Dissertation

Influence of cardiac output on the regional cerebral oxygenation in term neonates during the immediate neonatal transition

Einfluss von Herzzeitvolumen auf regionale zerebrale Oxygenierung bei Reifgeborenen unmittelbar nach der Geburt

submitted by

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz".

Certain parts of this thesis have been published in renowned journals before the preparation of this thesis was finally completed. Due to the publication policies of some journals, it was necessary to transfer the copyright to the journal's publishers. To avoid copyright infringement and self-plagiarism, I applied for the right to incorporate materials, including figures and tables, from my articles into this thesis. The journal's publishers, which hold the copyright on, granted back the right to include the articles within my dissertation, provided that proper credit is given to the original source. For transparency reasons one written permission has been included into the appendix of this dissertation. The other publisher Elsevier let the authors retain the right to include their own articles into their dissertation without further need for a written permission. A written correspondence is also included in the appendix.

This is a list of my published articles, which are partly included into this thesis.

1. Baik, N.; Urlesberger, B.; Schwaberger, B.; Freidl, T.; Schmolzer, G.M.; Pichler, G. Cardiocirculatory monitoring during immediate fetal-to-neonatal transition: a systematic qualitative review of the literature. *Neonatology* **2015,** *107,* 100-107.

2. Baik, N.; Urlesberger, B.; Schwaberger, B.; Schmolzer, G.M.; Kostenberger, M.; Avian, A.; Pichler, G. Foramen ovale (FO) - The underestimated sibling of ductus arteriosus (DA): Relevance during neonatal transition. *Early Hum. Dev.* **2016,** *103,* 137-140.

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Abstract

Background

The immediate transition from foetus to neonate includes substantial changes especially concerning the cardiovascular system. Furthermore, the brain is one of the most vulnerable organs to hypoxia during this period. The occurrence of brain injury like intraventricular haemorrhage is associated with development of hydrocephalus, poor neurological outcome and even death. According to current guidelines for postnatal stabilization, the recommended parameters for monitoring are heart rate (HR) and arterial oxygen saturation (SpO_2).
Recently, there is a growing interest for advanced monitoring of the cardio-circulatory system and the brain to get further and objective information of neonate's condition during the immediate postnatal transition after birth.

Aim of the study

The aim of this present study was to apply advanced cardio-circulatory and brain monitoring in term neonates and to investigate the potential influence of these cardio-circulatory parameters, especially cardiac output on the cerebral oxygenation.

Methods

This is a monocentric, prospective observational study. For non-invasive cardiac output measurements (NICOM) the electrical velocimetry (EV) method (Aesculon Monitor, Osypka medical, CA, USA) was used. Electrocardiogram (ECG) electrodes were placed on the left forehead, left side of the neck, left hemithorax, and left thigh. The pulse oximetry for SpO2 and HR measurements was placed on the right hand or wrist. The cerebral regional oxygen saturation ($crSO_2$)/ cerebral tissue oxygen index (cTOI) were measured using an INVOS cerebral/somatic oximeter monitor (Invos 5100C, Somanetics Corp, Troy, Michigan) with the neonatal sensor/ a NIRO200NX monitor (Hamamatsu; Japan). The near-infrared spectroscopy (NIRS)- transducer was positioned on the right frontoparietal forehead in each infant. Monitoring started at minute 1 and was continued until minute 15. At minute 5, 10 and 15 after birth, cardiac

output (CO) was calculated as an average out of six 10-second periods (with beat-to-beat analysis). The data of these 10-second periods were only accepted if the signal quality index (SQI) was ≥80%.

Immediately, after the end of NICOM and NIRS measurements (15 min after birth), an echocardiography was performed (Vivid 7 Pro, General Electric; USA) to evaluate the DA and FO. The blood pressure was measured non-invasively at the 15th minute of life using a neonatal cuff of appropriate size at the left upper arm (IntelliVue MP30 Monitor, Philips, Amsterdam, Netherlands).

Mean values of $crSO_2$, cTOI, SpO_2 and HR were calculated at minute 5,10 and 15 after birth. The cerebral fractional oxygen extraction (cFTOE) was calculated as (SpO_2-$crSO_2$)/SpO_2 or as (SpO_2-cTOI)/SpO_2.

Group differences in baseline characteristics were analysed using χ2 and Fisher's exact tests for discrete variables, and t-test or Mann-Whitney U test for continuous variables. Correlations were performed using Spearman's rank correlation coefficient or Pearson's correlation when appropriate. A p-value < 0.05 was considered statistical significant. The statistical analyses were performed using IBM SPSS Statistics 23.0.0 (IBM Corporation; Armonk, USA).

Results

During the study period, a total of 185 term neonates were enrolled. $crSO_2$, cTOI and SpO_2 parameters showed a statistically significant increase until minute 10 after birth. Accordingly, cFTOE showed a decrease during the observational period. HR decreased towards minute 10, afterwards to minute 15 it increased again. Cardiac output showed a decreasing tendency until minute 10 and stayed stable until minute 15. During the whole observational period, there was no significant correlation between CO and $crSO_2$/cTOI or cFTOE.

In our study population, we could identify 100 male and 85 female term neonates. $crSO_2$, cTOI, cFTOE, SpO_2 and heart rate were not significant different between male and female. Interestingly, males showed higher cardiac output compared to females

throughout the observational period. In both groups, there was no significant correlation between cardiac output and $crSO_2$, cTOI and cFTOE.

In our study population, we could identify 21 neonates, who have received respiratory support (RS group) and 164 term neonates (non-RS group), who didn't need respiratory support during the study period. $crSO_2$, cTOI and SpO_2 values showed an increase during the first 15 minutes. RS group showed significantly lower values of $crSO_2$, cTOI and SpO_2 compared to neonates in the non-RS group. RS group showed lower cardiac output levels compared to neonates in the non-RS group throughout the observational period. No significant correlation was observed between $crSO_2$ and mean arterial blood pressure (MABP), cTOI and MABP and between cFTOE and MABP.

82 out of 98 neonates showed predominantly left-to-right shunt via DA and 50 out of 82 neonates showed additionally left-to-right shunt via FO. No significant correlation could be observed between cTOI, the diameter of DA, or the diameter of FO. We observed a significant negative correlation between cTOI and the sum of the diameter of DA and FO.

Conclusion

The present work was the first study to investigate a possible influence between cardiac output and cerebral oxygenation in term infants during the immediate neonatal transition. In our study population, there was no significant correlation between CO and cerebral oxygenation.

Male neonates showed tendentially higher cardiac output compared to female neonates. Although, there was no significant correlation between cardiac output and cerebral oxygenation in male and female groups.

RS group showed lower cardiac output levels compared to neonates in the non-RS group. This might be due to positive intrathoracic pressure caused by the respiratory support.

In term infants there was no significant influence of MABP on cerebral oxygenation, suggesting that there is a well-functioning cerebral autoregulation.

A negative correlation was observed between the increasing sum of DA and FO diameters and cerebral oxygen saturation in term neonates 15 minutes after birth, suggesting that the only evaluation of DA might be insufficient to obtain the whole picture regarding the influence of left to right shunting on cardiac output and cerebral oxygenation during immediate neonatal transition.

Zusammenfassung

Hintergrund

Die postnatale Transition vom Fötus zum Neugeborenen beinhaltet wesentliche Veränderungen, insbesondere im Hinblick auf das Herz-Kreislauf-System. Besonders für Organe, welche anfällig auf die Hypoxie reagieren zum Beispiel das Gehirn, ist eine komplikationslose Transition sehr wichtig. Das Auftreten von Hirnblutungen ist mit der Entwicklung eines Hydrocephalus, einem schlechten neurologischen Outcome und sogar mit dem Tod assoziiert. Gemäß den aktuellen Richtlinien für die postnatale Stabilisierung, sind die einzigen empfohlenen Parameter während der postnatalen Transition von Neugeborenen die Überwachung der Herzfrequenz und der arteriellen Sauerstoffsättigung.
In letzter Zeit besteht ein wachsendes Interesse an der erweiterten Überwachung des Herz-Kreislauf-Systems und des Gehirns, um weitere und objektive Informationen über den Zustand des Neugeborenen während dieser vulnerablen Zeit des Lebens nach der Geburt zu erhalten.

Zielsetzung

Ziel dieser vorliegenden Studie war es, bei Neugeborenen eine erweiterte kardio-zirkulatorische und zerebrale Überwachung durchzuführen und den möglichen Einfluss dieser kardio-zirkulatorischen Parameter im speziellen Herzzeitvolumen auf die zerebrale Oxygenierung zu untersuchen.

Methoden

Diese Studie ist eine monozentrische, prospektive Beobachtungsstudie. Für nicht-invasive Herzzeitvolumenmessung (NICOM) wurde eine „electrical velocimetry“ (EV) - Methode (Aesculon Monitor, Osypka Medical, CA, USA) verwendet. EKG-Elektroden wurden auf der linken Stirnseite, der linken Halsseite, dem linken Hemithorax und dem linken Oberschenkel platziert. Für arterielle Sauerstoffsättigung (SpO_2) und Herzfrequenz-Messungen wurde ein Pulsoxymeter (IntelliVue MP30 Monitor, Philips, Amsterdam, Niederlande) an der rechten Hand oder am rechten Handgelenk platziert.

Die zerebrale regionale Sauerstoffsättigung ($crSO_2$) / der zerebrale Gewebesauerstoffindex (cTOI) wurde unter Verwendung eines INVOS-Monitors (Invos 5100C, Somanetics Corp., Troy, Michigan) / eines NIRO200NX-Monitors (Hamamatsu; Japan) gemessen. Der Nah-Infrarotspektroskopie (NIRS) Sensor auf der rechten fronto-parietalen Stirnseite positioniert. Die Überwachung begann in Minute 1 und wurde bis Minute 15 fortgesetzt. In den Minuten 5, 10 und 15 nach der Geburt wurde das Herzzeitvolumen (CO) als Durchschnitt von sechs 10-Sekunden-Perioden berechnet (mit Schlag-zu-Schlag-Analyse). Die Daten dieser 10-Sekunden-Perioden wurden nur zur Auswertung herangezogen, wenn der Signalqualitätsindex (SQI) ≥ 80% betrug.

Unmittelbar nach Beendigung der NICOM- und NIRS-Messungen (15 Minuten nach der Geburt) wurde eine Echokardiographie durchgeführt (Vivid 7 Pro, General Electric; USA), um Ductus arteriosus (DA) und Foramen ovale (FO) zu bewerten. Der Blutdruck wurde nicht-invasiv am linken Oberarm in der 15. Lebensminute gemessen (IntelliVue MP30 Monitor, Philips, Amsterdam, Niederlande).

Die Mittelwerte von $crSO_2$, cTOI, SpO_2 und Herzfrequenz wurden in den Minuten 5,10 und 15 nach der Geburt berechnet. Die zerebrale Sauerstoffextraktion (cFTOE) wurde berechnet als (SpO_2-$crSO_2$) / SpO_2 oder als (SpO_2-cTOI) / SpO_2. Die Gruppenunterschiede wurden unter Verwendung von exaktem Fisher‘s Test und t-Test oder Mann-Whitney-U-Test analysiert. Korrelationen wurden unter Verwendung des Spearman-Rangkorrelationskoeffizienten oder gegebenenfalls der Pearson-Korrelation durchgeführt. Die statistischen Analysen wurden unter Verwendung von IBM SPSS Statistics 23.0.0 (IBM Corporation; Armonk, USA) durchgeführt.

Ergebnisse

Während des Studienzeitraums wurden insgesamt 185 Neugeborene in die Studie eingeschlossen. In der gesamten Studienpopulation zeigten die Parameter $crSO_2$, cTOI und SpO_2 eine statistisch signifikante Steigung bis zur Minute 10 nach der Geburt. Folglich zeigte cFTOE eine Abnahme während der 15 Minuten nach der Geburt. Das Herzzeitvolumen zeigte eine abnehmende Tendenz bis Minute 10 und blieb bis Minute

15 nach der Geburt stabil. Während der gesamten Beobachtungsdauer gab es keine signifikante Korrelation zwischen CO, $crSO_2$ / cTOI und cFTOE.

