**Dissertation**

# The impact of glucose and the acid-base metabolism on the cerebral oxygenation of preterm and term neonates during the immediate transition after birth
## - an observational study

submitted by

**Dr. med. univ.**

**Mattersberger Christian**

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**Division of Neonatology**
**Department of Paediatrics and Adolescent Medicine**

under the Supervision of

**Assoz. Prof. Priv.-Doz. Dr.med.univ. Gerhard Pichler**

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# *Declaration*

*I hereby declare that this dissertation is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this dissertation. Due acknowledgement has been made in the text to all other materials used. Throughout this dissertation and in all related publications I followed the guidelines of "Good Scientific Practice".*

*Graz, 01.08.2021* *Mattersberger Christian*

## *Preface*

This dissertation offers an overview of my own original scientific work. Certain parts of it have already been published in the following article in the "Journal of Pediatrics & Frontiers in Pediatrics" before the preparation of this thesis was finally completed:

1. **C. Mattersberger , N. Baik-Schneditz, B. Schwaberger, G. M. Schmölzer, L. Mileder, E. Pichler-Stachl, B. Urlesberger , G Pichler**
   *Blood Glucose and Cerebral Tissue Oxygenation Immediately after Birth- An Observational Study.*
   **Institution:** Division of Neonatology; Research Unit for Neonatal Micro- and Macrocirculation, Department of Paediatrics, Medical University of Graz, Graz, Austria;
   Centre for the Studies of Asphyxia and Resuscitation, Royal Alexandra Hospital; and Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada
   The Journal of Pediatrics 2018 Sep; 200:19-23.

2. **C. Mattersberger, G. M. Schmölzer, B. Urlesberger, G. Pichler**
   *Blood Glucose and Lactate Levels and Cerebral Oxygenation in Preterm and Term Neonates-A Systematic Qualitative Review of the Literature.*
   **Institution:** Division of Neonatology; Research Unit for Neonatal Micro- and Macrocirculation, Department of Paediatrics, Medical University of Graz, Graz, Austria;
   Centre for the Studies of Asphyxia and Resuscitation, Royal Alexandra Hospital; and Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada
   Frontiers in Pediatrics 2020 Jul 29;8:361.

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*Disclosure:*

The sponsor had no involvement in (1) the study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

The authors have no conflicts of interest to disclose.

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## Abbreviations

| | |
|---|---|
| ARM | autoregulation mechanism |
| BE | base excess |
| BIC | bicarbonate |
| bpm | beats per minute |
| CBF | cerebral blood flow |
| CO | cardiac output |
| $crSO_2$ | cerebral regional oxygen saturation |
| CVR | cerebral vascular resistance |
| DO2 | oxygen delivery |
| EEG | electroencephalogram |
| FTOE | fractional tissue oxygen extraction |
| GLU | blood glucose level |
| HGB | hemoglobin |
| HHb | deoxyhemoglobin |
| HR | heart rate |
| IVC | inferior vena cava |
| LAC | lactate level |
| NIRS | near infrared spectroscopy |
| MABP | mean arterial blood pressure |
| O2Hb | oxyhemoglobin |
| pH | pH value |
| PVR | pulmonary vascular resistance |
| RR | blood pressure |
| $SpO_2$ | arterial oxygen saturation |
| SV | stroke volume |
| SVC | superior vena cava |
| tHb | total hemoglobin concentration |
| VO2 | oxygen consumption |

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# 1 Zusammenfassung

## 1.1 Hintergrund

Der zerebrale Autoregulationsmechanismus reguliert die Blutversorgung und die damit verbundene Sauerstoffversorgung des Gehirnes je nach Bedarf. Dieser Mechanismus und dessen jeweilige Einflussfaktoren sind bis heute nicht zur Gänze geklärt. Aktuelle Studien über Einfluss der zerebralen Sauerstoffversorgung von Neugeborenen beinhalten, zusätzlich zu den bereits bekannten kardiovaskulären sowie respiratorischen Einflussfaktoren, den Blutzuckerspiegel als metabolische Komponente *[Blutglukose-Spiegel (GLU)]*. Studien legen nahe, dass weitere metabolische Komponenten *[Laktat-level (LAC), pH-Wert (pH), Base-Excess (BE) und Bikarbonat (BIC)]* ebenfalls einen Einfluss auf den zerebralen Autoregulationsmechanismus und damit letztendlich auf die Sauerstoffversorgung des Gehirnes *[zerebral-regionale Sauerstoffsättigung (crSO2), zerebral fraktionierte Gewebssauerstoff Extraktion (FTOE)]* bei Neugeborenen haben könnten. Ziel dieser Dissertation ist es, mögliche Zusammenhänge zwischen kapillar gemessenen Blutglukose und Parameter des Säure-Base-Stoffwechsels und der zerebralen Sauerstoffversorgung während des Adaptationprozesses, direkt nach der Geburt, bei früh- und reifgeborenen Neugeborenen zu untersuchen.

## 1.2 Material und Methodik

Es wurde eine prospektive Beobachtungsstudie durchgeführt. Für die vorliegende Analyse wurden sekundäre Outcome-Parameter herangezogen. Früh- und reifgeborene Neugeborene, die durch einen Kaiserschnitt geboren wurden, wurden inkludiert, wenn i) eine zerebrale Nahinfrarot-spektrometrische Messung während der 15. Lebensminute nach der Geburt und ii) eine kapillare Blutanalyse zur Bestimmung der Blutglukose und Säure-Base-Stoffwechsel Parameter zwischen der 10. bis 20. Minute nach der Geburt,

durchgeführt wurden. Die Sauerstoffsättigung ($SpO^2$) sowie Herzfrequenz (HR) wurden mittels Pulsoximeter routinemäßig bestimmt. Zur Bestimmung potentieller Assoziationen wurden Korrelationsanalysen zwischen der Blutglukose und den einzelnen Parameter des Säure-Basen-Stoffwechsels und der zerebralen Oxygenierung durchgeführt.

## *1.3 Ergebnisse*

Von den 224 gemessenen Neugeborenen, die in die prospektive Beobachtungsstudie eingeschlossen wurden, konnten 36 Frühgeborene [Gestationsalter: 34.1 Schwangerschaftswoche (29.8-36.7), Geburtsgewicht: 1935g (1054-3006)] und 116 Reifgeborene [Gestationsalter: 38.9 Schwangerschaftswoche (37.0-41.4), Geburtsgewicht: 3235g (2090-4466)] Neugeborene in die vorliegende Analyse inkludiert werden. Der mediane crSO2 und FTOE Wert bei frühgeborenen Neugeborenen in der 15 Minute nach der Geburt betrug 83% (45-95) und 0.11 (0.01-0.47) und bei reifgeborenen Neugeborenen 83% (54-95) und 0.13 (0.01-0.41). Hohe GLU und LAC Werte sowie niedrige pH und BIC Werte zeigten einen signifikanten Zusammenhang mit einer niedrigen crSO2 sowie hohen FTOE Werten mit Ausnahme von BIC und FTOE welche jedoch einen Trend in Richtung eines positiven Zusammenhanges bei frühgeborenen Neugeborenen zeigten. Bei reifengeborenen Neugeborenen zeigte sich ein negativer signifikanter Zusammenhang zwischen GLU und der crSO2 sowie ein positiver signifikanter Zusammenhang zwischen BIC und FTOE. Weiters zeigte sich ein Trend in Richtung eines positiven Zusammenhanges zwischen pH und BE mit der FTOE sowie ein Trend in Richtung eines negativen Zusammenhanges zwischen BIC und crSO2.

## *1.4 Diskussion*

Es bestehen signifikante Zusammenhänge zwischen der Blutglukose und den untersuchten Parametern des Säure-Basen-Stoffwechsels und der zerebralen Sauerstoffversorgung sowohl bei früh- als auch reifgeborenen Neugeborenen während der Adaptation unmittelbar nach der Geburt. Frühgeborene Neugeborene haben im Vergleich zu reifen Neugeborenen ausgeprägtere Zusammenhänge.

# 2 Abstract

## 2.1 Objective

The cerebral autoregulation mechanism regulates the cerebral blood supply which depends on the oxygen demand of the brain. Its mechanisms and determining factors are currently not completely understood. Cardiovascular and respiratory components are still already known. Various studies on neonates reported that the blood-glucose-level (GLU) can have an impact on cerebral blood flow and subsequently on the cerebral oxygenation *[cerebral-regional-Oxygen-Saturation (crSO2) and cerebral Fractional-Tissue-Oxygen-Extraction (FTOE)]*. Further, current studies demonstrate that components of the acid-base-metabolism *[lactate (LAC), pH-value (pH), base-excess (BE), and bicarbonate (BIC)]* can also have an impact on the cerebral oxygenation in neonates. This dissertation aims at investigating potential associations between measured blood-glucose and parameters of the acid-base-metabolism and the cerebral oxygenation in preterm and term neonates during the immediate transition after birth.

## 2.2 Methods

A prospective observational study was performed and secondary outcome parameters were analyzed in the present study. Preterm and term neonates born by Cesarean section were included, for whom i) cerebral near-infrared-spectroscopy (NIRS) measurements were performed at the 15th minute after birth and ii) capillary measured blood-glucose and parameters of the acid-base-metabolism were taken between the 10th and 20th minute after birth. Routine monitoring was performed with pulse-oximetry [arterial-oxygen-saturation

($SpO^2$) and heart rate (HR)]. Correlation analyses were performed to investigate potential associations between the measured blood-glucose and parameters of the acid-base-metabolism and the cerebral oxygenation.

## 2.3 Results

**Results:** Out of 224 eligible neonates, who were included in the prospective observational study, 36 preterm neonates [Gestational age: 34.1 weeks (29.8-36.7), Birth weight: 1935g (1054-3006)] and 116 term neonates [Gestational age: 38.9 weeks (37.0-41.4), Birth weight: 3235 g (2090-4466)] fulfilled the inclusion criteria. Median crSO2 values at 15 minutes after birth were 83% (45-95) in preterm neonates and 83% (54-95) in term neonates. Median FTOE values at 15 minutes after birth were 0.11 (0.01-0.47) in preterm neonates and 0.13 (0.01-0.41) in term neonates. In preterm neonates, higher GLU and LAC values and lower pH values were associated with lower crSO2 and higher FTOE. BIC was significantly positively associated with crSO2. Only GLU was significantly negatively associated with the crSO2, and BIC was significantly positively associated with the FTOE in term neonates.

## 2.4 Conclusion

There are associations between the blood-glucose and the parameters of the acid-base metabolism and cerebral oxygenation in preterm and term neonates, but there associations are more pronounced in preterm neonates.

# 3 Introduction

## 3.1 Fetal cardiovascular physiology

The developing cardiovascular system of the fetus differ from the neonatal and adult circulations and undergoes enormous changes during fetal life and during the immediate transition after birth. The understanding of the physiology of the fetal circulation is crucial for the interpretation of hemodynamic assessments.[1] During fetal life, the circulation can be categorized into two parallel circuits with equal left and right ventricle pressures.[2] The placenta enriches the fetal blood with oxygen and nutrients. This is why the blood in the umbilical vein has the highest oxygen saturation in comparison to the blood of the rest of fetal circulation.[1,3] The oxygenated and nutrient-enriched blood from the placenta passes from the umbilical vein towards the neonatal heart through the liver or the *ductus venosus*, whereby the higher proportion passes through the liver.[4,5] The blood supply of the liver differs between the right and left liver lobe. The umbilical vein (UV) primarily supplies the left liver lobe, while the oxygen- and nutrient-depleted blood from the portal vein primarily serves the right liver lobe.[4] The blood of both lobes accumulates into the inferior cava vein before it reaches the right atrium. The blood of the *superior vena cava* (SVC) and *inferior vena cava* (IVC) enters the right *atrium*, and the thus enriched blood from the *inferior cava vein* is directed across the *foramen oval* to the left *atrium*.[3] A part of the right atrial blood supply, mainly consisting of the blood from the SVC, reaches the right ventricle and courses through the pulmonary trunk.[5] The blood flow through the lung is during the fetal period limited because of the high pulmonary vascular resistance (PVR) and is shunted through the ductus arteriosus into the descending aorta.[3] The intrapulmonary fluid is important for the development of the fetal lung and partly causal for the high PVR.[6,7] The relatively low oxygenated blood from the right ventricle supplies the lower body, while the relatively highly oxygenated blood from the left ventricle supplies the upper body, including the brain and coronary arteries.[3,8] To finally complete the circuit, the deoxygenated and nutrient-depleted blood passes through the two umbilical arteries to the placenta for the necessary replenishment with oxygen and nutrients.[6]

### 3.2 Physiological changes during the immediate transition

The transition from the fetal to the neonatal life is a rapid, complex process to ensure neonatal survival without the placenta.[3] During the adaptation, immediately after birth, the cardiovascular and respiratory system undergoes enormous changes including the necessary independence of the neonate to the placenta function. The primary aim of the adaptation is to ensure the blood supply and its related oxygenation of the vital organs during these enormous changes.[2] During these changes the neonatal lung takes over the function of the placenta.[8] Respiratory changes require anatomical and physiological adjustments.[9] Prior to the transition, the content of the lung fluid changes as a reaction to the cortisol induced surfactant production.[3,7] As the fetal lungs do not contribute to intrauterine oxygenation, there are several shunts to direct the blood away from the fetal lung.[3] Until the beginning of neonatal breathing, the pulmonary vascular resistance (PVR) decreases dramatically with a subsequent tenfold increase of pulmonary blood flow.[8] This effect is the result of lung inflation, oxygen and carbon dioxide tension changes of the intrapulmonary blood and other impact factors.[3,8] These changes lead to an increasing return of blood to the left atrium with consequent increase pressure in the left atrium above the pressure in the right atrium.[8] During and after birth, the lung must absorb the amniotic fluid to increase the alveolar airspace and enable it to become an efficient gas exchange organ.[7] Additionally, after cord clamping with subsequent elimination of the low resistant placenta, the systemic vascular resistance increases. All these complex changes lead to closure of the *foramen ovale*.[3] Subsequently, the progressive increase of oxygen in the neonatal blood leads to a progressive obliteration of the *ductus arteriosus*.[8] In contrast, the *foramen ovale* can remain open for years and is mostly asymptomatic.[10] However, a persistent *ductus arteriosus* is possible and more frequent in preterm neonates compared to term neonates.[11] Furthermore, a hemodynamic significantly relevant persistent *ductus arteriosus* is associated with neonatal morbidity.[11] Additionally the *ductus venosus* begins to obliterate whereby, the obliteration time of the ductus venosus depends on the week of gestation. It closes sooner in neonates with higher gestational age.[12] A widely used definition of the completion of the transition is the closure of the ductus.[13]

As described above, the fundamental aim of the adaptation process is to maintain an adequate oxygen supply during enormous cardiovascular and respiratory changes and its related independence of the neonate from the function of the placenta. That’s why, high priority vital organs were preferentially supplied with oxygen and nutrients enriched blood.

Consequently, blood flow toward vital organs is preserved by local vasodilatation, while non-vital organs tend to constrict in order to redistribute the blood mainly from the splanchnic vasculature.[2] This adaptation process is a complex mechanism and failure during the immediate transition after birth is possible and can lead to irreversible damages.

### 3.3 The neonatal delivery and the immediate transition after birth

The immediate transition after birth during adaptation is a highly complicated period. Approximately 99% of neonates start with spontaneous breathing within the first minute after birth without the need for basic resuscitation.[14] Of those needing help, a minority, approximately 16%, requires basic resuscitation including stimulation, suctioning, or mask ventilation.[14] The majority of ventilated neonates develop spontaneous breathing within 20 minutes.[15] Only 20% of the ventilated newborn neonates need an intubation.[15] Different maternal risk factors (i.e. infection, hypertension, and oligohydramnios) and neonatal risk factors (i.e. maturity born neonates, meconium-stained amniotic fluid, shoulder dystocia) are associated with an increased risk for requirement of respiratory support, whereby prematurity and meconium-stained amniotic fluid are considered to be the main risk factors for conditions requiring these kinds of support.[16] In neonates born by Cesarean section, the risk for respiratory support increases with decreased gestational age.[17] Nearly 12% of all newborn neonates are preterm neonates.[18] Further, decreased birth weight and severe malformations represent further risk factors for supportive care.[15] Despite constant improvement in medical techniques and medical care of preterm and term neonates, complications remain a problem in this vulnerable population.[19] During the adaptation, cerebral complications are possible and the risk of cerebral complications increases with decreased gestational age.[19] Between 10 and 15% of very preterm neonates will develop complications such as cerebral palsy or cognitive deficits.[20] Protective mechanisms, such as the cerebral autoregulation mechanism, have a crucial role in the prevention of irreversible damage to the neonatal brain.[21]

### 3.4 The cerebral autoregulation mechanism (ARM)

The aim of the cerebral ARM is the maintenance of a constant cerebral blood supply despite fluctuations in blood pressure to protect the brain from hyperperfusion or hypoperfusion and their related consequences. A sufficient working ARM can additionally be characterized as an adequate balancer of oxygen delivery (DO2) and oxygen consumption (VO2) regulated through cerebral blood flow (CBF).[2,21,22,23] The CBF depends on the cerebral perfusion pressure (CPP), which represents the pressure gradient from artery to vein and the cerebral vascular resistance (CVR). The CVR depends on different parameters, such as the diameters of arteries and arterioles, and blood viscosity, and must be overcome to create a blood flow in the cerebral vessels.[23] The cerebral ARM progressively improves during intrauterine development from the 23rd to the 33rd week of gestation.[21]

The capacity of the cerebral ARM and the resulting cerebral blood supply depends on the vasoreactivity, where the contractile responses of the vascular walls are initiated by nerve activity, circulating hormones, and paracrine signals from the perivascular tissue and immune cells.[24] The cerebral ARM and its capacity can be described as the relation between mean arterial blood pressure and cerebral blood flow. (see **Figure 1**) In a physiologic status, this relation forms a sigmoidal curve. The flat area, described as autoregulatory plateau or area with pressure reactivity, represents the capacity of the cerebral ARM to maintain the cerebral blood flow despite fluctuation in arterial blood pressure. Above the upper limit or below the lower limit of the autoregulatory plateau, the CBF is passive to blood pressure due to impaired vasoreactivity.[21] A further important clinical parameter is the critical closing pressure (CrCP), which represent the imbalance between intracerebral pressure and vascular wall tension. Decrease of arterial blood pressure below the critical closing pressure leads to a collapses of the cerebral arteries with following interruption of blood flow. The CrCP, predictable through the Aaslid formula, is a variable point and decreases with decreasing ABP and increases with gradual hypocapnia or the week of gestation.[21,25,26]

This sigmoidal relationship between the CBF and the arterial blood pressure demonstrate a well-functioning status of the ARM. Against them the passive pressure principle (PPP) describes a linear relationship between the arterial blood pressure and the CBF. This pathological status increases the risk of cerebral injury and/or persistent neurological disability.[21] Further, high coherence between cerebral oxygenation and arterial blood pressure indicates an impaired ARM, which is also associated with long-time neurologic impairment or death.[27] Optimizing the MABP and the CBF to maximize vasoreactivity may reduce the risk of brain injury in neonates.[21] A more detailed description of the pathophysiology of an impaired ARM is described in **section 4.6**.

