

Dissertation

Behaviour of cerebral blood volume (CBV) during neonatal transition in preterm infants with and without respiratory support

Verhalten des zerebralen Blutvolumens (CBV) bei Frühgeborenen in der Adaptationsphase mit und ohne Atemunterstützung

submitted by

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Declaration

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

Graz, September 2017

Bernhard Schwabegger

Preface

This dissertation offers an overview of my own original scientific work. Certain parts of it were already published within the following article (1) in the journal “Neonatology” before the preparation of this thesis was finally completed:

- (1) Schwabegger, B; Pichler, G; Binder-Heschl, C; Baik, N; Avian, A; Urlesberger, B.

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Abstract

The transition from fetal to neonatal life is dependent upon complex physiological changes in the respiratory and cardiovascular system. Major transitional changes at birth also affect the brain as the most vulnerable organ. Because of its prognostic importance, there is a special scientific interest in cerebral perfusion immediately after birth. Different methods to assess cerebral perfusion during postnatal transition have been introduced including near-infrared spectroscopy (NIRS) providing information on changes in cerebral blood volume (CBV). Transitional changes in CBV had not been investigated until we published the data of the *CBV study* (1) in which we evaluated CBV during immediate postnatal transition in healthy term infants plotting the physiological behaviour of CBV after birth by using NIRS. In this study we demonstrated a decrease in CBV in healthy term infants during immediate postnatal transition and hypothesized that this was due to changes within the autoregulatory capacity of cerebral vessels in reaction to increasing pO_2 and decreasing pCO_2 levels.

Recently, our research group showed that requirement for respiratory support (RS) after birth in preterm infants is associated with lower cerebral oxygenation compared to infants undergoing normal transition (2, 3). Therefore, the *CBV_RESUP study* (Cerebral Blood Volume in infants receiving Respiratory Support during neonatal transition study) was designed to investigate transitional changes in CBV in term and preterm infants with and without requirement for RS to estimate the potential influence of RS on the postnatal CBV behaviour. We observed a significant decrease of CBV in infants undergoing normal transition and in infants receiving RS. Interestingly, changes in CBV were smaller in the first seven minutes in neonates with RS. This study did not yet determine, whether RS itself or the condition of the infant leading to requirement for RS is responsible for the observed differences in CBV behaviour compared to healthy newborn infants.

In summary, the present data are the first describing CBV behaviour during immediate transition in healthy newborn infants and in newborn infants with requirement for RS. Our results are of particularly great interest, since

hemodynamic disturbances resulting in changes in cerebral perfusion are discussed to be an important pathway to ventilation-induced brain injury occurring as early as ventilation is initiated in the delivery room.

Zusammenfassung

Bei der postnatalen Adaptation Neugeborener kommt es zu komplexen physiologischen Veränderungen in verschiedenen Organsystemen wie Lunge oder Herz-Kreislaufsystem. Zu Umstellungen nach der Geburt kommt es aber auch im vulnerabelsten aller Organe, dem Gehirn. Aufgrund der prognostischen Relevanz gilt der zerebralen Durchblutung und ihren Änderungen in der unmittelbaren postnatalen Adaptationszeit ein besonderes wissenschaftliches Interesse. Unter anderem ist die Verwendung der Nahinfrarotspektroskopie (NIRS) zur Bestimmung relativer Änderungen des zerebralen Blutvolumens (CBV) eine Möglichkeit die zerebrale Perfusion in der Adaptationszeit zu evaluieren. Bis zur Veröffentlichung der *CBV-Studie* (1) gab es keine Daten zum physiologischen Verhalten des CBV unmittelbar nach der Geburt. Unter Verwendung von NIRS konnten wir in dieser Studie zeigen, dass es bei gesunden Reifgeborenen nach der Geburt zu einem signifikanten Abfall des CBV in den ersten 15 Lebensminuten kommt. Wir vermuten als zugrundeliegende Ursache für diese Beobachtung eine reaktive Vasokonstriktion in Folge von postnatalen Blutgasänderungen.

Unsere Studiengruppe konnte kürzlich zeigen, dass bei Frühgeborenen, die unmittelbar nach der Geburt eine Atemunterstützung benötigten, die zerebrale Oxygenierung im Vergleich zu normal adaptierenden Frühgeborenen signifikant niedriger war (2, 3). Vor diesem Hintergrund haben wir die *CBV_RESUP-Studie* (Cerebral Blood Volume in infants receiving Respiratory Support during neonatal transition study) durchgeführt, in welcher der postnatale Verlauf des CBV bei Früh- und Reifgeborenen mit und ohne Atemunterstützung untersucht wurde, um den potenziellen Einfluss einer Atemunterstützung auf die zerebrale Perfusion zu beleuchten. Es zeigte sich ein Absinken des CBV in der Gruppe von Neugeborenen mit komplikationsloser Adaptation sowie in jener Gruppe, in welcher die Neugeborenen postnatal eine Atemunterstützung benötigten. Allerdings war die Veränderung des CBV bei den beatmeten Neugeborenen in den ersten sieben Lebensminuten weniger stark ausgeprägt. Ob jedoch der Zustand des Neugeborenen, welcher zur Beatmungsnotwendigkeit geführt hat, oder die Atemunterstützung selbst die gefundenen Unterschiede der zerebralen

Perfusion erklären, konnte mit der *CBV_RESUP-Studie* vorerst nicht beantwortet werden.

Die in dieser Arbeit präsentierten Ergebnisse sind die ersten, welche physiologische Änderungen des CBV in der postnatalen Adaptationszeit bei gesunden Reifgeborenen und ein davon abweichendes Verhalten des CBV bei Früh- und Reifgeborenen aufzeigen, die unmittelbar nach der Geburt mittels Atemunterstützung versorgt werden mussten. Diese Daten sind von großem wissenschaftlichen Interesse insbesondere vor dem Hintergrund, dass Störungen der zerebralen Perfusion als wichtiger Faktor bei der Entstehung von beatmungsinduzierten Gehirnschäden diskutiert werden, die bereits bei der initialen Beatmung im Rahmen der Erstversorgung im Kreißsaal auftreten können.

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List of Abbreviations

aEEG	Amplitude-integrated electroencephalography
bpm	Beats per minute
CBF	Cerebral blood flow
CBV	Cerebral blood volume
cFTOE	Cerebral fractional tissue oxygen extraction
CPAP	Continuous positive airway pressure
crSO ₂	Cerebral regional tissue oxygen saturation
cTOI	Cerebral tissue oxygenation index
ΔCBV	Changes in cerebral blood volume
ΔHbO ₂	Changes in the concentration of oxygenated haemoglobin
ΔHbR	Changes in the concentration of reduced haemoglobin
ΔHbT	Changes in the concentration of total haemoglobin
ECG	Electrocardiography
FiO ₂	Fraction of inspired oxygen
Hb	(Large-vessel) haemoglobin concentration
HR	Heart rate
IQR	Interquartile range
IVH	Intraventricular haemorrhage
(M)ABP	(Mean) arterial blood pressure
NICOM	Non-invasive cardiac output monitoring
NIRS	Near-infrared spectroscopy
pCO ₂	Partial pressure of carbon dioxide
PEEP	Positive end-expiratory pressure
pO ₂	Partial pressure of oxygen
PPV	Positive pressure ventilation
prSO ₂	Peripheral regional tissue oxygen saturation
RS	Respiratory Support
rSO ₂	Regional tissue oxygen saturation
SD	Standard deviation
SpO ₂	Arterial oxygen saturation (measured by pulse oximetry)
SpO ₂ arm	Preductal arterial oxygen saturation
SpO ₂ leg	Postductal arterial oxygen saturation

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1 Introduction

1.1 *Neonatal transition*

The fetus resides intra-uterine in a relatively hypoxic environment as compared to extra-uterine life. The transition from fetal to neonatal life is dependent upon complex physiological changes in the respiratory and cardiovascular system (1).

During initiation of air breathing, lung liquid is cleared and the lungs aerate establishing a functional residual capacity. The lung aeration triggers a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow. This enables the commencement of effective pulmonary gas exchange (4, 5).

