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

DOI:
10.1016/j.earlhumdev.2014.04.008

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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CHAPTER 1

GENERAL INTRODUCTION
AND OUTLINE OF THE THESIS

Trijntje E. Schat
The main goal of this thesis is to investigate whether monitoring cerebral and splanchnic oxygenation by means of near-infrared spectroscopy (NIRS) could be useful in infants who develop necrotizing enterocolitis (NEC). NEC is currently the most common and deadliest gastrointestinal disease of prematurity.\textsuperscript{1} The first observations and reports of NEC can be traced back to the beginning of the nineteenth century. Back then, NEC was still considered a rare disease. However, with the founding of the first neonatal intensive care units in the 1960s, the prevalence of NEC increased rapidly.\textsuperscript{2} Despite improvements in neonatal care and extensive research regarding the pathophysiology of NEC, we are still unable to predict the onset of NEC, and offer appropriate and timely treatment, to counteract the devastating short- and long-term consequences with which NEC is associated.

**NECROTIZING ENTEROCOLITIS**

**Epidemiology**

NEC primarily affects preterm infants; more than 85\% of NEC cases occur in infants with a birth weight below 1500 grams or with a gestational age of less than 32 weeks.\textsuperscript{1,3,4} In those instances where NEC occurs in term and late preterm infants, an underlying condition is often present that causes intestinal hypoxia and/or hypoperfusion, such as congenital heart disease and intestinal anomalies.\textsuperscript{5,6} The most important factor that determines the prevalence of NEC is the neonatal intensive care unit in which an infant was cared for.\textsuperscript{7,8} Large multicenter and population based studies estimated the prevalence of NEC in very low birth weight infants at between 7 and 11\%.\textsuperscript{8-10}

**Pathophysiology**

The pathophysiology of NEC remains elusive; there are, however, several factors that are believed to predispose an infant to developing NEC. These factors include, amongst others, intestinal immaturity, enteral feeding, microbial colonization, and an imbalance in intestinal microvascular tone.\textsuperscript{1} It goes beyond the scope of this thesis to elaborate on the presumed role of each of these factors; only the role of intestinal perfusion will be further discussed. In 1969, Lloyd observed an association between severe, sustained asphyxia and gastrointestinal perforation. He was the first to propose that intestinal hypoxia might be one of the principal factors leading to the development of NEC and suggested that redistribution of blood flow to the brain, heart, and kidneys caused a markedly reduced intestinal perfusion (‘the diving reflex’).\textsuperscript{11} It is still believed that intestinal hypoperfusion and hypoxia play a considerable role in the development of NEC. In the neonatal rat model of NEC, which is currently the best accepted model, hypoxia-ischemia is one of the essential factors needed to generate NEC.\textsuperscript{12,13} Furthermore, it was found that the intestinal tissue of infants with NEC, whether diagnosed or suspected for NEC but not clinically or radiologically confirmed, was poorly perfused using intravenous fluorescein during laparoscopy.\textsuperscript{14} Additionally, a high resistance pattern of flow in the superior mesenteric artery was found in preterm infants with necrotizing enterocolitis, suggesting compromised intestinal blood flow.\textsuperscript{15,16} Currently,
the mechanism responsible for intestinal hypoxia is thought to be quite different from the one proposed by Lloyd. It is hypothesized that an imbalance between vasodilatory and vasoconstrictor regulation in favor of vasoconstriction contributes to ischemic injury.\textsuperscript{17-19} It remains unknown whether ischemic injury is (one of) the primary inciting factor(s) or is merely a secondary development as a result of intestinal inflammation and mucosal injury.\textsuperscript{19}

\textit{Clinical presentation and management}

Symptoms that indicate the presence of NEC can be of both abdominal and systemic origin, such as abdominal distention, feeding intolerance, apnea, bradycardia, and temperature instability.\textsuperscript{1,20} Common laboratory findings are leukocytosis, thrombocytopenia, metabolic acidosis, and increased C-reactive protein levels.\textsuperscript{20} Unfortunately, these symptoms and signs are nonspecific and can be found in the presence of a variety of other diagnoses, such as sepsis.\textsuperscript{20} The only signs that confirm the presence of NEC are pneumatosis intestinalis and/or portal venous gas on abdominal radiographic examination.\textsuperscript{1} These findings, however, might become evident only in advanced disease.

