Diplomarbeit

The influence of body temperature during immediate postnatal transition on cerebral oxygenation and short-term outcome

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Graz, am 24.07.2018 *Alisa Richter eh*

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II. Zusammenfassung

Zielsetzung: Das Ziel dieser Studie war es, den möglichen Einfluss der Körpertemperatur auf die regionale zerebrale Sauerstoffsättigung ($crSO_2$) des Neugeborenen während der ersten 15 Lebensminuten nach Entbindung per Sectio caesarea zu untersuchen. Des Weiteren sollte untersucht werden, ob sich reife Neugeborene und Frühgeborene hinsichtlich Körpertemperatur und $crSO_2$ während der postnatalen Adaptation unterscheiden und ob die Körpertemperatur mit einer erhöhten Rate an bakterieller Infektion, intraventrikulärer Hämorrhagie (IVH), periventrikulärer Leukenzephalomalazie oder nekrotisierender Enterokolitis (NEC) vergesellschaftet ist.

Methoden: Die Daten für diese retrospektive Studie wurden als explorative Parameter im Rahmen von prospektiv durchgeführten Beobachtungsstudien an der klinischen Abteilung für Neonatologie, Medizinische Universität Graz, erhoben. Für alle Studien lagen positive Ethikkommissionsvoten vor. Die schriftliche elterliche Zustimmung wurde für alle inkludierten Patienten und Patientinnen vor Studienteilnahme eingeholt.

Innerhalb der ersten 15 Minuten nach Entbindung erfolgte eine Messung der $crSO_2$ mittels Nahinfrarotspektroskopie (NIRS). Zusätzlich wurden folgende Parameter gemessen bzw. erhoben: Rektale Körpertemperatur in Lebensminute 15, Apgar-Werte in Lebensminute 1, 5 und 10, Geschlecht, Körpergewicht, Körperlänge, Kopfumfang, Notwendigkeit der respiratorischen Unterstützung bzw. Intubation und Komorbiditäten (early-/late onset-Sepsis, IVH, periventrikuläre Leukenzephalomalazie und NEC).

Die Daten wurden mit IBM SPSS Statistics 22 analysiert. Bedingt durch die Verteilung sind die Daten als Median (Minimum-Maximum) angeführt. Zur Datenanalyse verwendeten wir nicht-parametrische Tests (Mann-Whitney-U-Test). $crSO_2$ und rektale Körpertemperatur in Lebensminute 15 wurden mittels Spearman-Korrelation in Zusammenhang gesetzt. Ein p-Wert von unter 0,05 wurde als statistisch signifikant gewertet.

Ergebnisse: In dieser retrospektiven Studie wurden 568 Neugeborene (164 Früh- und 422 Reifgeborene) untersucht. Die mediane Körpertemperatur der gesamten Studienpopulation betrug 36,8°C (35,0-39,9). 461 der insgesamt 586 Neugeborenen (78,8%) waren normotherm (Körpertemperatur 36,5-37,5°C). Die

$crSO_2$ betrug 15 Minuten nach Geburt im Median 78,8% (15,9-95,0). Es gab keine signifikante Korrelation zwischen Körpertemperatur und $crSO_2$, weder für die gesamte Kohorte (ρ=0,011, p=0,816) noch für die Früh- (ρ=-0,071, p=0,446) oder die Reifgeborenen (ρ=0-054, p=0,316). Die Körpertemperatur war mit einer mittleren Differenz von 0,1°C bei Frühgeborenen jedoch signifikant niedriger (p=0,003). Bei den $crSO_2$-Werten gab es keine Unterschiede zwischen den zwei Gruppen (p=0,689). Es bestanden auch keine Unterschiede in der Körpertemperatur zwischen Neugeborenen mit neonatalen Komorbiditäten und jenen ohne.

Schlussfolgerung: Es zeigte sich keine Korrelation zwischen der rektal gemessenen Körpertemperatur und der $crSO_2$ bei Früh- und Reifgeborenen in der postnatalen Adaptation. Während bei der Körpertemperatur ein signifikanter Unterschied zwischen Früh- und Reifgeborenen bestand, zeigten sich keine Unterschiede in der $crSO_2$. Die postnatale Körpertemperatur unterschied sich nicht zwischen Patienten/PatientInnen mit bakterieller Infektion, IVH, periventrikulärer Leukenzephalomalazie oder NEC und jenen ohne diese Erkrankungen.

