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## CORRELATION OF ABDOMINAL rSO<sub>2</sub> WITH SUPERIOR MESENTERIC ARTERY VELOCITIES IN PRETERM INFANTS

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## Abstract

**Objective**—Near-infrared spectroscopy (NIRS) is used to monitor brain and kidney perfusion in at-risk premature and term neonates. Although NIRS holds potential for bedside monitoring of intestinal perfusion, there is insufficient evidence showing correlation with mesenteric blood flow. To determine if an association exists between abdominal regional oxygen saturation (A-rSO<sub>2</sub>) and mesenteric blood flow, we compared changes in A-rSO<sub>2</sub> to changes in blood flow velocity in the superior mesenteric artery (SMA) before and after feedings in very-low birthweight infants.

**Study Design**—A-rSO<sub>2</sub> was continuously monitored midline below the umbilicus for 3 days in 18 stable 25–31 week bolus-fed infants (median BW 1203g, median age 5 days). We compared change in SMA velocity from immediately before to 10 minutes and 60–120 minutes after feeding

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with change in A-rSO<sub>2</sub> over the same time. Spearman's rank correlation was used to ascertain if a significant association existed.

**Result**—Change in A-rSO<sub>2</sub> was significantly associated with change in systolic, diastolic, and mean SMA velocity from fasting to 60-120 minutes after feeding (p=0.016, 0.021, 0.010) and from 10 minutes after a feed to 60-120 minutes after feeding (p=0.009, 0.035, 0.032).

**Conclusion**—In very preterm infants, A-rSO<sub>2</sub> reflects blood flow in the SMA and can provide non-invasive continuous monitoring of intestinal perfusion. Further studies are indicated to determine the sensitivity of NIRS to detect early intestinal pathology in this population.

#### Keywords

mesenteric; splanchnic; near-infrared spectroscopy; very-low birthweight; premature

#### Introduction

Near-infrared spectroscopy (NIRS) is a non-invasive clinical tool with the potential to monitor splanchnic perfusion in very premature infants at increased risk for intestinal disorders. Disturbances in blood flow contribute to conditions such as feeding intolerance and necrotizing enterocolitis (NEC).<sup>1–5</sup> Blood flow velocities in the superior mesenteric artery (SMA) can be measured by Doppler ultrasound and correlated with gestational and post-natal age, in-utero growth restriction, feeding, intestinal dysmotility and necrotizing enterocolitis.<sup>2, 3, 6–11</sup> Preterm infants are able to regulate blood flow in the SMA in response to bolus milk feedings as early as the first day; the blood flow velocity increases during the first week after birth and greater postprandial increases are positively correlated with feeding tolerance.<sup>3, 12</sup> The widespread use of Doppler in daily clinical evaluation of neonates is limited due to cost, availability, and need for trained operators.<sup>3, 6, 8, 11</sup> Additionally, there are other important markers of organ health, such as how effectively oxygen is delivered and extracted in the target tissue bed, that cannot be measured by ultrasound.

NIRS measures vital organ oxygen delivery and consumption continuously through a surface sensor by measuring the ratio of light absorbed by different chromophores (oxyhemoglobin and deoxyhemoglobin) in the underlying organ bed to produce a venous-weighted measurement of regional oxygen saturation (rSO<sub>2</sub>). NIRS is especially suited to monitor intestinal perfusion in neonates. It is the only clinical tool that can provide immediate information to the clinician regarding response to mesenteric oxygen demand. Studies suggest correlation between A-rSO<sub>2</sub> and alterations in intestinal blood flow, such as left-to-right shunt associated with a patent ductus arteriosus or NEC.<sup>5, 13, 14</sup> Correlation has not yet been made between mesenteric blood flow and A-rSO<sub>2</sub> in healthy very preterm infants. The aim of this study was to determine if change in A-rSO<sub>2</sub> associated with feeds correlated with changes in Doppler blood flow velocity of the SMA. We hypothesized that changes in A-rSO<sub>2</sub> in response to feeding would correlate with increase in postprandial blood flow.