The course of NEC can be uncomplicated in which case the clinical symptoms and radiographic signs resolve gradually over days. However, progression to complicated NEC can be sudden with perforation, peritonitis, sepsis, and death in just a couple of hours. Since it remains impossible to predict the course of NEC, all infants who are suspected of NEC are treated uniformly, consisting of nil per mouth, gastric suctioning, and antibiotics, and by re-evaluation of abdominal symptoms and radiographic signs regularly. When a perforation is suspected or when an infant is clinically deteriorating, surgical treatment is required.

In order to help and guide clinicians in diagnosing and treating NEC, several staging systems have been developed.\textsuperscript{21-23} In our neonatal intensive care unit, the modified Bell’s staging system is used.\textsuperscript{22} This staging system defines three stages, each divided into two subcategories (Table 1).\textsuperscript{24} In case of Bell's stage 1, or suspected NEC, preterm infants have nonspecific abdominal and systemic symptoms suggesting NEC, but which cannot be confirmed by abdominal radiographic examination. Often, these infants are eventually diagnosed with diseases other than NEC. Bell’s stage 2 is frequently referred to as definite or proven NEC. Pneumatosis intestinalis, portal venous gas, or both are present on imaging findings. Finally, we distinguish Bell’s stage 3, or advanced NEC. This stage is characterized by deteriorating vital signs, such as hypotension and combined metabolic and respiratory acidosis. In addition to the radiographic signs described for Bell’s stages 1 and 2, pneumoperitoneum (‘free air’) can also be present. This finding warrants immediate surgical interference.

Although the use of the modified Bell’s staging system is widely employed, there are several limitations. Firstly, the stages described do not need to be followed in a sequential manner. Although it occurs rarely, the first sign of NEC can be pneumoperitoneum which classifies an infant directly into Bell’s stage 3. Secondly and more importantly, due to the nonspecific symptoms used to define Bell’s stage 1, many infants are classified as such and treated accordingly. The majority of these infants, however, are eventually diagnosed differently.
Table 1. Modified Bell’s staging criteria for necrotizing enterocolitis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>Systemic signs</th>
<th>Intestinal signs</th>
<th>Radiologic signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Suspected NEC</td>
<td>Temperature instability, apnea, bradycardia, lethargy</td>
<td>Increased pre-gavage residuals, mild abdominal distention, emesis, guaiac-positive stool</td>
<td>Normal or intestinal dilation, mild ileus</td>
</tr>
<tr>
<td>1B</td>
<td>Suspected NEC</td>
<td>Same as above</td>
<td>Bright red blood from rectum</td>
<td>Same as above</td>
</tr>
<tr>
<td>2A</td>
<td>Proven NEC – mildly ill</td>
<td>Same as above</td>
<td>Same as above, plus absent bowel sounds, with or without abdominal tenderness</td>
<td>Intestinal dilation, ileus, pneumatosis intestinalis</td>
</tr>
<tr>
<td>2B</td>
<td>Proven NEC – moderately ill</td>
<td>Same as above, plus mild metabolic acidosis, mild thrombocytopenia</td>
<td>Same as above, plus absent bowel sounds, definite abdominal tenderness, with or without abdominal cellulitis or right lower quadrant mass</td>
<td>Same as 2A, plus portal venous gas, with or without ascites</td>
</tr>
<tr>
<td>3A</td>
<td>Advanced NEC – severely ill, bowel intact</td>
<td>Same as 2B, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, and neutropenia</td>
<td>Same as above, plus signs of generalized peritonitis, marked tenderness, and distention of abdomen</td>
<td>Same as 2B, plus definite ascites</td>
</tr>
<tr>
<td>3B</td>
<td>Advanced NEC – severely ill, bowel perforated</td>
<td>Same as 3A</td>
<td>Same as 3A</td>
<td>Same as 2B, plus pneumoperitoneum</td>
</tr>
</tbody>
</table>

Modified from J.S. Lee and R.A. Polin.24 NEC - necrotizing enterocolitis.

