Dissertation

Arterial blood pressure and cerebral tissue oxygenation during immediate transition after birth in term and preterm neonates – a prospective pilot observational study

submitted by

Dr. med.univ. Daniel Pfurtscheller, BA

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Univ.Prof. Dr.med.univ. Gerhard Pichler

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Statutory Declaration

I hereby declare that this thesis is an original work of mine and that I have acknowledged all those individuals and organizations that have contributed to the research of this thesis by name. The acknowledgement has been made throughout this thesis and in all related publications and the guidelines of “Good Scientific Practice” have been followed as well.

Graz, Feb 19th 2025 Daniel Pfurtscheller

Disclosures

A review as well as the unpublished data served as basis for this thesis. I am the first author of this publication and included parts of it are in my thesis.

I informed all co-authors about the publication of this thesis. All co-authors have agreed to the inclusion of their illustrations, figures, and published data in the dissertation. and permission to reproduce illustrations and figures from their own publications has been granted.

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1 Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, 8036 Graz, Austria;
2 Research Unit for Neonatal Micro- and Macrocirculation, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, 8036 Graz, Austria;
3 Research Unit for Cerebral Development and Oximetry, Division of Neonatology, Medical University of Graz, 8036 Graz, Austria;

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Daniel Pfurtscheller[1,2,] , Christina H Wolfsberger[1,2,], Nina Höller[1,2,] , Bernhard Schwaberger[1,2,] , Lukas P Mileder[1,2,] , Nariae Baik-Schneditz[1,2,] , Berndt Urlesberger[1,2,] , Georg M Schmölzer[3,4,], Gerhard Pichler[1,2,]

1 Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria.

2 Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

3 Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, Royal Alexandra Hospital, Edmonton, Alberta, Canada.

4 Department of Pediatrics, Division of Neonatology Department of Pediatrics and Adolescent Medicine Medical, University of Alberta, Edmonton, Alberta, Canada.

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Abbreviations and Definitions

Abbreviations	Definition
ABP1	first harmonic of arterial pressure
CARM	Cerebral autoregulatory mechanism
CBF	Cerebral blood flow
CFTOE	Cerebral fractional tissue oxygen extraction
CO	Cardiac output
CPAP	Continuous Positive Airway Pressure
CPP	Cerebral perfusion pressure
CPPe	estimates CPP
CRIB	Clinical Risk Index for Babies
CrSO2	Cerebral regional oxygen saturation
CTOI	Cerebral tissue oxygen saturation index
CVR	Cerebral vascular resistance
DABP	Diastolic arterial blood pressure
ECG	Electrocardiogram
FTOE	Fractional tissue oxygen extraction
HHb	Deoxygenated hemoglobin
HR	Heart rate
IPPV	Intermittent Positive Pressure Ventilation
IVH	Intraventricular hemorrhage
MABP	Mean arterial blood pressure

NICOM	Non-invasive cardiac output measurement
NICU	Neonatal intensive care units
NIRS	Near infrared spectroscopy
O2HB	Oxygenated hemoglobin
PO	Pulse oximetry
PVL	Periventricular leukoencephalopathy
RCT	Randomized clinical trials
RDS	Respiratory distress syndrome
SABP	Systolic arterial blood pressure
SpO2	Arterial oxygen saturation
SV	Stroke volume
tHb	Total hemoglobin
TOI	Tissue oxygen saturation index
VO	mean blood flow velocity
VI	pulsatile amplitude of flow

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Abstract in German

Hintergrund und Ziel:

Das Ziel dieser Studie war es, den Einfluss des arteriellen Blutdrucks auf die zerebrale Gewebsoxygenierung (cTOI) und die zerebrale fraktionierte Sauerstoffextraktion (cFTOE) bei Früh- und Reifgeborenen während der unmittelbaren Transition nach der Geburt zu untersuchen.

Material und Methoden:

Zu diesem Zweck führten wir eine prospektive Beobachtungsstudie durch. Die Früh- und Reifgeborenen mit und ohne Atemunterstützung erhielten oszillometrische Blutdruckmessungen in den Minuten 5, 10 und 15 nach der Geburt sowie eine kontinuierliche zerebrale cTOI-Überwachung mit Nahinfrarotspektroskopie und eine kontinuierliche Überwachung der arteriellen Sauerstoffsättigung (SpO2) mit Pulsoximetrie während der ersten 15 Minuten nach der Geburt. CFTOE wurde aus cTOI und SpO2 berechnet. Anschließend wurde cTOI und cFTOE in den Minuten 5, 10 und 15 mit dem systolischen (SABP), diastolischen (DABP) und mittleren arteriellen Blutdruck (MABP) in allen Gruppen korreliert.

Ergebnisse:

Diese Studie umfasste 102 Früh- und Reifgeborene mit und ohne Atemunterstützung. Bei den Frühgeborenen mit Atemunterstützung korrelierte cTOI zu allen Zeitpunkten positiv mit DABP und auch mit MABP in Minute 15. CFTOE korrelierte zu allen Zeitpunkten negativ mit allen MABP- und DABP-Werten und auch mit dem SABP in Minute 5. Bei stabilen Frühgeborenen und Reifgeborenen mit und ohne Atemunterstützung korrelierten die Blutdruckwerte zu keinem Zeitpunkt mit cTOI oder cFTOE.

Schlussfolgerung:

Bei Frühgeborenen, die eine Atemunterstützung benötigten, korrelierte die zerebrale Oxygenierung (cTOI und cFTOE) zu allen Zeitpunkten während der ersten 15 Minuten nach der Geburt mit dem verschiedenen Werten des Blutdrucks, während bei stabilen Frühgeborenen und Reifgeborenen keine solchen Assoziationen beobachtet wurden.

Abstract in English

Background and Aim:

The aim of this study was to investigate the influence of arterial blood pressure on cerebral tissue oxygen saturation index (cTOI) and cerebral fractional tissue oxygen extraction (cFTOE) in preterm and term neonates during the immediate neonatal transition after birth.

Material and Methods:

For this purpose, we conducted a prospective observational study. Preterm neonates with and without respiratory support and term neonates with and without respiratory support received oscillometric blood pressure measurements at minutes 5, 10, and 15 after birth, a continuous cTOI monitoring with near-infrared spectroscopy and a continuous monitoring of arterial oxygen saturation (SpO2) with pulse oximetry during the first 15 minutes after birth. cFTOE was calculated out of cTOI and SpO2. Afterwards cTOI and cFTOE at minutes 5, 10, and 15 were correlated to systolic (SABP), diastolic (DABP), and mean arterial blood pressure (MABP) in all groups.

Results:

This study included 102 preterm and term neonates with and without respiratory support. In the preterm neonates with respiratory support cTOI correlated positively with DABP at all time points and it also correlated with MABP at minute 15. CFTOE correlated negatively with all MABP and DABP values at all time points and it also correlated with the SABP at minute 5. In stable preterm neonates and term neonates with and without respiratory support blood pressure values did correlate neither with cTOI nor with cFTOE at any time point.

Conclusion:

In compromised preterm neonates requiring respiratory support, cerebral oxygenation (cTOI and cFTOE) was associated with the different parameters of blood pressure at all time points during the first 15 minutes after birth, whereas no such associations were observed in stable preterm neonates and term neonates with and without respiratory support.

1. Introduction

1.1. Immediate transition period

The transition period from fetal-to-neonatal life is complex and one of the most difficult periods in life due to major remarkable physiological changes(2, 3). During this period the neonate undergoes extensive various physiological changes to adapt to the shift from Intrauterine to extrauterine environment (4). However the most crucial changes during the transition period occur in the pulmonary- and cardiovascular systems (5).

These changes are mainly triggered by the aeration of the lungs, which initiates the prior fluid filled aleveoli to expand and to increase surfactant production with the goal of air-filled lungs, to maintain a sufficient oxygen supply.

Simultaneously the prior mentioned aeration also lowers the pulmonary vascular resistance. As a result of this resistance drop, the blood flow gets redirected into the lungs which was bypassed prior by specific shunts such as the ductus arteriosus and the foramen ovale (4).

The ductus arteriosus is the connection between the pulmonary artery and the aorta and the foramen ovale is connection between the atria. Both shunts are vital for fetal life and upon birth with aeration of the lungs they gradually should close.

Due to the redirection of the blood flow, the pulmonary circulation in combination with the air-filled lungs are in charge for adequate oxygen supply for the whole neonate.

As a consequence of the new occurred blood pooling of the pulmonary circulation the systemic vascular resistance decreases initially and afterwards the systemic vascular resistance increases to a level where a balance is achieved between pulmonary resistance and systemic resistance, which allows a sufficient blood flow to the lungs as well as a sufficient blood flow to the remaining organs to maintain well oxygenated and nourished tissues (5, 6).

All these prior mentioned changes appear during the transition period contributing to the difficulties during this period.

The majority of neonates undergo this transition from intrauterine to extrauterine life successfully. However, approximately 10% require some clinical intervention during birth and up to 1% require even more extensive resuscitation (7).

However, these numbers are strongly influenced by certain risk factors such as the mode of delivery which increases the odds for the need of clinical intervention for the neonates.

For instance, neonates delivered by Cesarean section, face an increased likelihood of requiring respiratory support. Additionally, lower gestational age poses another risk factor, where lower gestational age is correlating positively with an increased probability of respiratory support (7, 8).

These prior mentioned influencing factors are leading to an increase of clinical intervention and consequently to an increase of complications, such as intraventricular hemorrhage (IVH) leading to cerebral palsy or cognitive deficits. In the literature the numbers vary around 10 to 15% of extremely premature neonates facing such complications (8, 9).

To prevent the neonate from these complications, essential protective mechanisms, such as cerebral autoregulation, play a pivotal role in safeguarding the neonatal brain from irreversible damage by maintaining a safe cerebral blood flow, regardless of the systemic blood pressure (10, 11).

1.2. The cerebral autoregulatory mechanism (cARM)

1.2.1 Physiology of cerebral autoregulatory mechanism

The oxygen supply of the brain relies on both oxygen delivery and consumption. Oxygen delivery is contingent upon the oxygen levels in hemoglobin, hemoglobin count and the cerebral blood flow (CBF). CBF, is determined by the cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR). The CPP is affected by two

major factors. The intracranial pressure (ICP) which can be neglected in neonates due to the open fontanelle and the systemic blood pressure making it therefore the strongest influence for CPP in neonates. Systemic blood pressure is strongly influenced by cardiac output as seen below in Figure 1. (12).