## **Materials and Methods**

#### Study design

We designed a prospective observational single-center trial that was approved by the Institutional Review Board at Vanderbilt University Medical Center. Informed consent was obtained for each enrolled subject by the mother, or by both parents if married. Enrolled outborn infants arrived at our institution within 24 hours of birth.

#### Inclusion criteria

Healthy premature infants born between  $23 \ 1/7 - 30 \ 6/7$  weeks with birthweight 1500 grams were enrolled. Infants were 14 days of age and tolerating enteral feeds of 10–20 ml/kg/day at start of study. The small volume of feeds was chosen to create a more homogeneous population, since the post-natal age of very premature infants becomes more discrepant with advancing feeding volumes. The neonatologist caring for the patient increased each infant's daily feeding by 10ml/kg/day as tolerated, following usual institutional practice.

#### **Exclusion criteria**

Infants were excluded if they had serious congenital malformations, known or suspected chromosomal anomalies, intrauterine growth restriction, congenital or acquired gastrointestinal anomalies (including atresia, gastroschisis, or omphalocele), history of necrotizing enterocolitis, use of inotropic support within 24 hours, known renal anomalies or disease, severe jaundice, known or suspected blood dyscrasia, or feeding intolerance within 12 hours of enrollment.

#### Study procedures

All infants admitted to the Vanderbilt Children's Hospital between October 2009 and November 2010 were screened for eligibility. Informed parental consent was obtained for each study participant. Infants were fed a gavage bolus by gravity of unfortified breast milk or preterm formula every three hours. Since the feeding volumes were small, all feeds occurred over 5 minutes or less. All infants received hyperalimentation in addition to enteral feeds at time of study.

#### Near-infrared spectroscopy

Infant/Neonatal sensors were placed midline below the umbilicus on each patient and ArSO<sub>2</sub> was measured using an optical spectroscopy system (INVOS 5100 and VitalSync, Covidien, Boulder, Colorado). A piece of gel-impregnated gauze (Mepitel, Mölnlycke, Sweden) was placed between the sensor and patient as an additional layer of protection from skin irritation. This technique has previously been described and does not interfere with NIRS measurements.<sup>15</sup> A-rSO<sub>2</sub> was measured continuously recorded at 30-second intervals for 72 hours.

#### Doppler ultrasound

Each infant received 1 set of three Doppler ultrasounds of the SMA on three consecutive days for a total of 9 ultrasounds per patient. Each set of 3 ultrasounds occurred surrounding one feeding on each day: the first ultrasound was performed immediately prior to a feed, the second ultrasound occurred 10 minutes after the gavage feeding was complete, and the third ultrasound was performed 60–120 minutes after the feed. Pediatric ultrasonographers trained for the study protocol performed the ultrasounds. All ultrasounds occurred during the daytime.

Imaging was obtained using pulsed Doppler ultrasound (Siemens Acuson Sequoia 512, Malvern, PA) and an 8.0 MHz transducer (Siemens 15L8, Malvern, PA). With the patient supine, scanning was performed immediately distal to the xiphoid process and perpendicular to the abdominal aorta. The origin of the SMA was identified in its long axis and the cursor placed one centimeter from the origin to obtain a waveform. When three stable waveforms were obtained, the waveforms were manually traced and systolic flow velocity, end diastolic velocity, and time-averaged mean flow velocities were automatically populated using the trace function of the machine. This was repeated once with a second set of three stable waveforms and the mean of the six values recorded to produce a single value for peak mean systolic flow velocity (PSV), mean end diastolic flow velocity (EDV) and time-averaged mean flow velocity (TAMV). Vessel volume and cross-sectional area were measured. A pediatric radiologist reviewed the studies for quality and consistency.

