

ORIGINAL ARTICLE

Normal cerebral, renal and abdominal regional oxygen saturations using near-infrared spectroscopy in preterm infants

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Objective: The aim of this study is to characterize baseline regional oxygen saturations (rSO₂) in stable preterm infants during the first weeks of life.

Study Design: Cerebral, renal and abdominal rSO₂ were continuously monitored from the time of birth to 21 days in twelve preterm infants of 29–34 weeks gestation. Regional saturations were evaluated for trends over time, variability and differences between gestational ages (GAs) and reported pediatric values.

Result: Both cerebral (66–83%) and renal (64–87%) rSO₂ baselines were within the range of reported neonatal values but consistently decreased over the first weeks of life ($P < 0.01$). The baseline abdominal rSO₂ was 32–66% and increased with GA ($P = 0.05$). The rSO₂ variability was lowest for cerebral measurements and highest at the abdomen. Abdominal rSO₂ variability decreased over time ($P \leq 0.05$).

Conclusion: Daily baseline rSO₂ in preterm infants changes over the first weeks of life, especially at the abdomen. Evolution in baseline rSO₂ over time may indicate regional developmental maturation of physiological oxygen balance.

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Introduction

In the neonatal population, assessments of vital organ oxygen delivery and consumption are complicated by vascular shunts, vasomotor immaturity, patient size and complex cardiovascular changes during postnatal adaptation. Although traditional measures of lactic acidosis, prolonged capillary refill time, temperature instability, apnea, bradycardia, decreasing blood

pressure and urine output are often readily available, they remain as indirect, nonspecific and insensitive markers of neonatal cardiovascular compromise.¹

A promising solution to continuous end-organ perfusion assessment in the neonatal intensive care unit (NICU) is the current generation of spatially resolved near-infrared spectroscopy (NIRS) devices; however, peer-reviewed normative neonatal data are lacking. Although some information can be extracted from previous studies measuring regional oxygen saturation (rSO₂) over short periods of time in premature infants during illness (Table 1), a comprehensive evaluation of rSO₂ over time has not been carried out. Before widespread use in the NICU, characteristics of normal rSO₂ in premature neonates should be established to appropriately interpret changes related to clinical pathology.⁵ The objective of this study was to evaluate the rSO₂ baseline trends and normal physiological variability seen in healthy, stable, preterm infants over the first weeks of life. To examine this, rSO₂ was continuously monitored at cerebral, renal and abdominal sites in sample of stable preterm infants from the time of birth up to 21 days.

Methods

In all, 14 stable premature infants between 24 and 36 weeks gestation admitted to the NICU at Vanderbilt University between April and September of 2008 were selected for monitoring. Patients at risk for potential problems with sensor interference and/or alterations in perfusion were excluded from analysis (Table 2).

The study had a prospective observational design and the institutional review board approval was obtained. After parental consent, monitoring was initiated within the first 12 h of life. rSO₂ was measured using neonatal sensors, which are approved by the Food and Drug Administration for use in preterm neonates (Somanetics 5100 INVOS System, Troy, MI, USA). A piece of gel-impregnated gauze (Mepitel, Mölnlycke, Sweden) was used as a barrier between the patient and sensor at all times. Somanetics laboratories confirmed INVOS signal integrity and validity when used in conjunction with the Mepitel (MD Wilder; personal communication) (Dr MD Wilder, personal communication, 2008).

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Table 1 Neonatal rSO₂ values with Somanetic NIRS systems and pediatric sensors