The cerebral ARM and its resulting cerebral oxygen saturation is complex and is still not completely understood. Different maternal and neonatal factors have an impact on the cerebral oxygen supply and oxygen consumption and are described in detail in **section 4.7**.[28,29]

Understanding the physiological and pathophysiological mechanisms of the cerebral ARM is crucial. This knowledge can be used to augment the autoregulatory capacity to prevent pressure passivity (see **section 4.6**) and its resulting neurologic impairments in neonates.[21]

### *3.5 Measuring the cerebral autoregulation mechanism*

There are currently different options to measuring the cerebral ARM. Each method has different advantages and disadvantages. Methods for quantifying the state of the autoregulatory system have evolved over time. The earlier approaches to measure the cerebral ARM used positron emission tomography (PET) or 133Xe clearance. However, these techniques are limited because of the lack of longitudinal continuous monitoring, radiation exposure, or its direct impact on the cerebral oxygen supply or consumption, and have therefore been replaced with newer methods.[22] Newer techniques enable indirect measurements of the cerebral ARM. Cerebral ultrasound enables the measurement of CBF velocity, whereas near-infrared spectroscopy (NIRS) allows measurement of the cerebral regional oxygen saturation.[19,30,31] Combinations of different techniques, such as NIRS and pulse oximetry, enable the CBF to be derived.[32,33] These improved techniques are non-invasive and enable real-time measurements during the immediate transition after birth.[34] Through an increase in medical techniques, real-time measurements of the cerebral blood supply and cerebral ARM are becoming possible and therefore allow potential impairments to be detected before irreversible cerebral damage occurs.

### *3.6 Pathophysiology of impaired cerebral ARM*

An impairment of the cerebral ARM can lead to both hypo- and hyperperfusion, which can increase the risk of injury with lasting neurologic disability.[21] As described already, this impairment of the ARM is called “pressure passivity“ (PPP) and is described as a linear correlation between the arterial blood pressure and the cerebral blood flow or the cerebral oxygenation.[21,27] Limitations in autoregulatory capacity of the cerebral ARM lead to an increased risk of cerebral ischemia during low blood pressure, and cerebral haemorrhage during high blood pressure.[23] The PPP was first detected in neonates suffering from asphyxia during birth, and in neonates with a respiratory distress syndrome.[35] Impairments of the cerebral ARM in neonates are possible and occur more frequently in preterm neonates, neonates with asphyxia and neonates with a congenital heart disease.[21] Neonatal and maternal factors can lead to an impaired cerebral ARM in neonates.[28] Reasons for an increased incidence of PPP in neonates are the incomplete development of the cerebral ARM particularly in preterm neonates, differences in consume/size relation of the neonatal brain, and differences in the autoregulatory capacity of cardiac cycle changes.[21,36] Further impact factors which increase the risk of impaired cerebral autoregulation mechanism are described in more detail in **section 4.7**.

A further important pathophysiological problem of an impaired cerebral ARM is the effect of cyclic disturbance during hemodynamic changes. These disturbances can result in a cycle of ischemia and reperfusion. This cycle leads to an inflammation with subsequent increase in oxygen demand and increased risk of cerebral injury during the next ischemic period in the neonatal brain.[22] A variety of factors or conditions have a disturbing effect on the cerebral ARM and can lead to an impaired ARM.

### 3.7 Factors disturbing the cerebral autoregulation mechanism

If the cerebral ARM is impaired, the compensatory effect fails. Consequently, a hypotensive or hypertensive condition leads to a reduced or increased CBF with possible initial imbalance between oxygen delivery and oxygen consumption.[2] Different factors have an impact on the capacity of the cerebral ARM and its resulting cerebral oxygenation.

An important factor for the capacity of the ARM is the development status of the cerebral ARM. Animal studies suggest the development of the cerebral ARM begins at approximately two-thirds of gestation. Following this, extreme preterm human neonates (<26-27 weeks of gestation) may lack the necessary arterial tone to regulate the cerebral blood flow.[36] Additionally, preterm neonates with an incompletely developed cerebral vascular system of the germinal matrix or white matter vascularisation have an increased risk of cerebral haemorrage.[21,37]

Shunts, especially the hemodynamically significant *ductus arteriosus,* have a negative effect on cerebral ARM and consequently on cerebral oxygen saturation.[38] Therefore, an improved effect on cerebral hemodynamics exists in medicamentously triggered closing processes of the hemodynamically significant shunts. Interestingly, this effect is not detectable in surgical closing procedures of the ductus.[38,39,40,41]

Anaemia is a possible condition, especially in preterm neonates. The hemoglobin concentration is important for the oxygen transportation and therefore relevant for the cerebral oxygen supply. Increased hemoglobin concentration in anemic preterm neonates can change the cerebral oxygenation.[42] Furthermore, the oxygen content is an independent regulator of the cerebral blood flow.[43]

Catecholamines are a common therapy option for the treatment of hypotension in critically ill neonates.[44] Catecholamines can have an impact on cerebral ARM and its oxygenation. Although, the effect of catecholamines on the cerebral ARM and its oxygenation is controversial. Animal studies demonstrate that dopamine does not negatively affect the CBF or the cerebral autoregulation capacity in newborn piglets, whereas other studies cannot demonstrate this effect. However, dopamine infusion in hypotensive neonates might cause increased adverse outcomes in neonates.[45]

Respiratory support in preterm neonates with respiratory distress syndrome can have a relevant impact on cerebral hemodynamics. Studies suggest an increased need for blood pressure support of neonates suffering from a respiratory distress syndrome. Further, a larger range of cerebral oxygenation in ventilated neonates with respiratory distress syndrome is detectable in this vulnerable population. Neonates with respiratory distress syndrome show significantly more periods of linear relationships between blood pressure and cerebral oxygenation. This phenomenon can demonstrate possible shortcomings of the cerebral ARM and can thus increase the risk of cerebral lesions.[46] Ventilation techniques such as high-oscillatory ventilation lead to a continuous increase of CBF with a good clinical outcome for extremely preterm infants.[47]

Common neonatal complications such as severe hypoxic-ischemic encephalopathy (HIE) are also relevant for the CBF in neonates.[48] Preterm neonates suffering from intraventricular hemorrhage (IVH) or other severe advanced events occur significantly more often in neonates with an impaired cerebral ARM compared to healthy neonates.[21] Furthermore, respiratory failures primarily lead to fluctuations in carbon dioxide tensions in the neonatal blood. Molecules such as carbon dioxide have an impact on the cerebral ARM and ultimately on cerebral oxygenation.[2,49] Different maternal factors are also relevant for the cerebral ARM of the neonatal brain during the first days after the transition. Maternal hemodynamic factors such as pregnancy-induced hypertension, cases with haemorrhage during labor and delivery or placental infarction, are associated with PPP in neonates. However, this association does not concern maternal fever, maternal chorioamnionitis or duration of ruptured membranes.[28]

Impaired cerebral ARM is still a problem in the neonatal period despite improvements in techniques and strategies. Currently, there are several hypotheses for the mechanisms of injury. If the compensatory capacity of the cerebral ARM fails, the impaired ARM leads to increased mortality and morbidity in neonates.[2]

## *3.8 Compensation mechanisms for an adequate cerebral oxygenation*

Under physiological conditions, cerebral oxygen delivery outweighs oxygen consumption. An increase in oxygen demand can be compensated by an increase in pulmonary oxygen uptake. The neonatal brain is further able to increase the level of oxygen extraction from the neonatal blood, whereas in healthy patients, the oxygen supply can be doubled without an increase in cardiac output.[2] Nevertheless, the CBF and the cerebral blood supply depend on cardiac output.[50] If the oxygen extraction capacity exceeds the maximum, the neonatal brain initiate the anaerobic metabolism to maintain the necessary energy provision.[2] Additionally, the neonatal brain is capable of capillary recruitment. This mechanism leads to the recruitment of unperfused capillaries to increase the surface area of the capillaries.[51]

If the different compensatory mechanisms fail or exceed capacity, there is an increase in intracranial pressure with a consequent decrease of organ perfusion resulting in dysoxia and, ultimately, cell death.[52]

# 4 Morbidities during the neonatal transition after birth

## 4.1 An adequate oxygen supply

During transition the necessary independents of the placental function are associated with increased risks for different complications.[53] On the one hand, organs like the neonatal brain, heart, adrenal glands, and renal cortex have a constantly high oxygen demand, whereas organs like the skeletal muscles or the gastrointestinal tract have a variable and function-dependent oxygen demand. On the other hand, the oxygen demand of the spleen or the skin can tolerate a very low oxygen supply.[2] Following this distribution, the rate of complications depends in particular on the oxygen demand and differs in different organs.

## 4.2 Cerebral morbidities

Inadequate oxygen supply of the neonatal brain leads to irreversible damage. Despite constant scientific progress in medicine, cerebral complications during the neonatal period remain a problem.[54] The neonatal brain is more frequently affected by irreversible damages through the requirement of a continuous oxygen delivery. Neonates, particularly prematurely born neonates, have a higher risk of cerebral complications such as intraventricular haemorrhage (IVH) or hypoxic-ischemic injury (HI) compared to term neonates. These complications are further associated with adverse neurologic outcomes.[22,54,55]

### 4.2.1 Intraventricular haemorrhage (IVH)

IVH, the most common type of intracranial haemorrhage in neonates, is one of the major cerebral complications. IVH occurs more frequent in neonates during the first days after birth and become rare after the first week.[19] The pathogenesis of IVH is multifactorial and includes intravascular, vascular, and extravascular components. **Table 1** gives an overview of the pathophysiological components for the development of an IVH in neonates. The most common origin of IVH are ruptures of small blood vessels in the subependymal germinal matrix and possible expansion to the ventricular system.[19]. **Table 2** gives an overview of the currently known clinical conditions that increase the risk to develop IVH in neonates.

| **Overview of components involved in developing IVH** | |
|---|---|
| **Intravascular Components** | CBV [31]<br>CBF [56,57]<br>Blood pressure [58]<br>Platelet capillary function [59]<br>Blood clotting capability [56]<br>Blood glucose level [60]<br>Hematocrit [61] |
| **Vascular Components** | Fragility and vulnerability of the Germinal Matrix blood vessels [56,62] |
| **Extravascular Components** | Poor support of the extravascular space [63]<br>Excessive fibrinolytic activity [63] |

**Table 1.:** Pathophysiological overview of the development of IVH in the neonatal brain; **CBF**= cerebral blood flow; **CBV**= cerebral blood volume

Two possible pathophysiological mechanisms can lead to IVH in the neonatal brain. Firstly, different pathologic conditions or medical interventions can lead to a fluctuating blood pressure with a consequent overwhelming of the immature fragile cerebral capillary bed and subsequent bursting of these vessels.[22] Secondly, different conditions compromise the venous blood flow return (i.e. pneumothorax, severe respiratory illness, mechanical ventilation) to the neonatal heart with a resulting increase of hydrostatic pressure and consecutive rupture of the vessels.[22,64] **Table 2** gives an overview of the currently known clinical conditions that increase the risk to develop IVH in neonates.

| **Overview of clinical conditions associated to IVH** | |
|---|---|
| **Maternal factors** | **Neonatal factors** |
| • absence of antenatal corticosteroid treatment before birth [61,62,65,]<br>• cesarean section [61] | • very low birth weight or low APGAR score [59,61]<br>• peri- or postnatal hypoxic events [19]<br>• severe respiratory distress syndrome (RDS) or pneumothorax [19]<br>• cerebral sinus thrombosis or thrombocytopenia [59]<br>• hypercapnia and acidosis [65,61]<br>• initial lower hematocrit and/or hypernatremia [61]<br>• long duration of hyperglycemia or use of insulin [60,61]<br>• neonatal infection or chorioamnionitis [66] |

**Table 2:** Summary of different maternal or neonatal clinical conditions that increase the risk of IVH in neonates.

Studies on histologic vascular characteristics confirm that IVH is primarily of venous origin.[67] Different classifications of IVH exist. One of them classifies IVH into 4 grades of severity, whereby with increasing grade, the haemorrhage expands from being strictly subependymally located to including the ventricular system and venous infarction.[19] The symptoms of IVH depend on the expansion of the haemorrhage and therefore on the degree of IVH. IVH are mostly clinically silent and therefore usually incidental findings.[19] The gestational age is the most important independent risk factor for the IVH but other factors are also relevant. (see **Table 2**.)

Preterm vessels are more fragile due to insufficient development of the vessels compared to term-born neonates. In particular vessels of the subarachnoid space or the germinal matrix are significantly more fragile compared to other vessels and are prone to tearing with possible irreversible cerebral damage.[56] This mechanism can explain the common origin of IVH in the germinal matrix. A further pathophysiological reason for this can be the progressive increase of the diameter of the veins during cerebrovascular development without a corresponding increase in vascular wall thickness in vessels of the germinal matrix until the 36th week of gestation.[68] Severe grades of IVH are distinctly associated with increased mortality and neurodevelopmental impairments.[69] Enlargement of the haemorrhage can lead to consecutive complications. The posthaemorrhagic ventricular dilatation (PHVD) is one of the major consecutive complications of severe IVH. But low-grade IVH is also related to PHVD or other complications, such as haemorrhagic parenchymal infarction with its possible consequent developmental delays, deafness, and blindness in neonates.[56,57,70,71] Intracerebral haemorrhage with PHVD can lead to a further reduction in cerebral perfusion.[72] Current investigations indicate differences in cerebral regional oxygen saturation in neonates suffering from IVH compared to neonates without IVH during the immediate transition after birth.[73] IVH with ventricular dilatation is further related to other consecutive complications, such as cystic periventricular leucomalacia.[74]

Cerebral ultrasound allows the diagnosis, classification and assessment of the progression of IVH.[19] Ultrasound examination demonstrate higher cerebral blood volume in neonates suffering from IVH compared to neonates without IVH.[31] Studies have demonstrated a beneficial effect of antenatal steroid or postnatal indomethacin application in low birth weight infants to reduce the risk of IVH.[75,76]

### 4.2.2 Hypoxic injury and hypoxic-ischemic encephalopathia (HIE)

Hypoxic injury is a very frequent cause of brain injury in neonates and is further associated with irreversible neurological impairments or death, despite improvements in both diagnosis and treatment.[77,78,79] The incidents of hypoxic injury depend on the gestational age and are more frequent in preterm neonates.[80] Neurologic long-term consequences such as cerebral palsy occur in approximately 15% of neonates with intrapartum hypoxic injury.[81] Moreover, hypoxic injury before, during or after birth is linked to hypoxic-ischemic encephalopathy (HIE). Most HIE occurs in the neonatal period and in 2.5‰ of all neonates born alive.[80,81] Mortality due to HIE in neonates is around 16%.[82] Different pathologic conditions, such as neonatal prematurity or prolonged labor, maternal anaemia or gestosis, are the major risk factors for HIE.[82] HIE can be classified into a mild, moderate, and severe form, of which the moderate and severe forms of HIE are more frequent compared to the mild form.[83]

Late sequelae of hypoxic injury include cystic periventricular leukomalacia (PVL), ventricular enlargement or porencephaly.[80] As a result of improvements in medical care, there is a significant decrease in incidents of preterm neonates suffering from cystic PVL, but, unfortunately, incidents of non-cystic PVL have remained stable in the last decades.[84]

The pathophysiology of the hypoxic injury is linked to a disturbed cerebral oxygenation, maternal or fetal infection, and/or inflammation.[77] Further, studies on neonates suffering from HIE demonstrate a failure in cerebral autoregulation with resulting hyperperfusion.[85]

It is possible to demonstrate a significant difference in CBF between the different grades of HIE in neonates at the neonatal intensive care unit.[33] Magnet Resonance Imaging (MRI) represents the gold standard for detection, assessment of severity and prediction of prognosis of hypoxic injuries in neonates.[86] Cerebral ultrasound (CU) examination represents an alternative option for the detection of hypoxic injuries in neonates. CU has the beneficial effect of serial bedside examinations without the need for sedation.[79] MRI as well as Computer Tomography (CT) can be used for accurately quantifying hypoxic injuries. Both methods are further able to assess the therapeutic effect, though CT is more suitable for subarachnoidal hemorrhage.[86] NIRS has the potential to detect cerebral autoregulation impairments in real time in neonates suffering from HIE. Studies demonstrate a high sensitivity and specificity of NIRS in the detection of neonatal asphyxia and its benefits as an outcome predictor in neonates with HIE.[87]

Currently, different therapeutic options for HIE exist, such as hypothermia, neuroprotective agent therapy, stem cells, melatonin, early administered caffeine, xenon, argon, or ibuprofen.[88,89] Nevertheless, the therapeutic window is very short and may vary from 2 to 6 hours after birth.[90] Consequently, rapid detection and early intervention are crucial for the course and outcome of neonates with HIE.