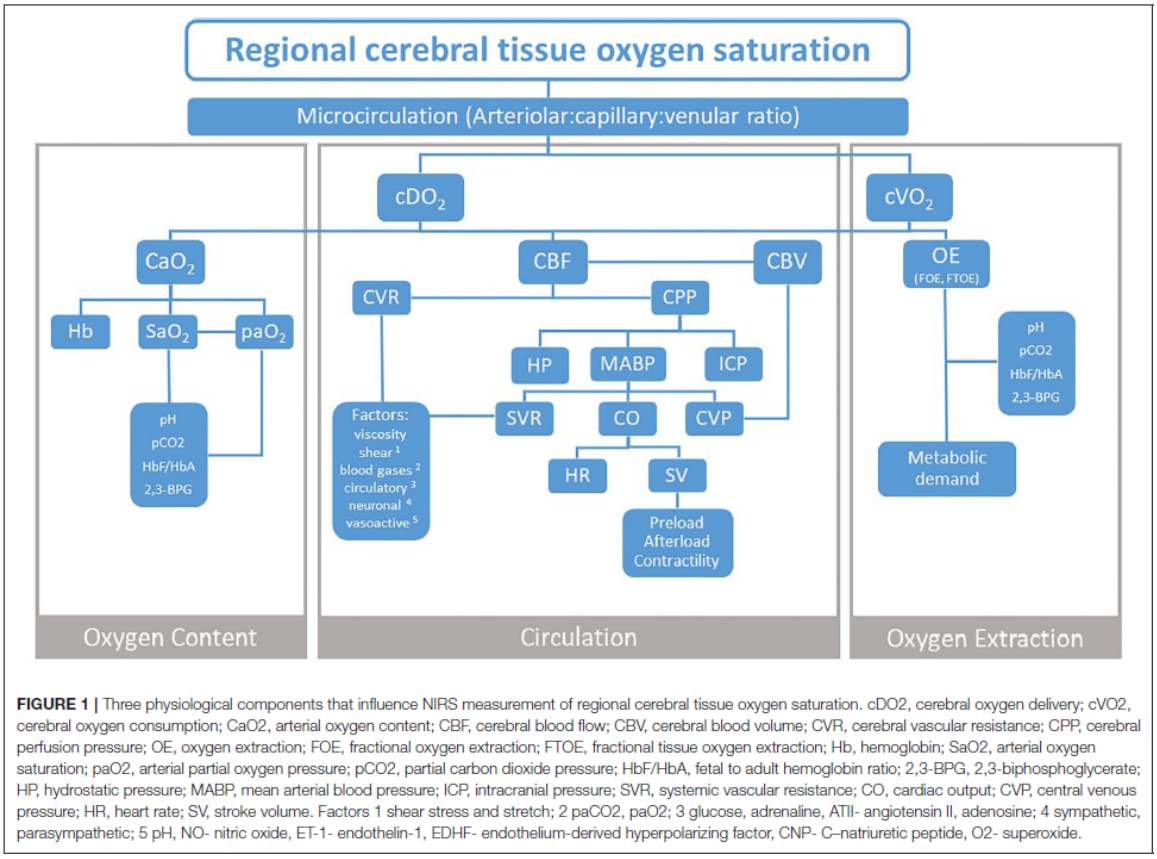

FIGURE 1 | Three physiological components that influence NIRS measurement of regional cerebral tissue oxygen saturation. cDO2, cerebral oxygen delivery; cVO2, cerebral oxygen consumption; CaO2, arterial oxygen content; CBF, cerebral blood flow; CBV, cerebral blood volume; CVR, cerebral vascular resistance; CPP, cerebral perfusion pressure; OE, oxygen extraction; FOE, fractional oxygen extraction; FTOE, fractional tissue oxygen extraction; Hb, hemoglobin; SaO2, arterial oxygen saturation; paO2, arterial partial oxygen pressure; pCO2, partial carbon dioxide pressure; HbF/HbA, fetal to adult hemoglobin ratio; 2,3-BPG, 2,3-biphosphoglycerate; HP, hydrostatic pressure; MABP, mean arterial blood pressure; ICP, intracranial pressure; SVR, systemic vascular resistance; CO, cardiac output; CVP, central venous pressure; HR, heart rate; SV, stroke volume. Factors 1 shear stress and stretch; 2 paCO2, paO2; 3 glucose, adrenaline, ATII- angiotensin II, adenosine; 4 sympathetic, parasympathetic; 5 pH, NO- nitric oxide, ET-1- endothelin-1, EDHF- endothelium-derived hyperpolarizing factor, CNP- C–natriuretic peptide, O2- superoxide.

Figure 1.: from Three Physiological Components that Influence Regional Cerebral Tissue oxygenation Saturation. (1)

Bearing that in mind, the cARM and its regulating influence on CBF rely mainly upon cerebral vasoreactivity. This cerebral vasoreactivity is triggered by neural activity, circulating hormones, and paracrine signals from perivascular tissues and immune cells. The cARM's capacity is defined by the relationship between the systemic mean arterial blood pressure and cerebral blood flow. Under normal physiological conditions, this relationship forms a s-shaped curve better known as Lassen's classic autoregulation curve (13) (Figure 2.).

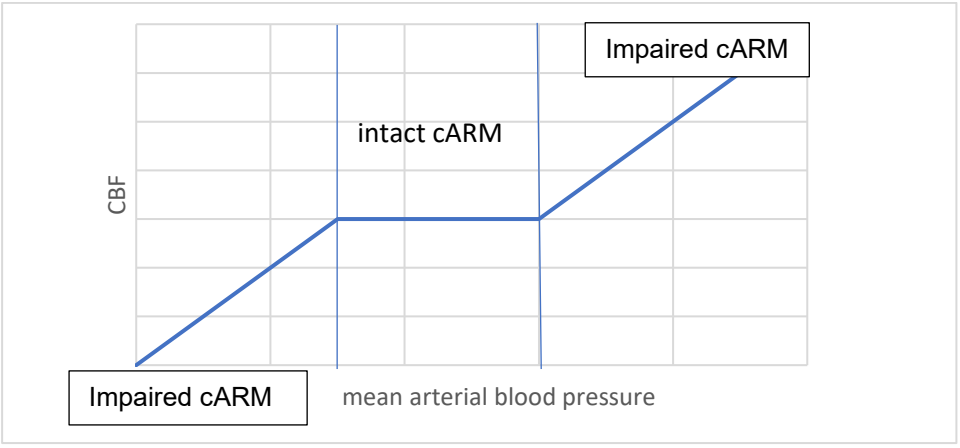

Figure 2.: *Relationship between the systemic mean arterial blood pressure and cerebral blood flow*.

This autoregulation curve describes that, if the systemic blood pressure is around the middle flat section, defined as the autoregulatory plateau or pressure reactivity zone, the brain is capable of maintaining CBF despite arterial blood pressure fluctuations. Below or above the cARM threshold a passive pressure-dependent cerebral perfusion occurs, which is defined with a positive correlation of the CBF and tissue oxygen saturation with the arterial blood pressure and a negative correlation of the arterial blood pressure with the cerebral oxygen extraction (14–16).

Talking about passive pressure dependent cerebral perfusion the critical closing pressure (CrCP) needs to be mentioned. This CrCP signifies the mismatch between ICP and the vascular wall tension. If the arterial blood pressure dips below the CrCP, cerebral arteries collapse and as a result, the flow of cerebral blood stops, leading to reduced oxygenated and nourished cerebral tissue. The CrCP can be determined using the Aslid formula (17). This formula estimates CPP (CPPe) by calculating the ratio of mean arterial blood flow velocity (VO) to the amplitude of the pulsatile component (VI). The ratio is afterward multiplied by the amplitude of the arterial pressure waveform's first harmonic (ABP1).

$$\mathbf{CPPe = (VO/VI) * ABP1}$$

Equation 1.

Furthermore, it needs to be mentioned, that the CrCP is strongly influenced by hypocapnia and gestational age (18, 19).

Bearing all this in mind the questions arise, which neonates are at risk of impaired cARM and how severe are the consequences of time spend with impaired cARM.

Impaired cARM is triggered by various factors. One frequently occurring in clinical routine is a low gestational age. According to the current knowledge preterm neonates are capable of cARM. However, as gestational age decreases, it seems that the threshold for impaired cARM to manifest becomes lower (20). That means that we have to be even more careful in more immature preterm neonates who are at higher risk for impaired cARM.

Besides gestational age also IRDS and sepsis are highly associated with impaired cARM. Whereby the link between cARM and IRDS are carbon dioxide levels and the link between cARM and sepsis is low blood pressure due to systemic inflammation and vascular response (13, 20–24).

Considering the autoregulation curve mentioned prior, it seems clear that also hypotension resembles a risk factor for impaired cARM. Besides that also low birthweight and a higher CRIB (Clinical Risk Index for Babies) score, both conditions also associated with lower blood pressure, are more likely to lose the capability for cARM (20–25).

1.2.2. Impaired cARM

Multiple studies have demonstrated a strong relationship between impaired cARM and the prevalence of intraventricular hemorrhage (IVH) (20, 22, 26). These studies consistently highlight the presence of impaired cARM both prior and during the IVH events, indicating a crucial association. Moreover, the onset of impaired cARM within the initial 24 hours after birth as well as the time period spent with impaired cARM appears to substantially increase the probability of IVH incidence (20, 26).

Additionally, noteworthy findings suggest a significant positive correlation between impaired cARM observed within the first day post-partum and subsequent abnormal neurodevelopmental outcomes at 16 months (27). This indicates a potential long-term impact of impaired cARM on neurological development.

In summary, prolonged periods of impaired cerebral autoregulation not only significantly increase the risk of IVH but also appear to correlate with adverse neurodevelopmental outcomes later in life. Which makes the understanding of the impact of impaired cARM crucial for evaluating the potential risk of both cerebral injury like IVH and impaired neurodevelopment in neonates.

1.3. Intraventricular Hemorrhage (IVH)

IVH is a major complication with a broad clinical appearance from unspecific symptoms such as lethargy or decreased responsiveness and irritability up to serious and potentially life-threatening situations with severe seizures, apnea and hypotonia (28). IVH is frequently observed in neonates, particularly those born preterm before 32 weeks of gestation or with a birth weight below 1500 gram (29) The risk is likely for a preterm neonate to develop an IVH in the first days whereas it becomes less likely one week after birth (9). The bleeding initiates typically in the so called periventricular germinal matrix (30). This region of minor resistance is located around the thalamocaudate groove and contains ganglional and glial precursor cells and numerous blood vessels making it therefore very susceptible for hemorrhage. The germinal matrix begins to diminish at a gestational age of 24 weeks and nearly disappears by 37 weeks of gestation, which explains the increased risk for IVH in preterm neonates (30).

During an IVH event the hemorrhage in the germinal matrix breaks through the ependyma and the blood enters the ventricular system and fills the lateral cerebral ventricle (30). Depending on the amount of blood in the lateral ventricle IVH can be classified into 4 different grades based on the extent of bleeding and the involvement of brain tissue (Figure 3.).

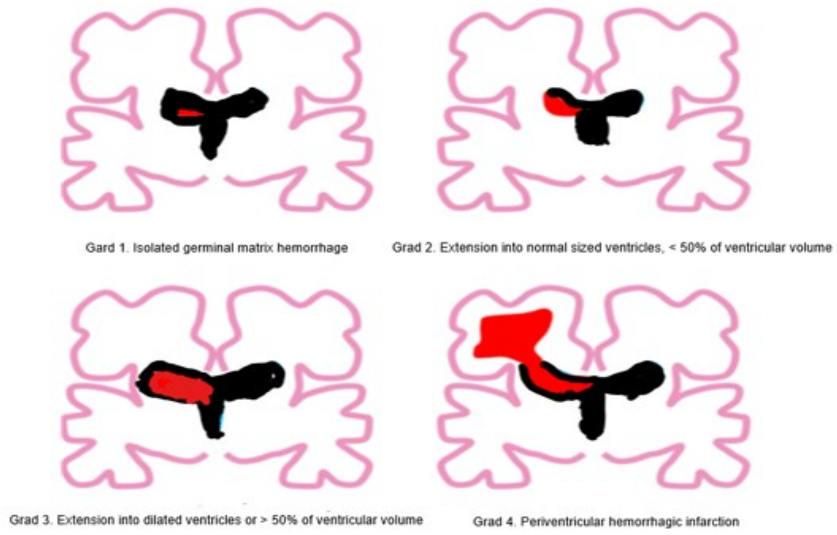

Figure 3. Classification of IVH

Several studies have shown that the grade of IVH is associated with morbidity and mortality, whereby higher grades of IVH have higher morbidity and mortality rates in neonates (29, 31, 32).

The number of neonates suffering from moderate to severe IVH over the last two decades in high income countries is stationary (29) considering, that approximately 50-75% of preterm neonates who survived a moderate to severe IVH demonstrate clinical presentation of cerebral palsy, some form of mental retardation and hydrocephalus with the age of 8 years (31, 32). It seems clear that IVH is still one of the major complications to be prevented to reduce morbidity and mortality in preterm neonates successfully.

Taking this into account and considering the pathogenesis of IVH which is multifactorial and consists of the beforementioned intrinsic fragile vessels of the germinal matrix and the fluctuation in the CBF, it seems reasonable that intact cARM reduces IVH by reducing CBF fluctuations as explained prior. However, in clinical routine the assessment of the neonates cARM, particularly in preterm neonates during immediate transition is still not established. The immediate transition period, however, is one of the most vulnerable phases in life. Therefore, combining various assessment tools to evaluate cARM seems to be desirable to support neonatologists in their decision making process for the best medical care for preterm neonates.

1.4. Assessment of a neonate during immediate transition

Bearing the above mentioned in mind, the assessment of the neonate is especially crucial during the transition period, in particular during the immediate transition.

1.4.1 Clinical Assessment (APGAR Score)

The most common used standardized approach for clinical assessing a neonate is the so called Apgar score, developed by Virgina Apgar in 1953 (33). This simple, yet effective clinical assessment tool helps medical staff to evaluate clinically a neonate's condition and to determine if any intervention is needed. The Apgar score is evaluating five essential criteria, such as skin color, heart rate, reflexes, muscle tone and breathing. In each of these criteria a score from zero to two is given and afterwards the scores are added together with a total score from zero to ten, whereby a score between seven and ten imply a stable neonate after birth (34). This easy, worldwide used score also has its downsides. One reason why it is often criticized, is that it has a high interobserver variability (35). Despite this variability a neonate with a total Apgar score of ten can be considered healthy and a neonate with a total Apgar score around one to three can be considered severely sick.

Another key point which is quite often criticized about the Apgar score is the applicability of the score on preterm neonates, which is an often highlighted limitation, prompting authors to explore for certain adaptations of the Apgar score specifically tailored for premature neonates (36). However, for various reasons, the Apgar score specifically tailored for premature neonates has not gained either widespread acceptance or widespread implementation into routine up to now (34, 36).

