

**Non-Invasive Regional Oxygen Saturation Measurement
in the Preterm Neonate**

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Laura Marrs

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Mentor: Dr. Gregory Martin, MD

For Oliver, the neonate from whom I have learned the most.

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Abstract

There are several, predictable complications of prematurity that are faced by premature infants. Patent ductus arteriosus is among them. This study is an evaluation of a near infrared spectroscopy device to see if the premature infants can be monitored in order to detect significant ductal steal secondary to symptomatic PDA. We hypothesize that in these cases, there would be a difference between renal and cerebral regional oxygenation. To evaluate a difference, it is essential to first establish baseline regional oxygenation values, which are scarce in current literature. There are many pathophysiologic states experienced by premature infants, such as hypoxic spells and intraventricular hemorrhage, which may affect the data. Therefore, the effects of abnormal brain activity on cerebral monitoring are also evaluated. Our preliminary data shows a mean cerebral reading of 77.5189 and a mean renal reading of 70.9105, both without any linear trends. Now that normative data for regional oxygen saturation in the preterm neonate has been established, this opens up a pathway for the study of additional states, such as the left to right shunt of sPDA, since there is now a standard for comparison.

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Introduction

When the life of the newborn begins with a rocky start, they are likely to end up in a neonatal intensive care unit (NICU).

NICU's commonly see babies who are premature, are one of a set of multiples, have congenital anomalies, suffer a traumatic birth, or are exposed to drugs or alcohol prenatally.

Delivery demands a dramatic change in circulation patterns following transition from within the womb to outside that are routine for the term infant, but may become problematic for preterm infants. Circulation in the fetus is successful in utero because a large supply of the blood from the pulmonary artery is transferred to the aorta by a vascular connection known as the ductus arteriosus. Since the lungs of the fetus are not oxygenating hemoglobin, this oxygenated blood from the umbilical vein is shunted past the lungs directly to the aorta in order to maximize the oxygenation of the brain and the rest of the body. This process is assisted by constriction of the pulmonary arteries, which increase the resistance to pulmonary circulation and allow the right ventricle to contribute to systemic circulation. The

ductus arteriosus is kept patent by prostaglandins produced in the placenta. (Doyle, et al. 2009)

Typically in the term infant, the ductus arteriosus gradually closes 10-15 hours after birth beginning on the side nearest the pulmonary artery and continuing toward the aorta. (Heymann, et al. 1975) This allows for the deoxygenated blood that is returned to the right side of the heart to pass properly into the pulmonary circulation to become oxygenated. The process of closure is assisted by the first breath, which expands the lungs, decreases pulmonary resistance, and allows for an increase in systemic oxygen concentration. In utero, the placenta was providing for a lower systemic resistance, but once the umbilical cord has been severed, this component is removed and the systemic resistance rises. These factors contribute to a change in circulation that no longer promotes the right to left shunting of blood through the ductus arteriosus. Furthermore, the duct is closed by the decrease in prostaglandins because of detachment of the placenta and an increase in bradykinin release by the now-expanded lungs. Finally, there is evidence that oxygen-sensitive potassium channels, activated by respiration, are also important to ductus arteriosus closure.

(Thebaud 2004, et al.) The remnant of the ductus arteriosus is known as the ligamentum arteriosum.

The ductus arteriosus may take much longer to close or fail to close at an early gestational age or secondary to hypoxia at birth. Full-term infants who experience hypoxia lack the benefits of the increasing oxygen saturation in closure of the PDA. Prematurity is a common cause of symptomatic PDA (sPDA) because of the underdevelopment of the cardiovascular system at birth, which greatly increases the probability of experiencing hypoxia. The consequences of this could be heart failure, pulmonary hypertension, and Eisenmenger's Syndrome. (Campbell 1968) Since the blood is now being shunted from left to right, systemic hypoperfusion may exist and an overload on the pulmonary circulation may develop, resulting in bronchopulmonary dysplasia, decrease in pulmonary function, or pulmonary hemorrhage. (Welty 2009) At least one study has shown that the left to right shunt decreases the blood available for systemic perfusion and infants with sPDA had lower abdominal aortic blood flow. (Shimada et al. 1994) Heart failure in these patients is a concern because of volume overload. The heart becomes tachycardic while trying to compensate for the oxygenated aortic blood being shunted away from systemic circulation

to the pulmonary artery and the infant may become tachypneic. A continuous murmur from the shunting blood may be auscultated in the left infraclavicular area. Furthermore, the neonate may experience difficulty eating and poor growth, which can complicate the already delicate situation of a preterm infant's survival.

