The course of cerebral, renal, and splanchnic oxygen tissue extraction in preterm infants in the first 48 hours after the diagnosis of a clinical sepsis

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Abstract

**Background:** Sepsis is an important cause of circulatory failure in newborn infants admitted to the neonatal intensive care unit (NICU) and is associated with severe morbidity and mortality. Conventional hemodynamic parameters are insufficient to detect circulatory failure in these infants in a timely manner. Near infrared spectroscopy (NIRS) is a non-invasive method that can be used to measure the regional tissue oxygenation and calculate the fractional tissue oxygen extraction (FTOE), an indicator of tissue perfusion. Since cerebral perfusion could be maintained due to cerebral autoregulation in infants with sepsis at risk of circulatory failure, monitoring of the oxygenation of somatic organs might give a better impression of systemic blood flow in these infants.

**Aim:** To analyze the course of cerebral, renal, and splanchnic FTOE (cFTOE, rFTOE, sFTOE) in preterm infants in the first 48 hours after the diagnosis of a sepsis.

**Methods:** As part of the **NEonatal Monitoring of tissue Oxygenation in newborn infants at risk of circulatory failure (NEMO) study,** preterm infants, who were admitted to the Neonatal Intensive Care of the University Medical Center Groningen (UMCG) between August 2011 and June 2012, were selected. Inclusion criteria consisted of a gestational age < 32 weeks and a clinically suspected sepsis. Hemodynamic parameters were collected prospectively. After informed consent was obtained, NIRS monitoring was started within 24 hours after the diagnosis of a sepsis and was continued for 48 hours. Neonatal NIRS-Somasensors were placed on the left frontoparietal side of the newborns head, the left posterior flank between T10 and L2, and below the umbilicus. To identify the course of cFTOE, rFTOE, and sFTOE in the first 48 hours after diagnosis, mean FTOE values were calculated every 3 hours for 48 hours. We related the course in the first 24 hours and between 24 and 48 hours after diagnosis to blood culture positivity, to the administration of dopamine and dobutamine and to conventionally used hemodynamic parameters.

**Results:** Fourteen infants were included with a mean gestational age of 28 weeks (standard deviation (SD) 2), a mean birth weight of 1088 grams (SD 337) and a mean postnatal age at clinical presentation of 11 days (SD 11). sFTOE measurements were not available in three infants. The blood culture was positive in six infants. Three infants received dopamine and dobutamine for circulatory support. Median cFTOE, rFTOE, and sFTOE in the first 24 hours after diagnosis were 0.21 (range -0.03 – 0.60), 0.32 (range 0.04 – 0.83), and 0.55 (range 0.07 – 0.82), respectively. Median cFTOE, rFTOE, and sFTOE values between 24 and 48 hours were 0.22 (range -0.04 – 0.52), 0.34 (range 0.08 – 0.83), and 0.56 (range 0.29 – 0.83), respectively. rFTOE was significantly lower in the first 24 hours after diagnosis in infants with a positive blood culture compared to infants with a negative blood culture. Furthermore, significant higher cFTOE values were seen during the entire study period in infants who received dopamine and dobutamine. Finally, significant positive correlations were observed between cFTOE and heart rate (r=0.482) and sFTOE and pH (r=0.636). A significant negative correlation was found between rFTOE and pH (r=-0.291).

**Conclusion:** Cerebral perfusion seems to be maintained within the normal range in the first 48 hours after diagnosis of a sepsis in preterm infants. On the contrary, somatic perfusion seems to be decreased, possibly to ensure an adequate perfusion to the brain. Further studies in a larger population are necessary to confirm these results.
Samenvatting

Achtergrond: Sepsis is een veelvoorkomende oorzaak van circulatoir falen bij prematuren en is geassocieerd met ernstige morbiditeit en mortaliteit. Conventionele monitoring methoden zijn onvoldoende om circulatoir falen in een vroeg stadium op te sporen. Met behulp van near infrared spectroscopy (NIRS) is het mogelijk geworden om op een non-invasieve manier een continue meting uit te voeren van de weefseloxygenatie, waarmee de fractionele zuurstofextractie (FTOE) kan worden berekend, een indicator van weefselperfusie. Aangezien de cerebrale perfusie gehandhaafd kan blijven door cerebrale autoregulatie tijdens dreigend circulatoir falen, zou men met het monitoren van de oxygenatie van somatische organen mogelijk eerder een pasgeborene kunnen identificeren met een verminderde systemische bloeddoorstroming.

Doel: Het vaststellen van het beloop van de cerebrale, renale en splanchnische FTOE (cFTOE, rFTOE, sFTOE) in prematuren in de eerste 48 uur na het vaststellen van een sepsis.


Resultaten: Veertien patiënten werden geïncludeerd met een gemiddelde amenorroeduur van 28 weken (standaarddeviatie (SD) 2), een gemiddeld geboortegewicht van 1088 gram (SD 337) en een gemiddelde postnatale leeftijd van 11 dagen (SD 11). sFTOE waarden waren niet beschikbaar in drie kinderen. Zes kinderen bleken een positieve bloedkweek te hebben. Drie kinderen kregen dopamine en dobutamine toegediend bij een insufficiënte circulatie. Mediane cFTOE, rFTOE en sFTOE in de eerste 24 uur na diagnose waren 0,21 (range -0,03 – 0,60), 0,32 (range 0,04 – 0,83) en 0,55 (range 0,07 – 0,82) respectievelijk. Mediane cFTOE, rFTOE en sFTOE tussen 24 en 48 uur waren 0,22 (range -0,04 – 0,52), 0,34 (range 0,08 – 0,83) en 0,56 (range 0,29 – 0,83) respectievelijk. rFTOE was significant lager in de eerste 24 uur na diagnose in kinderen met een positieve bloedkweek. Tevens werden significant hogere cFTOE waarden vastgesteld gedurende de gehele studieperiode bij kinderen die behandeld werden met dopamine en dobutamine. Tenslotte werden er significante positieve correlaties gevonden tussen cFTOE en hartfrequentie (r=0,482) en sFTOE en pH (r=0,636) en een significante negatieve correlatie tussen rFTOE en pH (r=-0,291).