These prior mentioned limitations regarding the Apgar score and the difficulty in clinical assessment of neonates can be compensated with additional monitoring devices.

Therefore the latest guidelines of the European Resuscitation Council (ERC) as well as of the American Heart Association (AHA) concerning the support of neonatal

transition and resuscitation recommended additional monitoring in form of an electrocardiography (ECG) and/or pulse oximetry (PO) (36, 37).

1.4.2 Electrocardiography (ECG)

The ECG, as prior mentioned is one of the monitoring methods recommended by ERC and AHA (36, 37). The ECG is a device that records the electrical activity of the heart over a certain period of time and produces a graph that displays the hearts electrical activity as a waveform. Due to this waveform the rhythm, the HR, and potential abnormalities can be detected. This information helps to assess a neonate's cardio-circulatory system (37). However, it needs to be taken into account that the ECG alone has its limitations, specifically in cardio-circulatory conditions with normal electrical activity and reduced cardiac output (37).

Despite this limitation, the ECG is proven to be a feasible tool during transition and its accuracy concerning the HR compared to PO has been shown to be superior especially within the first two minutes after birth where a difference of up to 60 beats per minute (bpm) between ECG and PO has been demonstrated. This difference narrows down to about 20 bpm after a few minutes. Whereby PO seems to show in average lower HR values compared to ECG (38).

Considering the prior mentioned differences, HR references for the ECG were published to improve the accuracy in the evaluation of the neonate's cardio-circulatory status (39).

Besides accuracy the ECG is also superior to the PO in terms of the signal acquisition time, as shown in two randomized clinical trials (RCTs) (13, 14). In these trials the ECG parameters were gained about 50 seconds prior to the PO parameters (40, 41).

1.4.3. Pulse oximetry (PO)

The PO is the second recommended monitoring method by the ERC and AHA (36, 37). The PO is a device that emits two wavelengths (red and infrared) into the tissue. Depending on the oxygenated hemoglobin content of the red blood cells, the absorption of the light varies. These differences in the absorption of the light are measured and with that information oxygen saturation levels can be calculated (42).

The biggest advantage of PO over the ECG is, that it also gives information about the oxygen saturation of the blood and the perfusion. This is crucial particularly e.g. in terms of a pulseless electrical activity (PEA), when the ECG seems normal due to normal electrical activity despite reduced cardiac output and consequently reduced perfusion (43).

Furthermore, the information gained by PO about the oxygen saturation of the blood helps to guide intervention during the immediate transition period and therefore well-known references for arterial oxygen saturation (SpO2) were published (36, 37). Despite its slower signal acquisition time compared to the ECG, it is still a feasible tool for evaluating neonates in the immediate transition period (36, 37, 44).

Both monitoring methods (ECG and PO) recommended by the ERC and AHA (44, 45) provide crucial additional information during immediate transition period beside the clinical assessment. This information about the neonate’s condition, helps to enhance the accuracy of the assessment of the neonate during immediate transition and improves neonatal care (43–45).

However, both monitoring methods do not provide enough data to adequately evaluate a neonate’s cardio-circulatory status (45). Therefore, blood pressure might also be considered, because blood pressure is a parameter which is strongly associated with the cardio-circulatory status (46).

1.4.4. Blood pressure

Blood pressure parameters can be obtained using either an arterial catheter or oscillometric methods involving a blood pressure cuff. Each approach has its advantages and its disadvantages, and the clinician must decide which measurement is feasible and which is adequate for which condition.

1.4.4.1. Invasive blood pressure measurement

The invasive method by using an arterial catheter is acknowledged for its higher accuracy and its continuous blood pressure assessment. However, its implementation faces practical limitations, particularly during the immediate transition period after birth, due to the time required for arterial catheter insertion. Furthermore the risk of arterial thrombosis has to be considered, especially in preterm neonates with a relative higher risk for developing arterial thrombosis, according to the study of Cohen et al.(47)

Therefore, while arterial catheterization still stands as the gold standard for accuracy, its utility might be limited in time-sensitive situations such as the immediate transition period. Furthermore, the level of invasiveness needs to be considered.

1.4.4.2. Non-invasive blood pressure measurement

Oscillometric methods, though less precise but also less associated with complications such as arterial thrombosis, provide an alternative for rapid blood pressure evaluation during the immediate transition period (48). As prior mentioned oscillometric blood pressure measurement methods are shown to be feasible in the immediate transition period and its accuracy is acceptable (48, 49). Furthermore, it is a save method even for the lowest gestational age groups (49, 50). In general, oscillometric blood pressure measure devices are working by inflating a blood pressure cuff which detects the vibrations or so-called oscillations in the artery due to the blood flow. This information

is then analyzed by an algorithm to determine systolic arterial blood pressure (SABP), diastolic arterial blood pressure (DABP) and mean arterial blood pressure (MABP) (48). Whereby SABP resembles the peak of the blood flow and the DABP the point of the lowest blood flow. MABP is calculated by a specific formula from DABP and SABP.

$$\mathbf{MABP = DABP + 1/3\ (SABP - DABP)}$$

Equation 2.

Oscillometric blood pressure measurements are already commonly used in neonatal intensive care units (NICU). However, it is not regularly used during the immediate transition period. One of the main reasons is, that although we have reference ranges (50), it is still hard to interpret those values and further harder to decide when and if it is necessary to start an intervention based on the blood pressure values gained (51, 52). Some NICUs ,as a rule of thumb, consider the gestational age to be the lower MABP threshold (53). However there is no evidence that this rule of the thumb is an adequate blood pressure value for a neonate and therefore reference ranges during the immediate transition needed to be considered more (51, 52, 54).

Besides blood pressure a further parameter reflecting the cardio-circulatory status is cardiac output (CO).

1.4.5. Cardiac output (CO)

Likewise blood pressure also CO can be measured with different mthods, with each method having its advantages and disadvantages.

1.4.5.1. CO by thermodilution

CO gives a good overview of the cardio-circulatory status but the process to maintain CO values can be difficult. The gold standard method for CO is the so called thermodilution which has limited applicability and feasibility during the immediate transition period in the neonatal population due to the fact, that it needs a central line, which is also very invasive (55). Thermodilution is a method whereby a certain amount of a cold saline solution is given via a central catheter placed in the pulmonary artery. The cold saline solution lowers the temperature in the bloodstream. These temperature changes are measured and with that information cardiac output can be maintained. This method, despite being the most invasive one, has the highest accuracy. However, considering the neonatal population during immediate transition this method does not meet the feasibility criteria needed and is far too invasive as mentioned prior. Therefore, in neonates, non-invasive CO measurements are preferred.

1.4.5.2. CO by non-invasive cardiac output measurement (NICOM)

One of the most essential non-invasive CO measurement methods is the echocardiography which provides the highest accuracy among the non-invasive CO measurements, whereby its accuracy is still just acceptable compared to the thermodilution method (56, 57).

1.4.5.3. CO by Echocardiography

For estimating CO by echocardiography, a trained investigator is required who performs an echocardiography examination and does a doppler assessment to gain the stroke volume (SV). Once the SV is estimated it is multiplied with the HR to gain CO. The advantage of this CO examination is that it is non-invasive and still has a remarkable accuracy. However, the challenge with this CO measurement method is that it is difficult to measure accurately SV in neonates, who are not calm and moving, and therefore it requires highly trained staff to achieve high precision. Furthermore, the echocardiographic assessment requires a certain amount of space and time which makes the feasibility during immediate transition challenging, as echocardiography may interfere with resuscitation procedures, especially in terms of severely impaired neonates, where the CO measurement would be of importance.

These disadvantages are the main reasons why it is not been applied in routine yet. Consequently, other methods have been established to assess CO non-invasively during immediate transition, like the electrical cardiometry.

1.4.5.4. Electrical cardiometry

One approach for NICOM is the so called electrical cardiometry method. This method relies on an electrical field build by several sensors. These sensors are comparable to ECG sensors and are attached to the neonate. As the heart pumps blood through the heart, the electrical field changes due to impedance changes. These impedance changes happen because the red blood cells align during the systole and as a result of this the conductivity changes. The changes of the electrical field are monitored and afterwards this information is transformed through special algorithms to maintain CO values.

One of the biggest advantages of the electrical cardiometry method is that it provides continuous non-invasive CO measurements. Also, the limit of precision seems to be acceptable if the signal quality index is above 80% (58).Furthermore, it also seems

feasible during immediate transition in terms of the signal acquisition time (59). However, there are certain limitations. This method lacks precision in sick neonates and the algorithm relies further on accurate height and weight for precise CO measurements, which can be challenging to obtain during resuscitation procedures (56). However, considering the studies (60, 61) demonstrating that between 60% to 76% of measurements did not meet the required signal quality index of above 80% hinders electrical cardiometry methods to be applied in routine.

1.4.5.5. Bioreactance method

The bioreactance method differs from the prior mentioned electrical cardiometry in that the bioreactance method measures phase shifts in electrical signals related to blood flow velocity in the aorta (56). Comparable to the electro cardiometry method several sensors are applied. These sensors both, apply a specific thoracic voltage and measure the resulting signals. However, unlike electro cardiometry the time delay between measured thoracic voltage and applied thoracic voltage is gained. This time delay is the so-called phase shift and is influenced by the amount of blood flowing through the aorta. With this information an algorithm can calculate a SV and a CO (58).

One of its biggest advantages is that that it provides continuous non-invasive CO measurements.

However equal to the electrical cardiometry also this method is doable in terms of the signal acquisition time, but the feasibility during the immediate transition is questionable, with the first signals maintained about eight minutes after birth (62, 63). This is a long time period if it is considered that the neonate should be almost completely adapted after this time period to extra uterine life.

Furthermore, the accuracy is also quite often questioned. The CO values gained by bioreactance are in general below CO values gained via echocardiography but within an acceptable range. However, it needs to be clear that when using NICOM device there are no studies in neonates comparing NICOM devices with thermodilution which is the gold standard method for CO measuring. It is only compared to

echocardiography a method where precision is around 30% compared to the gold standard method (58, 62).

Apart from all mentioned monitoring devices near- infrared spectroscopy (NIRS) should be mentioned.

NIRS is a device which is not used in routine yet. However, it possesses huge potential, especially combined with other monitor devices.

1.4.6 Near-infrared spectroscopy (NIRS)

NIRS was first described and published by Jöbsis et al in 1977 (64). The foundation of NIRS is that it uses the physical properties of the organic tissue towards light in the near infrared spectrum. The organic tissue itself is transparent towards light in the near infrared spectrum around a wavelength of (700-1000 nm). However, light with this wavelength is absorbed, scattered or reflected differently by oxygenated or deoxygenated hemoglobin, myoglobin and cytochrome oxidase. This property of the prior mentioned chromophores reduces the returned infrared light, and the changes of this returned infrared light can be converted directly into changes of oxygenated or deoxygenated hemoglobin. With this information it is possible to obtain the concentration of oxygenated hemoglobin (O2HB) and deoxygenated hemoglobin (HHb) as well as total hemoglobin (tHb) throughout a straightforward Equation(64).

$$\mathbf{tHb = O2Hb + HHb}$$

Equation 3.

From the prior mentioned formula tissue oxygen saturation index (TOI) can be derived with the following Equation (65, 66).

$$\mathbf{TOI = O2Hb / tHb}$$

Equation 4.

TOI reflects the tissue oxygen saturation, and its value depends on oxygen delivery and consumption. The value itself can be derived through dividing oxygenated hemoglobin with total hemoglobin. And it reflects the share of oxygenated hemoglobin to the total hemoglobin concentration (65–67).

The tissue's oxygen extraction, known as fractional tissue oxygen extraction (FTOE), can also be calculated using a straightforward equation, when SpO2 and TOI is known. It involves subtracting the tissue oxygenation index (TOI) from the arterial blood oxygen saturation (SpO2) and then dividing this difference by SpO2 (65, 67).

FTOE = (SpO2 - TOI) / SpO2

Equation 5.

Understanding the principle of NIRS as well as the calculations to gain TOI and FTOE lead to the understanding of the various possibilities depending on where the device is placed. With this tool it is possible to measure various vital organs such as kidney, splanchnic tissue, or even peripheral muscles. However, the most promising organ to be measured is the brain, due to the brain being the most vulnerable organ concerning hypoxia and therefore information about its wellbeing is especially during a difficult period such as the immediate transition helpful for the physician in charge of the neonate to guide further intervention. A further advantage of NIRS is that it is feasible during immediate transition with studies showing faster signal acquisition time with NIRS compared to PO during immediate transition. In average within the first two minutes after birth, a signal is obtained with NIRS (68–70). Also, dislocation happens rarely in initially correctly applied sensor. Besides all the prior mentioned advantages, one of NIRS greatest advantage is that it provides continuous and non-invasive data (71).

