Cerebral and splanchnic oxygenation and necrotizing enterocolitis in preterm infants
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CHAPTER 6

USING NEAR-INFRARED SPECTROSCOPY TO PREDICT THE DEVELOPMENT OF NECROTIZING ENTEROCOLITIS

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Submitted
ABSTRACT

Objectives: To investigate whether cerebral, liver, and infraumbilical regional tissue oxygen saturation ($rSO_2$) and fractional tissue oxygen extraction (FTOE) could be used to diagnose necrotizing enterocolitis (NEC) and complicated NEC (Bell’s stage 3B or death) during its early stages.

Methods: A prospective observational cohort study of preterm infants with suspected or diagnosed NEC. We compared mean 8-hour cerebral, liver, and infraumbilical $rSO_2$ and FTOE values of infants with suspected and definite NEC and of infants with uncomplicated and complicated NEC in the first 48 hours after onset of NEC symptoms. Furthermore, we determined cut-off values by generating receiver operating characteristics curves in case of significant differences in the first 8-hour mean values of $rSO_2$ between infants with suspected and definite NEC and between infants with uncomplicated and complicated NEC.

Results: We included 33 patients: 13 without NEC, 10 with uncomplicated NEC, and 10 with complicated NEC. We found no significant differences in the first 24 hours after onset of NEC symptoms in $rSO_2$ and FTOE values between infants with suspected and definite NEC. In preterm infants with complicated NEC, we observed significantly lower cerebral, liver, and infraumbilical $rSO_2$ values and higher FTOE values within 24 hours after onset of NEC symptoms in comparison to infants with uncomplicated NEC. A continuous cerebral $rSO_2 \leq 71\%$ and liver $rSO_2 \leq 59\%$ in the first 8 hours after onset of NEC symptoms predicted the onset of complicated NEC with a sensitivity of 1.00 and specificity of 0.80, and a sensitivity of 1.00 and specificity of 1.00, respectively.

Conclusions: By measuring cerebral and splanchnic oxygenation it may be possible to differentiate complicated NEC in preterm infants from uncomplicated NEC. NIRS monitoring did not prove useful for distinguishing between suspected and definite NEC.
INTRODUCTION

Necrotizing enterocolitis (NEC) is the most devastating gastrointestinal disease in the neonatal intensive care unit. It is associated with detrimental short-term and long-term outcomes, including high mortality rates and impaired neurodevelopmental outcome.\textsuperscript{1,2} Currently, we lack the tools and tests to reliably diagnose NEC in its early stage and to predict its progression to becoming a complicated disease (i.e. perforated bowel corresponding to Bell’s stage 3B, or death).

Near-infrared spectroscopy (NIRS) might be a useful bedside tool to diagnose the earliest stages of NEC. In previous studies it was found that NIRS measurements differed between preterm infants with and without bowel ischemia.\textsuperscript{3-5} NIRS measures regional tissue oxygen saturation (rSO\textsubscript{2}) non-invasively. Using simultaneous measurements of transcutaneous arterial oxygen saturation (SpO\textsubscript{2}), fractional tissue oxygen extraction (FTOE) can be calculated.\textsuperscript{6} It reflects the balance between oxygen supply and consumption in tissue and can, therefore, be used as an indicator of inadequate tissue perfusion and oxygenation.\textsuperscript{6} Since bowel ischemia seems to be strongly associated with the development of NEC, complicated NEC in particular,\textsuperscript{7} measuring splanchnic tissue oxygen saturation and extraction might help the clinician to diagnose NEC from its earliest stage onward.