Recent research focuses on the postnatal transition period, when the lungs replace the placenta as organs of gas exchange, and major changes in oxygen content of the newly born occur. Major transitional changes at birth also affect the brain as the most vulnerable organ. Because of its prognostic importance, there is a special scientific interest in cerebral perfusion and oxygenation immediately after birth (1).

1.2 *Monitoring during neonatal transition*

In order to assess the neonate's condition, the latest guidelines on resuscitation and support of neonatal transition recommend the use of pulse oximetry and electrocardiography (ECG) monitoring in the delivery room (6).

Immediately after birth, clinical assessment, pulse oximetry and/or ECG might not always reflect a potentially compromised cardiocirculatory status or impaired cerebral oxygenation. The introduction of cardiocirculatory and/or cerebral monitoring might be useful to guide medical interventions by providing additional information to improve oxygen delivery to the brain.

1.2.1 Pulse oximetry

Pulse oximetry enables non-invasive continuous monitoring of the arterial oxygen saturation (SpO₂) as well as heart rate (HR). The monitoring of SpO₂ during neonatal stabilisation using pulse oximetry may assist to avoid serious damage caused by hyper- and hypoxia (7-9).

By using pulse oximetry at the right arm (SpO₂arm) and lower leg (SpO₂leg) the pre- and postductal arterial oxygen saturations may be measured, reflecting the SpO₂ in arteries originating from the aorta proximally and distally from the ductal orifice. Most of the available studies evaluating oxygen saturation levels in newborn infants immediately after birth investigated SpO₂arm values. Whereas in healthy term infants SpO₂arm rises from approximately 50% to >90% within the first 10 minutes after birth (10-12), SpO₂arm is slightly lower in healthy preterm infants at each time point during this period (11-13). Recently, we investigated the course of SpO₂arm in preterm infants with and without requirement for respiratory support (RS) and found significantly lower values for SpO₂arm in infants receiving RS compared to those infants with normal neonatal transition (2, 3).

Mariani et al. (2007) were the first authors describing the course of SpO₂leg in term infants during undisturbed postnatal transition. They demonstrated significant higher values for SpO₂arm compared to SpO₂leg throughout the first 15 minutes after birth (14). Recently, our study group added data from preterm infants showing similar courses compared to the study of Mariani et al. (2, 3, 14).

1.2.2 Electrocardiography (ECG)

An increasing HR that exceeds the threshold value of 100 beats per minute (bpm) is currently the most important parameter indicating adequate postnatal transition. The recent guidelines on resuscitation and support of neonatal transition recommend the use of ECG for evaluating HR in newborn infants requiring medical support (6).

Reference ranges of HR during postnatal transition have been established. Dawson et al. (2010) described HR changes of healthy newborn infants in the delivery room demonstrating a significant increase during the first 5 minutes after birth with a slower increase in preterm compared to term infants (15). In another cohort of neonates with delayed cord clamping and immediate skin-to-skin contact lower HR values combined with a slower increase in the first 3 minutes were shown (16). Moreover transitional HR changes are affected by the mode of delivery and maternal anaesthesia (15, 17).

In those studies HR assessment was performed by using pulse oximetry. Although modern pulse oximeters give an accurate heart rate also in newborn infants requiring medical support (18), HR assessment by using ECG during transition is more reliable and faster than pulse oximetry and therefore recommended in the guidelines for those infants (6, 19). However, ECG monitoring does not replace the need to use pulse oximetry assessing the oxygenation status of the newborn (6).

1.2.3 Cardiocirculatory monitoring

In addition to an increase of HR, transitional changes of the cardiocirculatory system includes a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow and left ventricular output (5, 15, 20). These cardiovascular changes are initiated by the onset of air breathing resulting in lung aeration and by an increase in systemic vascular resistance due to cord clamping (4, 5, 20).

During immediate transition, clinical assessment and the routinely used monitoring with pulse oximetry and/or ECG does not always reflect accurately a potentially compromised cardiocirculatory status. Therefore, further cardiocirculatory monitoring might be beneficial to guide and optimize hemodynamic management to improve oxygen delivery to tissues, especially to the brain (21).

Oscillometric blood pressure monitoring in neonates immediately after birth might be of some value in future, considering that our study group has established normative data recently (22).

Current research focuses on further cardiocirculatory monitoring methods during transition including non-invasive cardiac measurements by using echocardiography (20, 23) or electrical velocimetry, an upcoming modification of non-invasive cardiac output monitoring (NICOM) (24, 25). During immediate transition, these methods are technically challenging and frequently affected by movement artefacts. Therefore, an introduction in clinical routine remains questionable. Beyond that, the use of echocardiography and NICOM for research purposes might improve knowledge about cardiocirculatory changes during postnatal transition influencing cerebral perfusion and oxygenation (21).

1.2.4 Cerebral monitoring

Inadequate cerebral perfusion and compromised oxygen delivery to the brain during immediate postnatal transition may cause perinatal cerebral injury including intraventricular haemorrhage (IVH) (26) or periventricular leukomalacia (27), which frequently lead to subsequent neurodevelopmental morbidity (28, 29). Therefore, the use of cerebral monitoring during immediate transition is potentially beneficial and may guide medical interventions by providing additional information to optimize oxygen delivery to the brain (30).

Recent research focuses on various methods to evaluate cerebral changes during postnatal transition, including sequential measurements of cerebral perfusion using Doppler sonography (23), continuous measurements of cerebral activity by using amplitude-integrated electroencephalography (aEEG) (31, 32) and continuous monitoring of cerebral tissue oxygenation with near-infrared spectroscopy (NIRS) (1-3, 26, 31, 33-42).

Doppler sonography and aEEG are technically challenging and frequently affected by artefacts during neonatal transition (30). Therefore, both techniques seem to be of limited value for routine clinical practice. In contrast, NIRS provides continuous monitoring and is feasible even in very low birth weight infants immediately after birth (30).

1.2.4.1 Near-infrared spectroscopy (NIRS)

NIRS is a spectroscopic method that allows non-invasive measurements of cerebral tissue oxygenation on the one hand, and changes in cerebral total haemoglobin concentrations (ΔHbT) providing information on cerebral blood volume (CBV) on the other hand (43, 44).

As brain oxygenation during fetal to neonatal transition is crucial, there has been an increasing interest in the continuous monitoring of the cerebral regional tissue oxygen saturation (crSO_2) by using NIRS (45). The first reports on crSO_2 in newborn infants during the postnatal transition period by using NIRS were published by Isobe et al. in 2000 and 2002 (46, 47). Since then, several studies have shown that NIRS measurements during the immediate postnatal transition are feasible – even in very low birth weight infants (2, 3, 26, 31, 33-38, 40-42). In term infants, crSO_2 is significantly increasing within the first minutes after birth reaching a plateau after 7 to 8 minutes, which is earlier compared to the courses of SpO_2 or peripheral regional tissue oxygen saturation (prSO_2) (40, 42). After approximately 10 minutes of age crSO_2 is decreasing again progressively until minute 20 (23). Recently, reference ranges and centile charts of crSO_2 during the first 15 minutes after birth using different NIRS devices have been published by our study group (33, 37). Interestingly, the crSO_2 values within the first 10 minutes after birth were not significantly different in term infants after vaginal delivery versus caesarean section, while there were significant differences in SpO_2 and HR with lower values for newborn infants after caesarean section (37, 41, 47, 48).

Urlesberger et al. (2010) were the first who presented different dynamics in the courses of crSO_2 as well as pre- and postductal prSO_2 during postnatal transition with the highest saturation levels for the brain, indicating the potential for preferential oxygen delivery to the brain (40). We demonstrated in preterm infants receiving RS due to mild respiratory distress that crSO_2 and prSO_2 levels were not different within the first 8 minutes after birth suggesting that those infants temporarily lost the ability to modify oxygen delivery to various tissue compartments in regards to the supply needs of the organ systems (2). The

underlying reasons for this observation are unknown, but it may be speculated that cardiovascular factors play an important role.

