Tissue oxygenation monitoring in newborn infants at risk of circulatory failure
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The association between multisite near-infrared spectroscopy and routine hemodynamic measurements in relation to short-term outcome in preterms with clinical sepsis

Michelle E. van der Laan, Trijntje E. Schat, Annelies J. Olthuis, H. Marike Boezen, Arend F. Bos, Elisabeth M.W. Kooi

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**Background:** The added clinical value of multisite near-infrared spectroscopy (NIRS) monitoring to detect low organ tissue perfusion in preterm infants at risk of circulatory failure remains unclear.

**Objectives:** To evaluate the associations between multisite NIRS measurements and clinical signs of circulatory failure in relation to short-term outcome in preterm infants with clinical sepsis.

**Methods:** Prospective cohort study of preterm infants (gestational age <32 weeks) with clinical sepsis. We monitored cerebral, renal, and intestinal oxygen saturation using NIRS for 72 h following sepsis workup and calculated fractional tissue oxygen extraction (FTOE). We recorded clinical signs of circulatory failure every 8 h. We analyzed the associations between FTOE values, clinical signs of circulatory failure, and short-term outcome.

**Results:** In 28 preterm infants with clinical sepsis, intraindividual and interindividual associations between NIRS values and clinical signs of circulatory failure were weak. At several points of time during the study period, cerebral and renal FTOE were higher in infants who developed intestinal complications compared with infants who did not, while clinical signs of circulatory failure never differed between groups. After correcting for multiple testing, significant differences disappeared.

**Conclusions:** The associations between multisite FTOE values and clinical signs of circulatory failure were weak in preterm infants with clinical sepsis. Nevertheless, in contrast to clinical signs of circulatory failure, cerebral and renal FTOE values were associated with adverse short-term intestinal outcome in the uncorrected analyses. Multisite NIRS monitoring might help to detect critically low tissue oxygen delivery leading to adverse intestinal outcome not detected by routine hemodynamic measurements.
Introduction

Circulatory failure is an important cause of mortality and morbidity in preterm infants. Although monitoring tissue oxygen delivery is essential to guide adequate treatment during circulatory failure, it is challenging in preterm infants since the possibilities for invasive hemodynamic monitoring are limited. Routine clinical hemodynamic measurements, such as blood pressure and capillary refill time (CRT), are poor predictors of systemic blood flow as estimated by functional echocardiography (1,2). Biochemical indicators of tissue oxygen delivery, such as serum lactate and base excess, only become abnormal after a prolonged period of inadequate tissue perfusion and have to be obtained intermittently and invasively.

Near-infrared spectroscopy (NIRS) is a noninvasive method to assess tissue oxygen delivery and consumption. With NIRS, regional tissue oxygen saturation (rSO₂), which reflects the venous weighted oxygen saturation of the underlying tissue, can be measured continuously. When transcutaneous arterial oxygen saturation (spO₂) is measured simultaneously, fractional tissue oxygen extraction (FTOE) can be calculated (3). If tissue oxygen metabolism is constant, FTOE may serve as an indicator of tissue perfusion.

Increasingly, NIRS is used to monitor oxygenation and perfusion at multiple sites in newborn infants at risk of circulatory failure of various causes (4,5). As cerebral blood flow may be preserved due to cerebrovascular autoregulation in newborn infants with circulatory failure, monitoring somatic tissue beds, e.g. intestines or kidneys, could be a better and more timely indicator of low systemic blood flow than cerebral NIRS monitoring. There is, however, little evidence to support the added clinical value of multisite NIRS monitoring for diagnosing compromised tissue perfusion in preterm infants.

A frequent cause of circulatory failure in preterm infants is sepsis. Our aim was to explore the clinical value of multisite NIRS monitoring in the diagnosis of circulatory failure in a cohort of preterm infants with clinical sepsis. For this purpose we explored the association between clinical signs of circulatory failure and multisite NIRS measurements during the first 72 h following sepsis workup. Furthermore, we explored the ability of routine clinical hemodynamic measurements as well as multisite NIRS measurements to detect critically low tissue oxygen delivery by determining the association of both with short-term outcome.