Our first aim was to investigate the diagnostic value of splanchnic NIRS monitoring to discriminate between definite NEC (Bell’s stages 2 & 3) and suspected NEC (Bell’s stage 1) at the onset of the disease. Our second aim was to determine whether splanchnic NIRS monitoring could be used to discriminate between infants with NEC that would develop without complications (uncomplicated NEC) and infants with NEC that would develop with complications (complicated NEC). The latter was defined as the infant developing a bowel perforation requiring surgery (Bell’s stage 3B), or death. We hypothesized that as a result of hypoxic and/or necrotic intestinal tissue splanchnic rSO\textsubscript{2} values would be lower and splanchnic FTOE values would be higher in preterm infants who developed (complicated) NEC.
METHODS

Patient population

Between October 2010 and October 2012 we conducted a prospective observational cohort study in the neonatal intensive care unit of University Medical Center Groningen, a tertiary referral center. The study was registered in the Dutch Trial Registry under number NTR3239. We included preterm infants without abdominal wall defects who were suspected of having NEC or who had already been diagnosed with NEC. Abdominal radiographs were made as soon as possible after suspicion of NEC; the diagnosis was confirmed if pneumatosis intestinalis was present. The modified Bell’s staging criteria were used for diagnosis. In case of definite NEC (minimal Bell’s stage 2), our protocol indicates that sequential abdominal radiographs be taken every 8 to 12 hours until it is evident that radiographic signs of NEC have resolved and clinical signs have stabilized.

Written informed parental consent was obtained in all cases. The study was approved by the institutional ethics review board of University Medical Center Groningen.

Near-infrared spectroscopy

We used the INVOS 5100C near-infrared spectrometer (Covidien, Mansfield, MA, USA) in combination with the neonatal SomaSensors (Covidien) to measure oxygen saturation values of cerebral tissue and in the splanchnic region. We placed the SomaSensors to the left or right frontoparietal side of the infant’s head to measure cerebral tissue oxygen saturation ($r_{cSO_2}$). The oxygen saturation of the splanchnic region was measured at two abdominal locations: below the right costal arch to measure liver tissue oxygen saturation ($r_{livSO_2}$), and infraumbilically on the central abdominal wall to measure intestinal tissue oxygen saturation ($r_{inSO_2}$). The sensors were held in place by elastic bandaging or Mepitel (Mölnlycke, Sweden) and were only removed temporarily during routine nursing care, clinical assessments, and radiographic examinations. Afterwards, they were replaced onto the same location. NIRS monitoring started as soon as possible after NEC was suspected or diagnosed and was continued for 48 hours. Simultaneously, we measured $SpO_2$ and calculated FTOE with the equation: $FTOE = (SpO_2 - rSO_2) / SpO_2$. We previously reported on the feasibility and safety of monitoring oxygenation in both the liver and infraumbilical region and the correlation and agreement between these measurements. The infants reported in that article are also part of the study group described in this manuscript. However, we did not report any findings concerning the course of $rSO_2$ and FTOE values in relation to the development of definite NEC and complicated NEC.

Clinical variables

Prospectively, we collected neonatal characteristics including gestational age, postnatal age at first NIRS measurement, birth weight, and gender. Furthermore, we documented the presence or absence of anemia (defined as a hemoglobin level < 8.0 mmol/L),
thrombocytopenia (defined as a platelet count < 150 x 10^9/L), and metabolic acidosis (defined as pH < 7.30 and HCO₃⁻ < 22 mmol/L) within 24 hours before and 24 hours after onset of NEC symptoms. Furthermore, we registered signs of circulatory failure and patency of the ductus arteriosus (determined by echocardiography) during the first 48 hours after onset of NEC symptoms, and treatment for a patent ductus arteriosus before the onset of NEC symptoms. Circulatory failure was defined as hemodynamic instability and scored by the need for volume expansion or the use of inotropes or both, from one hour before onset of NEC symptoms until the first 48 hours after onset, or until surgery, whichever came first. Onset of NEC symptoms was defined as the time of the first abdominal radiographic examination after clinical suspicion of NEC, including the radiographs done in the referring hospitals. After completion of the study a panel of four experts (MS, JBFH, AFB, EMWK), blinded for the NIRS measurements, initially classified the infants independently of one another into onset and end-stage modified Bell’s stages using clinical and radiological parameters. For those infants who had been classified differently by the individual panel members the final Bell’s stage was determined by consensus.