Unsere Studienpopulation setzte sich zusammen aus 100 männlichen und 85 weiblichen Neugeborene.
$crSO_2$, cTOI, cFTOE, SpO_2 und Herzfrequenz unterschieden sich nicht signifikant zwischen männliche und weibliche Neugeborene. Interessanterweise zeigten männliche Neugeborene im Vergleich zu weiblichen Neugeborenen ein höheres Herzzeitvolumen. In beiden Gruppen gab es keine signifikante Korrelation zwischen Herzzeitvolumen und $crSO_2$, cTOI und cFTOE.

In unserer Studienpopulation konnten wir 21 Neugeborene mit respiratorischer Unterstützung (RS-Gruppe) und 164 Neugeborene ohne respiratorische Unterstützung (non-RS-Gruppe) identifizieren. Die RS-Gruppe zeigte signifikant niedrigere Werte von $crSO_2$, cTOI und SpO_2 im Vergleich zu Neugeborenen in der non-RS-Gruppe. Weiters, zeigte die RS-Gruppe im Vergleich zu Neugeborenen in der non-RS-Gruppe niedrigeres Herzzeitvolumen.

Es wurde keine signifikante Korrelation zwischen $crSO_2$ und mittleren arteriellen Blutdruck (MABP), cTOI und MABP und zwischen cFTOE und MABP beobachtet.

82 von 98 Neugeborenen zeigten überwiegend einen Links-Rechts-Shunt über DA und 50 von 82 Neugeborenen zeigten zusätzlich einen Links-Rechts-Shunt über FO. Es konnte keine signifikante Korrelation zwischen cTOI, dem Durchmesser von DA oder dem Durchmesser von FO beobachtet werden. Wir beobachteten aber eine signifikante negative Korrelation zwischen cTOI und der Summe der Durchmesser von DA und FO.

Schlussfolgerung

Die vorliegende Arbeit ist die erste Studie, die den Einfluss von Herzzeitvolumen auf zerebrale Oxygenierung bei reifen Neugeborenen während der neonatalen Adaptationsphase untersuchte. In unserer Studienpopulation gab es keine signifikante Korrelation zwischen CO und zerebraler Oxygenierung.

Männliche Neugeborene zeigten im Vergleich zu weiblichen Neugeborenen ein tendenziell höheres Herzzeitvolumen. Es gab jedoch keine signifikante Korrelation zwischen Herzzeitvolumen und zerebraler Oxygenierung bei männlichen und weiblichen Neugeborenen.

Die RS-Gruppe zeigte niedrigeres Herzzeitvolumen im Vergleich zu Neugeborenen in der non-RS-Gruppe. Dies ist in erster Linie auf den positiven intrathorakalen Druck bei der Atemunterstützung zurückzuführen.

In unserer Studienpopulation gab es keinen signifikanten Einfluss von MABP auf die zerebrale Oxygenierung, was auf eine gut funktionierende zerebrale Autoregulation in unserer Studienpopulation schließen lässt.

Eine negative Korrelation wurde zwischen der zunehmenden Summe von DA- und FO-Durchmessern und zerebraler Oxgenierung bei reifen Neugeborenen 15 Minuten nach der Geburt beobachtet. Die alleinige Evaluierung von DA könnte nicht ausreichend sein, um den Einfluss von Links-Rechts-Shunt auf das Herzzeitvolumen und die zerebrale Oxygenierung nach der Geburt zu beurteilen.

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List of Abbreviations

HR	Heart rate
SpO_2	Arterial oxygen saturation
DV	Ductus venosus
DA	Ductus arteriosus
FO	Foramen ovale
PVR	Pulmonary vascular resistance
ECG	Electrocardiogram
PO	Pulse oximetry
BP	Blood pressure
CO	Cardiac output
SVR	systemic vascular resistance
SBP	Systolic blood pressure
MBP	Mean blood pressure
MABP	Mean arterial blood pressure
DBP	Diastolic blood pressure
CS	Caesarean section
VD	Vaginal delivery
LVO	Left ventricular output
LVSV	Left ventricular stroke volume
LtoR	Left-to-right shunting via the ductus arteriosus
EV	Electrical velocimetry
NICOM	Non-invasive cardiac output monitoring
TEB	Thoracic electrical bioimpedancemetry
SV	Stroke volume
aEEG	Amplitude integrated electroencephalography
NIRS	Near infrared spectroscopy
VLBW	Very low birth weight
Nm	Nanometers
Hb	Hemoglobin
Mb	Myoglobin
CtOx	Cytochrome aa3
cTOI	Cerebral tissue oxygen index
$crSO_2$	Cerebral regional oxygen saturation

s	second
cFTOE	Cerebral fraction tissue oxygenation extraction
SD	Standard deviation
IQE	Interquartile range
RS	Respiratory support
Non-RS	Non-respiratory support
CPAP	Continuous positive airway pressure
PPV	Positive pressure ventilation
PEEP	Positive end expiratory pressure
PIP	Peak inflation pressure
CBV	Cerebral blood volume

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1 Introduction

1.1. Neonatal transition

The transition from fetal to newborn life causes complex physiological processes affecting all vital organ systems. Major changes triggered by lung aeration especially involves the cardiovascular system. (1)

(1)

1.1.1. The fetal circulation

At the beginning of the pregnancy, the first heart beats can be observed from the 4th week, and already around the 8th week the heart is fully developed. (2) At the timepoint of 11th weeks of gestation, the fetal circulation is completely established. (3) The main difference between fetal and neonatal circulation is the bypass of the non-functional lungs through the presence of the placenta. Furthermore, the fetal circulation has three short connections, also called “shunts”, which switch the systemic circulation in parallel instead of in series. These three shunts (ductus venosus, ductus arteriosus and foramen ovale) are arrangements that make the fetal circulation a well-functioning system for intra-uterine life. (4)

Ductus venosus (DV): This connection is located between the umbilical vein and the vena cava inferior. It distributes the main volume of oxygenated blood from the placenta into the vena cava inferior, bypassing the liver.
Ductus arteriosus (DA): This shunt is the connection between the pulmonary artery and the aorta and it serves to bypass the pulmonary circulation.
Foramen ovale (FO): Through this connection the blood passes directly from the right atrium into the left atrium, bypassing the pulmonary circulation. (5)

The placenta provides oxygenated blood via umbilical vein. About 80% of the oxygenated blood flows directly into the vena cava inferior through DV, bypassing the liver. The other 20 % passes the liver and reaches the vena cava inferior through the liver veins.

This oxygenated blood in the vena cava inferior merges with the deoxygenated blood returning from the lower part of the body and flows into the right atrium, where it is partly mixed with the deoxygenated blood from the vena cava superior.
The major part of the blood flows via foramen ovale into the left atrium and consequently into the left ventricle, bypassing the right ventricle and the pulmonary circulation.

From there, the blood is pumped into the aorta and supplies the upper body with a relatively high oxygenated blood. The remaining blood, which does not flow through the foramen ovale and mainly derived from the superior vena cava, flows from the right atrium into the right ventricle and is pumped into the pulmonary artery. Due to the high vascular resistance in the pulmonary circulation and due to the unfolded lung, blood takes the path of lowest resistance and flows through the DA into the aorta and supplies the lower body. Through the two umbilical arteries, the blood flows back to the placenta and can be re-enriched with oxygen.

The highest oxygen saturation is found in the umbilical vein and the lowest is measured in the abdominal vena cava inferior. (6) The oxygenated blood in the fetal circulation has lower oxygen saturation and lower partial pressure of oxygen compared to the oxygenated blood in the extra-uterine circulation. However, to achieve adequate oxygenation, the hemoglobin concentration in the fetal blood is about 20 g/dl and the oxygen affinity of the fetal hemoglobin is above that of the maternal blood. (7)
In addition, fetal oxygen consumption is significantly lower due to decreased metabolism. It also comes in utero to a different blood distribution of the oxygenated blood: the brain and the heart are supplied with the most highly oxygenated blood. (8)

1.1.2. Changes in cardio-circulatory system from intra-uterine to extra-uterine life

These physiological arrangements of fetal circulation, which are described above, provides the fetus advantages in utero, but they are not beneficial to survival after birth. After separation of the newborn from the placenta by clamping the cord, a rapid switch to pulmonary gas exchange is essential within few minutes after birth. This alteration not only includes a quick transition from liquid- to air filled lungs, but also a major adaptation of the fetal cardiovascular system. (9) Especially, pulmonary vascular resistance has to drop quickly to increase pulmonary perfusion as the sole recipient of right ventricular output. This is not only important for establishment of lungs gas exchange, but also essential for increasing pulmonary blood flow to become the source of preload for the left ventricular output. (10)

The newborn undergoes all of these events within minutes after birth and they are critical for the extra-uterine survival. All of these events are triggered by a single incident: lung aeration. Lung aeration leads to the decrease in pulmonary vascular resistance (PVR), consequently it comes to the increase of pulmonary blood flow, which initiates dramatic reorganization of newborns circulation. Lung aeration combined with umbilical cord clamping leads into the closing of the major shunts resulting in separation of the pulmonary and systemic circulations. (1)

Recently, there is a growing interest in neonatal transition research concerning changes in cardio-vascular system. Many study groups attempt different monitoring methods (11) to observe these changes more precisely for getting a better understanding.

1.2. Monitoring during neonatal transition

To objectify the newborn's condition during this vulnerable transition period, Virginia Apgar developed a scoring system based on clinical assessments (12), which is called Apgar score and widely used all over the world. However, there is significant inter-observer and intra-observer variability in clinical assessments using Apgar score. (13, 14) In order to assess the neonate's condition objectively, the latest guidelines in support of neonatal transition and resuscitation recommend, besides the clinical

evaluation, the use of electrocardiography (ECG) and pulse oximetry in the delivery room. (15) These monitoring methods enable non-invasive continuous monitoring of the SpO_2 as well as HR, but they do not provide information about potentially compromised cardiocirculatory status resulting in severely limited oxygen transport to tissue. (11)

1.2.1. Pulse oximetry (PO)

Pulse oximetry provides continuous information noninvasively about arterial oxygen saturation (SpO_2) as well as heart rate. Dawson et al. has already established the reference range for SpO_2 in term infants during the first 10 minutes after birth who did not receive oxygen or other interventions in the delivery room. (16) With defined reference ranges, Pulse oximetry is used in the delivery room to guide oxygen supply during neonatal transition to avoid hyper- and hypoxia. (17)

1.2.2. Cardiocirculatory monitoring

1.2.2.1. Heart rate

The latest guidelines for neonatal resuscitation recommend monitoring of the heart rate to guide the supporting assessments during neonatal transition. (15) Most of the studies carried out in human neonates immediately after birth monitored heart rate using pulse oximetry or ECG or the combination of both. (11) (Table 1)

Author/year	Gestation	Mode of delivery	Method used	Infants	Tendency first 15 min	Respiratory support	First measurement	
							heart rate, bpm	time after birth, min
Brady [10], 1962	–	CS/VD	ECG	112	–	yes	152[a]/125[b]	2
Bustos [22], 1975	term	VD	–	23	increase	no	170	3–5
Meier-Stauss [13], 1990	preterm/term	CS	PO/ECG	53	–	yes	158	2
Gonzales [18], 1998	term	VD/CS	PO	380	increase	yes	133 VD/108 CS	1
Toth [15], 2002	preterm/term	VD	PO	50	decrease	no	157	2
Kopotic [16], 2002	preterm	–	PO	15	–	yes	110	2–3
Kamlin [14], 2008	preterm/term	–	PO/ECG	55	–	yes	–	2
Dawson [17], 2009	preterm	–	PO	126	increase	yes	<100	1
Dawson [19], 2010	preterm/term	VD/CS	PO	468	increase	no	96	1
van Vonderen [11], 2014	term	CS	ECG	24	stable	no	157	2
Noori [20], 2012	term	VD	PO	20	decrease	no	169	3–7
van Vonderen [12], 2014	term	CS	ECG	24	stable	no	158	2
Smit [21], 2014	term	VD	PO	109	increase	no	61	1

CS = Cesarean section; VD = vaginal delivery; PO = pulse oximetry. [a] Infants with onset of respiration before cord clamping. [b] Infants with onset of respiration after cord clamping.