Diagnosis and monitoring of sPDA is currently done by echocardiography. A chest x-ray may show an increased cardiac silhouette and ECG findings are usually not specific.

Current practice on treatment of sPDA in the preterm infant is lacking in consensus among different NICUs and even varies by practitioners in groups because there has never been a large-scale randomized controlled trial to determine the most advantageous course. The three routes that are currently available include observation, pharmacologic treatment, and a surgical approach.

The first treatment approach, conservative observation, has been advocated because it avoids the potential hazards of the other two treatments, allows time for what is the likely natural course of the sPDA, to close, and also avoids exposing the neonate to the risks of treatment, only to have the common occurrence of the sPDA reopening. (Philips 2011) Additionally, though it is known that the presence of a

sPDA increases morbidity in the preterm infant, treatment of the sPDA has not been shown to produce any decrease in morbidity in this patient population. (Benitz 2010)

The second treatment approach is pharmacologic management, typically the administration of indomethacin, which decreases the synthesis of the prostaglandins required to keep the sPDA open. Side effects of this drug can include rising creatinine levels, renal failure, gastrointestinal perforation, and platelet dysfunction. Intravenous ibuprofen has also been found effective for sPDA closure. (Van Overmeire et al. 2000)

Surgical ligation is an option that has typically been reserved for patients when pharmacologic management has failed and has risks of its own, including infection, death, intraventricular hemorrhage and respiratory compromise. (Philips 2011)

An additional option, percutaneous intervention, has been used in children and adults, as the sPDA can be closed with a device inserted with a catheter into the femoral vein or artery.

On the topic of monitoring, a technology known as NIRS, or near infrared spectroscopy, has been used in adult and pediatric populations to monitor a regional saturation of oxygen. These light emitting

sensors are similar to those used in pulse oximetry, but reflect a weighted average of arterial (20%), capillary (5%), and venous blood (75%). This weighting toward venous saturations allows for a measurement of a change in perfusion if there is less oxygen delivery, such as anemia or poor perfusion, increased oxygen extraction, such as sepsis or seizure activity, or an increase in venous proportion, such as cardiac tamponade.

This technology allows scientists to infer regional perfusion. It emits light from a sensor that travels through skin and bone, which is variably absorbed by the hemoglobin (depending on its oxygenation). The rest of the light is scattered and goes back to detectors on the skin where it is measured and processed to give a reading of regional oxygenation. (Somanetics 2005)

NIRS technology has been studied and utilized in various settings for the adult, pediatric, and neonatal patient. In the neonate, NIRS technology has been applied to congenital heart disease patients and some studies have focused on sPDA. For example, one NIRS study has concluded that sPDA does not inhibit cerebral blood flow. (Zaramella, et al. 2006) Other studies have since concluded that a sPDA does limit cerebral oxygenation and increase cerebral oxygen

extraction due to ductal steal. (Lemmers, et al. 2008) There was also some concern raised for cerebral oxygenation during and following the surgical ligation procedure to correct sPDA. One study showed that the procedure itself did not have a negative effect on cerebral oxygenation in patients undergoing ligation. (Vanderhaegen, et al. 2008)

Also using NIRS, the hemodynamic changes taking place due to ductal steal of oxygenated blood from systemic circulation, which lead to mesenteric desaturation, have been illustrated. This was remedied after ligation of the sPDA . (Meier, et al. 2008) Finally, another study used NIRS technology in extremely low birth weight infants by measuring tissue oxygen saturation in the brain, lung, deltoid, and kidney. The tissue oxygen saturation of the left deltoid and the kidney were lower for infants that needed treatment for sPDA, compared to those who did not, and increased to a value more similar to those not requiring treatment after the administration of indomethacin to close the sPDA, suggesting that the post-ductal steal phenomenon has been previously observed in this population. (Underwood, et al. 2007)

NIRS Applications in the Preterm Infant

The original aim at the inception of this scholarly project was to answer the question, “can near infrared spectroscopy be used effectively to detect differences in cerebral and renal regional oxygen saturation in preterm neonates with patent ductus arteriosus when compared to normative saturations for age-matched patients?”