## 4.3 Other neonatal morbidities

### 4.3.1 Necrotizing enterocolitis (NEC)

Necrotizing enterocolitis (NEC) is an inflammatory gastrointestinal disease of the small and large bowels and may have an impact on the neurodevelopment of neonates. NEC mainly affects preterm neonates. Mucosal injury, necrosis and intestinal perforation are the main characteristics of this feared complication. Studies on animal models suggest a link between NEC and cerebral changes. Furthermore, early interventions during NEC may have an impact on cerebral inflammation and subsequently an influence on cerebral neurological outcomes.[91]

### 4.3.2 Bronchopulmonary dysplasia (BPD)

Bronchopulmonary dysplasia (BPD) is a further common long-term complication in extremely preterm neonates and can lead to irreversible lung damage with hypertension in the pulmonary vessels and a consequent increase in late neonatal mortality.[92] The incidence of BPD increases with decreased gestational age and ranges between 12 and 32% of preterm neonates born before the 32th week of gestation.[93] The etiology of BPD is multifactorial. Interestingly, the effects of supplemental oxygen and antenatal steroid to cause a BPD has not been completely established.[93] Factors such as fetal growth restriction, persistent ductus arteriosus or mechanical ventilation increase the risk of BPD, whereas factors like vitamin A and caffeine application decrease its risk.[93] It is furthermore significant that postnatal factors, such as early-onset sepsis, increase the risk of BPD by 2.4 times.[94] Finally, current reviews describe a direct relation of oxidative stress between BPD and HIE.[95]

# 5 Assessment of neonates during the immediate transition after birth

The assessment of the neonatal hemodynamics, especially in critically ill neonates or during the immediate transition after birth is still a challenge.

## 5.1 Clinical assessment of neonates

The clinical assessment, summarized as the APGAR score, includes the respiratory rate, heart rate, muscle tone, skin colour and the reflexes of the neonates during the immediate transition after birth. It is an easy to apply, standardized assessment tool which is still clinically relevant today.[96,97,98] This score was used as a predictive index of mortality, morbidity, later neurologic disability and developmental disorders.[99] Nevertheless, this predictive value lacks sensitivity and specificity in long-term neurologic outcomes.[99] To protect the newborn neonate the assessment of a sufficient organ perfusion and subsequent adequate oxygen supply is important.

For the assessment of a sufficient organ perfusion or oxygenation, the systemic blood flow (SBF) is an important parameter. Assessing the SBF clinically through factors such as heart rate or capillary refilling time during the neonatal immediate transition is possible but inaccurate.[2] Consequently, additional neonatal assessment tools by means of monitoring techniques during the adaptation is crucial but remains difficult.[100]

## 5.2 Monitoring techniques

Invasive and non-invasive techniques for the assessment of neonatal hemodynamics during the immediate transition, additionally to the clinical assessment, are available.

### 5.2.1 Non-invasive monitoring

In particular in prematurely born neonates, non-invasive monitoring techniques are preferred and recommended for assessment in neonates during the immediate transition after birth.[100,101] Techniques such as pulse oximetry and electrocardiogram (ECG) are routinely performed, whereby in addition non-invasive measuring of the arterial blood pressure, amplitude-integrated EEG (aEEG), transcutaneous pCO2 monitoring and temperature have been demonstrated to be feasible tools for non-invasive monitoring of neonates during the immediate transition after birth.

#### 5.2.1.1 Systemic blood pressure

Non-invasively measured arterial blood pressure (ABP) is one of the most frequently used monitoring techniques to assess the hemodynamic status of the neonate at the NICU. But non-invasive monitoring of ABP to assess the hemodynamic status is an imperfect bedside test on the first day after birth.[102] The systemic blood pressure or ABP is one of the main determinants of the CBF. Disturbance of ABP influences the CBF.[36,45] Premature neonates have a lower blood pressure compared to term neonates.21 Reference ranges and their relationship to invasively measured ABP are known.[103] Until today it is still a problem to identify the optimal ABP for preterm neonates. According to the current state of knowledge, an adequate minimum of ABP is still the gestational age reported in weeks.[104] It is problematic that an impaired systemic blood flow is also possible during normal ABP.[102] Consequently, the ABP is one of many components of the hemodynamic status and CBF but other determinants are also relevant. Nevertheless, during the transition, the ABP is an important parameter for the cerebral oxygenation more in preterm compared to term neonates.[105] Finally, current studies demonstrate no differences in ABP between neonates with and without cerebral complications such as IVH.[73] These results demonstrate the importance of other parameters to assess neonatal hemodynamics.

#### 5.2.1.2 Electrocardiogram (ECG)

A progressive increase in HR during the immediate transition after birth is currently the most important parameter for an adequate fetal to neonatal transition.[106] Non-invasive measured HR through ECG during these timepoint is feasible and currently a part of the resuscitation guidelines.[107] The sensitivity and specificity of HR monitoring through ECG or pulse oximetry in neonates during after birth and during advanced resuscitation delivers an excellent accuracy.[108] However, the application of ECG can be applied more quickly compared to pulse oximetry during after birth.[109] In addition, the ability of ECG to measure the neonatal HR during after birth is the most accurate method compared to other currently possible methods.[110]

#### 5.2.1.3 Pulse oximetry

Pulse oximetry, considered as a routine monitoring, measures the arterial oxygen saturation ($SpO^2$) and heart rate (HR) non-invasively and continuously, without a need for calibration.[111,112] The $SpO^2$ of the fetus directly before birth is approximately 40% to 60%

and decreases during labor.[112,113] Directly after the transition, the SpO$^2$ rises slowly in the neonate.[114] It is possible to measure the SpO$^2$ in neonates during the immediate transition after birth and current guidelines recommend the use of pulse oximetry for guiding interventions during the immediate transition after birth.[9,115] Furthermore, it is possible to measure the SpO$^2$ in neonates during resuscitation through pulse oximetry to guide the amount of supplemental oxygen.[115,116] Additionally, a regular pulse oximeter is able to measure the pulsatile index (PI). The PI describes a ratio between pulsatile and non-pulsatile contributors to light absorption and is thus an additional parameter in monitoring the hemodynamics of neonates.[111] The use of pulse oximetry during the immediate transition after birth is recommended, but unfortunately does not provide information about adequate oxygen supply of the neonatal brain.[117] Studies on neonates suffering from IVH demonstrate lower cerebral oxygenation without changes in SpO$^2$ values during immediate transition after birth.[118]

#### *5.2.1.4 Amplitude integrated Electroencephalogram (aEEG)*

An adequate cerebral oxygen supply depends on oxygen delivery and consumption. The cerebral oxygen consumption depends further on the cerebral activity.[119] aEEG provides a non-invasive, continuous, real-time assessment of cerebral activity.[120] The cerebral activity is an reliable diagnostic outcome parameter in neonates.[119] Seizure during the neonatal period, especially in neonates suffering from cerebral complications, such as HIE, is a common problem and the aEEG allow seizures to be detected and classified.[119,121,122,123] The aEEG is further able to estimate the neurologic outcome in neonates with cerebral complications.[119] The use of aEEG during the immediate transition after birth as well as during resuscitation is feasible.[120] The aEEG is able to detect differences in cerebral activity pattern and sleep wake cycle or the likelihood of seizure between neonates with or without intracranial haemorrhage.[124] Simultaneously assessment of neonates through EEG and NIRS is possible and increases the predictive value.[125] Nevertheless, this method is limited by the technical difficulties of sampling and interpretation due to artifacts.[126]

#### 5.2.1.5 Temperature

The body temperature management of neonates, especially during the immediate transition after birth, is of crucial importance. The body temperature has an impact on the cerebral oxygen metabolism. The World Health Organisation (WHO) recommends a body temperature of between 36.7C° and 37.7C°. A reduction of one degree can increase the risk of IVH and increase mortality by approximately one third.[127,128] Neonates, especially preterm neonates, are at a high risk of hypothermia because of their unfavourable surface area/body mass ratio, immature skin, and a lack of brown adipose tissue.[127] Animal studies demonstrate a reducing effect of cerebral oxygen metabolism during hypothermia in rats.[129] Consequently, therapeutic hypothermia is one of the most common treatments of neonates suffering from HIE.[130] Further, hypothermia also has an impact on the cerebral oxygen supply. Hypothermia results in a reduced CBF and consequently a decrease in cerebral oxygenation.[130]

#### 5.2.1.6 Near infrared spectroscopy (NIRS)

NIRS is a non-invasive, real-time monitoring system which measures the cerebral oxygenation based on the principle absorption of near infrared light. The NIRS is described in detail in **section 7.1**.

### 5.2.2 Invasive monitoring

#### 5.2.2.1 Temperature management

The body temperature management of neonates, especially during the immediate transition after birth, is of crucial importance. The body temperature has an impact on the cerebral oxygen metabolism. The World Health Organisation (WHO) recommends a body temperature of between 36.7C° and 37.7C°. A reduction of one degree can increase the risk of IVH and increase mortality by approximately one third.[127,128] Neonates, especially preterm neonates, are at a high risk of hypothermia because of their unfavourable surface area/body mass ratio, immature skin, and a lack of brown adipose tissue.[127] Animal studies demonstrate a reducing effect of cerebral oxygen metabolism during hypothermia in rats.[129] Consequently, therapeutic hypothermia is one of the most common treatments of neonates suffering from HIE.[130] Further, hypothermia also has an impact on the cerebral oxygen supply. Hypothermia results in a reduced CBF and consequently a decrease in cerebral oxygenation.[130]

#### 5.2.2.2 Blood gas analysis (BGA)

An analysis of blood gas provides information about the circulation, the immediate oxygen metabolic status and the predictive outcomes of the neonate, and is recommended for all high-risk deliveries and in all neonates with a low APGAR score.[98,131] BGA can be carried out during pregnancy by cordocentesis, during labor by sculp puncture as well as during and immediately after transition by puncture of the umbilical vessels.[132] BGA of the umbilical cord in healthy term neonates is simple and minimally disruptive, whereby the blood of the umbilical vein represents the placental function and the blood of the umbilical arteries represents the status of the neonate.[132,133] BGA of the umbilical cord is considered the best way to assess neonatal oxygenation during the delivery.[133] Furthermore, BGA of capillary blood after birth in neonates can also be carried out. BGA carried out on capillary blood is highly correlated to BGA carried out on the venous blood in concern to the partial pressure of oxygen in neonates.[134] Blood gas monitoring in neonates at the NICU is used to reduce the risk of retinopathy of prematurity, respiratory distress syndrome, and/or to guide ventilator support.[104] Furthermore, components of the BGA have the potential to be a predictor of multiple organ dysfunction syndrome, preeclampsia or hemorrhage in neonates.[135] The BGA provides different prognostic parameters, such as oxygen content, carbon dioxide content, blood glucose level, lactate level, pH level, level of bicarbonate, and the base excess.

#### 5.2.2.2.1 Oxygen content

Oxygen is one of the major inorganic substrates of the cerebral metabolism. Both hyperoxia and hypoxia can cause cerebral tissue damage during neonatal transition.[136] Oxygen can be used during resuscitation, although an initial use of room air compared to 100% oxygen should be preferred in term neonates.[137] Studies on ultrasound examinations demonstrate a reduced effect of hyperoxia on the CBF velocity in term and preterm neonates.[138] Paradoxically, the arterial pressure of oxygen (pO$^2$) is the least valuable parameter of the BGA to evaluate oxygenation because of the effect of the dissociation curve and the affinity of oxygen to hemoglobin.[139] Nevertheless, the partial pressure of oxygen is associated with the cerebral oxygen saturation.[140]

#### 5.2.2.2.2 Carbon dioxide (CO$^2$)

CO$^2$ is the product of energy metabolism and has an impact on cerebral ARM.[141] Compared to the arterial pO$^2$, the level of CO$^2$ has a more pronounced effect on CBF velocity in term and preterm neonates.[138] According to current knowledge, hypercapnia has an impact on the vascular tone. CO$^2$ leads to a vasodilatation of the cerebral arterial vessels with a consequently increased perfusion. Further, CO$^2$ also has an impact on the oxygen supply because, an increase in CO$^2$ causes a right shift of the oxygen dissociation curve and an increased oxygen-carrying capacity with consequently increased oxygen to the tissues.[142] Studies demonstrate a positive correlation between CO$^2$ and cerebral regional oxygen saturation, and a negative correlation between CO$^2$ and fractional-tissue oxygen extraction in neonates during the first day of life.[143] Additionally, hypercapnia can lead to a decrease in the electrical activity of the neonatal brain with a consecutive decrease in oxygen consumption.[144] Nevertheless, an increased level of CO$^2$ above 45 mmHg indicates pressure passive perfusion and a consequent cerebral ARM failure.[145,146] Interestingly, the vascular reactivity of the cerebral vessels to CO$^2$ seems to be reduced in mechanically ventilated neonates during the first days of life.[147] Animal studies demonstrate further that the hypercapnia induced effects of increased CBF and cerebral metabolism persist for several hours.[148] CO$^2$ can be used for different thoracoscopic surgical techniques, such as thoracoscopic repair of congenital diaphragmatic hernia or esophageal atresia. Despite this, studies show a systemic effect of the CO$^2$ pneumothorax on the acid-base balance of the neonate.[149] Current investigations demonstrate a negative correlation between the level of $CO^2$ and cerebral regional oxygen saturation during total video-assisted thoracoscopic radiofrequency ablation in patients with atrial fibrillation. Despite this, the effect of $CO^2$ on the cerebral oxygenation seems to be relatively small.[140]

#### 5.2.2.2.3 Blood glucose level (GLU)

Glucose is a major essential substrate for the cerebral energy metabolism, and a restricted blood glucose supply can result in cerebral damage.[51] During the adaptation, in order to maintain the GLU independently of the placental supply, the neonate experiences an increase in catecholamine and glucagon levels and a decrease of insulin. Due to this, the neonatal liver starts to increase glucose production on the basis of gluconeogenesis and glycogenolysis to ensure a stable GLU.[3] Initial hypoglycemia is a risk factor for perinatal brain injury.[150] Hyperglycemia affects the majority of preterm neonates during the first days of life and is highly associated with cerebral alteration and the degree of severity of IVH.[60] Current studies show a relationship between the GLU and the cerebral hemoglobin content in preterm neonates.[151] Also, studies demonstrate a negative effect of hyperglycemia on the ARM, the cerebral energy metabolism, and outcome in patients.[152]

#### 5.2.2.2.4 Lactate (LAC)

LAC is the oxidized product of pyruvate and is increased during an inadequate cellular oxygenation. Consequently, LAC represents the anaerobic metabolic energy maintenance system.[80,153] Studies during delivery demonstrate that the arterial umbilically measured LAC level is primarily of fetal origin.[154] Consequently, detecting the arterial umbilical LAC can be a predictor of an inadequate oxygenation of the neonate during delivery. Reference ranges of the parameters of the umbilical artery and vein BGA on healthy neonates have been published.[133] Lactate is comparable to the pH and base excess in sensitivity, specificity, and positive and negative predictive values in relation to morbidity and mortality in neonates during the delivery.[155] Consequently, hyperlactaemia is a predictor for mortality in critically-ill patients. 80% of critically-ill patients at the intensive care unit with LAC values above >10mmol/l die.[156] Specifically, persistent LAC is a strong predictor for severe encephalopathy during the first hour of life.[153] Further, LAC in relation to pyruvate can represent a high predictor of HIE in neonates.[153]

### *5.2.2.2.5 pH*

Acidosis, respiratory as well as metabolic acidosis, is the result of inadequate oxygen supply. The pH level of the umbilical artery is the most sensitive indicator for hypoxia during delivery and have been used to evaluate adaptation.[132] Existing functional placenta defects and other disturbances during the delivery will affect the oxygen supply and $CO^2$ elimination.[132] Both effects result in acidemia and have enormous effects on the cardiovascular system, such as disturbed myocardial performance, reduction of blood pressure and heart rate, and reduction of sensibility of catecholamines to cardiac contractility.[157] Acidosis has a right shifting effect on the dissociation curve and, thus, to the oxygen delivery of the hemoglobin to the tissue. In contrast, alkalosis, for example, shifts the dissociation curve to the left with a consequently reduced unloading of oxygen from the hemoglobin.[158,159] Compensation mechanisms, such as the stimulating effect of alkalosis to 2,3-diphosphoglycerate production to normalise the dissociation curve, are less developed in fetuses compared to adult humans.[147] Depending on the tissue, severe acidosis and alkalosis lead to a vasoconstriction or vasodilatation with subsequent changes in systemic perfusion.[160] In particular, metabolic acidosis is, in combination with intrapartum asphyxia, a strong indicator for severe complications in preterm neonates.[161] Increased acidosis is associated with a low APGAR score, increased perinatal mortality, and impaired neurodevelopmental outcomes in neonates.[132] Furthermore, low arterial cord pH during the delivery is strongly associated with HIE, PVL, and an increased risk of cerebral palsy in neonates.[162] Despite this, the results of the investigation of pH of the umbilical blood and IVH in preterm neonates are controversial. However, some studies demonstrate the impact of very low umbilical cord arterial pH and the increased occurrence of severe IVH and seizure in both preterm and term neonates.[162,163,164] Nevertheless, mild to moderate hypercapnic acidosis seems to have some neuroprotective properties and may improve the survival rate of neonates with cerebral ischemic insults.[142] Moreover, the mode of delivery is also relevant for the level of acidosis, respiratory acidosis, for instance, dominates in vaginal delivery.[165] Reference ranges of the pH in healthy neonates as well as of asphyctic neonates have been published.[133,166] The level of pH is further related to other factors of the BGA like buffers (bicarbonate or base excess) or LAC.