Conclusie: In prematuren met een sepsis wordt in de eerste 48 uur na het vaststellen van de diagnose een cerebrale perfusie gevonden binnen de normale range. Echter, systemische perfusie lijkt verminderd te zijn, wellicht om een adequate cerebrale perfusie te kunnen waarborgen. Grotere studies met meer patiënten zijn nodig om deze resultaten te bevestigen.
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1. Introduction

1.1 Neonatal sepsis

Sepsis is an important cause of circulatory failure in newborn infants admitted to the neonatal intensive care unit (NICU) and is associated with severe morbidity and mortality. Neonatal sepsis is worldwide the leading cause of death in the first month of life and is responsible for more than 1 million deaths annually.\(^1,2\) Mortality rates can exceed 70% for extremely low birth weight (ELBW) infants.\(^3\)

Regarding morbidity, infection in the newborn infant is associated with prolonged hospitalization and an increased risk of neonatal complications, such as respiratory distress syndrome, bronchopulmonary dysplasia, and severe intraventricular hemorrhage or periventricular leukomalacia.\(^4,5\)

On the long term, sepsis is also associated with adverse outcomes. Several studies have found that there is an association between sepsis in ELBW infants and neurodevelopmental impairment. Stoll et al conducted a large cohort study among 6093 ELBW infants with a follow-up visit at 18 to 22 months.\(^6\) They concluded that there is an association between a neonatal infection and an increased risk of neurodevelopmental and growth impairment in early childhood. Similar results have been found by Bassler et al.\(^7\) They concluded that neonatal infection, in addition to bronchopulmonary dysplasia, brain injury, and severe retinopathy, further corresponded with an increased risk of a late death or survival with neurosensory impairment. The incidence of adverse neurodevelopmental outcome is estimated to be around 30% of extremely preterm infants surviving to childhood.\(^6,8\)

Improvement in reducing the incidence of sepsis in preterm infants is therefore necessary, considering the adverse outcomes delineated above.

1.2 Clinical presentation

Sepsis is defined as a microbiologically proven infection or a high clinical suspicion on an infection, in the presence of a systemic inflammatory response syndrome (SIRS). The presentation of sepsis in newborn infants born before 37 weeks of gestation can be very diverse and therefore, unlike in other age groups, no specific criteria for the sepsis continuum have been defined.\(^9\) To diagnose a sepsis in preterm infants, physicians principally rely on the observed clinical signs. Overt symptoms may be respiratory distress or significant apnea, cyanosis, hypotension, bradycardia, poor perfusion, acidosis, and lethargy. Nevertheless, nonspecific symptoms, such as feeding intolerance, self-resolving apnea or bradycardia, mild tachypnea or tachycardia, abnormal serum glucose level, or decreased activity, can be the only warning signs for the development of a fulminant clinical deterioration. Furthermore, the physiologic transitional period after birth complicates the interpretation of symptoms. Physicians should therefore always keep in mind that a sepsis may be present in preterm infants with minimal and nonspecific symptoms.\(^10\) Although evidence has indicated that physicians are able to make an accurate judgment based on clinical grounds whether or not an infection is present, sepsis in preterm infants remains a clinical challenge for every doctor working with this category of patients.\(^11,12\) Moreover, microbiologically confirmed sepsis by a positive blood culture is the exception that proves...
the rule; only 20% of the blood cultures drawn after 72 hours of life in preterm infants who are clinically suspected for a sepsis are found to be positive.5

1.3 Hemodynamics

The hemodynamic response of preterm infants to septic shock is much more variable than the response that is seen in adults and older children. Contributing factors in this matter are immature structure and function of cardiomyocytes, limited ability to increase contractility and stroke volume and the transitional physiology seen in newborns.13

Briefly, the hemodynamic response that is seen in newborn infants can be classified in three groups:

1. Hyperdynamic state with a high cardiac output and low systemic vascular resistance; referred to as warm shock;
2. Hypodynamic state with low cardiac output and normal-to-low systemic vascular resistance;
3. Hypodynamic state with low cardiac output and high systemic vascular resistance, referred to as cold shock.

Animal models suggest low cardiac output states in response to neonatal sepsis.14 Contradictorily, de Waal et al. showed a high right and left cardiac output and a low systemic vascular resistance after volume support in preterm infants with sepsis.15 Besides these contradictory findings, hemodynamic states can change during the disease process.16 Therefore, it is difficult to describe the hemodynamic response in preterm infants accurately. Further research is necessary to investigate the hemodynamics in preterm infants with a sepsis.

1.4 Treatment

Treatment of a suspected hemodynamic failure due to sepsis in neonates is based on the interpretation of a combination of clinical and biochemical parameters which are used to assess systemic blood flow and tissue oxygenation. It is demonstrated however, that low systemic blood flow in newborn infants is poorly predicted by clinical parameters such as blood pressure and capillary refill time.17,18 Biochemical parameters as serum lactate and blood gas values, give a better impression of systemic blood flow. These parameters, however, will only disarrange after significant injury has already developed. Furthermore, they have to be obtained invasively and intermittently.19

It is of great importance to adequately identify newborns with low systemic and cerebral blood flow and commence therapy once this is recognized, since serious injury to the brain and to somatic organs can develop due to underperfusion. With the current diagnostic possibilities however, there is a risk of over- and undertreatment of newborn infants with a sepsis. Undertreatment will occur when infants with low cerebral or systemic blood flow are not hypotensive or do not have an increased serum lactate. These infants do not get treated while they are at risk of developing brain injury or organ damage. Overtreatment will occur when infants with hypotension but normal cerebral and systemic blood flow receive treatment such as volume expansion or inotropic agents. In this situation, iatrogenic damage can develop due to adverse side effects. Liet et al investigated the effect of
dopamine administered to hypotensive preterm infants. He found that dopamine can induce increased arterial pulmonary pressure relative to arterial systemic pressure. Caution must therefore be taken in preterm infants who are susceptible of developing persistent pulmonary hypertension. Volume expansion in newborns increases the risks of a patent ductus arteriosus and congestive heart failure and is associated with abnormal neurodevelopmental outcome and adversely affects lung function in the perinatal period.