For various reasons, there were delays in analysis of the normative data and progression into the second phase of the study to look at the previously described inquiry into comparing the data from infants with sPDA to those in the normative study. Some of these delays included initial growing pains in the IRB process in the scholarly project curriculum, the author’s own coursework, and delays due to safety concerns regarding the INVOS device. These concerns mainly consisted of skin irritation and abrasions due to the adhesive on the INVOS sensors, though the sensors were changed following 24 hours of monitoring, as per manufacturing instructions. This issue was reported and followed by the research nurse, who developed a gentler method for removing the sensors, which minimized erythema and ecchymoses on the sensitive, premature skin. For these reasons, and to keep within the timeline of the scholarly project, it was decided that

this project would focus on the normative value analysis instead, while the process of looking into obtaining the sPDA data is ongoing. At least one other study has noted similar safety concerns and took measures such as changing out the sensor every 48 hours rather than 24 hours in order to minimize trauma to the skin and extensive training of staff to prevent and monitor any adverse skin events secondary to the adhesive sensors. (Cortez, et al. 2011)

Due to the change of analytic direction, a new scholarly question is now being focused on, which seeks to answer, “when establishing normative values of cerebral and renal regional oxygenation in preterm neonates, do the mean rSO₂ readings follow a linear trend in time over a period of five days?”

If the health of the preterm neonate declines with complications due to ductal steal from a sPDA, medical or surgical intervention may be necessary. With the assistance of NIRS technology, if it were established that the technology could effectively detect regional oxygen saturation differences, it may be possible to establish new guidelines for clinicians to intervene when a medically fragile infant presents with sPDA in order to optimize their chances for survival and decrease morbidity. Eventually, NIRS technology may be used to monitor drug

titrations in an attempt to close the sPDA as well. The technology offers a noninvasive alternative to measure oxygenation compared to blood gasses, and could provide continual real-time feedback for monitoring or treatment purposes. Although there are examples in the literature of using NIRS technology to study sPDA, especially as a screening tool, there has yet to be a study comparing the regional oxygen saturation to established normative values, which was the original aim of this study. It was further hypothesized that the difference between cerebral and renal oxygen saturation would be greater in those infants with sPDA due to the decrease in oxygenation of the kidney secondary to ductal steal from post-ductal organs. The brain's blood supply, originating from the common carotids, is preductal and is hypothesized to not be affected by this phenomenon, leaving a greater difference between the two values in those research subjects with sPDA compared to those without this condition.

One NIRS study has specifically looked at comparing large and moderate size sPDAs and the cerebral and renal regional oxygenation was not found to be different based upon the size of the sPDA, though mesenteric regional oxygenation was found to be decreased on those neonates on NCPAP. (Petrova, et al. 2011) However, this study did not

compare the data to normative values for preterm neonates without sPDA.

With the incidence of sPDA's on the rise, this work is timely and significant. sPDA's are being seen more often due to the increases in survival of preterm infants. Although the incidence of sPDA is only 0.02%-0.04% in term infants, this will increase dramatically as the gestational age decreases, reaching approximately 60% of neonates born before 28 weeks of gestation.(Mullins 1990) (Freedom, et al. 1992)

Case Report of NIRS Application in a Term Infant

Traditionally oxygenation measurements have reflected systemic determinations, but, as described, NIRS is a technology used to monitor regional oxygen saturation. It is increasingly emerging as an important measure of function in the critical care of neonates. As a case in point the correlation of regional cerebral oxygenation with the onset of seizure activity in an infant with neonatal encephalopathy secondary to respiratory failure is reported. Initially in this patient, normal regional cerebral saturations were detected, with subsequent decreases occurring just prior to the beginning of seizure activity.

The male neonate weighed 2,977 g and was delivered by caesarian section at 40 weeks gestation to a gravida 3, para 3, African American woman. His mother states that the pregnancy and delivery were uneventful. The infant had Apgar scores of 9 at 1 minute and 9 at 5 minutes. He was discharged after birth and was reportedly doing well. His only past medical history consisted of surgical repair of bilateral inguinal hernias.

The infant presented to the ER on the 27th day of life in full arrest. The infant required full resuscitation which included volume, intubation, and inotropic support. The infant's history at this time was notable for an apneic event temporally related to a formula aspiration. He was transported to the NICU on an epinephrine drip, where he arrived in critical condition with only intraosseous access.

The mother had been hospitalized recently for pneumonia and left two days before the infant's admission against medical advice. Additionally, a sibling was being treated with antibiotics for upper respiratory symptoms. The infant was reported to have a ten day history of cough upon admission and subsequently pneumonia was confirmed by chest radiograph.

Treatment of the infant's respiratory failure was managed with high frequency oscillatory ventilation followed by a transition to high humidity nasal cannula. The infant was originally treated with ampicillin and gentamycin and later with Cefepime, Vancomycin, and Tamiflu due to suspicion of H1N1 infection, despite negative direct fluorescent antibodies for influenza. Blood, urine, and CSF cultures were negative for bacteria, but the child completed a treatment course for clinical sepsis.