Table 1: Heart rate monitoring in neonates immediately after birth
Reproduced from (11) with permission of Neonatology/Karger (11)

A prompt increase in HR immediately after birth is currently the most important parameter for adequate fetal- to-neonatal transition. (15) If HR is <100/min, the resuscitation guidelines suggest providing respiratory support. (15) However, several studies have reported HR <100/min to be common in term and preterm infants. (18, 19) Furthermore, the changes of heart rate might be strongly connected with cord clamping time and lung aeration: Brady et al. could observe a significant decrease in HR, when the umbilical cord was clamped before lung aeration and it lung aeration could be achieved before cord clamping, HR remained stable before and after cord clamping. (20)

There are further aspects, which can influence the changes in heart rate immediately after birth: mode of delivery and maternal anaesthesia. Two studies could observe

significantly higher HR in vaginally delivered neonates compared to those born by caesarean section. This observation could be an effect of maternal general anaesthesia. (19, 21)

Resuscitation, either with 100% oxygen or with air in preterm neonates, had a similar effect on HR with a rising tendency. (18) Kopotic et al (22) described similar observations during neonatal resuscitation with 100% oxygen in a small number of extremely preterm neonates.

Few studies compared between PO and ECG and came to the conclusion, that there is a good accuracy between PO and ECG. (23) However, it has been reported that ECG placement can be applied more quickly and ECG provides heart rate faster compared to PO. (24)

1.2.2.2. Blood pressure (BP)

Blood pressure is a composite of cardiac function and peripheral circulation as determined by cardiac output (CO) and systemic vascular resistance (SVR), respectively, and is therefore an important indicator of appropriate circulation.(11) Several studies described blood pressure during neonatal transition using the doppler ultrasound method (25) and the oscillometric technique.

Author/year	Gestation	Mode of delivery	Method used	Infants	First measurement, mm Hg		
					SBP	MBP	DBP
Marx [23], 1976	term	VD/CS	Doppler	134	67.7±0.6	48.0±0.6	–
Winberg [25], 1989	term	CS	oscillometric	16	67	45	32
Salihoglu [24], 2012	preterm/term	VD/CS	oscillometric	982	63.82±12.24	49.01±11.40	37.76±11.63
van Vonderen [11], 2014	term	CS	oscillometric	24	68.3±18.3	51.2±15.4	41.6±16.0
Pichler [26], 2014	preterm/term	VD/CS	oscillometric	108	62 (60–66)	49 (42–52)	42 (35–45)

SBP = Systolic BP; MBP = mean BP; DBP = diastolic BP; CS = cesarean section; VD = vaginal delivery.

Table 2: Blood pressure monitoring in neonates immediately after birth
Reproduced from (11) with permission of Neonatology/Karger (11)

Recently, our study group has established the reference ranges of BP in preterm and term neonates during the immediate transition. (26) Comparable values of blood pressure have been reported by further studies during immediate transition period in term infants receiving no medical support. (25, 27-29) Further aspects, which have an influence on BP is the gestational age, the birth mode and gender: BP values have been described to be lower in preterm infants compared to term infants and increase with increased gestational age. (26, 28) Neonates after vaginal birth had significantly higher BP values compared to neonates born via caesarean section. (25, 26, 28)

There is until now no study describing blood pressure measured invasively during the immediate neonatal transition.

1.2.2.3. Cardiac function

1.2.2.3.1. Echocardiography

To describe cardiac function, many studies performed functional echocardiography during neonatal transition. (27, 29-31)

Author/year	Gestation	Mode of delivery	Infants	Tendency first 15 min	First measurement	
					LVO, ml/kg/min	LVSV, ml/kg
Winberg [25], 1989	term	CS	16	–	238	1.55
Noori [20], 2012	term	VD	20	increase (LVO/LVSV)	168±42	1.01±0.23
van Vonderen [11], 2014	term	CS	24	increase (LVO/LVSV)	151±47	1.0±0.3
van Vonderen [12], 2014	term	CS	24	increase (LVO/LtoR shunting)	161±50	–

CS = Cesarean section; VD = vaginal delivery; LtoR = left-to-right shunting via the ductus arteriosus.

Table 3: Cardiac function monitoring in neonates immediately after birth
Reproduced from (11) with permission of Neonatology/Karger (11)

Stroke volume determines HR and cardiac output. In term neonates, three studies reported an increase in left ventricular output (LVO) and left ventricular stroke volume (LVSV) within the first 10 min. (27, 30, 31) In addition, shunting through a persistent

ductus arteriosus has been described, becoming increasingly more left to right during the first 10 min after birth. (30, 31)

Echocardiography has the ability to noninvasively measure cardiac functions during the immediate fetal- to-neonatal transition. However, the use of echocardiography is limited due to i) inability to measure cardiac function continuously, ii) dependence on ability and experience of the examiner, iii) parameters need to be defined prior measurements to limit time on echocardiography and not to interfere with resuscitation procedures, and iv) currently no reference values during immediate transition period are available. (11)

1.2.2.3.2. Electrical velocimetry (EV) monitoring

EV monitoring is a new method of non-invasive cardiac output monitoring (NICOM), based on a modified impedance cardiography technology. This method has already been validated compared with echocardiography in neonates with excellent correlations. (32, 33) Our study group made first measurements in a larger cohort of term infants during neonatal transition using this technique. (34)

Cardiac output is a parameter, which represents the global hemodynamic cardiac function. Thoracic electrical bioimpedancemetry (TEB) is a way to capture this parameter non-invasively. In 1966, Kubicek et al presented for the first time a model for stroke volume calculation by impedance changes across the thorax. (35) This technique was modified in 80s. (36, 37)

The classical TEB method is based on the change of resistance depending on the change in intrathoracic fluid volume during a heartbeat. This method takes advantage of the different electrical conductivity of the various biological tissues: Blood has good conductivity, while the conductivity of muscles and adipose tissue can be almost neglected.

The EV is based on the assumption that the disordered biconcave erythrocytes align themselves parallel to the bloodstream for approximately 60ms before the aortic valve. In the course of systole to diastole, they are then disordered again and this alteration leads to the change in the thoracic electrical bio impedance. The change in the

erythrocyte orientation leads to an increase or decrease in the thorax electrical conductivity.

During a systole, there is a decrease in the intrathoracic fluid volume, which corresponds exactly to the stroke volume (SV). As a result, there is an increase in intrathoracic resistance and this is used to calculate the stroke volume. Thus, the method allows to measure the stroke volume non-invasively and to calculate the cardiac output.

1.2.3. Cerebral monitoring

The brain is one of the most vulnerable organs to hypoxia during fetal to neonatal transition. The recommended routine monitoring during neonatal transition are SpO_2 and heart rate. Unfortunately, these parameters do not provide information about cerebral perfusion or oxygenation or brain activity. (38) Around 30% of very preterm neonates tend to develop brain injury, including peri/intraventricular haemorrhage, mostly during the first 3 postnatal days (39) leading to development of hydrocephalus, poor neurological outcome and even death. (40) Therefore, additional cerebral monitoring during this vulnerable phase of life might potentially be beneficial and may influence interventions to optimize oxygen delivery to the brain to potentially affect survival with improved short- and long-term neurological outcomes.

For evaluation of cerebral changes during neonatal transition, research groups applied various methods: (38)

i) Doppler sonography: sequential measurements of cerebral perfusion (41)
ii) Amplitude integrated electroencephalography (aEEG): continuous measurement of cerebral activity (42)
iii) Near infrared spectroscopy (NIRS): continuous measurement of cerebral oxygenation (43-45)

Doppler sonography and aEEG have their limitations: they are technically difficult to perform during the neonatal transition, especially when neonates need interventions. Furthermore, Doppler sonography cannot be continuously applied and aEEG is prone to artefact, so that these methods are not optimal for clinical everyday routine. NIRS seems at the moment the most favourable method, since it provides continuous data monitoring and is feasible even in very low birth weight (VLBW) infants receiving resuscitation interventions. (38)

1.2.3.1. Measurement principle of Near-Infrared Spectroscopy

The technique of NIRS is based on the principle that biological tissue is relatively permeable to near-infrared light. The in NIRS used light is in a wavelength range of 700-1000 nanometres (nm). (46, 47) The light is reflected, absorbed or scattered by the tissue.

The reflection depends on the tissue surface and the angle of incidence of the light and can be reduced with increasing wavelength.

The scattering is influenced by the tissue composition and the absorption depends on the individual molecular characteristics. (48, 49) Chromophores (colour carriers) belong to these molecules and can absorb light of different wavelengths. The most important chromophores for the NIRS are haemoglobin, myoglobin and cytochrome aa3. Oxygenated, deoxygenated haemoglobin and myoglobin have different absorption characteristics, resulting in a different absorption spectrum at different wavelengths for each one. (50) Changes in the concentration of these chromophores lead to absorption changes of the emitted light.

The absorption maximum of oxygenated haemoglobin is 920nm and of deoxygenated haemoglobin is 760nm. Since haemoglobin and myoglobin have partly the same absorption spectra, and their absorption maxima overlap, it is not possible to exactly differentiate these substances, but the absorption of the near infrared light by myoglobin is negligible, since it accounts for only about 10%. (51)

Cytochrome aa3, which is part of the mitochondrial respiratory chain and thus part of cellular energy production, has its absorption maximum at 830nm, and absorbs near-infrared light by only 2-5%, so it plays a subordinate role for NIRS and can be neglected as well. (47)

According to these findings the optimal wavelength would be 700-1000 nm. If a shorter wavelength is chosen, the penetration of the light into the tissue would be only 1 cm and the absorption and scattering of haemoglobin would be too strong. (46, 52) If a wavelength above 1000 nm is chosen, the absorption of the near infrared light by fluid would be too high. (52)

When a wavelength of 820 nm is selected, the total haemoglobin concentration can be measured, since at this wavelength an equivalent absorption of oxygenated and deoxygenated haemoglobin occurs. (49)

Thus, with NIRS, a change in the concentration of oxygenated and deoxygenated haemoglobin and by their summation, a change in the total haemoglobin concentration in the tissue can be determined. (47)

1.2.3.2. Cerebral monitoring with NIRS

In 1977, the NIRS was introduced by Frans F. Jöbsis as a monitoring method for non-invasive measurement of oxygenation in different tissue regions, such as brain, kidney, intestinal tract, and muscle. (46) In neonatology, this method was first demonstrated in 1985 by Brazy et al. (53) Over the last decades, there have been numerous studies focusing on NIRS, and in research field NIRS has its significant value for better understanding for tissue oxygenation.

NIRS is now a promising technique for measuring the cerebral perfusion of preterm and term neonates and numerous studies have already been conducted on the use of NIRS to measure cerebral oxygenation. (47, 50, 52, 54)

Our study group has investigated difference topics with using NIRS

i) changes in cerebral hemodynamic and oxygenation in preterm and term neonates during periodic breathing and apnoea. (55-58)
ii) effect of tilting on cerebral hemodynamic in preterm- and term neonates with and without periventricular leukoencephalomalacia. (59, 60)
iii) observation study of cerebral and pre- and post-ductal peripheral muscular oxygen saturation in term infants during neonatal transition. (43)
iv) differences in cerebral oxygenation in term neonates after caesarean section and after vaginal delivery. (44)
v) differences in cerebral oxygenation in preterm neonates with and without mild respiratory support during neonatal transition. (61)

vi) observational study of cerebral blood volume behaviour during neonatal transition in term and preterm with and without respiratory support. (62, 63)

vii) randomised controlled study to investigate the effect of sustained lung inflation on cerebral blood volume. (64)

Most clinical studies using NIRS in a neonatal intensive care unit examined changes in cerebral oxygenation at different stages of the neonatal adaptation phase, starting from the first few minutes postnatally with and without respiratory support (43, 65, 66) over the first day of life (67) towards the first week of life. (68, 69)

Recently, our study group have published reference ranges and centile charts of cerebral oxygenation during the first 15 minutes after birth using different NIRS devices. (70, 71) Thus, cerebral tissue oxygen index (cTOI) is equivalent to the cerebral regional oxygen saturation ($crSO_2$) of different NIRS devices of other companies.

