General discussion and future perspectives

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Diagnosing circulatory failure in neonates is difficult because modes for invasive hemodynamic monitoring are limited in these small infants and no gold standard for assessing tissue oxygen delivery is available. A more direct continuous measurement of actual tissue oxygen delivery is needed to adequately guide therapeutic interventions aimed at timeously improving impaired tissue oxygen delivery in infants with circulatory failure, in order to improve short-term and long-term outcome. A non-invasive method that aims to measure tissue oxygen delivery and consumption continuously at the bedside is near-infrared spectroscopy (NIRS). However, the clinical additional value in diagnosing and treating critically low tissue oxygen delivery in infants at high risk of circulatory failure remains unclear.

The main aim of this thesis was therefore to explore the potentially additional value of monitoring regional tissue oxygen saturation of multiple organs using near-infrared spectroscopy in the clinical management of infants at high risk of hypoxic-ischemic organ injury due to circulatory failure. Our first aim was to explore the agreement between multisite NIRS measurements and available hemodynamic, biochemical and echocardiographic measurements indicating circulatory failure or abnormal circulation. Our second aim was to explore the effect of commonly used interventions in neonatology on cerebral NIRS measurements. We formulated the following research questions.

(1) What is the association between routine hemodynamic measurements and multisite NIRS measurements in relation to short-term outcome in preterm infants at risk of circulatory failure due to clinical sepsis (Chapter 2)?

(2) How does cardiac output as assessed by Doppler echocardiography correlate with multisite NIRS measurements in preterm infants at risk of circulatory failure due to clinical sepsis (Chapter 3)?

(3) Do echocardiographic parameters of ductal hemodynamic significance relate to multisite NIRS measurements in preterm infants at risk of circulatory failure due to patent ductus arteriosus (Chapter 4)?

(4) Does retrograde blood flow in the ascending or descending aorta signify impaired cerebral or renal tissue oxygen delivery in infants at risk of circulatory failure due to cardiac left-sided obstructive lesions (Chapter 5)?

(5) What is the effect of balloon atrial septostomy on cerebral oxygenation in neonates with transposition of the great arteries (Chapter 6)?

(6) Does treatment with volume expansion improve cerebral oxygenation in preterm infants with clinical signs of poor perfusion (Chapter 7)?

In this discussion, we will first provide answers to our research questions and summarize our main findings. Then we will focus on our main outcomes and compare our outcomes with the available literature. Finally, we will focus on limitations, implications and future perspectives.
Main findings

(1) What is the association between routine hemodynamic measurements and multisite NIRS measurements in relation to short-term outcome in preterm infants with clinical sepsis (Chapter 2)?

To answer this question, we monitored cerebral, renal, and intestinal regional tissue oxygen saturation (rSO$_2$) and clinical signs of circulatory failure during the first 72 hours following sepsis workup in 28 preterm infants with clinical sepsis. Furthermore, we determined the presence of adverse cerebral and intestinal outcome within 14 days of sepsis workup. We found poor inter- and intraindividual associations between multisite NIRS measurements and commonly used clinical signs of circulatory failure. Adverse intestinal and cerebral outcome occurred in four and six infants respectively. In the absence of correcting for multiple testing, cerebral and renal fractional tissue oxygen extraction (FTOE) were, in contrast to clinical signs of circulatory failure, associated with adverse intestinal outcome. In this study, we could not demonstrate an association between multisite NIRS values, or clinical signs of circulatory failure, and adverse cerebral outcome.

(2) How does cardiac output as assessed by Doppler echocardiography correlate with multisite NIRS measurements in preterm infants with clinical sepsis (Chapter 3)?

For the purpose of this study, assessment of cardiac output using Doppler echocardiography and multisite tissue oxygenation using NIRS was performed within 48 hours following sepsis workup, and repeated at least 24 hours later, in preterm infants with clinical sepsis. Echocardiographic measurements of cardiac output, corrected for intra- and extracardiac shunts, were associated with intestinal FTOE, but not with cerebral and renal FTOE, during the first 48 hours after sepsis workup. Changes in cardiac output measurements were not associated with observed changes in FTOE values.

(3) Do echocardiographic parameters of ductal hemodynamic significance relate to multisite NIRS measurements in preterm infants with clinical signs of patent ductus arteriosus (Chapter 4)?