Knowing all this, the question arises, why it is not yet a routine monitoring device. One of the main reasons is its questioned precision. In the study of Skov et al (72) 1991 where NIRS was compared to the invasive 133Xe clearance technique in 19 neonates, they demonstrated that both methods are close to zero in low range areas concerning

the CBF and in high range areas NIRS may underestimate CBF. Further studies showed that the precision of NIRS correlates with tissue homogeneity and that precision is higher in term neonates than in preterm neonates (71, 73). Bearing in mind that the studies with the questionable precision are older ones and that nowadays the initial problem with the lack in precision gets better due to improvement of the technology and the sensors, and about latter particular point especially due to adapting sensors for neonates (74, 75). As a result of that, the precision nowadays reaches levels comparable to PO (74).

Another often criticized point of this technology is the differences between devices, leading to different percentiles for each device. These differences are caused by the different algorithms which are used to gain values. This problem is solved by published normative data for each device (76).

Summarized NIRS monitoring has a big potential for assessing a neonate however the latest COSGOD III Trail showed that although it improves outcome in neonates especially in regards to cerebral injury it is not yet significantly improving outcome (77). The reason for these results may be due to the hard endpoints in combination with the high threshold of statistical significance considering the time of NIRS monitoring. Besides maybe a more specific answer can be given after the two years follow-up of the cohort has been done. However, it is essential to consider whether the chosen intervention settings were appropriate. In cases where they might not have been effective, and probably a multimodal approach incorporating various monitored values such as blood pressure could lead to an improved assessment of the neonates and consequently also leads to a higher quality of medical care in neonates during immediate transition.

One approach for such a multimodal approach would be combining NIRS with oscillometric blood pressure.

1.4.7 NIRS and blood pressure

Cerebral NIRS monitoring and blood pressure measurements were described prior and the combination of these devices holds substantial promises. Because cerebral NIRS monitoring, and blood pressure measurements give insights into the dynamics of cerebral autoregulation. By concurrently assessing blood pressure and a non-invasive continuous NIRS monitoring of the cerebral oxygenation the interplay between blood pressure variations and cerebral perfusion can be detected, especially if considered that in terms of neonates with an impaired cARM the CPP mainly relies on the systemic blood pressure (20).

So, the combination of these two non invasive monitoring methods is promising and presents a novel avenue for investigating cerebral autoregulation and further gives a chance to understand how blood pressure impacts cerebral perfusion dynamics. Besides it may help to target an optimal blood pressure threshold and therefore help physicians in their decision-making process of improving short and long-term outcomes in term and preterm neonates by preventing IVH and cerebral impairment (21, 22).

1.5. Objectives

NIRS monitoring of the cerebral oxygenation in neonates during the immediate transition after birth combined with systemic blood pressure measurements raise the opportunity to monitor cARM in neonates during this difficult period of life. Currently one study demonstrated impaired cARM at minute 15 after birth in preterm neonates in need of respiratory support by combining systemic blood pressure measurements with NIRS monitoring (78). A major limitation of this study was that only one single blood pressure measurement was performed. To enhance our understanding of cARM during immediate transition, we combined systemic blood pressure measurements and cerebral tissue oxygen saturation index (cTOI) and cerebral fractional tissue oxygen

extraction (cFTOE) gained with NIRS during the first 15 minutes after birth in term and preterm neonates.

The aim of this thesis is to analyze the potential influence of blood pressure on cTOI and cFTOE within the first 15 minutes after birth in term and preterm neonates with and without respiratory support, when most cardio-circulatory changes and aeration of the lung take place.

2. Materials and Method

2.1. Design

The present study is a prospective observational study which was conducted at the Division of Neonatology, Department of Pediatrics and Adolescent Medicine, at the Medical University of Graz, Austria between July 2022 and November 2023. The Regional Ethics Committee approved the studies (Austria: 1026/2022 (34-221 ex 21/22)). Written parental consent was obtained before birth for all neonates included in the study.

2.2. Inclusion and Exclusion Criteria

Preterm and term neonates delivered by cesarean section during July 2022 and November 2023 with a written parental consent were eligible for the present observational study.

Exclusion criteria were, if there was no decision to conduct full life support or an absence of written informed consent. Furthermore, neonates with major congenital malformations and umbilical artery pH below 7.0 were excluded.

2.3. Monitoring

Demographics and antepartum medical history of neonates were collected from patient charts. After ceasarean section all neonates were routinely transferred to the resuscitation table immediately after birth.

Cord clamping time was performed according to routine between 30 - 60 seconds after birth.

During the first 15 minutes after birth SpO2 and HR were routinely obtained by pulse oximetry, with the sensor being placed on the right hand or wrist (Intelli Vue MP 30 Monitor, Philips, Amsterdam, The Netherlands). TOI was measured in addition by NIRS, which was performed with a cerebral oximeter monitor (T-NIRS, Hamamatsu Photonics K.K., Hamamatsu, Japan) using a neonatal sensor. The sensor was placed on the left frontoparietal head of the neonate and secured with an elastic bandage (Peha-haft, Harmann, Heidenheim, Germany) or with a modified continuous positive airway pressure cap.

cFTOE was calculated with the following equation:

$$\mathbf{cFTOE = (SpO2 – cTOI)/ SpO2}$$

Equation 6.

Arterial blood pressure was measured non-invasively at minute five, ten and 15 after birth with an oscillometric blood pressure cuff (Intelli Vue MP 30 Monitor, Philips, Amsterdam, The Netherlands) of appropriate size (#1, #2 or #3) on the right calf. Cuff size diameter was chosen according to the circumference of the infant's right calf. The right calf was chosen to avoid interference with the pulse oximetry measurements at the infant's right hand or wrist.

All data were continuously stored in a polygraphic system (alpha trace digital MM, BEST Medical Systems, Vienna, Austria) for further analyses.

2.4. Statistical analysis

The cohort was stratified into four groups based on gestational age and the need for respiratory support:

- term neonates without respiratory support
- term neonates with respiratory support
- preterm neonates without respiratory support
- and preterm neonates with respiratory support

Demographic and clinical data are presented as mean and standard deviation (SD) for normally distributed data or as median and interquartile range (IQR) for not normally distributed data.

For comparisons of baseline characteristics between term neonates and preterm neonates with and without respiratory support for non-continuous variables, the Chi-square test or Fisher's exact test was used. For continuous variables, Student's t-test or Mann-Whitney U test was applied as well as Kruskal-Wallis test.

Correlation analyses between the NIRS parameters (TOI and cFTOE) at minute five, ten and 15 and the blood pressure values (SABP, DABP and MABP) at minute five, ten and 15 were calculated for preterm and term neonates with and without respiratory support using Pearson's correlation for normally distributed data and Spearman's rank correlation for skewed distributions. A Kolmogorov – Smirnov and Shapiro-Wilk Test was performed prior for establishing normality.

A p-value < 0.05 was considered statistically significant. These values were considered in an explorative sense so that no multiple testing corrections were performed. All statistical analyses were performed using IBM SPSS Statistics 26 (IBM Corporation, Armonk, NY, USA).

Furthermore, a mixed model was performed in collaboration with the Institute of Medizinische Informatik, Statistik und Dokumentation.

2.5. Primary aim

The aim of this thesis is to analyze the potential influence of blood pressure on cTOI and cFTOE within the first 15 minutes after birth in term and preterm neonates with and without respiratory support.

2.6. Primary hypotheses

Non-invasively measured blood pressure correlates with cTOI and cFTOE within the first 15 minutes after birth in term and preterm neonates with and without respiratory support, with higher blood pressure being associated with higher cerebral oxygenation and lower fractional oxygen extraction.

3. Results

3.1. Participants

Between July 2022 and November 2023. 102 preterm and term neonates were included in the prospective observational studies. Fifty-one term neonates and 51 preterm neonates were split into two groups each depending on the need of respiratory support (Figure 4.).

Figure 4.

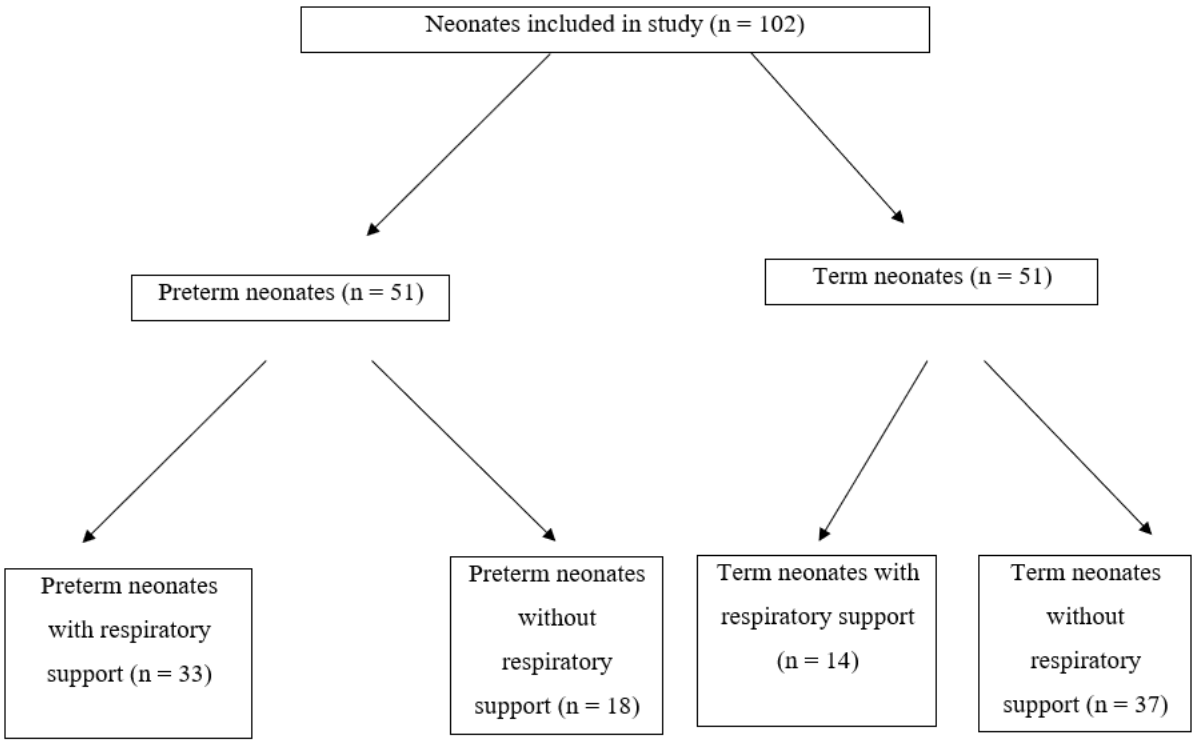

Figure 4.: Flow-diagram illustrating the study cohort.

The reason for cesarean section in term neonates were labor arrest (respiratory support n = 4 / no respiratory support n = 6), breech position (n = 2 / n = 5), repeat cesarean section (n = 6 / n = 16), macrosomia (n = 1 / n = 3), and other reasons (n = 1 / n = 7).

The reasons for preterm birth and cesarean section were preterm labor (respiratory support n = 6 / no respiratory support n = 3), premature rupture of membranes (n = 8 / n = 5), preeclampsia , HELLP syndrome or maternal hypertension (n = 5 / n = 3), intrauterine growth restriction (n = 5 / n = 2), and other reasons (n = 9 / n = 5).

In this study, respiratory support was defined as any application of supplemental oxygen or any form of respiratory assistance, including CPAP (Continuous Positive Airway Pressure) or IPPV (Intermittent Positive Pressure Ventilation).

None of the neonates received surfactant or vasoactive pharmacologic therapy such as vasopressors or inotropes, within the first 15 minutes after birth.

3.2. Demographic and clinical data

3.2.1. Term and preterm neonates

The term and preterm neonates exhibit expected differences across several parameters, regardless of the need for respiratory support. The groups vary significantly in gestational age and birth weight. Additionally, differences in APGAR scores reflect the higher proportion of neonates requiring respiratory support in the preterm group. There is also a notable gender difference between the groups, with a higher percentage of boys among preterm neonates. (Table 1.a.)

