Cerebral and splanchnic oxygenation and necrotizing enterocolitis in preterm infants

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ABDOMINAL NEAR-INFRARED SPECTROSCOPY IN PRETERM INFANTS: A COMPARISON OF SPLANCHNIC OXYGEN SATURATION MEASUREMENTS AT TWO ABDOMINAL LOCATIONS

Trijntje E. Schat, Michelle E. van der Laan, Maarten Schurink, Jan B.F. Hulscher, Christian V. Hulzebos, Arend F. Bos, Elisabeth M.W. Kooi
ABSTRACT

**Background**: Splanchnic tissue oxygenation monitoring has been performed at both the liver and the infraumbilical regions. It is unknown whether these measurements could be substituted one for the other when interpreting splanchnic oxygenation since they have not been measured simultaneously before.

**Aims**: To evaluate the feasibility and safety of liver and infraumbilical near-infrared spectroscopy (NIRS) monitoring in preterm infants with suspected necrotizing enterocolitis (NEC) and to assess the correlation and agreement between NIRS measurements performed simultaneously at the two abdominal locations.

**Study design and subjects**: This study was part of a prospective observational cohort study. Preterm infants who were suspected of NEC or who had been diagnosed with NEC were included.

**Outcome measures**: Liver oxygen saturation and infraumbilical oxygen saturation were monitored simultaneously and continuously for 48 hours by NIRS.

**Results**: NIRS monitoring was performed in 20 out of 24 infants for the entire 48-hour study period. No adverse effects were observed. Values of liver and infraumbilical oxygen saturation correlated weakly (Spearman's rho = 0.244, \( P < .001 \)). On the Bland-Altman plot liver oxygen saturation was higher than infraumbilical oxygen saturation (mean difference 6.6%, SD 22.5%).

**Conclusions**: Using NIRS as method for monitoring oxygen saturation simultaneously in both the liver and infraumbilical regions is safe and feasible. Additionally, we demonstrated that values of liver and infraumbilical oxygen saturation cannot be randomly substituted one for the other for the purpose of assessing splanchnic oxygenation.
INTRODUCTION

Near-infrared spectroscopy (NIRS) is a non-invasive tool that can be used to continuously measure the oxygen saturation of underlying tissue.\(^1\) It is being used increasingly to investigate splanchnic oxygen saturation. Various locations, including the liver and infraumbilical regions, have been selected for placing the NIRS sensors for this purpose.\(^2\)\(^-\)\(^10\)

Although this new technique seems promising for assessing splanchnic oxygen saturation, location-specific characteristics have been identified that may interfere with the reliability of the measurements. The infraumbilical region covers non-solid and moving tissue. Movements of the intestines within the abdominal cavity as well as peristaltic movements may alter the reflected signal despite static sensor placement.\(^11\) The liver, a solid and non-moving organ, relies on the portal vein for approximately 75% of its blood supply and on the hepatic artery for the remaining 25%. Due to the hepatic arterial buffer response, no direct linear relationship exists between the contributions of the two vessels to the hepatic blood supply, thus limiting the potential use of NIRS to monitor splanchnic oxygenation.\(^12\) To date, it remains unclear whether liver and infraumbilical oxygen saturation measurements obtained by NIRS can be substituted one for the other for interpreting splanchnic oxygenation, since splanchnic oxygen saturation in the liver and infraumbilical regions have not been monitored simultaneously before. Additionally, it is difficult to compare the liver and infraumbilical oxygen saturation values reported in the literature due to discrepancies between study groups and study methods.

The primary aim of this study was to evaluate the feasibility and safety of monitoring splanchnic oxygen saturation in the liver and infraumbilical regions simultaneously by NIRS in preterm infants with suspected necrotizing enterocolitis (NEC). Our secondary aim was to compare the liver measurements with the infraumbilical measurements and to assess the correlation and agreement between the oxygen saturation values obtained at the two abdominal locations.