To answer this question, we measured cerebral, renal, and intestinal rSO$_2$ in infants suspected of a hemodynamically significant ductus arteriosus within the first two weeks after birth on the day of echocardiography. We demonstrated that a patent ductus arteriosus did not affect cerebral and renal oxygen saturation and extraction, whether or not the duct was echocardiographically classified as hemodynamically significant. We also demonstrated that retrograde diastolic blood flow in the descending aorta in the presence of a patent ductus arteriosus, compromised neither cerebral nor renal oxygenation. Other echocardiographic variables indicative for a hemodynamically significant ductus arteriosus, such as increased ductal diameter, increased end diastolic blood flow velocity in the left pulmonary artery and increased left atrial to aortic root ratio, were also not associated with impaired cerebral or renal oxygenation. We did, however, observe that in preterm infants with patent ductus arteriosus with
retrograde diastolic blood flow in the descending aorta, median intestinal rSO\textsubscript{2} was nearly half of median intestinal rSO\textsubscript{2} in infants with patent ductus arteriosus without retrograde diastolic blood flow in the descending aorta. This difference did not reach statistical significance as our study was underpowered with regard to intestinal NIRS measurements.

(4) Does retrograde blood flow in the ascending or descending aorta signify impaired cerebral or renal tissue oxygen delivery in infants with cardiac left-sided obstructive lesions (Chapter 5)?

For the purpose of this study, we assessed cerebral and renal tissue oxygen saturation and extraction in infants with cardiac left-sided obstructive lesions during the first four days of admission and correlated both to the presence of retrograde blood flow in the ascending aorta and retrograde diastolic blood flow in the descending aorta. We did not find an adverse effect of retrograde blood flow in the ascending aorta on cerebral oxygenation. Although renal rSO\textsubscript{2} values in infants with cardiac left-sided obstructive lesions were lower than in healthy term infants, we did not find an additional adverse effect of diastolic back flow in the descending aorta.

(5) What is the effect of balloon atrial septostomy on cerebral oxygenation in neonates with transposition of the great arteries (Chapter 6)?

We measured cerebral tissue oxygen saturation and extraction in neonates with transposition of the great arteries. We demonstrated that cerebral rSO\textsubscript{2} improved in accordance with transcutaneous arterial oxygen saturation (spO\textsubscript{2}) shortly after balloon atrial septostomy and that cerebral rSO\textsubscript{2} continued to improve during the next 24 hours, whereas spO\textsubscript{2} remained stable. Furthermore, we demonstrated that, in our series, cerebral rSO\textsubscript{2} was higher at baseline, but lower on the second day of admission, in neonates who did not undergo balloon atrial septostomy compared with neonates who did undergo balloon atrial septostomy.

(6) Does treatment with volume expansion improve cerebral oxygenation in preterm infants with clinical signs of poor perfusion (Chapter 7)?

In this observational study, we assessed cerebral fractional tissue oxygen extraction before, during, and one hour after volume expansion treatment in preterm infants with clinical signs of poor perfusion. Simultaneously, we measured mean arterial blood pressure (MABP). We found a small increase in MABP during and after volume expansion, but no change in cerebral FTOE during or after volume expansion. We also did not observe a simultaneous reduction in cerebral FTOE in the small subgroup of infants who did show an increase in MABP of more than 2 mm Hg after volume expansion.
General discussion

Part I
The first part of this thesis focused on the agreement between clinical signs of circulatory failure, cardiac output, and echocardiographic measurements suggesting hemodynamic compromise or abnormal circulation on one hand and multisite NIRS measurements on the other hand in infants at high risk of hypoxic-ischemic organ injury due to circulatory failure of various causes.

Clinical signs of circulatory failure
Due to the lack of a gold standard for assessing tissue perfusion and oxygenation and limited available options for invasive hemodynamic monitoring, clinical assessment concerning the diagnosis and treatment of impaired tissue perfusion in neonates is based on interpreting several hemodynamic and biochemical indicators of systemic blood flow and tissue oxygen saturation. We explored the association between these clinical signs of circulatory failure and cerebral, renal, and intestinal FTOE as measured by near-infrared spectroscopy during the first 72 hours following sepsis workup in preterm infants at high risk of circulatory failure due to clinical sepsis (Chapter 2). In accordance with clinical practice (1), we chose to combine several frequently used hemodynamic and biochemical indicators of systemic blood flow and tissue oxygenation into one, not validated, but clinical practice reflecting, assessment score: the circulatory failure score (CFS). To our surprise, we never observed significant positive correlations between the CFS and FTOE values, reflecting poor agreement in the estimation of end-organ tissue oxygen delivery between both monitoring methods.