Methods

This was a prospective, observational cohort study in which all preterm infants admitted to the neonatal intensive care unit of the University Medical Center Groningen, who developed clinical sepsis between September 2011 and March 2013, were eligible.
Patients
Preterm infants (gestational age <32 weeks), who showed clinical signs suggesting sepsis as evaluated by the attending clinician were included within 24 h of sepsis workup. Infants were suspected of sepsis in the presence of clinical signs such as increased frequency of apnea and bradycardia, lethargy, temperature instability, and poor peripheral circulation (increased CRT, cold extremities, gray skin color). Infants with major congenital defects were excluded. The study was approved by the ethical review board of the University Medical Center Groningen. Written informed parental consent was obtained in all cases.

Multisite near-infrared spectroscopy measurements
We used an INVOS 5100C near-infrared spectrometer and neonatal SomaSensors (Covidien, Mansfield, Mass., USA) to measure cerebral rSO$_2$ (r$_c$SO$_2$), renal rSO$_2$ (r$_r$SO$_2$), and intestinal rSO$_2$ (r$_m$SO$_2$). Cerebral and renal monitoring commenced at the time of inclusion and continued for 72 h. Additionally, r$_m$SO$_2$ was measured twice daily for 2 h in infants weighing >1,000 g who did not have an umbilical catheter. Sensors were placed on the frontoparietal side of the infant’s head to measure r$_c$SO$_2$, on the lateral posterior flank to measure r$_r$SO$_2$, and just below the umbilicus to measure r$_m$SO$_2$. Replacement of the sensors was documented by the nurse and after replacement 5 min were allowed for the measurement to stabilize. NIRS data were downloaded and stored for off-line analysis. We calculated FTOE for each location as: FTOE = (spO$_2$-rSO$_2$)/spO$_2$. Increasing FTOE either represents decreasing tissue oxygen delivery or increasing tissue oxygen consumption.

Demographic and clinical variables
Prospectively, we collected all infants’ routinely measured clinical and biochemical hemodynamic parameters, i.e. heart rate, mean arterial blood pressure, spO$_2$, urine output, blood gas values (pH, base excess, HCO$_3$), serum lactate, and central CRT, which was assessed at the sternum with a blanching time of 5 s. Other characteristics, collected from the infants’ medical charts, were gestational age, birth weight, postnatal age, C-reactive protein levels, the results of blood and liquor cultures, the need for mechanical ventilation, treatment of circulatory failure, and the results of cardiac and cranial ultrasound scans and abdominal X-rays.

Circulatory failure score
The presence of clinical signs of circulatory failure was evaluated every 8 h following sepsis workup by calculating a circulatory failure score (CFS). The CFS has not been validated previously, but is a reflection of a clinical evaluation of signs of circulatory failure. The score was composed of the presence or absence of six clinical indicators of circulatory failure: tachycardia (heart rate >180 b.p.m.), hypotension (mean arterial blood pressure less than postmenstrual age), oliguria (urine output <1.0 ml/kg/h), prolonged CRT (CRT ≥3 s), high serum lactate (serum lactate >2.5 mmol/l), and metabolic acidosis (pH <7.30 in the presence of serum HCO$_3$ <22 mmol/l or base excess <6). The total CFS could range from 0 (no signs of
circulatory failure) to 6 (all signs of circulatory failure present). Mean mean arterial blood pressure and heart rate were calculated from the values measured during the hour preceding the CFS assessment.

**Data selection and missing data**

NIRS data were excluded from analyses in case of documented malplacement of the sensors and in case of baseline changes >50% after documented replacement of the sensors. Missing NIRS data were not replaced. Missing data concerning signs of circulatory failure were scored as present when preceded and followed by a present sign and as absent when preceded and followed by an absent sign. If this was not the case, missing data were not replaced.

**Short-term outcome**

Adverse somatic short-term outcome was defined as the occurrence of a single intestinal perforation (SIP) or necrotizing enterocolitis (NEC) of Bell's stages II or III within 14 days of sepsis workup. Adverse cerebral short-term outcome was defined as worsening or new-onset periventricular echodensities, new-onset intraventricular hemorrhage (IVH), or seizures within 14 days of sepsis workup.