1.5 Near infrared spectroscopy

Near infrared spectroscopy (NIRS) is a relatively new monitoring method in neonatal intensive care. It was first described by Jöbsis in 1977, but it was not until 1985 that NIRS was first used in a clinical trial in preterm infants born below 32 weeks of gestation. Currently, NIRS is used as a routine clinical monitoring technique in critically ill newborn infants admitted to the NICU of the University Medical Center Groningen (UMCG).

NIRS allows us to continuously measure tissue oxygenation in a non-invasive way. It therefore seems to be a good monitoring technique to assess cerebral and systemic blood flow in addition to the currently used hemodynamic parameters. NIRS measures the regional tissue oxygenation (rSO2). The rSO2 reflects the saturation in a mixed vascular bed, dominated by venules. When simultaneous measurements of the transcutaneous arterial oxygen saturation (SpO2) are collected, the fractional tissue oxygen extraction (FTOE) can be calculated, using the following equation:

\[ \text{FTOE} = \frac{\text{SpO2} - \text{rSO2}}{\text{SpO2}} \]

FTOE is thought to reflect the balance between oxygen supply and oxygen extraction and could therefore be used as an indicator for inadequate tissue perfusion and oxygenation.

1.6 Multi-site near infrared spectroscopy

In several studies, tissue perfusion and oxygenation with NIRS in different somatic tissue beds in addition to the brain (multi-site NIRS) in newborns at risk of circulatory failure have been monitored. Since cerebral blood flow and tissue oxygenation may be preserved by cerebral autoregulation during low systemic blood flow, somatic tissue oxygenation could provide better information about organ perfusion. For example, Hanson et al studied the tissue oxygenation in somatic tissue beds and in the brain in children with acute dehydration. Only the somatic tissue beds showed an increase in rSO2 with rehydration whereas cerebral rSO2 remained unchanged throughout rehydration.

In some of the studies mentioned previously, the findings of NIRS were correlated with clinical and biochemical parameters used in clinical practice to assess systemic blood flow. A strong correlation was found between cerebral, abdominal, and renal tissue oxygenation on one hand and serum lactate and central venous oxygen saturation on the other hand. A combination of cerebral and somatic tissue oxygenation measurements correlated even better with serum lactate. This suggests that multi-site NIRS monitoring could be a better indicator for low systemic blood flow than one site (cerebral) NIRS monitoring only.
Studies evaluating cerebral and somatic tissue oxygenation measured by NIRS in preterm infants below 32 weeks gestation diagnosed with a sepsis have not yet been conducted. Performing these studies could give us a better understanding of the hemodynamic consequences of a sepsis in preterm infants. Furthermore, multi-site NIRS monitoring could possibly be used to identify newborn infants with low systemic blood flow at risk of brain injury and organ damage earlier and more adequate. This could help to guide adequate therapy and thereby to improve the outcome of preterm infants with sepsis.

1.7 Aim

The aim of this observational cohort study was to identify the course of cerebral, renal, and splanchnic tissue oxygen extraction during the first 48 hours in preterm infants diagnosed with a sepsis.

Furthermore, we were interested if the course of cerebral, renal, and splanchnic tissue oxygen extraction could be related to:
- the presence of a positive blood culture;
- the administration of dopamine and/or dobutamine;
- conventionally used hemodynamic parameters.

1.8 Hypothesis

We hypothesized that:
- cerebral, renal, and splanchnic FTOE in infants with a positive blood culture will not differ from infants with a negative blood culture;
- cerebral FTOE is similar in infants who were and infants who were not treated with dopamine and/or dobutamine, attributable to intact cerebral autoregulation. However, we expect higher renal and splanchnic FTOE values in infants treated with dopamine and/or dobutamine, due to a greater deal of circulatory insufficiency and therefore more compromised blood flow to somatic organs;
- cerebral, renal, and splanchnic FTOE relate to the conventionally used hemodynamic parameters.
2. Methods

2.1 Design and patients

We conducted a prospective observational cohort study. As part of the *NEonatal Monitoring of tissue Oxygenation in newborn infants at risk of circulatory failure (NEMO)* study, preterm infants, who were admitted to the NICU of the UMCG between August 2011 and June 2012, were initially selected. Inclusion criteria for the purpose of this study included a gestational age < 32 weeks and a clinically suspected sepsis. After informed consent was given, monitoring with NIRS was started within 24 hours after sepsis work up. Infants with chromosomal or congenital abnormalities, infants with a congenital heart disease and infants who were treated with intensive phototherapy were excluded from the study group.

The protocol for this study was approved by the review board of the UMCG. Written informal parental consent was obtained in all cases.

2.2 Study procedures

Cerebral, renal, and splanchnic rSO2 measurements were recorded continuously for 48 hours after the clinical diagnosis of a sepsis. Only the first 48 hours were recorded, since hemodynamic states tend to progress and change principally during the first 48 hours after commencing treatment for sepsis.\(^\text{16}\)

2.3 Physical principles of NIRS

We used an INVOS 5100C near-infrared spectrometer (Somanetics Corporation, Troy, MI) to measure the regional tissue oxygenation in the brain, the left kidney, and the abdomen using neonatal Somasensors (Somanetics Corporation).