#### Statistical analyses

Spearman's rank correlation was used to measure the relationship between the change in systolic, diastolic and mean blood flow velocity in the SMA before and at two post-prandial points (10 minutes after feeding and 60–120 minutes after feeding) compared with the change in A-rSO<sub>2</sub> values over the same time period. A p-value <0.05 was considered statistically significant.

A-rSO<sub>2</sub> values were recorded at 30-second intervals. The median A-rSO<sub>2</sub> for the 10 minutes prior to each Doppler ultrasound was calculated. Median, rather than mean, values were used due to the small sample size. Since all the infants in the study were clinically well and without abdominal pathology, prolonged periods of very low A-rSO<sub>2</sub> (A-rSO<sub>2</sub>=15) without any variability for >50% of the time were deemed to be poor quality measurements inconsistent with biological readings and were not included in the initial analysis. This approach has been previously described.<sup>15</sup>

Data was entered in a Redcap database (Vanderbilt Institute for Clinical and Translational Research). The statistical analyses were done using R version 2.12.1 (2010-12-16).

## Results

#### **Demographic features**

Twenty-five patients were enrolled; seven were withdrawn before beginning the study due to parental preference (n=2), clinical instability, sepsis, or feeding intolerance (n=3),

hemodynamically significant PDA (n=1) or technical difficulties (n=1). Altogether, 18 infants were included in the analysis. Infant and maternal characteristics are presented in Table 1 and Table 2. The median post-natal age at time of study was 5 days. Infants were all well at time of study.

#### Doppler

Previous studies have documented increased velocity of blood flow in the superior mesenteric artery during the first week following birth. We used the Kruskal-Wallis test to determine if the A-rSO<sub>2</sub> or SMA velocities varied by day of study. A-rSO<sub>2</sub> values were not significantly different from day 1 to day 3 of the study. The immediate post-prandial (10 minutes after feed) systolic, diastolic, and mean velocities differed by day of study with all three velocities increasing from day 1 to day 3 (p-value=0.013, 0.015, 0.005, respectively). (Table 3)

#### Change in A-rSO<sub>2</sub> associated with change in SMA blood flow velocity

The NIRS sensors provided consistent A-rSO<sub>2</sub> values in the infraumbilical location. The median A-rSO<sub>2</sub> for the 10-minute period before each Doppler ultrasound was calculated and used as baseline for analysis. The change in systolic, diastolic, and mean ultrasound velocity from before feeding (fasting) to 10 minutes after feeding was compared to the change in median A-rSO<sub>2</sub> at each point. The same method was used to compare before feeding to 60–120 minutes after feed as well as 10 minutes after feeding to 60-120 minutes after feeding. Spearman's rank correlation was used to ascertain if any association existed.

There was a significant association between the change in SMA systolic, diastolic and mean Doppler velocity and the change in A-rSO<sub>2</sub> for two time periods: before a feed (fasting) to 60-120 minutes, and from immediately after a feeding (10 minutes post-prandial) to 60-120 minutes after feeding. The change in SMA Doppler velocities from before feeding to 10 minutes after feeding was not significantly associated with the change in A-rSO<sub>2</sub> over the same time period. (Table 4) There was no association between change in A-rSO<sub>2</sub> and change in superior mesenteric artery vessel volume during feedings.

#### **Additional Analyses**

There was no evidence of a correlation between number of days to full feeds and degree of change in A-rSO<sub>2</sub> with feeding. Own-mother milk was provided in 79% of feedings. There was no difference in A-rSO<sub>2</sub> between infants fed breast milk and those fed formula (Wilcoxon test). No infants developed intestinal disturbances during the study although three infants were later treated for Bell Stage I necrotizing enterocolitis at age 9–35 days. One was ultimately diagnosed with milk protein allergy, one developed unclassified "medical NEC" treated with 1 day of bowel rest at an outlying hospital after being transported out for convalescent care, and one infant developed circulatory shock with a distended abdomen. Exploratory laparotomy showed no gross evidence of intestinal disease, no bowel was resected, and his urine culture subsequently grew *Enterobacter cloacae*. There was considerable heterogeneity in this group and lack of definitive evidence for true necrotizing enterocolitis in each case. Median A-rSO<sub>2</sub> and change in A-rSO<sub>2</sub> was not

significantly different in this group at time of study from the infants who did not subsequently develop abdominal disturbances.