**Statistical analysis**

To determine the relationship between the CFS and NIRS data, mean values of cerebral FTOE (cFTOE), renal FTOE (rFTOE), and intestinal FTOE (intFTOE) were calculated during the hour preceding every CFS assessment. This resulted in one assessment per infant per 8-hour period following sepsis workup. The Spearman rank correlation and Mann-Whitney tests were used when appropriate to determine the association between FTOE values, CFS, and signs of circulatory failure.

To determine whether clinical deterioration, as defined by the onset of new signs of circulatory failure, was accompanied or preceded by deterioration of FTOE values in an individual infant, the FTOE values of the assessments at 16 and 8 h prior to clinical deterioration and during the presence of circulatory failure were tested using the Wilcoxon signed-rank test.

To relate the course of the FTOE and the CFS to short-term outcome, we calculated mean cFTOE and rFTOE for every 8-hour period following sepsis workup and subsequently analyzed differences in the course of the mean 8-hour FTOE values and CFS between groups at different time points using the Mann-Whitney U test. SPSS 22.0 (IBM Corp., Armonk, N.Y., USA) was used for all statistical analyses. A p value <0.05 was considered statistically significant. We corrected for multiple testing using a Bonferroni correction. We chose to also show the uncorrected results as this was mainly a hypothesis-generating study.
Chapter 2

Results

Patient characteristics
From the 73 eligible infants who were born between August 2011 and February 2013, 37 (51%) developed clinical sepsis of which 28 (76%) were included. Five had early-onset and 23 had late-onset clinical sepsis. Table 1 provides the patient characteristics.

NIRS measurements
Multisite NIRS measurements were started after a median of 6.9 h (range: 0-22.5) after sepsis workup. We were able to measure $r_t\text{SO}_2$ and $r_c\text{SO}_2$ in all infants and $r_{int}\text{SO}_2$ in 18 infants. NIRS measurements were continued for 72 h in 23 infants. In 5 infants, NIRS measurements were discontinued after a median of 58 h (range: 27-68) after sepsis workup due to death, surgery for NEC stage IIIB, ductal ligation, intensive phototherapy, or discharge to a high care ward.

Paired measurements of FTOE values and routine hemodynamic measurements
Table 2 shows median FTOE values, median CFS, and the occurrence of signs of circulatory failure per 8-hour period following sepsis workup. The CFS never showed a significant positive correlation with FTOE values during the study period (Table 3). The $c \text{FTOE}$ was higher during episodes of tachycardia (19 episodes in 8 infants) and a CRT $\geq$3 s (44 episodes in 18 infants; Table 4). The $\text{intFTOE}$ was higher during episodes of hypotension (3 episodes in 3 infants; Table 4). After Bonferroni correction, none of these differences were significant. An increasing CFS was observed 31 times in 22 infants. FTOE values neither changed directly before nor between 16 and 8 h before the occurrence of an increasing CFS.

FTOE values, clinical signs of circulatory failure, and short-term outcome
Four infants developed intestinal complications and 6 developed cerebral complications, all within 8 days of the end of the study period. Of the 4 infants with intestinal complications, 3 infants developed NEC stage III one, 9, and 11 days after sepsis workup, and 1 infant developed an SIP 6 days after sepsis workup. Cerebral and renal FTOE were higher in infants who developed intestinal complications at different points of time during the study period (Figure 1), while median CFS (range: 0-1.5 and 0-1 in infants with and infants without intestinal complications, respectively) was not higher at any point during the study period in comparison to infants who did not develop intestinal complications. After applying a Bonferroni correction, these differences were not significant.

Of the 6 infants with cerebral complications, one developed IVH grade II and one developed seizures during the study period. Three infants developed worsened periventricular echodensities and one developed IVH grade I after the study period confirmed by cranial ultrasound scans. FTOE values and median CFS (range: 0-1 and 0-1 in infants with and infants without cerebral complications, respectively) were not significantly different between infants who did or did not develop cerebral complications at any point during the study period (Figure 2).
<table>
<thead>
<tr>
<th>TABLE 1. Patient characteristics</th>
<th>N = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, weeks</td>
<td>27.7 (26.0-31.6)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>980 (560-1810)</td>
</tr>
<tr>
<td>Postnatal age, days</td>
<td>9.8 (0.1-33.4)</td>
</tr>
<tr>
<td>Weight at inclusion, g</td>
<td>1,085 (630-2400)</td>
</tr>
<tr>
<td>Time between sepsis workup and inclusion, h</td>
<td>6.9 (0-22.5)</td>
</tr>
</tbody>
</table>

