Cerebral and splanchnic oxygenation and necrotizing enterocolitis in preterm infants
Schat, Trijntje

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CHAPTER 5

CEREBRAL AND INTESTINAL OXYGENATION IN RELATION TO THE DEVELOPMENT OF NECROTIZING ENTEROCOLITIS


Submitted
ABSTRACT

Objectives: To investigate whether cerebral and intestinal regional tissue oxygen saturation (rSO$_2$) and fractional tissue oxygen extraction (FTOE) values predict the onset of necrotizing enterocolitis (NEC).

Methods: A prospective case-control study. Infants with gestational age (GA) < 32 weeks and birth weight (BW) < 1200 grams were included. For every NEC case we matched two controls based on GA, BW, and presence of a hemodynamically significant patent ductus arteriosus. Cerebral and intestinal oxygenation were monitored two hours daily during the first five days after birth and once a week thereafter until five weeks after birth or until NEC developed. Kaplan-Meier analyses were used to assess the ability of near-infrared spectroscopy (NIRS) measurements to predict the development of NEC.

Results: We included ten infants (median (range) GA 27.1 (24.6-29.4) weeks, BW 903 (560-1630) grams) who developed NEC at median postnatal day 13 (range, 4-43 days), and 20 matched controls. Infants with cerebral rSO$_2$ < 70% in the first 48 hours after birth developed NEC significantly more often than infants with cerebral rSO$_2$ ≥ 70% ($P = .005$). Intestinal FTOE was higher in infants who developed NEC compared with controls during the last NIRS measurement before NEC onset (median 0.65 vs. 0.44, $P = 0.04$), which was performed at a median of 2 (range, 1-7) days prior to NEC development.

Conclusions: Cerebral NIRS monitoring early after birth might be valuable to predict the onset of NEC. Additionally, our results suggest that intestinal perfusion is impaired before the onset of clinical NEC.
INTRODUCTION

Necrotizing enterocolitis (NEC) is the most severe gastrointestinal disease in preterm infants, with mortality rates up to 40%.\(^1\) Short- and long-term gastrointestinal and neurodevelopmental impairment occurs frequently.\(^2\) Preventing development of NEC is currently considered the best strategy to minimize these devastating short- and long-term consequences.\(^6\)

Near-infrared spectroscopy (NIRS) measures regional tissue oxygen saturation (\(r\text{SO}_2\)) non-invasively. When transcutaneous arterial oxygen saturation (\(\text{SpO}_2\)) is obtained simultaneously, fractional tissue oxygen extraction (FTOE) can be calculated.\(^7\) FTOE is thought to reflect the balance between oxygen delivery and oxygen consumption, and might therefore be used as an early indicator of inadequate tissue perfusion.\(^7\) As bowel ischemia is hypothesized to play a role in NEC development, NIRS could be a helpful tool for predicting the onset of NEC in preterm infants.\(^8,9\) Patel et al. found lower intestinal \(r\text{SO}_2\) (\(r\text{int}\text{SO}_2\)) values in the first week of life in preterm infants who later developed NEC compared to infants who did not develop NEC.\(^10\) Additionally, it was found that \(r\text{int}\text{SO}_2\) was lower and showed less variability just before NEC onset, when symptoms were not yet present.\(^11\)

Measurements of cerebral \(r\text{SO}_2\) (\(r\text{c}\text{SO}_2\)) might provide additional information concerning the underlying mechanism responsible for NEC development, since impaired intestinal perfusion might be the result of a compromised systemic circulation. Simultaneous measurements of cerebral and intestinal \(r\text{SO}_2\) values might help to determine whether this is indeed the case. We therefore investigated the possibility to use cerebral and intestinal NIRS measurements in the first days after birth to differentiate high-risk infants who went on to develop NEC from those who did not. Furthermore, we compared cerebral and intestinal \(r\text{SO}_2\) and FTOE values of the last measurement before the onset of NEC between infants who developed NEC and those who did not.