METHODS

Ethical statement

This study was part of a prospective observational cohort study registered with the Dutch Trial Registry under number NTR3239. The study was approved by the ethical review board of University Medical Center Groningen. Written informed parental consent was obtained in all cases.

Patients and procedures

We included preterm infants admitted to the neonatal intensive care unit of University Medical Center Groningen between October 2010 and March 2012, who were suspected of NEC or who had been diagnosed with NEC. Suspected NEC is defined as Bell’s stage 1, in which case only non-specific symptoms of abdominal disease, such as gastric retention,
abdominal distension, and mild ileus, are present.\textsuperscript{13,14} Infants with abdominal wall defects were excluded. Monitoring splanchnic oxygen saturation by NIRS commenced as soon as possible after suspected or diagnosed NEC and was continued for 48 hours.

\textit{Near-infrared spectroscopy}

We used the INVOS 5100C near-infrared spectrometer (Covidien, Mansfield, MA, USA) in combination with the neonatal SomaSensors (Covidien) to measure splanchnic oxygen saturation continuously and simultaneously in both the liver and infraumbilical regions. Near-infrared light is emitted using two wavelengths (730 and 810 nm). By measuring the quantity of reflected light as a function of wavelength, the spectral absorbance of the underlying tissue can be calculated. Since oxygenated and deoxygenated hemoglobin have different absorption spectra, NIRS can differentiate between the two. The ratio of oxygenated hemoglobin to total hemoglobin reflects the regional tissue oxygen saturation ($rSO_2$). The SomaSensor has a shallow and deep detector; on 3 and 4 cm distance from the near-infrared optode respectively. By subtracting the measurement of the shallow detector from the deep detector, oxygenation values of the deep detector, which reflect the tissue beneath the skin, are calculated. The depth of the signal is estimated to be around 15 to 20 mm.\textsuperscript{15}

For this study, we placed the neonatal SomaSensors just below the right costal arch to measure liver oxygen saturation ($r_{\text{lv}}SO_2$) and just below the umbilicus on the central abdomen to measure intestinal oxygen saturation ($r_{\text{int}}SO_2$). The SomaSensors were held in place by elastic bandaging and were removed only during moments of routine nursing care, clinical assessment, and radiographic examination; afterwards they were replaced onto the same location. There was no overlap between the sensors at any time. $r_{\text{lv}}SO_2$ and $r_{\text{int}}SO_2$ were measured every 6 seconds for 48 hours. The measurements were saved on the INVOS 5100C near-infrared spectrometer and were downloaded at the end of the study and stored off-line for future analysis. Afterward we only removed data obtained during documented incorrect sensor placement.

\textit{Clinical variables}

We prospectively collected neonatal characteristics including gestational age, postnatal age at first NIRS measurement, birth weight, and gender. We documented the following characteristics as well: respiratory support at the time of NEC suspicion/diagnosis, mean systemic blood pressure in the first hour after start of NIRS monitoring, patency of the ductus arteriosus (PDA) from 48 hours before NEC suspicion/diagnosis until the first 48 hours after NEC suspicion/diagnosis or until surgery took place, whichever came first, whether or not the PDA was hemodynamically significant, the first lactate value, and need for fluid resuscitation and inotropes for circulatory support from 1 hour before NEC suspicion/diagnosis until 48 hours after NEC suspicion/diagnosis, or until surgery took place, whichever came first.
Hemodynamically significant PDA was defined as a diastolic forward flow in the branches of the pulmonary artery, a diastolic backflow in the descending aorta, and a left ventricular end diastolic diameter $> p 95$.

**Statistical analysis**

We used medians (range) to describe sample characteristics. To determine and compare the courses of $r_{lvSO_2}$ and $r_{intSO_2}$, we calculated mean 1-hour and mean 12-hour values of 5-minute measurements of $r_{lvSO_2}$ and $r_{intSO_2}$ during the 48-hour study period. The 5-minute measurement is based on one oxygen saturation value obtained during these 5 minutes. The differences between the simultaneously obtained 12-hour mean values of $r_{lvSO_2}$ and $r_{intSO_2}$ were analyzed using the Wilcoxon signed rank test.