**Confirmed diagnosis**

- Culture-proven sepsis: 11 (39)
  - CNS 7
  - Staphylococcus aureus 2
  - Escherichia coli 1
  - GBS 1
- Culture-proven sepsis-meningitis: 1 (4)
  - Enterobacter cloacae (BC) 1
  - Klebsiella oxytoca (LC) 1
- Blood culture negative, CRP >10 9 (32)
- Blood culture negative, CRP ≤ 10 6 (21)
- NEC Bell’s stage IIIB 1 (4)

**Maximum CRP**

15.5 (0-221)

**Mechanical ventilation**

13 (46)

**Volume expansion**

15 (54)

- Saline 9
- Blood transfusion 13

**Inotropes**

4 (14)

- Dopamine 3
- Dopamine + dobutamine 1

**PDA confirmed during or before the study period**

17 (61)

- Hemodynamically significant\(^a\) 11

**Mortality during NICU stay**

6 (21)

- During study period 1

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Data are shown as medians (range) or as n (%) when appropriate.

\(^a\): A PDA was considered hemodynamically significant when predominantly left to right shunting occurred across the ductus arteriosus in the presence of at least one of the following criteria: left atrial to aortic root ratio >1.4, end diastolic blood flow velocity in the left pulmonary artery > 0.2 m/s, and retrograde diastolic blood flow in the descending aorta. CNS = Coagulase-negative staphylococcus; GBS = group B streptococcus; CRP = C-reactive protein; BC = blood culture; LC = liquor culture; PDA = patent ductus arteriosus; NICU = neonatal intensive care unit.
<table>
<thead>
<tr>
<th>Hours after sepsis workup</th>
<th>0-7</th>
<th>8-15</th>
<th>16-23</th>
<th>24-31</th>
<th>32-39</th>
<th>40-47</th>
<th>48-55</th>
<th>56-63</th>
<th>64-71</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in study, n</td>
<td>19</td>
<td>23</td>
<td>28</td>
<td>28</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>cFTOE</td>
<td>0.21</td>
<td>0.25</td>
<td>0.28</td>
<td>0.29</td>
<td>0.25</td>
<td>0.28</td>
<td>0.26</td>
<td>0.27</td>
<td>0.31</td>
</tr>
<tr>
<td>(0.04-0.48)</td>
<td></td>
<td>(0.02-0.45)</td>
<td>(0.06-0.57)</td>
<td>(0.08-0.55)</td>
<td>(-0.02-0.58)</td>
<td>(0.04-0.62)</td>
<td>(0.01-0.61)</td>
<td>(0.03-0.48)</td>
<td></td>
</tr>
<tr>
<td>rFTOE</td>
<td>0.32</td>
<td>0.31</td>
<td>0.36</td>
<td>0.30</td>
<td>0.37</td>
<td>0.39</td>
<td>0.34</td>
<td>0.34</td>
<td>0.30</td>
</tr>
<tr>
<td>(0.07-0.81)</td>
<td></td>
<td>(0.09-0.80)</td>
<td>(0.05-0.78)</td>
<td>(0.17-0.81)</td>
<td>(0.04-0.81)</td>
<td>(0.14-0.76)</td>
<td>(0.18-0.82)</td>
<td>(0.15-0.51)</td>
<td></td>
</tr>
<tr>
<td>intFTOE</td>
<td>0.30</td>
<td>0.51</td>
<td>0.55</td>
<td>0.49</td>
<td>0.55</td>
<td>0.54</td>
<td>0.54</td>
<td>0.60</td>
<td>0.44</td>
</tr>
<tr>
<td>(0.12-0.84)</td>
<td></td>
<td>(0.01-0.80)</td>
<td>(0.27-0.84)</td>
<td>(0.32-0.83)</td>
<td>(0.27-0.81)</td>
<td>(0.23-0.85)</td>
<td>(0.50-0.84)</td>
<td>(0.22-0.83)</td>
<td></td>
</tr>
<tr>
<td>N=9</td>
<td>N=9</td>
<td>N=10</td>
<td>N=12</td>
<td>N=11</td>
<td>N=12</td>
<td>N=9</td>
<td>N=7</td>
<td>N=8</td>
<td></td>
</tr>
<tr>
<td>CFS</td>
<td>1 (0-3)</td>
<td>0 (0-3)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (11%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3 (16%)</td>
<td>1 (4%)</td>
<td>3 (11%)</td>
<td>2 (7%)</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
<td>2 (8%)</td>
<td>3 (12%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>CRT ≥3 s</td>
<td>5 (26%)</td>
<td>6 (26%)</td>
<td>6 (21%)</td>
<td>5 (18%)</td>
<td>4 (15%)</td>
<td>6 (23%)</td>
<td>4 (15%)</td>
<td>6 (23%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>4 (21%)</td>
<td>4 (17%)</td>
<td>2 (7%)</td>
<td>5 (18%)</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
<td>6 (23%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Oliguria</td>
<td>2 (11%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lactate &gt;2.5 mmol/l</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Data are shown as medians (range) or as n (%) when appropriate.
### TABLE 3. The association between cFTOE, rFTOE, and intFTOE and the CFS during all CFS-assessments and per 8-hour period following sepsis workup