There are several explanations for this poor agreement. The absolute FTOE values might not be good indicators of actual tissue oxygen delivery since it is known that NIRS has its shortcomings concerning precision and accuracy (2) and that rSO₂ and FTOE values are influenced by factors such as gestational age and postnatal age (3-6). On the other hand, clinical signs of circulatory failure might not accurately reflect actual tissue oxygen delivery either (7). This is supported by previous studies that demonstrated poor associations between clinical signs of circulatory failure and systemic blood flow as assessed by Doppler echocardiography (8-10). The fact that we observed both cerebral and renal FTOE, in contrast to clinical signs of circulatory failure, to be associated with adverse intestinal outcome, supports this second explanation. Our results indicate that multisite NIRS monitoring might help to detect critically low tissue oxygen delivery not detected by routine hemodynamic measurements.

Cardiac output and superior vena cava flow using Doppler echocardiography
Within neonatology there is increasing interest in using Doppler echocardiography to assess cardiac output in preterm infants (11,12). Measurements of interest in these infants include, in addition to right ventricular output and left ventricular output, measurements that are less sensitive to the presence of extra- and intracardiac shunts, such as superior vena cava (SVC) flow and descending aorta flow (13,14). Several studies have provided reference values of cardiac output and SVC flow for preterm and term infants at different stages of transition (13-20). These studies have demonstrated associations between
adverse outcome and SVC flow during the first day of life in extremely preterm infants (18-20). Others however have raised concerns concerning the precision and repeatability of SVC flow and cardiac output measurements and found poor associations between cardiac output as measured with Doppler echocardiography and cardiac output as determined by magnetic resonance imaging scans (17,21). Furthermore, an adequate cardiac output does not necessarily reflect an adequate tissue oxygen supply.

In Chapter 3 we explored the associations between SVC flow, right and left ventricular output corrected for patent ductus arteriosus and patent foramen ovale flow respectively and cerebral, renal, and intestinal tissue oxygen delivery as measured by NIRS in preterm infants at risk of low cardiac output and impaired tissue oxygen delivery due to clinical sepsis. Previous studies performed in very low birth weight infants in the first 24 to 48 hours of life found a weak to no positive correlation between SVC flow and cerebral oxygenation (10,22,23). Associations between cardiac output measurements and renal and intestinal tissue oxygenation measurements have never been studied before. We did not find an association between cerebral or renal FTOE and SVC flow nor between cerebral or renal FTOE and cardiac output corrected for shunts in our group. These results indicate that infants with high cerebral or renal tissue oxygen extraction as measured by NIRS, suggestive of impaired cerebral and renal tissue oxygen delivery, during the first 48 hours after sepsis workup cannot be identified by means of cardiac output measurements, including SVC flow.

We did however find a negative correlation between cardiac output corrected for shunts and intestinal FTOE. Our findings therefore suggest that low cardiac output during clinical sepsis is associated with low intestinal oxygen delivery or high intestinal oxygen consumption, possibly as a result of preferential blood flow to the brain.

**Echocardiographic indicators of abnormal circulation due to patent ductus arteriosus or congenital heart disease**

In Chapters 4 and 5 we assessed the association between echocardiographic indicators of abnormal circulation and multisite tissue oxygenation in infants at high risk of circulatory failure due to patent ductus arteriosus (PDA) or cardiac left-sided obstructive lesions (LSOL).

Neonates with congenital heart disease are at risk of impaired neurodevelopmental outcome, possibly due to cerebral hypoxia-ischemia (24-26). In infants with LSOL, which include infants with hypoplastic left heart syndrome, aortic coarctation, aortic interruption and critical aortic stenosis, upper and/or lower body perfusion may be duct dependent. In fetuses, duct dependent filling of the ascending aorta has been associated with decreased cerebrovascular resistance, possibly as compensation for impaired cerebral oxygenation (27). We found that, in neonates with LSOL, the presence of retrograde blood flow in the ascending aorta during the first days of admission was not related to preoperative low cerebral and renal tissue oxygen supply (Chapter 5). This observation challenges the postnatal use of blood flow direction in the ascending aorta as risk factor for impaired cerebral tissue oxygen delivery.