Near infrared light, having a wavelength between 700 and 1000 nm, penetrates biological tissue much better than visible light which covers the wavelength spectrum of 450 – 700 nm.\(^\text{38}\) NIRS is based on the principle that near infrared light is absorbed and reflected by chromophores in the underlying tissue.\(^\text{26}\) The chromophores used most often by NIRS are oxygenated and deoxygenated hemoglobin and cytochrome AA3. The distinct absorption spectra of oxygenated and deoxygenated hemoglobin are shown in Figure 1.

The absorption spectra of oxygenated and deoxygenated hemoglobin are similar at 800 nm, also known as the isobestic point. To determine the ratio of oxygenated and deoxygenated hemoglobin, changes in absorption at two different wavelengths, below and above the isobestic point at 730 and 805 nm, are used. The NIRS spectrometer subsequently calculates the ratio of oxygenated hemoglobin to the total amount of hemoglobin, expressing it as an absolute value: rSO2.
Figure 1. Absorption spectra of oxygenated (HbO2) and deoxygenated (Hb) at different wavelengths.

2.4 NIRS measurements

To measure the cerebral, renal, and splanchnic rSO2, neonatal NIRS-Somasensors were placed on the left frontoparietal side of the newborns head, the left posterior flank between T10 and L2, and below the umbilicus, respectively. Elastic bandages or Mepitel® were used to keep the Somasensors in place and to avoid skin irritation. Before participation into the study, consultation with the attending doctor was done to decide whether or not the abdominal Somasensor could be placed based on the size of the newborn. During the study period, measurements of SpO2 were simultaneously recorded. Subsequently, the fractional tissue oxygen extraction could be calculated, using the following formula: FTOE = (SpO2 – rSO2)/SpO2. All measurements were measured at a frequency of 0.2 Hz and were stored off-line for analysis.

2.5 Clinical and biochemical variables

Clinical and biochemical parameters to assess systemic blood flow and tissue oxygenation were prospectively collected and were stored for off-line analysis. These included heart rate, blood pressure, urinary output, blood gas values (pO2, pCO2, pH, and base excess) and serum lactate. These data were gathered as part of clinical routine. Furthermore, additional data from the patients’ medical charts were gathered, including gestational age, birth weight, postnatal age, gender, APGAR scores and received treatment for circulatory failure (volume expansion and inotropic agents).

2.6 Circulatory failure score

To correlate clinical and biochemical data with NIRS measurements, we calculated mean values of mean arterial blood pressure (MABP), heart rate, cerebral FTOE, renal FTOE, and splanchnic FTOE one hour preceding every blood gas drawing. Every blood gas drawing was defined as a clinical evaluation moment; the number of clinical evaluation moments was
dependent on the clinical condition of each preterm infant. A total circulatory failure score (CFS), indicating the severity of circulatory insufficiency, was calculated for every clinical evaluation moment. The CFS was composed of the following clinical indicators:

- Tachycardia, a heart rate > 180 beats per minute;
- Hypotension, MABP < postmenstrual age;
- Oliguria, diuresis < 1.0 ml/kg/h;
- High serum lactate, > 2.50 mmol/l;
- Metabolic acidosis, pH < 7.30 in the presence of serum HCO₃ < 22 mmol/l or HCO₃ < 24 mmol/l in the presence of a pCO₂ < 4.5 kPa.

In all infants each indicator was scored as 0 (not present) or 1 (present), so that the CFS could range from 0 (no clinical signs of circulatory failure) to 5 (all clinical signs of circulatory failure).

2.7 Data processing and statistics

To identify the course of cerebral, renal, and splanchnic FTOE in the first 48 hours after diagnosis, mean FTOE values were calculated for every 3 hours, creating 16 time periods per infant. Before FTOE values were calculated, rSO₂ measurements were screened for insufficiency. When rSO₂ measurements were missing for more than 1 hour per time period, SpO₂ measurements were adjusted accordingly. Furthermore, when readings of rSO₂ were missing for more than 150 minutes per time period, we considered data to be too insufficient to be used to calculate FTOE values reflecting oxygen extraction for that particular time period.

To analyze the course of cerebral, renal, and splanchnic FTOE between infants with a positive blood culture compared to infants with a negative blood culture and infants who received dopamine and dobutamine compared to infants who did not receive those inotropic agents, mean values of cerebral, renal, and splanchnic FTOE were calculated over 24 hour periods in each infant. Differences in the course of cerebral, renal, and splanchnic FTOE between the groups were analyzed using the Mann Whitney U test.

To evaluate the relation between clinical and biochemical variables on one hand and paired cerebral, renal, and splanchnic FTOE on the other hand, the Spearman’s rank order correlation was calculated.

SPSS 20.0 (SPSS Inc. Chicago, IL) was used for statistical analysis. A p-value of <0.05 was considered significant.
3. Results

Patient characteristics

Fourteen infants were included in this observational cohort study with a mean gestational age of 28 weeks (standard deviation (SD) 2), a mean birth weight of 1088 grams (SD 337) and a mean postnatal age at clinical presentation of 11 days (SD 11). Blood culture was positive in six infants; the blood culture of the remaining eight infants showed no growth. One infant, however, was diagnosed with a rhinovirus pneumonia, in another infant sputum culture was positive for klebsiella and in three infants bacterial growth was found on the tip of the umbilical catheter that had been removed. Fluid administration was administered in five infants and circulatory support by means of dopamine and/or dobutamine in three infants. Two infants died, one infant 29 hours after the onset of sepsis and the other infant two months after birth due to bronchopulmonary dysplasia. Six infants had clinical signs of circulatory failure, defined as a CFS ≥ 1. In two infants, no blood gas drawings were performed during the study period; a CFS of 0 was assigned to these infants (patients 5 and 10). The characteristics of the 14 infants are shown in Table 1.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>GA (weeks)</th>
<th>BW (grams)</th>
<th>PNA (days)</th>
<th>Gender</th>
<th>Apgar</th>
<th>Blood culture</th>
<th>Fluid administration</th>
<th>Dopamine/Dobutamine</th>
<th>Death</th>
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<td>1810</td>
<td>26</td>
<td>M</td>
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GA, gestational age; BW, birth weight; PNA, postnatal age; F, female; M, male; CNS, coagulase-negative staphylococcus; GBS, Group B streptococcus; Staph, staphylococcus; N, no; Y, yes; Max CFS, maximum circulatory failure score