Two observational studies described a possible association between IVH in preterm neonates and an increased burden of cerebral hypoxia defined as $crSO_2$ values below the 10th percentile of the published reference values (37) during the first 15 minutes after birth (26, 34). Therefore, a continuous cerebral monitoring aiming at a reduction of burden of cerebral hypoxia during immediate transition might be beneficial. Very recently, a randomized controlled trial of our study group (the COSGOD trial) demonstrated that a reduction of burden of cerebral hypoxia after birth is feasible by using NIRS monitoring to guide respiratory and supplemental oxygen support (38). A bigger randomized controlled trial to prove if the use of NIRS during neonatal stabilisation improves neonatal outcome is needed.

ΔHbT reflecting CBV dynamics is another promising NIRS derived parameter which might be useful during postnatal transition (49). While most of the NIRS studies reported on $crSO_2$ levels (2, 3, 26, 31, 33-38, 40-42), $\Delta HbT/CBV$ was not investigated in humans during immediate postnatal transition until now. The aim of this dissertation was to describe the transitional CBV changes in healthy newborn infants for the first time and to evaluate differences in the CBV behaviour by comparing term and preterm infants with and without RS during immediate postnatal transition (1, 39).

1.3 ***Cerebral Hemodynamics***

Along with the changes in systemic and pulmonary blood flow, organ perfusion is also altered during fetal to neonatal transition. As the brain is the most vulnerable organ system of the infant, cerebral perfusion is of great interest. Different methods to assess cerebral perfusion during postnatal transition have been introduced including Doppler sonography and NIRS providing information on cerebral blood flow (CBF) velocity and changes in CBV, respectively (30). However, presently the relationship between CBF and CBV in newborn infants remains unclear.

By using Doppler sonography, a decrease in CBF velocity was demonstrated in term and preterm infants within the first 30 minutes after birth (23, 50-52). CBF changes were presumed to be caused by an increase in intracranial vascular resistance in response to an increase in arterial oxygen content to protect the brain from excessive oxygen exposure (23, 50). Another possible explanation might be the changing shunt direction via the ductus arteriosus (DA) from predominantly right-to-left to predominantly left-to-right shunting with a consecutive increase in left ventricular stroke volume (23, 53). That might be the reason why in term infants with predominantly left-to-right shunting through the DA significantly higher crSO₂ values were found compared to infants without shunt flow 15 minutes after birth (54). However, due to an increase in left ventricular stroke volume and in SpO₂ within the first minutes after birth, oxygen delivery to the brain is rising during immediate postnatal transition.

Using NIRS is another approach that might be helpful to evaluate cerebral hemodynamics after birth. It has been shown in newborn infants during immediate postnatal transition that crSO₂ is reflecting both, cerebral oxygenation and cerebral perfusion (2). Physiologically, the crSO₂ and SpO₂ levels are increasing consistently within the first minutes. Despite a further increase of SpO₂, crSO₂ is achieving a steady plateau after 8 minutes of age, and is decreasing again in the further course accompanied by an increase of the cerebral fractional tissue oxygen extraction (cFTOE) after 8 min of age, which can easily be explained by a decrease in CBF (23, 37, 47).

Most of the NIRS studies (2, 3, 26, 31, 33-38, 40-42) in newborn infants reported on cerebral oxygenation, displaying crSO₂ and/or cFTOE. Although NIRS technology measuring changes in total haemoglobin reflecting CBV behaviour was previously available, it was not investigated in humans during postnatal transition until now. The only available animal study demonstrated a CBV decrease in ventilated lambs during postnatal transition (55). However, ventilation itself might have influenced the findings on cerebral perfusion in this study.

We demonstrated in preterm infants who received RS due to mild respiratory distress a lower cerebral oxygenation caused by lower arterial oxygen content and compromised cerebral perfusion (2). Whether the respiratory distress or the ventilatory strategies, or both, were responsible for this findings is presently unclear. However, cerebral perfusion is dependent on cardiac output and regional vascular resistance. Gullberg et al. (1999) demonstrated changes of stroke volume in neonates depending on mean airway pressure, presuming an influence of RS to cardiac output (56). Given the known association between low CBF and brain injury (57), the impact of supplemental oxygen and RS on cerebral perfusion at birth needs to be studied intensively.

1.4 ***Respiratory Support (RS)***

Preterm birth is a major determinant of neonatal mortality and morbidity. According to the World Health Organization (WHO), the worldwide incidence of preterm birth ranges from 6.2 to 11.9% (58). One of the major problems of preterm infants are pulmonary complications due to the underdeveloped lungs including respiratory distress at birth and consecutive requirement of RS. Hence, approximately 90% of extremely preterm infants (born at <28 weeks gestation age) require any kind of RS after birth (59).

Recent guidelines on resuscitation and support of neonatal transition recommend the initiation of positive pressure ventilation (PPV) in term and preterm infants with inadequate or absent breathing efforts and low heart rate (HR) despite tactile stimulation (6). Preterm infants which are breathing and showing signs of respiratory distress should be supported by continuous positive airway pressure (CPAP) (6, 60).

Even though RS may be crucial for the survival of the preterm infant, it can increase the incidence of lung and brain injury, especially in extremely preterm infants who are already at an elevated risk (59). Therefore, any kind of RS needs to be applied with caution. Further research is needed to reduce requirement of RS and improve ventilatory strategies to achieve a better pulmonary and cerebral outcome in those infants.

Despite RS and supplemental oxygen to achieve targeted oxygen saturations, it was demonstrated that SpO₂ as well as cerebral and peripheral rSO₂ values in preterm infants who received RS were significantly lower compared to preterm infants with normal neonatal transition (2, 3). We found remarkable differences of the oxygenation parameters in various tissue compartments over time indicating that the decreased rSO₂ levels in infants with RS are not only caused by lower SpO₂ levels, but also by a compromised perfusion (2). Thus, it can be speculated that both, neonatal pathologies causing respiratory distress and RS itself may have a negative impact on the cardiocirculatory system during postnatal stabilisation.

1.4.1 Supplemental oxygen and continuous positive airway pressure (CPAP)

Preterm infants frequently need RS in the delivery room due to respiratory distress (59). Vento et al. (2009) demonstrated that postnatal stabilisation with low supplemental oxygen resulted in significantly decreased late morbidity such as chronic lung disease (61). In another study Vento et al. (2013) did show that preterm infants receiving continuous positive airway pressure without supplemental oxygen attained stable SpO₂ values earlier compared to spontaneously breathing infants as recorded in the nomogram of Dawson et al. (2010) (12, 62). However, there is a scientific dispute, if reference ranges of healthy term infants are appropriate to serve as SpO₂ targets for infants with requirement for RS. The amount of supplemental oxygen which should be applied during postnatal stabilisation, especially in preterm infants, is still a matter of debate. While an undersupply of oxygen to tissues has been early recognized as being hazardous to newborn infants, more recent work addresses to the negative effects of an oversupply caused by oxygen toxicity (63). More detailed information about oxygen delivery to different tissue compartments during neonatal transition may help in finding a key to titration of supplemental oxygen (2, 3, 40).

By applying CPAP via face mask during postnatal stabilisation, a positive pressure is applied on the thoracic cavity which may have a significant impact on the cardiocirculatory system (64, 65). Increased intra-thoracic pressure may impair

venous return to the heart leading to increased cerebral venous pressure with a potential increase in CBV (66). Venous pooling due to a decrease in venous return to the heart may increase the regional venous portion within the brain, resulting in a decrease of crSO₂ values. On the other hand, increased intra-thoracic pressure may impair cerebral blood supply to the brain by a reduction of cardiac stroke volume in response to a decrease in the end diastolic volume (Frank-Starling law), which may decrease CBV in case of impaired autoregulation (2, 39). This effects might even be pronounced with increasing mean airway pressures used in PPV.

1.4.2 Positive Pressure Ventilation (PPV)

During postnatal stabilisation many preterm infants require RS to assist lung aeration and establish a functional residual capacity, which seems to be the key to successful neonatal resuscitation. Recent guidelines on resuscitation and support of neonatal transition recommend the initiation of PPV in those term and preterm infants in which the breathing efforts are absent or inadequate and heart rate is not rising despite initial tactile stimulation (6). For the first five inflations it is recommended to maintain the initial inflation pressure for 2–3 seconds (6). The optimum pressure, inflation time and flow to establish an effective functional residual capacity has not been determined (6).