Both preterm infants as well as term infants with PDA are at risk of impaired organ blood flow due to systemic to pulmonary shunting when pulmonary vascular resistance falls after birth. Several echocardiographic variables have been proposed that may signify a PDA with hemodynamic consequences. These
variables include the presence of increased antegrade diastolic blood flow in the left pulmonary artery, an increased left atrial to aortic root ratio and the presence of ductal steal associated with retrograde diastolic blood flow in the descending aorta (28-30). In Chapter 4 we found no differences in cerebral, renal, and intestinal rSO$_2$ or FTOE between preterm infants with and preterm infants without a hemodynamically significant ductus arteriosus (HSDA). Individual echocardiographic signs indicative of a HSDA, such as increased ductal diameter, increased end diastolic blood flow velocity in the left pulmonary artery and increased left atrial to aortic root ratio, were not associated with impaired cerebral or renal oxygenation. These results are in line with other studies that also failed to show an association between cerebral and renal oxygen delivery and a HSDA (31-33). Our results suggest poor agreement between echocardiographic variables that are currently used to identify infants with a HSDA, and actual tissue oxygen delivery.

Several studies have demonstrated that ductal shunting occurs mainly from the postductal, lower body, circulation (30,34-36). Groves et al. reported preserved superior vena cava flow but decreased descending aorta flow in preterm infants with PDA and retrograde diastolic blood flow in the descending aorta as compared with infants with PDA without retrograde diastolic blood flow in the descending aorta during the first 48 hours after birth (34). We did not find an effect of retrograde diastolic blood flow on renal oxygen saturation and extraction in preterm infants with PDA (Chapter 4) nor in infants with LSOL in whom the ductus arteriosus was kept open with prostaglandin E1 (Chapter 5). Therefore, we speculate that, at least in the groups of patients with retrograde diastolic blood flow in the descending aorta that we included, a potentially diminished blood flow in the descending aorta did not lead to compromised renal oxygen delivery.

Some studies have suggested that especially the mesenteric circulation might be at risk of impaired tissue perfusion in the presence of a PDA in preterm infants (33,37). In infants with congenital heart disease there is evidence that suggests that diastolic backflow in the descending aorta is associated with decreased intestinal perfusion. Carlo et al. found that persistent diastolic backflow in the descending aorta was a risk factor for developing necrotizing enterocolitis, probably due to mesenteric circulatory insufficiency as a consequence of a 'steal' phenomenon (38). Therefore, it might be useful to monitor intestinal FTOE in these infants. Regarding the effect of a patent ductus arteriosus on intestinal oxygen saturation and extraction, our results were unfortunately inconclusive because intestinal NIRS measurements were not feasible in most infants due to the presence of an umbilical catheter taped to the infra-umbilical skin, leaving no space for adequate infra-umbilical sensor placement. Nevertheless, we observed median intestinal rSO$_2$ in preterm infants with PDA and retrograde diastolic blood flow in the descending aorta to be nearly half of that in infants with PDA without retrograde diastolic blood flow in the descending aorta. However, the difference did not reach statistical significance as our study was underpowered with regard to intestinal NIRS measurements.

**Overall agreement**

Part I of this thesis focused on the agreement between clinical and echocardiographic indicators of hemodynamic compromise or abnormal circulation and multisite NIRS measurements in infants at high risk of circulatory failure due to various causes. Our main findings are summarized in Table 1.
### Table 1. Main Findings Part I

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Cardiac output</th>
<th>Echocardiographic indicators of abnormal circulation due to PDA or CHD</th>
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<tbody>
<tr>
<td></td>
<td>CFS</td>
<td>Individual clinical signs of circulatory failure</td>
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<td></td>
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<td>not significant</td>
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<td>Preterm infants with clinical sepsis (Chapters 2&amp;3)</td>
<td>Cerebral FTOE</td>
<td>↑ during tachycardia</td>
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<tr>
<td></td>
<td>Renal FTOE</td>
<td>Not significant</td>
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<td></td>
<td>Intestinal FTOE</td>
<td>↑ during hypotension</td>
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<tr>
<td>Preterm infants with clinical signs of PDA (Chapter 4)</td>
<td>Cerebral FTOE</td>
<td>NI</td>
</tr>
<tr>
<td></td>
<td>Renal FTOE</td>
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<td></td>
<td>Intestinal FTOE</td>
<td>NI</td>
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<tr>
<td>Infants with cardiac left-sided obstructive lesions (Chapter 5)</td>
<td>Cerebral FTOE</td>
<td>NI</td>
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<td>Renal FTOE</td>
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<td>Intestinal FTOE</td>
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Abbreviations: PDA, patent ductus arteriosus; CHD, congenital heart disease; CFS, circulatory failure score; SVC, superior vena cava; RVO-PFO, right ventricular output minus patent foramen ovale flow; LVO-DA, left ventricular output minus ductus arteriosus flow; HSDA, hemodynamically significant ductus arteriosus; FTOE, fractional tissue oxygen extraction; NA, not applicable; NI, not investigated.
As stated above, poor agreement was found between multisite NIRS measurements and clinical signs of circulatory failure and echocardiographic indicators of abnormal circulation in preterm infants with clinical sepsis or PDA and in infants with LSOL. Cardiac output corrected for shunts was associated with intestinal, but not cerebral or renal, FTOE in preterm infants with clinical sepsis.