Table 1.a.) Demographic and clinical data from term and preterm neonates

	term neonates (n = 51)	preterm neonates (n = 51)	p-value
Gestational age, weeks	38.8 (± 1.6)	34.7 (± 1.0)	<0.001*
Birth weight, g	3375 ± 440	2239 ± 482	<0.001*
Female n (%)	39 (76)	13 (25)	0.003*
Umbilical artery pH	7.31 (± 0.05)	7.31 (± 0.05)	0.160
Apgar 1 min	9 (7 – 9)	8 (4 – 9)	0.004*
Apgar 5 min	9 (8 – 10)	10 (7 – 10)	<0.001*
Apgar 10 min	9 (9 – 10)	10 (8 – 10)	<0.001*

Data are presented as mean ± SD, median (IQR), or n (%).

* p-values indicate a significant difference between preterm neonates with and without respiratory support

3.2.2. Term neonates with and without respiratory support

Regarding the term neonates the gestational age did not show a significant difference between term neonates with and without respiratory support concerning gestational age unlike the pattern observed in the preterm neonates (Table 1.b.).

However, similar to the preterm neonates, the term neonates with and without respiratory support did not differ in terms of birth weight, gender and umbilical artery pH (Table 1.a.).

Furthermore, likewise the preterm neonates, the term neonates with and without respiratory support differ as expected in terms of Apgar score (Table 1.b.).

Table 1.b.) Demographic and clinical data from term neonates with and without respiratory support

	with respiratory support (n = 14)	stable (n = 37)	p-value
Gestational age, weeks	38.3 (37.3 - 40.7)	38.9 (37.4 - 41.4)	0.165
Birth weight, g	3318 ± 392	3287 ± 401	0.608
Female	7 (50)	19 (50)	0.932
Umbilical artery pH	7.31 (7.21 – 7.38)	7.32 (7.17 – 7.41)	0.950
Apgar 1 min	8 (7 – 9)	9 (7 – 9)	<0.001*
Apgar 5 min	9 (8 – 9)	10 (8 – 10)	<0.001*
Apgar 10 min	10 (9 – 10)	10 (9 – 10)	<0.001*

Data are presented as mean ± SD, median (IQR), or n (%).

* p-values indicate a significant difference between term neonates with and without respiratory support.

3.2.3. Preterm neonates with and without respiratory support

Demographic and clinical data showed a significant difference in gestational age between preterm neonates with and without respiratory support. Specifically, neonates in need of respiratory support had a lower gestational age. Furthermore, preterm neonates with and without respiratory support unsurprisingly differed in terms of Apgar score, whereby neonates requiring respiratory support showed lower values, reflecting their more compromised condition after birth (Table 1.c.).

However, no significant differences were found between the two groups in terms of birth weight, gender, or umbilical artery pH (Table1.c.).

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Table 1.c.) Demographic and clinical data from preterm neonates with and without respiratory support

	with respiratory support (n = 33)	Stable (n = 18)	p-value
Gestational age, weeks	34.3 (30.9 - 36.9)	35.6 (33.0 - 36.9)	0.014*
Birth weight, g	2197 ± 514	2314 ± 421	0.362
Female n (%)	8 (16)	5 (28)	0.841
Umbilical artery pH	7.31 (7.17 – 7.38)	7.33 (7.23 – 7.39)	0.394
Apgar 1 min	8 (4 – 9)	9 (8 – 9)	<0.001*
Apgar 5 min	9 (7 – 10)	10 (9 – 10)	<0.001*
Apgar 10 min	9 (8 – 10)	10 (9 – 10)	<0.001*

Data are presented as mean ± SD, median (IQR), or n (%).

* p-values indicate a significant difference between preterm neonates with and without respiratory support.

3.3. Monitoring parameters

3.3.1. Term and preterm neonates

Term neonates and preterm neonates showed significant differences in all blood pressure values at five minutes, and in mean arterial blood pressure (MABP) and systolic arterial blood pressure (SABP) at ten and 15 minutes. Heart rate also differed between the groups at five minutes, with preterm neonates showing an unexpectedly lower heart rate, possibly due to the higher proportion of neonates receiving respiratory support in this group. Additionally, preterm neonates had significantly higher cTOI values, likely reflecting both respiratory support and supplemental oxygen administration.

No significant differences were observed between the groups in cFTOE, heart rate at ten and 15 minutes, or diastolic blood pressure at ten and 15 minutes (Table 2.).

Table 2.) NIRS parameters, EKG-parameters, and blood pressure values at 5,10 and 15 minutes after birth of term and preterm neonates

	Term neonates (n = 51)	Preterm neonates (n = 51)	p-value
NIRS parameters			
5min cTOI,	70 ± 10	69 ± 6	0.371
5min cFTOE	0.26 ± 0.18	0.21 ± 0.09	0.099
10min cTOI,	72 ± 11	80 ± 6	<0.001*
10min cFTOE	0.09 ± 0.02	0.18 ± 0.09	0.300
15min cTOI,	73 ± 5	80 ± 6	<0.001*
15min cFTOE	0.10 ± 0.14	0.18 ± 0.10	0.318
ECG parameters			
5min Puls, bpm	156 ± 19	144 ± 17	<0.001*
10min Puls, bpm	154 ± 19	150 ± 13	0.093
15min Puls, bpm	157 ± 14	157 ± 14	0.364
Blood pressure parameters			
5min SABP, mmHg	68 ± 13	58 ± 11	<0.001*
5min DABP, mmHg	42 ± 12	42 ± 9	<0.001*
5min MABP, mmHg	51 ± 10	42 ± 9	<0.001*
10min SABP, mmHg	64 ± 10	59 ± 11	0.005*
10min DABP, mmHg	37 ± 10	35 ± 11	0.187
10min MABP, mmHg	47 ± 10	43 ± 10	0.032*
15min SABP, mmHg	64 ± 9	58 ± 11	0.002*
15min DABP, mmHg	37 ± 9	35 ± 9	0.232
15min MABP, mmHg	46 ± 7	43 ± 9	0.046*

Data are presented as mean ± SD, or median (IQR). Bpm, beats per minute; cTOI, cerebral tissue oxygenation index; cFTOE, cerebral fractional tissue oxygen extraction; DABP, diastolic arterial blood pressure; ECG, electrocardiogram; MABP, mean arterial blood pressure; NIRS, near-infrared spectroscopy; SABP, systolic arterial blood pressure.

* p-value indicates a significant difference between preterm neonates with respiratory support and stable term neonates.

3.3.2. Term neonates with and without respiratory support

The term neonates with and without respiratory support showed significant differences in the monitoring parameters, including HR at five minutes, cFTOE at 15. Further, the SABP differed significantly at minute five. Whereby term neonates with respiratory support showed likewise preterm neonates, lower cFTOE and HR levels and higher SABP values (Table 3).

Table 3.) NIRS parameters, EKG-parameters, and blood pressure values at 5,10 and 15 minutes after birth of term neonates with and without respiratory support

	with respiratory support (n = 14)	Stable (n = 37)	p-value
NIRS parameters			
5min cTOI,	68 ± 5	69 ± 7	0.426
5min cFTOE	0.28 ± 0.24	0.22 ± 0.04	0.439
10min cTOI,	75 ± 6	71 ± 17	0.470
10min cFTOE	0.21 ± 0.05	0.23 ± 0.05	0.885
15min cTOI,	75 ± 6	73 ± 4	0.082
15min cFTOE	0.21 ± 0.06	0.59 ± 0.15	0.003*
ECG parameters			
5min Puls, bpm	146 ± 20	165 ± 15	0.010*
10min Puls, bpm	156 ± 12	152 ± 22	0.470
15min Puls, bpm	159 ± 17	158 ± 15	0.603
Blood pressure parameters			
5min SABP, mmHg	74 ± 14	66 ± 13	0.036*
5min DABP, mmHg	44 ± 15	41 ± 12	0.319
5min MABP, mmHg	55 ± 14	50 ± 12	0.112
10min SABP, mmHg	68 ± 9	64 ± 9	0.123
10min DABP, mmHg	41 ± 13	33 ± 7	0.233
10min MABP, mmHg	50 ± 12	44 ± 7	0.090
15min SABP, mmHg	62 ± 8	64 ± 10	0.313
15min DABP, mmHg	39 ± 9	34 ± 8	0.427
15min MABP, mmHg	47 ± 8	45 ± 6	0.752

Data are presented as mean ± SD, or median (IQR). Bpm, beats per minute; cTOI, cerebral tissue oxygenation index; cFTOE, cerebral fractional tissue oxygen extraction; DABP, diastolic arterial blood pressure; ECG, electrocardiogram; MABP, mean arterial blood pressure; NIRS, near-infrared spectroscopy; SABP, systolic arterial blood pressure.

* p-value indicates a significant difference between preterm neonates with respiratory support and stable term neonates.

3.3.3. Preterm neonates with and without respiratory support

The preterm neonates with and without respiratory support showed significant differences in the monitoring parameters, including HR at five minutes, cFTOE at ten and 15 minutes and cTOI at five and ten minutes. Further the SABP differed significantly at minute ten. Whereby preterm neonates with respiratory support showed lower cTOI, cFTOE and HR levels and higher SABP values (Table 4.).

Table 4.) NIRS parameters, EKG-parameters, and blood pressure values at 5,10 and 15 minutes after birth of preterm neonates with and without respiratory support

	with respiratory support (n = 33)	Stable (n = 18)	p-value
NIRS parameters			
5min cTOI,	66 ± 9	77 ± 8	0.023*
5min cFTOE	0.22 ± 0.10	0.12 ± 0.07	0.258
10min cTOI,	78 ± 7	81 ± 5	0.168
10min cFTOE	0.15 ± 0.05	0.15 ± 0.06	<0.001*
15min cTOI,	79 ± 6	81 ± 5	0.031*
15min cFTOE	0.15 ± 0.07	0.18 ± 0.06	<0.001*
ECG parameters			
5min Puls, bpm	141 ± 16	158 ± 17	0.014*
10min Puls, bpm	149 ± 13	148 ± 12	0.483
15min Puls, bpm	158 ± 14	157 ± 12	0.601
Blood pressure parameters			
5min SABP, mmHg	59 ± 12	55 ± 9	0.276
5min DABP, mmHg	34 ± 9	29 ± 8	0.444
5min MABP, mmHg	43 ± 10	39 ± 8	0.296
10min SABP, mmHg	61 ± 11	51 ± 10	0.036*
10min DABP, mmHg	36 ± 11	33 ± 9	0.233
10min MABP, mmHg	44 ± 10	39 ± 8	0.085
15min SABP, mmHg	60 ± 11	52 ± 10	0.183
15min DABP, mmHg	36 ± 9	33 ± 9	0.181
15min MABP, mmHg	44 ± 8	40 ± 9	0.110

Data are presented as mean ± SD, or median (IQR). Bpm, beats per minute; cTOI, cerebral tissue oxygenation index; cFTOE, cerebral fractional tissue oxygen extraction; DABP, diastolic arterial blood pressure; ECG, electrocardiogram; MABP, mean arterial blood pressure; NIRS, near-infrared spectroscopy; SABP, systolic arterial blood pressure.

* p-value indicates a significant difference between preterm neonates with respiratory support and stable term neonates.

3.4. Correlation analyses

Table 5 illustrates the correlation analyses of cTOI and cFTOE with the blood pressure parameters (SABP, DABP, MABP) at minute five, ten and 15 after birth for term and preterm neonates with and without respiratory support.

Preterm neonates with respiratory support showed significant positive correlations of cTOI with DABP at five, ten and 15 minutes and with MABP at 15 minutes.

Further preterm neonates with respiratory support showed a negative correlation of cFTOE with all blood pressure values at five minutes and with DABP and MABP at ten and 15 minutes after birth.

In preterm neonates without respiratory support as well as in term neonates with and without respiratory support, neither cerebral regional oxygen saturation (crSO2) nor cFTOE correlated with blood pressure measurements (Table 5.).