Two hours after admission to the NICU, the infant developed seizures that were characterized by myoclonic jerking of the lower extremities. These were initially treated with Phenobarbital. When the clinical seizures continued Keppra was added. On this therapy, the seizure occurrences decreased. They did occur, however, when the child was stimulated.

Initial MRI and EEG findings shortly after admission were normal. A second EEG was performed at thirty days of life with abnormal findings, showing many multifocal clonic seizures, but inconsistent with hypoxic ischemic encephalopathy. A repeat EEG at 36 days of life showed abnormal waves over the bilateral temporal and

occipital lobes, but no clinical or electrographic seizures. A repeat MRI on the 43rd day of life was also normal.

Cerebral and renal oxygen saturations were measured using NIRS technology, specifically Somanetic's INVOS oximeter, throughout this hospitalization. No side effects of this technology were noted in this case. Interictal regional saturation was found to be at this child's baseline; however, regional saturations dropped just prior to the onset of seizure activity and only gradually improved after the seizure activity had stopped.

Following continued improvement in breathing and feeding, on the 46th day of life, the infant was discharged with plans for continued therapy on Phenobarbital and Keppra.

This case showcases the versatility of the NIRS technology, though this particular patient was not included in the normative value study because the infant was full term and therefore did not pass the exclusion criteria.

Methods

For the normative value study, the original goal was to enroll 25 premature infants between 28-32 weeks of gestation in order to collect 14 days of continuous data recording from a cerebral and somatic regional oximeter after consent from their guardians. Subjects were to be excluded from the study if they had any major congenital anomaly, were withdrawn by their guardian, received vasopressor medication, experienced asphyxia, or if they had a five minute APGAR score less than seven. Following consent, infants were resuscitated and managed with a normal standard of care regardless of participation status in the study. Then a regional oximeter was applied over the forehead and over the renal area in the T10-L2 region, with the INVOS regional oximeter device blinded to the healthcare providers. Continuous data was collected and analyzed to establish normative values of regional oxygenation in the preterm neonate.

Results

The data consist of repeated rSO₂ measurements on nine pre-term patients, which was the final number accrued that did not meet any of the exclusion criteria. Cerebral and somatic readings were taken every five seconds for days 2 through 6 of each patient's life. The first 24 hours of data was eliminated due to what was felt to be measurement error in several of the subjects, as misplacement of the sensors could not be excluded. The patients represent a sample from the population of pre-term infants, suggesting that the patients should be treated as random effects. Furthermore, the observations within each (region of) each patient are highly correlated. The correlation must be taken into account to obtain valid standard errors. For each region, as well as for the difference of readings between regions, we obtain an estimate of the mean rSO₂ values over the course of days 2 through 6 of each patient's life using a linear mixed model, treating patients as random effects and modeling each patient's error covariance matrix with a first-order autoregressive structure. Furthermore, we test for a linear trend in the values using a random-

coefficient model, modeling correlated patient random-slopes and random-intercepts. We analyze the data using SAS 9.2.

Cerebral rSO2 values

Figure 1 presents cerebral readings at a rate of one measurement per hour. The mixed-model estimate for the mean cerebral reading is 77.5189 with a standard error of 1.9220 on 8 degrees of freedom, yielding a 95% confidence interval of (73.0868, 81.9510) for the population mean. The interpretation of this interval is that if we were to repeat this experiment many times, 95% of these replications would produce a confidence interval that contained the true population mean. Given the data observed on our nine subjects, we believe that the mean cerebral rSO2 value for the population of pre-term infants who do not have one of the conditions listed in the exclusion criteria for the study falls somewhere between 73 and 82. This is a wide interval, but it reflects the large amount of variation in the data, which can be seen in Figure 1.

A useful aspect of mixed models is that they partition the total variance in the data between inter-subject and intra-subject variance. The estimated variance component for the random patient-intercept

(inter-subject variance) is 33.0636, and the estimated error variance (intra-subject variance) is 39.8614. That is, the patient-to-patient variability in mean cerebral rSO₂ readings is about the same size as the within-patient variability. If the inter-subject variability is large relative to the intra-subject variability, it may indicate that the predictive ability of the model is of limited. The variability can be reduced, improving the predictive ability of the model, by adding significant covariates to the model. Furthermore, the variability reflects measurement error due to sensor placement, and could potentially be reduced with careful, standardized application of the sensors to the patients. In this data set, with only eight degrees of freedom for testing fixed effects, we have a limited ability to test for significance of covariates to avoid confounding factors. The specific effects that were tested are discussed later, but none of them were significant.