Due to the lack of a gold standard for assessing tissue oxygen delivery, we could not validate multisite NIRS measurements as actual measurement of tissue oxygen delivery. Therefore, as a substitute, we chose to relate them to imperfect indicators of end-organ tissue oxygen delivery and abnormal circulation. However, currently, clinical decisions regarding the diagnosis and therapy of circulatory failure are based on these imperfect indicators. Based on our observations, we cannot conclude which measurement method is best for detecting critically low tissue oxygen delivery. It could be that NIRS monitoring lacks the precision and accuracy to detect tissue hypoxia. It seems probable however that NIRS actually measures end-organ tissue oxygen delivery and therefore adds information to the current diagnostic possibilities. We found some evidence for this assumption in Chapter 2 in which we found cerebral and renal FTOE to be associated with adverse intestinal outcome while clinical signs of circulatory failure never differed between groups.

If NIRS actually measures end-organ tissue oxygen delivery, the poor agreement that was found between clinical and echocardiographic indicators of hemodynamic compromise or abnormal circulation and multisite NIRS measurements indicates that these indicators cannot be used to identify those infants with impaired tissue oxygenation.

Pathophysiology of cardiac output distribution during circulatory failure

In Chapter 3 we found that low cardiac output corrected for shunts in preterm infants with clinical sepsis was associated with increased intestinal, but not cerebral or renal, FTOE. In Chapter 2 we found increased intestinal, but not cerebral or renal, FTOE during episodes of hypotension. In Chapter 4 we observed median intestinal, but not cerebral or renal, rSO₂ in preterm infants with PDA and retrograde diastolic blood flow in the descending aorta to be nearly half of that in infants with PDA without retrograde diastolic blood flow in the descending aorta. These three observations indicate a more decreased regional tissue oxygen delivery in the mesenteric region in comparison to the kidney and the cerebrum. Since sympathetic stress responses will cause a redistribution of cardiac output during early stages of shock in which preferential blood flow to the brain and heart may compromise mesenteric and renal perfusion, and since cerebral blood flow is normally under strict cerebrovascular autoregulation in most newborn infants (39), it is to be expected that the cerebrum will be less vulnerable than the kidneys or the intestines for low output states. Both our observations however, also suggest a higher vulnerability for hypotension and low output states for the intestines than for the kidneys. We can only speculate that the fact that the kidney is a high flow low oxygen utilization organ compared to the intestines, that have a higher metabolic oxygen demand, may make it less vulnerable for low output states than the intestines (40,41). This speculation is supported by the findings of Bronicki et al. who found that extubation led to an increase in venous oxygen saturation and cerebral oxygen saturation in infants who had undergone repair of Tetralogy of Fallot at the expense of a decrease in intestinal rSO₂ while renal rSO₂
remained stable (42). Furthermore, measuring renal rSO\textsubscript{2} may be difficult in preterm infants as the tissue underneath the sensor will encompass more than only the perirenal tissue in very small infants, thereby possibly limiting its use, as compared with the intestinal sensor which will cover mainly intestinal tissue, even in the smallest infants.

In Chapter 3 we further demonstrated a positive correlation between SVC flow and intestinal FTOE, suggesting a decreased intestinal blood flow or an increased intestinal oxygen consumption in the presence of higher SVC flow. We can only speculate that preserved cerebral blood flow may have compromised intestinal blood flow in the presence of limited cardiac output. The negative correlation between the ratio of SVC flow to systemic blood flow and intestinal FTOE that was found supports this hypothesis. Our findings are supported by the findings of Li et al. and Bronicki et al. who found evidence for a tradeoff of cerebral and splanchnic circulation after elevation of p\textsubscript{CO\textsubscript{2}} in neonates after the Norwood procedure and after extubation in neonates after repair of Tetralogy of Fallot (42,43).