Initial ventilatory strategies are discussed to have an impact on development or prevention of lung and brain injury (55, 67-71). Even though there is growing evidence that ventilation-induced injuries occur as early as ventilation is initiated in the delivery room, PPV immediately after birth is presently one of the least controlled interventions a preterm infant will likely face (59). By using a respiratory function monitor, Schmölder et al. (2010) demonstrated dangerously high tidal volumes during postnatal stabilisation in more than 85% of preterm infants receiving PPV via face mask (72), which might have hazardous effects on the lungs (73, 74) and the brain (55, 75).

The pathways to the ventilation-induced brain injury include a complex inflammatory cascade (74) resulting in a localized cerebral inflammatory response with an increase in oxidative stress (55, 75). In newborn infants with immature or

absent mechanisms of autoregulation (76), another pathway is haemodynamic disturbance with variable blood flow to the brain. Compromised cerebral blood flow might be caused by an increased pulmonary resistance and decreased cardiac output due to over-distension of alveoli and compression of pulmonary capillaries (55, 59). This indicates the need of strategies to improve initial RS during postnatal stabilisation and to monitor cerebral haemodynamics and its disturbances, which potentially may result in brain injury (77).

Regardless of the initial ventilatory strategy after birth, manual or mechanical PPV may have detrimental effects on the brain of preterm infants who are already at high risk for cerebral injuries due to the immaturity of the brain (59). This underlines the necessity to improve strategies for initial RS during postnatal stabilisation and to monitor the brain during immediate transition emphasising disturbance of cerebral hemodynamics which potentially result in brain injury (77).

2 Objectives

2.1 *Aim of the CBV study*

The aim of the *CBV study* (Cerebral Blood Volume during neonatal transition study) was to evaluate changes in CBV during immediate postnatal transition in healthy term infants to plot the physiological behaviour of CBV after birth by using NIRS (1).

2.2 *Aim of the CBV_RESUP study*

The aim of the *CBV_RESUP study* (Cerebral Blood Volume in infants receiving Respiratory Support during neonatal transition study) was to investigate the transitional changes in CBV in term and preterm infants with and without requirement for RS by using NIRS, to estimate the potential influence of RS on the postnatal CBV behaviour.

3 Methods

3.1 *Materials*

After birth initial medical care was performed in a 'Giraffe' incubator (GE Healthcare; United Kingdom) or on a resuscitation cot ('CosyCot', Fisher & Paykel Healthcare; New Zealand). NIRS measurements were carried out with a 'NIRO 200-NX' tissue oxygenation monitor (Hamamatsu; Japan). HR and SpO₂ were measured by a pulse oximeter (M1193A Neonate Silicon Wrap, Philips; the Netherlands). The vital signs including blood pressure and rectal body temperature were displayed on the 'IntelliVue MP30/X2' monitor (Philips; the Netherlands). In newborn infants with respiratory distress syndrome RS was applied by using a 'Neopuff Infant T- Piece Resuscitator' (Perivent, Fisher & Paykel Healthcare; New Zealand) and a round face mask of appropriate size (LSR Silicon mask no. 0/0 or 0/1, Laerdal; Norway). A 'Florian Neonatal Respiratory Function Monitor' (Acutronic Medical Systems; Switzerland) captured ventilation variables: tidal volume, face mask leak, positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO₂). For later analysis all parameters and the video recordings were stored using a multichannel system 'alpha-trace digital MM' (BEST Medical Systems; Austria). Echocardiography was performed within the CBV study by using the 'Vivid 7 Pro' ultrasound machine (General Electric; USA) with the 10 MHz sector transducer.

3.2 *Near-infrared spectroscopy (NIRS)* (1)

NIRS is a continuous non-invasive method to measure changes in the concentration of oxygenated (ΔHbO_2) and reduced haemoglobin (ΔHbR). Changes in total haemoglobin (ΔHbT) can be calculated by using the following equation:

$$\Delta HbT (\mu\text{mol/l}) = \Delta HbO_2 + \Delta HbR$$

ΔHbT ($\mu\text{mol/l}$) may be converted to changes in cerebral blood volume (ΔCBV) by using a previously described relationship (49). ΔCBV (ml/100 g brain) is calculated

by the following equation, in which Hb represents the large-vessel haemoglobin concentration (g/dl):

$$\Delta CBV \text{ (ml/100 g brain)} = \Delta HbT * \frac{0.89}{Hb}$$

This method does not allow measurements of absolute CBV, but allows measurements of changes in CBV in proportion to the total haemoglobin concentration, if Hb and the large vessel to cerebral haematocrit ratio remain constant. We presume that abrupt changes in Hb during our short-term observation were not likely to occur, since serious bleedings were not observed.

Moreover by using NIRS technology the cerebral tissue oxygenation index (cTOI) may be evaluated:

$$cTOI \text{ (\%)} = \frac{\Delta HbO2}{\Delta HbT}$$

Thus cTOI is equivalent to the crSO₂ of different NIRS devices of other companies. NIRS measurements were conducted over the whole study period of the first 15 minutes after birth using a sample rate of 2 Hz. The interoptode distance was 4 cm, and a differential path length factor of 3.85 was chosen (78).

3.3 **Methods of the CBV study**

3.3.1 **Study design (1)**

The *CBV study* (Cerebral Blood Volume during neonatal transition study) was designed as observational single-centre based study and conducted at the neonatal intensive care unit of the Medical University of Graz (Austria, Europe). The Regional Committee on Biomedical Research Ethics approved the study protocol. Between September 2010 and March 2014 term infants delivered by elective caesarean section were included, provided written informed consent was obtained from parents prior to birth. The measurements were performed on the resuscitation cot at the neonatal intensive care unit, where all infants after caesarean section were routinely observed for approximately 15 minutes after birth. Infants born vaginally were not included, to avoid delay of immediate skin-to-

skin contact with the mother. The exclusion criteria were requirement for RS during transition period and congenital malformations.

3.3.2 Procedure (1)

After the delivery by caesarean section immediate cord clamping (<30 seconds) was performed, which was standard of care at our department at that time. The term infants were promptly placed on the resuscitation cot under an overhead heater. Without disturbing routine medical care the NIRS transducer was fastened with gauze bandage on the newborn's right forehead by additional scientific staff members. NIRS measurements were carried out over the first 15 minutes after birth. Additionally preductal SpO₂ and HR were continuously monitored by a pulse oximeter fixed on the right wrist. Singular measurements of blood pressure and rectal body temperature were recorded between minute 10 and 15 after birth. After completing NIRS measurements, a neonatologist performed an echocardiography for assessing ductal patency and flow within the first 30 minutes after birth. We measured the internal ductal diameter with pulsed Doppler echocardiography and colour flow mapping three times and averaged the results. During the entire study period infants were lying in supine position.

3.3.3 Statistics (1)

Data of Δ HbT, cTOI, SpO₂ and HR are presented as mean and \pm standard deviation (SD). Δ HbT values for each minute after birth were calculated by subtracting the HbT value at minute 15 after birth from the HbT value of each minute. The 15 minute value was used as reference value, because at that time point NIRS signal quality was the best. In this analysis we investigated the changes in Δ HbT, cTOI, SpO₂ and HR within the first 15 minutes after birth using a linear mixed model with fixed effects for time. A first order autoregressive covariance structure was used. Post-hoc analysis for changes between each minute was performed. A p-value <0.05 was considered statistical significant. Statistical analyses were performed using SPSS Statistics 20.0.0 (IBM; USA).

3.4 **Methods of the CBV_RESUP study**

3.4.1 **Study design**

The *CBV_RESUP study* (Cerebral Blood Volume in infants receiving REspiratory SUPport during neonatal transition study) was designed as a post-hoc analysis of data collected as primary and secondary outcome parameters in prospective observational studies or randomized controlled trials at the Medical University of Graz; Austria (1, 25, 33, 39). Between October 2010 and January 2015 term and preterm infants delivered by caesarean section with and without the need of RS were included after a written informed consent was obtained from the parents prior to birth. Due to technical reasons the NIRS measurements couldn't be performed in the delivery room next to the mother. Therefore, vaginally born infants were excluded to avoid a delay or disturbance of immediate skin-to-skin contact with the mother. Within the mentioned time period many newborn infants in our centre were included to other studies (2, 3, 26, 31, 32, 37, 38) in which cerebral NIRS measurements were conducted by using a different device ('INVOS 5100 C', Covidien, USA) and therefore couldn't be enrolled into the *CBV_RESUP study*, in which the NIRS measurements were performed by using a 'NIRO 200-NX' tissue oxygenation monitor (Hamamatsu; Japan). Further exclusion criteria were presence of congenital malformations, inherited disorders of metabolism, decision to not provide full life support and application of sustained lung inflations during postnatal stabilisation.