To determine the variability of the measurements, we calculated each infant’s daily intraindividual variability, defined as the daily percentage of time that 1-hour mean $r_{lvSO_2}$ or $r_{intSO_2}$ values were 15% or more below or above the infant’s daily mean.\textsuperscript{16}

To compare the two abdominal locations at which we monitored splanchnic oxygen saturation, we determined the correlation coefficient of the mean 1-hour period values of $r_{lvSO_2}$ and $r_{intSO_2}$, using the Spearman rank test. Furthermore, to determine if the direction of change in oxygen saturation was comparable between $r_{lvSO_2}$ and $r_{intSO_2}$ values, we calculated the differences between consecutive 1-hour measurements for $r_{lvSO_2}$ and $r_{intSO_2}$ values independently, leading to 47 delta values per child. We analyzed the correlation between these delta $r_{lvSO_2}$ and $r_{intSO_2}$ values using the Spearman rank test. Finally, we constructed a Bland-Altman plot to assess the agreement between the measurements of the two locations.

Since our primary aim was to assess the feasibility and safety of monitoring in both the liver and infraumbilical regions and to assess the correlation and agreement between oxygen saturation values measured at the two abdominal locations, we did not analyze the correlation between NIRS measurements and type of treatment and/or patient outcome.

We used the Statistical Package for the Social Sciences (IBM SPSS Statistics 22, IBM Corp., Armonk, New York, USA) for all statistical analyses. Statistical significance was defined as $P < .05$.

**RESULTS**

**Patient characteristics**

We included 24 infants with a median gestational age of 28.4 weeks (range, 25.0-35.9), a median birth weight of 1279 grams (range, 570-2400), and a median postnatal age at the first measurement of 9 days (range, 3-41). The patient characteristics are presented in Table 1.
Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>28.4 (25.0-35.9)</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>1279 (570-2400)</td>
</tr>
<tr>
<td>Male</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Postnatal age at first $r_{l\text{iv}}\text{SO}<em>2$ and $r</em>{i\text{nt}}\text{SO}_2$ measurement (days)</td>
<td>9 (3-41)</td>
</tr>
<tr>
<td>Respiratory support</td>
<td></td>
</tr>
<tr>
<td>None/lowflow</td>
<td>9 (38)</td>
</tr>
<tr>
<td>CPAP</td>
<td>4 (17)</td>
</tr>
<tr>
<td>SiPAP/NIMV</td>
<td>3 (12)</td>
</tr>
<tr>
<td>SIMV/SIPPV</td>
<td>7 (29)</td>
</tr>
<tr>
<td>HFOV</td>
<td>1 (4)</td>
</tr>
<tr>
<td>PDA</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Hemodynamically significant</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Mean systemic blood pressure in the first hour after NEC onset (mmHg) (n = 11)</td>
<td>35 (19-66)</td>
</tr>
<tr>
<td>Lactate (mmol/L) (n = 14)</td>
<td>2.1 (1.0-5.5)</td>
</tr>
<tr>
<td>Circulatory support</td>
<td></td>
</tr>
<tr>
<td>Fluid resuscitation</td>
<td>13 (54)</td>
</tr>
<tr>
<td>Inotropes</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

Data are shown as either median (range) or as n (percentage). CPAP - continuous positive airway pressure; HFOV - high-frequency oscillatory ventilation; NIMV - nasal intermittent mandatory ventilation; PDA - patent ductus arteriosus; $r_{l\text{iv}}\text{SO}_2$ - liver tissue oxygen saturation; $r_{i\text{nt}}\text{SO}_2$ - infraumbilical tissue oxygen saturation; SIMV - synchronized intermittent mandatory ventilation; SiPAP - synchronised intermittent positive airway pressure; SIPPV - synchronous positive pressure ventilation.

