. Epub 2021 Feb 24.
10. Pichler G, Goeral K, Hammerl M, et al.; COSGOD III study group. Cerebral regional tissue Oxygen Saturation to Guide Oxygen Delivery in preterm neonates during immediate transition after birth (COSGOD III): multicentre randomised phase 3 clinical trial. *BMJ.* 2023 Jan 24;380:e072313. doi: 10.1136/bmj-2022-072313. Erratum in: *BMJ.* 2023 May 15;381:p1102. doi: 10.1136/bmj.p1102.
11. Hansen ML, Pellicer A, Hyttel-Sorensen S, et al. Cerebral Oximetry Monitoring in Extremely Preterm Infants. *N Engl J Med.* 2023 Apr 20;388(16):1501-1511. doi: 10.1056/NEJMoa2207554.
12. Tina LG, Frigiola A, Abella R, et al. Near Infrared Spectroscopy in healthy preterm and term newborns: correlation with gestational age and standard monitoring parameters. *Curr Neurovasc Res.* 2009 Aug;6(3):148-54. doi: 10.2174/156720209788970090. Epub 2009 Aug 1.
13. Fuchs H, Lindner W, Buschko A, et al. Brain oxygenation monitoring during neonatal resuscitation of very low birth weight infants. *J Perinatol.* 2012 May;32(5):356-62. doi: 10.1038/jp.2011.110. Epub 2011 Aug 18.
14. Pichler G, Binder C, Avian A et al. Reference ranges for regional cerebral tissue oxygen saturation and fractional oxygen extraction in neonates during immediate transition after birth. *J Pediatr.* 2013 Dec;163(6):1558-63. doi: 10.1016/j.jpeds.2013.07.007. Epub 2013 Aug 22.
15. Hoeller N, Baik-Schneditz N, Schwaberg B, et al. Cerebral and peripheral muscle oxygenation and perfusion: Course in moderate and late preterm neonates during the first day after birth. *Physiol Int.* 2020 Jul 17;107(2):267-279. doi: 10.1556/2060.2020.00028.
16. Sirc J, Dempsey EM, Miletin J. Cerebral tissue oxygenation index, cardiac output and superior vena cava flow in infants with birth weight less than 1250 grams in the first 48 hours of life. *Early Hum Dev.* 2013 Jul;89(7):449-52. doi: 10.1016/j.earlhumdev.2013.04.004. Epub 2013 Apr 26.
17. Naulaers G, Morren G, Van Huffel S, et al. Cerebral tissue oxygenation index in very premature infants. *Arch Dis Child Fetal Neonatal Ed.* 2002 Nov;87(3):F189-92. doi: 10.1136/fn.87.3.f189.
18. Lemmers PM, Toet M, van Schelven IJ, van Bel F. Cerebral oxygenation and cerebral oxygen extraction in the preterm infant: the impact of respiratory distress syndrome. *Exp Brain Res.* 2006 Aug;173(3):458-67. doi: 10.1007/s00221-006-0388-8. Epub 2006 Feb 28.
19. Takami T, Sunohara D, Kondo A, et al. Changes in cerebral perfusion in extremely LBW infants during the first 72 h after birth. *Pediatr Res.* 2010 Nov;68(5):435-9. doi: 10.1203/PDR.0b013e3181f2bd4d
20. Hyttel-Sorensen S, Austin T, van Bel F, et al. Clinical use of cerebral oximetry in extremely preterm infants is feasible. *Dan Med J.* 2013 Jan;60(1):A4533.
21. Alderliesten T, Dix L, Baerts W, et al. Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates. *Pediatr Res.* 2016 Jan;79(1-1):55-64. doi: 10.1038/pr.2015.186. Epub 2015 Sep 21.
22. Chock VY, Smith E, Tan S, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early brain and abdominal oxygenation in extremely low birth weight infants. *Pediatr Res.* 2022 Oct;92(4):1034-1041. doi: 10.1038/s41390-022-02082-z. Epub 2022 May 5.
23. Mohamed MA, Frasketi MJ, Aly S, El-Dib M, Hoffman HJ, Aly H. Changes in cerebral tissue oxygenation and fractional oxygen extraction with gestational age and postnatal maturation in preterm infants. *J Perinatol.* 2021 Apr;41(4):836-842. doi: 10.1038/s41372-020-00794-w. Epub 2020 Aug 22.
24. Howarth CN, Leung TS, Banerjee J, Eaton S, Morris JK, Aladangady N. Regional cerebral and splanchnic tissue oxygen saturation in preterm infants - Longitudinal normative measurements. *Early Hum Dev.* 2022 Feb;165:105540. doi: 10.1016/j.earlhumdev.2022.105540. Epub 2022 Jan 16.
25. Thilo EH, Park-Moore B, Berman ER, Carson BS. Oxygen saturation by pulse oximetry in healthy infants at an altitude