3.4.2 **Procedure**

After cord clamping, routinely performed within 30 seconds after birth, infants were placed on the resuscitation table under an overhead heater by the midwives. The newborn infants were dried and stimulated by using warm cotton diapers to induce effective breathing. In case of obvious or suspected upper airway obstruction immediate suction of the oropharynx was performed. If necessary, RS was provided via face mask according to recent guidelines (79-81) either by applying PPV or CPAP depending on the breathing efforts of the patient. The pre-set FiO₂

was 0.21 in term infants and 0.3 in preterm infants and was adapted to achieve defined oxygen saturation targets during immediate postnatal transition (12).

As soon as possible, scientific staff members fixed the NIRS transducer on the newborn's right forehead by using gauze bandage without disturbing routine medical care. Additionally, preductal SpO₂ and HR were continuously monitored by using pulse oximetry on the right wrist. The measurements were conducted over the first 15 minutes after birth. Singular measurements of blood pressure and rectal body temperature were recorded between minute 10 and 15 after birth.

3.4.3 Statistics

In each neonate, ΔHbT values for each minute after birth were calculated by subtracting the mean ΔHbT value at minute 15 from the mean ΔHbT value of the related minute. The 15 minute value was used as reference value, because at that time point NIRS signal quality was most stable and reliable. Next, ΔHbT values were converted to ΔCBV . For the calculation either the actual Hb level of the individual (from routinely performed blood sampling within 30 minutes after birth) or the averaged group Hb of term or preterm infants (if the individual value was not available) was used.

Demographic variables are presented as absolute and relative counts, mean and SD or median and interquartile range (IQR), as appropriate. Comparisons of categorical baseline characteristics between infants with and without RS and between preterm and term infants were made using chi-square test, t-test or Mann Whitney U-test, as appropriate. Data of ΔCBV , cTOI, SpO₂ and HR are presented as mean and 95% confidence interval (95% CI). We investigated the courses of ΔCBV , cTOI, SpO₂ and HR within the first 15 minutes after birth using a linear mixed model with fixed effects for time, RS (with RS vs. without RS), and gestational age (preterm vs. term). Since most of preterm neonates (82.2%) required RS and most of term neonates (88.1%) did not receive RS, we tested a model including RS without considering gestational age (model 1) and a model including RS and gestational age (model 2). The decision, which of these models to be used was based on a REML-based likelihood ratio test. A first order

autoregressive covariance structure was used. Post-hoc analyses for differences between groups for each minute were performed for the comparison of RS groups (with RS vs. without RS) and if model 2 was chosen also for gestational age groups (term infants vs. preterm infants). A p-value <0.05 was considered statistical significant. Statistical analyses were performed using SPSS Statistics 20.0.0 (IBM; USA).

4 Results

4.1 Results of the CBV study (1)

109 term infants (55 female) with mean gestational age of 38+6 weeks (± 7 days) and mean birth weight of 3242 (± 481) g were enrolled. Demographic and clinical data of the study population are summarized in Table 1.

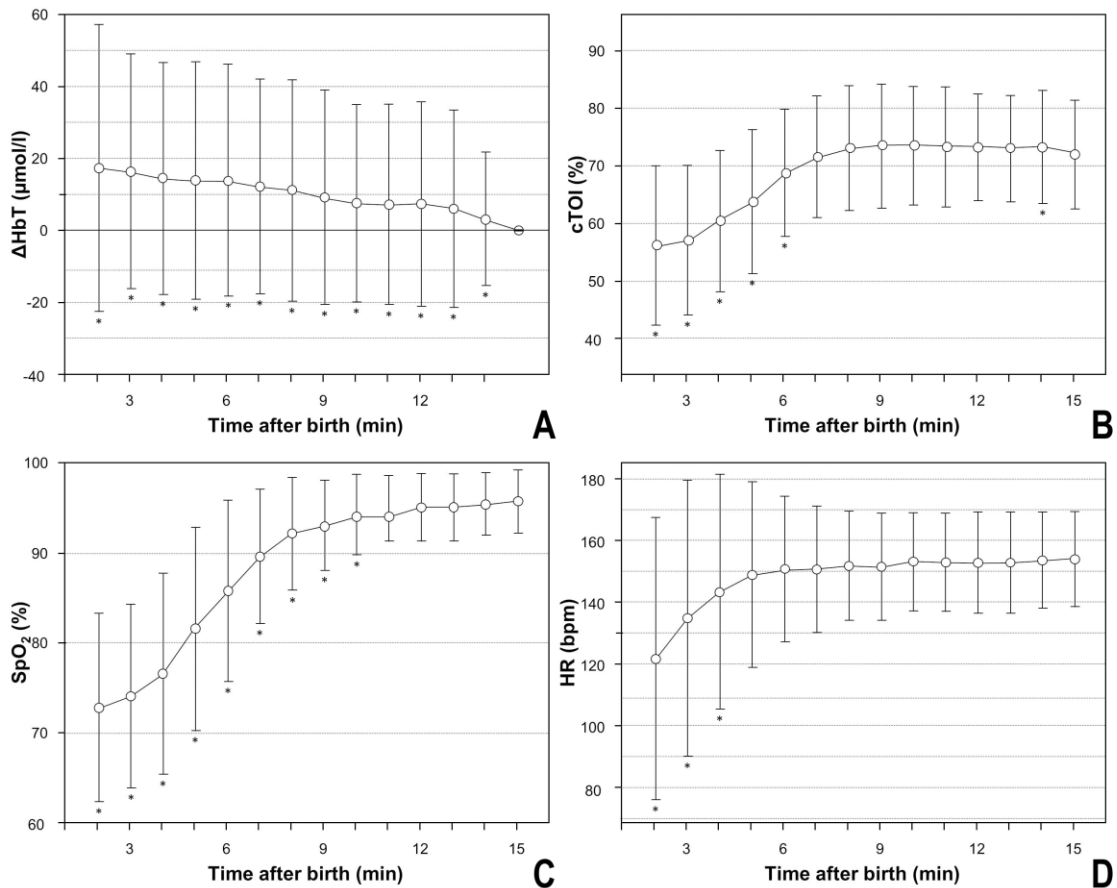
Table 1: Demographic and clinical characteristics of the study population (CBV study) (1)

	Study population (n = 109)
Gestational age (wk), mean (\pmSD)	38.8 (1.0)
Gestational weight (g), mean (\pmSD)	3242 (481)
Head circumference (cm), mean (\pmSD)	34.8 (1.3)
Female sex, n (%)	55 (50.4)
Apgar at 1 min, median (IQR)	9 (9 – 9)
Apgar at 5 min, median (IQR)	10 (10 – 10)
Apgar at 10 min, median (IQR)	10 (10 – 10)
pH umbilical artery, mean (\pmSD)	7.28 (0.05)
Haemoglobin (g/dl) in umbilical cord blood, mean (\pmSD)	15.9 (1.6)
Systolic arterial blood pressure (mmHg) at 10 min, mean (\pmSD)	64.7 (9.6)
Mean arterial blood pressure (mmHg) at 10 min, mean (\pmSD)	45.0 (7.9)
Diastolic arterial blood pressure (mmHg) at 10 min, mean (\pmSD)	35.0 (10.2)
Rectal body temperature ($^{\circ}$C) at 15 min, mean (\pmSD)	36.7 (0.3)

4.1.1 Δ HbT and Δ CBV (1)

Related to a reference value at minute 15 after birth (min), a significant decrease of HbT was observed for each minute. HbT was gradually decreasing, starting with a Δ HbT of 17 (\pm 40) μ mol/l at minute 2, and values of 16 (\pm 33) μ mol/l at minute 3, 14 (\pm 32) μ mol/l at minute 4, 14 (\pm 33) μ mol/l at minute 5 and 8 (\pm 27) μ mol/l at minute 10 (Figure 1A).