Marker of intestinal damage in NEC

A protein that represents the degree of intestinal damage in infants with NEC is intestinal fatty acid-binding protein (I-FABP). I-FABP is a small intracellular protein that plays an important role in the fatty acid metabolism and transport.25 It is primarily located in epithelium cells of the small bowel, with only trace amounts in the stomach and large intestine.25 Normally,
I-FABP is present in very small quantities in the circulation. However, levels rapidly increase in the event of compromised cell membrane integrity, such as occurs in acute intestinal ischemia and inflammation, including NEC. Because I-FABP has a low molecular weight, it passes through the glomerular filter, and can be easily and rapidly detected in the urine. Since the bladder serves as a storage site, I-FABP levels in urine represent the secretion of I-FABP over a longer period of time, whilst I-FABP levels in plasma represent the immediate secretion by enterocytes. It was found that I-FABP levels in both plasma and urine are associated with the development of NEC and its severity. However, determining I-FABP levels is not yet sufficiently accurate to be considered diagnostic for NEC.

Outcome and complications

Despite significant progress in the field of neonatology, the short- and long-term consequences of NEC have not improved. Overall, mortality rates range between 9 and 40%, and increase with lower birth weight and severity of NEC. Other complications include intestinal stricture, abdominal abcess, cholestasis, and short bowel syndrome. Moreover, it was found that infants who survived NEC, specifically those who were treated surgically, had neurodevelopmental impairments later on.

NEAR-INFRARED SPECTROSCOPY

Since an impaired intestinal perfusion seems to play an essential role in the development of NEC, being able to detect this altered perfusion may give the clinician an early warning about the onset and progression of this disease. It was proposed that NIRS monitoring could be helpful in identifying infants with impaired bowel perfusion.

Technique

In 1977, Jöbsis introduced NIRS as a method to non-invasively monitor the oxygen saturation of tissue. A couple of years later the first report appeared that demonstrated that NIRS could be used at the bedside to monitor cerebral oxygen saturation in sick preterm infants. NIRS is based on the fact that light in the near-infrared range (wavelengths between 700 and 1000 nm) can be effectively transmitted through biological tissue over longer distances. Within these wavelengths, the majority of near-infrared light will be absorbed by oxygenated and deoxygenated hemoglobin, each of which have a distinct absorption spectrum. The remaining light will be either reflected or scattered. NIRS measures the spectral absorption for oxygenated and deoxygenated hemoglobin separately, and then calculates the ratio of oxygenated hemoglobin to total hemoglobin. This measurement represents the oxygen uptake in tissue and is referred to as regional tissue oxygen saturation ($rSO_2$). Approximately 75 to 80% of this value forms a representation of the saturation of venous blood, 5% forms the capillary compartment and the remaining forms arterial blood.

For the purpose of this thesis, we used the INVOS 5100C spectrometer (Covidien, Mansfield, MA, USA) with neonatal SomaSensors (Covidien). The SomaSensor has one light emitting...
diode that emits two wavelengths into underlying tissue, i.e. 730 and 810 nm. A shallow and a deep detector, at 30 and 40 mm distance from the emitter respectively, receive the light as a function of wavelength. The shallow detector provides information about surface tissue oxygen saturation and the deep detector information about the oxygen saturation of deeper tissues. The \(rSO_2\) is calculated by subtracting the oxygen saturation of the surface path from the deeper path and represents the venous weighted oxygen saturation of tissues at a depth of approximately 20 mm.\(^{48,50}\)

When the transcutaneous arterial oxygen saturation (\(SpO_2\)) is measured simultaneously, the fractional tissue oxygen extraction (FTOE) can be calculated: 

\[
FTOE = \frac{(SpO_2 - rSO_2)}{SpO_2}
\]

It is thought that FTOE reflects the balance between tissue oxygen supply and tissue oxygen consumption and might therefore be an early indicator of impaired tissue perfusion.\(^{52}\) High FTOE values can indicate two possibilities: (1) increased oxygen extraction due to increased metabolism at the tissue level, or (2) increased oxygen extraction due to decreased blood flow to the tissue that is being measured.