- of 1610 m (5280 ft). What is normal? *Am J Dis Child*. 1991 Oct;145(10):1137-40. doi: 10.1001/archpedi.1991.02160100069025.
26. Levesque BM, Pollack P, Griffin BE, Nielsen HC. Pulse oximetry: what's normal in the newborn nursery? *Pediatr Pulmonol*. 2000 Nov;30(5):406-12. doi: 10.1002/1099-0496(200011)30:5<406::aid-ppul7>3.0.co;2-c.
 27. Morgan MC, Maina B, Waiyego M, Mutinda C, Aluvaala J, Maina M, English M. Oxygen saturation ranges for healthy newborns within 24 hours at 1800 m. *Arch Dis Child Fetal Neonatal Ed*. 2017 May;102(3):F266-F268. doi: 10.1136/archdischild-2016-311813. Epub 2017 Feb 2.
 28. Richard D, Poets CF, Neale S, Stebbens VA, Alexander JR, Southall DP. Arterial oxygen saturation in preterm neonates without respiratory failure. *J Pediatr*. 1993 Dec;123(6):963-8. doi: 10.1016/s0022-3476(05)80395-6
 29. Ze B, Liu L, Yang Jin GS, et al. Near-Infrared Spectroscopy Monitoring of Cerebral Oxygenation and Influencing Factors in Neonates from High-Altitude Areas. *Neonatology*. 2021;118(3):348-353. doi: 10.1159/000514403 Epub 2021 Jun 9.
 30. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr*. 1978 Apr;92(4):529-34. doi: 10.1016/s0022-3476(78)80282-0
 31. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, Brotherton T. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg*. 1978 Jan;187(1):1-7. doi: 10.1097/00000658-197801000-00001
 32. R Core Team. R: A language and environment for statistical computing. [Internet]. Vienna, Austria; 2021. Last accessed 08/11/2024 Available from: <https://www.R-project.org/>
 33. Dix LM, van Bel F, Baerts W, Lemmers PM. Comparing near-infrared spectroscopy devices and their sensors for monitoring regional cerebral oxygen saturation in the neonate. *Pediatr Res*. 2013 Nov;74(5):557-63. doi: 10.1038/pr.2013.133. Epub 2013 Aug 13.
 34. Schneider A, Minnich B, Hofstätter E, Weisser C, Hattinger-Jürgenssen E, Wald M. Comparison of four near-infrared spectroscopy devices shows that they are only suitable for monitoring cerebral oxygenation trends in preterm infants. *Acta Paediatr*. 2014 Sep;103(9):934-8. doi: 10.1111/apa.12698 Epub 2014 Jun 10.
 35. van Bel F, Mintzer JP. Monitoring cerebral oxygenation of the immature brain: a neuroprotective strategy? *Pediatr Res*. 2018 Aug;84(2):159-164. doi: 10.1038/s41390-018-0026-8. Epub 2018 Aug 16. Erratum in: *Pediatr Res*. 2018 Nov;84(5):786. doi: 10.1038/s41390-018-0127-4
 36. SafeBoosC trial group. SafeBoosC Physiology-based treatment guideline [Internet]. Physiology-based treatment guideline. [cited 2023 May 11]. Available from: <https://www.rigshospitalet.dk/english/departments/julian-e-marie-centre/department-of-neonatology/research/safeboosc/Sider/physiology-based-treatment-guideline.aspx>
 37. Suppan E, Pichler G, Binder-Heschl C, Schwabegger B, Urlesberger B. Three Physiological Components That Influence Regional Cerebral Tissue Oxygen Saturation. *Front Pediatr*. 2022 Jun 13;10:913223. doi: 10.3389/fped.2022.913223.
 38. Baerts W, Lemmers PM, van Bel F. Cerebral oxygenation and oxygen extraction in the preterm infant during desaturation: effects of increasing FiO₂ to assist recovery. *Neonatology*. 2011;99(1):65-72. doi: 10.1159/000302717. Epub 2010 Jul 15.
 39. Kenosi M, O'Toole JM, Livingston V, et al. Effects of Fractional Inspired Oxygen on Cerebral Oxygenation in Preterm Infants following Delivery. *J Pediatr*. 2015 Nov;167(5):1007-12.e1. doi: 10.1016/j.jpeds.2015.07.063. Epub 2015 Sep 16.
 40. Waitz M, Schmid MB, Fuchs H, Mendler MR, Dreyhaupt J, Hummler HD. Effects of automated adjustment of the inspired oxygen on fluctuations of arterial and regional cerebral tissue oxygenation in preterm infants with frequent desaturations. *J Pediatr*. 2015 Feb;166(2):240-4.e1. doi: 10.1016/j.jpeds.2014.10.007. Epub 2014 Nov 18.

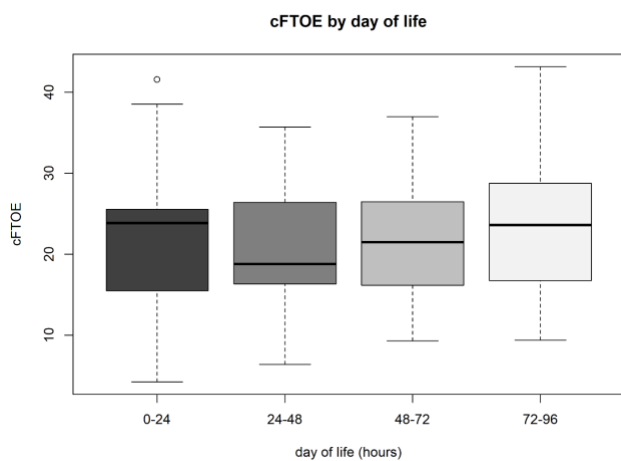
Supplemental:

Figure 2: rcSO₂ by day of life



Median regional cerebral oxygen saturation rcSO₂ by day of life

Figure 3: cFTOE by day of life



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