The inter-subject variability may be used along with the confidence interval for the mean to construct a “prediction interval.” The prediction interval yields a range in which the mean of the observations on a new patient would be expected to fall. A 95% prediction interval for the mean cerebral reading of a new patient is

(61.8166, 93.22119). This is a wide interval, but it reflects the large amount of variation in the data. If a new patient were to have a mean cerebral rSO₂ reading outside of this range, it would indicate that their readings were significantly different from the normative value established by this study. The size of this interval may limit its utility, but it could be minimized in future studies if either measurement error due to sensor placement is reduced, or significant predictors for deviations in mean rSO₂ readings (e.g. a particular medical condition) is identified.

A random-coefficient model did not detect a significant linear trend in the cerebral rSO₂ readings. That is, there did not appear to be either a linear increase or decrease, on average, in the cerebral rSO₂ readings over days two through six after delivery in the sampled patients. As a result, the mean reading, described above, provides a sufficient description of the rSO₂ readings, without depending on the number of days since delivery.

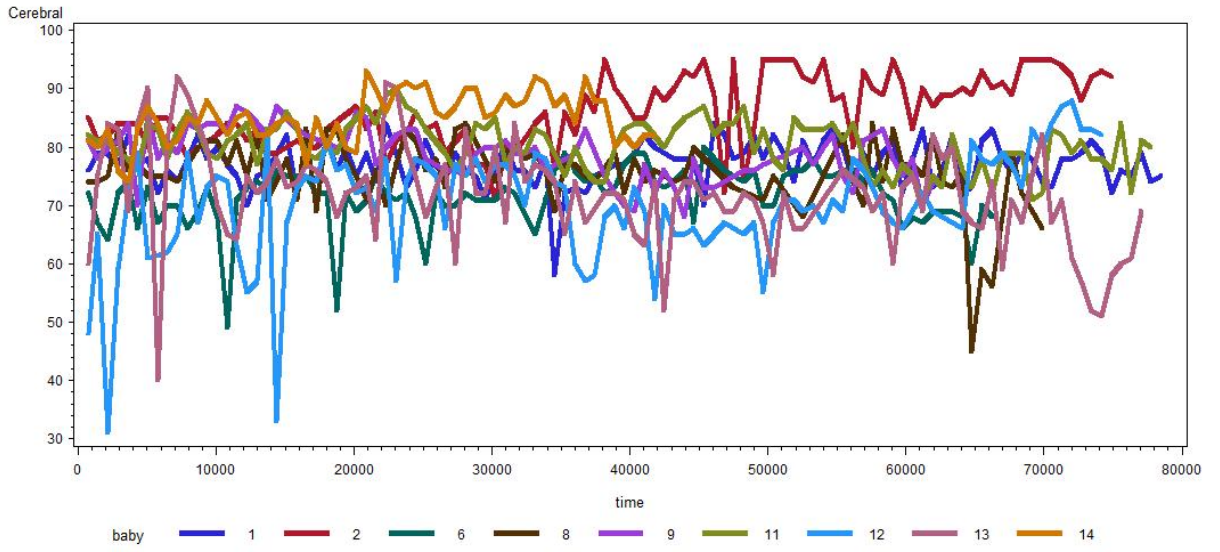


Figure 1 Cerebral readings (1 per hour)

Somatic rSO2 values

Figure 2 presents somatic readings at a rate of one measurement per hour. The mixed-model estimate for the mean somatic reading is 70.9105 with a standard error of 3.0838 on 8 degrees of freedom, yielding a 95% confidence interval of (63.8023, 78.0187). The estimated variance component for the random patient-intercept is 84.1705, showing patient to patient variability, and the estimated error variance is 220.24, showing within patient variability. A 95% prediction interval for the mean somatic reading of a new patient is (45.8204, 96.0006). A random-coefficient model did not detect a significant linear trend in the somatic rSO2 readings.