Site/source	rSO ₂ (%)	N	Population characteristics
<i>Cerebral</i>			
Somanetics (Dr MD Wider, personal communication, 2008) ²	60–80		Adult and pediatric
Petrova ²	66 ± 10	10	>7 days old; 24–32 weeks GA; SaO ₂ >85%
Lemmers ³	70 ± 8	38	6–72 h old; <32 weeks GA
<i>Renal</i>			
Somanetics (Dr MD Wider, personal communication, 2008)	5–15% above cerebral		Adult and pediatric
Petrova ²	80 ± 10	10	>7 days old; 24–32 weeks GA; SaO ₂ >85%
Li ⁴	40–83	11	4–92 days old; post Norwood
<i>Abdominal</i>			
Somanetics (Dr MD Wider, personal communication, 2008)	5–15% above cerebral		Adult and pediatric
<i>Vanderbilt pilot data (neonatal sensors)</i>			
Cerebral	78 ± 9	7	6–72 h old; >37 weeks GA
Renal	88 ± 6	7	6–72 h old; >37 weeks GA
Abdominal	68 ± 13	7	6–72 h old; >37 weeks GA

Abbreviations: GA, gestational age; NIRS, near-infrared spectroscopy; rSO₂, regional oxygen saturation; SaO₂, arterial oxygen saturation.

Table 2 Exclusion criteria

<i>Potential sensor interference</i>	
Disorders of/nonkeratinized skin	
Hydrops/anasarca	
Severe jaundice	
Congenital anomaly	
Small for gestational age	
<i>Potentially altered perfusion</i>	
Pneumatosis/Necrotising Enterocolitis (NEC)/perforation	
Encephalopathy/seizure	
Congenital heart disease (including clinically significant PDA)	
Indomethacin treatment	
Renal failure	
5-min Apgar <5	
Hypotension requiring pressors	
<i>Other confounding factors</i>	
Chromosomal abnormality	
Inborn errors of metabolism	

As the neonatal sensors were recently developed, seven term newborns were studied to ensure they returned similar rSO₂ values to those achieved with the Somanetic pediatric sensors (Table 1).

Sensors were placed over the forehead for cerebral (rSO₂-C), right posterior-lateral flank for renal rSO₂ and infraumbilical abdomen for abdominal (rSO₂-A) regional saturations. Because of the contour of the neonatal abdomen and possible confounding contribution of the liver, infraumbilical probe placement was chosen to best sample mesenteric tissue.

rSO₂ was measured every 30 s for 21 days or until discharge. Sensors were removed for 6 h of skin rest every 48 h and skin integrity was inspected daily. Sensors were reused as long as a value was returned. Individual sensors lasted from 1 to 10 days. Neither signal degradation nor augmentation was noted during new sensor placement. Clinicians were blinded to saturation values.

Data were filtered and aligned by hour of life using a MatLab program (The Mathworks, Natick, MA, USA). Isolated drop-out rSO₂ values with continuous data for 5 min before and after were interpolated. Sensors with correct skin contact and placement always had some degree of variability. Data with no variability were determined to be inconsistent with biological readings and periods with <5 min of continuous data were removed.

Daily mean rSO₂ at each site was calculated for each individual subject and also for the group. They were then plotted against postnatal age defining individual and group rSO₂ baseline values. Daily intraindividual variability was defined as the percentage of time each day that a subject's rSO₂ measurements were either 15 above or below their daily mean rSO₂. For each individual, every 30 s rSO₂ value was compared with the subject's mean for that site for that day and then averaged. The percentage of time outside the ± 15 range was calculated daily at each site for each subject and the group.

Differences in daily mean rSO₂ and variability between gestational age (GA) groups (29–30 and 32–33 weeks) were assessed with the Mann–Whitney *U* for independent samples. Weekly changes were evaluated using Wilcoxon signed-rank test and Friedman analysis of variance for repeated measures. Change over time was also assessed by comparing the slopes of rSO₂

baselines to zero. Daily mean rSO₂ were compared with a range of expected values based on previously published preterm measurements (except abdominal that has no published values) and industry reported pediatric norms with single sample *t*-tests (cerebral 60–80, renal 65–95, abdominal 65–95)(Table 1). Hemoglobin concentration and daily weights extracted from the chart were correlated to daily mean rSO₂ values with linear regression at all the three sites.