#### 5.2.2.2.6 Bicarbonate level (BIC)

Buffers are important for proton elimination and, in particular, the BIC buffer is the most important buffer system and contributes approximately 35% to this effect.[167] The level of BIC is related to acidosis or alkalosis.[132] The level of BIC has a high relevance for the oxygen supply, because it has an impact on vasoreactivity through an endothelium-dependent mechanism.[24] With decreased pH and increased BIC levels, the risk of cerebral palsy increases.[162] An umbilical artery BIC level above 16eMq/L during and after birth is associated with perinatal asphyxia.[168] Reference ranges of BIC levels in healthy neonates have been published.[133] BIC infusions are used as buffers in neonates suffering from acidosis. This infusion can be used to improve the myocardial function in acidotic patients.[157] Unfortunately, BIC infusion leads to hyperosmolarity and $CO^2$ generation with disturbing effects on the myocardial or cerebral function. This mechanism can explain the increase on mortality of BIC infusion during cardiopulmonary resuscitation.[157] Besides, prospective randomized, double-blind, trials on the effects of BIC buffer infusion during cardiopulmonary resuscitation on patients with cardiac arrest cannot demonstrate a beneficial effect despite very rare cases of arterial alkalosis as possible side effect of BIC.[169] Finally, the use of sodium BIC infusion is further linked to IVH, even though current studies do not suggest this association.[170]

#### 5.2.2.2.7 Base excess (BE)

The BE, calculated out of pH, BIC, partial pressure of $CO^2$ and hemoglobin content through the “Van Slyke” equation, is the best marker for a metabolic conditional acidosis.[132,171] The BE quantifies the magnitude of the metabolic acidosis and the supposed risk factors for central neurologic injury.[172] Umbilical arterial and vein BE differences can be used for a differentiation between short- and long-term asphyxia of the neonate.[173] Studies demonstrate the negative relationship between the BE and cerebral oxygen saturation in adult patients with atrial fibrillation during total video-assisted thoracoscopic radiofrequency ablation.[140] Finally, BE is used clinically to assess the tissue perfusion or effectiveness of implemented interventions.[174] Reference ranges of BE in neonates suffering from asphyxia have been published.[133,166]

To measure the cerebral perfusion and related cerebral oxygen supply is at the centre of the assessment of neonates, particularly during the immediate transition, and this remains a challenge today. Additional innovative techniques for the real-time assessment of cerebral oxygenation are necessary and can possibly lead to minimization of irreversible damage in neonates.[22]

## *6 Near-infrared spectroscopy (NIRS)*

### *6.1 Principles of near-infrared spectroscopy*

Measuring cerebral oxygenation continuously is a crucial step towards an understanding of cerebral ARM and the prevention of neurological complications in critically-ill neonates. NIRS represents a non-invasive, real-time monitoring technique to detect cerebral oxygenation and hemodynamics. The basic principle of NIRS is that the biological tissue is relatively transparent to light in the near-infrared light spectrum. Oxy- and deoxyhemoglobin molecules reduce the returned light by absorption or scattering. Both principles reduce the intensity of the returning light. Consequently, changes of the infrared light can be converted into relative concentration changes of deoxy- and oxyhemoglobin.[175,176]

This phenomenon allows us to identify and quantify the relative concentration of the desired molecules. This differentiation of the desired molecules is based on different absorption spectra of the respective molecules. Thus, this optical mechanism allows us to detect oxyhemoglobin **($O^2Hb$)**, deoxyhemoglobin **(HHb)**, and total hemoglobin **(tHb)** concentration.[176] The following equation describes the relation between the desired molecules.

$$\mathbf{tHb = O^2Hb + HHb}$$

*Equation 1.*

It is possible to determine the relative value of cerebral regional oxygen saturation **($crSO^2$)** derived from the formula described above.

$$\mathbf{crSO^2 = \frac{O^2Hb}{tHb}}$$

*Equation 2.*

$crSO^2$ represents a state of hemodynamic stability and is the result of oxygen delivery and consumption.[177] The resulting $crSO^2$ represents the percentage of the oxygen-saturated portion of hemoglobin in the measured tissue.

The fractional tissue oxygen extraction (FTOE) represents the extraction of oxygen from the neonatal blood measured with NIRS and pulse oximetry and is calculated by the following equation:

$$\mathbf{FTOE} = \frac{(\mathbf{SpO^2 - crSO^2})}{\mathbf{SpO^2}}$$

*Equation 3.*

In order to identify an adequate oxygen delivery, the cerebral oxygen consumption is crucial. Fractional oxygen extraction (FOE) is an indicator of the level of oxygen consumption and is measurable through invasive measurements of CBF and *Jugular bulb* oxygen saturation.[178] Animal studies on piglets have demonstrated that the FTOE, measured with NIRS, is well correlated with FOE, measured through invasive techniques.[178] The increase of FTOE in the neonatal brain seems to be a compensatory mechanism.[179]

With the help of frequency-domain or time of flight NIRS, it is further possible to measure the cerebral blood volume **(CBV)** using the following equation.[180]

$$\mathbf{CBV} = \frac{(\mathbf{tHb\ x\ MW_{Hb}})}{\mathbf{HGB\ x\ D_{bt}}}$$

*Equation 4.*

The **CBV** is given in mL/100 g; $\mathbf{MW_{Hb}}$ is the molecular weight of hemoglobin (64,500 g/Mol) and $\mathbf{D_{bt}}$ is the brain tissue density (1.05 g/mL).[180]
The arterial oxygen content **($CaO^2$)** and venous oxygen content **($CvO^2$)** are important for the understanding of oxygenation. Both are measurable through the following equations:[181]

$$\mathbf{CaO^2 = Hb\ x\ (SaO^2/100)\ x\ 1.39}$$

*Equation 5.*

$$\mathbf{CvO^2 = Hb\ x\ (SjvO^2/100)\ x\ 1.39}$$

*Equation 6.*

$\mathbf{SaO^2}$ represents the arterial oxygen saturation whereas $\mathbf{SjvO^2}$ represents the jugular venous oxygen saturation.

With the help of NIRS, it is possible to measure the cerebral oxygen delivery (**COD**), cerebral oxygen consumption (**$CMRO^2$**) and the **CBF.**[33,180]

$$\mathbf{COD = CBF \ x \ CaO^2}$$

*Equation 7.*

$$\mathbf{CMRO^2 = CBF \ x \ (CaO^2 - CvjO^2)}$$

*Equation 8.*

## 6.2 Methodical principles of NIRS:

There are differences in methodical approaches in NIRS monitoring:

a. Continuous-wave (intensity measurement)
b. Time-domain (intensity and time measurement)
c. Frequency-domain (intensity and time measurement)

**Figure 3** illustrates the different methodical principles of the NIRS technique.[182] Continuous-wave techniques are based on the principle of intensity measurements and are therefore more sensitive to haemoglobin changes compared to the time-domain technique.[182,183] In contrast, time- and frequency-domain techniques additionally allow the measuring of the time of flight with resulting absolute values of O2Hb, HHb, tHb and crSO2.[176,182] Furthermore, new technical approaches, such as functional NIRS (fNIRS), allow the detection of cerebral activity non-invasively through NIRS.[182] Improvements in techniques allow for 3-D tissue oxygenation measurements with a depth of up to 3cm.[184]

### 6.3 Area of application

The NIRS sensor can be positioned above the region of interest and fixed in clinical conditions with glue or an elastic band.[185] There are differences in tissue oxygen saturation in different organs. Studies have demonstrated a preserved oxygenation of vital organs compared to other organs, such as kidney or splanchnic tissue.[186] Following this principle, the relationship between central and peripheral NIRS measurements can be further used to identify possible centralization.[187] NIRS can be used to analyse and monitor different tissue oxygenation, such as cerebral oxygenation[119], renal oxygenation and perfusion[188], splanchnic oxygenation[189], oxygenation of the peripheral muscle[190], liver oxygenation[191], and mesenteric oxygen saturation[186].

### 6.4 Accuracy of NIRS

The accuracy of NIRS measurements increase over time and depend on different factors. Studies on the reproducibility of inter-neonate variation and between-neonate variation demonstrate an accuracy of 5.2% and 6.9%, respectively. As a result, there are different reference ranges for different devices and different tissues.[186,188,189,190,191,192,193] The accuracy of NIRS measurements furthermore depends on the tissue homogeneity of the measured tissue.[194] Fortuitously, the use of NIRS as a trend monitoring method can provide information about the changes in oxygenation and there is a possibility of improving the accuracy.[176] Other reproducibility studies on NIRS detect a variability of 4.2% between neonates and only a third of the measurement errors can be traced to this variability.[195] NIRS measurements to calculate the CBF are closely related to invasive techniques, such as 133Xe measurements.[32] The accuracy of NIRS measurements has been increased by technical improvements. Current studies demonstrate that the accuracy of NIRS measurements in a clinical setting is below 1.85%.[196] Consequently, the accuracy of NIRS measurements seem to be comparable with the precision of pulse-oximetry,[197] though different devices of NIRS are available and the accuracy of the different devices varies.[176,194]

NIRS monitoring in the clinical setting has both advantages and disadvantages, and both will be described below.

## 6.5 Advantages of NIRS

NIRS measurements have several advantages in clinical use. A NIRS light source is non-ionizing, non-invasive and thus painless for the neonate.[198] Technical studies on phantoms to investigate the exact accuracy of NIRS demonstrate excellent correlations.[196,199] The accuracy of NIRS measurements seems to be comparable with the precision of the current guided routine monitoring techniques such as pulse-oximetry.[197] NIRS monitoring enable the CBF to be measured non-invasively and is comparable to invasive methods, such as Xe133, whereas the differences between both methods are close to zero in a low range.[32] This possibility for long-range measurements of the NIRS increases the accuracy and thus further enables the re-evaluation of the clinical intervention.[176] A further advantage of NIRS is the applicability in the clinical setting. Results of NIRS measurements can be obtained very quickly – in fact within 2 minutes after birth, thus enabling the monitoring of neonates during the immediate transition after birth directly on the resuscitation table.[100] The use of NIRS monitoring during the immediate transition after birth is independent of the mode of delivery and NIRS monitoring is also possible in special conditions, such as in very low birth weight infants during cardiorespiratory resuscitation.[200,201,202,203] Moreover, continuous, long-time measurements, bedside monitoring as well as the simultaneous monitoring of different regions of interest can be carried out. Interestingly, studies demonstrate no differences in oxygenation between different simultaneously measured cerebral regions.[176,204,205] Consequently, measuring only one cerebral region should be sufficiently reliable for obtaining information, and simplifies the application of cerebral NIRS measurements.[176] Additional NIRS monitoring to the routine monitoring can lead to a reduction in the time of cerebral hypoxia and thus to lower morbidity and mortality.[206] As described before, NIRS monitoring of neonates during the immediate transition can detect cerebral oxygenation deficits in neonates, something which is still not achievable using routine monitoring.[73] Finally, NIRS monitoring is also usable during different surgical procedures as well as in inter-hospital patient transport.[207,208]

## 6.6 Disadvantages and limitations of NIRS

Despite a number of advantages, the NIRS technology also has disadvantages and limitations. The NIRS light is sensitive to all penetrated tissue and thus limited to use on superficial tissue. Due to this, all extracranial tissue and blood flow will contaminate the accuracy of the emitted light.[209] However, this effect is relatively small in neonates, because the tissue is thin and therefore has less impact compared to adult patients.[176,198] The emitted light can also be disturbed by subjacent vessels. However, with an increasing diameter of the vessels, the influence on emitted light decreases.[210] Therefore, the emitted light has a relatively small effect on the large vessels compared to the small vessels. Despite this, the measured cerebral oxygenation are the relation of arterial and venous saturation weighted out of the compartment size. This weighting factor varies between time, tissue and, in particular, between healthy and diseased tissue. Determination of the precise weighting factor is not possible at present.[176] The penetration of near-infrared light is limited to half of the distance from the light emitter to the sensor. This is why NIRS measurements only detect oxygen saturation in a thin superficial layer of the neonatal brain. However, this seems to be sufficient in neonates.[100] As described above, the emitted intensity of NIRS light is reduced by oxy- and deoxyhemoglobin. Other molecules, such as cytochrome aa3 or bilirubin, also have an effect on near-infrared light, but this effect appears only at very low levels of oxygenation.[198,211] The position of the sensor and the patient influences the results of NIRS measurements.[212,213] Consequently, investigations must be standardized to reduce this effect. Furthermore, in contrast to monitoring techniques, such as pulse oximetry, there is no existing gold-standard method to compare and test the accuracy of NIRS in vivo.[176] Finally, there are a variety of NIRS devices, sensors and algorithms and this leads to discrepancies in interpretation and comparability between measurements of the different devices.[176] Nevertheless, comparability studies and reference ranges for different devices have been published.[193,214]

## 6.7 Links between NIRS, cerebral ARM and neurologic outcome

As described above, the cerebral ARM is a mechanism to maintain the CBF on a constant level. With the help of cerebral NIRS measurements in combination with pulse oximetry, it is possible to calculate the CBF based on Fick´s principle in adults and neonates.[33] Furthermore, it is possible to use NIRS on neonates during the immediate transition after birth.[126] With this principle, it is also possible to detect the cerebral ARM and its impairment (PPP) during this time period in this vulnerable population.[215] The application of NIRS additionally allows the detection and assessment of the cerebral injury status and its evolution.[180] Cerebral oxygenation measurements indicate that an increased duration of PPP is associated with an adverse neurologic outcome.[215]

## 6.8 NIRS immediate after the transition

NIRS measurements during the immediate transition after birth in healthy term [200] and preterm neonates [201] as well as during cardiorespiratory resuscitation [202] is feasible. NIRS monitoring in special conditions, such as during the resuscitation of very low birth weight neonates during the first minutes after birth is also possible.[201] Additionally, it is possible to demonstrate that the feasibility of NIRS measurements is independent of the mode of delivery.[203] Despite detectable differences in the routine monitoring of term neonates born through vaginal or elective Cesarean section, there seems to be no measurable difference concerning the $crSO^2$ between the different modes of delivery.[216] In concern to this, investigations of neonates during the immediate transition after birth demonstrate significantly lower $crSO^2$ in neonates suffering from IVH compared to neonates without IVH.[73] Furthermore, it is also possible to demonstrate differences in CBV between neonates with brain injury compared to those without brain injury.[180] NIRS measurements during delivery room resuscitation might help to minimize cerebral injury in the preterm neonatal brain.[127] NIRS monitoring to reduce the time of hypoxia during the immediate transition after birth might be associated with improved short-term neurologic outcomes in preterm neonates.[217]

Investigations indicate the importance of NIRS during the immediate transition after birth to identify in timely manner neonates with a high risk of developing cerebral injury.

### *7 Objective*

NIRS measurements can deliver continuous, real-time monitoring of cerebral oxygenation in neonates during the immediate transition after birth. Current studies describe the association between blood-glucose and the different parameters of the acid-base metabolism and its impact on cerebral oxygenation in the neonatal period after immediate transition. Thus, blood-glucose and parameters of the acid-base metabolism might also have an important impact on cerebral oxygenation in neonates during the immediate transition after birth.

The aim of this dissertation is therefore to investigate the potential influences of blood-glucose (GLU) and the acid-base metabolism (LAC, pH, BE, BIC) on the cerebral tissue oxygenation in the immediate transition period at 15 minute after birth in term and preterm neonates.

# *7 Methods:*

## *7.1 Study design*

A prospective observational study “Carbon dioxide during the immediate transition after birth: course and influence on cerebral oxygenation” was carried out at the Medical University Hospital of Graz, Austria. Ethical approval (EC number: 27-465 ex 14/15) was obtained before inclusion of the first patient.

The present dissertation was part of this prospective observational study and analyzed secondary outcome parameters.

### *7.1.1 Eligible Patients included in “Carbon dioxide during the immediate transition after birth: course and influence on cerebral oxygenation”*

Between October 2015 and September 2018, neonates delivered by elective Cesarean section were included in the prospective observational study, if there was a decision to conduct full life support and written informed consent was obtained from the parents prior to the birth. The exclusion criteria were the following: disturbing effects of measurements during cardiopulmonary resuscitation during the transition period, no decision to conduct full life support or absence of written informed consent and congenital malformations (e.g. congenital diaphragmatic hernia).

### 7.1.2 Procedure

The antepartum medical history was collected before birth, and demographics were documented for each neonate.

After delivery by Cesarean section, the cord was routinely immediately clamped after 30 seconds, which was the standard of care in Graz at that time. The neonates were brought to the resuscitation table and were placed under an overhead heater in a supine position. Following this, the neonates were dried and stimulated. Resuscitation was performed according to neonatal resuscitation guidelines by a dedicated resuscitation team composed of a neonatologist and a nurse who were not involved in the study.[9,116] Without disturbing the routine medical care, the NIRS transducer was fixed with a gauze bandage or below the CPAP hood on the neonate's right forehead by the scientific staff members. NIRS measurements were collected during the first 15 minutes after birth. Additionally, preductal $SpO^2$ and HR were continuously measured by a pulse oximeter fixed onto the right wrist. Singular measurements of blood pressure and rectal body temperature were recorded between the 5th and 15th minutes after birth. Blood samples were taken by heel prick according to the discretion of the attending neonatologist.

## 7.2 Monitoring

Cerebral oxygenation ($crSO^2$ & FTOE) was investigated with an INVOS 5100 (*Covidien, Minnesota, USA*), using neonatal sensors to measure the relative oxygenation through NIRS (see equation 2 *on page 38*). To determine the $SpO^2$ and HR, a pulse-oximetry (*MR7CDS1 Radical 7, Chemomedica, Austria / IntelliVue MP70, Philips, Netherland*) was used. Blood pressure and central temperature measurements were measured with Intellivue MP70 (*Philips, Netherland*).. Respiratory support was provided through continuous positive airway pressure or positive pressure ventilation using a T-Piece (*Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand*). Default settings that were used were a gas flow of 8 L/min peak inflation pressure of 24 cm H2O, positive end-expiratory pressure of 5cm H2O and a FiO2 of 0.21 for term neonates and FiO2 of 0.30 for preterm neonates below the 35 week of gestation according the guidelines.[9] Metabolic parameters were measured using a blood gas analyzer (*ABL 800 Flex, Fa. Drott, Wiener Neustadt, Austria*). All variables were stored by using a multichannel system alpha-trace digital MM (*BEST Medical Systems, Vienna, Austria*) for subsequent analysis. Values of the $SpO^2$, HR and crSO2 were stored every second, while the sampling rate for $crSO^2$ was one per eight seconds. For the present study, parameters obtained during a 60-second period at the 15th minute after birth were analyzed. Mean values for $SpO^2$, HR and $crSO^2$ were calculated in the 15th minute after birth. $crSO^2$ and $SpO^2$ were eliminated as quality criterion values if $crSO^2$ was higher than $SpO^2$.[218] FTOE was calculated with the following formula: $SpO^2$-$crSO^2$/$SpO^2$.[219]

## 7.3 Patients

From the eligible patients included in the prospective observational study neonates were included in the present analysis, if cerebral NIRS measurements during the 15th minute after birth were available and a capillary blood gas analysis to detect the blood glucose level (GLU) and the parameters of the acid-base-metabolism (LAC, pH, BE, BIC) between 10 and 20 minutes after birth was performed.