The mean (\pm SD) decrease of HbT of 17 (\pm 40) μ mol/l from minute 2 to minute 15 represents a decrease of CBV of 1.0 (\pm 2.2) ml/100g brain.



bpm, beats per minute; *cTOI*, cerebral tissue oxygenation index; *HbT*, total haemoglobin; *HR*, heart rate; *SpO₂*, arterial oxygen saturation

Figure 1: Courses of Δ HbT (A), cTOI (B), SpO₂ (C) and HR (D) during the first 15 minutes after birth (CBV study) (1)

Values are mean (\pm SD); * $p < 0.05$, significances are calculated from each minute in relation to a reference value at 15 min for each parameter.

4.1.2 cTOI, SpO₂ and HR (1)

cTOI was significantly increasing between minute 3 and 8 and then reached a steady state at a level of approximately 73% until minute 14. Between minute 14 and 15 cTOI decreased significantly (Figure 1B). SpO₂ values were significantly increasing within the first 10 minutes, and reached a steady state in the further course (Figure 1C). HR was significantly rising and reached a steady state at minute 5 (Figure 1D).

4.1.3 Echocardiography (1)

A cardiac ultrasound was performed in 83 of 109 (76.1%) neonates between minute 15 and 30 after birth. A predominantly left-to-right shunt via ductus arteriosus Botalli was identified in 71 infants (85.5%) and a bidirectional shunt in 11 infants (13.3%). A predominantly right-to-left shunt wasn't observed in this population; in 1 (1.2%) infant no flow via ductus arteriosus was seen. The average diameter of ductus arteriosus was 1.95 (± 0.7) mm.

4.2 *Results of the CBV_RESUP study*

In total, in 204 neonates measurements were performed during the study period including 45 preterm infants (37 with and 8 without RS) and 159 term infants (19 with and 140 without RS) born at a mean gestational age of 33+3 weeks (± 15 days) and 38+6 weeks (± 6 days), respectively. Thus, 56 newborn infants received RS during the transitional period, whereas 148 had a normal neonatal transition without the need of RS. Hb values were available in 19.6% of the included infants with a mean Hb of 16.2 (± 2.5) g/dl.

Demographic and clinical data of newborn infants with and without RS during immediate postnatal transition are summarized in Table 2.

Table 2: Demographic and clinical characteristics of newborn infants with and without RS (CBV_RESUP study)

	With RS (n = 56)	Without RS (n = 148)	p-value
Gestational age (wk), mean (\pmSD)	35.0 (3.2)	38.7 (1.2)	<.001
Gestational weight (g), mean (\pmSD)	2382 (916)	3232 (502)	<.001
Head circumference (cm), mean (\pmSD)	32.2 (3.3)	34.6 (1.5)	<.001
Female sex, n (%)	31 (55)	76 (51)	.609
Apgar at 1 min, median (IQR)	8 (8 – 8)	9 (9 – 9)	<.001
Apgar at 5 min, median (IQR)	9 (9 – 9)	10 (10 – 10)	<.001
Apgar at 10 min, median (IQR)	9 (9 – 10)	10 (10 – 10)	<.001
pH umbilical artery, median (IQR)	7.29 (7.27 – 7.31)	7.29 (7.27 – 7.32)	.695
Rectal body temperature ($^{\circ}$C) at 15 min, mean (\pmSD)	36.7 (0.5)	36.7 (0.3)	.794
Haemoglobin (g/dl) in umbilical cord blood, mean (\pmSD)	17.4 (3.1)	15.3 (1.6)	.002
Systolic APB (mmHg) at 10 min, mean (\pmSD)	60.2 (9.4)	66.0 (9.4)	<.001
Mean APB (mmHg) at 10 min, mean (\pmSD)	41.2 (8.9)	45.4 (7.8)	.003
Diastolic APB (mmHg) at 10 min, mean (\pmSD)	32.7 (9.4)	35.0 (10.3)	.186

APB, arterial blood pressure; RS, respiratory support

Demographic and clinical data of preterm and term infants – irrespective of whether RS was applied or not – are summarized in Table 3.

Table 3: Demographic and clinical characteristics of preterm and term infants (CBV_RESUP study)

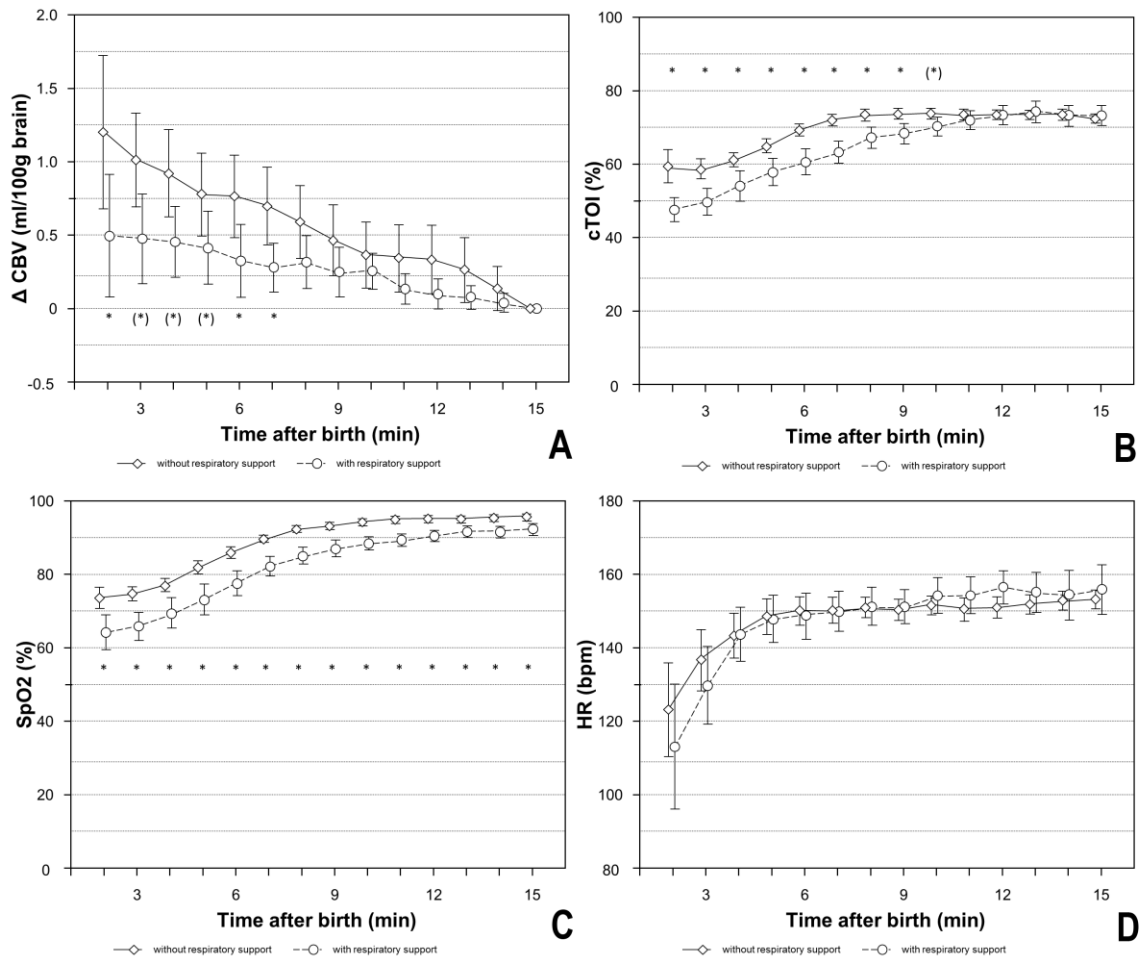
	Preterm Infants (n = 45)	Term infants (n = 159)	p-value
Gestational age (wk) , mean (\pm SD)	33.5 (2.1)	38.9 (0.9)	<.001
Gestational weight (g) , mean (\pm SD)	1900 (1442 – 2580)	3260 (2954 – 3480)	<.001
Head circumference (cm) , median (IQR)	30.5 (29.0 – 38.0)	35.0 (34.0 – 35.5)	<.001
Female sex , n (%)	26 (58)	81 (51)	.418
Apgar at 1 min , median (IQR)	8 (8 – 8)	9 (9 – 9)	<.001
Apgar at 5 min , median (IQR)	9 (8 – 9)	10 (10 – 10)	<.001
Apgar at 10 min , median (IQR)	9 (9 – 10)	10 (10 – 10)	<.001
pH umbilical artery , mean (\pm SD)	7.30 (0.04)	7.28 (0.05)	.015
Rectal body temperature (°C) at 15 min , mean (\pm SD)	36.7 (0.6)	36.7 (0.3)	.546
Haemoglobin (g/dl) in umbilical cord blood , mean (\pm SD)	18.0 (3.0)	15.2 (1.6)	<.001
Systolic APB (mmHg) at 10 min , mean (\pm SD)	59.1 (10.0)	65.8 (9.2)	<.001
Mean APB (mmHg) at 10 min , mean (\pm SD)	40 (35 – 47)	45 (40 – 50)	.002
Diastolic APB (mmHg) at 10 min , median (IQR)	32 (27 – 38)	35 (28 – 42)	.090