METHODS

Patient population

We performed a case-control study. Patients and controls were derived from a prospective observational cohort study performed at the neonatal intensive care unit (NICU) of University Medical Center Groningen between October 2012 and February 2014. The study was registered in the Dutch Trial Registry under number NTR4153. In the large cohort study we included 100 consecutive preterm infants at high risk for developing NEC. High risk was defined as being born at a gestational age (GA) of less than 30 weeks, with a birth weight (BW) below 1000 grams, at a GA of less than 32 weeks with a BW below 1200 grams, the presence of cardiac disease leading to impaired intestinal blood flow, or being born from a mother who received indomethacin for tocolysis. Infants with abdominal wall defects and infants who could not be measured with NIRS within 72 hours after birth were excluded.

We obtained written informed parental consent in all cases. The study was approved by the institutional ethics review board of University Medical Center Groningen.
For the present case-control study, we selected all NEC cases and matched two controls to each infant who developed NEC, using the following criteria, in descending order of importance: GA, BW, and the presence of a hemodynamically significant patent ductus arteriosus (PDA).

**NEC diagnosis**

NEC was diagnosed by the attending radiologist when pneumatosis intestinalis, portal venous gas, or both were present on abdominal radiographic examination.12 Afterwards, five consultants classified the infants according to modified Bell’s stages.12 Consensus was reached in all cases.

**Near-infrared spectroscopy**

We used the INVOS 5100C monitor (Covidien, Mansfield, MA, USA) with neonatal SomaSensors (Covidien) to measure $r_{cSO_2}$ and $r_{intSO_2}$. We placed the sensor on the left or right frontoparietal side of the head to measure $r_{cSO_2}$ and centrally just below the umbilicus to measure $r_{intSO_2}$. Sensors were kept in place using Mepitel (Mölndlycke, Sweden) or an elastic bandage.

We performed NIRS measurements two hours daily, from day one to five after birth, and weekly thereafter until the fifth week (day 36 after birth), until the infant was discharged from the NICU, or until NEC developed, whichever came first.

The first NIRS measurement was classified into either day one (< 24 hours after birth) or day two (> 24 hours < 48 hours after birth). Timing of sequential NIRS measurements was based on the date of the first NIRS measurement.

**Clinical variables**

We collected the following clinical data from patient reports: GA, BW, gender, postnatal age at time of NEC onset, multiple gestations, the administration of antenatal steroids, cause of prematurity, Apgar scores at one and five minutes, administration of antibiotics in the first 48 hours after birth, continuation of antibiotics more than 48 hours after birth, mortality, and length of NICU stay. Furthermore, we documented ventilator use, presence of a hemodynamically significant PDA, and use of medication (inotropes, red blood cell transfusions, volume expansion, ibuprofen).

**Data analysis and statistical analysis**

We collected cerebral and intestinal $rSO_2$ values once every 6 seconds and $SpO_2$ once every 5 seconds. We then matched $SpO_2$ values that corresponded temporally to the $rSO_2$ values. Next, FTOE values were calculated for the cerebral and intestinal region separately, using the synchronized $rSO_2$ and $SpO_2$ values. We allowed the first 10 minutes of each NIRS measurement for stabilization. As a result, 110 minutes of available data could be used to calculate the daily mean values of $r_{cSO_2}$, $r_{intSO_2}$, cFTOE, and intFTOE.
First, we determined whether $r_{cSO_2}$, $r_{intSO_2}$, cFTOE and/or intFTOE values predicted the onset of NEC. We therefore used the first measurement after birth, which was obtained on either day one or two. Since it was found that low $rSO_2$ values corresponded to the onset of NEC, we chose to use the 25th percentile for $r_{cSO_2}$ and $r_{intSO_2}$ values and the 75th percentile for cFTOE and intFTOE values as a cut-off. We compared infants with $rSO_2$ and $r_{intSO_2}$ values below the 25th percentile to infants with $rSO_2$ and $r_{intSO_2}$ values above the 25th percentile. Similarly, we compared infants with cFTOE and intFTOE values below the 75th percentile to infants with cFTOE and intFTOE values above the 75th percentile. We performed Kaplan-Meier analyses to determine whether the occurrence of NEC was significantly different between the aforementioned groups. We used the log-rank test to determine if there were significant differences in the Kaplan-Meier plots for the different groups: low versus high $rSO_2$ and FTOE values. Then, we performed a logistic regression analysis for those variables that had significantly different Kaplan-Meier curves and calculated odds ratios.