To address our first aim, we classified the infants into two groups: infants with suspected NEC (Bell’s stage 1) and infants with definite NEC (Bell’s stages 2 & 3). For our second aim, we analyzed the differences between infants with uncomplicated NEC and infants with complicated NEC (Bell’s stage 3B, or death as a consequence of NEC).

**Statistical analysis**

We used SPSS 22.0 software for Windows (IBM SPSS Statistics 22, IBM Corp., Armonk, New York, USA) for the statistical analyses.

RcSO₂, rlivSO₂, and rinSO₂ values were recorded by the INVOS 5100C every 6 seconds. SpO₂ was registered every 5 minutes. We then matched one rSO₂ value that corresponded time wise to every SpO₂ value, leaving one measurement per 5 minutes for rSO₂ and SpO₂. Next, we constructed six 8-hour periods starting from onset of NEC symptoms (first abdominal radiographic examination) and calculated 8-hour means of rcSO₂, rlivSO₂, rinSO₂, cerebral FTOE (cFTOE), liver FTOE (livFTOE), and intestinal FTOE (intFTOE) values. Means of rSO₂ and FTOE values were only used for further analyses if they were based on at least 30 minutes of available values.

The Mann-Whitney test was used to compare the 8-hour mean values of rSO₂ and FTOE between infants with suspected NEC and definite NEC and between infants with uncomplicated NEC and complicated NEC. Next, a receiver operating characteristics (ROC) curve was constructed of the rSO₂ values that were statistically significantly different between groups in the first 8 hours after onset of NEC symptoms to assess sensitivity and specificity and to determine potential cut-off values to predict the development of definite and complicated NEC within 48 hours after onset of NEC symptoms.

Finally, we determined the variability of the rcSO₂, rlivSO₂, and rinSO₂ measurements separately during the first 48 hours after onset of NEC symptoms, by calculating each infant’s daily
intraindividual variability, defined as the daily percentage of time that one-hour mean rSO$_2$ values were 15% or more below or above the infant’s daily mean.$^{10}$

To test whether there were differences between groups we used the chi-square test or Fisher exact test for categorical data and the Mann-Whitney test for continuous data. A $P$ value of $< .05$ was considered statistically significant.

Since this study was of an exploratory nature, we refrained from performing extensive statistical analyses. Because clinical and radiographic symptoms and signs are evaluated every 8 to 12 hours in our neonatal intensive care unit, we decided to calculate 8-hour mean values of NIRS measurements in order to investigate the possibility of using rSO$_2$ and FTOE values in routine clinical care.

RESULTS

A total of 33 infants were included for final analysis (Figure 1). NIRS monitoring commenced after a median of 7 hours (range, 1-32) after onset of NEC symptoms. We were able to measure both r$_{liv}$SO$_2$ and r$_{int}$SO$_2$ in 24 infants. In seven infants we were unable to measure r$_{liv}$SO$_2$: in three infants due to shortage of equipment, and in four infants due to simultaneous inclusion in another multisite NIRS study in which renal rather than liver oxygen saturation was measured. In two infants we were unable to measure r$_{int}$SO$_2$: in one infant because we could not place the sensor due to the presence of an umbilical venous catheter taped to the infraumbilical skin, and in the other infant due to shortage of equipment.

We were able to calculate 8-hour mean r$_{c}$SO$_2$ values for 156, r$_{liv}$SO$_2$ for 115, and r$_{int}$SO$_2$ for 135 time periods out of the possible 198 (6 x 33 time periods). Median (range) time of available r$_{c}$SO$_2$, r$_{liv}$SO$_2$, and r$_{int}$SO$_2$ values every 8 hours was 450 (35-480), 370 (50-480), and 375 (30-480) minutes, respectively.