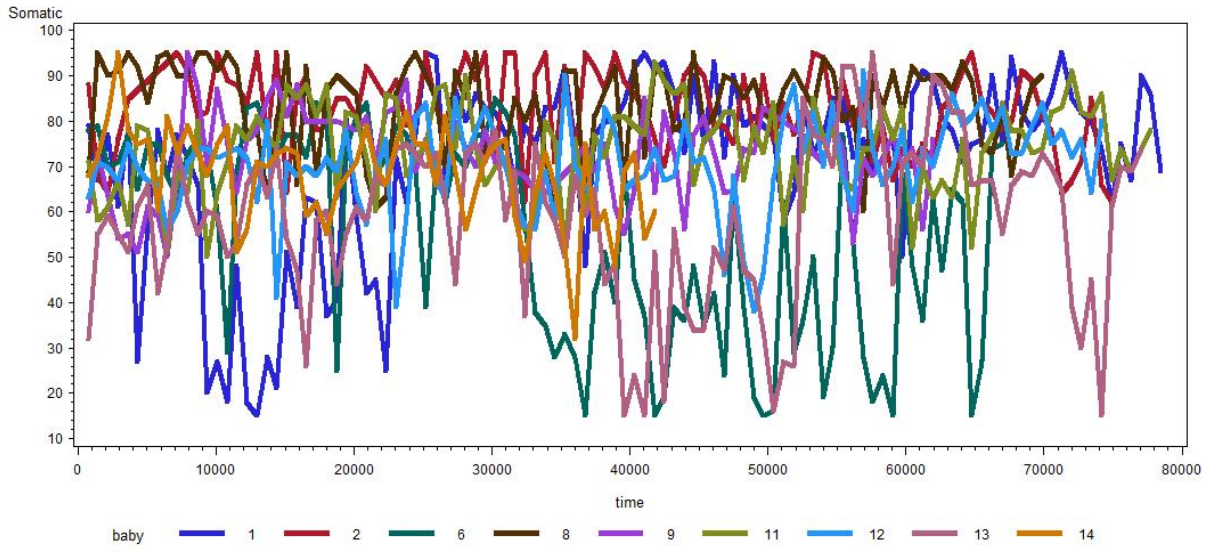


Figure 2 Somatic rSO2 readings (1 per hour)

Difference between cerebral and somatic readings

Figure 3 presents somatic readings at a rate of one measurement per hour. The mixed-model estimate for the mean difference is 6.7178 with a standard error of 2.6217 on 8 degrees of freedom, yielding a 95% confidence interval of (0.672149, 12.76345), which shows that the mean cerebral reading is significantly higher than the mean somatic reading. The estimated variance component for the random patient-intercept is 60.3257, and the estimated error variance is 231.21. A 95% prediction interval for the mean difference between cerebral and somatic readings in a new patient is (-14.5511, 15.8954), meaning that it would not be surprising, based on this data set, to observe a new patient with a mean somatic reading higher than their cerebral reading. A random-coefficient model did not detect a significant linear trend in the difference between the rSO₂ readings.

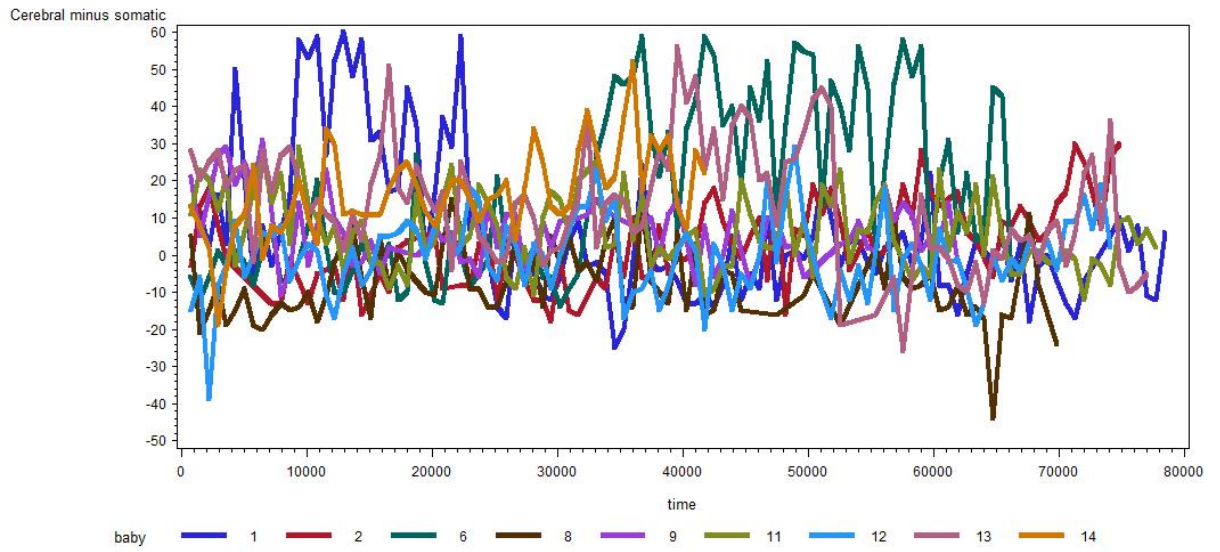


Figure 3 Difference between cerebral and somatic readings

Discussion

In some instances, changing the sensor led to a shift in the mean rSO₂ readings. The INVOS readings for pre-term infants may be more sensitive to sensor placement than in adults due to the sensor being able to probe further into tissue, such as white matter in the brain, secondary to obvious anatomic differences in size between the two populations. (Adelson, et al. 1999) This could lead to difficulties when attempting to use the INVOS system with neonatal patients, and may contribute to the large variance observed in our data.