**Difficulties concerning multisite NIRS monitoring**

Somatic NIRS monitoring may have several disadvantages as compared with cerebral NIRS monitoring. First, physiological variability of renal and intestinal NIRS measurements has been reported to be higher than that of cerebral NIRS measurements (3,44). Therefore, identifying deterioration in organ tissue oxygen delivery might be difficult as it is to be expected that baseline changes of >20%, which some authors use in monitoring algorithms based on cerebral NIRS monitoring (45), might reflect normal physiological variation. This could possibly also be the explanation for the associations between cerebral, but not renal and intestinal, FTOE and tachycardia and prolonged capillary refill time that we found in Chapter 2, as subtle associations might not be detected due to this high physiological variability. Second, applying extra sensors to the infant may interfere with daily care while handling of infants should be minimal in neonatal intensive care to avoid distress. Third, we found it difficult to apply intestinal NIRS sensors in preterm infants due to the small size of the infant and/or due to the presence of an umbilical catheter taped to the infra-umbilical skin.

**Part II: Improving cerebral tissue oxygen delivery**

Measuring actual cerebral tissue oxygen delivery in addition to current diagnostic possibilities in infants with an indication for treatment may have additional clinical value for two reasons. First, it can help to identify those infants in need of treatment because of impaired cerebral tissue oxygen delivery. Second, it can help to determine if treatment indeed leads to improved cerebral tissue oxygen delivery. In Part II of the thesis we therefore monitored the effect of interventions on cerebral oxygenation in two groups of infants at high risk of adverse neurodevelopmental outcome: 1) infants with transposition of the great arteries and 2) infants with hypotension accompanied by clinical signs of poor perfusion. These conditions may lead to predominantly hypoxic hypoxia and ischemic hypoxia, respectively.
Balloon atrial septostomy

In Chapter 6 we assessed the effect of balloon atrial septostomy (BAS) on cerebral oxygen saturation and extraction in neonates with transposition of the great arteries (TGA). Severity and duration of exposure to preoperative hypoxemia and acidosis have been identified as major risk factors for preoperative brain injury and motor delay in infants with TGA (46,47). BAS aims at relieving hypoxemia by improving mixing of oxygenated and deoxygenated blood at the atrial level and has therefore been suggested to be a neuroprotective intervention (47), although its effect on cerebral oxygenation has never been studied before.

We found cerebral oxygenation to be severely compromised in neonates with TGA with poor interatrial mixing. Median cerebral rSO$_2$ in neonates with TGA was 42% preceding BAS as measured by the INVOS in combination with the pediatric sensor, which is below critically low rSO$_2$ values established in other studies (48-52). Two studies that used either piglet models of graded hypoxia-ischemia or graded hypoxia demonstrated that cerebral rSO$_2$ values below 30-45% for more than 30 minutes led to cerebral lactate accumulation, EEG changes, decreased ATP, and ischemic brain injury (48,49). Dent and Hoffman et al. established cutoff values of prolonged cerebral rSO$_2$ <45-55% postoperatively after Norwood 1 palliation in infants with hypoplastic left heart syndrome to be associated with adverse outcome. They demonstrated that these low cerebral rSO$_2$ values were associated with new or worsened postoperative periventricular leukomalacia and poorer neurodevelopmental outcome at age 4 to 5 (50,52). These thresholds and exposure times may differ depending on the nature of the tissue hypoxia (hypoxic hypoxia vs. ischemic hypoxia). However, also in neonates with TGA who are mainly at risk of hypoxic hypoxia, lower preoperative cerebral rSO$_2$ values have been associated with poorer cognitive and motor scores at the age of 12 months (53). A second study on cerebral oxygenation in neonates with TGA showed a trend toward a less favourable neurodevelopmental outcome in neonates with a preoperative cerebral rSO$_2$ <35%, as compared with neonates with higher preoperative cerebral rSO$_2$ (51). As they used different sensors (INVOS small adult sensor) with a baseline difference of approximately 10% with the sensors used in the studies of Dent and Hoffman et al (INVOS pediatric sensor) (54,55), this critically low value seems similar to previously found values (45%) in patients with hypoplastic left heart syndrome.

BAS led to direct improvement in preductal spO$_2$ and to a delayed improvement in cerebral rSO$_2$ to what are probably more "safe" values of 48%, 2 hours after BAS and 64%, 24 hours after BAS (Chapter 6). BAS could therefore be regarded as a neuroprotective intervention in these neonates. As the occurrence of preoperative periventricular leukomalacia was previously associated with severity and duration of hypoxemia (47), we speculate that earlier application of balloon atrial septostomy could reduce the time of impaired cerebral tissue oxygen saturation and possibly minimize the risk of brain injury in these neonates even more. However, as critically low values in neonates with congenital heart disease have predominantly been established in the post- and intraoperative period in infants with hypoplastic left heart syndrome, more research concerning critically low preoperative values in infants with predominantly hypoxemic conditions as TGA is warranted.