Next, we determined the course of cerebral and intestinal $rSO_2$ and FTOE in individual infants. We used the Mann-Whitney test to assess differences in median values of the last cerebral and intestinal $rSO_2$ and FTOE values before NEC development between preterm infants who developed NEC and infants who did not.

Finally, we determined the variability of cerebral and intestinal $rSO_2$ measurements of the first NIRS measurement after birth and of the last NIRS measurement prior to NEC development. For this purpose, we divided the 110 minutes of NIRS data that were available for each day in eleven blocks of 10-min and subsequently calculated means of $r_{cSO_2}$ and $r_{intSO_2}$ values for every 10-min block. We compared each 10-min mean with the infant’s daily mean and determined the amount of 10-min means that were 15% below or under the daily mean. We used the Mann-Whitney test to determine whether there were significant differences in variability between the two groups during the first NIRS measurements after birth, and during the last NIRS measurements prior to the development of NEC.

In order to test differences in clinical parameters between infants who developed NEC and infants who did not, we used the chi-square test or Fischer exact test for categorical data and the Mann-Whitney test for continuous data. We used SPSS 22.0 software for Windows (IBM SPSS Statistics 22, IBM Corp., Armonk, New York, USA) for statistical analyses. We considered a $P$ value < .05 to be statistically significant.

RESULTS

Of the 99 infants that were included in the study protocol, 11 preterm infants developed NEC of whom 10 infants with available NIRS measurements (Figure 1). From the remaining 88 included infants, 20 were matched to the 10 preterm infants with NEC and served as a control group. Of the ten infants with NEC, two infants were eventually classified as Bell’s stage 2 and eight infants as Bell’s stage 3 of whom six infants developed a bowel perforation.
None of the infants with NEC nor any of the control infants had cardiac diseases or had received indomethacin antenatally.

Median postnatal age at time of NEC onset was 13 (range, 4-43) days. In preterm infants who developed NEC, we were able to calculate mean $r_c$SO$_2$ values for 62/64 (97%) 2-hour periods and mean $r_{int}$SO$_2$ values for 20/64 (31%) 2-hour periods. In preterm infants who did not develop NEC, we were able to calculate mean $r_c$SO$_2$ values for 122/128 (95%) 2-hour periods and mean $r_{int}$SO$_2$ values for 41/128 (32%) 2-hour periods. Placing the infraumbilical sensor was often not possible due to the presence of an umbilicus venous catheter taped to the infraumbilical skin and/or due to lack of space in very low birth weight and small for gestational age infants.

We present clinical characteristics of the study population in Table 1. Apart from significantly higher mortality rates in preterm infants with NEC compared to controls, no other differences were observed.

![Flow diagram of the study](image)

**Figure 1.** Flow diagram of the study.

_Cerebral and intestinal rSO$_2$ and FTOE values in the first days after birth and the development of NEC_

In 21/30 patients (70%) the first NIRS measurement was performed within 24 hours (day one) after birth, and in 9/30 (30%) between 24 hours and 48 hours (day two) after birth. All infants were monitored in the cerebral region (30/30: 100%) and seven infants also in the intestinal region (7/30: 23%). SpO$_2$ values were not significantly different between infants
who developed NEC compared to infants who did not (median: 91% (range, 48-99%) versus 90% (range, 84-97%), \(P = .69\)).