<table>
<thead>
<tr>
<th>CFS</th>
<th>cFTOE</th>
<th>rFTOE</th>
<th>intFTOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>0.067</td>
<td>-0.007</td>
<td>-0.125</td>
</tr>
<tr>
<td>N=214</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hours after sepsis workup</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-7</td>
<td>0.259</td>
<td>-0.007</td>
<td>-0.199</td>
</tr>
<tr>
<td>N=15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-15</td>
<td>-0.112</td>
<td>0.226</td>
<td>-0.639</td>
</tr>
<tr>
<td>N=22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-23</td>
<td>-0.087</td>
<td>-0.139</td>
<td>-0.418</td>
</tr>
<tr>
<td>N=26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-31</td>
<td>0.252</td>
<td>-0.028</td>
<td>-0.839**</td>
</tr>
<tr>
<td>N=27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32-39</td>
<td>0.014</td>
<td>-0.431*</td>
<td>0.000</td>
</tr>
<tr>
<td>N=25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-47</td>
<td>0.010</td>
<td>0.073</td>
<td>0.268</td>
</tr>
<tr>
<td>N=25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48-55</td>
<td>0.072</td>
<td>0.226</td>
<td>0.261</td>
</tr>
<tr>
<td>N=26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56-63</td>
<td>0.204</td>
<td>0.031</td>
<td>0.144</td>
</tr>
<tr>
<td>N=25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64-71</td>
<td>0.216</td>
<td>0.064</td>
<td>0.218</td>
</tr>
<tr>
<td>N=23</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are shown as Spearman rank correlation coefficients, * p < 0.05, ** p < 0.01
We demonstrated that in preterm infants with clinical sepsis there were few intraindividual and interindividual associations between clinical signs of circulatory failure and multisite NIRS measurements measured simultaneously. High cerebral and renal FTOE were, however, before correction for multiple testing associated with the occurrence of NEC or SIP within 14 days of sepsis workup, while clinical signs of circulatory failure were not. To our knowledge, this is the first study that explored the usefulness of multisite NIRS measurements in this specific group of infants.