Table 5) Correlation analysis of term and preterm neonates with and without respiratory support

		5 Minutes				10 Minutes				15 Minutes			
		Term neonates				Term neonates				Term neonates			
		Resp. support		Stable		Resp. support		Stable		Resp. support		Stable	
		CTOI	CFTOE	CTOI	CFTOE	CTOI	CFTOE	CTOI	CFTOE	CTOI	CFTOE	CTOI	CFTOE
SABP	p	0.44	0.31	0.52	0.06	0.89	0.82	0.94	0.66	0.38	0.36	0.73	0.63
	r	0.24	0.32	0.11	-0.31	0.04	-0.07	-0.01	-0.08	0.25	-0.28	0.06	0.12
MABP	p	0.78	0.14	0.62	0.20	0.90	0.81	0.29	0.76	0.73	0.59	0.46	0.81
	r	0.09	0.46	0.09	-0.22	0.04	0.07	-0.18	0.05	0.10	0.16	-0.12	0.06
DABP	p	0.98	0.07	0.24	0.27	0.84	0.67	0.32	0.57	0.77	0.13	0.27	0.98
	r	0.01	0,54	0.20	-0.19	-0.06	0.13	-0.17	0.10	-0.09	0.44	-0.19	0.08

		5 Minutes				10 Minutes				15 Minutes			
		Preterm neonates				Preterm neonates				Preterm neonates			
		Resp. support		Stable		Resp. support		Stable		Resp. support		Stable	
		CTOI	CFTOE	CTOI	CFTOE	CTOI	CFTOE	CTOI	CFTOE	CTOI	CFTOE	CTOI	CFTOE
SABP	p	0.18	0.00**	0.12	0.42	0.77	0.07	0.30	0.75	0.15	0.15	0.91	0.92
	r	0.24	-0.52	0.40	-0.23	0.05	-0.32	0.27	-0.09	0.26	-0.26	-0.03	-0.03
MABP	p	0.15	0.00**	0.34	0.51	0.08	0.02*	0.92	0.60	0.04*	0.00***	0.86	0.89
	r	0.26	-0.53	0.25	-0.19	0.31	-0.41	0.03	0.14	0.36	-0.61	-0.05	0.04
DABP	p	0.04*	0.00**	0.75	0.54	0.03*	0.00***	0.76	0.41	0.03*	0.00***	0.92	0.85
	r	0.36	-0,52	0.08	-0.17	0.37	-0.57	-0.08	0.22	0.39	-0,53	-0.03	0.05

cTOI cerebral tissue oxygenation index, cFTOE cerebral fractional tissue oxygen extraction, DABP diastolic arterial blood pressure, SABP systolic arterial blood pressure, MABP mean arterial blood pressure.

*p<0,05, **P<0,01; ***P<0,001

3.5. Mixed Model

Further a mixed model for every blood pressure value with cFTOE and cTOI was performed.

3.5.1. SABP and cTOI

The analysis shows that there was no influence of the SABP in terms of cTOI, regardless of gestational age and the need for respiratory support. (Table 5.a.)

Table 5.a.) Mixed Model for SABP and cTOI

Dependent Variable: cTOI
Random Factor: Patient
Fixed Factors: Minute, Group, Mean Arterial Pressure
Interactions: Group + Systolic Arterial Pressure, Group + Minute
Correlation Structure: Autoregressive 1

	numDF	denDF	F-value	p-value
as.factor(minute)	2	167	0.417	0.659
group	3	95	1.520	0.214
SABP	1	167	0.465	0.496
group: SABP	3	167	2.120	0.100
as.factor(minute):group	6	167	1.439	0.202
as.factor(minute):SABP	2	167	0.402	0.670
as.factor(minute):group:SABP	6	167	0.818	0.558

	Beta.CI	P.value
(Intercept)	66.086 (56.49,75.68)	0.000
as.factor(minute)10	3.228 (-9.56,16.02)	0.622
as.factor(minute)15	-3.467 (-18.22,11.29)	0.646
Group Preterm with resp. support	-14.311 (-28.23,-0.4)	0.047
Group Preterm without resp. support	-10.349 (-29.17,8.48)	0.284
Group Term with resp. support	-1.951 (-21.46,17.56)	0.845
SABP	0.049 (-0.09,0.19)	0.496
Preterm with resp. support: SABP	0.212 (-0.01,0.43)	0.058
Preterm without resp. support:SABP	0.31 (-0.01,0.63)	0.061
Group Term with resp. support:SABP	0.004 (-0.27,0.28)	0.975

3.5.2. ***SABP and cFTOE***

The analysis shows that there was no influence of the SABP in terms of cFTOE, regardless of gestational age and the need for respiratory support. (Table 5.b.)

Table 5.b.) Mixed Model for SABP and cFTOE

Dependent Variable: CFTOE
Random Factor: Patient
Fixed Factors: Minute, Group, Mean Arterial Pressure
Interactions: Group + Systolic Arterial Pressure, Group + Minute
Correlation Structure: Autoregressive 1

	numDF	denDF	F-value	p-value
as.factor(minute)	2	168	0.565	0.569
group	3	95	0.364	0.779
SABP	1	168	2.760	0.099
group: SABP	3	168	0.727	0.538
as.factor(minute):group	6	168	0.596	0.733
as.factor(minute):SABP	2	168	0.510	0.601
as.factor(minute):group:SABP	6	168	0.376	0.894

	Beta.CI	P.value
(Intercept)	0.35 (0.21,0.49)	0.000
as.factor(minute)10	0.065 (-0.12,0.25)	0.493
as.factor(minute)15	-0.044 (-0.26,0.17)	0.683
Group Preterm with resp. support	0.052 (-0.14,0.25)	0.599
Group Preterm without resp. support	-0.071 (-0.33,0.19)	0.595
Group Term with resp. support	-0.05 (-0.33,0.22)	0.720
SABP	-0.002 (0,0)	0.099
Preterm with resp. support: SABP	-0.002 (0,0)	0.215
Preterm without resp. support:SABP	0 (0,0)	0.857
Group Term with resp. support:SABP	0.001 (0,0)	0.749

3.5.3. MABP and cTOI

The MABP in the mixed model shows a significant influence on cTOI in moderate to late preterm neonates with respiratory support. (Table 6.a.).

Table 6.a.) Mixed model for MABP and cTOI

Dependent Variable: cTOI
Random Factor: Patient
Fixed Factors: Minute, Group, Mean Arterial Pressure
Interactions: Group + Mean Arterial Pressure, Group + Minute
Correlation Structure: Autoregressive 1

	numDF	denDF	F-value	p-value
as.factor(minute)	2	167	1.537	0.218
group	3	95	3.583	0.017
MABP	1	167	0.609	0.436
group:MABP	3	167	3.399	0.019
as.factor(minute):group	6	167	0.971	0.447
as.factor(minute):MABP	2	167	0.564	0.570
as.factor(minute):group:MABP	6	167	0.383	0.889

	Beta.CI	P.value
(Intercept)	66.064 (57.53,74.6)	0.000
as.factor(minute)10	10.856 (-1.41,23.12)	0.085
as.factor(minute)15	7.977 (-5.65,21.6)	0.253
Group Preterm with resp. support	-16.443 (-28.88,-4)	0.011
Group Preterm without resp. support	2.016 (-13.95,17.98)	0.805
Group Term with resp. support	5.281 (-10.45,21.01)	0.512
MABP	0.067 (-0.1,0.24)	0.436
Preterm with resp. support: MABP	0.345 (0.08,0.61)	0.012
Preterm without resp. support:MABP	0.114 (-0.25,0.48)	0.540
Group Term with resp. support:MABP	-0.13 (-0.42,0.16)	0.386

3.5.4. ***MABP and cFTOE***

The MABP in the mixed model shows a significant influence of the MABP on cFTOE regardless of gestational age or the need of respiratory support (Table 6.b.).

Table 6.b.) Mixed model for MABP and cFTOE

Dependent Variable: CFTOE
Random Factor: Patient
Fixed Factors: Minute, Group, Mean Arterial Pressure
Interactions: Group + Mean Arterial Pressure, Group + Minute
Correlatioɑ Structure: Autoregressive 1

	numDF	denDF	F-value	p-value
as.factor(minute)	2	168	0.817	0.443
group	3	95	1.086	0.359
MABP	1	168	4.040	0.046
group:MABP	3	168	1.384	0.250
as.factor(minute):group	6	168	0.455	0.841
as.factor(minute):MABP	2	168	0.881	0.416
as.factor(minute):group:MABP	6	168	0.401	0.877

	Beta.CI	P.value
(Intercept)	0.356 (0.24,0.47)	0.000
as.factor(minute)10	0.001 (-0.17,0.17)	0.995
as.factor(minute)15	-0.106 (-0.3,0.09)	0.278
Group Preterm with resp. support	0.003 (-0.17,0.18)	0.977
Group Preterm without resp. support	-0.117 (-0.34,0.11)	0.307
Group Term with resp. support	-0.162 (-0.38,0.05)	0.145
MABP	-0.002 (0,0)	0.046
Preterm with resp. support: MABP	0.356 (0.24,0.47)	0.000
Preterm without resp. support:MABP	0.001 (-0.17,0.17)	0.995
Group Term with resp. support:MABP	-0.106 (-0.3,0.09)	0.278

3.5.5. ***DABP and cTOI***

The DABP in the mixed model shows a significant positive influence of the DABP on cTOI in late to preterm neonates with respiratory support (Table 7.a.).

Table 7.a.) Mixed model for MABP and cTOI

Dependent Variable: cTOI
Random Factor: Patient
Fixed Factors: Minute, Group, Diastolic Arterial Pressure
Interactions: Group + Diastolic Arterial Pressure, Group + Minute
Correlation Structure: Autoregressive 1

	numDF	denDF	F-value	p-value
(Intercept)	1	167	332.007	0.000
as.factor(minute)	2	167	3.250	0.041
Group	3	95	4.545	0.005
DABP	1	167	2.229	0.137
group: DABP	3	167	3.302	0.022
as.factor(minute):group	6	167	1.521	0.174
as.factor(minute): DABP	2	167	1.593	0.206
as.factor(minute):group: DABP	6	167	0.814	0.561

	Beta.CI	P.value
(Intercept)	3.607 (0.54,6.67)	0.000
as.factor(minute)10	3.729 (0.65,6.81)	0.022
as.factor(minute)15	-14.71 (-23.24,-6.18)	0.019
Group Preterm with resp. support	-8.268 (-16.95,0.41)	0.001
Group Preterm without resp. support	-0.529 (-11.63,10.57)	0.065
Group Term with resp. support	0.005 (-0.18,0.19)	0.926
DABP	0.189 (-0.04,0.42)	0.958
Preterm with resp. support: DABP	0.052 (-0.17,0.27)	0.107
Preterm without resp. support: DABP	-0.163 (-0.43,0.1)	0.648
Group Term with resp. support: DABP	3.607 (0.54,6.67)	0.226

3.5.6. ***DABP and cFTOE***

The mixed model shows a significant negative influence of DABP on cFTOE regardless of gestational age or the need of respiratory support (Table 7.b.)

Table 7.b.) Mixed model for MABP and cFTOE

Dependent Variable: CFTOE
Random Factor: Patient
Fixed Factors: Minute, Group, Diastolic Arterial Pressure
Interactions: Group + Diastolic Arterial Pressure, Group + Minute
Correlation Structure: Autoregressive 1

	numDF	denDF	F-value	p-value
as.factor(minute)	2	168	1.548	0.216
Group	3	95	1.914	0.133
DABP	1	168	5.389	0.021
group: DABP	3	168	1.850	0.140
as.factor(minute):group	6	168	0.486	0.818
as.factor(minute): DABP	2	168	1.899	0.153
as.factor(minute):group: DABP	6	168	0.454	0.841

	Beta.CI	P.value
(Intercept)	0.347 (0.25,0.44)	0.000
as.factor(minute)10	-0.047 (-0.19,0.1)	0.528
as.factor(minute)15	-0.116 (-0.25,0.02)	0.088
Group Preterm with resp. support	-0.03 (-0.17,0.11)	0.685
Group Preterm without resp. support	-0.162 (-0.34,0.02)	0.085
Group Term with resp. support	-0.171 (-0.34,0)	0.056
DABP	-0.003 (0,0)	0.021
Preterm with resp. support: DABP	-0.001 (0,0)	0.552
Preterm without resp. support: DABP	0.002 (0,0.01)	0.445
Group Term with resp. support: DABP	0.004 (0,0.01)	0.064

3.5.7. ***Comparison of cFTOE and cTOI Values in term and preterm neonates with and without Respiratory Support***

Further alle measured values of cFTOE and the cTOI in all patients of each group are presented graphically in figure 5.