By nature, pre-term infants are predisposed to a variety of medical issues – especially respiratory issues – that may affect rSO₂ readings. Thus, our estimate of normative rSO₂ readings in pre-term infants is associated with large standard errors, producing wide confidence intervals. A few subjects produced rSO₂ readings that appeared to be sporadic and different from the behavior shown by the readings of the majority of patients. However, these patients did not meet any of the relatively weak exclusion criteria and were included in the analysis. It may be useful for future studies to study more patients, spending less time on each patient. This study planned to collect 14

consecutive days of readings from each patient. After examining the data, it would be sufficient to collect data from each patient during a single 24 hour period. We did not observe any trends in the data that would require more than one day's worth of measurements.

Furthermore, this would likely increase the number of patients willing to participate in the study. With only 9 subjects, we do not have enough degrees of freedom to test for the significance of covariates with several categories, such as race. Effects for birth weight, gender, one-minute APGAR, and method of delivery were tested one at a time, but none of the effects were significant, even without the requisite multiple-comparisons correction to the level of each test (e.g. a Bonferroni correction).

The data contain information about sPDA in the subjects, but only one of the four patients with confirmed sPDA did not meet one of the exclusion criteria, making it impossible for us to test for the effect of sPDA, since the sPDA effect would be confounded with a random subject effect (we would not know if the effect were due to the sPDA or to characteristics of the particular subject). Furthermore, some of the subjects in the study who did not have confirmed cases of sPDA were later thought to have had sPDA. If testing for the effect of sPDA, the

presence of misclassified subjects in the study could lead to reduced power (i.e., reduced sensitivity).

It is difficult to find published normative data for regional cerebral and renal oxygenation values as of the writing of this paper. One larger-scale study has reported specific median normative values for preterm and term cerebral regional oxygenation based on gestational age in the first six hours of life. The article assumed independence and unlike the analysis described in this data, didn't take into account the complex correlation structure in the data. As a result, their P values were too small and some of their reported statistically significant differences are likely to be invalid. We are in the process of contacting the journal to notify them of the issue as of the writing of this paper. (Tina, et al. 2009) To illustrate the nature of the error, we note that our mixed model did not detect a significant difference between male and female rSO₂ readings in our data (p-value 0.3275). However, the naïve ordinary least squares analysis (t-test) indicates a highly significant gender effect (p-value <0.0001) on the same data. This stark difference in the results is due to the incorrect assumption of independence made by the t-test. We expect

observations on the same patient to be similar, and we certainly expect consecutive observations made on the same patient to be related.

In another study, normative values were given for premature babies for splanchnic tissue, as measured in the periumbilical region. They, similar to this analysis, reported no linear relationship in time for the regional oxygenation data outside of the confidence interval, but the interesting finding was a decrease in splanchnic tissue oxygenation in those preterm neonates with feeding intolerance when compared to those without intolerance. Cerebral and renal measurements were not recorded and therefore cannot be compared with the values in this data set. (Cortez, et al. 2011)

NIRS has been studied and utilized in various settings for the adult, pediatric, and neonatal patient. In the neonate, NIRS has been applied in many situations, especially to congenital heart disease patients, patients in a state of low cardiac output, and patients suffering from hypoxic ischemic encephalopathy.

Some exploration has been done in the area of applying NIRS to patients with seizures. For example, in a preliminary study, NIRS was successful at providing noninvasive and continuous monitoring of cerebral oxygenation in the periictal period, which showed preictal

increase in cerebral oxygenation, seizure activity associations with decreased cerebral oxygen availability, and the ability to differentiate between electrographic and electroclinical seizures based on their patterns of fluctuating oxygenated hemoglobin levels. (Adelson, et al. 1999)