Course of cerebral, renal, and splanchnic tissue oxygen extraction in the first 48 hours after the onset of sepsis

NIRS monitoring was started at a median of 2 hours (range 0 – 21 hours) after the clinical diagnosis of sepsis and was continued in all infants for 48 hours, except for one infant in whom NIRS monitoring was stopped after 24 hours due to clinical deterioration eventually leading to her death, 5 hours later. Abdominal NIRS monitoring was not performed in three infants because the small size of these infants did not allow for the placement of a sensor
below the umbilicus. There were no adverse skin effects of sensor placement in all infants in the 48 hour study period.
As a result of standard care and absent NIRS readings due to inadequate placement of the sensors, we were not able to calculate mean cerebral, renal, and splanchnic rSO2 values for every three hours in every patient. As a result, from the total of 14 x 16 time periods, mean cerebral rSO2 could be calculated for 215, mean renal rSO2 for 195 and mean splanchnic rSO2 for 66 time periods.
The 48 hour course of cerebral, renal, and splanchnic tissue oxygen extraction is shown in Figure 2. Median cerebral, renal, and splanchnic FTOE in the first 24 hours after diagnosis were 0.21 (range -0.03 – 0.60), 0.32 (range 0.04 – 0.83) and 0.55 (range 0.07 – 0.82), respectively. Median cerebral, renal, and splanchnic FTOE values between 24 and 48 hours were 0.22 (range -0.04 – 0.52), 0.34 (range 0.08 – 0.83) and 0.56 (range 0.29 – 0.83), respectively. More variability was observed in splanchnic FTOE in comparison with cerebral and renal FTOE.
The course of cerebral, renal, and splanchnic FTOE in the first 48 hours after the diagnosis of a sepsis. Data are shown in box and whisker plots.

Course of cerebral, renal, and splanchnic tissue oxygen extraction in relation to the presence of a positive blood culture

The course of cerebral, renal, and splanchnic FTOE in relation to blood culture is shown in Figure 3. Infants with a positive blood culture showed a similar cerebral FTOE in the first 48 hours after diagnosis compared with infants with a negative blood culture (median 0.20 vs. 0.23, \( p=0.29 \) within 24 hours; median 0.21 vs. 0.23, \( p=0.68 \) between 24 and 48 hours). Renal FTOE was significantly lower in the first 24 hours after diagnosis in infants with a positive blood culture compared to infants with a negative blood culture (median 0.29 vs. 0.45, \( p=0.01 \)). This difference was not found between 24 and 48 hours (median 0.34 vs. 0.35, \( p=0.77 \)). In addition, no differences were found in splanchnic FTOE between infants with a positive blood culture compared to a negative blood culture (median 0.58 vs. 0.42, \( p=0.54 \) within 24 hours; median 0.49 vs. 0.59, \( p=0.96 \) between 24 and 48 hours).
Figure 3. The course of cerebral, renal, and splanchnic FTOE in the first 24 hours and between 24 and 48 hours after the diagnosis of a sepsis in infants with a negative and positive blood culture. Data are shown in box and whisker plots. * indicates a p<0.05

Course of cerebral, renal, and splanchnic tissue oxygen extraction in relation to the administration of dopamine and dobutamine

Three infants received dopamine and/or dobutamine for circulatory insufficiency during the study period. Two infants only received dopamine and one infant received dopamine as well as dobutamine. Administration of dopamine was already started in one infant at the start of this study and was stopped 34 hours after the start of the study. In the second infant, dopamine was administered nine hours after the start of the study and was continued until after the study period ended. The third infant received dopamine as well as dobutamine. Dobutamine was administered six hours after the start of the study and was stopped 30 hours after the start of the study. Dopamine was started 19 hours after the start of the study and was continued for 11 hours. All three infants received volume expansion as well.
The course of cerebral, renal, and splanchnic FTOE in relation to the administration of dopamine and dobutamine is displayed in Figure 4. Significant differences were seen in cerebral FTOE between infants who did and infants who did not receive dopamine and dobutamine within 24 hours and between 24 and 48 hours after diagnosis (0.32 vs. 0.20, \( p < 0.001 \); 0.25 vs. 0.21, \( p = 0.005 \), respectively). There were no significant differences between these two groups for renal FTOE (0.40 vs. 0.31, \( p = 0.44 \) within 24 hours; 0.25 vs. 0.34, \( p = 0.35 \) between 24 and 48 hours) and splanchnic FTOE (0.44 vs. 0.56, \( p = 0.62 \) in the first 24 hours; 0.55 vs. 0.56, \( p = 0.82 \), between 24 and 48 hours after diagnosis).
Figure 4. The course of cerebral, renal, and splanchnic FTOE in the first 24 hours and between 24 and 48 hours after the diagnosis of a sepsis in infants who received dopamine and dobutamine and infants who did not. Data are shown in box and whisker plots. * indicates a p<0.05

Course of cerebral, renal, and splanchnic tissue oxygen extraction in relation to conventional used hemodynamic parameters

A total of 65 blood gas drawings were performed in the study group during the 48 hour study period with a median of four blood gas drawings per infant (range 0 – 13). Since the amount of blood gases taken was dependent on the clinical condition of an infant, two infants were evaluated as being clinically stable and therefore no blood gas drawings were performed in these infants. Furthermore, lactate measurements were only taken when considered clinically necessary as decided by the attending neonatologist. In total, only four lactate measurements were available. Since no splanchnic FTOE values were available during the one hour preceding the lactate measurement, no correlation coefficient between sFTOE and serum lactate could be calculated.