The values of the 25th percentile of \(r_c\text{SO}_2\) and \(r_m\text{SO}_2\) were 70% and 30%, respectively. The values of the 75th percentile of cFTOE and intFTOE were .23 and .65, respectively.

Infants with \(r_c\text{SO}_2\) values below the 25th percentile (n=7) developed NEC significantly more often in the first 43 days after birth than infants with \(r_c\text{SO}_2\) values above the 25th percentile (n=23), \(P = .005\) (Figure 2). The occurrence of NEC was not significantly different between infants with \(r_m\text{SO}_2\) values below and above the 25th percentile, or between infants with cFTOE and intFTOE values below and above the 75th percentile.

### Table 1. Patient characteristics of preterm infants with NEC and their matched controls.

<table>
<thead>
<tr>
<th></th>
<th>NEC cases (n = 10)</th>
<th>Controls (n = 20)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>27.1 (24.6-29.4)</td>
<td>27.6 (25-29.7)</td>
<td>.58</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>903 (560-1630)</td>
<td>960 (615-1330)</td>
<td>.88</td>
</tr>
<tr>
<td>Male:Female</td>
<td>6:4</td>
<td>10:10</td>
<td>.71</td>
</tr>
<tr>
<td>Multiple gestations</td>
<td>3 (30)</td>
<td>4 (20)</td>
<td>.66</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>9 (90)</td>
<td>18 (90)</td>
<td>.99</td>
</tr>
<tr>
<td>Reason prematurity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPROM (&gt;24h)</td>
<td>3 (30)</td>
<td>3 (15)</td>
<td>.37</td>
</tr>
<tr>
<td>Spontaneous premature birth</td>
<td>3 (30)</td>
<td>10 (50)</td>
<td>.44</td>
</tr>
<tr>
<td>Induced birth – maternal</td>
<td>2 (20)</td>
<td>2 (10)</td>
<td>.58</td>
</tr>
<tr>
<td>Induced birth – fetal</td>
<td>2 (20)</td>
<td>4 (20)</td>
<td>.99</td>
</tr>
<tr>
<td>Induced birth – maternal and fetal</td>
<td>-</td>
<td>1 (5)</td>
<td>.99</td>
</tr>
<tr>
<td>Apgar score 1 min</td>
<td>4 (1-7)</td>
<td>5 (2-10)</td>
<td>.18</td>
</tr>
<tr>
<td>Apgar score 5 min</td>
<td>7 (1-9)</td>
<td>7 (3-10)</td>
<td>.74</td>
</tr>
<tr>
<td>Antibiotics &lt; 48 hours after birth</td>
<td>8 (80)</td>
<td>17 (85)</td>
<td>.99</td>
</tr>
<tr>
<td>Antibiotics &gt; 48 hours after birth</td>
<td>7 (70)</td>
<td>13 (65)</td>
<td>.99</td>
</tr>
<tr>
<td>Hemodynamically significant PDA</td>
<td>5 (50)</td>
<td>8 (40)</td>
<td>.71</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>5 (50)</td>
<td>8 (40)</td>
<td>.71</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>7 (70)</td>
<td>16 (80)</td>
<td>.65</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>8 (80)</td>
<td>13 (65)</td>
<td>.68</td>
</tr>
<tr>
<td>RBC transfusion in 48 hours before NEC onset</td>
<td>3 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid resuscitation</td>
<td>6 (60)</td>
<td>8 (40)</td>
<td>.44</td>
</tr>
<tr>
<td>Inotropes</td>
<td>4 (40)</td>
<td>3 (15)</td>
<td>.18</td>
</tr>
<tr>
<td>Length NICU stay (days)</td>
<td>46 (6-89)</td>
<td>39 (9-103)</td>
<td>.73</td>
</tr>
<tr>
<td>Death</td>
<td>4 (40)</td>
<td>1 (5)</td>
<td>.03</td>
</tr>
</tbody>
</table>

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

Abbreviations: NEC - necrotizing enterocolitis; NICU - neonatal intensive care unit; PDA - patent ductus arteriosus; PPROM - preterm premature rupture of membranes; RBC - red blood cell.
Using logistic regression analysis, we found that the risk of NEC increased with an odds ratio of 9.00 (95% CI 1.33-61.14, \( P = .03 \)) when infants had \( r_c \text{SO}_2 \) values < 70%.