For analysis two groups were defined: preterm and term neonates. Preterm neonates are defined as neonates born before the 37th week of gestation and term neonates are born after the 37th week of gestation.

The exclusion criteria for the present analyses were absence of $crSO^2$ measurements at the 15th minute after birth as well as the absence of a capillary blood gas analysis between the 10th and 20th minutes after birth.

## 7.4 Statistics

Data are presented as mean and standard deviation for normally distributed continuous variables, and median (interquartile range, IQR) when the distribution was skewed.

Baseline characteristics and measured parameters ($SpO^2$, HR, $crSO^2$, FTOE, and GLU, LAC, pH, BE, BIC) of term and preterm neonates were compared. Categorical demographic variables were compared with the use of the chi-square test or Fisher’s exact test. Continuous variables were compared using the t-Test or Mann–Whitney-U test, as appropriate. The association between $crSO^2$/FTOE and blood-glucose and the parameters of the acid-base metabolism were analysed using Spearman’s rank correlation coefficient or Pearson's correlation when appropriate. A p-value <0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics 26 (IBM Corporation; Armonk, USA).

## 7.5 Hypotheses

### 7.5.1 Primary Hypothesis

The blood-glucose level and parameters of the acid-base metabolism measured in capillary blood (LAC, pH, BE, BIC) influences the cerebral oxygenation in term and preterm neonates during the immediate transition after birth.

### 7.5.2 Secondary Hypothesis

Higher GLU and LAC are associated with lower $crSO^2$ and higher FTOE in preterm and term neonates during the immediate transition after birth.

Lower pH, BE and BIC are associated with higher $crSO^2$ and lower FTOE in preterm and term neonates during the immediate transition after birth.

Influence of the parameters of the acid-base metabolism on cerebral oxygenation differs between preterm and term neonates.

# 8 Results

## 8.1 Participants

Out of 224 eligible neonates, we included 36 preterm neonates and 116 term-born neonates in the present analyses. The most common reason for exclusion was a lack of $crSO^2$ or $SpO^2$ values taken at the 15th minute after birth, no or late blood sample taking or invalid FTOE values. The flow diagram (**Figure 3**) describes the numbers and characteristics of excluded neonates in detail.

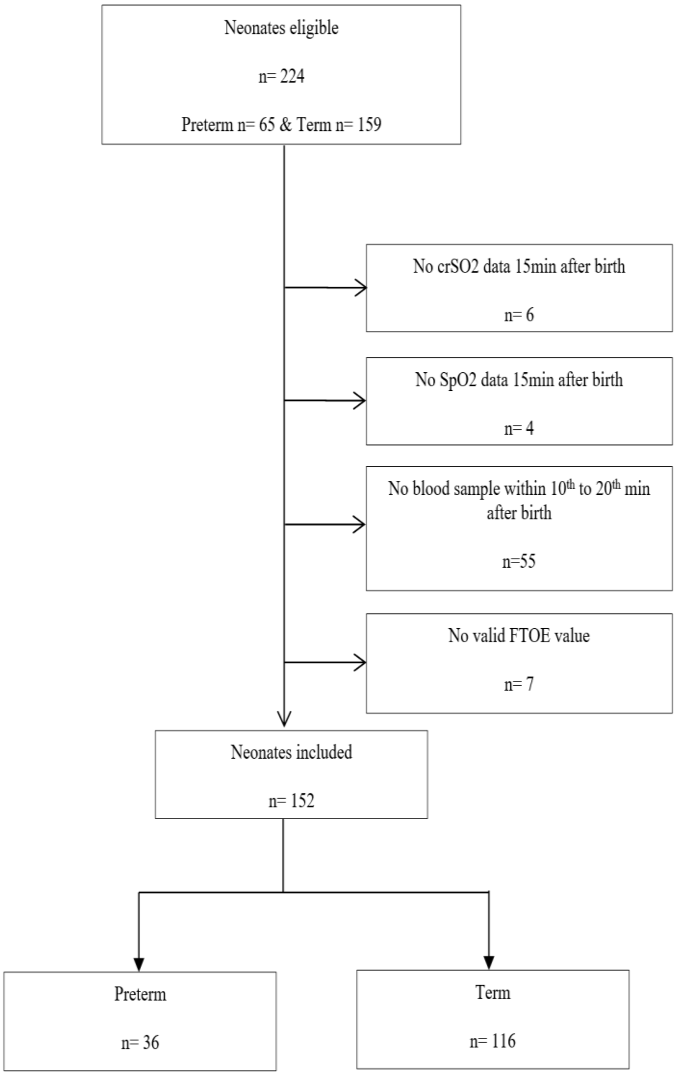


**Figure 1.:** Flow-diagram illustrating inclusion and exclusion of the investigated study population. $\mathbf{SpO^2}$= arterial oxygen saturation, $\mathbf{crSO^2}$= cerebral regional oxygen saturation, **FTOE**= fractional tissue oxygen extraction.

### 8.2 Descriptive data

Of the included neonates during delivery, 146 (96.0%) mothers received regional anesthesia and 6 (3.9%) mothers received general anesthesia for the Cesarean section.

Indications for a Caesarean section were previous Caesarean sections [n=38 (25.0%)], breech presentation [n=8 (5.2%)], transverse presentation [n=5 (3.3%)], multiple birth [n=16 (10.5%)], pre-eclampsia and eclampsia [n=4 (2.6%)], intrauterine growth restriction [n=17 (11.2%)], placenta praevia [n=5 (3.3%)], CTG abnormality [n=1 (0.7%)], fetal or maternal infection [n=7 (4.6%)] and others [n=51 (33.6%)].

### 8.3 Outcome measurements

In preterm neonates, data of the blood gas analysis is missing for GLU [n= 4, *(11.1%)*], LAC [n= 4 *(11.1%)*], pH [n= 2 *(5.5%)*], BE [n= 1 *(2.8%)*], and BIC [n= 4 *(11.1%)*].

In term neonates, data of the blood gas analysis is missing for GLU [n= 7 *(6.0%)*], LAC [n= 8 *(6.9%)*], pH [n= 3 *(2.6%)*], BE [n= 4 *(3.4%)*], and BIC [n= 6 *(5.2%)*].

The mean time point, when the blood samples were taken, was 17 minutes (13-20) in preterm and 16 minutes (11-20) in term neonates after birth.

### 8.4 Demographic data and routine monitoring

Demographic data and routine monitoring of preterm and term neonates are presented in table 3.

### 8.5 Respiratory support

12 (33%) preterm neonates and 9 (8%) term-born neonates received supplemental oxygen.

17 (47%) preterm neonates received mask ventilation and 0 (0%) preterm neonates were intubated during the immediate transition after birth.

19 (16%) preterm neonates received mask ventilation and 0 (0%) term neonates were intubated during the immediate transition after birth.

Group comparison

### 8.6 Group comparison

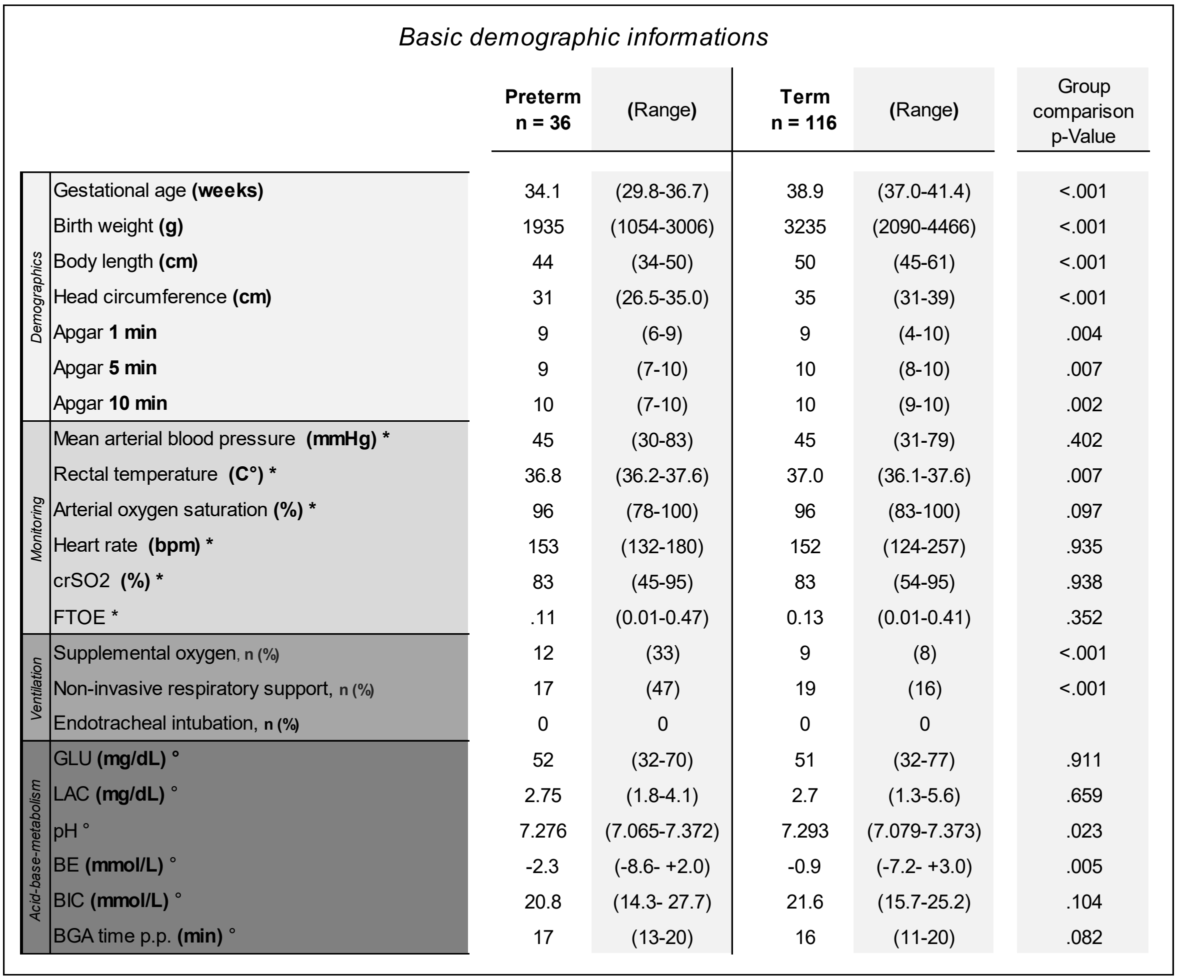
In addition to gestational age, body length, head circumference and birth weight, there was a significant difference in mean of the APGAR in minute 1, 5 and 10, rectal temperature, pH, and BE between term and preterm neonates. Further, there was a significant difference in preterm and term neonates received supplemental oxygen and face mask for ventilator support. There were no significant differences in mean cerebral oxygenation parameters or time of blood gas analysis postpartum between preterm and term neonates.

## 8.7 Main results

### 8.7.1 Acid-base metabolic parameters

The blood glucose level (GLU) and the parameters of the acid-base metabolism (LAC, pH, BE and BIC) of preterm neonates at 15 minutes after the transition are 52 mg/dL, 2.7 mg/dL, 7.27, -2.3 mmol/L, 20.8 mmol/L, respectively (table 3). The numbers and percentages of measured blood-glucose level and the parameters of the acid-base metabolism (LAC, pH, BE and BIC) of preterm neonates during the 10-20 minutes after the transition are 32 (89%), 32 (89%), 34 (94%), 35 (97%), 32 (89%), respectively.

The blood glucose level (GLU) and the parameters of the acid-base metabolism (LAC, pH, BE and BIC) of term-born neonates at 15 minutes after the transition are 51 mg/dL, 2.7 mg/dL, 7.29, -0.9 mmol/L, 21.6 mmol/L, respectively (table 3). The numbers and percentages of measured blood-glucose level (GLU) and parameters of the acid-base metabolism (LAC, pH, BE and BIC) of term neonates during the 10-20 minutes after the transition are 149 (95%), 148 (95%), 153 (98%), 152 (97%), 150 (96%), respectively.



Basic demographic informations

| | | Preterm n = 36 | (Range) | Term n = 116 | (Range) | Group comparison p-Value |
|---|---|---|---|---|---|---|
| Demographics | Gestational age **(weeks)** | 34.1 | (29.8-36.7) | 38.9 | (37.0-41.4) | <.001 |
| | Birth weight **(g)** | 1935 | (1054-3006) | 3235 | (2090-4466) | <.001 |
| | Body length **(cm)** | 44 | (34-50) | 50 | (45-61) | <.001 |
| | Head circumference **(cm)** | 31 | (26.5-35.0) | 35 | (31-39) | <.001 |
| | Apgar **1 min** | 9 | (6-9) | 9 | (4-10) | .004 |
| | Apgar **5 min** | 9 | (7-10) | 10 | (8-10) | .007 |
| | Apgar **10 min** | 10 | (7-10) | 10 | (9-10) | .002 |
| Monitoring | Mean arterial blood pressure **(mmHg) *** | 45 | (30-83) | 45 | (31-79) | .402 |
| | Rectal temperature **(C°) *** | 36.8 | (36.2-37.6) | 37.0 | (36.1-37.6) | .007 |
| | Arterial oxygen saturation **(%) *** | 96 | (78-100) | 96 | (83-100) | .097 |
| | Heart rate **(bpm) *** | 153 | (132-180) | 152 | (124-257) | .935 |
| | crSO2 **(%) *** | 83 | (45-95) | 83 | (54-95) | .938 |
| | FTOE * | .11 | (0.01-0.47) | 0.13 | (0.01-0.41) | .352 |
| Ventilation | Supplemental oxygen, **n (%)** | 12 | (33) | 9 | (8) | <.001 |
| | Non-invasive respiratory support, **n (%)** | 17 | (47) | 19 | (16) | <.001 |
| | Endotracheal intubation, **n (%)** | 0 | 0 | 0 | 0 | |
| Acid-base-metabolism | GLU **(mg/dL) °** | 52 | (32-70) | 51 | (32-77) | .911 |
| | LAC **(mg/dL)** ° | 2.75 | (1.8-4.1) | 2.7 | (1.3-5.6) | .659 |
| | pH ° | 7.276 | (7.065-7.372) | 7.293 | (7.079-7.373) | .023 |
| | BE **(mmol/L)** ° | -2.3 | (-8.6- +2.0) | -0.9 | (-7.2- +3.0) | .005 |
| | BIC **(mmol/L)** ° | 20.8 | (14.3- 27.7) | 21.6 | (15.7-25.2) | .104 |
| | BGA time p.p. **(min)** ° | 17 | (13-20) | 16 | (11-20) | .082 |

**Table 3:** Basic demographic information of basic information, monitoring parameters, ventilation parameters, blood-glucose level, acid-base metabolism in preterm and term neonates after the transition after birth with median (range) and group comparison (p-value). **bpm**= beats per minute, **GLU**= blood glucose level, **LAC**= blood lactate, **pH**= pH value, **BE**= base excess, **BIC**= bicarbonate, **min**= minute, *= in the 15th minute after birth, °= between the 10th to the 20th minute after birth.

An overview of the basic demographic information of the included neonate is given in **Table 3**

### 8.7.2 *Cerebral regional oxygen saturation*

Five (12%) preterm neonates had $crSO^2$ values <10th centile and nine (21%) >90th centile at 15 minutes after birth according published reference ranges.[214]
Four (3%) term neonates had $crSO^2$ values <10th centile and 24 (21%) >90th centile according published reference ranges.[214].

### 8.7.3 *Fractional tissue oxygen extraction*

Three (7%) preterm neonates had FTOE values <10th centile and three (7%) >90th centile at 15 minutes after birth according published reference ranges.[214]
26 (22%) term neonates had FTOE values <10th centile and three (3%) >90th centile according published reference ranges.[214]

### 8.7.4 *Blood-glucose and acid-base metabolism*

There are no existing reference ranges for the blood-glucose level or the acid-base metabolic parameters measured in the capillaries in neonates during the immediate transition after birth, therefore comparison to reference ranges was not possible.

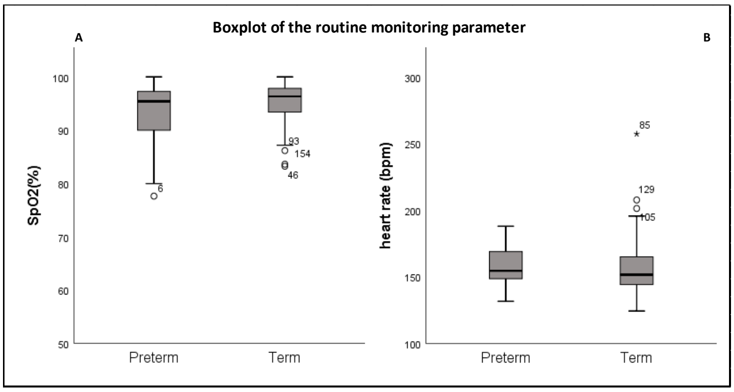


**Figure 2.:** Box-whisker plots of routine monitoring parameter of preterm and term neonates at the 15th minute after birth. **A**= arterial oxygen saturation (%); **B**=heart rate (bpm) measured with pulse oximetry. The boxes represent the 25th and 75th percentile of the measurements with the median in the center, the whiskers represent the range of the measurements. The numbered stars represent outliers. $SpO^2$= peripheral oxygen saturation.