Table 2 shows the correlation coefficients found between conventional hemodynamic parameters on one hand and cerebral, renal, and splanchnic FTOE values on the other hand. Significant positive correlations were observed between cFTOE and heart rate and sFTOE and pH. A significant negative correlation was found between rFTOE and pH.

Table 2. Non-parametric correlations between cerebral, renal, and splanchnic FTOE and hemodynamic variables.

<table>
<thead>
<tr>
<th></th>
<th>FTOE c r</th>
<th>p-value</th>
<th>FTOE r r</th>
<th>p-value</th>
<th>FTOE s r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCO2</td>
<td>-0.104</td>
<td>0.417</td>
<td>0.017</td>
<td>0.901</td>
<td>-0.342</td>
<td>0.276</td>
</tr>
<tr>
<td>MABP</td>
<td>-0.045</td>
<td>0.739</td>
<td>0.045</td>
<td>0.759</td>
<td>-0.204</td>
<td>0.548</td>
</tr>
<tr>
<td>HR</td>
<td>0.482*</td>
<td>0.000</td>
<td>0.179</td>
<td>0.195</td>
<td>0.486</td>
<td>0.109</td>
</tr>
<tr>
<td>pH</td>
<td>-0.074</td>
<td>0.565</td>
<td>-0.291*</td>
<td>0.033</td>
<td>0.636*</td>
<td>0.026</td>
</tr>
<tr>
<td>Serum lactate</td>
<td>-0.035 (n=4)</td>
<td>0.965</td>
<td>0.174 (n=3)</td>
<td>0.888 (n=0)</td>
<td>0.043</td>
<td>0.895</td>
</tr>
<tr>
<td>Diuresis</td>
<td>0.048</td>
<td>0.707</td>
<td>-0.166</td>
<td>0.231</td>
<td>0.043</td>
<td>0.895</td>
</tr>
</tbody>
</table>

MABP, mean arterial blood pressure; HR = heart rate. * indicates significant correlation.
4. Discussion

We have presented the course of cerebral, renal, and splanchnic FTOE in preterm infants in the first 48 hours after the diagnosis of a clinical sepsis. Furthermore, a significant relation between renal FTOE in the first 24 hours after diagnosis and the presence of a positive blood culture and a significant relation between cerebral FTOE in the first 48 hours after diagnosis and the administration of dopamine and dobutamine was found. Finally, significant positive correlations were seen between cerebral FTOE and heart rate and between splanchnic FTOE and pH. A significant negative correlation was found between renal FTOE and pH.

The first objective of this study was to describe the course of cerebral, renal, and splanchnic FTOE in the first 48 hours after the diagnosis of sepsis. Median cerebral, renal, and splanchnic FTOE values in the first 24 hours after diagnosis were 0.21, 0.32, and 0.55, respectively. Median cerebral, renal, and splanchnic FTOE values between 24 and 48 hours were 0.22, 0.34, and 0.56, respectively. Furthermore, in our study marked variability was observed in splanchnic FTOE in comparison with cerebral and renal FTOE. This has been previously described by Cortez et al. In a study performed previously in our center, a median cerebral FTOE value of 0.20 was found in stable preterm infants on day 15 after birth. This is comparable to the FTOE values we found in this cohort study. A possible explanation for the similarity could be the presence of an adequate cerebral autoregulation (CAR) in these preterm infants. CAR is a property of cerebral arteries to maintain cerebral perfusion at a constant level despite a great deal of variation in blood pressure. Since sufficient oxygen supply to the brain tissue is therefore maintained, oxygen extraction would not vary if CAR is present. Hahn et al conducted a study in preterm infants with a gestational age < 32 weeks and found no association between postnatal inflammation and CAR, suggesting an adequate functioning of CAR in these infants. However, impaired CAR has been demonstrated in sick preterm infants as well. One might argue that the infants in our study group were not circulatory insufficient enough, demonstrated by the low CFS values, to cause an inadequate CAR. No definite conclusions can be drawn on this matter; nevertheless, in our study group cerebral oxygen extraction and therefore cerebral perfusion seems to be comparable to the values previously described in stable preterm infants.

Data on renal and splanchnic FTOE in stable preterm infants are scarce; in a study conducted by Petrova et al., renal FTOE values were calculated for stable preterm infants under nasal positive end expiratory pressure (PEEP). A mean renal FTOE value of 0.23 was found in these infants at a mean postconceptual age of 31.7 weeks. Cortez et al. evaluated the use of splanchnic NIRS monitoring in preterm infants during the first 14 days after birth. A mean splanchnic FTOE of 0.54 was found in stable preterm infants on postnatal day 11 and 0.48 on postnatal day 12. Higher renal and splanchnic FTOE values were found in our study group. The higher FTOE values could be explained by either a decreased perfusion, or an increased oxygen consumption. The hemodynamic consequences of sepsis on somatic organs in the preterm infant are not yet fully understood. However, as mentioned in the introduction of this manuscript, de Waal et al. found low systemic vascular resistance in preterm infants with sepsis treated with volume expansion. This is in contradiction with the higher renal and splanchnic FTOE values we found, which suggests a decreased blood flow and thus high systemic vascular resistance instead. Since warm shock in pediatric patients is mostly observed in the early
stages of sepsis, whereas in more advanced stages of the disease process signs of cold shock are acknowledged, higher FTOE values might indicate this progression of sepsis in our study group.\textsuperscript{47} The higher FTOE values could also be explained by an increased oxygen consumption by the renal and splanchnic tissue beds. In a recent study of Tran et al however, decreased oxygen consumption in the kidney in adult mice with sepsis was observed.\textsuperscript{48} Again, this is in contradiction with the findings of this study. We hypothesize that in this study group, decreased blood flow to the somatic organs due to circulatory insufficiency may explain the higher FTOE values. It is well described that this redistribution of blood can be a protective mechanism during states of hemodynamic instability to preserve cerebral perfusion and thereby oxygen supply to the brain.\textsuperscript{49}