Figure 2. Kaplan-Meier plots illustrating the occurrence of NEC in infants with \( r_c \text{SO}_2 \) values below (---) and above (-----) the 25\(^{th}\) percentile (A) and infants with cFTOE values below (-----) and above (---) the 75\(^{th}\) percentile (B) on the first measurement on day one or two.
Cerebral and intestinal oxygenation in relation to the development of necrotizing enterocolitis

The course of cerebral and intestinal rSO₂ and FTOE in individual infants who developed NEC did not reveal any specific patterns. No significant differences of these values were found between the last and the penultimate measurement before NEC. The last NIRS measurement before NEC development was obtained at a median of 2 (range, 1-7) days prior to NEC development; median postnatal day was 8 (range, 3-36) days. SpO₂ values were not significantly different between infants who developed NEC and infants who did not (median 92% (range: 86-100%) versus 90% (range: 84-99%), P = .16). We found significantly higher intFTOE values in preterm infants who developed NEC than in infants who did not develop NEC (median 0.65 (range, 0.49-0.84) versus 0.44 (range, 0.17-0.70), P = .04, Figure 3D). Furthermore, r_intSO₂ tended to be lower and cFTOE values higher in infants who developed NEC compared to controls (r_intSO₂, median 33% versus 48%, P = .09, Figure 3B; cFTOE, median 0.36 versus 0.24, P = .08, Figure 3C).

Variability
We did not find significant differences for the variability between infants with and infants without NEC in the first NIRS measurement after birth (r_cSO₂, median (range) 0% (0%-0%) versus 0% (0%-33%), P = .16; r_intSO₂, median 0% (0%-18%) versus 5% (0%-9%), P = .63), nor in the last NIRS measurement prior to NEC onset (r_cSO₂, median 0% (0%-3%) versus 0% (0%-18%), P = .24; r_intSO₂, median 0% (0%-18%) versus 0% (0%-0%), P = .13).
Figure 3. Median values of $r_c \text{SO}_2$ (A), $r_{\text{int}} \text{SO}_2$ (B), cFTOE (C), and intFTOE (D) of the last NIRS measurement prior to NEC onset in infants who developed NEC and their controls. Data are shown in box and whisker plots. Dots represent outliers.

* indicates $P < .05$ and § $P < .10$. 
DISCUSSION

In this study we found that \( r_{SO_2} \) values might be useful to predict the onset of NEC in preterm infants. The probability of developing NEC was nine-fold higher in infants with \( r_{SO_2} \) values < 70% in the first two days after birth compared with infants with \( r_{SO_2} \) values ≥ 70%. Furthermore, we found significantly higher intestinal FTOE values in the week prior to NEC development in preterm infants who developed NEC compared with matched controls. Variability did not differ between preterm infants who went on to develop NEC and infants who did not.

Our results suggest that monitoring \( r_{SO_2} \) might be helpful in identifying infants who will develop NEC. We found that infants with \( r_{SO_2} \) values < 70% in the first 48 hours after birth had a nine-fold higher risk of developing NEC. This finding suggests that infants who go on to develop NEC have impaired cerebral oxygenation as early as within 48 hours after birth. We offer several explanations for this finding. First, low \( r_{SO_2} \) values might be caused by low \( SpO_2 \) values as it was recently found that low \( SpO_2 \) values were associated with NEC development. However, we did not find lower \( SpO_2 \) values in infants who developed NEC compared to controls (median 91% versus 90%, \( P = .69 \)). Nonetheless, since we only measured two hours daily, we might have missed episodes in which infants were in the lower \( SpO_2 \) range. Secondly, low \( r_{SO_2} \) values might be the result of a low systemic perfusion. Because several clinical factors such as ventilatory status and presence of PDA were not different between cases and controls, we believe that lower \( r_{SO_2} \) values cannot be explained by these factors. Still, infants who go on to develop NEC may be relatively underperfused at birth due to variables we did not investigate, such as inflammation, maternal medication, and/or a more pronounced left to right flow across the PDA. The inciting event or chain of events that lead to development of NEC may therefore be set off before, during and/or just after birth. Further research in a larger patient population is warranted to investigate this hypothesis.