NIRS measurements in infants with suspected and definite NEC

Twenty infants developed Bell’s stages 2 or 3 and thirteen infants ultimately did not have NEC (Bell’s stage 1). Clinical diagnoses of the infants without NEC were sepsis (n=3), delayed passage of meconium (n=2), bloody stools of unknown cause (n=2), gastroenteritis (n=2), sigmoid volvulus (n=1), CPAP belly (n=1), and abdominal symptoms of unknown cause (n=2). Table 1 contains the patient characteristics of infants with suspected NEC and definite NEC. Infants with definite NEC underwent surgery significantly more often and had a higher mortality rate than infants with suspected NEC. Additionally, we found a trend towards a higher prevalence of anemia in preterm infants with suspected NEC than in infants with definite NEC.

In Table 2 we present the courses of rSO$_2$ and FTOE values. We found no significant differences between the two groups in the first 24 hours after onset of NEC symptoms. From 24 hours onwards, however, preterm infants with definite NEC had significantly higher median r$_{int}$SO$_2$ values in comparison to infants with suspected NEC. Furthermore, median
intFTOE was significantly lower between 32 and 48 hours after onset of NEC symptoms in preterm infants with definite NEC in comparison to infants with suspected NEC.

**NIRS measurements in infants with uncomplicated and complicated NEC**

Ten out of twenty infants with definite NEC developed complicated NEC and the other ten infants developed NEC without complications. Of the infants with complicated NEC two were diagnosed with Bell’s stage 3A. Both died as a consequence of NEC 5 and 35 days after onset of the symptoms. The other eight infants were found to have a perforation (Bell’s stage 3B). Seven infants were operated on with a median time of 33 hours (range, 9-165) between onset of NEC symptoms and surgery. The other infant was too unstable clinically for surgery. Five infants were taken for surgery during the study period. NIRS monitoring in these infants was stopped after a median of 10 hours (range, 5-33) after onset of NEC symptoms. Of the infants with a perforation, five died as a consequence of NEC. Ischemic necrosis was confirmed by our pathologist using tissue macroscopy and microscopy in all infants with Bell’s stage 3B.

In Table 3 we provide the patient characteristics of infants with an uncomplicated and a complicated course of NEC. Infants with complicated NEC were significantly younger, received inotropes more often, underwent surgery more often, and had a higher mortality rate than infants with uncomplicated NEC.

We present the courses of rSO₂ and FTOE values in Table 4. Preterm infants with complicated NEC had significantly lower median r_cSO₂ values throughout the entire study period and significantly higher cFTOE values from 8 hours onwards. Furthermore, we found lower
Table 1. Patient characteristics of infants with suspected and definite NEC.

<table>
<thead>
<tr>
<th></th>
<th>Suspected NEC (n = 13)</th>
<th>Definite NEC (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>28.3 (27.0-31.7)</td>
<td>28.2 (25.0-35.9)</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>1190 (570-1690)</td>
<td>1333 (740-2400)</td>
</tr>
<tr>
<td>Male:Female</td>
<td>5:8</td>
<td>14:6</td>
</tr>
<tr>
<td>PNA at first NIRS measurement (days)</td>
<td>13 (4-36)</td>
<td>10 (3-41)</td>
</tr>
<tr>
<td>Anemia (%)</td>
<td>8 (62)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Metabolic acidosis (%)</td>
<td>2 (17) (n = 12)</td>
<td>3 (16) (n = 19)</td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td>3 (23)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Treated PDA before onset study (%)</td>
<td>2 (15)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>PDA during study (%)</td>
<td>4 (31)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Hemodynamically significant</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>RBC transfusion (%)</td>
<td>4 (31)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Fluid resuscitation (%)</td>
<td>5 (38)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Inotropes (%)</td>
<td>0 (-)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>0 (-)</td>
<td>9 (45)*</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0 (-)</td>
<td>7 (35)*</td>
</tr>
</tbody>
</table>

Data are expressed as median (range) or as numbers unless specified otherwise.