Results

Population characteristics

In all, 14 preterm infants were enrolled with two exclusions; one for receiving therapeutic indomethacin and one for prolonged nasal continuous positive airway pressure (nCPAP) spatially interfering with the cerebral measurement. Altogether, 12 subjects were included in the analysis. Six were between 29 and 30 weeks gestation and six were between 32 and 33 weeks gestation. Each GA group included one set of twins. In the 29–30 week GA group, all subjects were monitored continuously for 21 days. In the 32–33 week GA group, subjects were monitored continuously from 5 to 15 days until discharge. Prenatal and nursery characteristics are summarized in Table 3. Although absence of a PDA was not routinely confirmed by echocardiogram (ECHO), four subjects included in the analysis received ECHOs for evaluation of a murmur (one small muscular ventricular septal defect (VSD), two patent foramen ovale (PFO) and one small restrictive patent ductus arteriosus (PDA). None of these subjects had changes in clinical management.

Table 3 Maternal, neonatal and postnatal characteristics (*n* = 12)

Characteristic	Data
Maternal steroids, <i>n</i> (%)	10 (83)
Pregnancy-induced hypertension, <i>n</i> (%)	3 (25)
Preeclampsia, <i>n</i> (%)	2 (17)
Placental abruption, <i>n</i> (%)	2 (17)
Cesarean section, <i>n</i> (%)	7 (58)
Chorioamnionitis, <i>n</i> (%)	2 (17)
Gestational age, median (range) (in weeks)	31 (29–33)
Birth weight, median (range) (in g)	1640 (1278–2110)
Male gender, <i>n</i> (%)	5 (42)
SNAPPE-II score, median (range)	21 (0–34)
Change in hematocrit, median (range)	–8 (–22–+2)
Days on mechanical ventilation, median (range)	1 (0–2)
Days on FiO ₂ >0.3, median (range)	0 (0–2)
Clinical sepsis, <i>n</i> (%)	3 (25)
DOL initial enteral feed, median (range)	1 (1–4)
Days to full enteral feeds, median (range)	10 (5–21 ⁺)
Number of blood transfusions <i>n</i> (%)	0 (0)

Abbreviations: DOL, day of life; SNAPPE-II, Score for Neonatal Acute Physiology Perinatal Extension, Version II.

Skin safety assessments

Skin integrity was evaluated daily as a measure of sensor safety. One infant developed a small linear bruise underneath a flank sensor. No skin concerns prompted removal of any sensors during the study period.

Regional saturation (rSO₂): baselines

The daily mean rSO₂ for preterm infants was determined at each site for each GA group plotted against time (Figure 1). The average slope of cerebral baselines was –1.01 and weekly mean rSO₂-C significantly decreased over time (*P* < 0.0001). There were no