ABP, arterial blood pressure

4.2.1 Δ CBV

In the whole study population a significant decrease in CBV was observed within the first 15 minutes after birth ($p < .001$). Furthermore we observed a trend toward smaller Δ CBV in neonates with RS ($p = .097$), while the courses of Δ CBV were

comparable between groups ($p = .655$). Differences of ΔCBV between groups reached statistical significance ($p < .05$) at minutes 2, 6 and 7. The ΔCBV values at minutes 3, 4 and 5 showed a trend ($p < .10$) toward a difference between groups (Figure 2A). The inclusion of the gestational age did not result in a significant better model fit ($p = 0.172$), meaning that gestational age could not explain further differences in ΔCBV between neonates.



bpm, beats per minute; CBV, cerebral blood volume; cTOI, cerebral tissue oxygenation index; HR, heart rate; SpO₂, arterial oxygen saturation

Figure 2: Courses of ΔCBV (A), cTOI (B), SpO₂ (C) and HR (D) during the first 15 minutes after birth in newborn infants with and without respiratory support (CBV_RESUP study)

Values are mean (95% CI); * $p < 0.05$, significances are calculated for group comparisons for each minute.

4.2.2 cTOI, SpO₂ and HR

In the whole study population cTOI ($p < .001$) and SpO₂ values ($p < .001$) showed a significant increase during immediate postnatal transition. We found significant differences in cTOI and SpO₂ levels between newborn infants with and without RS after birth showing significantly lower values in those infants who received RS (cTOI: $p = .023$; SpO₂: $p < .001$). By comparing both groups, cTOI levels did not equalize before the 9th minute of age, whereas the differences of SpO₂ continued until the end of the observational period of 15 minutes after birth (Figure 2B-C). cTOI and SpO₂ values did not show significant differences comparing term to preterm infants (cTOI: $p = .577$; SpO₂: $p = .595$).

HR increased significantly ($p < .001$) in the study population. This significant increase was mainly due to an increase within the first 5 minutes after birth. HR values were higher in newborn infants with RS compared to newborn infants without RS ($p = .007$) (Figure 2D) and were higher in term compared to preterm infants ($p = .003$).

5 Discussion

5.1 *Discussion of the CBV Study*

5.1.1 CBV (1)

To the best of our knowledge the *CBV study* is the first study that investigated changes in CBV during immediate postnatal transition in healthy human newborn infants. CBV was continuously decreasing over the whole study period of 15 minutes. This finding is in accordance with animal data, which showed a CBV decrease during resuscitation of ventilated preterm lambs (55). However, RS itself might have a significant influence on cerebral hemodynamics. Term infants of the present study underwent undisturbed neonatal transition without need for any kind of RS, which alludes to the fact, that this CBV decrease may display a physiological process. Thus, changes in blood gases during transition from fetal to neonatal life might play an important role. As the first breaths aerate the lungs after birth, pulmonary vascular resistance rapidly decreases and pulmonary blood flow increases. Consecutively, the entire right ventricular output passes through the lungs, as they assume the function of gas exchange (82). Therefore, the partial pressure of oxygen (pO_2) rises dramatically and the partial pressure of carbon dioxide (pCO_2) levels decrease during the first minutes of life.

The pO_2 levels have shown to increase from 15 – 20 mmHg (2.0 – 2.7 kPa) at birth to 46 – 57 mmHg (6.1 – 7.6 kPa) by 10 minutes of age (83). The impact of changes in pO_2 levels on CBV during postnatal transition has not been subject of investigation in previous studies. However, it has been shown that hypoxaemia is a potent vasodilatory stimulus to cerebral vessels with a similar vessel response across fetal, neonatal and adult humans (84). Vasodilatation occurs below a pO_2 threshold of approximately 50 mmHg (6.7 kPa), the point at which SpO_2 starts to fall significantly as plotted in the oxygen-haemoglobin dissociation curve (84). In preterm lambs Wong et al. (2010) have shown a CBV decrease with an increase

in pO₂ by using NIRS (85). Thus, we hypothesize that the CBV decrease after birth was mainly caused by the postnatal increase of cerebral pO₂ levels.

Furthermore it was reported that pCO₂ at birth is 49 – 76 mmHg (6.5 – 10.1 kPa) and decreases to 46 – 57 mmHg (6.1 – 7.6 kPa) by 10 minutes of age (83). A CBV decrease in consequence of falling pCO₂ levels has been demonstrated in preterm and term infants (49). An increase in cerebrovascular reactivity to changing pCO₂ levels with gestational age has been shown (49). Whereas this mechanism might be of lower importance in preterm infants, in general a decrease of pCO₂ levels accounts for cerebral vasoconstriction (49).

Noori et al. (2012) have demonstrated a drop of cerebral blood flow (CBF) using Doppler sonography in preterm infants after birth (23). In this paper the reduction in CBF was presumed to be caused by an increase in arterial oxygen content and/or changes in shunting via ductus arteriosus during transition time. However, the relationship of CBF and CBV in newborn infants remains unclear. In monkeys (86) and adults (87) a nonlinear relationship of CBF and CBV was found.

After birth, ductus arteriosus shunting changes from predominantly right-to-left to predominantly left-to-right shunting with a responsive increase in left ventricular stroke volume (23, 53). That might be the reason why in term infants with predominantly left-to-right shunting via the ductus arteriosus significantly higher cerebral regional oxygen saturation values were found compared to infants without shunt flow (54). Due to the increase in left ventricular output and in arterial oxygen saturation within the first minutes after birth, oxygen delivery to the brain is rising.

In our study we demonstrated an average decrease of CBV of 1.0 (\pm 2.2) ml/100g brain during postnatal transition. This value is particularly remarkable when it is related to the absolute numbers of CBV in newborn infants. A wide variation of CBV in newborn infants has been reported by using NIRS technology. While Wyatt et al. (1990) have shown a CBV of 2.22 ml/100g at an age of 4 – 240 hours in preterm and term infants (44), Baenziger et al. (2007) estimated the CBV to be approximately 6 ml/100g in preterm infants at 4 hours of age (88). Recently,

Fujioka et al. (2014) has shown significant differences of CBV in term (2.45 ml/100g) and preterm infants (1.97 ml/100g) at 3 – 72 hours of age (89).

Taking into consideration the amount of CBV decrease within this short-term observation, one has to acknowledge a significant autoregulatory capacity of cerebral vessels. Any impairment of this autoregulatory capacity may have the potential of being an influential factor for the development of brain damage. It remains speculative that immaturity of such an autoregulatory capacity in extreme premature infants may lead to different behaviour of CBV during transition, thus playing an important role in the development of intraventricular haemorrhage.