Abbreviations: NEC - necrotizing enterocolitis; NIRS - near-infrared spectroscopy; PDA - patent ductus arteriosus; PNA - postnatal age; RBC - red blood cell.

Circulatory failure was defined as hemodynamic instability and scored by the need for volume expansion or the use of inotropes or both, from 1 hour before NEC onset until the first 48 hours after NEC onset, or until surgery, whichever came first.

Statistical differences between the two groups are marked by * (< .05) or † (< .10).

Higher \( r_{\text{ivSO}_2} \) and higher \( \text{livFTOE} \) values in preterm infants with complicated NEC than in infants with uncomplicated NEC in three time periods (0-8 hours, 24-32 hours, and 40-48 hours). Finally, \( r_{\text{intSO}_2} \) was significantly lower and \( \text{intFTOE} \) higher between 8 and 16 hours and \( r_{\text{intSO}_2} \) significantly higher and \( \text{intFTOE} \) lower between 24 and 32 hours after onset of NEC symptoms.

In Figure 2 we present the courses of the cerebral and splanchnic \( r\text{SO}_2 \) values in the first 48 hours after onset of NEC symptoms in infants with suspected NEC, uncomplicated NEC, and complicated NEC separately.

**ROC curves**

We generated ROC curves for \( r\text{SO}_2 \) and \( r_{\text{ivSO}_2} \) to differentiate between infants with uncomplicated and complicated NEC, since only these values showed significant differences between the groups in the first 8 hours after onset of NEC symptoms. The area under the \( r_{\text{ivSO}_2} \) ROC curve was 0.88 (95% confidence interval (CI) 0.64-1.00, \( P = .047 \)) and the area under the \( r_{\text{ivSO}_2} \) curve was 1.00 (CI 1.00-1.00, \( P = .014 \)). Taking a threshold value for \( r_{\text{ivSO}_2} \) of 71%, \( r_{\text{ivSO}_2} \) detected the presence of complications with a sensitivity of 1.00 (CI
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Taking a threshold value for $r_{\text{livSO}_2}$ of 59%, $r_{\text{livSO}_2}$ detected the presence of complications with a sensitivity of 1.00 (CI 0.40-1.00) and specificity of 1.00 (CI 0.46-1.00).

Variability

In Table 5 we present the intraindividual variability. Variability measurements were neither significantly different within 24 hours after onset of NEC symptoms between infants with suspected and definite NEC, nor between infants with uncomplicated and complicated NEC. Between 24 and 48 hours, however, infants with definite NEC had significantly lower variability of $r_{\text{intSO}_2}$ measurements in comparison to infants with suspected NEC. Moreover, infants with complicated NEC had a significantly higher variability of $r_{\text{SO}_2}$ and lower variability of $r_{\text{intSO}_2}$ measurements than infants with uncomplicated NEC.

DISCUSSION

Our study suggests that NIRS monitoring can be useful in preterm infants with definite NEC to differentiate in the first 8 hours after onset of symptoms between those infants who would develop complicated NEC and those who would not. The low oxygen saturation values and high oxygen extraction values of splanchnic and cerebral tissue are associated with the progression to a bowel perforation or death. Furthermore, we demonstrated that...
Using near-infrared spectroscopy to predict the development of necrotizing enterocolitis in the early stages of the disease with clinical signs pointing to NEC, NIRS monitoring did not help to differentiate between infants with definite NEC and infants who were diagnosed differently. Distinguishing between NEC and other intestinal diseases is often difficult as symptoms are not specific. It is important, however, to be able to distinguish NEC from other abdominal illnesses as different diseases require different treatments. Early recognition of patients in need for surgery could also benefit the patient. To our knowledge no studies to date have investigated the possibility of NIRS monitoring to differentiate between preterm infants with suspected and preterm infants with definite NEC. Because hypoxia and/or necrosis of the bowel wall is present in preterm infants with NEC, we hypothesized that the rSO\textsubscript{2} values obtained in the splanchnic region would be lower and FTOE values higher than those measured in preterm infants who did not have NEC. Interestingly, in contrast to our hypothesis, we did not find significant differences between these two groups during the first 24 hours after onset of NEC symptoms. Perhaps the underlying conditions which were finally diagnosed in preterm infants with suspected NEC, such as volvulus and sepsis, had similar effects on the splanchnic rSO\textsubscript{2} and FTOE values obtained with NIRS as those observed in the early stages of the disease with clinical signs pointing to NEC, NIRS monitoring did not help to differentiate between infants with definite NEC and infants who were diagnosed differently.