Adverse effects of BAS have also been reported. It has been suggested that BAS is a major risk factor for the development of preoperative brain injury, particularly stroke, in neonates with TGA (56,57).
Mukherjee et al. demonstrated that BAS was associated with nearly twice the risk of clinically recognized stroke in 8681 neonates with TGA (56). However, Applegate and Lim did not find this association in 2000 children with TGA (58). Furthermore, MRI studies have suggested that decreased arterial oxygenation and the presence of an intact ventricular septum, and not BAS, are associated with preoperative brain injury (47,59). Nevertheless, the risk of thrombosis remains a possible adverse risk factor associated with BAS.

Although spO\textsubscript{2} correlated strongly with cerebral rSO\textsubscript{2}, we still identified an infant with, for a cyanotic heart defect, a relatively normal spO\textsubscript{2} of 77% and a very low cerebral rSO\textsubscript{2} of 35%. This suggests that, although low spO\textsubscript{2} identified most infants with impaired cerebral oxygen delivery, monitoring cerebral oxygenation might be of additional value in identifying those infants at risk of adverse outcome due to cerebral hypoxia.

**Volume expansion**

Treated hypotension has been associated with adverse outcome in preterm infants (60). Volume expansion is the treatment of choice for preterm infants with hypotension or other signs of poor perfusion. The purpose of administering volume expansion is to increase cerebral and other organ perfusion, thereby improving tissue oxygen delivery and preventing adverse outcome. Several studies, however, have failed to show an effect of volume expansion on outcome in preterm infants (61,62). There are several explanations for this finding. First, the indication for volume expansion may be inadequate as blood pressure may not adequately reflect cerebral perfusion nor cerebral tissue oxygen delivery (7,8,63,64), resulting in over- and undertreatment of preterm infants with (in)adequate tissue oxygen delivery. Second, volume expansion itself may be inadequate to increase an impaired cerebral oxygen delivery. Bonestroo et al. indeed reported volume expansion to be ineffective in improving cerebral oxygenation in preterm infants with hypotension thereby possibly explaining the absence of an effect of volume expansion on outcome in preterm infants with hypotension (65).

As stated above, hypotension itself might be an inadequate indication for volume expansion as it is often not related to cerebral perfusion. Dempsey et al. demonstrated similar neurodevelopmental outcomes in infants with a mean blood pressure below their gestational age who showed clinical signs of good perfusion compared with normotensive preterm infants (66). Therefore, a more comprehensive approach in which infants are only treated when clinical signs of impaired perfusion are present has been suggested (67). Possibly, only these infants will benefit from volume expansion. In Chapter 7 we therefore assessed the effect of volume expansion on cerebral oxygen delivery as reflected by cerebral FTOE in preterm infants with not only hypotension but also at least one clinical sign of poor perfusion. Although we did find a small rise in MABP following volume expansion, we did not find an effect on cerebral FTOE, suggesting no effect of volume expansion on cerebral oxygen delivery even in infants with clinical signs of poor perfusion. As we did not monitor renal or intestinal oxygen delivery, we cannot exclude that volume expansion in these infants may be beneficial for lower body tissue oxygen delivery.

As some infants had a cerebral FTOE in the normal range, we speculate that clinical signs of poor perfusion may still not identify those infants with low cerebral tissue oxygen delivery. This statement
is supported by the fact that we also did not find associations between clinical signs of poor perfusion and cerebral FTOE in preterm infants with clinical sepsis (Chapter 2) and by the fact that part of the infants that were included still had a cerebral FTOE in the normal range. We speculate that a comprehensive approach in identifying infants with hypotension and clinical signs of circulatory failure with actual impaired end-organ tissue oxygen delivery should include measurements of actual end-organ tissue oxygen delivery such as cerebral FTOE. A suggestion that is supported by the recent study of Alderliesten et al. that showed that not hypotension but low cerebral oxygenation was related to lower neurodevelopmental outcome at the age of 18 months in preterm infants without PDA treated for hypotension and their matched controls (68). A randomized controlled trial to investigate the effect of volume expansion in preterm infants with signs of poor perfusion combined with a proven affected cerebral oxygen delivery may be warranted.