Lately, two observation studies (65, 72) in preterm neonates with IVH demonstrated increased burden of cerebral hypoxia below the 10^{th} percentile of published reference ranges (71), leading to the result, that a further cerebral monitoring to reduce the burden of cerebral hypoxia during neonatal transition might be beneficial.

The COSGOD trial, a randomized controlled trial of our study group could demonstrate that a reduction of burden of cerebral hypoxia after birth is feasible by using NIRS monitoring to guide respiratory and oxygen support. (73)

1.2.4. Connection of cardiac output and cerebral oxygenation

In recent years, our study group has shown that cerebral oxygenation increases slowly in the first 15 minutes after birth. (43, 44) This was observed in both preterm and term newborns.

The oxygen supply of the brain depends on oxygen delivery and cardiac output and the evaluation of cardio circulatory status in the first minutes of life remains challenging.

So far, our study group recently published reference ranges of blood pressure in the first minutes after birth. (26) We discovered, however, an association with the heart rate and open ductus arteriosus. (74) Furthermore, we were able to present cardiac output data in lager cohort of term neonates immediately after birth, suggesting the NICOM using EV method is feasible during the postnatal stabilization. (34) In order to investigate and understand a possible influence of the cardio-circulatory factors for the cerebral oxygenation during immediate neonatal transition, we performed in the present study different monitoring of cardio-circulatory parameters and analysed the connection between these parameters and cerebral oxygenation.

2 Objectives

2.1. Aim of the study

2.1.1. Main objective

The aim of this study was to use the new non-invasive procedure to measure hemodynamic changes with a focus on cardiac output during the first 15 minutes immediately after birth and to investigate the connection and the influences of cardiac output on cerebral oxygenation in term neonates.

2.1.2. Secondary objectives

i) Difference in gender; to investigate, if there is a difference between male and female term neonates concerning vital parameters (SpO_2, HR, $crSO_2$ and cardiac output) and the influence of cardiac output on cerebral oxygenation

ii) Difference in respiratory support; to investigate if there is a difference between those neonates receiving respiratory support and those with no need of respiratory support concerning vital parameters (SpO_2, HR, $crSO_2$ and cardiac output) and the influence of cardiac output on cerebral oxygenation

iii) Mean arterial blood pressure (MABP); to investigate the influence of MABP on cerebral oxygenation.

iv) Shunting via FO and DA; to investigate the influence of shunting via Foramen ovale and ductus arteriosus on the cerebral oxygenation

3 Methods

This is a monocentric, prospective observational study conducted in the period from September 2013 to March 2017 at the Division of Neonatology at the Department of Paediatrics and Adolescent Medicine, Medical University of Graz. This study is approved by the Regional Committee on Biomedical Research Ethics at the University. (EC number 25-342 ex 12/13)

3.1. Patients

3.1.1. Inclusion criteria

We included term infants with a gestational age of at least 37 weeks, fulfilling following criteria:

i) written informed consent by the parents prior to birth
ii) delivery through caesarean section.

3.1.2. Exclusion criteria

Exclusion criteria were

i) decision not to provide full life support
ii) congenital malformation
iii) any structural heart disease

3.1.3. Dropout

A dropout out of the study on parental request was possible at any time. All parents were told at the beginning of the study that they could quit the study at any time and without any reason. Consequently, their children will automatically leave the study and

their data were not further analysed. Furthermore, they were assured that their decision would have no influence on the further care and medical care of their children.

3.2. Materials

3.2.1. Pulse oximetry

For monitoring of SpO_2 and HR, a pulse-oximetry was placed around the right wrist/hand (IntelliVue MP30 Monitor, Philips, Amsterdam, Netherlands).

3.2.2. Blood pressure

The blood pressure was measured non-invasively at the 15th minute of life using a neonatal cuff of appropriate size at the left upper arm (IntelliVue MP30 Monitor, Philips, Amsterdam, Nether- lands).

3.2.3. NICOM using Electrical Velocimetry

The cardiac output was measured by the Aesculon EV monitoring system (Osypka, Berlin, Germany). Four surface ECG electrodes (forehead, left side of the neck, left hemithorax, and left thigh) are used to obtain a current flow. This small alternate electrical current flows through the thorax from the outer ECG electrodes and the inner electrodes measure the resulting voltage. A major contributing factor to conductance (1/impedance) of the electrical current is blood flow in the ascending aorta. The impedance to the flow of current varies according to the alignment of red blood cells in the ascending aorta. (34)

Recently, Noori et al. (32) analysed a non-invasive EV device for cardiac output monitoring in neonates and compared the results with echocardiography. They described, EV had similar accuracy and precision compared to echocardiography

when the EV signal quality index (SQI) was ≥80%. The SQI is a composition of two measures. First, the signal has to meet certain shape and timing requirements. Second, the magnitude derived from the signal has to fall within statistically predetermined limits. Therefore, the SQI is an indication for signal strength over a number of cardiac cycles. If for example the SQI is 80%, that means 8 of 10 cardiac cycles met the established criteria and thereby were acceptable. Using NICOM, we always analysed periods of 10 seconds (s), and these measurements were used to calculate a mean value for minute 5, 10 and 15 after birth. (34)

3.2.4. NIRS

The cerebral regional oxygen saturation ($crSO_2$) was measured using an INVOS cerebral/somatic oximeter monitor (Invos 5100C, Somanetics Corp, Troy, Michigan) with the neonatal sensor. The cerebral tissue oxygen index (cTOI) was measured using an NIRO200NX monitor (Hamamatsu; Japan).

3.2.5. Echocardiography

Echocardiography was performed (Vivid 7 Pro, General Electric; USA) to evaluate the DA and FO.

3.3. Anamnestic and demographic data

The following anamnestic data were collected for all patients:

i) Gestational age
ii) Gender
iii) Birth weight
iv) Head circumference
v) APGAR values (minute 5, 10 after birth)

vi) Arterial ph value of the umbilical cord

vii) Need for respiratory support during the measurement period

3.4. Calculated parameter

3.4.1. Calculation of cerebral fractional tissue oxygen extraction (cFTOE)

cFTOE shows the oxygen consumption of the brain. The following formula can then be used to calculate the FTOE: [(SpO_2-$crSO_2$or cTOI) / SpO_2]. (75) In our study, a mean cFTOE was calculated for each patient at minute 5, 10 and 15 after birth.

3.5. Study design

A stopwatch was started when the neonate was fully delivered. After cord clamping, which was routinely performed after 30 seconds, neonates were brought to the resuscitation table and placed with an overhead heater in supine position. The neonates after caesarean section are routinely observed by a neonatologist (who was not member of the research team). Measurement/monitoring was performed during the first 15 min after birth. For non-invasive CO measurements, the Aesculon monitor was used. Before starting the measurement, the skin was cleaned from vernix and the four surface ECG electrodes were placed on the left forehead, left side of the neck, left hemithorax, and left thigh. The pulse oximetry for arterial oxygen saturation and HR measurements was placed on the right hand or wrist. The cerebral regional oxygen saturation ($crSO_2$)/ cerebral tissue oxygen index (cTOI) were measured using an INVOS cerebral/somatic oximeter monitor (Invos 5100C, Somanetics Corp, Troy, Michigan) with the neonatal sensor / a NIRO200NX monitor (Hamamatsu; Japan). The transducer was positioned on the right frontoparietal forehead in each infant. The sensor on the forehead was secured with cohesive conforming bandage (Peha-haft, Harmann, Heidenheim, Germany).

Monitoring started at minute 1 and was continued until minute 15. At minute 5, 10 and 15 after birth, CO was calculated as an average out of six 10-second periods (with

beat-to-beat analysis). The data of these 10-second periods were only accepted if the SQI was ≥80%.

If respiratory support was required, it was started using continuous positive airway pressure (CPAP) and/or positive pressure ventilation (PPV) via an appropriate sized round silicone face mask (Fischer & Paykel Healthcare, Auckland, New Zealand). Respiratory support was provided with a T-piece – a continuous flow, pressure-limited device with a built-in manometer and positive end expiratory pressure (PEEP) valve. The default settings used were a gas flow of 6-8 L/min, peak inflation pressure (PIP) of 24-28 cmH2O, PEEP of 5-6 cmH2O and FiO2 0.21. Resuscitation was performed according to latest guideline recommendations. (15)

Immediately, after the end of NICOM and NIRS measurements (15 min after birth), an echocardiography was performed (Vivid 7 Pro, General Electric; USA) to evaluate the DA and FO. After excluding any form of structural heart disease, ductal and FO patency was assessed. If there was a left to right flow through DA and FO was detectable, the diameter of DA and FO was measured. Ductal patency was directly assessed from left parasternal location in the parasternal short axis view. We measured the internal ductal diameter three times with pulsed Doppler echocardiography plus colour flow mapping. Then we averaged the results of the measurements. Based on fulfilling the following echocardiographic criteria, a patency of ductus arteriosus was diagnosed as being haemodynamically important: a left atrium to aortic root diameter ratio of 1.4, internal ductal diameter N 1.4 mm/kg. FO size and patency were using the subcostal 4-chamber view. We measured the FO diameter three times with pulsed Doppler echocardiography plus colour flow mapping and averaged the results of the measurements. (76)

The blood pressure was measured non-invasively at the 15th minute of life using a neonatal cuff of appropriate size at the left upper arm (IntelliVue MP30 Monitor, Philips, Amsterdam, Nether- lands).

3.6. Statistics

All variables were stored by using a multichannel system alpha-trace digital MM (BEST Medical Systems, Vienna, Austria) for subsequent analysis. Values of the SpO_2, and HR were stored every second, and the sample rate of $crSO_2$/ cTOI was 0.13Hz/ 2Hz.

Baseline characteristic are presented as means with 95%CImean ± standard deviation (SD) for normally distributed continuous variables and medians with interquartile range (IQE) when the distribution was skewed. Categorical variables are given with numbers and percent. Group differences in baseline characteristics were analysed using $\chi 2$ and Fisher's exact tests for discrete variables, and t-test or Mann-Whitney U test for continuous variables.

Mean values of $crSO_2$, cTOI, SpO_2 and HR were calculated at minute 5,10 and 15 after birth. The cerebral fractional oxygen extraction (cFTOE) was calculated as (SpO_2-$crSO_2$)/SpO_2 or as (SpO_2-cTOI)/SpO_2.

Correlations were performed using Spearman's rank correlation coefficient or Pearson's correlation when appropriate. A p-value < 0.05 was considered statistical significant. The statistical analyses were performed using IBM SPSS Statistics 23.0.0 (IBM Corporation; Armonk, USA).

3.6.1. Analyses for secondary aims

3.6.1.1. Difference in gender

To investigate the difference in gender, we divided the study population into two groups: male and female. The mean of vital parameters ($crSO_2$, cTOI, cFTOE, SpO_2, HR and CO) were compared between the two groups. A correlation analysis was performed between $crSO_2$, cTOI, cFTOE and CO individually.

3.6.1.2. Difference in respiratory support

To investigate the difference in respiratory support, we divided the study population into two groups: neonates receiving respiratory support and neonates with no need of respiratory support. The mean of vital parameters ($crSO_2$, cTOI, cFTOE, SpO_2, HR and CO) were compared between the two groups. A correlation analysis was performed between $crSO_2$, cTOI, cFTOE and CO individually.