The second objective of this study was to relate the course of cerebral, renal, and splanchnic FTOE to the presence of a positive blood culture. Blood cultures in preterm infants are difficult to withdraw and in clinical practice blood inoculated into culture bottles may often not exceed the 0.5 ml.\textsuperscript{50} One can imagine that these small samples in conjunction with low-density bacteremia, may lead to a substantial risk of not finding a causative organism. As a result, the actual incidence of positive blood cultures in preterm infants who present with signs of sepsis may be underestimated. Therefore, we expected not to find any differences in cerebral, renal, and splanchnic FTOE between infants with a positive and negative blood culture as all these infants showed clinical signs of sepsis. Surprisingly, a significant lower renal FTOE was found in the first 24 hours after diagnosis in infants with a positive blood culture in comparison with infants in whom the blood culture was negative (\(p=0.01\)). No other significant differences were observed between the two groups.

The comparable cerebral FTOE in infants with a positive and infants with a negative blood culture is in conjunction with our hypothesis and underscores the fact that the incidence of positive blood cultures may be underestimated. Furthermore, CAR might have played a role in this matter. The presence of an intact CAR causes cerebral perfusion to be maintained in normal ranges during fluctuations in blood pressure. Even in preterm infants who might be hemodynamically more challenged, this autoregulatory process might be the reason for finding similar cerebral FTOE measurements between the two groups.

Second, infants with a positive blood culture had lower renal FTOE measurements in the first 24 hours after the diagnosis of a sepsis compared to infants with a negative blood culture. Several explanations can be mentioned. First of all, lower renal FTOE values can be explained by increased blood flow to the renal tissue bed. It has been previously suggested by Biban et al. that the early hemodynamic response to sepsis in children consists of a low flow state with increased blood flow to somatic organs, but high vascular resistance represents the later response to sepsis.\textsuperscript{47} It could be speculated that a positive blood culture is related to a more advanced stage of sepsis and that this would be associated with more severe hemodynamic derangements represented by increased vascular resistance. This would be in contradiction with our findings. Secondly, lower renal FTOE may result from decreased oxygen consumption. This has been demonstrated by Tran et al, who found decreased oxygen consumption rates in the kidney from septic adult mice.\textsuperscript{48} This second theory seems most likely to elucidate our findings. However, we would like to stress the fact that the studies mentioned were performed in animal models or older children and therefore the applicability to preterm neonates can be questioned.
Finally, no differences were found in splanchnic FTOE between infants with a positive and negative blood culture. First of all, this could be explained by the great variability found in splanchnic FTOE measurements.40 Second, only a few measurements of splanchnic rSO2 were available and consequently only few splanchnic FTOE values could be calculated. This could have led to an incorrect representation of the results.

The third objective of this study was to relate the course of cerebral, renal, and splanchnic FTOE to the administration of dopamine and dobutamine. Median cerebral FTOE in infants who received dopamine and dobutamine was significantly higher during the entire study period in comparison with infants who were not treated with dopamine and dobutamine. The increased cerebral FTOE in infants who received dopamine and dobutamine could be explained by either cerebral vasoconstriction or a decreased systemic blood flow in the presence of an inadequate CAR, leading to diminished cerebral blood flow (CBF). This could have been the effect of the administered dopamine and dobutamine or could have been caused by the ongoing sepsis.

Dopamine has a principally positive inotropic and a peripheral vasoconstrictive effect in the newborn period, with a probable vasodilatory effect in renal, cerebral, and coronary circulations. Dobutamine exerts its effect mainly through an increase in cardiac output, without causing the same peripheral vasoconstriction observed when using dopamine.51 Since vasoconstriction could have deleterious effects on the cerebral circulation due to decreased cerebral blood flow, recent studies have focused on cerebral hemodynamics in hypotensive preterm infants treated with dopamine. In a recent study in newborn piglets it was found that dopamine causes cerebral vasodilation but does not alter cerebral rSO2 readings; the authors suggest a concurrent increase in cerebral metabolic rate and thus an increased oxygen consumption to be the cause of these findings.52 The higher cerebral FTOE values we found in our study might reflect this increase in oxygen consumption in infants who were treated with dopamine and dobutamine. Furthermore, the ongoing sepsis might have caused the higher cerebral FTOE we found in preterm infants who received dopamine and dobutamine. A possible explanation might be the presence of an impaired CAR in these infants. However, as previously described, it remains unclear whether or not CAR is present in preterm infants with a sepsis. Additionally, Hahn et al. demonstrated in a recent study the possibility of dopamine leading to an impaired CAR.52 All things considered, it is not well understood if CAR in preterm infants with a sepsis treated with dopamine and dobutamine is adequate or not.