**NIRS and NEC**

Studies investigating intestinal perfusion with NIRS in both animals and humans showed promising results. Fortune and colleagues were the first to find a difference in NIRS measurements between infants with and infants without bowel ischemia.\(^{44}\) Instead of measuring intestinal tissue alone, they also measured the oxygen saturation of cerebral tissue. They used the cerebral \(rSO_2\) value as a reference to calculate the cerebro-splanchnic oxygenation ratio (CSOR) and found that a CSOR < 0.75 predicted the development of bowel ischemia with a sensitivity of 0.90 and a specificity of 0.96. Additionally, several reports were published which showed increasing splanchnic \(rSO_2\) values in infants who were recovering from NEC, demonstrated by improved clinical and radiographic signs and symptoms.\(^{53,54}\) Finally, it was found that intestinal \(rSO_2\) values were low with little variability in two infants, several days prior to NEC development.\(^{55}\)

It was also suggested that infants in whom NEC develops already have an altered intestinal perfusion from birth onwards.\(^{56,57}\) A study using a piglet model showed that abdominal NIRS readings were indeed lower on the first day after birth in piglets that developed NEC compared to those that did not.\(^{56}\) This finding was recently confirmed in a large study performed in preterm infants with a gestational age of less than 32 weeks and a birth weight below 1500 grams.\(^{57}\)

However, there are some concerns regarding monitoring \(rSO_2\) in the intestinal region. Since the bowel is a hollow organ, enteric contents, such as meconium and air, may be measured in stead of or concomitantly with intestinal tissue.\(^{58,59}\) It was found that meconium can alter the reflected signal considerably.\(^{60}\) Furthermore, peristalsis and movements of the gut within the abdominal cavity may alter the tissue that is being sampled during static sensor placement. For these reasons, it was suggested that the liver region could be a better site for monitoring \(rSO_2\) of intestinal tissue.\(^{58}\) The liver not only receives oxygenated blood
from the hepatic artery, but deoxygenated blood, that already passed the intestine, from the portal vein as well. Moreover, the liver is a solid and non-moving organ. Finally, since impaired splanchnic perfusion might be the result of a compromised systemic circulation, it would also be interesting to measure cerebral oxygenation values.

In this thesis we define the oxygenation of intestinal tissue as splanchnic oxygenation. We measured this oxygenation using NIRS at two abdominal locations: in the infraumbilical region on the central abdomen (intestinal or infraumbilical oxygenation), and the liver region, located at the right upper quadrant just below the costal margin (liver oxygenation).

**OUTLINE AND AIMS OF THE THESIS**

Our main aim was to investigate whether monitoring cerebral, liver, and intestinal oxygenation could be useful in infants who develop NEC. To this end, we first investigated the feasibility and validity of monitoring cerebral and splanchnic oxygenation by NIRS. Second, we investigated whether these NIRS measurements can be used for three purposes, i.e. (1) identifying infants who go on to develop NEC in infants with a high risk of developing NEC, (2) identifying infants with definite NEC in infants with abdominal signs and symptoms, and (3) identifying infants with complicated NEC in infants with established NEC. Complicated NEC was defined as the infant developing a bowel perforation requiring surgery (Bell’s stage 3B), or death.

The specific research questions were (chapters which focus on each question are indicated in brackets):

1. Is it feasible to study splanchnic oxygenation simultaneously in two abdominal regions in infants with suspected and definite NEC? Can liver and infraumbilical oxygen saturation values substitute each other for the purpose of assessing splanchnic oxygenation? (Chapter 2)
2. Can cerebral and splanchnic FTOE values be used as markers for intestinal damage in infants with NEC? (Chapter 3)
3. Do preterm infants with NEC show impaired cerebrovascular autoregulation more often than infants without NEC? (Chapter 4)
4. Can we differentiate high-risk infants who develop NEC from those who do not by monitoring cerebral and intestinal oxygenation as early as in the first days after birth? (Chapter 5)
5. Can we, in an early stage of the disease, differentiate infants with definite NEC from infants with suspected NEC, and infants with complicated NEC from infants with uncomplicated NEC by monitoring cerebral, liver, and intestinal oxygenation? (Chapter 6)
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