## Discussion

Intestinal dysfunction and disease are significant morbidities for premature infants and an easily accessible bedside monitoring tool could provide real-time information and add to the repertoire of the clinician assessing an at-risk infant. Change in A-rSO<sub>2</sub> correlates with change in SMA blood flow velocity before and after feedings in very premature infants during the first two weeks after birth. This suggests that A-rSO<sub>2</sub> reflects intestinal blood flow and can be used to monitor intestinal perfusion in this population.

Comparing blood flow velocities to regional oxygenation is not without challenges because they are inherently measuring two different, but not unrelated, aspects of oxygen delivery to the organs. While Doppler measures merely the blood flow velocity to the intestines, NIRS measures the oxygen delivery to an organ bed and subsequent extraction of provided oxygen through the interrogation of local chromophores. It was important to investigate if any relationship existed between the two different modalities, since abdominal NIRS is currently being used in premature infants without a complete understanding of how the measurements relate to underlying intestinal physiology. In this study there was an association between change in A-rSO<sub>2</sub> and change in SMA blood flow velocity from fasting and 10 minutes after feeding to 60-120 minutes after feeding. There was no association between change in ArSO<sub>2</sub> and blood flow velocities from fasting to 10 minutes after feeding. While Doppler blood flow had already increased in response to feeding, the A-rSO<sub>2</sub> had not yet changed, indicating that this time period was too short to detect a change in O<sub>2</sub> consumption.

There is growing evidence that it is not merely the absolute value of A-rSO<sub>2</sub> or even the amount of change in A-rSO<sub>2</sub> that provides the most physiologically useful information but rather the degree of variability, with periods of either low or exaggerated variability representing an abnormal state.<sup>13</sup> Several authors have noted increased daily variability in A-rSO<sub>2</sub> compared to cerebral and renal sites, about 15–22% change from daily mean at any given time.<sup>15, 16</sup>

One of the challenges faced in the routine clinical use of abdominal NIRS in the newly-born very-preterm infant is that A-rSO<sub>2</sub> is often low and can be invariable for long periods of time in the absence of clinical pathology. While this is likely due in part to the physiologic transition from fetal to neonatal circulation, this may also represent limitations in application of the current technology to this population. The INVOS regional oximetry system used in this study provides rSO<sub>2</sub> values between 15–95. In very premature infants within the first week of life, it is not uncommon to have long periods of 15 in the absence of clinical pathology. In our experience, infants who experienced long periods of time without A-rSO<sub>2</sub> variability always had A-rSO<sub>2</sub> measurements of 15, the lowest reading that the machine provides. This low value was present despite good sensor placement, and in the absence of clinical pathology. To date, it is unclear whether prolonged periods of 15 are due to truly low values, which may actually be less than 15, or limitations of the technology. Cortez et al. noted periods of extremely low A-rSO<sub>2</sub> in two infants with developing necrotizing

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enterocolitis.<sup>13</sup> This same phenomenon occurred in the absence of pathology in this study. This might represent an adaption of the circulatory system in early post-natal life when low feeding volumes exert low demand on the splanchnic bed.

Achieving clinically relevant A-rSO<sub>2</sub> monitoring requires understanding the significance of variability in the early post-natal days when normative values change almost daily, as well as variation in an individual throughout a single day. The clinical interpretation of long periods of low A-rSO<sub>2</sub> lacking variability is as yet unclear. In the very preterm infant with an immature transition to neonatal circulation, we are unable to identify whether a low A-rSO<sub>2</sub> represents hypoperfusion, increased demand by the intestine, or another process. However, our novel data shows that A-rSO<sub>2</sub> does reflect changes in mesenteric blood flow and sets the stage for further research in this area. There are currently very limited data on how abdominal NIRS monitoring affects patient outcomes and we recommend caution in routinely implementing this modality outside of investigation until more is known about clinical effect. Despite being a non-invasive device, harm could still be done through reliance on an emerging modality if it alters patient management.<sup>17</sup> Future studies need to focus on developing algorithms that calculate and describe patient-specific daily A-rSO<sub>2</sub> variability over the first weeks of life in very premature infants.