| Patient characteristics of infants with uncomplicated and complicated NEC. |
|---------------------------------|-----------------|-----------------|
| Uncomplicated NEC (n = 10)      | Complicated NEC (n = 10) |
| Gestational age (weeks)         | 30.9 (25.7-35.9)  | 27.2 (25.0-34.0)* |
| Birth weight (grams)            | 1518 (740-2400)  | 1035 (790-2280)* |
| Male:Female                     | 6:4              | 8:2              |
| PNA at first NIRS measurement (days) | 10 (3-41)  | 10 (7-22)  |
| Anemia (%)                      | 3 (30)           | 3 (30)           |
| Thrombocytopenia (%)            | 1 (10)           | 4 (40)           |
| Metabolic acidosis (%)          | 1 (11) (n = 9)   | 2 (20)           |
| Mechanical ventilation (%)      | 2 (20)           | 4 (40)           |
| Treated PDA before onset study (%) | 1 (10)  | 4 (40)  |
| PDA during study (%)            | 1 (10)           | 4 (40)           |
| Hemodynamically significant     | 0                | 2                |
| RBC transfusion (%)             | 3 (30)           | 4 (40)           |
| Fluid resuscitation (%)         | 4 (40)           | 8 (80)           |
| Inotropes (%)                   | 0 (-)            | 6 (60)*         |
| Surgery (%)                     | 1 (10)           | 8 (80)*         |
| Death (%)                       | 0 (-)            | 7 (70)*         |

Data are expressed as median (range) or as numbers unless otherwise specified.

Abbreviations: NEC - necrotizing enterocolitis; NIRS - near-infrared spectroscopy; PDA - patent ductus arteriosus; PNA - postnatal age; RBC - red blood cell.

Circulatory failure was defined as hemodynamic instability and scored by the need for volume expansion or the use of inotropes or both, from 1 hour before NEC onset until the first 48 hours after NEC onset or until surgery took place, whichever came first. Differences between the two groups are marked by * (< .05) or § (< .10).
### Table 4. RSO₂ and FTOE values in the first 48 hours after onset of NEC symptoms in preterm infants with uncomplicated and complicated NEC.