NIRS monitoring

NIRS monitoring was started within 48 hours after suspected or diagnosed NEC and was continued for 48 hours in twenty infants. In one infant, data were partially lost due to technical problems. In three other infants, NIRS monitoring was stopped after a median of 4 hours (range, 3-11) due to progressive circulatory failure leading to the death of one infant an hour later and due to abdominal surgery for NEC in the other two infants. Three infants were not monitored in the liver region due to shortage of equipment. Two infants were not monitored in the infraumbilical region. In one infant this was because of the inability to place the SomaSensor due to the presence of an umbilical venous catheter, and because of shortage of equipment in the other. In none of the infants did we observe adverse skin effects due to sensor placement during the 48-hour study period. Routine care was not hindered by the sensors either.

We were able to calculate mean $r_{l\text{iv}}\text{SO}_2$ values for 817 (71%) and mean $r_{i\text{nt}}\text{SO}_2$ values for 773 (67%) 1-hour periods out of a possible 1152 (48 hours × 24 infants). After excluding the data of the infants who had been monitored at only one location due to shortage of equipment...
(n = 4), simultaneously acquired measurements were available for 647 (67%) 1-hour periods out of the possible 960 (48 hours × 20 infants).

**Course of \(r_{\text{lv}} \text{SO}_2\) and \(r_{\text{int}} \text{SO}_2\)**

Figure 1 illustrates the 48-hour course of \(r_{\text{lv}} \text{SO}_2\) and \(r_{\text{int}} \text{SO}_2\) measurements. Oxygen saturation values measured by NIRS in the region of the liver were not significantly different from oxygen saturation values obtained in the infraumbilical region. There was a tendency, however, for higher \(r_{\text{lv}} \text{SO}_2\) values between 12 and 36 hours compared to \(r_{\text{int}} \text{SO}_2\) values (Table 2). The percentage of intraindividual variability of both \(r_{\text{lv}} \text{SO}_2\) and \(r_{\text{int}} \text{SO}_2\) values for each day is presented in Table 3.

**Table 2.** Comparison of median liver and infraumbilical oxygen saturation values during the 48-hour study period.

<table>
<thead>
<tr>
<th>Hours</th>
<th>(r_{\text{lv}} \text{SO}_2) Median</th>
<th>(r_{\text{lv}} \text{SO}_2) Range</th>
<th>(r_{\text{int}} \text{SO}_2) Median</th>
<th>(r_{\text{int}} \text{SO}_2) Range</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 12</td>
<td>62%</td>
<td>22% - 90%</td>
<td>51%</td>
<td>15% - 83%</td>
<td>.212</td>
</tr>
<tr>
<td>12 - 24</td>
<td>62%</td>
<td>15% - 86%</td>
<td>56%</td>
<td>22% - 72%</td>
<td>.070</td>
</tr>
<tr>
<td>24 - 36</td>
<td>60%</td>
<td>16% - 92%</td>
<td>49%</td>
<td>18% - 86%</td>
<td>.068</td>
</tr>
<tr>
<td>36 - 48</td>
<td>51%</td>
<td>25% - 86%</td>
<td>49%</td>
<td>25% - 76%</td>
<td>.408</td>
</tr>
</tbody>
</table>

\(r_{\text{lv}} \text{SO}_2\) - liver oxygen saturation; \(r_{\text{int}} \text{SO}_2\) - infraumbilical oxygen saturation.

**Table 3.** Median percentage of time 1-hour mean \(r_{\text{lv}} \text{SO}_2\) and \(r_{\text{int}} \text{SO}_2\) measured 15% below or above the daily mean.

<table>
<thead>
<tr>
<th>Hours</th>
<th>Variability (r_{\text{lv}} \text{SO}_2) (%)</th>
<th>Variability (r_{\text{int}} \text{SO}_2) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 24</td>
<td>13 (0-33)</td>
<td>13 (0-50)</td>
</tr>
<tr>
<td>24 - 48</td>
<td>14 (0-78)</td>
<td>13.5 (0-50)</td>
</tr>
</tbody>
</table>

Data are shown as median (range).