III. Abstract

Objective: The primary aim of this study was to investigate the potential correlation between body temperature and regional cerebral oxygen saturation ($crSO_2$) in neonates during the first 15 minutes of life after delivery by caesarean section. Furthermore, we looked for differences in body temperature and $crSO_2$ between term and preterm neonates and analysed, whether body temperature is associated with bacterial infection, intraventricular haemorrhage (IVH), periventricular leukomalacia or necrotizing enterocolitis (NEC).

Methods: Data for this retrospective analysis were collected as part of prospective observational studies at the Division of Neonatology, Medical University of Graz. For all studies, approval by the local Ethics Committee and written parental consent prior to study inclusion were obtained.

Within 15 minutes after delivery, $crSO_2$ was measured by near-infrared spectroscopy (NIRS). In addition, the following parameters were measured/obtained: rectal body temperature in minute 15, Apgar scores in minutes 1, 5 and 10, sex, body weight, body length, head circumference, need for respiratory support or intubation, and comorbidities (early-/late onset-sepsis, IVH, periventricular leukomalacia and NEC).

The data were analysed with IBM SPSS Statistics 22. Due to their distribution, data are given as median (minimum-maximum). We used non-parametric tests (Mann-Whitney-U test) for data analyses. For the correlation between rectal body temperature and $crSO_2$, we used Spearman's correlation. A p-value of below 0.05 was deemed statistically significant.

Result: In this retrospective study 568 neonates (164 preterm and 422 term neonates) were included. The median body temperature of the whole cohort was 36.8°C (35.0-39.9). 461 of the 586 neonates (78.7%) were normothermic (body temperature 36.5-37.5°C). Median $crSO_2$ was 78.8% (15.9-95.0) 15 minutes after birth. There was no significant correlation between body temperature and $crSO_2$ neither for the whole group (ρ=0.011, p=0.816) nor for preterm (ρ=-0.071, p=0.446) or term neonates (ρ=0.054, p=0.316). However, body temperature was significantly lower in preterm neonates with a mean difference of 0.1°C (p=0.003). $crSO_2$ did not differ between groups (p=0.689). In addition, there were no

differences in body temperature between neonates with comorbidities and those without.

Conclusion: There was no correlation between rectally measured body temperature and $crSO_2$ in preterm and term neonates during postnatal transition. While there was a significant difference in body temperature between preterm and term neonates, there was none in $crSO_2$. Postnatal body temperature was not different between patients who developed bacterial infection, IVH, periventricular leukomalacia or NEC and those who did not.

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VI. Abbreviations

cm	centimetre(-s)
$crSO_2$	cerebral regional tissue oxygenation saturation
e.g.	example given
Hb	deoxygenated haemoglobin
HbO_2	oxygenated haemoglobin
i.e.	id est (this is)
IVH	intraventricular haemorrhage
mm	millimetres
NEC	necrotizing enterocolitis
NIRS	near-infrared spectroscopy
p	probability
pCO_2	partial pressure of carbon dioxide
TOI	tissue oxygenation index
°C	degrees Celsius
%	percent
ρ	correlation coefficient

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1 Introduction

1.1 *Fetal and neonatal thermoregulation*

Biologists divide the wildlife to which the humankind belongs in two fractions: the poikilothermic and the homoeothermic. The poikilothermics are capable of adapting their body temperature to the ambient temperature and the seasons. Humans belong to the group of the so-called homoeothermic species. Their body temperature depends on many complex biochemical and physiological processes, aiming at reaching a temperature around 37 degrees Celsius (°C). For neonates it is not easy to keep the body temperature stable, and this is why they need a higher surrounding temperature compared to adults. (1)

The temperature of a fetus inside the uterus depends mainly on the maternal temperature, because the mother's heat is constantly permeating via the placental surface and the amnion to the fetus. (2) The amnion is a thin, transparent, non-vascular layer and a part of the amnion sac. Because of the steady circulation, the fetal temperature depends on the maternal temperature until birth and is normally 0.3°C to 0.5°C higher than the maternal temperature. (2)

At the moment the fetus is born, thermal conditions change extremely, as the extrauterine environment is 10-15°C cooler compared to intrauterine temperature. In order to adjust to the new surroundings, the homoeothermic response to reach a core temperature around 37.0°C begins right after delivery. (2)