<table>
<thead>
<tr>
<th>Hours</th>
<th>$r_{SO_2}$ unNEC</th>
<th>$r_{SO_2}$ cNEC</th>
<th>$r_{IV,SO_2}$ unNEC</th>
<th>$r_{IV,SO_2}$ cNEC</th>
<th>$c_{FTOE}$ unNEC</th>
<th>$c_{FTOE}$ cNEC</th>
<th>$Liv_{FTOE}$ unNEC</th>
<th>$Liv_{FTOE}$ cNEC</th>
<th>$Int_{FTOE}$ unNEC</th>
<th>$Int_{FTOE}$ cNEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-8</td>
<td>83% (5)</td>
<td>65%* (5)</td>
<td>69% (5)</td>
<td>37%* (4)</td>
<td>77% (3)</td>
<td>43% (5)</td>
<td>0.13 (5)</td>
<td>0.42§ (3)</td>
<td>0.28</td>
<td>0.45* (3)</td>
</tr>
<tr>
<td>8-16</td>
<td>81% (7)</td>
<td>55%* (7)</td>
<td>76% (7)</td>
<td>44% (4)</td>
<td>70% (6)</td>
<td>32%* (7)</td>
<td>0.17 (7)</td>
<td>0.38* (7)</td>
<td>0.22</td>
<td>0.53 (4)</td>
</tr>
<tr>
<td>16-24</td>
<td>81% (8)</td>
<td>54%* (8)</td>
<td>67% (8)</td>
<td>42% (4)</td>
<td>61% (7)</td>
<td>51% (4)</td>
<td>0.17 (8)</td>
<td>0.37* (6)</td>
<td>0.31</td>
<td>0.59 (4)</td>
</tr>
<tr>
<td>24-32</td>
<td>78% (9)</td>
<td>58%* (9)</td>
<td>60% (8)</td>
<td>31%* (5)</td>
<td>54% (8)</td>
<td>66%* (2)</td>
<td>0.21 (9)</td>
<td>0.35* (7)</td>
<td>0.37</td>
<td>0.64* (5)</td>
</tr>
<tr>
<td>32-40</td>
<td>73% (10)</td>
<td>59%* (6)</td>
<td>59% (9)</td>
<td>53% (4)</td>
<td>48% (9)</td>
<td>59% (4)</td>
<td>0.22 (10)</td>
<td>0.35* (6)</td>
<td>0.39</td>
<td>0.44 (4)</td>
</tr>
<tr>
<td>40-48</td>
<td>75% (10)</td>
<td>55%* (5)</td>
<td>62% (9)</td>
<td>39%* (3)</td>
<td>47% (9)</td>
<td>55% (4)</td>
<td>0.24 (10)</td>
<td>0.38* (5)</td>
<td>0.37</td>
<td>0.59* (3)</td>
</tr>
</tbody>
</table>

Data are expressed as median values with the number of infants studied between brackets. Statistical differences between the two groups are marked by * ($<$ .05) or § ($<$ .10).
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in NEC. The higher prevalence of anemia in infants without NEC might also have contributed to the lower $rSO_2$ values in this group, since a low concentration of hemoglobin corresponds to lower oxygen saturation values.\textsuperscript{11}

Although our results need to be confirmed in a larger patient population, this study suggested that NIRS did not serve the additional purpose of being able to distinguish between NEC and other intestinal diseases during the early stages of the disease.

Our second aim was to determine the value of splanchnic NIRS monitoring to predict a complicated course in preterm infants with definite NEC. In the first 24 hours after NEC onset, we demonstrated that both splanchnic and cerebral oxygen saturations were lower and that splanchnic and cerebral oxygen extractions were higher in preterm infants who developed complicated NEC.

We offer several explanations for these findings. First, blood flow to the splanchnic bed may be reduced due to the presence of ischemic/necrotic bowel. A second explanation relates to illness severity. This might have been so severe in those infants who developed complicated NEC.

![Figure 2](image.png)

**Figure 2.** $R_cSO_2$, $r_{av}SO_2$, and $r_{iv}SO_2$ values in infants with suspected NEC, uncomplicated NEC, and complicated NEC. Data are shown in box and whisker plots. Dots and stars represent outliers.

- Suspected NEC
- Uncomplicated NEC
- Complicated NEC
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complicated NEC that circulatory insufficiency ensued in the early stage of NEC. Perfusion to less essential organs, such as the intestine, will be affected first. When insufficiency becomes more severe, however, the cerebral perfusion will also be compromised. Indeed, cerebral oxygen saturation was lower and extraction was higher in preterm infants with complicated NEC than in preterm infants with uncomplicated NEC.

A third explanation would be that preterm infants with uncomplicated NEC might have had higher splanchnic oxygen saturation and lower oxygen extraction values due to a relatively increased intestinal blood flow compared to preterm infants with complicated NEC, caused by the inflammatory response seen in NEC. Increased blood flow velocities in the superior mesenteric artery and the celiac axis, the major contributors of blood flow to the intestinal tissue, have been shown in preterm infants with NEC compared to preterm infants without abdominal disease. Moreover, McNeill et al. reported infraumbilical saturation values of 35% to 55% ten days after birth for relatively stable preterm infants between 29 to 33 weeks of gestation. We found a higher median saturation level of 77% in the first 8 hours after onset of NEC symptoms in preterm infants with uncomplicated NEC.