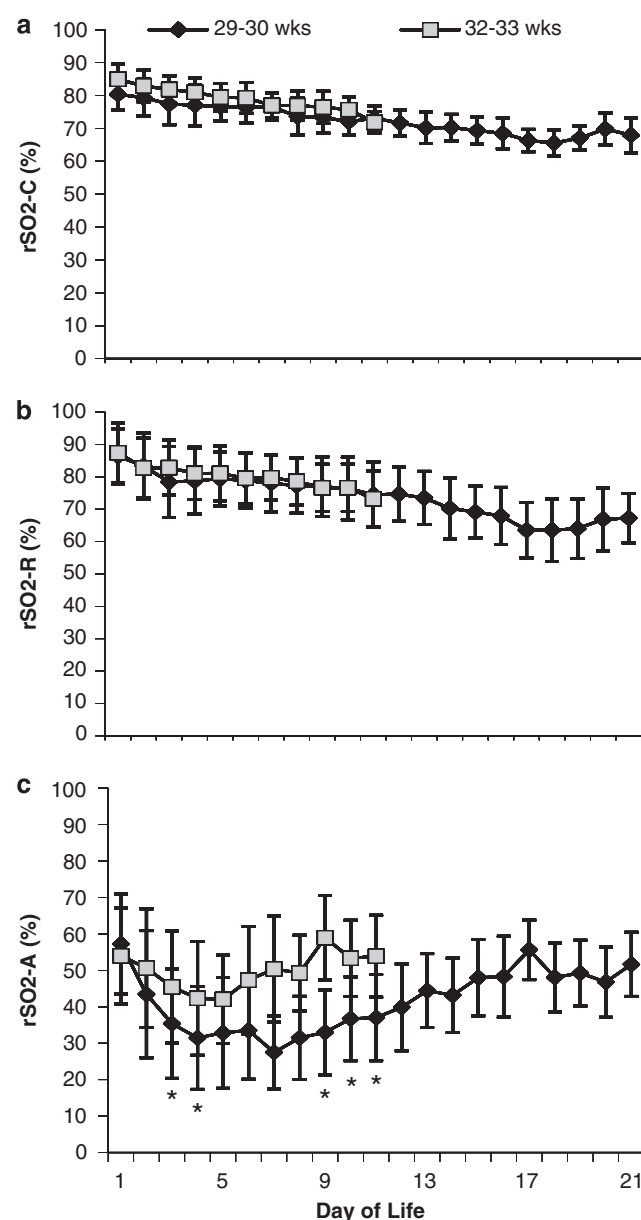


Figure 1 Daily mean rSO₂ ± s.d. demonstrating interindividual daily variability at cerebral (a), renal (b) and abdominal (c) sites for two GA groups. *n* = 6 for each GA group. *Significant difference from 32 to 33 weeks (*P* < 0.05).

significant differences in cerebral measurements between GA groups.

The average slope of renal baselines was -0.85 and weekly mean renal rSO_2 significantly decreased over time ($P < 0.0001$). There were no significant differences in renal measurements between GA groups. The relationship between cerebral and renal values within individuals was not consistent.

The abdominal rSO_2 demonstrated a curvilinear baseline different from the renal and cerebral sites (Figure 1c). The median nadir was at day of life (DOL) 7 (range 3–9) for 29–30 weeks and DOL 4.5 (range 3–8) for 32–33 weeks. Individual daily mean abdominal rSO_2 ranged widely from 18 to $80 \pm 11\%$. The older GA group had significantly higher daily means on DOL 3, 4, 9, 10, 11 and a significantly higher weekly mean in the second week of life ($P \leq 0.05$). There were no abdominal baseline slope differences between the GA groups. The daily mean abdominal rSO_2 was outside the range of industry reported normal values ($P < 0.001$) (Dr MD Wider, personal communication, 2008).

Combined daily mean rSO_2 at each site with 95% confidence intervals (CI) for DOL 1–21 are available.

Regional saturation (rSO_2): variability

Although both cerebral and renal rSO_2 showed almost 40% variability between individuals, the amount of variation within each individual throughout the day was much less. On average, cerebral rSO_2 varied ± 15 from the daily mean $< 1\%$ of the day (95% CI 0–1.6%) and renal rSO_2 8% (95% CI 4.5–10.7%). There were no differences in cerebral or renal variability between GA groups or over time (Figure 2). Abdominal daily variability was higher at 16% (95% CI 7.0–25.4), spending up to 40% of the day ± 15 from the daily mean but decreased over time ($P \leq 0.05$). There were no significant differences between renal and abdominal variability by the third week of life ($P \leq 0.05$) (Figure 2).

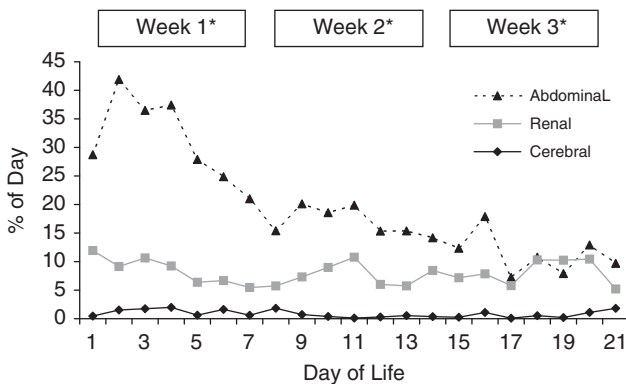


Figure 2 Mean percentage of time rSO_2 measured 15% above or below an individual's daily mean at each site. Data are representative of daily intraindividual variability from baseline. * $P \leq 0.05$; abdominal variability is significantly less each week with no significant difference between renal and abdominal means during week 3.