The automatic, somatic and endocrine systems are responsible for temperature regulation in infants. The hypothalamus receives information from the thermal receptors in skin and core, which detect changes in temperature from a certain point and then respond with thermogenesis. (3) However, as producing heat requires adequate oxygenation, it is not possible for respiratory distressed neonates with hypoxemia to produce enough heat to increase body temperature by themselves. (2)

There are several options for an increase in neonatal heat production:

- by metabolic gain in cellular activity.
- by shivering thermogenesis.
- by non-shivering thermogenesis

Especially the non-shivering thermogenesis plays a significant role in neonates after birth. It takes place in the brown adipose tissue, which contains many fat vacuoles and mitochondria with huge stores of glycogen. Mitochondria are double-membraned organelles which are part of eukaryotic cells. Their main role is to produce energy for the cell, but they also have a very good connection to the blood and nerve supply. The brown adipose tissue first develops in the fetus between 26 to 30 weeks of gestation and remains for several weeks after birth. It is found around the great vessels, in the mediastinum, the kidneys and the adrenal glands. Other reservoirs are in the nape, the axilla and between the shoulder blades. The brown appearance derives from the higher number of mitochondria inside the adipocytes. (4)

To produce heat the adenosine triphosphate synthesis inside the mitochondria becomes uncoupled from the oxidative process, being triggered via noradrenaline and beta-3-receptors. As a result, the only function of the mitochondria is the heat production. An elevation in oxygen consumption and additionally an increase of free fatty acids takes place, which leads to an elevation of the body temperature. (5)

In healthy, term born neonates, shivering thermogenesis also is of some relevance, but heat production is more efficient via non-shivering thermogenesis.

Premature infants have a diminished capacity to produce heat by shivering and possess a lower amount of brown adipose tissue. (6) However, they may increase body heat by maximal constriction of skin blood vessels. This effect is even more profound in term born neonates. (7)

Another action found in most of the neonates to conserve heat is active flexion of the extremities to decrease the exposed surface area and to increase motor activity, thus gaining energy and heat by adenosine triphosphate synthesis. (8)

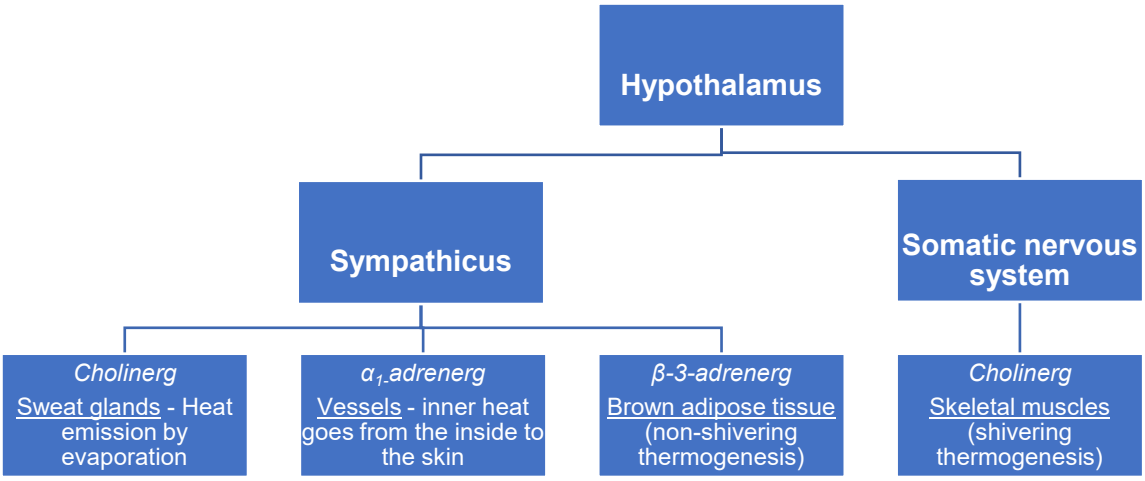

Figure 1 – Regulation of thermogenesis (1)