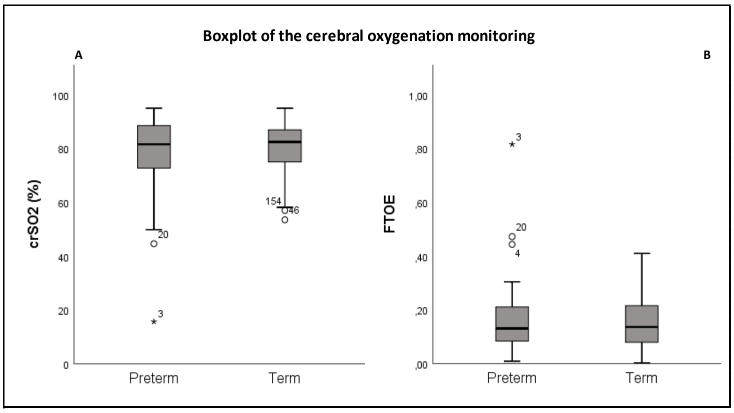


**Figure 3.:** Box-whisker plots of the cerebral oxygenation monitoring measured with near-infrared spectroscopy of preterm and term neonates at the 15th minute after birth. **A**= cerebral regional oxygen saturation **(%)**; **B**= fractional tissue oxygen extraction. The boxes represent the 25th and 75th percentile of the measurements with the median in the centre, the whiskers represent the range of the measurements. The numbered stars represent outliers. $crSO^2$= cerebral regional oxygen saturation; FTOE= fractional tissue oxygen extraction.

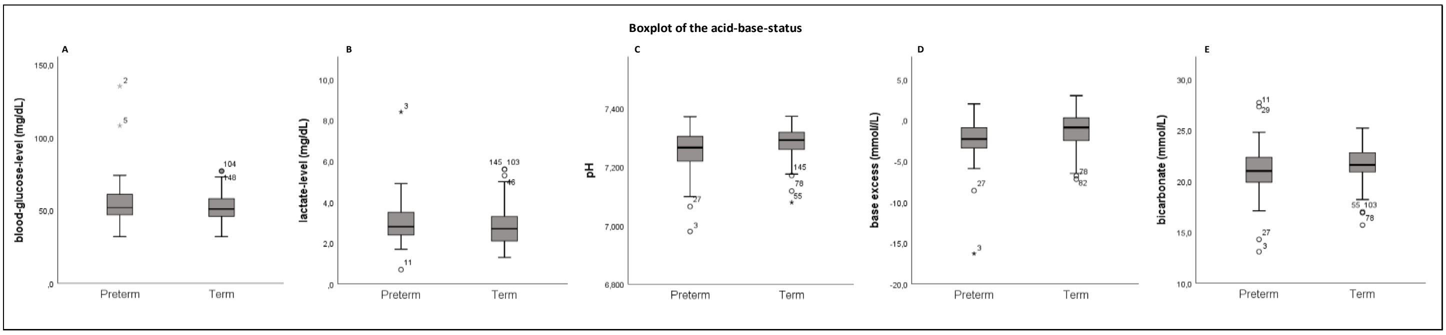


**Figure 4.:** Box-whisker plots of the blood-glucose level and the acid-base-metabolic parameter measured in capillary blood of preterm and term neonates measured between **the 10th and 20th** minute after birth. **A**= GLU **(mg/dL), B**= LAC **(mg/dL)**, **C**= pH, **D**= BE **(mmol/L)**, **E**= BIC **(mmol/L).** The boxes represent the 25th and 75th percentile of the measurements with the median in the center, the whiskers represent the range of the measurements. The numbered stars represent outliers. GLU= blood-glucose level; LAC= lactate level; pH= pH level; BE= base excess; BIC= bicarbonate.

**Figures 4** to **6** show the boxplots of the routine monitoring parameters, cerebral oxygenation monitoring and acid-base-metabolic parameters of preterm and term neonates during the immediate transition after birth.

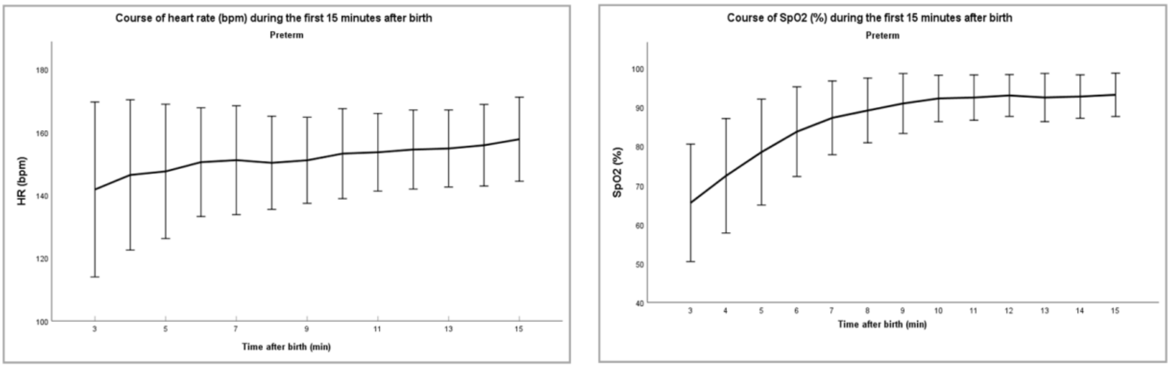


**Figure 5:** Course of routine monitoring measured with pulse oximetry of preterm neonates immediately after the transition. **A**= heart rate **(bpm)** during the first 15 minutes after birth **B**= preductal arterial oxygen saturation during the first 15 minutes after birth. **HR** = heart rate, **SpO$^2$** = arterial oxygen saturation. Mean value of SpO$^2$ and HR with **25th** and **75th** percentile, respectively.

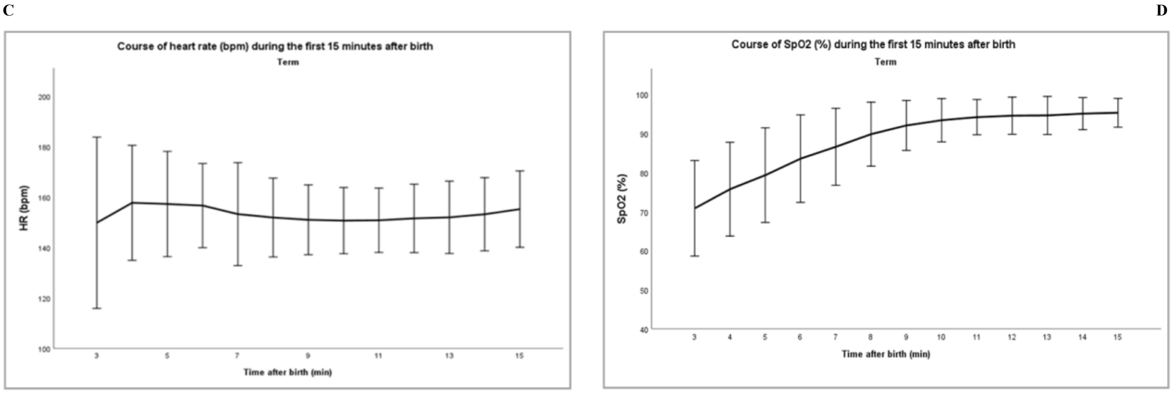


**Figure 6:** Course of routine monitoring measured with pulse oximetry of term neonates immediately after the transition. **C**= mean heart rate (bpm) with standard deviation during the first 15 minutes after birth; **D**= mean preductal measured arterial oxygen saturation with standard deviation during the first 15 minutes after birth. **HR** = heart rate, **SpO$^2$** = arterial oxygen saturation. Mean value of SpO$^2$ and HR with **25th** and **75th** percentile, respectively.

**Figures 7 and 8** provide the course of the course of routine monitoring in preterm and term neonates during the 15 minutes after birth measured with pulse oximetry.

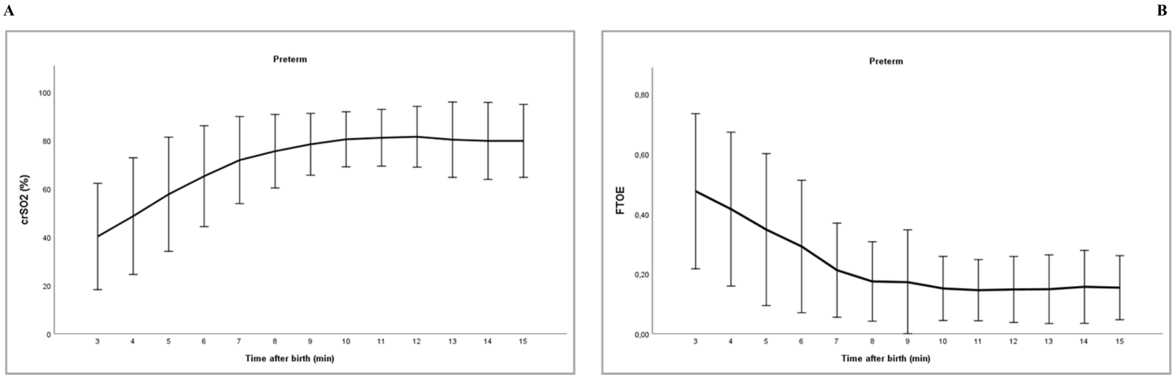


**Figure 7:** Course of cerebral oxygenation **(crSO$^2$ (%), FTOE)** during the first 15 minutes after the transition after birth in preterm neonates. **A**= mean values of **crSO$^2$ (%)** during the first 15 minutes after birth, **B**= mean values of **FTOE** during the first 15 minutes after birth; Mean value of crSO2 and FTOE with 25th and 75th percentile, respectively; **crSO2**= cerebral regional oxygen saturation, **FTOE**= Fractional tissue oxygen extraction.

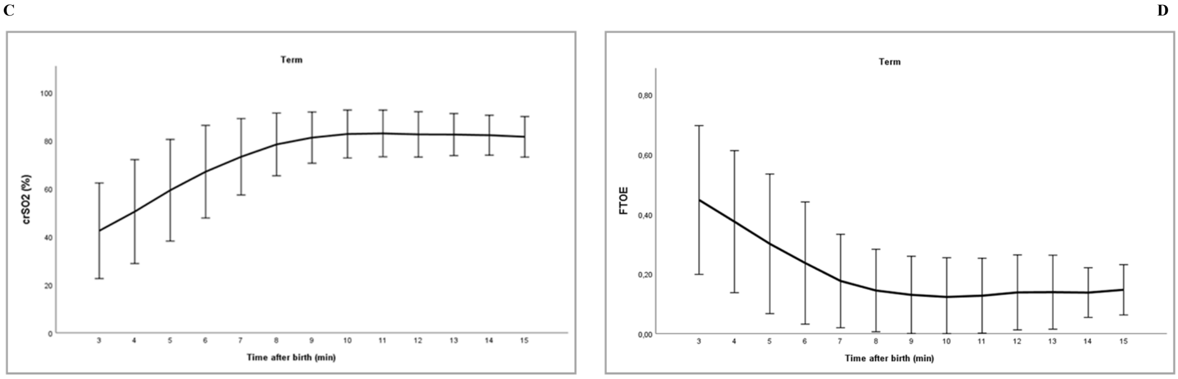


**Figure 8:** Course of cerebral oxygenation **(crSO$^2$ (%), FTOE)** during the first 15 minutes after the transition after birth in preterm neonates. **C**= mean values of **crSO$^2$ (%)** during the first 15 minutes after birth, **D**= mean values of **FTOE** during the first 15 minutes after birth; Mean value of **crSO$^2$** and **FTOE** with 25th and 75th percentile, respectively; **crSO$^2$**= cerebral regional oxygen saturation, **FTOE**= Fractional tissue oxygen extraction.

**Figures 9 and 10** illustrate the course of crSO$^2$ (%) and FTOE in preterm and term neonates during the first 15 minutes after the transition after birth.

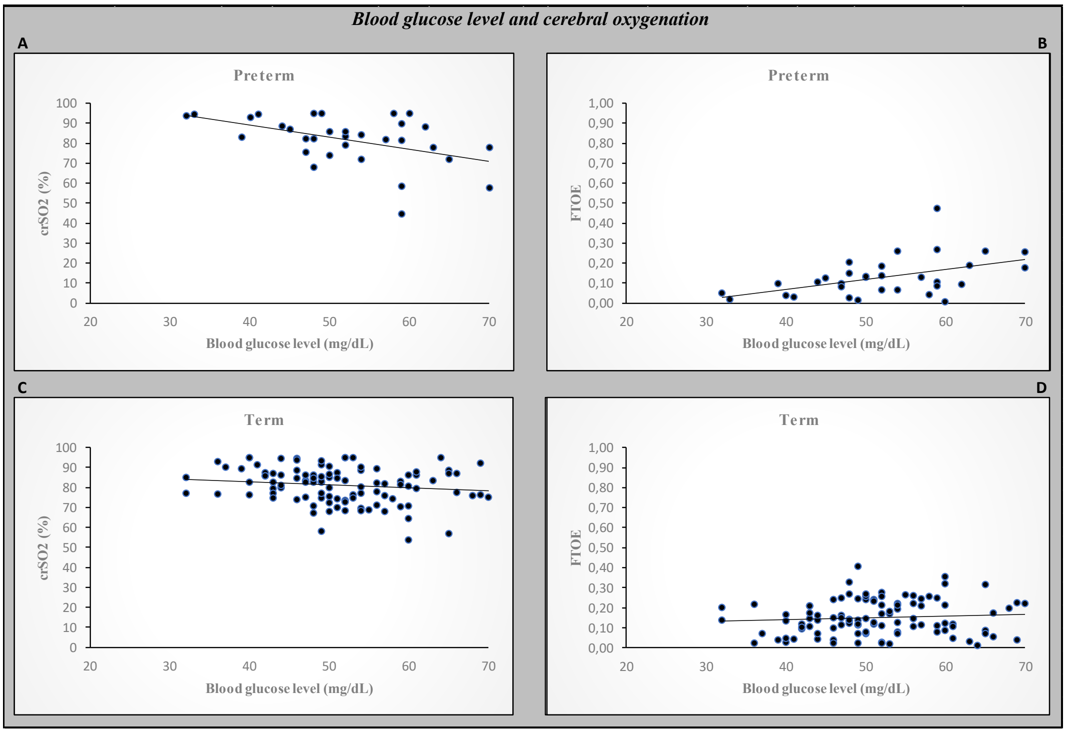


**Figure 9:** Correlation between **$crSO^2$ (%)** and **GLU (mg/dL)** and **FTOE** with **GLU (mg/dL)** in preterm **(A&B)** and at term **(C&D)** neonates. **A**, q = -.408 P= .020; **B**, q = .454 P = .009; **C**, q = -.195, P = .042; **D**, q = .116, P = .232; **$crSO^2$ (%)** = cerebral regional oxygen saturation, **FTOE** = fractional tissue oxygen extraction, **GLU** = blood glucose level.

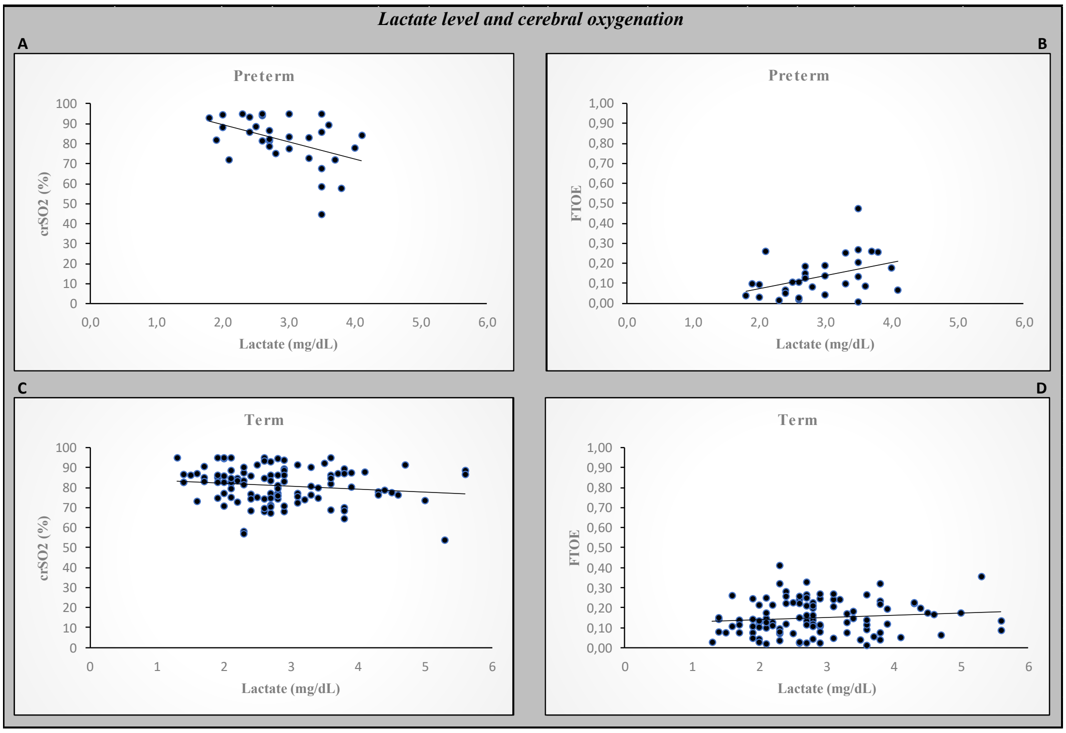


**Figure 10:** Correlation between **$crSO^2$ (%)** and **LAC (mg/dL)** and **FTOE** with **LAC (mg/dL)** in preterm **(A&B)** and at term **(C&D)** neonates. **A**, q = −.428, P = .015; **B**, q = .435, P = .013; **C**, q = -.133, P = .170; **D**, q = .124, P = .200; **$crSO^2$ (%)** = cerebral regional oxygen saturation, **FTOE** = fractional tissue oxygen extraction, **LAC** = lactate level.