Due to the lack of a gold standard for assessing tissue perfusion and oxygenation in preterm infants, assessment of tissue perfusion in the neonatal intensive care unit is based on interpreting several clinical and biochemical indicators of systemic blood flow. Our first objective was to explore the agreement...
between clinical signs of circulatory failure and absolute FTOE values. To this end, we attempted to mimic clinical assessment of tissue perfusion by calculating a CFS. In our cohort, FTOE values never showed positive correlations with the CFS, suggesting poor agreement in the interpretation of organ blood flow between both monitoring methods. There are several explanations for this finding. First, the absolute FTOE values might not be good indicators of organ blood flow since it is known that NIRS measurements are influenced by factors such as Hb level, gestational age, and postnatal age (6-10). Second, clinical signs of circulatory failure might not reflect organ blood flow well either: previous studies have demonstrated poor associations between clinical signs of circulatory failure and systemic blood flow as assessed by Doppler echocardiography (1,2,10). Third, sepsis-associated microvascular dysfunction might have influenced the association between routine hemodynamic measurements, which predominantly reflect macrohemodynamics, and NIRS measurements, which might be affected by a disturbed microcirculation (11-12).
Composing a CFS might diminish the discriminative power of detecting low organ blood flow as some clinical signs of circulatory failure might reflect impaired organ blood flow better than others. Therefore, we also explored the associations between NIRS values and individual signs of circulatory failure. We found intFTOE to be higher during episodes of hypotension, indicating a more decreased rSO₂ in the mesenteric region in comparison to the kidney and the cerebrum (Table 4). Furthermore, cFTOE was higher during episodes of tachycardia and CRT ≥ 3 s, while renal and mesenteric FTOE values did not differ. Previously, associations were found in neonates between a prolonged CRT and low superior vena cava flow (1,2) and low cardiac index (13). We cannot offer a clear explanation for not finding different somatic FTOE values during episodes of prolonged CRT and tachycardia, other than the smaller sample and larger physiological variability of somatic NIRS measurements compared with cerebral NIRS measurements (6).

Ultimately, the main goal of monitoring tissue oxygen delivery consists of guiding appropriate therapeutic interventions to improve impaired tissue oxygen delivery which, if left untreated, might result in organ damage. Several studies have found low abdominal rSO₂ values in infants who developed or already showed signs of NEC (14-16). As we could only measure intFTOE in 18 infants, we were unable to assess the association between the course of intFTOE and the development of intestinal complications. Nevertheless, the 4 infants in our cohort who developed NEC or SIP within 8 days of the end of the study did show higher cFTOE and rFTOE during several 8-hour periods following sepsis workup, while the CFS of these infants was never higher compared to infants who did not develop intestinal complications. Although these results were only significant without correcting for multiple testing, these findings suggest that NIRS measurements might help to detect impaired tissue oxygen delivery leading to intestinal ischemia and/or hypoxia, independent of signs of circulatory failure.

Previously, periventricular echodensities, periventricular leukomalacia, and IVH in preterm infants were associated with low and high cFTOE values during the first 24 h to the first 2 weeks after birth in comparison to controls (17-20). Surprisingly, we neither found different NIRS values nor different CFS at any point in time between infants who did and infants who did not develop adverse cerebral short-term complications. We cannot rule out that the events leading to the development of cerebral complications might have occurred outside of the monitoring period. Furthermore, inflammatory rather than hemodynamic characteristics may have played a role in the development of cerebral complications.

We recognize several limitations of this study. First, we studied a heterogeneous cohort of preterm infants with clinical sepsis, which included infants with culture-proven sepsis as well as infants with no culture- or laboratory-proven sepsis. We do, however, believe that these infants represent the typical clinical scenario of infants at risk of circulatory failure who deserve intensive monitoring of tissue oxygen supply to prevent critically low tissue oxygen delivery. Second, few clinical signs of circulatory failure were observed with a median CFS of zero during most of the study period. However, when signs of circulatory failure were present, they were not always accompanied by high FTOE values. Furthermore, high FTOE values associated with adverse intestinal outcome were observed, which suggests that a critically low oxygen supply may have been present during the study period in the absence of clinical signs of circulatory failure. Third, as the number of patients and the signs of circulatory failure were limited, we
had to include multiple measurements per infant when comparing individual signs of circulatory failure
with FTOE values. Fourth, as we only monitored regional oxygenation during the first 72 h following
sepsis workup, we cannot rule out that events leading to an adverse outcome within 14 days of sepsis
workup have occurred outside of the monitoring period. Fifth, since this was an exploratory study, we
might have found statistically significant associations between variables due to multiple testing.

Conclusions

Multisite FTOE values showed poor inter- and intraindividual associations with clinical signs of circula-
tory failure in preterm infants with clinical sepsis. Nevertheless, in contrast to clinical signs of circulatory
failure, cerebral and renal FTOE values were associated with adverse short-term intestinal outcome in
the uncorrected analyses. Multisite NIRS monitoring might help to detect critically low tissue oxygen
delivery leading to adverse intestinal outcome not detected by routine hemodynamic measurements in
preterm infants with clinical sepsis.

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