1.2 *Temperature measurement*

There are several options to measure a neonate's body temperature, including invasive and non-invasive measurement. The most common non-invasive devices are the mercury-in-glass thermometer and the electronic thermometer. Both can be used to measure temperature rectally or axillary. The advantage of the electronic thermometer is the short measurement time compared to the mercury-in-glass thermometer. Another non-invasive option is temperature measurement via the skin. For this, small pin-shaped or round sensors have to be placed below the patient's body or on the skin via the adhesive side of the electrodes. Especially for small preterm neonates, this is a very convenient possibility offering continuous measurement. Disadvantages of this method are the higher costs of the sensors and that they are single-use products. As cutaneous pressure marks can be found often in vulnerable preterm neonates, the electrodes shall be changed frequently. (9)

Measuring locations (9):

- Rectal measurement: Depending on the depth of measurement, the body core temperature of a healthy term born neonate is about 36.9°C. The temperature sensor or thermometer should be inserted rectally for not more than 5cm in term and 2cm in preterm neonates. The location of the thermometer plays a significant role. A distance of 25mm from the sensor to the anus results in a temperature discrepancy of 1°C between body core and measured temperature. Having positioned the thermometer next to the anus, measured temperature can be up to 3°C below core temperature. It has to be kept in mind that rectal temperature measurement bears the danger of intestinal perforations.

- Axillary measurement: This method represents the easiest form of non-invasive central temperature measurement in neonates.

- Cutaneous measurement: The skin measurement is a non-invasive method and can be conducted intrascapularly, prehepatically or on the extremities using adhesive sensors. The temperature reference ranges are equal to the invasive measurement.

- Oesophageal/urinary bladder measurement: Temperatures measured by these methods are invasive and thus more complicated and complication prone, yet they correlate directly with the body core temperature and should be between 36.5°C and 37.5°C in healthy newborn infants. For oesophageal measurement, the sensor is located in a thin-walled feeding tube at the level of the cardiac cavity, while measurement in the urinary bladder uses a urine catheter with temperature probe.

1.3 *Normothermia*

Normal body temperature for a newborn infant is defined as a core temperature between 36.5°C and 37.5°C. (10) Yet, based on neonatal physiology, heat loss and consequent hypothermia or hyperthermia may occur fast after birth.

1.4 *Hypothermia*

The temperature regulation of infants is different to adults. Infants can only tolerate a limited range of environmental temperature, so they are more vulnerable to hypothermia as well as hyperthermia. It is important to note that a naked neonate exposed to an environmental temperature of 23°C at birth suffers the same heat loss as does a naked adult at 0°C. (10)

1.4.1 Definition

The World Health Organization classifies a body core temperature in neonates of 36.0°C-36.4°C as mild hypothermia (or cold stress), 32.0°C-35,9°C as moderate hypothermia and a body core temperature of less than 32.0°C as severe hypothermia. (10) The reasons for hypothermia can be exogenous, because of a cold environment, wet skin, or cold breathing gas. Hypothermia can also be caused by endogenous reasons such as hypoxia, asphyxia, sepsis, shock or cerebral haemorrhage. (9)

According to a systematic review published in 2013, hypothermia is a common medical problem for infants born in hospitals (prevalence 32%-85%) as well as at home (prevalence 11%-92%). (11)

A selection of risk factors, that are associated with hypothermia after birth, are listed below.

1.4.2 Environmental factors

Environmental temperature after birth is of special importance in the case of home deliveries. (12) Two Indian studies showed correlation between lower ambient

temperatures and a higher incidence of neonatal hypothermia. (13, 14) The prevalence of body temperatures below 36,5°C among neonates after home deliveries in Haryana, Northern India, was 11% overall, with a range from 3% in the summer to 19% in the winter. (13)
However, studies undertaken in South Asia and Nepal demonstrated that neonatal hypothermia is a global problem and does not only occur in regions with lower ambient temperatures and cold seasons, but also in tropical countries with generally warm climates. (15-18)

1.4.3 Neonatal physiology

Independent of their gestational age neonates have a high risk of losing body temperature after birth, and preterm and small-for-gestational age infants are particularly vulnerable. The heat loss of the neonate per unit body weight has been estimated to be approximately four times higher than that of an adult. (7) The reason for this rapid heat loss is that neonates have a larger surface area in relation to their body weight and a thinner layer of subcutaneous fat. (19)

Basically, there are four main mechanisms of heat loss in neonates (Table 1), comprising:

- Evaporation
- Conduction
- Convection
- Radiation

The main reason for heat loss after birth is evaporation of amniotic fluid from the neonate's skin surface. This occurs rapidly during and after birth, when the wet neonate changes the environment from the consistently warm uterus to the relatively drier and cooler delivery room. (20) During the evaporation process the liquid on the body surface of the neonate changes into the gaseous phase, resulting in a decrease of body temperature.