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## Maternal Characteristics

Characteristic	Data
Age	23 (18–34)*
Gravida	1 (1–10)*
Preterm Labor	8 (44)**
Premature Rupture of Membranes	7 (7)**
PIH or Preeclampsia	8 (44)**
Steroids >24 hrs prior to delivery	5 (29)**

\*Median (range)

\*\* n (%)

#### Infant Characteristics

Characteristic	Data
Gestational Age (weeks)	28 (25–31)*
Birthweight (grams)	1203 (810–1550)*
Male	9 (50%)
Race	
Black American	3 (17%)
Caucasian	11 (61%)
Hispanic	1 (6%)
Multiple Races	3 (17%)
Postnatal Age at Study Start (days)	5 (2–7)*
Days to Full Feeds (120 ml/kg/d)	14.5 (7–23)*
Apgar at 1 min	7 (1–9)*
Apgar at 5 min	8 (2–9)*

\*Median (range)

A-rSO2 and SMA velocity (m/s) by day of study

A-rSO <sub>2</sub>		Day 1			Day 2			Day 3		<i>p</i> value
Pre-prandial	28	34	44	26	41	56	18	34	42	0.820
Immediate Post-prandial	16	30	46	23	35	42	15	38	44	0.970
60–120 min Post-prandial	18	32	50	34	45	48	26	36	39	0.350
Doppler Velocity (m/s)										
Systolic										
Pre-prandial	0.420	0.570	0.690	0.510	0.580	0.740	0.640	0.670	0.810	0.068
Immediate Post-prandial	0.380	0.480	0.610	0.650	0.680	0.770	0.550	0.610	0.770	$0.013^{*}$
60–120 min Post-prandial	0.520	0.680	0.740	0.640	0.760	0.810	0.600	0.710	0.820	0.280
Diastolic										
Pre-prandial	0.076	060.0	0.131	0.087	0.140	0.172	0.105	0.142	0.153	0.062
Immediate Post-prandial	0.084	0.111	0.159	0.142	0.174	0.203	0.148	0.160	0.214	$0.015^{*}$
60–120 min Post-prandial	0.140	0.170	0.250	0.200	0.220	0.250	0.140	0.160	0.260	0.360
Mean										
Pre-prandial	0.210	0.240	0.330	0.210	0.280	0.320	0.240	0.280	0.340	0.530
Immediate Post-prandial	0.190	0.260	0.300	0.340	0.380	0.400	0.290	0.350	0.410	$0.005^*$
60–120 min Post-prandial	0.230	0.260	0.360	0.300	0.320	0.360	0.230	0.260	0.360	0.270
a b c represent the median $b$ ,	and the l	ower and	upper liı	nits of ra	nge <i>a</i> and	$1_c$				

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\* *p*-value <0.05

Change in A-rSO2 Compared to Change in SMA Doppler Velocity

Change during Feeding	P value
A-rSO2 compared to Systolic Velocity	
Change from 3 to 2	$0.009^{*}$
Change from 3 to 1	0.016*
Change from 2 to 1	0.984
A-rSO2 compared to Diastolic Velocity	
Change from 3 to 2	0.035*
Change from 3 to 1	0.021*
Change from 2 to 1	0.985
A-rSO2 compared to Mean Velocity	
Change from 3 to 2	0.032*
Change from 3 to 1	$0.010^{*}$
Change from 2 to 1	0.850

\* Statistically significant

KEY: 1 - Preprandial, 2 - 10 min post-prandial, 3 - 60-120 min post-prandial