Difficulties concerning individual treatment decision making based on cerebral NIRS monitoring

In Chapters 6 and 7 we demonstrated a beneficial effect of balloon atrial septostomy and no effect of volume expansion on cerebral oxygenation in neonates with transposition of the great arteries and preterm infants with clinical signs of poor perfusion respectively. We speculated that in both groups of infants, cerebral NIRS monitoring might help to identify those infants with compromised cerebral oxygenation in need of treatment. However, concerns have been raised regarding the accuracy and precision of cerebral rSO$_2$ as measured by NIRS. Previous studies have described a high replacement variability with limits of agreement of up to 18% (55,69,70). Therefore, one should be careful when making clinical decisions regarding individual patients based on absolute NIRS values. Still, evidence is accumulating that suggests that critically low values as measured by NIRS are present (50-53,68,71-83), although these thresholds may vary according to the group and nature of the risk studied.

Limitations of this thesis

The most important limitation of this thesis is an important limitation of neonatal intensive care as there is no gold standard of actual organ tissue oxygen delivery in neonates. The results of this thesis are therefore based on the associations between imperfect indicators of tissue oxygen delivery and abnormal circulation. These, however, are the available monitoring methods that can non-invasively be used to estimate tissue oxygenation and that are currently widely used in neonatal intensive care. Second, as all included chapters in this thesis were hypothesis-generating in nature, we did not always correct for multiple testing. Therefore, we might have found significant results due to multiple testing. Third, all included studies are single center studies with small sample sizes limiting generalisability. Fourth, we included heterogenous groups of infants. We do, however, believe that the heterogeneity of the included groups of infants reflects clinical practice and that it therefore increases the applicability of our results. Fifth, except for Chapter 2, we did not relate our findings to short- or long-term outcome and are therefore unable to define critical thresholds leading to organ damage.
Conclusions, implications and future perspectives
The aim of this thesis was not to establish near-infrared spectroscopy as a monitoring tool in neonatology, but to explore its usefulness in the detection of circulatory failure and in the monitoring of treatment effects in newborn infants at high risk of circulatory failure. We can therefore not draw firm conclusions concerning the additional value of NIRS in diagnosing circulatory failure. In this thesis however, we found poor agreement between multisite NIRS values and other techniques suggesting a compromised tissue perfusion or abnormal circulation as clinical signs of circulatory failure and Doppler echocardiography. This leaves the possibility that multisite NIRS monitoring might indeed give additional information concerning critically low tissue oxygen delivery leading to organ damage. A suggestion that is supported by the association between adverse short-term intestinal outcome and NIRS measurements that was found in Chapter 2 and by increasing evidence concerning the association between NIRS measurements and adverse outcomes in various patient groups (50-53,68,71-83). Furthermore, we found a beneficial and no effect respectively of two interventions that were previously thought to be beneficial for cerebral oxygen supply. Our findings in Part II may have implications for the clinical care of neonates with transposition of the great arteries and preterm infants with clinical signs of poor perfusion. They support the early application of balloon atrial septostomy in neonates with persistent hypoxemia and acidosis due to poor interatrial mixing to decrease the duration of severely impaired cerebral oxygenation, since increasing evidence suggests that these critically low cerebral rSO$_2$ values are associated with impaired neurodevelopmental outcome in neonates with transposition of the great arteries (51,53). Furthermore, they support a more comprehensive diagnostic approach in identifying those infants in need of volume expansion to improve cerebral oxygen delivery as no effect was found on cerebral oxygenation after volume expansion in infants with clinical signs of poor perfusion. Future research should focus on the addition of NIRS to diagnostic models to determine if volume expansion, and other treatments that may improve cerebral oxygen delivery as red blood cell transfusions and inotropes, are able to improve cerebral oxygen delivery in infants whose cerebral oxygenation is impaired.

Our findings in Part I do not have direct implications for clinical care, but predominantly have implications for future research. Our results suggest a possible additional value of NIRS as a non-invasive monitor in detecting critically low tissue oxygen delivery compared to available non invasive methods. As critically low NIRS values may differ concerning the etiology of circulatory failure, larger groups of infants with similar clinical pathology (i.e. clinical sepsis, patent ductus arteriosus, congenital heart disease) should be included to determine critically low and high absolute values and baseline changes of cerebral, renal, and intestinal rSO$_2$ and FTOE associated with adverse outcome. When critically low values have been defined, randomized controlled trials are warranted to first determine the safety and next the additional value of treatment strategies to keep NIRS values within these predefined limits. In preterm infants during the first few days of life, such a RCT is now being performed (84). When these randomized clinical trials demonstrate that NIRS monitoring contributes to the early detection of tissue hypoxia and ischemia and improved short-term and long-term outcome, NIRS can be established as a routine monitoring tool in neonatal intensive care.
References


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