The scatter plots of the blood glucose level (GLU) and the parameter of the acid-base-metabolism parameters (LAC) and cerebral oxygenation (crSO2 and FTOE) of preterm and term neonates are illustrated in **Figures 11 to 12.**

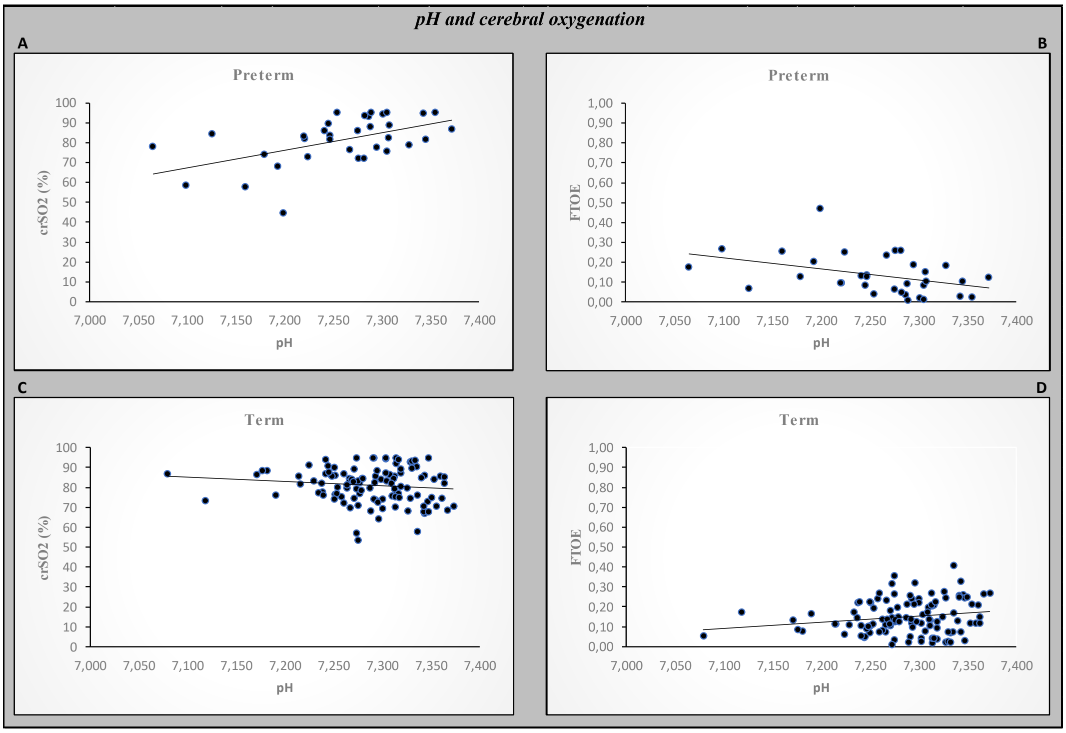


**Figure 11:** Correlation between **crSO$^2$ (%)** and **pH** and **FTOE** with **pH** in preterm **(A&B)** and at term **(C&D)** neonates. **A**, q = .501, P= .003; **B**, q = -.425, P = .012; **C**, q = -.129, P = .173; **D**, q = .163, P = .085; **crSO$^2$ (%)** = cerebral regional oxygen saturation, **FTOE** = fractional tissue oxygen extraction.

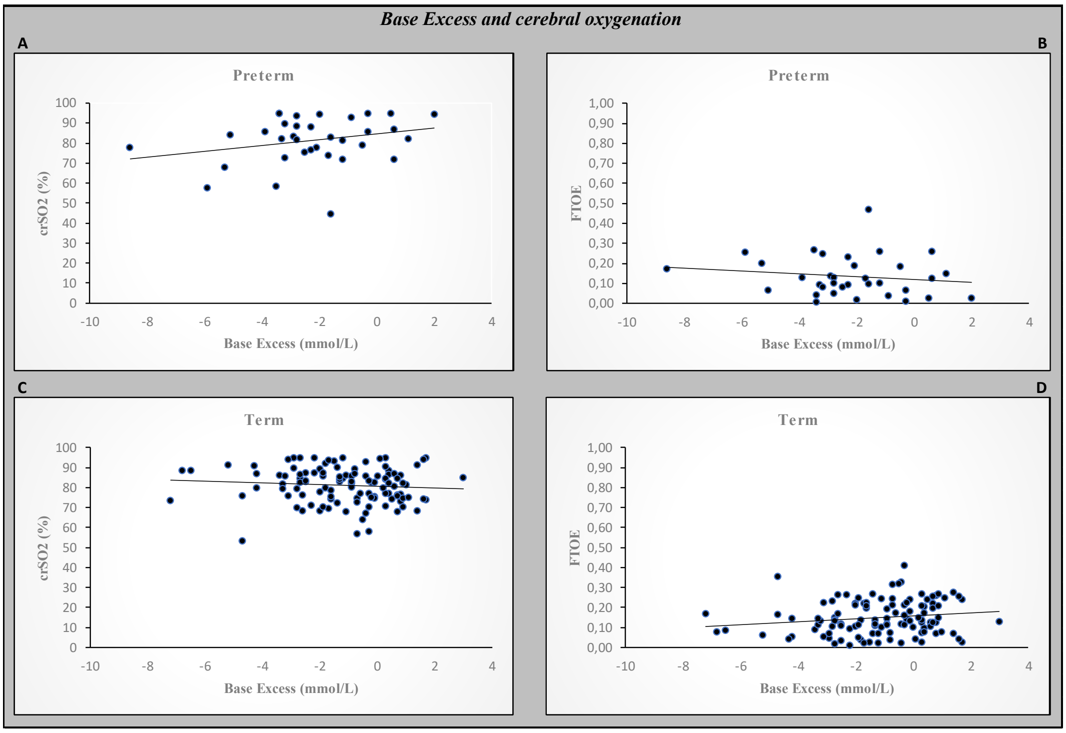


**Figure 12:** Correlation between **crSO$^2$ (%)** and **BE (mmol/L)** and **FTOE** with **BE (mmol/L)** in preterm **(A&B)** and at term **(C&D)** neonates. **A**, q = .187, P = .290; **B**, q = -.163, P = .358; **C**, q = -.149, P = .118; **D**, q = .184, P = .052; **crSO$^2$ (%)** = cerebral regional oxygen saturation, **FTOE** = fractional tissue oxygen extraction, **BE** = base excess.

The scatter plots of the parameter of the acid-base-metabolism parameters (pH and BE) and cerebral oxygenation (crSO2 and FTOE) of preterm and term neonates are illustrated in **Figures 13 to 14.**

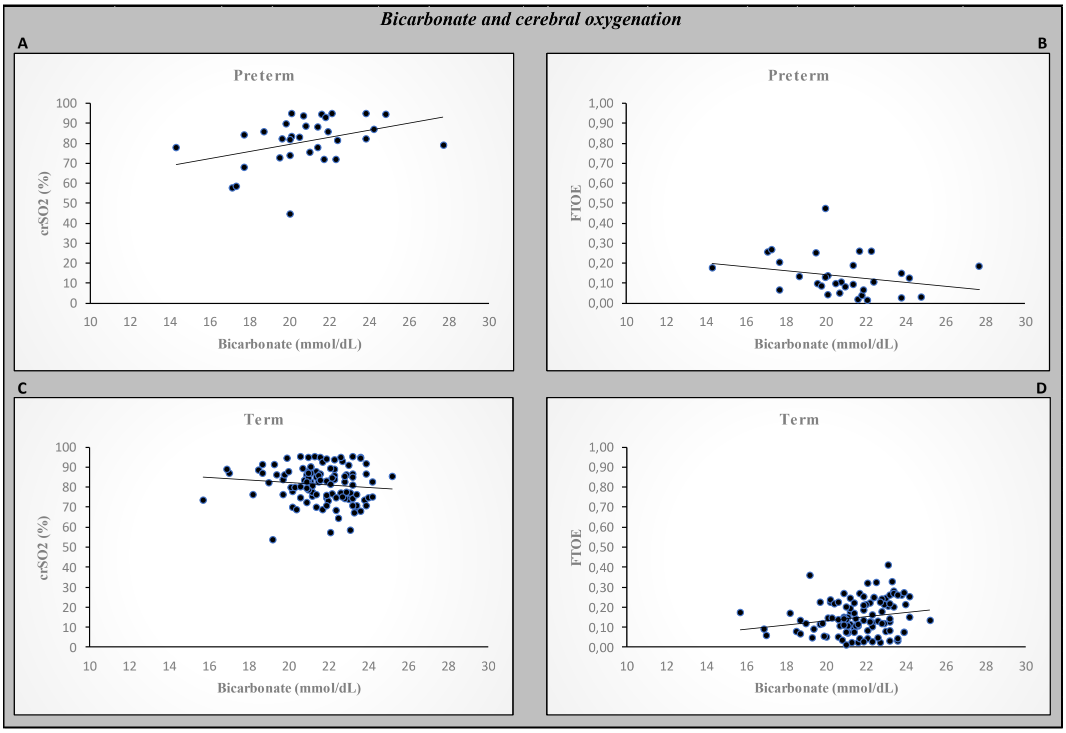


**Figure 13:** Correlation between **crSO$^2$ (%)** and **BIC (mmol/L)** and **FTOE** with **BIC (mmol/L)** in preterm **(A&B)** and at term **(C&D)** neonates. **A**, q = .399, P = .04; **B**, q = -.346, P = .052; **C**, q = -.169, P = .078; **D**, q = .212, P = .026; **crSO$^2$ (%)** = cerebral regional oxygen saturation, **FTOE** = fractional tissue oxygen extraction, **BIC** = bicarbonate.

The scatter plots of the parameter of the acid-base-metabolism parameters (BIC) and cerebral oxygenation (crSO2 and FTOE) of preterm and term neonates are illustrated in **Figures 15.**

### *8.7.5 Correlation analysis*

There was a significant negative correlation between crSO$^2$ and GLU in preterm and term-born neonates. There was a significant positive correlation between FTOE and GLU in preterm but not in term-born neonates. The correlations in preterm neonates were more pronounced compared to term neonates **(see Table 4).**

Correlation analyses between LAC and crSO$^2$ showed a significant negative correlation, and LAC and FTOE showed a significant positive correlation in preterm neonates. There is no significant correlation between LAC and crSO$^2$ and FTOE in term-born neonates.

Correlation analyses between pH and BIC on crSO$^2$ showed a significant positive correlation, and pH on FTOE showed a significant negative correlation in preterm neonates. There was a trend to a negative correlation between BIC and FTOE. There were no significant correlations between pH and BE on crSO$^2$ in term neonates, while a significant positive correlation between BIC on FTOE in term neonates was visible. There was a trend to a negative correlation between BIC and crSO$^2$ in term neonates. No correlation between pH, BE and FTOE was found, even though there was a trend towards positive correlations in term neonates. There was no correlation between LAC and FTOE in term neonates.

***Correlation analysis***

| | ***Preterm*** | | | | ***Term*** | | | |
|---|---|---|---|---|---|---|---|---|
| | crSO2 **(%)** | p-value | FTOE | p-value | crSO2 **(%)** | p-value | FTOE | p-value |
| *GLU* ***(mg/dL)*** | -.408 | .020 | .454 | .009 | -.195 | .042 | .116 | .232 |
| *LAC* ***(mg/dL)*** | -.428 | .015 | .435 | .013 | -.133 | .170 | .124 | .200 |
| *pH* | .501 | .003 | -.425 | .012 | -.129 | .173 | .163 | .085 |
| *BE* ***(mmol/L)*** | .187 | .290 | -.163 | .358 | -.149 | .118 | .184 | .052 |
| *BIC* ***(mmol/L)*** | .399 | .024 | -.346 | .052 | -.169 | .078 | .212 | .026 |

**Table 4:** Results of the Spearman correlation analysis showing correlations between the parameters of cerebral oxygenation **(crSO$^2$ (%), FTOE),** and the blood-glucose level **(GLU)** and acid-base metabolic parameters **(LAC pH, BE & BIC)**. **crSO$^2$**= cerebral regional oxygen saturation, **FTOE**= Fractional tissue oxygen extraction, **GLU**= blood glucose level, **LAC**= blood lactate, **pH**= pH value, **BE**= base excess, **BIC**= bicarbonate

**Table 4** gives an overview of the correlation analysis of cerebral oxygenation with the acid-base metabolic parameters and the blood glucose level in term and preterm neonates during the immediate transition after birth.

# 9 Discussion

To the best of our knowledge, this is the first study that demonstrated a significant correlation between the blood-glucose and parameters of the acid-base metabolism and cerebral oxygenation in preterm and term neonates during the immediate transition after birth, whereby preterm neonates showed more and stronger associations compared to term-born neonates.

Early identification of an imbalance between cerebral oxygen supply and cerebral oxygen consumption in the neonatal brain is very important, especially during the immediate transition after birth. Both, hypoxia and hyperoxia during the immediate transition after birth are associated with an increased risk of cerebral injury.[218] However, there is no clear consensus on how the blood-glucose level or the parameters of the acid-base metabolism have an impact on the cerebral oxygenation in neonates during the immediate transition after birth.

Currently existing literature on the association between the blood-glucose level and parameters of the acid-base-metabolic and cerebral oxygenation in the neonatal period reveal conflicting results.[151,158-159,220-234]

Some studies demonstrate correlations between the blood glucose or the parameters of the acid-base-metabolic and the cerebral tissue oxygenation[151,158-159,220,223-226,232-234], whereas others describe the absence of such correlations.[221-222,227-231]

*GLU and cerebral oxygenation*

GLU is essential for the neonatal cerebral metabolism and hypoglycemia or hyperglycemia is associated with an increased risk of brain damage, including IVH or ROP and increased morbidity.[51,227,239-241] Our study demonstrates a negative correlation between GLU and $crSO^2$ and a positive correlation between GLU and FTOE in preterm neonates. Furthermore, there was a negative correlation between GLU and $crSO^2$ and no correlation between GLU and FTOE in term neonates during the immediate transition after birth.

Similar results have been published in very preterm neonates admitted to an intensive care unit during the first 6 hours of life[155] in very low birth weight neonates during the first 7 days of life[227], in critically-ill neonates during the Norwood procedure[229], in neonates during the first 72 hours after the Norwood procedure[230] and, in preterm and term neonates during the 15th minute after birth[238]. In contrast, other studies in preterm neonates during the first 3 days after birth[225] and in critically-ill neonates and infants, who have been free of cerebral disease or trauma for up to 1 year and who were admitted to the intensive care unit[226] did not demonstrate any correlations between GLU and $crSO^2$ or FTOE.

*LAC and cerebral oxygenation*

LAC, the anaerobic metabolic energy maintenance system, increases during an imbalance in cellular oxygenation.[153] Our study demonstrated a negative correlation between LAC and $crSO^2$ and a positive correlation between LAC and FTOE in preterm but not in term neonates during the immediate transition after birth.

Similar results have been published for extremely preterm neonates during the first days after birth.[233] In contrast, other studies in paediatric patients during surgical heart procedures[158], in critically-ill neonates, in infants, who have been free of cerebral disease or trauma for up to 1 year and who were admitted to the intensive care unit[222] and, in neonates with prenatally diagnosed congenital heart disease during the first 72 hours after birth[229] did not demonstrate any correlations between LAC and $crSO^2$ or FTOE.

*pH and cerebral oxygenation*

Both, respiratory as well as metabolic acidosis may result from inadequate oxygen delivery and impaired gas exchange. The pH level measured in the umbilical arteries is the most sensitive indicator of fetal hypoxia during delivery and can be used for evaluating neonatal adaptation.[132] Our study demonstrated a significant positive correlation between pH and $crSO^2$ and a significant negative correlation between the pH and FTOE in preterm but not in term neonates during the immediate transition after birth. However, there was a trend toward a positive correlation between pH and FTOE in term neonates.

Similar results have been published in studies of neonates and infants undergoing thoracoscopic repair of congenital diaphragmatic hernia and esophageal atresia[224] and in fetuses shortly before birth[220]. In contrast to these two studies, other studies demonstrated a negative correlation between pH and $crSO^2$ in paediatric patients during surgical heart procedures[158] and in term neonates suffering from hypertrophic pyloric stenosis during correction of metabolic alkalosis[159]. Against them, other studies demonstrated the absence of correlation between pH and $crSO^2$ or FTOE in critically-ill neonates and infants who have been free of cerebral disease and trauma for up to 1 year and who were admitted to the intensive care unit[222], in very preterm neonates during the first 6 hours of life admitted to an intensive care unit[151], in neonates and children during cardiopulmonary bypass surgery[227], in extremely preterm neonates with very low birth weight during sodium BIC infusion for correction of metabolic acidosis during the first postnatal week[228], in term born infants with prenatally diagnosed congenital heart disease during the first 72 hours after birth[229], in clinically stable preterm infants in the intensive care unit[230] and, in term neonates with persisting pulmonary hypertension[231].

*BE and cerebral oxygenation*

The BE quantifies the magnitude of the metabolic acidosis and represents a risk factor for central neurologic injury and is also an important prognostic marker for short- and long-term outcome in asphyxiated neonates.[172,173] Our study demonstrated the absence of correlation between BE and $crSO^2$ or FTOE in preterm and term neonates. Despite this, there was a trend towards a positive correlation between BE and FTOE in term neonates. Similar to our results, other studies demonstrated the absence of a correlation between BE and $crSO^2$ or FTOE in critically-ill neonates and infants up to 1 year without cerebral diseases or trauma in the intensive care unit[222], in extremely preterm neonates with very low birth weight during sodium BIC correction of metabolic acidosis during the first postnatal week[228] and in clinically stable preterm neonates in the neonatal intensive care unit[230]. In contrast, other studies could demonstrate a negative correlation between BE and the cerebral oxygenation in term-born infants suffering from hypertrophic pyloric stenosis during correction of metabolic alkalosis[159], in fetuses shortly before birth[220] and in extremely preterm neonates during BIC administration during the first 24 postnatal hours[232].

*BIC and cerebral oxygenation*

Buffers are important for proton elimination and, particularly, the BIC buffer is the most important buffer system and contributes approximately one third to this effect.[167] Our results demonstrate a positive correlation between BIC and $crSO^2$ and a trend towards a negative correlation between BIC and FTOE in preterm neonates. Furthermore, there seems to be a trend towards a negative correlation between BIC and $crSO^2$ and a significant positive correlation between BIC and FTOE in term neonates during the immediate transition after birth.