As opposed to \( r_{SO_2} \) values, \( r_{int}SO_2 \) values within the first days after birth were not associated with NEC development later on. We were, however, only able to measure \( r_{int}SO_2 \) in seven (7/30, 23%) preterm infants. In the very preterm and small for gestational age infants space was lacking for adequate sensor placement. The presence of an umbilical venous catheter taped to the skin hindered sensor placement as well. The resultant small sample size may have limited our ability to detect significant differences in intestinal oxygenation values between the two groups. However, our experience indicates that monitoring at the infraumbilical region is accompanied with practical difficulties in preterm infants in the first days after birth, limiting the usefulness of this measurement procedure in clinical practice.

Patel et al. recently demonstrated that \( r_{int}SO_2 \) values were lower in the first week after birth in infants who later developed NEC compared with infants who did not. We did not find such a difference, perhaps because of the small sample size of this study. Differences between study designs might also explain the dissimilar findings. In the study of Patel et al. infants with NEC were of lower GAs and had lower BWs than their controls, whilst our cases...
were comparable with controls regarding GA and BW. It has been reported that intestinal rSO$_2$ measurements might be dependent on GA.$^{14}$ Furthermore, Patel et al. measured daily for five minutes,$^{10}$ whilst we measured continuously for two hours every day. All other factors being equal, a more robust measurement should have made our chance of finding a difference greater rather than smaller.

With regard to the last NIRS measurement prior to NEC onset, we found approximately one and a half times higher intFTOE values in preterm infants with NEC than in controls. This finding supports the hypothesis that infants who develop NEC have decreased intestinal perfusion prior to the development of NEC.$^{8,9}$ As a predictor of NEC in individual infants this measurement is not clinically useful, because of the large intra-individual range of the intFTOE values. However, it provides insight into the role of intestinal perfusion in the pathophysiology of NEC. Further studies are needed to investigate the possibility of using intestinal oxygenation values to predict the onset of NEC.

With regard to the variability measurements, we did not find significant differences between infants with NEC and their matched controls. Cortez et al. suggested that loss of variability pointed towards the development of NEC.$^{11}$ Possibly, the method we used to determine the variability might not be sensitive enough to detect subtle changes. Further research is warranted to assess the usefulness of using variability for detecting an infant at risk for developing NEC.

In order to be able to adequately interpret our results, we have to keep in mind that the current NIRS technology has limitations. Since there are different NIRS devices, each with their own algorithm, our results are only representative for the INVOS 5100C device.$^{16-18}$ Moreover, peristalsis, gut movements, air, and stools complicate the interpretation of intestinal NIRS measurements.$^{14,19,20}$

The strength of this study is that we matched the infants who developed NEC to controls, based on GA, BW, and presence of hemodynamically significant PDA. Moreover, we measured two hours daily. A limitation is that we were not able to apply the infraumbilical sensor in every infant due to lack of space or the presence of an umbilical catheter. As a result, we were unable to obtain r$_{int}$SO$_2$ values in the smallest infants, which could have biased our results.

**CONCLUSIONS**

Cerebral rSO$_2$ values in the first two days after birth are predictive for NEC in preterm infants with a GA of less than 32 weeks. Although impaired intestinal perfusion is possibly present before the onset of NEC, the usefulness of monitoring intestinal oxygenation values to predict the onset of NEC needs to be investigated further.

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