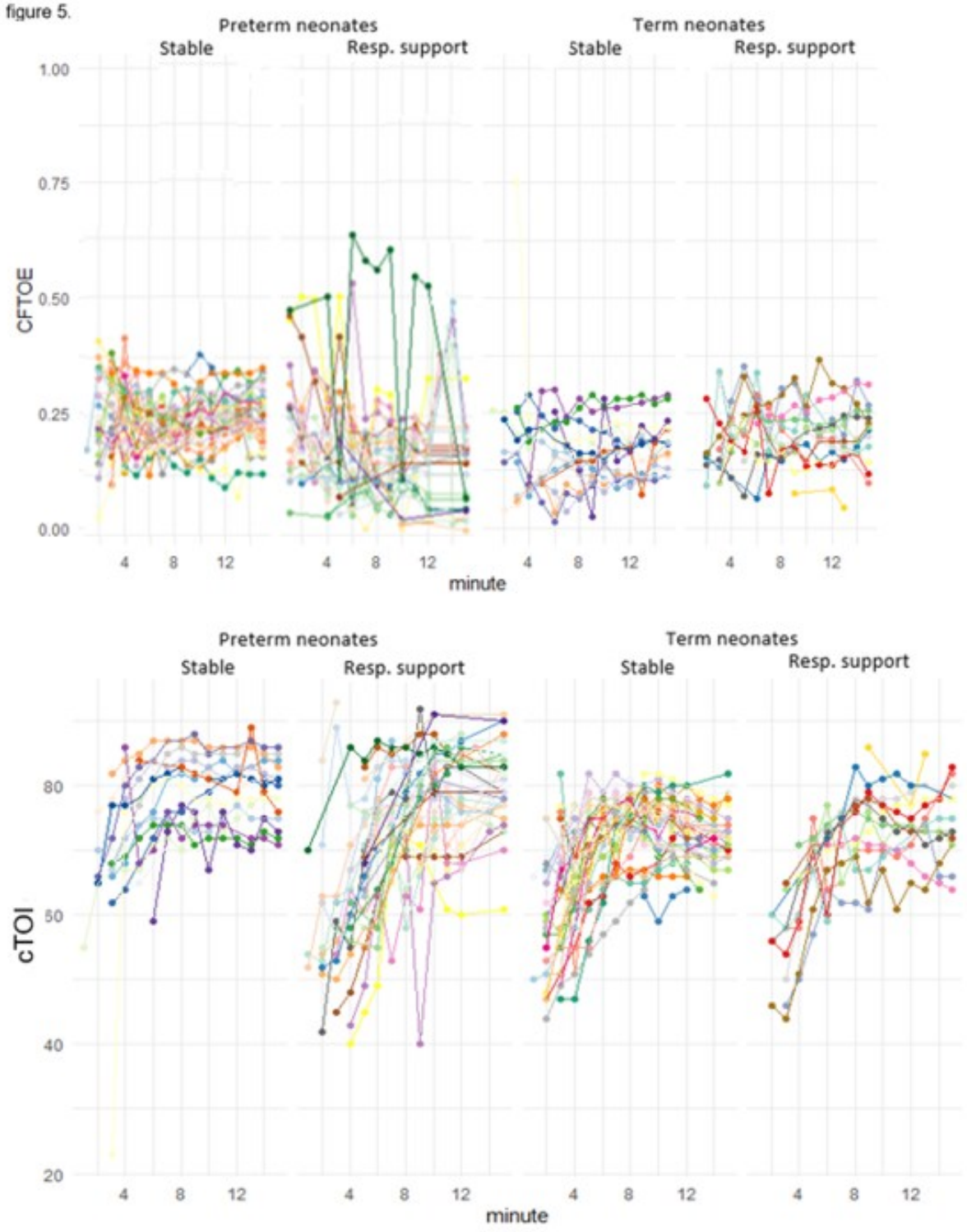
In term neonates, cFTOE values are displayed in two graphs for those with and without respiratory support.

Both groups appear similar between stable neonates and those receiving respiratory support, with comparable levels and distribution patterns (Figure 5). Likewise, the cTOI values for term neonates with and without respiratory support are closely matched, mirroring the trends observed for cFTOE, with similar data distributions (Figure 5).

In preterm neonates, cFTOE values are presented in two graphs for neonates with and without respiratory support. The respiratory support group shows greater variability, with more scattered data points compared to the stable group. Both groups start from similar initial values; however, the respiratory support group generally demonstrates lower cFTOE values at five and ten minutes compared to stable preterm neonates (Figure 5).

Regarding cTOI, preterm neonates in the respiratory support group again display a more dispersed range of values. Similar to the trends seen in cFTOE, both groups start at similar initial values. However, preterm neonates with respiratory support demonstrate higher cTOI values at five and ten minutes on average compared to the stable preterm group (Figure 5).

figure 5.


Preterm neonates
Stable
Resp. support
Term neonates
Stable
Resp. support
CFTOE
1.00
0.75
0.50
0.25
0.00
4
8
12
minute
Preterm neonates
Stable
Resp. support
Term neonates
Stable
Resp. support
cTOI
80
50
40
20
4
8
12
minute

3.5.8. Mixed Model Analysis of cFTOE and cTOI in Relation to Blood Pressure Among Term Neonates with Respiratory Support and Preterm Neonates (with and without Respiratory Support) Compared to Stable Term Neonates

Additionally, a mixed model analysis was conducted to compare the groups with stable term neonates for each minute (Table 8), revealing a clear difference in all blood pressure values for preterm neonates, regardless of the need for respiratory support. Whereby the difference in cFTOE becomes more pronounced over time, while for cTOI, significant differences were initially observed only in stable preterm neonates. However, over time, these differences also became more pronounced and significant in preterm neonates requiring respiratory support.

4

Table 8.) Mixed Model Analysis of cFTOE and cTOI in Relation to Blood Pressure Among Term Neonates with Respiratory Support and Preterm Neonates (with and without Respiratory Support) Compared to Stable Term Neonates.

		5 Minutes			10 Minutes			15 Minutes		
		Term neonates	Preterm neonates		Term neonates	Preterm neonates		Term neonates	Preterm neonates	
cFTOE		Resp. support		Stable	Resp. support		Stable	Resp. support		Stable
SABP	p	0.983	0.007**	0.005**	0.253	0.000***	0.002**	0.214	0.000***	0.014*
	est.	0.032	0.020	0..028	0.028	0.019	0.027	0.026	0.019	0.026
MABP	p	0.761	0.005**	0.004**	0.137	0.000***	0.002**	0.230	0.000***	0.012*
	est.	0.030	0.020	0.026	0.026	0.019	0.025	0.025	0.019	0.025
DABP	p	0.632	0.004**	0.005**	0.126	0.000***	0.001**	0.191	0.000***	0.011*
	est.	0.029	0.021	0.026	0.026	0.019	0.024	0.025	0.019	0.024

		5 Minutes			10 Minutes			15 Minutes		
		Term neonates	Preterm neonates		Term neonates	Preterm neonates		Term neonates	Preterm neonates	
cTOI		Resp. support		Stable	Resp. support		Stable	Resp. support		Stable
SABP	p	0.900	0.876	0.001**	1.000	0.000*	0.013*	0.594	0.000***	0.001**
	est.	2.430	1.600	2.192	2.210	1.517	2.137	2.042	1.534	2.047
MABP	p	0.993	0.950	0.004**	0.999	0.000***	0.024*	0.721	0.000***	0.002**
	est.	2.289	1.578	2.033	2.052	1.477	1.955	1.973	1.467	1.877
DABP	p	1.000	0.974	0.010*	0.996	0.000***	0.021*	0.639	0.000***	0.002**
	est.	2.222	1.586	2.000	2.027	1.486	1.880	1.983	1.466	1.849

cTOI cerebral tissue oxygenation index, cFTOE cerebral fractional tissue oxygen extraction, DABP diastolic arterial blood pressure, SABP systolic arterial blood pressure, MABP mean arterial blood pressure.

*p<0,05, **P<0,01; ***P<0,001

4. Discussion

To our knowledge, this is the first study that comprehensively describes ABP measurements in combination with NIRS during the critical first 15 minutes after birth better known as the immediate transition period in term and preterm neonates, with and without the need for respiratory support. This study aims to analyze the potential influence of blood pressure on cTOI and cFTOE during the immediate transition, when most cardio-circulatory changes take place.

4.1. Term neonates

In stable term neonates with and without the need for respiratory support, we did not observe a correlation between SABP, DABP or MABP with cTOI or cFTOE at minute five, ten and 15. These results suggest that regardless of time passed after birth, term born neonates are capable of maintaining cerebral autoregulation thereby ensuring a constant cerebral blood flow. These findings are in line with the current literature. For instance, animal studies on piglets have shown that term born piglets possess the ability to sustain cerebral autoregulation immediately after birth (79). In this study the cerebral autoregulation was assessed equally to our study by blood pressure measurements and NIRS monitoring. Additionally, Baik et al (80) demonstrated, that MABP does not influence crSO2 and cFTOE at minute 15 after birth, regardless of the necessity for respiratory support in term neonates. These observations are consistent with our study and do confirm an intact cerebral autoregulation immediately after birth in term neonates, irrespective of the need of respiratory support.

4.2, Stable moderate to late preterm neonates

In moderate to late preterm neonates without respiratory support, we observed similar findings during the immediate transition period as in term neonates. Our data showed that all three blood pressure parameters (SABP, MABP and DABP) did not correlate

with the cTOI and cFTOE at five, ten and 15 minutes after birth. These results suggest, similarly to the prior described term born neonates, that moderate to late preterm neonates possess an intact cerebral autoregulation. These findings are supported by the literature. For instance, Pfurtscheller et al. (78) demonstrated similar results in their cohort of moderate to late preterm neonates, showing no correlation between MABP and crSO2 or cFTOE in stable moderate to late preterm neonates at minute 15 after birth.

In conclusion our results support that both, term neonates with and without respiratory support, as well as stable moderate to late preterm neonates, maintain stable cTOI and cFTOE values independent of variations in SABP, MABP and DABP. These findings suggest an effective cerebral vascular regulation and indicate an intact cerebral autoregulation in these groups (19, 22, 26).

4.3. Moderate to late preterm neonates in need of respiratory support

In contrary to the findings mentioned prior, our study showed a correlation between different arterial blood pressure parameters and cerebral oxygenation in moderate to late preterm neonates in need of respiratory support during the immediate transition period.

4.3.1 Systolic blood pressure parameters

However, our study revealed that the systolic blood pressure parameters did not show any correlation with cTOI at all three time points during the immediate transition period. This is different to the study of Pfurtscheller et al. (78) which reports a correlation between the systolic blood pressure values and crSO2 15 minutes after birth. Although, it is important to note, that in Pfurtscheller et al.'s study (78), the correlation between the systolic blood pressure value and crSO2 was the one correlation with the least significance among blood pressure parameters and crSO2, with a p-value of 0,02.

In comparison, considering our study, we observed a trend suggesting a potential correlation between SABP, with a p-value approaching significance, concluding with a

p-value of 0.15. This trend indicates that for SABP, although not statistically significant in our current sample, a larger sample size might be necessary to detect a statistical significance in the relationship between SABP and crSO2 similar to that demonstrated by Pfurtscheller et al. (78) in his cohort. This potential for achieving significance with a larger cohort suggests that our findings may align more closely with Pfurtscheller et al.'s study (78) than initially apparent.

Furthermore, the observed discrepancies may also be attributed to physiological factors such as the presence of an open ductus arteriosus, a remanent of the fetal circulation as discussed prior in the introduction section. This anatomical structure can shunt blood away from the systemic circulation, particularly during episodes of higher systemic vascular pressure, redirecting the blood from the heart back to the lungs, where it recirculates. Consequently, this circulating blood is effectively missing from the systemic vascular system, which is affecting oxygen delivery and blood pressure parameters, particularly during the systolic phase. Therefore, the open ductus arteriosus play a critical role in the relationship between SABP and cTOI.

Considering the correlation between SABP and cFTOE, our study demonstrated a significant finding at the fifth minute after birth in moderate to late preterm neonates receiving respiratory support. However, in our study this correlation diminished at ten minutes and persisted only as a trend at 15 minutes after birth, with a p value of 0.15. These results are contrary to the current literature, particularly the study by Pfurtscheller et al. (78), which showed a significant correlation of SABP and cFTOE at 15 minutes after birth. In Pfurtscheller's study (78), likewise, crSO2 also cFTOE shows a lower significance compared to other blood pressure values with a p-value of 0,03. This discrepancy between our results and those of Pfurtscheller et al, may be due to several factors.

Firstly, similar to the prior mentioned correlation between cTOI and SABP the sample size in our study might have been insufficient to detect a consistent significant correlation after five minutes. A larger cohort could potentially reveal more robust correlations, aligning more closely with Pfurtscheller et al 's (78) findings. Secondly, like already mentioned with the correlation between cTOI and SABP the physiological

influence of the ductus arteriosus on the systolic blood pressure parameters needs to be taken into consideration and may explain these results.

4.3.2. Mean arterial blood pressure

Regarding the MABP and cTOI, our study showed that these two values did not correlate at five and ten minutes after birth in moderate to late preterm neonates in need of respiratory support. However, as time progressed, the correlation approached significance. Ultimately MABP and cTOI becoming significant at 15 minutes after birth. This observation suggests that the relationship between MABP and cTOI in moderate to late preterm neonates in need of respiratory support strengthens during the first minutes after birth.

Contrary to our findings Baik et al. (80) did not demonstrate a correlation between crSO2 and MABP. It is important to note, that Baik et al.'s study included a mixed cohort of late to moderate preterm neonates, both with and without respiratory support, which could affect the comparability of their findings with ours. Therefore, the heterogeneity of Baik's cohort may affect possible correlations.