3.6.1.3. MABP

A correlation analysis was performed to investigate if there was an association between cTOI, $crSO_2$, cFTOE and MABP in our study population

3.6.1.4. DA+FO

A correlation analysis was performed to investigate if there was a connection between cTOI and the diameter of DA and FO, individually. Furthermore, to get the whole input of the left to right shunt on the cerebral tissue oxygenation, we added the diameter of PDA and FO, when there was a left-to-right shunt. As the next step we performed the correlation analyses between the sum of DA/FO diameters and the cerebral tissue oxygenation. (76)

4 Results

During the study period, between September 2013 and March 2017, a total of 185 term neonates were enrolled. Demographic and clinical characteristics of the study population are presented in table 4.

	Study population (n=185)
Gestational age (weeks), – mean (SD)	38.7 ± 0.8
Birth weight (g), – mean (SD)	3252.1 ± 513
Birth length (cm), mean (SD)	50.5 ± 2.4
Head circumference (cm), mean (SD)	34.8 ± 1.3
Female sex, n (%)	85 (45.9)
Apgar score at 5 minutes, – median (range)	10 (9-10)
Apgar score at 10 minutes, – median (range)	10 (10-10)
Umbilical artery pH – mean (SD)	7.29 ± 0.04
Caesarean section, n (%)	185 (100)
Cord clamping within 30 seconds, n (%)	185 (100)
Respiratory support, n (%)	21 (11.4)

Table 4: Demographic and clinical characteristics of the study population

4.1. Course of Cerebral Oxygenation ($crSO_2$, cTOI), cFTOE, SpO_2, HR and cardiac output at minute 5,10,15 after birth

The courses of vital parameters at the time points 5,10 and 15 minutes after birth of the whole study population are presented in table 5. $crSO_2$, cTOI and SpO_2 parameters showed a statistically significant increase until minute 10 after birth, which is comparable with results of numerous other study groups. Accordingly, cFTOE showed consequently a decrease during the study period. Heart rate decreased towards minute 10, afterwards to minute 15 it increased again.

	Minute 5 after birth	Minute 10 after birth	Minute 15 after birth	p- value between minute 5 and 10/ between minute 10 and 15
$crSO_2$ (%) mean (SD)	61.7 ± 21.2	81.6 ± 10.4	81.3 ± 10.5	0.00/0.74
cTOI (%) mean (SD)	63.9 ± 11.8	73.1 ± 7.8	73.0 ± 7.5	0.00/0.89
cFTOE mean (SD)	0.23 ± 0.15	0.17 ±0.09	0.19 ± 0.08	0.00/0.02
SpO^2 (%) mean (SD)	80.7 ± 11.5	93.4 ± 5.4	95.4 ± 3.6	0.00/0.00
HR (beat per minute) mean (SD)	146 ± 14.4	143 ± 12.0	147 ± 13.1	0.02/0.01
CO (ml/kg/min) mean (SD)	194.3 ± 34.1	191.0 ± 35.9	191.8 ± 38.0	0.2/0.9

Table 5: Courses of vital parameters at 5, 10 and 15 minutes after birth of study population

The results of cardiac output measurements are additionally presented in figure 1. Cardiac output showed a decreasing tendency until minute 10, which didn't reach significance and stayed stable until minute 15.

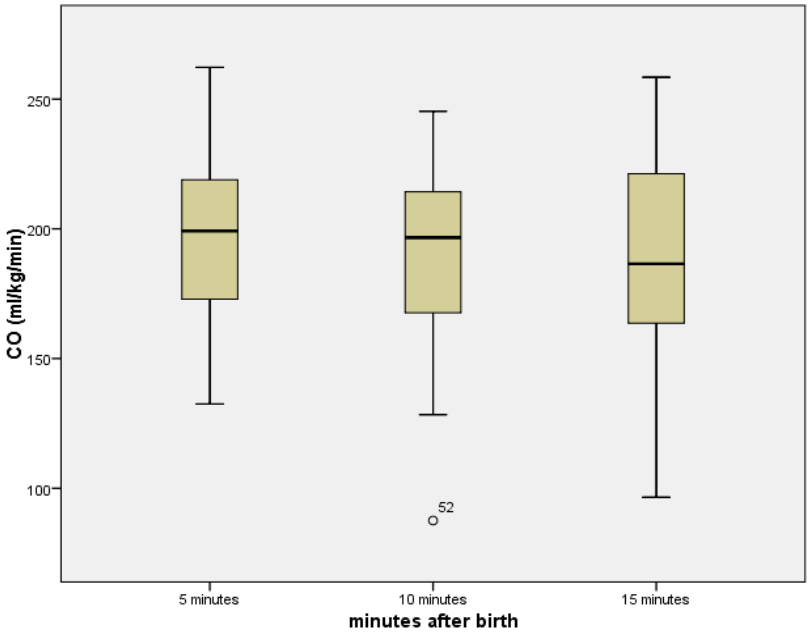

Figure 1: Course of cardiac output in whole study population at minute 5, 10 and 15 after birth.

4.2. Correlation between cardiac output and cerebral oxygenation / cFTOE at minute 5,10,15 after birth

The results of correlation analyses between cardiac output and $crSO_2$/cTOI and cFTOE are presented in table 6.

		$crSO_2$	cTOI	cFTOE
Cardiac Output	Minute 5 after birth			
	ρ	0.20	0.13	0.12
	P value	0.26	0.53	0.43
	Minute 10 after birth			
	ρ	0.10	0.23	-0.17
	P value	0.57	0.13	0.15
	Minute 15 after birth			
	ρ	-0.12	0.27	-0.07
	P value	0.48	0.06	0.53

Table 6: Correlation analyses between CO and $crSO_2$/cTOI and cFTOE

During the whole observational period, there was no significant correlation between cardiac output $crSO_2$/cTOI and cFTOE.

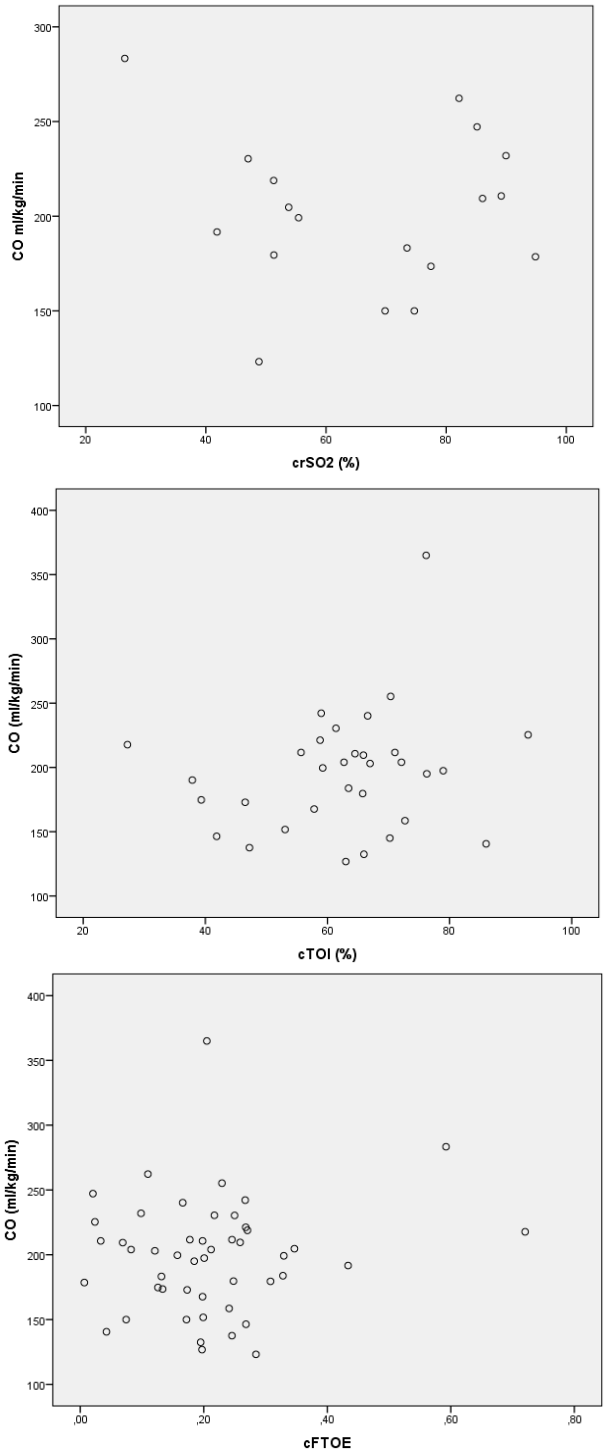

Figure 2: Correlation analyses between CO and $crSO_2$/cTOI and cFTOE at minute 5 after birth

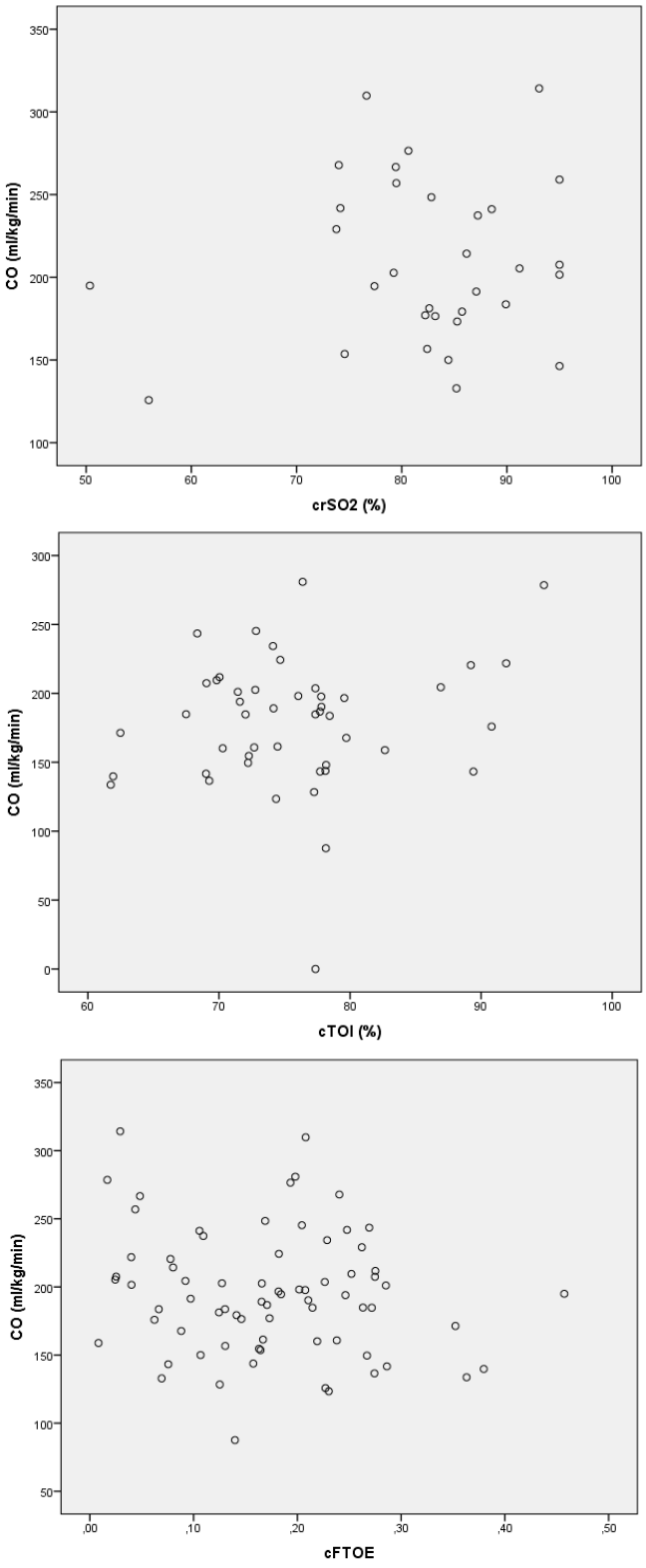

Figure 3: Correlation analyses between CO and crSO2/cTOI and cFTOE at minute 10 after birth