5.1.2 cTOI, SpO₂ and HR (1)

cTOI was significantly increasing within the first 7 minutes after birth. Recently, our study group presented two publications with reference ranges for regional cerebral tissue oxygenation of term infants without need for RS by using two different NIRS devices [NIRO 200 NX (Hamamatsu; Japan) and INVOS 5100C (Covidien, USA)] (33, 37). Mean cTOI levels of the CBV study population were very similar to the percentiles of Baik et al. (2015) representing NIRS measurements with NIRO 200NX. In contrast, cTOI levels of our study population showed lower values when compared to the INVOS percentiles of Pichler et al. (2013) with an exception in the 2nd and 3rd minute after birth. However, values of regional tissue oxygenation measured with different NIRS devices have to be interpreted with caution, although comparative studies with all the widely used devices have been published (90).

Dawson et al. (2010) published reference ranges for preductal SpO₂ in the first 10 minutes after delivery (12). Our findings of SpO₂ were very similar to Dawson's percentiles of term infants.

HR was significantly increasing within the first 5 minutes of age and showed a similar course compared to the 25th percentile of the defined reference ranges (15) and compared to the 75th percentile of a cohort of newborn infants with delayed cord clamping and immediate skin-to-skin contact (16).

5.2 ***Discussion of the CBV_RESUP Study***

As far as we know the *CBV_RESUP study* is the first study that incorporates detailed analysis of CBV in term and preterm infants with and without the need of RS during immediate postnatal transition. We observed a significant decrease in CBV within the first 15 minutes after birth in both groups, but the Δ CBV was smaller in the first seven minutes in neonates with RS. Whether RS itself or the condition of the infant leading to requirement for RS is responsible for the observed CBV behaviour cannot be explained in detail with the present data.

Our findings are in accordance with recently published data by our study group demonstrating a significant decrease in CBV in healthy term infants after birth (1). We hypothesized that the transitional CBV decrease reflected a physiological response to changing blood gases within the autoregulatory capacity of cerebral vessels as pO_2 increases and pCO_2 decreases postnatally (1). Blood gas changes may occur to a different extent in different individuals during postnatal immediate transition, but generally during neonatal transition the changes in pO_2 are more distinct, compared to changes in pCO_2 . Furthermore, our study group demonstrated that preterm infants receiving RS during neonatal transition showed significantly lower $crSO_2$ values compared to infants without requirement of RS (2, 3). Thus, decreased cerebral oxygenation in infants receiving RS potentially may be accompanied by cerebral vasodilatation to increase cerebral blood flow and improve oxygen delivery (91). The extent of CBV decrease due to cerebral vasoconstriction might substantially depend on pO_2 levels, which increase less rapidly in infants requiring RS immediately after birth (2, 3, 92).

Furthermore, our research group has shown that in ventilated preterm infants who developed IVH in the first days of life $crSO_2$ was significantly lower during immediate transition compared to infants within the normal range of $crSO_2$ and no IVH in the further course (26). This is especially remarkable since SpO_2 and HR was not different in those two groups of infants suggesting that differences in $crSO_2$ were mainly caused by differences in cerebral perfusion potentially resulting in a less pronounced CBV decrease in ventilated infants with IVH and low $crSO_2$ values after birth (26).

However, it has been shown that initial RS immediately after birth is a considerable risk factor for cerebral injury and local brain inflammation in newborn neonates, particularly in preterm infants who already are at a high risk due to brain immaturity (59). Even though there is growing evidence that ventilation-induced injuries occur as early as ventilation is initiated in the delivery room, PPV immediately after birth still is one of the least controlled interventions in preterm infant (59). By using a respiratory function monitor, potentially harmful high tidal volumes were demonstrated during postnatal stabilisation in more than 85% of preterm infants receiving PPV via face mask (72). These high tidal volumes might influence cerebral perfusion and might have hazardous effects on the brain (55, 75). Therefore, further research is needed to optimize initial ventilatory strategies to potentially achieve improved cerebral outcome in newborn infants.

5.3 **Limitations** (1, 39)

NIRS measurements were performed by using a NIRO 200-NX (Hamamatsu, Japan), because it was the only available NIRS device which supported CBV measurements. We included preterm infants into the *CBV_RESUP study*, but needed to exclude extremely low birth weight infants, because at the time of the initiation of the studies NIRS probes of Hamamatsu were pretty bulky and not suitable for measurements on the smallest of our preterm infants. Therefore, our data do not permit conclusions about CBV behaviour in extremely low birth weight infants.

Due to technical reasons NIRS measurements were not performed in the delivery room next to the mother. To avoid delay or disturbance of immediate skin-to-skin contact with the mother vaginally born newborn infants were excluded. Since all the included infants were delivered by elective caesarean section, we have no information on courses of CBV and cTOI in vaginally delivered infants. This is particularly noteworthy, although our study group already described that there were no differences in cerebral tissue oxygenation in term infants with respect to mode of delivery (elective caesarean vs vaginal delivery) (41).

The standard of care at our centre at the time when the studies were conducted was immediate cord clamping performed within the first 30 seconds after birth. It remains unclear, whether delayed cord clamping would have resulted in a different CBV behaviour. It has been shown that delayed cord clamping of 60 and 180 seconds resulted in an increase of blood volume by about 16 ml/kg and 23 ml/kg body weight, respectively (93). Nevertheless in term infants cardiac output in relation to early and delayed cord clamping was not different between 2 and 4 hours after birth (94). In preterm infants it has been shown that delayed cord clamping resulted in a higher blood flow in the superior vena cava at 24 hours after birth (95) and in an improvement of cerebral oxygenation (88) at 4 and 24 hours after birth. Apart from that, CBV was not different at the age of 4 and 24 hours in early compared to delayed cord clamping (88). However, there is a lack of data regarding changes in cerebral hemodynamics during postnatal transition in relation to the time of cord clamping.

It has been shown that cerebral vasoreactivity is dependent on pO_2 and pCO_2 levels in human newborn infants (49, 84). Unfortunately, we cannot provide continuous data for pO_2 or pCO_2 , which might be beneficial for the interpretation of the CBV results. However, we continuously observed SpO_2 which is closely linked to pO_2 on the one hand, and $cTOI$ on the other hand. In preterm infants and in most of the infants who received RS we obtained capillary blood gases for pO_2 and pCO_2 evaluation at one time point (15 minutes after birth). In contrast, mainly due to ethical concerns, no blood samples were obtained in newborn infants who underwent normal postnatal transition and did not receive any kind of medical support. Thus, pO_2 and pCO_2 values cannot be provided for those healthy newborn infants.

Furthermore, the conversion of NIRS derived ΔHbT to ΔCBV requires the individual Hb levels of every single patient. Unfortunately, it wasn't possible to obtain Hb levels in each patient, because the Regional Committee on Biomedical Research Ethics did not authorize blood sampling exclusively for study purposes. Therefore, in absence of the individual levels we used mean Hb values of the respective study group for calculating ΔCBV .

In addition, no data were collected on the impact of RS on cardiac output and the superior vena cava flow indicating the extent of venous return from the brain in ventilated infants. Anyhow, we performed echocardiography only within the *CBV study* in which healthy term infants were exclusively included.

6 Conclusions

The *CBV study* (1) demonstrated a decrease in CBV in healthy term infants during immediate postnatal transition. This likely reflects a physiological process showing changes within the autoregulatory capacity of cerebral vessels in reaction to increasing pO₂ and decreasing pCO₂ levels. Our data add important information for a better understanding of haemodynamic processes during transition period. The study results serve as reference ranges of the physiological CBV behaviour in healthy newborn infants and may be compared with data of preterm or term infants receiving RS to identify differences in CBV courses with potential risks for cerebral damage (1).

The *CBV_RESUP study* was the first study that incorporated detailed analyses of CBV in preterm and term infants with and without requirement of RS during immediate postnatal transition. We observed a significant decrease of CBV in infants undergoing normal transition and in infants which received either PPV or CPAP. Interestingly, Δ CBV was smaller in the first seven minutes in neonates with RS. This study did not yet determine, whether RS itself or the condition of the infant leading to requirement for RS is responsible for the observed differences in CBV compared to healthy newborn infants. Our results are of particularly great interest, since hemodynamic disturbances resulting in changes in cerebral perfusion are discussed to be an important pathway to ventilation-induced brain injury occurring as early as ventilation is initiated in the delivery room.

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8 Appendix

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