In contrast to Baik et al., our study is in line with the findings of Pfurtscheller et al. (78), who also reported a significant positive correlation between MABP and cTOI in a comparable cohort with moderate to late preterm neonates in need of respiratory support during the immediate transition period.

Considering MABP and cFTOE our study revealed a significant negative correlation between MABP and cFTOE at five, ten and 15 minutes after birth. This indicates that higher MABP is associated with lower cFTOE, suggesting impaired cerebral autoregulation in late to moderate preterm neonates in need of respiratory support.

However, the level of significance decreases slightly at ten minutes and reaches its peak at 15 minutes. This trend underscores the dynamic nature of cerebral hemodynamics during the immediate transition period.

Our results are consistent with the existing literature. Both Baik et al. and Pfurtscheller et al. reported (78, 80) a significant negative correlation between MABP and cFTOE at 15 minutes after birth in late to moderate preterm neonates.

4.3.3 Diastolic arterial blood pressure

In our study the analysis of the DABP and cTOI revealed a significant positive correlation at five, ten and 15 minutes after birth. Notably, the level of significance increases from five to ten minutes and reaches its peak at 15 minutes after birth. This pattern shows a strengthening of the relationship between DABP and cTOI in preterm neonates in need of respiratory support during the first minutes after birth.

Our results are similar to the findings reported by Pfurtscheller et al. (78), who also demonstrated a significant positive correlation between DABP and crSO2 in moderate to late preterm neonates in need of respiratory support during immediate transition 15 minutes after birth.

Furthermore, our study demonstrated a significant negative correlation between DABP and cFTOE at five, ten, and 15 minutes after birth. Additionally, the level of significance for this correlation increased from five to ten minutes, reaching its peak again at 15 minutes after birth. This trend mirrors the patterns observed with cTOI, and indicates a progressive strengthening of the relationship between DABP and cFTOE in preterm neonates in need of respiratory support during the immediate transition period.

Our results were again in line with the existing literature. For instance, previous studies had also shown a significant negative correlation between DABP and cFTOE in moderate to late preterm neonates in need of respiratory support during immediate transition period, in particular shown at 15 minutes after birth (78).

…

In contrary to the previously described intact cerebral autoregulation observed in term neonates and stable preterm neonates, our findings reveal a different picture for the preterm neonates in need of respiratory support. Considering our results, in this group, cTOI is increasing and cFTOE is decreasing with rising blood pressure values (19, 22, 26).

The observed increasing cTOI and decreasing cFTOE while rising blood pressure implies cerebral perfusion to be passively dependent on systemic blood pressure in these neonates during immediate transition (20, 23, 27).

These findings show that preterm neonates who need respiratory support reveal a high level of vulnerability during the immediate transition due to impairment of cerebral autoregulation. This unstable supply has significant implications for the neurodevelopmental outcomes, as periods of over- or under perfusion can potentially lead to brain injury in form of IVH or developmental delays as shown in literature (26, 81–83).

4.4. Risk factors for impaired cerebral autoregulation

According to the literature, one pronounced risk factor affecting cerebral autoregulation in neonates is the overall condition of the neonate itself. Taking the neonates health status into account, it is not surprising that conditions such as sepsis has an impact on cerebral autoregulation. While inflammation due to sepsis is known to influence cerebral autoregulation, the extent of this impact is still on debate. Some studies suggest that impaired cerebral autoregulation in neonates with sepsis is due to the associated hypotension, which resembles another risk factor for the loss of autoregulation, rather than the inflammation itself (23, 84). Considering our study, the neonates did not exhibit signs of hypotension or sever inflammation. So, the observed loss of the cerebral autoregulation must be contributed to other risk factors. One factor is respiratory distress syndrome (RDS), which is associated with the loss of cerebral autoregulation in sick neonates (15, 21). This might explain the results in our group of preterm neonates with respiratory support, where impaired cerebral autoregulation was observed.

However, this explanation does not account for the intact autoregulation noted in the group of term neonates also receiving respiratory support.

These differences suggest that additional factors must be considered to fully understand the determinants of cerebral autoregulation in neonates. Therefore, other risk factors needed to be considered, like the clinical risk index for babies (CRIB) II score, which is often used to assess the severity of illness and predict outcomes in preterm neonates. Whereby higher CRIB II scores have been associated with a greater risk of losing cerebral autoregulation, indicating that the overall severity of a neonate’s condition, rather than any single factor, might play a crucial role (85, 86).

However, it is important to note that the CRIB II score is typically applied to neonates born at 32 weeks of gestation or earlier, and therefore it is not entirely applicable to our study's cohorts, which included preterm neonates with a mean gestational age of 34 and 35 weeks. Despite this limitation, our results indicate that gestational age itself remains a critical risk factor influencing cerebral autoregulation. It seems that preterm neonates are more vulnerable to disruptions in cerebral blood flow regulation due to an underdeveloped autoregulatory mechanism. This vulnerability is compounded in the presence of additional stressors, which is in line with the existing literature (87–89).

This discussion on gestational age naturally leads to an important question, if *preterm neonates are even capable of cerebral autoregulation immediately after birth*.

This question has been the focus of several studies, and the current evidence suggests that late to moderate preterm neonates are indeed capable of maintaining a constant CBF due to intact cerebral autoregulation (57, 78, 87, 90). In our study, we showed that in the multi mixed model, preterm neonates significantly differ from stable term neonates in cTOI and cfTOE at each time point, considering the blood pressure, regardless of respiratory support. However, preterm neonates with respiratory support exhibited more pronounced differences.

These findings are in line with our correlation analysis in the cohort of late to moderate preterm neonates requiring respiratory support during the immediate transition period, where correlations between blood pressure and cFTOE or cTOI suggest impaired cerebral autoregulation. In contrast, no such correlation were demonstrated in preterm neonates without respiratory support indicating intact cerebral autoregulation in this group.

Considering these results, it seems that the situation appears to be more complex. So showed Gilmore et al. (88) that preterm neonates are prone to experience episodes of impaired cerebral autoregulation. This susceptibility suggests that preterm neonates are capable to maintain cerebral autoregulation, however they are under imminent risk of losing this regulatory capacity due to certain conditions discussed prior.

Taking this into consideration it makes sense that preterm neonates, who already show a tendency to lose cerebral autoregulation, are particularly vulnerable to losing the

ability to maintain CBF regardless of arterial blood pressure values, when additional stressors, such as the need of respiratory support, is present. This need for respiratory support likely exacerbates their physiological instability, leading to a loss of cerebral autoregulation and as a result, preterm neonates in need of respiratory support exhibits a more passive, pressure-dependent cerebral perfusion, as observed in our study where arterial blood pressure correlated with cTOI and cFTOE.

However, considering blood pressure monitoring it is still not clear, *which blood pressure parameter would be the most relevant in preterm neonates.*

The majority of literature focuses on MABP, and therefore, when investigating cerebral autoregulation in neonates, this is the best investigated blood pressure parameter in combination with NIRS. Given the previously discussed influence of the ductus arteriosus on the SABP, it is not surprising that the correlation between SABP and cTOI was not detectable, with significant findings for cFTOE observed only at 5 minutes. These findings are in line to the mixed model analysis, which did not show any significant influence of SABP on cTOI or cFTOE across all groups during the entire 15 minutes of the immediate transition regardless of gestation or respiratory support.

On the other hand, MABP did show an influence on cFTOE in the correlation analysis, and at 15 minutes after birth it also significantly affected cTOI. These findings are consistent with the mixed model results, which showed a relationship between MABP and cTOI and with cFTOE in the preterm group with respiratory support during the immediate transition period. This result is not that pronounced as expected at first and could be due to the limitations in calculating MABP in preterm neonates, which involve summing DABP with the product of one-third of the pulse pressure (the difference between SABP and DABP). Given that SABP can be unreliable in neonates due to the influence of the arterial duct, the accuracy of MABP as a parameter must be questioned to a certain degree, too.

This concern is supported by the existing literature, indicating that MABP measurements in neonates can be inaccurate when derived using formulas like mentioned above, normally typically applied to adults (91, 92). So do some researchers recommend to adjust the coefficient used in the calculation, suggesting that the

difference between SABP and DABP should be multiplied by a factor ranging from 0.45 to 0.50, rather than one-third, to have a better approximation in neonates (91).

Bearing all this in mind it seems that DABP is the most robust and reliable parameter during immediate transition for neonates. Unlike SABP, DABP is hardly influenced by the arterial duct and therefore making it a more reliable and stable indicator of systemic and cerebral hemodynamics. This aligns with our study, where DABP consistently showed strong correlations with both cTOI and cFTOE across all time points in preterm neonates with respiratory support. Moreover, also the mixed model analysis showed a significant influence of DABP on cTOI and cFTOE, particularly in preterm neonates requiring respiratory support.

These results prompt a reevaluation of the focus on MABP as primary blood pressure parameter especially in neonates during the immediate transition. Furthermore, MABP has also to be reevaluated as primary parameter in combination with NIRS for investigating cerebral autoregulation in neonates during immediate transition.

Besides, the studies assessing the prior described CrCP in combination with the cerebral autoregulation suggest that DABP is the major factor in terms of cerebral perfusion. Because, if the DABP falls below the CrCP, the CBF ceases and blood flow will only occur during the systole (93). This consistent interruption at regular intervals of the CBF is a sign of impaired cerebral autoregulation. This condition significantly elevates the risk of severe complications such as IVH and periventricular leukoencephalopathy (PVL) (93).

The inability to maintain constant CBF and the associated perfusion fluctuations are particularly detrimental to the neural tissue of preterm neonates. These episodes of impaired cerebral autoregulation did not pose an immediate threat but also increase the likelihood of long-term neurodevelopmental impairments, emphasizing the importance of monitoring and managing the CBF in this vulnerable population.

Therefore, to avoid such adverse outcomes, it is crucial for clinicians to know whether the cerebral autoregulation is intact or not in neonates. In cases where the neonates show an impaired cerebral autoregulation, it is essential to maintain the blood pressure stable without fluctuations and around the autoregulatory plateau. This plateau was

described prior, in the discussion section and it describes the region where CBF remains stable. This ensures adequate and consistent cerebral perfusion and reduces the risk for adverse outcomes.

To assess the autoregulatory status, NIRS monitoring in combination with blood pressure measurements, specifically in combination with DABP seems to be an ideal tool. By combining these two medical devices clinicians can gain a deeper insight into the cerebrovascular stability of the neonate and with this information the clinician can reduce the risk of adverse outcomes.

4.4. Strengths and Limitations

One of the greatest strengths of this study is its prospective study design, which allows a systematic approach to evaluate the influence of blood pressure on cerebral oxygenation during the immediate transition. This methodology enhances the robustness and reliability of the findings. Additionally, the study benefits form a relatively large sample size, consisting of 102 neonates (51 preterm and 51 term). This is quite substantial for a single-center study, particularly during the critical period of immediate transition after birth.

Despite its strengths, this study possesses several limitations that need to be acknowledged. One limitation is the small number of neonates in some of the subgroups, which may reduce the statistical power to detect differences. However, although the numbers are limited in some sub-groups there are still significant results. Additionally, the arterial duct, was not documented via cardiac sonography. Although this information would be noteworthy, the ductus arteriosus is typically still open within the first 15 minutes after birth. Lastly, the preterm neonate groups differ in terms of gestational ages. This variation could interfere with the results. That was the reason a mixed model analysis was applied to reinforce the issue and help to ensure further robustness despite these differences.

4.5 Conclusion

This study shows a significant association in compromised late to moderate preterm neonates requiring respiratory support between cTOI and cFTOE with blood pressure and especially with the diastolic blood pressure during the first 15 minutes after birth. This association was absent in stable preterm and term neonates whether they required respiratory support or not.

These results suggest that compromised late to moderate preterm neonates requiring respiratory support during immediate transition show impaired cerebral autoregulation, a condition where the ability to maintain stable CBF despite changes in systemic blood pressure is compromised. As a result of this the brain suffers from a passive pressure cerebral perfusion. This is a condition where the CBF gets overly dependent on systemic blood pressure and its fluctuations. The resulting inconstant CBF is known as a risk factor for IVH and subsequent neurodevelopmental disturbances.

Therefore, this study suggests that NIRS monitoring in combination with blood pressure measurements during immediate transition is crucial to identify early episodes of impaired cerebral autoregulation and to reduce the potentially associated risk which goes hand in hand with it.

Moreover, this study shows, that the current focus on the MABP as the primary marker for systemic blood pressure should be reevaluated in preterm neonates, considering that it promotes the often-overlooked DABP which seems to play a more crucial role in ensuring stable CBF.

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