Median values of renal FTOE and splanchnic FTOE were not significantly different between the groups during the 48 hour study period. Since the infants treated with dopamine and dobutamine were possibly hemodynamically more insufficient than the infants who did not receive dopamine and dobutamine, one might expect to find increased renal and splanchnic FTOE due to a favorable blood flow to the brain at the expense of somatic organs such as the kidney and the abdomen and thereby preserving cerebral perfusion. This would result in an increased oxygen consumption by the renal and mesenteric tissue and thus a higher renal and splanchnic FTOE. However, direct vasodilatory effects of dopamine and dobutamine on renal and mesenteric arteries were found in neonatal piglets53 and this, on the contrary, could lead to a decrease in renal and splanchnic FTOE values due to increased perfusion. Since no differences were found between infants who did and infants who did not receive dopamine and dobutamine, the two previously described mechanisms might neutralize each other which may have resulted in the observed results. However, these
explanations remain highly speculative, as no direct measurements of organ blood flow were available. Furthermore, we acknowledge that, due to a limited amount of data of renal and splanchnic FTOE, small changes could have remained undetected due to the small sample size.

Our fourth objective was to analyze the relation between cerebral, renal, and splanchnic FTOE on one hand and conventional used hemodynamic parameters on the other hand. A significant positive correlation was found between cerebral FTOE and heart rate and splanchnic FTOE and pH. Furthermore, a negative correlation was found between renal FTOE and pH; no further significant correlations were found. The positive correlation between cerebral FTOE and heart rate has been described before and designates that cerebral FTOE can be related to clinical indicators of systemic blood flow.\textsuperscript{54} To date, no studies have been performed exploring the correlation between renal and splanchnic FTOE and conventional used hemodynamic parameters, other than serum lactate and central venous oxygen saturation.\textsuperscript{35-37} During impaired global tissue perfusion, oxygen delivery to somatic organs might be impaired and could cause tissue acidosis and consequently a fall in pH.\textsuperscript{55} Since we hypothesized that inadequate somatic organ blood flow was also related to an increase in tissue oxygen consumption, we suspected to find a negative correlation between renal and splanchnic FTOE on one hand en pH on the other hand. This theory is supported by our finding of a negative correlation between renal FTOE and pH. However, a positive correlation between splanchnic FTOE and pH was found. We can think of several explanations. First of all, the variability observed in splanchnic FTOE measurements might be the reason that a positive correlation between splanchnic FTOE and pH was found. Second, decreased bowel motility, such as observed during ileus, a known complication in preterm infants with a sepsis, might cause lower oxygen consumption and therefore lower FTOE values. However, these explanations are highly speculative and further research is necessary to investigate this properly. A possible explanation for the lack of correlations that were found is the small amount of measurements performed. Another explanation might be that cerebral, renal, and splanchnic FTOE do not give a good insight in the circulatory status of preterm infants with a sepsis. However, as mentioned previously, several studies found good correlations between cerebral, renal, and splanchnic FTOE on one hand and lactate and central venous oxygen saturation on the other hand, suggesting that multi-site NIRS monitoring might be a good indicator of systemic blood flow.\textsuperscript{35-37} Finally, it can be speculated that FTOE measurements are better and earlier indicators than conventional used hemodynamic parameters for an impaired organ blood flow and that this might be the reason that no correlations were found.

There are several limitations concerning our study. First of all, a relative small number of infants were included in this study. This may have resulted in existing relations and differences remaining undetected, whereas in a larger sample size this would not be the case. However, since we designed this study to be an observational cohort study and did not aim at providing answers but generating hypotheses instead, we belief this design is adequate for this purpose. Second, we would like to stress the fact that NIRS provides an estimation of the regional oxygen supply-demand relationship in mixed venous blood and not a definite and absolute
value of tissue oxygenation. This is demonstrated by our finding of four negative FTOE values in one infant. However, it is possibly not the value at a specific time moment that is clinically important, but the real-time changes in rSO2 instead.56

Third, due to inadequate sensor placement and the changing gas-fluid-surfaces in the splanchnic area, the renal and splanchnic tissue oxygen saturation measurements might not truly reflect the oxygen saturation of the renal and splanchnic tissue bed.57 However, since feasibility of renal and abdominal NIRS monitoring is reported in various studies,33,35,36,40 we believe somatic NIRS monitoring does give a good impression of the renal and splanchnic oxygen saturation.

Fourth and finally, we used blood gas drawings to relate conventional hemodynamic parameters to NIRS measurements. In some infants, no blood gas drawings were performed, while the sicker infants had comparatively more blood gas drawings. This might pose the risk of biased correlation coefficients. However, we decided to use this approach, because we believe that the associations are not infant-bound.
5. Conclusion

This study has presented the course of cerebral, renal, and splanchnic FTOE in preterm infants in the first 48 hours after the diagnosis of a sepsis. Since our study was designed to be an observational cohort study, no definite conclusions about the clinical relevance of our data can be drawn. However, our findings do suggest that preterm infants with a sepsis have a compromised systemic blood flow in order to preserve cerebral perfusion. Lower renal FTOE measurements were found in the first 24 hours after diagnosis of a sepsis in infants with a positive blood culture. This might reflect a true difference due to decreased oxygen consumption in a septic kidney. Furthermore, the administration of dopamine and dobutamine was associated with higher cerebral FTOE values in septic preterm infants during the entire 48 hour study period, possibly caused by an impaired CAR or an increased cerebral metabolic rate due to the administration of dopamine. Since increased oxygen consumption during hypoxic states might lead to cerebral damage, one must keep in mind that prescribing inotropic agents might have negative consequences on the preterm brain. Finally, no strong correlations were found between cerebral, renal, and splanchnic FTOE on one hand and conventionally used hemodynamic parameters on the other hand. Since only a limited amount of measurements were performed, it is difficult to draw definite conclusions about the absence or presence of possibly existing relations. More research in a larger group of patients is necessary to investigate a possible role of multi-site NIRS in preterm infants diagnosed with a clinical sepsis.
6. References


42. Caicedo A, de Smet D, Naulaers G et al. Cerebral tissue oxygenation and regional oxygen saturation can be used to study cerebral autoregulation in prematurely born infants. Pediatr Res 2011;69:548-553.