Finally, the younger gestational age of infants with complicated NEC in comparison to infants with uncomplicated NEC might have contributed to the differences we found for splanchnic rSO₂ and FTOE values between these two groups. This assumption, however, is based on a study performed in relatively healthy preterm infants who were fed normally. The effect of NEC and its treatment on splanchnic oxygen saturation values makes an interpretation of the effect of gestational age on these values difficult, if not impossible.

Regarding variability measurements, we did not find any significant differences between preterm infants with suspected and definite NEC, and between infants with complicated NEC in Table 5.

### Table 5

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Suspected NEC</th>
<th>Definite NEC</th>
<th>P Value</th>
<th>Uncomplicated NEC</th>
<th>Complicated NEC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24</td>
<td>rSO₂ (%)</td>
<td>0 (0-39)</td>
<td>0 (0-14)</td>
<td>.106</td>
<td>0 (0-6)</td>
<td>.433</td>
</tr>
<tr>
<td></td>
<td>rSO₂ (%)</td>
<td>21 (0-44)</td>
<td>6 (0-42)</td>
<td>.421</td>
<td>12 (0-42)</td>
<td>.302</td>
</tr>
<tr>
<td></td>
<td>rSO₂ (%)</td>
<td>16 (0-48)</td>
<td>15 (0-55)</td>
<td>.667</td>
<td>15 (0-55)</td>
<td>.999</td>
</tr>
<tr>
<td>24-48</td>
<td>rSO₂ (%)</td>
<td>0 (0-14)</td>
<td>0 (0-33)</td>
<td>.951</td>
<td>0 (0-0)</td>
<td>.017*</td>
</tr>
<tr>
<td></td>
<td>rSO₂ (%)</td>
<td>13 (4-67)</td>
<td>13 (0-86)</td>
<td>.421</td>
<td>13 (4-86)</td>
<td>.393</td>
</tr>
<tr>
<td></td>
<td>rSO₂ (%)</td>
<td>22 (0-78)</td>
<td>4 (0-25)</td>
<td>.022*</td>
<td>17 (0-25)</td>
<td>.022*</td>
</tr>
</tbody>
</table>

Data are expressed as median (range).

Abbreviations: NEC - necrotizing enterocolitis; rSO₂ - cerebral tissue oxygen saturation; rSO₂ - liver tissue oxygen saturation; rSO₂ - infraumbilical tissue oxygen saturation. Intraindividual variability is defined as the daily percentage of time that one-hour mean rSO₂ values were 15% or more below or above the infant’s daily mean.

* Indicates P < .05
and uncomplicated NEC in the first 24 hours after onset of NEC symptoms. Although Cortez et al. suggested that loss of variability might be helpful to predict the onset of NEC our study suggests that these measurements might not be useful once NEC is suspected or diagnosed. In this study we have shown that values of $r_c SO_2 \leq 71\%$ and $r_m SO_2 \leq 59\%$ predicted complicated NEC with a sensitivity of 1.00 and specificity of 0.80 and sensitivity of 1.00 and specificity of 1.00, respectively. These results suggest that monitoring cerebral and splanchnic $rSO_2$ might be helpful in clinical practice in predicting the course of NEC. However, we would like to stress the fact that these findings are based on measurements performed in a small sample size. Additionally, we did not control for potential confounders, such as gestational age and vasopressor medications. Our results, therefore, warrant further research in a larger patient population before we can be confident of its usefulness.

CONCLUSIONS

Our findings suggest that monitoring oxygen saturation and extraction at the cerebral and splanchnic region in preterm infants can help us to differentiate between complicated and uncomplicated NEC. However, we found no relevant added-value for NIRS in the diagnostic process of preterm infants with suspected NEC.

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