Similarly, one case study has cited the phenomenon of decreased cerebral oxygenation during seizure activity. Since, in the above described neonate's case, the seizures were localized to one hemisphere, researchers had the ability to observe more pronounced regional oxygen saturation index vacillations in the focus of seizure activity when compared to the unaffected hemisphere. (Shuhaiber, et al. 2004) This method of localization is complicated when using NIRS because the measurement is limited to the area directly underlying the sensor, and thus may not measure the specific area of interest. The area reached by the diode, only a few centimeters, may very well not be at the depth necessary to specify a focus. However, NIRS has been shown to be useful in at least lateralizing the focus when placed over the frontal cortex due to marked desaturation during seizure activity on the ipsilateral side. (Steinhoff, et al. 1996) NIRS's ability to lateralize seizure foci may be further augmented or superior to current

single photon emission computed tomography studies. (Watanabe, et al. 2002)(Shichiri, et al. 2001)

In the case report of the neonate with seizures, cerebral oxygenation was found to decrease during seizure activity because of the clonic nature of the seizures. Clinicians must consider the underlying pathophysiology of the patient when interpreting regional oximetry. For example, convulsive seizures and complex partial seizures may tend to show an increase in cerebral oxygenation utilization, while absence seizures and rapidly secondarily complex partial seizures were associated with an ictal decrease. (Haginoya, et al. 2001)(Sokol, et al. 2000)

Seizures in neonates may be clinically silent or subtle and because of the necessity of discovering if a specific anticonvulsant therapy is beneficial, EEG needs to be performed for monitoring. NIRS may have some role in augmenting monitoring in this population. (Arca, et al. 2006) For hospitals that do not have the ability to perform continuous EEG monitoring, NIRS may be a viable alternative for assistance in detection, management, and treatment of seizures. Additionally, NIRS may have the capability to lower treatment costs

by removing the necessity for continuous EEG monitoring in some cases.

NIRS is likely to become an increasingly popular device for managing seizures due to its noninvasive nature, ability to provide objective measurements of regional oxygenation, and the capability to have real-time information to correlate with seizure activity and therapeutic interventions. Currently, although clinicians must be cautious of possible artifacts during their interpretation, continuous EEG is the standard of care in NICU's for the constant monitoring of epilepsy, but the advent of NIRS has the potential to change this, with some advocating for the combination of continuous EEG with NIRS for the best in brain oxygen disparity detection. (Toet, et al. 2009)

Future Work

Our mixed model analysis was appropriate here because we had information on several patients. For future work, the appropriate method of analysis for observations on a single patient is via autoregressive moving average (ARMA) models. This class of models accounts for the correlation of the repeated rSO₂ readings to calculate accurate point estimates and standard errors. The mixed model approach will also be useful for future studies with several patients. We recommend more stringent exclusion criteria for future studies, and monitoring the subjects for only a single 24 hour period. This would narrow the population to which inference from the study may be drawn, but a more focused study would likely see less patient-to-patient variation in the data, allowing for practically significant conclusions to be drawn about the data. Most importantly, for characteristics such as sPDA that change in a patient over time, the patients can be used as their own control. This is known in the design of experiments literature as “blocking.” This would greatly increase the sensitivity of the test by eliminating all of the patient-to-patient variation from the model, as well as likely decreasing the error variance. For example, if a subject were diagnosed with sPDA, they

could be monitored for 24 hours on the INVOS, and then for another 24 hours once the sPDA were confirmed to have closed by echocardiography.

Similar to the normative data study, the protocol for carrying out a study to look at the effect of sPDA on regional oxygen saturation, patients will be consented by their guardians for enrollment in this study. Participation will not alter resuscitation standards at birth or any other medical or surgical management during their time in the NICU. Patients with known sPDA between the gestational ages of 28-32 weeks will be enrolled in the study. Two measurements will be taken of regional oxygen saturation by attaching an INVOS monitor sensor to the skin on the forehead over the brain and another over the kidney in order to determine the effect that the patent ductus arteriosus is having on the patients' hemodynamics. If monitoring were to continue beyond 24 hours, the sensor would be changed. The INVOS screen will be blinded during the data collection. This data will be compared to normative values for neonates of comparable gestational ages without a sPDA. Data collection for the study would take place at Phoenix Children's Hospital NICU at Banner Good Samaritan.

Conclusion

This study describes the establishment of some normative values for cerebral and renal regional tissue oxygenation in the preterm neonate. This is the first step for studying other relationships of regional oxygenation, such as any potential differences seen in infants with sPDA in order to determine if there is variation from the norm.

The case report featured the observation of a correlation between decreased cerebral oxygen saturation, and thus perfusion, and seizure activity in a neonate. While this conclusion provides potential applications to seizure management in neonates, further studies need to be done to validate our observation.

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