Influence of hemoglobin concentration and weight

The effect of hemoglobin concentration on rSO_2 in this population with evolving anemia was evaluated. All the three sites demonstrated a moderate-strength, positive correlation between rSO_2 and [Hgb]. Coefficients of determination (r^2) indicated that hemoglobin concentration contributed from 30 to 50% of the variation seen in rSO_2 (Figures 3a–c).

Large weight changes over the first weeks of life may affect rSO_2 sensor depth reading. Weight had a weak positive correlation to rSO_2 at the abdominal site only. The coefficient of determination that indicated 20% of variance in rSO_2 -A was attributable to changes in weight (Figures 3d–f).

Discussion

Despite increasing use in the NICU, little is known about neonatal rSO_2 safety and normative values, including the potential effects of gestational and postnatal age.^{2,6} This study confirms that continuous, long-term rSO_2 monitoring of premature infants in the NICU is both safe and feasible. Our findings indicate that neonatal daily baseline rSO_2 values not only change with postmenstrual age, but also decrease in variability as measured by the amount of time the rSO_2 spends away from the daily mean value. These findings have important implications for using rSO_2 as an indication of pathology in preterm infants during the first weeks of life. These data provide a basis from which to interpret changes in rSO_2 , stimulate speculation about normal transitional physiology, highlight the importance of longer rSO_2 sampling periods, and introduce the use of abdominal rSO_2 measurements in neonatal populations.

A valid concern for introduction of NIRS to the NICU is skin safety. To address this we used a Mepitel barrier, often used for wound care even in extremely low birth weight infants. Although this necessitated more frequent repositioning of the sensor, it enabled easy frequent removal for examination without skin disruption. Importantly, we found no adverse skin effects using this technique and believe that in conjunction with Mepitel, long-term NIRS monitoring can be safe in even the youngest GAs.

By eliminating significant pathology and monitoring over time, we attempted to isolate the normal characteristics of rSO_2 unique to prematurity and postnatal age. In this circumstance, changes in the rSO_2 baseline over time may represent developmental maturation of the physiological control of oxygen delivery and utilization at regional organ vascular beds. This in turn could provide new insight into physiological patterns during neonatal transition in premature infants in addition to potential early identification and management of perfusion altering disease states.

The group mean cerebral rSO_2 fell within the expected range of 60–80%; however, several subjects demonstrated cerebral values