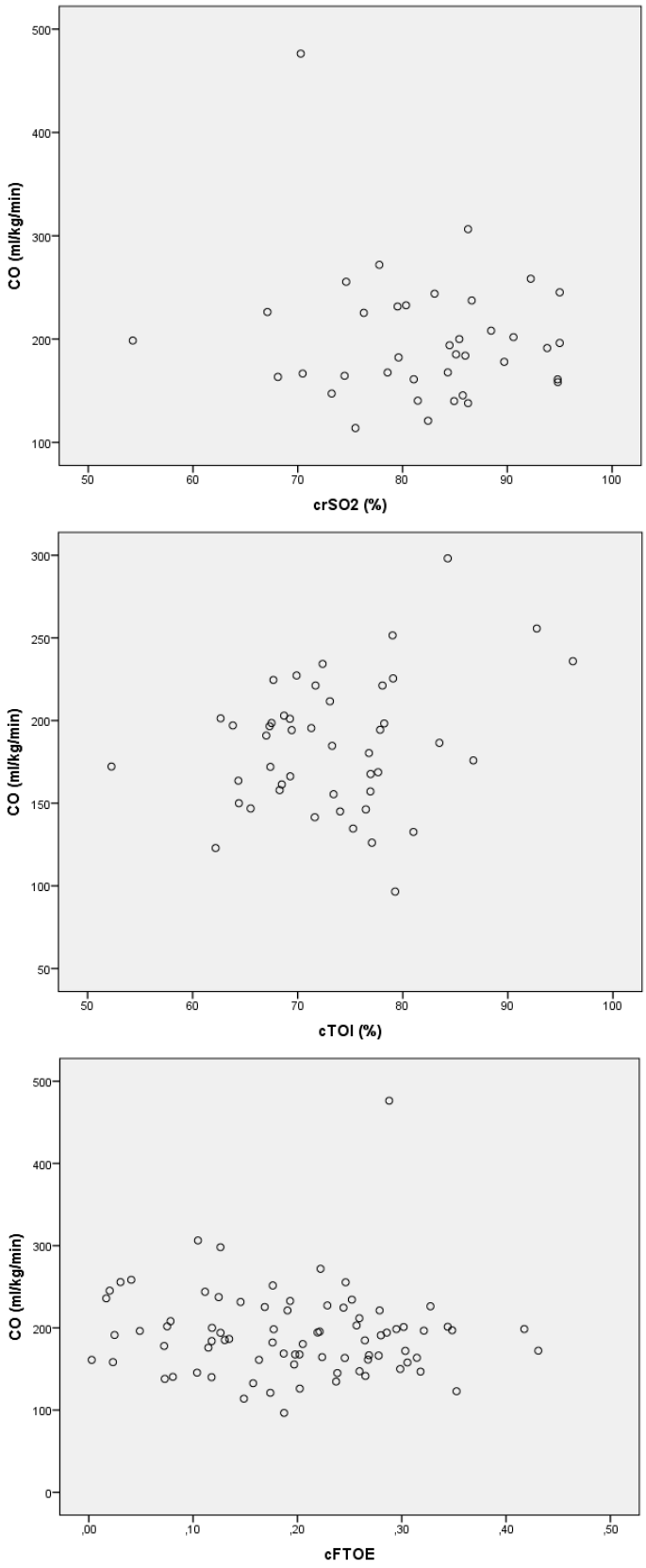

Figure 4: Correlation analyses between CO and crSO2/cTOI and cFTOE at minute 15 after birth

4.3. Difference in gender

In our study population, we could identify 100 male and 85 female term neonates. The demographic data of these two groups are shown in table 7. Concerning the demographic data, there was no significant difference between male and female group.

	Male (n=100)	**Female (n=85)**	**p value**
Gestational age (weeks), – mean (SD)	38.7 ± 0.9	38.7 ± 0.8	0.8
Birth weight (g), – mean (SD)	3248.9 ± 510	3255.7 ± 519	0.85
Birth length (cm), mean (SD)	50.5 ± 2.2	50.4 ± 2.6	0.24
Head circumference (cm), mean (SD)	35.0 ± 1.3	34.6 ± 1.3	0.89
Apgar score at 5 minutes, – median (range)	10 (9-10)	10 (9-10)	0.68
Apgar score at 10 minutes, – median (range)	10 (10-10)	10 (10-10)	0.49
Umbilical artery pH – mean (SD)	7.29 ± 0.05	7.29 ± 0.04	0.27
Caesarean section, n (%)	100 (100)	85 (100)	-
Cord clamping within 30 seconds, n (%)	100 (100)	85(100)	-

Table 7: Demographic and clinical characteristics of male and female neonates

4.3.1. Course of vital parameters at minute 5,10,15 after birth in male and female

	Minute 5 after birth			minute 10 after birth			minute 15 after birth		
	Male	Female	P value	Male	Female	P value	Male	Female	P value
$crSO_2$ (%)	63.9 ± 20.0	57.0 ± 22.5	0.16	82.5 ± 10.5	80.1 ± 10.0	0.31	81.8 ± 9.0	81.3 ± 7.7	0.78
cTOI (%)	64.2 ± 9.6	63.7 ± 13.5	0.83	73.1 ± 6.8	73.1 ± 8.4	0.98	72.2 ± 7.1	73.7 ± 7.6	0.35
cFTOE	0.22 ± 0.14	0.24 ± 0.15	0.32	0.17 ± 0.09	0.18 ± 0.09	0.34	0.18 ± 0.09	0.20 ± 0.08	0.39
SpO_2 (%)	81.5 ± 10.8	79.7 ± 12.4	0.3	93.8 ± 5.4	92.7 ± 5.6	0.16	95.6 ± 3.3	95.1 ± 4.0	0.36
HR (beat per minute)	145.5 ± 15.2	150.9 ± 15.5	0.2	150.8 ± 13.3	152.8 ± 15.0	0.37	149.6 ± 12.0	152.5 ± 18.3	0.38
CO (ml/kg/min)	206.1 ± 52.5	189.5 ± 33.9	0.16	195.7 ± 49.3	189.1 ±40.3	0.5	202.6 ± 61.8	177.2 ± 34.4	0.02

Table 8: Courses of vital parameters at 5, 10 and 15 minutes after birth of male and female neonates

In following vital parameters ($crSO_2$, cTOI, cFTOE, SpO_2 and heart rate), there was no significant group difference between male and female during the whole observational period.

Interestingly, males showed higher cardiac output compared to females throughout the observational period and this difference turned statistically significant at minute 15 after birth.

4.3.2. Correlation between cardiac output and cerebral oxygenation/cFTOE at minute 5,10,15 after birth in female and male

4.3.2.1. Male

		$crSO_2$	cTOI	cFTOE
Cardiac Output	Minute 5 after birth			
	ρ	-	-	-
	P value	-	-	-
	Minute 10 after birth			
	ρ	0.37	0.12	-0.17
	P value	0.12	0.59	0.29
	Minute 15 after birth			
	ρ	-0.10	0.21	-0.12
	P value	0.63	0.33	0.42

Table 9: Correlation analyses between CO and crSO2/cTOI and cFTOE in male neonates

4.3.2.2. Female

		$crSO_2$	cTOI	cFTOE
Cardiac Output	Minute 5 after birth			
	ρ	-0.47	0.31	0.34
	P value	0.19	0.89	0.08
	Minute 10 after birth			
	ρ	-0.49	0.34	-0.19
	P value	0.07	0.10	0.29
	Minute 15 after birth			
	ρ	0.04	0.40	-0.05
	P value	0.90	0.124	0.77

Table 10: Correlation analyses between CO and crSO2/cTOI and cFTOE in female neonates

In both groups, there was no significant correlation between cardiac output and $crSO_2$, cTOI and cFTOE. Unfortunately, due to missing data, the correlation analysis in male group at minute 5 was not possible.

4.4. Difference in respiratory support

In our study population, we could identify 21 term neonates, who have received respiratory support (RS group) and 164 term neonates (non-RS group), who didn't need respiratory support during our observational period. The demographic data of these two groups are shown in table 11. Concerning the demographic data, there was no significant difference between RS and non-RS group.

	RS group (n=21)	Non-RS group (n=164)	p value
Gestational age (weeks), – mean (SD)	38.3 ± 0.7	38.8 ± 0.8	0.87
Birth weight (g), – mean (SD)	3071.6 ± 574	3275.9 ± 501	0.52
Birth length (cm), mean (SD)	49.6 ± 2.4	50.6 ± 2.4	0.89
Head circumference (cm), mean (SD)	34.6 ± 1.4	34.8 ± 1.3	0.95
Apgar score at 5 minutes, – median (range)	9 (9-9)	10 (10-10)	0.00
Apgar score at 10 minutes, – median (range)	9 (9-9)	10 (10-10)	0.00
Umbilical artery pH – mean (SD)	7.29 ± 0.04	7.29 ± 0.04	0.47
Caesarean section, n (%)	21 (100)	164 (100)	-
Cord clamping within 30 seconds, n (%)	21 (100)	164 (100)	-

Table 11: Demographic and clinical characteristics of RS group and Non-RS group

4.4.1. Course of cardiac output at minute 5,10,15 after birth in RS group and non-RS group

In the whole study population $crSO_2$, cTOI and SpO_2 values showed an increase during the first 15 minutes. We could observe differences in $crSO_2$, cTOI and SpO_2 values between the RS group and non-RS group, RS group showing significantly lower values compared to neonates in the non-RS group. Neonates in the RS group tended to have lower heart rate throughout the observational period, but this difference didn't reach significance. Additionally, the most interesting observation is the behaviour of cardiac output. In both groups we observed decreasing tendency during the first 15 minutes after birth. RS group showed lower cardiac output levels compared to neonates in the non-RS group throughout the observational period.

	Minute 5 after birth			Minute 10 after birth			Minute 15 after birth		
	RS group	Non-RS group	P value	RS group	Non-RS group	P value	RS group	Non-RS group	P value
$crSO_2$ (%)	36.8 ± 18.4	65.5 ± 18.7	0.00	75.5 ± 14.7	82.5 ± 9.4	0.04	80.4 ± 11.3	81.8 ± 8.1	0.6
cTOI (%)	54.3 ± 11.6	65.0 ± 11.5	0.00	71.1 ± 4.7	73.4 ± 7.9	0.4	75.1 ± 5.8	72.8 ± 7.5	0.41
cFTOE	0.33 ± 0.21	0.22 ± 0.14	0.00	0.16 ± 0.09	0.17 ± 0.09	0.46	0.16 ± 0.08	0.19 ± 0.09	0.13
SpO_2 (%)	66.9 ± 10.8	82.5 ± 10.4	0.00	87.7 ± 6.5	94.0 ± 4.9	0.00	93.1 ± 3.9	95.7 ± 3.5	0.03
HR (beat per minute)	142 ± 24.1	149.3 ± 14.5	0.32	148.5 ± 14.7	152.2 ± 14.0	0.27	147.1 ± 18.0	151.3 ± 14.9	0.46
CO (ml/kg)	192.9 ± 40.3	197.1 ± 43.9	0.83	189.7 ± 60.9	192.3 ± 44.3	0.7	172.9 ± 45.4	193.3 ± 53.3	0.26

Table 12: Courses of vital parameters at 5, 10 and 15 minutes after birth of RS group and non-RS group

4.4.2. Correlation between cardiac output and cerebral oxygenation/cFTOE at minute 5,10,15 after birth in RS group and non-RS group

Due to small data number, is was not possible to perform correlation analyses between cardiac output and cerebral oxygenation in respiratory support group.