\(r_{\text{lv}} \text{SO}_2\) - liver oxygen saturation; \(r_{\text{int}} \text{SO}_2\) - infraumbilical tissue oxygen saturation.

**Correlation and agreement between \(r_{\text{lv}} \text{SO}_2\) and \(r_{\text{int}} \text{SO}_2\)**

We determined the correlation between the \(r_{\text{lv}} \text{SO}_2\) and \(r_{\text{int}} \text{SO}_2\) values obtained simultaneously during the entire 48-hour study period and found a Spearman’s rho of 0.244, \(P < .001\). The values representing the change in hourly means of \(r_{\text{lv}} \text{SO}_2\) and \(r_{\text{int}} \text{SO}_2\) were not significantly correlated with each other, Spearman’s rho 0.062, \(P = .131\). The Bland-Altman plot revealed a mean difference in oxygen saturation between \(r_{\text{int}} \text{SO}_2\) and \(r_{\text{lv}} \text{SO}_2\) of 6.6% (SD 22.5%), with \(r_{\text{lv}} \text{SO}_2\) being the highest (Figure 2).
Abdominal near-infrared spectroscopy in preterm infants: A comparison of splanchnic oxygen saturation measurements at two abdominal locations

**DISCUSSION**

With this study we demonstrated that it is safe and feasible most of the time to use NIRS as method for monitoring tissue oxygen saturation simultaneously at the liver and infraumbilical region. Furthermore we demonstrated that $r_{\text{lv}}\text{SO}_2$ and $r_{\text{int}}\text{SO}_2$ values cannot be randomly substituted one for the other for the purpose of assessing splanchnic oxygenation in this population.

**Figure 1.** The course of mean liver and infraumbilical oxygen saturation measurements in preterm infants during the first 48 hours after diagnosis of suspected NEC. Error bars represent ± 1 SD.
Abdominal near-infrared spectroscopy in preterm infants: A comparison of splanchnic oxygen saturation measurements at two abdominal locations

NIRS is a non-invasive bedside tool that can be used to monitor tissue oxygenation continuously and as such it seems to be a promising technique, particularly in vulnerable preterm infants. We demonstrated that in preterm infants with suspected NEC it is feasible, for most infants and most of the time, to measure tissue oxygen saturation simultaneously at two abdominal locations. We did not observe any adverse skin effects nor was routine care hampered. Other studies did report adverse skin effects in a few cases.\textsuperscript{7,16} A possible explanation for this difference may be the considerably longer monitoring times in these studies of 14 up to 21 days after birth, compared to the 48-hour period in our study.

We were unable to monitor $r_{\text{int}}SO_2$ and $r_{\text{liv}}SO_2$ simultaneously in five infants. In four infants this was due to shortage of equipment. In one infant, $r_{\text{liv}}SO_2$ monitoring was not performed due to the lack of space for the sensor because of an umbilical venous catheter taped to the infraumbilical skin, in accordance with local protocol. Theoretically, this situation could be easily overcome. Most preterm infants, however, need intensive, routine care during which clinical procedures and devices might inhibit adequate sensor placement. Nevertheless, our data showed that rarely adequate sensor placement was not possible at all. We were able to monitor liver and infraumbilical oxygen saturation simultaneously 67\% of the time.

Because we measured tissue oxygen saturation simultaneously in the liver and infraumbilical regions, we were able to compare the courses of $r_{\text{liv}}SO_2$ and $r_{\text{int}}SO_2$ values during the study period. The $r_{\text{liv}}SO_2$ values (median, 51-62\%) were not significantly different from the $r_{\text{int}}SO_2$ values (median, 49-56\%). There was, however, a tendency for higher oxygen saturation values in the region of the liver compared to the saturation values obtained in the infraumbilical region. There may be several explanations for this finding. Firstly, this tendency could

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Bland-Altman plot: $r_{\text{int}}SO_2$ versus $r_{\text{liv}}SO_2$.}
\end{figure}
be attributable to lower oxygen consumption by the liver compared to the intestine in conjunction with the unique portal and arterial hepatic blood supply. A second explanation might be the presence of air, meconium, and/or bilirubin in the preterm intestinal tract. Finally, the underlying intestinal pathophysiological condition might also have played a role. Further studies are needed to delineate the differences in baseline values between \( r_{\text{liv}}\text{SO}_2 \) and \( r_{\text{int}}\text{SO}_2 \) values and the role of NEC in influencing these oxygen saturation values.