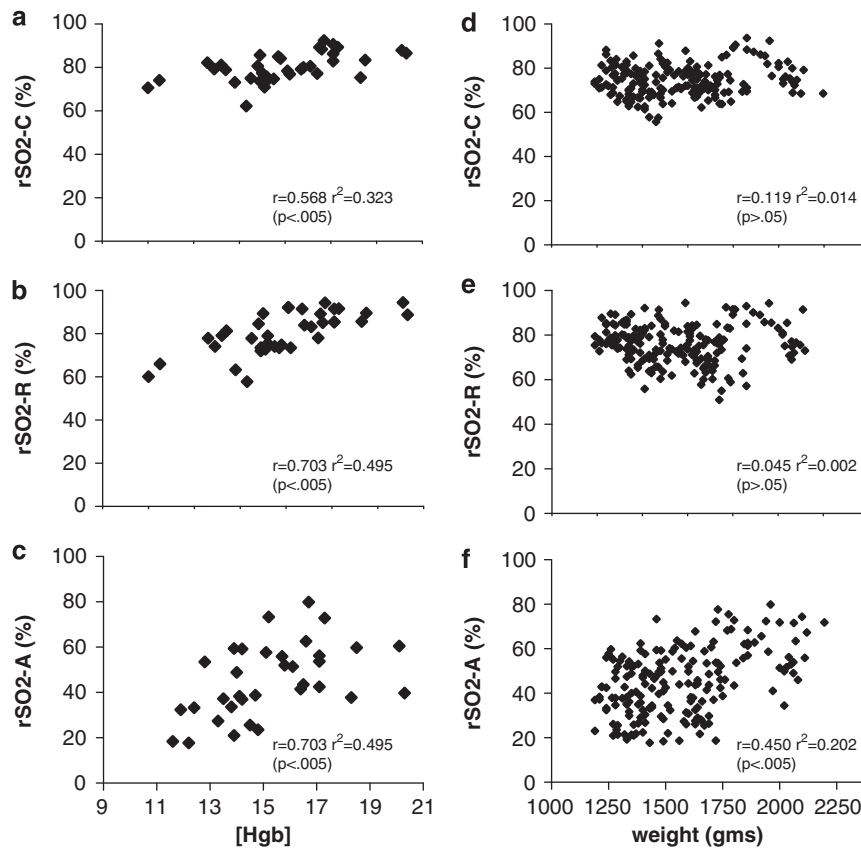


Figure 3 Correlation between hemoglobin concentration [Hgb] (g per 100 ml) and rSO_2 at cerebral (a), renal (b) and abdominal (c) sites. Correlation between weight (g) and rSO_2 at cerebral (d), renal (e) and abdominal (f) sites.

consistently above 80% during the first week of life before declining. The etiology of an initially higher and gradually declining rSO_2 -C in the early days of life is unclear. A pattern of decreasing cerebral rSO_2 contrasts the increase in cerebral artery blood flow described for this time period.^{7,8} These novel data suggest a gradual increase in cerebral oxygen demand even during a physiological rise in oxygen delivery through increased blood flow. This contradicts previously published findings in which Naulaers *et al.*⁹ found that increased cerebral oxygenation values over the first 3 days of life presumably attributed to increased blood flow. This contradiction may be explained as the Naulaers study sampled infants over 30 min in contrast to our more robust 24 h measurement. In addition, Naulaers used tissue oxygenation index (a different NIRS technology), which has not been equivalent to rSO_2 .¹⁰ In contrast, Lemmers *et al.*³ did not see any change in cerebral oxygenation over DOL 1–3. The important difference here includes a shorter sampling period of 60 min twice daily. Such conflicting data highlights the importance of comparing similar technologies in this field and potential downfalls of shorter sampling periods, which may underestimate the degree of inherent variability.

The group mean renal rSO_2 also fell within the expected range (65–95), but did not always maintain the same relationship to the

cerebral measurement. Renal rSO_2 was higher than cerebral for a majority of the days monitored in 10 out of 12 subjects, but did not reach significance. We speculate that these differences in cerebro-renal rSO_2 relationship may be related to intermittent ductal influences on cerebro-renal blood flow. Similar to the cerebral site, decreasing rSO_2 contrasts the increase in renal artery blood flow typical of this time period and may reflect increased renal oxygen consumption outweighing delivery.^{7,11,12}

The unique abdominal rSO_2 pattern suggests regional changes in oxygen balance not mirrored at the cerebral or renal sites. As Doppler studies indicate a progressive increase in superior mesenteric artery flow over the first days to weeks of life,^{7,13} the rSO_2 -A pattern suggests a change in intestinal oxygen consumption around DOL 3–9. A net increase in intestinal oxygen utilization over the first days of life may switch to a net increase in oxygen delivery. This could reflect physiological compensations for the increasing metabolic demand of advancing enteral feeds.

Abdominal rSO_2 was also the only site with differences between GA groups. Although not reaching significance, the younger GA group reached an rSO_2 -A nadir later and deeper than the 32–33 week group. Although these differences may be related to feeding schedules, the pattern suggests a possible GA-dependent

maturation in the ability of the mesenteric vasculature to provide for the increasing metabolic activity of the intestinal tract. Although cyclic changes in rSO_2 -A were noted in association with feeds, in-depth analysis of such responses were beyond the scope of this paper.