4.5. Correlation between MABP and cerebral oxygenation

No significant correlation was observed between $crSO_2$ and MABP (ρ = -.07; p =0.49), cTOI and MABP (ρ = -.10; p =0.33) and between cFTOE and MABP (ρ =-.04 p =0.6) in term infants.

		$crSO_2$	cTOI	cFTOE
MABP	ρ	-0.07	-0.10	-0.04
	P value	0.49	0.33	0.6

Table 13: Correlation analyses between MABP and $crSO_2$/cTOI and cFTOE

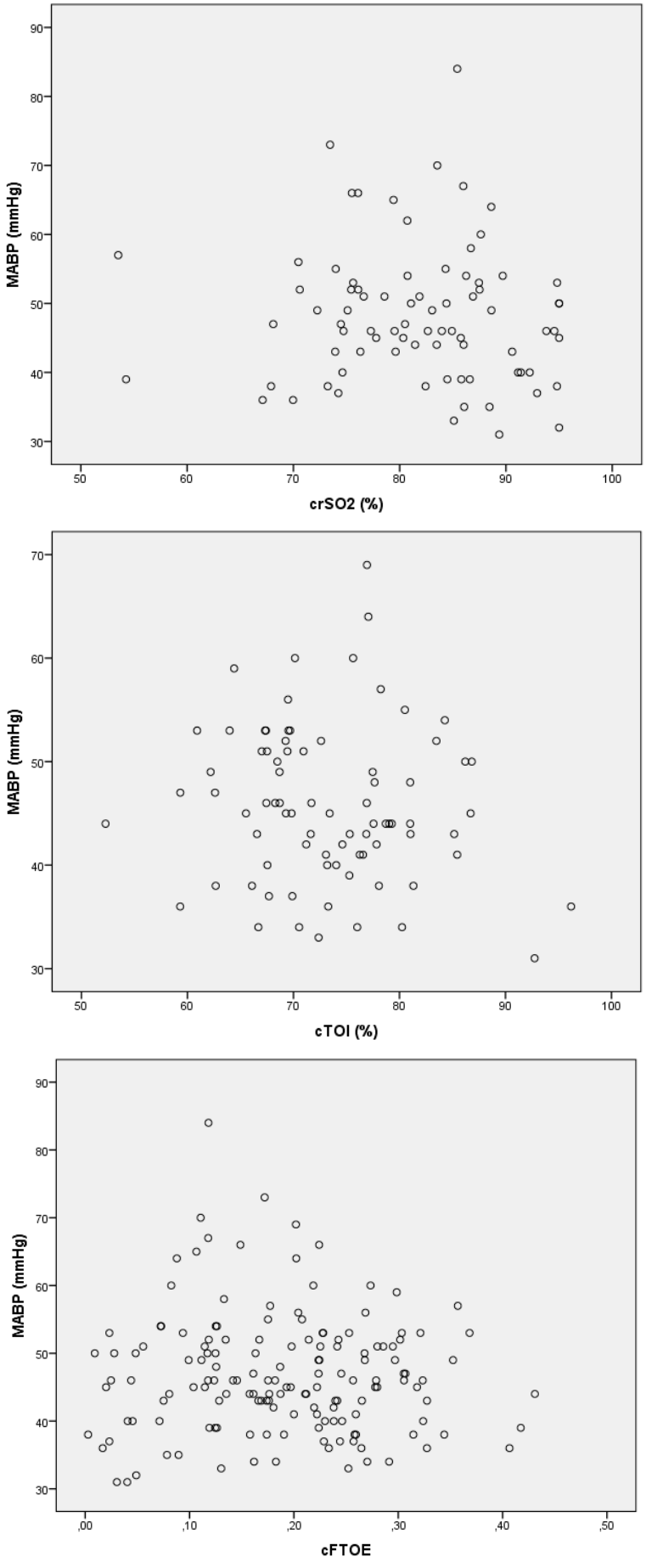

Figure 5: Correlation analyses between MABP and $crSO_2$/cTOI and cFTOE

4.6. Correlation between DA, PFO and cerebral oxygenation

The echocardiography measurement was performed in 98 neonates. 82 out of 98 neonates showed predominantly left-to-right shunt via DA with a mean diameter of 2.2 ± 0.8 mm. 50 out of 82 neonates showed left-to-right shunt via FO with a mean diameter of 2.7 ± 0.7 mm.

No significant correlation could be observed between cTOI, the diameter of DA (figure 6), or the diameter of FO (figure 7). Nevertheless, we observed a significant negative correlation between cTOI and the sum of the diameter of DA and FO (figure 8). cTOI decreased with increasing combined diameter of DA and FO.

		DA	FO	DA + FO
cTOI	ρ	-0.09	-0.16	-0.32
	P value	0.4	0.27	0.02

Table 14: Correlation analyses between cTOI and DA, FO and DA+FO

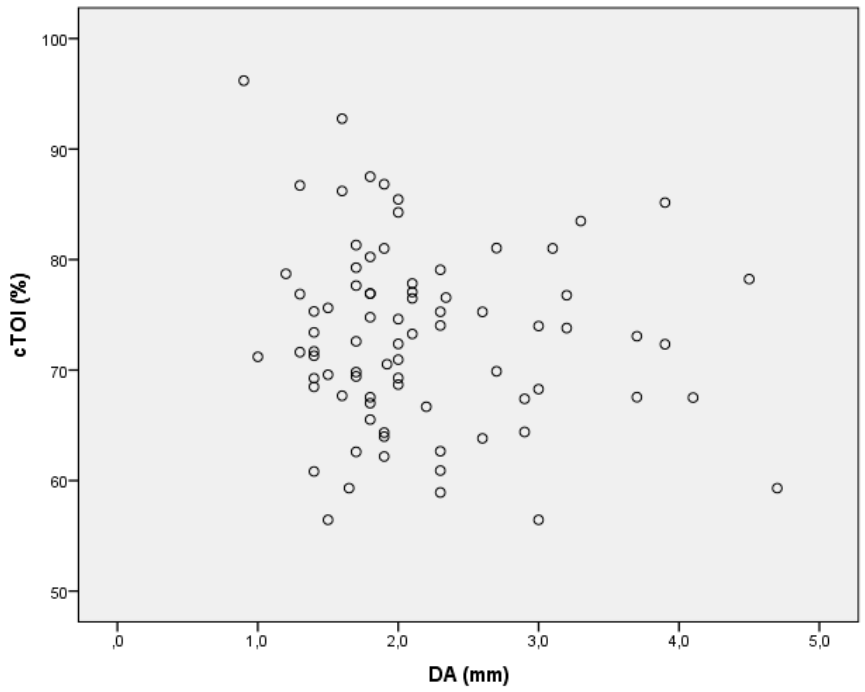

Figure 6: Correlation analysis between cTOI and DA of the study population
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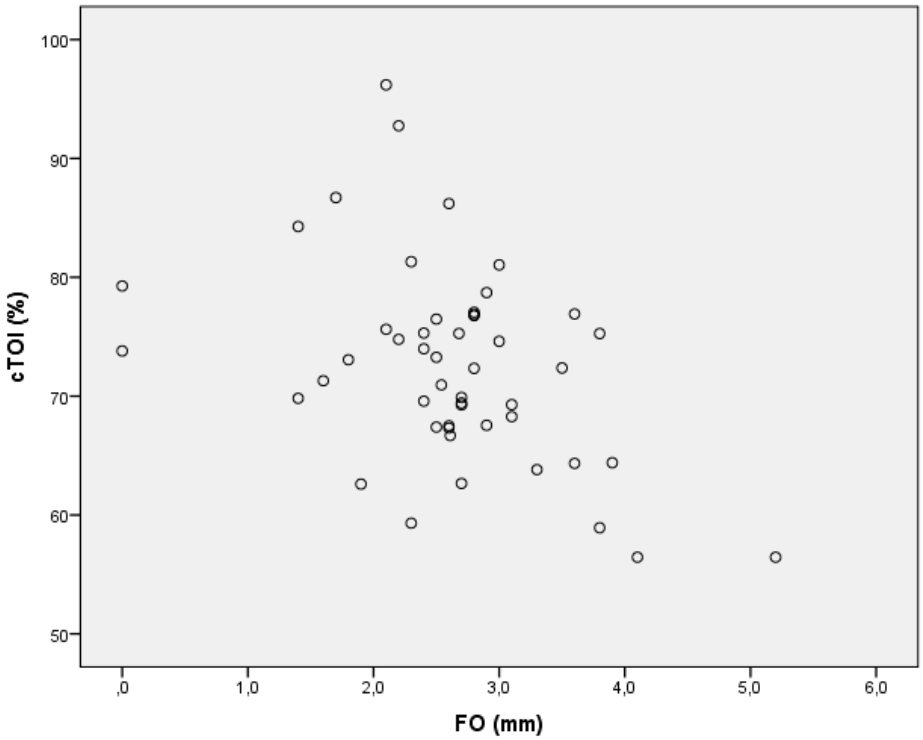

Figure 7: Correlation analysis between cTOI and FO of the study population
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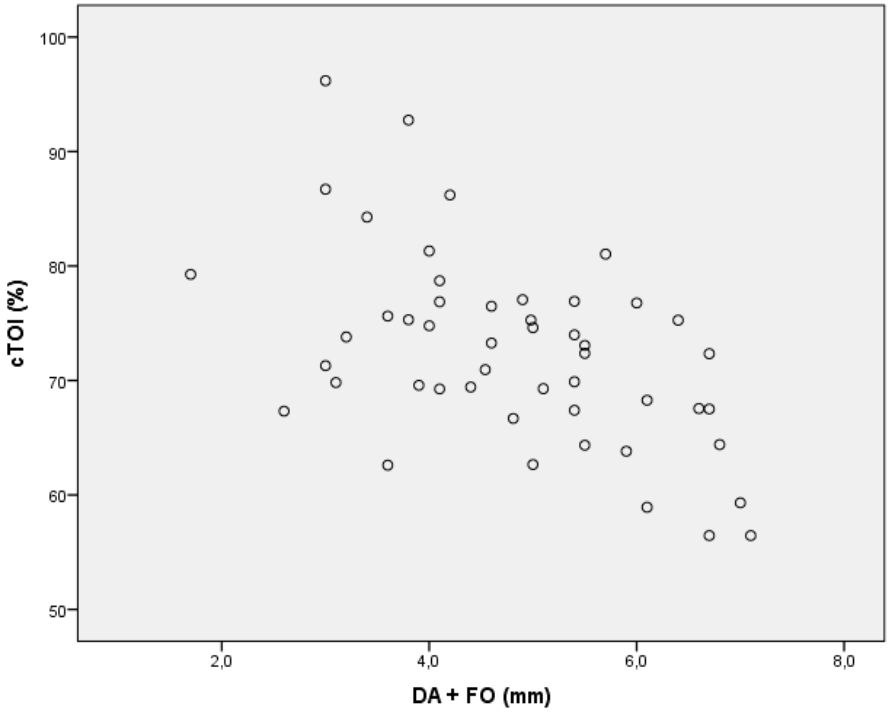

Figure 8: Correlation analysis between cTOI and DA+FO of the study population
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5 Discussion

5.1. Courses of CO and correlation between CO and cerebral oxygenation/cFTOE

Most published haemodynamic changes during the immediate neonatal transition described an increase in heart rate and a decrease in pulmonary vascular resistance after cord clamping and lung aeration. (31, 77) Few research groups in resent studies published data of changes in cardiac output, mostly using echocardiography. (77, 78) Lately, our research group published data of cardiac output using EV measurement in a larger cohort of term neonates after caesarean section. (34) CO decreased significantly from minute 4 to minute 10, increased significantly from minute 10 to minute 11 and stayed stable afterwards.