Similar results have been published in extremely preterm neonates during BIC administration during the first 24 postnatal hours[232] and in term-born infants suffering from hypertrophic pyloric stenosis during correction of metabolic alkalosis[159]. In contrast, other studies demonstrated the absence of correlation between BIC and crSO$^2$ or FTOE in extremely preterm neonates with very low birth weight during sodium BIC correction of metabolic acidosis during the first week after birth [228] and in clinically stable preterm infants in the intensive care unit [230].

Currently existing publications demonstrated conflicting results. *Aldricht et al. 1994* investigated potential correlations between parameters of the acid-base status, measured in umbilical arterial and venous cord blood, and the cerebral oxygenation in the fetus during delivery. Similar to our results of the pH measured in capillary blood, the umbilical artery and venous pH showed a significant positive correlation with crSO$^2$. Furthermore, they demonstrated a significant negative correlation between BIC and the cerebral oxygenation of the fetus during delivery. Of interest, low crSO2 was related to both respiratory and metabolic acidosis during delivery.[220] *Naulaers et al. 2002* described an increase of cerebral oxygenation from day 1 to day 3 after birth in neonates with a postmenstrual age of 28 weeks. In contrast to our study, this study demonstrated the absence of correlation between GLU, pH and BIC to the measured cerebral oxygenation.[221] *Weiss M. et al. 2005* investigated different laboratory and vital parameters, and cerebral oxygenation in critically-ill term-born neonates and infants. Pearson correlation analysis of arterially measured pH, LAC and BE with the cerebral tissue oxygenation index demonstrated, similar to our results, the absence of significant correlations.[222] The cerebral oxygen supply in neonates is also related to the cerebral haemoglobin content. *Von Siebenthal K. 2005* investigated cerebral haemoglobin content in neonates during the first 6 hours of life. They described different parameters that influence the cerebral haemoglobin concentration of neonates, and found that GLU was negatively correlated to the cerebral haemoglobin concentration. Interestingly, the pH level of the umbilical arteries at birth was not correlated with the cerebral haemoglobin concentration.[151] *Vanderhaegen et al. 2010* reported on glycemia and cerebral NIRS measurements in very low birth weight neonates during the first 7 days of life. They detected, similar to our findings, a significant negative correlation between the level of GLU and crSO$^2$ as well as a significant positive correlation between GLU and FTOE. Interestingly, this correlation remained significant after correction for MABP, SpO$^2$ and transcutaneously measured CO$^2$ pressure.[223] *Bishay M. et al. 2011* described the effect of increased CO$^2$ absorption during thoracoscopic repair of congenital diaphragmatic herniation and esophageal atresia in neonates and infants.

Laparoscopic procedure with $CO^2$ was associated with hypercapnia and acidosis.[224] Despite this, the course of the pH and the cerebral oxygenation differed from our findings. We assume that the induced pneumothorax of the laparoscopic procedure can lead to a consecutive decrease of blood return to the neonatal heart and/or that the increased level of $CO^2$ possibly influences cerebral oxygenation. Interestingly, the decrease of $crSO^2$ during thoracoscopic repair did not recover during the first 24 hours after surgery in the majority of the neonates. This may indicate the slow recovery of the cerebral changes and therefore the impact of these long-term effects on the neonatal brain. *Amigoni et al. 2011* investigated variables that could have an impact on NIRS measurements in neonatal and pediatric patients during surgical heart procedures. In this study, a significant inverse correlation between pH and $crSO^2$ was observed. In contrast to this, no correlation between LAC and cerebral oxygenation could be detected. A possible explanation for the difference in results to our study was the small number of investigated populations compared to our study or the effect of the cardiopulmonary bypass on the cerebral oxygenation.[158] *Zhang et al. 2012* investigated systemic and cerebral oxygen transport in critically-ill neonates during the Norwood procedure and demonstrated a significant negative correlation of elevated GLU levels with the $crSO^2$ as well as with the cardiac output. Further, GLU elevation tended towards a positive correlation with LAC and indicated the link between GLU and LAC. They concluded that an increased GLU level affected the cellular function in all systems and in critically-ill patients, and pro-inflammatory cytokines upregulated the glucose transporters, which resulted in increased glycolysis, superoxide, and nitric oxide production. Following this, nitric oxide and superoxides led to peroxynitrite formation that resulted in disturbed mitochondrial function and adenosine triphosphate production with a consequently disturbed cellular energy metabolism.[225] *Li J. et al. 2012* investigated an impaired balance between oxygen delivery and oxygen consumption measured with mass spectroscopy and NIRS in neonates during the first 3 days after the Norwood procedure. A correlation analysis demonstrated that the $crSO^2$ was significantly influenced by all parameters that influence the systemic oxygen transport including GLU. These results regarding the correlation between GLU and $crSO^2$ were concordant with our findings for preterm and term neonates. Moreover, the researchers concluded that early improvements of systemic and regional oxygen transport might have an important impact on the long-term outcome.[226] *Menke J. et al. 2013* investigated different vital parameters and NIRS measurements during cardiopulmonary bypass surgery in neonates and children. The results demonstrated that central perfusion pressure, central venous pressure and central temperature, in contrast to the pH level, had a significant correlation with the cerebral oxygenation or the cerebral hemoglobin content. They concluded that acidosis might occur during hypovolemia with a consequently decreased cerebral blood flow and cerebral blood volume.[227] We assume that the effect of cardiopulmonary bypass or the small number of patients in contrast to our study might have an effect on the findings. *Mintzer J.P. et al. 2015* investigated the effect of sodium BIC correction in extremely preterm neonates with low birth weight suffering from metabolic acidosis and its effect on the cerebral oxygenation during the first 7 days after birth. The study detected a decrease of BE and an increase of the pH after a correction of BIC but without discernible effects or benefits for crSO$^2$ or FTOE.[228] These findings were in contrast to our results. A possible explanation of this phenomenon is the effect of increased BIC on osmolarity. Furthermore, an increased level of BIC led to a CO$^2$ generation with an increase in CO$^2$ and a consecutive impact on the cerebral blood flow. Both mechanisms could have an impact on the cerebral oxygenation and, ultimately, on the results of the study. *Mebius MJ et al. 2016* investigated the cerebral oxygenation of term-born infants with prenatally diagnosed congenital heart disease during the first 3 days after birth and did not find a correlation between the LAC or pH and the cerebral oxygenation.[229] In relation to the gestational age of the investigated population, these results are concordant with our results. *Hunter C.L. et al. 2017* assess correlations between crSO$^2$ and parameters of arterially measured BGA in clinically stable preterm infants. In contrast to the detected correlations between the parameters of hemoglobin, oxyhemoglobin and respiratory rate, no significant correlations between the pH and BIC and cerebral oxygenation were found.[230] Nevertheless, similar to our resutls, they demonstrated the absence of correlation between BE and cerebral oxygenation. We assume that the significantly smaller numbers of preterm neonates compared to our study are a possible reason for the difference in findings compared to our study. *Nissen M. et al. 2017* investigated the influence of metabolic alkalosis and its effect on the cerebral oxygenation in mostly term-born infants with hypertrophic pyloric stenosis. They observed an inverse correlation between corrected metabolic alkalosis and cerebral oxygenation. Furthermore, cerebral oxygenation was significantly inversely correlated with the level of BIC and BE. They assumed that the cerebral oxygenation during alkalosis might be influenced by the physiologically decreased oxygen release of hemoglobin. Furthermore, it is possible that the pH or CO$^2$ induced vasoconstrictory effect with a consecutive reduction of cerebral blood flow could be an explanation for this finding.[159] With regard to the missing significance concerning our results in term-born neonates, the course of the correlation is concordant with these findings. We expect that with an increased number of term-born neonates we would have a significant correlation between the parameters of the acid-base metabolism and the cerebral oxygenation. Further, *Mebius MJ et al. 2018* demonstrated the absence of a correlation between the clinical parameters pH, pCO$^2$, RR, nitrogen monoxide or sedative therapy and crSO$^2$ or FTOE in term-born neonates with persisting pulmonary hypertension during the first 72 hours after birth.[231] This study demonstrated, similar to our results the absence of correlation in term neonates. *Katheria A.C. et al. 2017* described hemodynamic changes during sodium BIC administration in extremely preterm neonates during the first 24 hours of life. BIC administration led to an increase in pH and a decrease in BE and CO$^2$ with a consecutive increase of crSO2 without changes in FTOE. Interestingly, the BIC administration did not affect the cardiac output. These findings differ from our results. The researchers assumed that the increased cerebral oxygenation without an effect on the cerebral extraction was related to a compensatory increase of CBF as a consequence of the decreased ABP. Additionally, BIC administration induced hyperosmolar peripheral and cerebral vasodilatation that was exaggerated during early postnatal transition.[232] *Baik N. et al. 2017* demonstrated that further relevant factors have an impact on cerebral oxygenation, such as mean arterial blood pressure, which showed a significantly negative correlation with the cerebral oxygenation in preterm but not in term neonates during the immediate transition after birth.[235] The findings demonstrated differences in correlations between preterm and term neonates. It can be assumed that this effect concerns the development of the ARM to compensate disturbance during and after the delivery. With increase in gestational age, the capacity of the cerebral ARM to compensate for inadequate oxygenation increases. Following this, term neonates are more able to compensate an imbalance in cerebral oxygenation compared to preterm neonates during the immediate transition after birth. This explains, why correlations in term neonates in contrast to preterm neonates are less pronounced. *Janaillac M. et al. 2018* published similar findings and demonstrated a weak correlation between LAC and cerebral tissue oxygenation as well as a weak correlation between the pH and the cerebral tissue oxygenation during the hemodynamic assessment of extremely preterm neonates during the first 3 days of life.[233] However, none of these correlations were significant and they suggested that this clinical parameter should not be taken to assess the hemodynamic status in preterm infants by itself.

We assume that the blood-glucose level and different parameters of the acid-base metabolism can have a potential influence on the cerebral oxygenation of the neonatal brain during the immediate transition after birth.

Firstly, Skov et. al demonstrated that with increased levels of GLU, the CBV decreased. They described this phenomenon as "recruitment of the vessels". With a decrease in GLU, previously unperfused capillaries are recruited for maintenance of the cerebral glucose transport into the neurons of the neonatal brain.[51] This mechanism can explain our findings of the increased cerebral oxygenation due to the increased perfusion under the assumption of constant oxygen consumption. Furthermore, the effect of GLU on an increase in cerebral hemoglobin concentration suggested the relevance in this field.[151]

Secondly, LAC is, due to the lesser permeability of the placenta and the selective increase by anaerobe conditions, an unspecific chemical marker for neonatal hypoxia during the delivery.[154] LAC indicates tissue hypoxia and is thus an indication for an imbalance between oxygen demand and oxygen supply. A compensatory increase of the blood flow during this status is necessary to prevent induced cellular damage by hypoxia. Further, increased LAC can also be the result of hyperglycolysis and is therefore related to the level of GLU.[225] Studies demonstrated the relation between LAC, glutamate and the level of extracellular potassium. The level of extracellular potassium was inversely related to the CBF, intracranial pressure and, finally, to a fatal outcome in patients after brain injury.[236,237] Furthermore, LAC led to a relative hypovolemia due to redistribution, to a pulmonary vasoconstriction and a reduction in cardiac stroke volume as a result of reduced cardiac contractility with consequential inadequate cardiac output.[238] Consequently, increase in LAC levels might affect the cardiac output with a consequent decrease in oxygen delivery and a resulting decrease in crSO2. Additionally, increase of LAC leads to a decrease in pH with consequential effects on the neonatal heart, too.[239]

Thirdly, the pH level represents a relation of oxygen supply and demand and has an enormous effect on the total organism. A deficit of oxygen supply leads to an increase in acid products with a consecutive decrease in the pH. Following this, decreased pH can be compensated by increase in blood flow initiated through an increase in the diameter of the arterial vessels. This leads to a replenishment of the tissue with the necessary substrates and the removal of the metabolic products.[24] Consequently, it is explainable why a very low pH above the border of the compensation capacity of the ARM is associated with IVH, PVL, HIE or cerebral palsy in neonates during the immediate transition after birth.[162] Furthermore, acidosis leads on one hand to a reduced contractility of cardiomyocytes with a consequent reduction in cardiac output as a consequence of reduced responsiveness to catecholamine that would suggest a negative correlation of pH and cerebral oxygenation.[240] On the other hand, it leads to the redistribution of blood from the peripheral venous system into the lungs with increased left atrial pressure.[240] Additionally, depending on the tissue, severe acidosis and alkalosis lead to a vasoconstriction or vasodilatation[160], whereby acidosis leads usually to vasodilation of cerebral vessels with increase in cerebral blood flow and oxygenation.[158] This mechanism can be considered as a compensation mechanism following regional imbalance between oxygen supply and oxygen demand to increase the blood flow. This compensation mechanism can be underdeveloped in preterm neonates, which could explain our results regarding a detected association in preterm but not in term neonates. Finally, elevated blood pH stimulates central and peripheral chemoreceptors, resulting in a respiratory depression with subsequent hypercapnia. Hypercapnia has a dilatating effect on cerebral vessels and may further increase the cerebral blood flow and consequentially increase cerebral oxygenation.[159]

Fourthly, the BE was calculated from pH, BIC, partial pressure of $CO^2$, and Hb content and is further inversely correlated with $crSO^2$ in neonates with metabolic and respiratory acidosis during the delivery.[132,171,220] Following this, BE gives an overview of the individual relation of all parameters included in the *Van Slyke* equation. With an increased level of BE, the incidence of HIE, cerebral palsy and mortality increased. Furthermore, the BE is an indicator of shock and efficacy of resuscitation and reflective of the true volume deficit.[241] It can be assumed that increased BE demonstrates a centralisation with its resulting hemodynamic problems for the oxygen delivery. In our study the BE was mainly in the normal range. Following this, we assume that the above described effect of BE on the cerebral oxygenation was not visible.

Fifthly, the BIC buffer system is the most important buffer and administration of BIC in extremely preterm neonates can lead to an increase of $crSO^2$. BIC can have an enormous effect on the pH as infusion of sodium BIC leads to a transient increase in cardiac output, aortic blood flow, systolic blood pressure and transcutaneously measured $pCO^2$ and $pO^2$ in neonates with mechanical ventilation.[242] Furthermore, infusion of BIC in mechanically ventilated neonates decreases the pulmonary artery blood pressure and the cardiac after load that might again effect the cardiac output and oxygen supply to the brain.[242] Finally, an increase in BIC leads to a $CO^2$ generation with a resulting increase in CBF.[243] Whether this effect is related to BIC or to its consecutive increase of osmolarity or the effect of $CO^2$

generation is questionable. Finally, the BIC level is related to the LAC and BE levels in extremely preterm neonates during the first day of life.[232]

### *9.1 Strengths and Limitations*

One of the strengths of this study is that the analysed data were recorded prospectively as secondary outcome parameters of a prospective observational study. A further strength of this study is the inclusion of different potentially influencing parameters that could have an impact on the cerebral oxygenation. Additionally, this study includes a homogeneous population of neonates, which allows some degree of generalization.

Cerebral oxygenation depends on many factors. Thus, this study is limited by the lack of exclusion of other possible factors impacting on the respiratory or cardiovascular systems. However, this study aimed to indicate an additional impact of the blood-glucose or the acid-base metabolism on the cerebral oxygenation. Further limitations include the sample size, especially of preterm neonates. The sample size of preterm neonates was smaller compared to term-born neonates. However, despite the lower number of preterm neonates identified associations were pronounced compared to term neonates. A further limitation concerns the time differences between the time point BGA and the cerebral NIRS measurements. In some neonates, there were up to five minutes between the final $crSO^2$ measurement and taking the blood sample. Nevertheless, it can be assumed that the blood-glucose level and the parameters of the acid-base metabolism did not change significantly within these five minutes.

The different parameters of the acid-base metabolism are related and interfere with each other. Whether only one or more factors are responsible for our findings is unclear. Additionally, there are no existing reference ranges of parameters for the acid-base-metabolic parameters or the blood-glucose level measured from capillary blood samples in neonates during the first 15 minutes after birth, which makes a comparison to normal values measured from arterial blood samples difficult. Moreover, the comparability of parameters such as LAC is complicated, because the level of LAC is related to gestational age.[244] A further limitation concerns the absence of continuous measuring of the blood-glucose level or acid-base-metabolic parameters. However, from an ethical point of view, measuring these biochemical indicators of organ hypoperfusion, such as LAC, cannot be measured continuously.[245] One further limitation might be that $crSO^2$ is the result of oxygen delivery and consumption, and both are influenced by various parameters. On the one hand, oxygen delivery is influenced by cerebral perfusion, which depends on cardiac output and vascular resistance, whereby the latter depends on the cerebral ARM.[246,247] On the other hand, oxygen delivery is further influenced by the oxygen content of the arterial blood depending on the hemoglobin concentration and the oxygen saturation ($SpO^2$).[246] However, despite these multifactorial influences on cerebral oxygenation, the present study demonstrated an association of the blood-glucose level and the parameters of the acid-base metabolism with the cerebral oxygenation that is most probably due to changes in oxygen consumption and cerebral perfusion/autoregulation. The use of ventilatory support has a direct or indirect effect on cerebral metabolism, vascular tone, and the cerebral ARM. Ventilatory support generally affects in particular preterm neonates with worse BGA values. This effect could have biased the $crSO^2$ and FTOE.

Our study was not designed to identify a cause-and-effect relationship. Randomized clinical trials are necessary to provide information on the causal relationship between parameters of the blood-glucose level and the parameters of the acid-base metabolism with the cerebral oxygenation.

## 9.2 Conclusion

There are statistically significant associations between the blood glucose and the parameters of the acid-base metabolism and the cerebral oxygenation in preterm and term neonates during the immediate transition after birth. Preterm neonates have more pronounced associations compared to term neonates. Further studies to test for causality and to identify the role of each factor on the cerebral oxygenation in neonates are necessary.

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