Potential concerns with abdominal rSO_2 measurement involve the increased variability in values and the related uncertainty of what tissue is being sampled. As the intestine is a hollow, peristalsing organ, the specific tissue sampled may change frequently despite static sensor placement. Measurement fluctuations are therefore expected to be greater and may represent saturation differences between enteral mucosa, smooth muscle and/or enteric contents. In addition, with infraumbilical placement, there is potential for intestinal displacement from bladder distension; however, in our experience, infants with urinary catheters demonstrate similar variability at the abdominal site. Although infraumbilical placement may inadvertently sample posterior pelvic or abdominal wall muscles in the smallest infants, supraumbilical sensor placement may sample the liver, stomach and spleen in the neonate. In our experience, supraumbilical placement returns rSO_2 values very similar to the renal site, and different from infraumbilical. Lateral abdominal placement presents difficulty in maintaining adequate skin contact due to the contour of the abdomen.

In our experience, because of the large variability of the abdominal signal, we recommend caution in interpreting low absolute abdominal rSO_2 values in young preterm infants. Many of our subjects registered rSO_2 -A at 15% for long periods (hours) while tolerating feeds with good sensor pick-up and appropriate sensor positioning.

The promising benefit of rSO_2 is the potential for real time assessments of change in regional tissue oxygen balance. The significance of such a change depends on the inherent variability of that measurement. Many pediatric intensive care units and operating rooms use an acute drop in cerebral rSO_2 from baseline (10–20% change), or an absolute rSO_2 -C value below 50% as a trigger for intervention. These numbers have been extrapolated from both animal and human data correlating rSO_2 with structural ischemia.^{14–17} Without knowing the true ischemic rSO_2 thresholds at each site in neonates, we opted to assign a change of 15 from the daily mean (baseline) as an indicator of possible clinical change and evaluated how often the rSO_2 hit that mark over the course of a day in a stable patient. We defined this as rSO_2 variability.

The cerebral rSO_2 remained fairly constant, spending <1% of the day on an average outside the ± 15 range, thus by making changes from baseline values potentially meaningful as indicators of clinical change. The renal and abdominal rSO_2 were more variable, spending $\sim 10\%$ of the day ± 15 from the daily mean thereby making changes more difficult to interpret as pathologic, especially in the first 2 weeks of life. This variability highlights the

importance of establishing an individual's baseline over an adequate amount of time and suggests a greater role in long-term monitoring at the renal and abdominal sites.

A potential confounding factor to interpret rSO_2 in the premature infant is the presence of anemia. Preterms are prone to iatrogenic and/or physiological anemia, and hemoglobin concentration is an important contributor to oxygen delivery that weakly correlates with rSO_2 in adults.¹⁸ Similarly, the natural decline in fetal hemoglobin may affect rSO_2 . We found only moderate correlations between rSO_2 and hemoglobin concentration explaining 30–50% of the changes seen. The contribution of fetal hemoglobin is more difficult to evaluate, but studies suggest that the switch to hemoglobin A is likely delayed beyond our period of observation in this GA group.¹⁹ Although anemia appears to contribute to rSO_2 variability, it does so only to a minor degree.

Weaknesses of this study include small numbers and subject attrition in the third week for the older GA group. In addition, slight differences in sensor repositioning could have introduced some variability.

Reflecting changes in the balance between oxygen consumption and delivery, these neonatal rSO_2 patterns suggest the presence of a longer transitional period to ex-utero steady state than perhaps traditionally recognized. Future studies should identify time to steady state baseline for all sites and further define abdominal characteristics as the field moves toward detecting and managing pathological physiology using regional oximetry technology in the NICU.

Conclusion

This paper characterizes for the first time normal rSO_2 patterns in a sample of stable premature infants using the Somanetics NIRS system. We have shown that baseline rSO_2 in preterm infants change during the first weeks of life, change with postnatal age and may be GA dependent at the abdomen. Such characteristics are important to recognize and establish in moving toward interpretation of rSO_2 in the NICU.

Conflicts of interest

Dr McNeill used NIRS equipment donated by Somanetics Corp. to complete this research. Dr Engelhardt is a member of an unsalaried neonatal research panel working with Somanetics Corporation. Dr Gatenby and Dr McElroy declare no conflict of interest.

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