In the present study, we observed a decreasing tendency in cardiac output from minute 5 (194ml/kg/min) until minute 10 (191ml/kg/min), which didn't reach significance and stayed stable until minute 15 (191ml/kg/min) after birth. Van Vonderen et al. (27) described in a study using echocardiography an increase of cardiac output from minute 2 (151 ml/kg/min) to minute 5 (203 ml/kg/min) and afterwards stable tendency until minute 10 (201 ml/kg/min). A further study described an increasing tendency of cardiac output in the first 20 minutes after birth, which didn't reach significance. CO was 168 ml/kg/min at p1, 186 ml/kg/min at p2, and 189 ml/kg/ min at p3. (31) These findings are absolutely comparable with the results in present study.

Compared with echocardiography EV provides an optimal opportunity to monitor cardiac output continuously and objectively. Additionally, it has already been shown in larger cohort of term infants after caesarean section (34) and in smaller cohort of vaginally born neonates receiving delayed cord clamping (79), that this method is feasible to apply already in the delivery room.

Noori et al. compared EV measurement with echocardiography in 20 healthy neonates during the two days of life. They performed left ventricular output measurements with EV and echocardiography and there was no significant difference between these two methods, confirming EV measurement has comparable accuracy and precision as echocardiography concerning cardiac output measurement. (31)

To our knowledge, this is first study presenting correlation data between cardiac output and cerebral oxygenation in term infant during the immediate neonatal transition. In our study population of 185 term infants after caesarean section, we couldn't observe any significant correlation between cardiac output and cerebral oxygenation.

Several studies described lower cerebral oxygenation values in preterm neonates already immediately after birth who suffered cerebral injury in the following days. (65, 80) As a recent study described a possible connection between lower left ventricular output using echocardiography and development of intraventricular haemorrhage during the first day of life (81), the open question was, whether cardiac output immediately after birth plays a role concerning cerebral oxygenation.

However, in the present study, we couldn't observe any correlation in term infants. But it has to be considered, that our study population of term infants is not at risk to suffer any cerebral injury and our results might be a sign of functioning autoregulation.

The next step would be to apply cardiac output monitoring in preterm neonates to rule out the influence of cardiac output on oxygen transport to brain.

5.2. Difference in gender

From birth to old age, females demonstrate a survival advantage compared to males, suggesting that males are more prone to adverse environmental factors during gestation and childhood. (82) Throughout the whole life, it is well known, that an increased male mortality is present, but this disparity is predominantly evident, if it comes to newborn period and especially concerning preterm neonates. (83) Lately, there are many study groups focusing their research on gender differences. (82-86)

As far as we know, this is first study describing gender difference in a larger cohort concerning cardiac output immediately after birth.

In the present study, we could observe in following vital parameters ($crSO_2$, cTOI, cFTOE, SpO_2 and Heart rate), no significant group difference between male and female during the whole observational period.

Interestingly, males showed higher cardiac output compared to females throughout the observational period and this difference turned statistically significant at minute 15 after birth.

Male neonates tend to show lower heart rates than female neonates, even if the differences were not significant, suggesting that males had higher stroke volumes than females, resulting in higher cardiac output.

Until now other study group could describe concerning cardiovascular outcomes in preterm infants, that male neonates had lower blood pressure than females on the first day of life (87) and extremely preterm males require more often treatment for hypotension during the first week of life. (88)

The exact aetiology of gender specific differences stays unknown and is likely to be multifactorial. However, there are clear disparities concerning cardiovascular system between males and females. Recognition of such differences and consideration of such are important steps to optimize clinical and research results for both sexes.

5.3. Difference in respiratory support

To the best of our knowledge, this is the first study describing the difference in behaviour of cardiac output changes immediately after birth between term neonates with and without respiratory support. In both groups we observed decreasing tendency during the first 15 minutes after birth. RS group showed lower cardiac output levels compared to neonates in the non-RS group throughout the observational period.

According to European resuscitation guideline around 5 % of term born neonates need respiratory support after birth (Resuscitation guideline). When it comes to preterm birth the number of need for respiratory support after birth increases up to 90% in extremely preterm infants. (89)

As there are complex changes going on during neonatal transition, the whole effect of respiratory support on ongoing changes is not well investigated yet.

During postnatal stabilization, application of CPAP via face mask, may have an impact on the cardiocirculatory system, due to application of a positive pressure on the thoracic cavity. (90, 91) The increased intra-thoracic pressure may result in a reduction of cardiac output as a consequence of a decrease in the end diastolic volume due to a decrease of venous return to heart. This interpretation supports our observed results that the cardiac output tends to be lower in the respiratory support group.

Lately, our study group performed detailed analysis of cerebral blood volume (CBV) in term and preterm infants with and without the need of RS during immediate postnatal transition. We could observe a significant decrease in CBV within the first 15 minutes after birth in both groups, but the ΔCBV was smaller in the first seven minutes in neonates with RS. (63) This might be a sign of venous pooling in the brain due to reduced venous return to heart.

Due to small sample number, it was not possible to perform a correlation analyses between cardiac output and cerebral oxygenation in this specific subgroup.

With the result of present study, we could add the information that term neonates receiving respiratory support during postnatal stabilization, tend to have lower cardiac

output vales compared to those without respiratory support. As respiratory support seems to have an impact on cardio-circulatory system, it might be noteworthy to investigate the cardiac output in preterm neonates with higher risk of suffering respiratory and cardiocirculatory complication during the perinatal period.

5.4. MABP and cerebral oxygenation

In our study population of term infants, we observed no correlations between cerebral oxygenation ($crSO_2$/ cTOI) and MABP and between cFTOE and MABP.
With the umbilical cord clamping at birth, the transition from foetus to neonates is initiated and huge changes occur especially in cardio-circulatory system. (92) These changes result in an increase of systemic vascular resistance causing an increase in systemic arterial pressure already over the first four heart beats after cord clamping. (93) Consequently, it comes to a reduction of venous return leading to reduced cardiac output, which remains reduced, until the increase of pulmonary blood flow (in response to lung aeration) comes up and evolves to the source of preload for the left ventricle output. (94) Considering these facts, there are huge changes concerning cardio-circulatory system and blood pressure immediately after birth. So, the question comes up: Is there any connection to observe during the immediate neonatal transition between circulation changes and cerebral oxygenation?

In critical ill preterm infants during the first days of life, it has already been described in several studies, that they showed blood pressure dependent variations in cerebral oxygenation. (95-97) This observed phenomenon suggests impaired autoregulation in these neonates. (96)

In the recent study, our study group has shown that MABP has an impact on cerebral oxygenation in preterm infants during the immediate neonatal transition. (98)
In comparison, term infants showed stables values of cerebral oxygenation independently from the MABP, which might be due to an effective vascular autoregulation. (96) This surveillance is comparable with the findings in this present study.

Cerebral autoregulation is indeed a complex process, which is still not well studied in preterm as well as in term neonates. Several factors are discussed to have an impact: the vascular muscle tone, sympathetic nervous system, the partial pressure of carbon dioxide and oxygen, endocrine substances, infant's activity and medications. It is still unclear, whether there is a developmental aspect during the first minutes and/or hours of life.

However, in the present study, we couldn’t obverse any correlation between cerebral oxygenation/cFTOE and MABP in term infants during the immediate neonatal transition, suggesting effective autoregulation in our study population.

5.5. DA, FO and cerebral oxygenation

In our study population, in 83 % of term neonates the presence of predominant left-to-right shunt via DA was seen; 60 % of these neonates showed LR shunting via FO as well. When the correlation analyses were performed separately concerning the diameter of DA and FO, we couldn't observe any correlation between cerebral oxygenation and the diameter of DA und FO. There was though a significant correlation to cerebral oxygenation, when the diameters of DA and FO with presence of left-to-right shunt were added; with increasing diameters there was a decrease in cerebral oxygen saturation.

Oxygen delivery to the brain is dependent on cardiac output and oxygen content. In our study population, SpO_2 and heart rate were not related to the change in DA and FO diameters, leading to the result, that changes in cerebral oxygenation were correlated to changes in cardiac output.

With cord clamping, there are huge changes concerning the pressure in the systemic as well as in the pulmonary circulation influencing the shunt direction via DA and FO. (99, 100) This change in shunt direction via DA, from right to left to left to right could be observed in fetal lambs as the consequence of pressure gradient change between systemic and pulmonary system. (101)

Our study group has already described increased cerebral oxygen saturation in neonates with the presence of LR shunting via DA, suggesting cardio circulatory relevance cerebral oxygenation during neonatal transition.(74)

However, the findings of the present study suggest, that the single evaluation of the DA shunt presence might be insufficient to get the complete impact on the cerebral oxygenation.

The decrease of cerebral oxygenation can be explained by high LR-shunt volume, leading to an overload of the right circulation system. This might be contributed to higher shunt volume, resulting in higher LR steal phenomenon from the left atrium via FO and from the aortic post-ductal flow via DA. In the present study, we observed LR

shunt via the FO in 81% of neonates indicating that it is a physiological event during immediate transition. The transient presence and gradual closure of the two shunts after birth allows the cardiac output to come into balance after cord clamping and during lung aeration. However, LR shunting through DA also reduces systemic venous return, which would reduce right ventricular preload and output, unless it is compensated for LR flow through the FO. (76)

5.6. Limitation

We recognize several limitations to our study.

First, we only included neonates born by caesarean section. Due to technical reasons all the measurements were not possible to perform in the delivery room next to the mother. Since all neonates after caesarean section were brought to resuscitation table and observed by neonatologist for 10 to 15 minutes, we performed the measurement in those neonates. We did not include vaginally born neonates to avoid delay of immediate bonding with the mother. Therefore, we don't have any information about cardiac output measurements in vaginally born neonates. Recent studies showed that mode of delivery might influence haemodynamic parameters and cerebral oxygenation during neonatal transition. (19, 21, 44) We might have observed some difference in vaginally born neonates.

Second, our study population contains exclusively term neonates. As we observed stable values concerning cardiac output during the immediate neonatal transition in term neonates, the question comes up, if there will be some difference to observe in especially very low birth weight preterm neonates needing extended respiratory and/or medical support.

Third, since we only accepted and analysed the cardiac output measurements, if the signal quality index was >80% to guarantee the reproducibility with the other already approved methods, we had to exclude many NICOM measurements. In many cases the activity and movements of the neonates have influenced the NICOM measurements. Further studies are needed before introducing this method into clinical routine.

Forth, at the time, as we conducted the study, the standard of care at our centre was to clamp the umbilical cord within the first 30 seconds after birth. As it has already been shown, that delayed cord clamping result in an increase of blood volume (102) and in different behaviour concerning cerebral oxygenation/ cFTOE in the first minutes of life (103), it is noteworthy to mention that we might have observed a difference in neonates receiving delayed cord clamping time.

6 Conclusion

The present work was the first study to investigate a possible influence between cardiac output and cerebral oxygenation in term infants during the immediate neonatal transition. In term infants after caesarean section, there was no significant correlation between CO and cerebral oxygenation.

Male neonates showed tendentially higher cardiac output compared to female neonates. This difference was statistically significant at 15 minutes after birth. Although, there was no significant correlation between cardiac output and cerebral oxygenation in male and female groups.

RS group showed lower cardiac output levels compared to neonates in the non-RS group throughout the observational period. In both groups we observed decreasing tendency during the first 15 minutes after birth. This might be firstly, due to positive intrathoracic pressure caused by respiratory support and secondly, due to reduced venous return.

In term infants there was no significant influence of MABP on cerebral oxygenation, suggesting that there is a well-functioning cerebral autoregulation.

A negative correlation was observed between the increasing sum of DA and FO diameters and cerebral oxygen saturation in term neonates 15 minutes after birth, suggesting that the only evaluation of DA might be insufficient to obtain the whole picture regarding the influence of left to right shunting on cerebral oxygenation during immediate neonatal transition.

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8 Appendix

Sehr geehrte Dr. Nariae Baik,

ich danke Ihnen für Ihre Anfrage. Diesbezüglich freut es uns, Ihnen hiermit die Genehmigung zu erteilen, den Artikel

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