We observed a high variability in the \( r_{\text{liv}}\text{SO}_2 \) (13-14%) and \( r_{\text{int}}\text{SO}_2 \) values (13-13.5%). Our variability measurements were consistent with those previously reported for the infraumbilical region.\(^{16}\) McNeill \textit{et al.} speculated that these fluctuations might result from saturation differences between enteral mucosa, smooth muscle, and/or enteric contents in a hollow, moving organ\(^{16}\) whereas the liver is a solid, non-moving organ comparable to renal tissue. Since renal oxygen saturation values showed less variability,\(^{16}\) one would also expect \( r_{\text{liv}}\text{SO}_2 \) values to be less variable. However, we also found a high variability in the \( r_{\text{liv}}\text{SO}_2 \) values. A possible explanation could be that the liver oxygen saturation values reflected the highly variable infraumbilical oxygenation values, for the blood supply to the liver consist for a large part of this splanchnic perfusion. It is also possible that besides the liver, intestinal tissue was measured at the right costal margin. We placed the SomaSensor where we anatomically would expect the liver to be located in these infants, which we did not confirm by ultrasonography. Therefore, we do not know for sure whether we solely measured liver tissue. This is, however, generally the case in a clinical setting.

We found a weak correlation between liver and infraumbilical oxygen saturation values, a lack of correlation between values representing the change in hourly means of both measurements, and the Bland-Altman plot revealed relatively large discrepancies between the \( r_{\text{liv}}\text{SO}_2 \) and \( r_{\text{int}}\text{SO}_2 \) values. These findings suggest that absolute values as well as trends in tissue oxygen saturation values measured at the right lower costal region and infraumbilical region differ, which could be explained in several ways. First, both sites have different origins of perfusion as stated before. Second, intestinal movements and passage of air and stools, influence mainly the infraumbilical measurements. Third, the inaccuracy of the NIRS technique and SomaSensors itself could have played a role. Fluctuations in oxygen saturation values have been reported, measured in the same infant and at the same location.\(^{17}\)

Because of the large discrepancies between liver and infraumbilical oxygen saturation measurements, it seems erratic to interchange \( r_{\text{liv}}\text{SO}_2 \) and \( r_{\text{int}}\text{SO}_2 \) values at a specific time point, thus limiting or even abolishing their potential for comparison and substitution in research or clinical practice. In the absence of a gold-standard for measuring splanchnic blood flow for a prolonged period of time, we were unable to assess the validity of the two NIRS measurements. We realize that this was a limitation of our study.

In conclusion, this study showed that the NIRS technique was feasible and safe for measuring tissue oxygen saturation in the liver and infraumbilical regions simultaneously in preterm infants with suspected NEC. Additionally, we demonstrated that the \( r_{\text{liv}}\text{SO}_2 \) and \( r_{\text{int}}\text{SO}_2 \) values were highly variable in time and that correlation and agreement between the
values is poor, which limits the potential for comparison and substitution. Further studies are needed to investigate the tissue or substance that is being measured by NIRS in the liver and infraumbilical regions and to explore the baseline values and trends of both liver and infraumbilical NIRS monitoring in preterm infants with abdominal symptoms and diseases. Furthermore, since the aim of this study was to investigate the feasibility of NIRS for monitoring in both the liver and infraumbilical regions simultaneously, and to compare the values obtained at the two locations, we did not assess the value of these measurements for predicting the onset of NEC. Larger groups of patients are required to determine the potential value of liver and/or infraumbilical NIRS monitoring in order to predict the onset and course of NEC in preterm infants.

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