Heat may also be lost by conduction, when the naked neonate gets in direct contact with colder surfaces (e.g. resuscitation table, weighing scale). Convection occurs if the neonate is exposed to a cooler surrounding environment and, by this, loses heat through diffusion. Radiation refers to the transfer of electromagnetic energy, i.e. heat, from the neonate to cooler objects without being in direct contact with each other. (10)

In addition to conditions like prematurity and intrauterine growth restriction, perinatal asphyxia and hypoglycaemia are highly associated with hypothermia after birth. (21-25)

Mechanisms of heat loss in neonates (4)		
Mechanism	***Definition***	***Interventions***
Evaporation	This occurs on wet newborn skin and depends on humidity of the surrounding air on air speed	• Polyethylene or vinyl bags • Increase humidity of the environment • Dry well • Decrease air currents
Conduction	Transferation of heat via contact from one area of higher temperature to another surface with a lower temperature	• Warming mattress • Using warm blankets to cover cold surfaces • Prewarming surfaces with radiant warmers
Convection	Heat transfer which takes place by diffusion from the neonate's body surface to the surrounding air	• Swaddle infant • Put a hat on a well-dried head • Use prewarmed gas for resuscitation
Radiation	Transfer of electro-magnetic energy from one body surface to the surrounding surfaces. This is not dependent on the ambient temperature, air speed or other mechanisms of heat loss	• Prewarming of the delivery room • Avoid keeping warmers to external walls, windows or direct sunlight

Table 1 – Mechanisms of heat loss in neonates (modified from 4)

1.4.4 Newborn care practices

Newborn care practices during the hours after birth play an important role in maintenance of normothermia. Various habits and rituals are performed after deliveries. A common tradition in countries where home deliveries are predominant is massage and oil applications, which shall protect the neonate from hypothermia. Studies on their effects are conflicting. It has been shown that these measures can also have negative effects on the skin as a protection layer and may lead to heat loss. (23, 26, 27)

Another frequently used practice is early bathing, which has been associated with unwanted hypothermia especially in cold regions. Hence, early bathing should be avoided at least for six hours post partum even in warm regions. (28, 29)

1.4.5 Socioeconomic factors

Besides a lack of knowledge among healthcare professionals regarding neonatal temperature management especially in low-income countries, neonatal hypothermia is more common in inexperienced, young mothers, who often derive from a family with low socioeconomic status. (30) In addition, there is also an association between neonatal hypothermia and women who already gave multiple births. (22)

1.5 *Hypothermia and neonatal morbidity/mortality*

An Indian study which focused on morbidities and mortality in hypothermic neonates found a case fatality rate ranging from 39.3 % for mild hypothermia to 80% for severe hypothermia. Fatality rates increased to 71.4% with additional hypoglycaemia, to 83.3% with hypoxia and up to 90.9% with shock. (31)

The potential consequences of hypothermia in neonates are (9):

- Metabolic acidosis
- Hypoglycaemia
- Increased oxygen consumption → hypoxaemia
- Apnoea

- Bradycardia
- Arterial hypotension
- Increased risk of a persistent fetal circulation and pulmonary hypertension
- Dysfunction of the coagulative system → increased risk of haemorrhage
- Increased mortality in the first week of life

In addition, chronic hypothermia leads to constant loss of energy and poor body growth and impaired neurocognitive development.

A study from 2006 with a cohort of 5227 low birth weight infants found no association between body temperature after birth and the rates of necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH) or duration of mechanical ventilation. On the contrary, they found that for every 1°C decrease in admission temperature, the odds of patients to develop a late-onset sepsis increased by 11% and the number of deaths by 28%, proving admission temperature to be inversely related to neonatal mortality. (32)

1.6 *Therapeutic hypothermia*

Hypothermia is used as a therapy for asphyxiated neonates with hypoxic-ischaemic encephalopathy. There is either the possibility of whole-body cooling, where the neonate is placed on a cooling mattress or blanket which gets circulated with cold fluid, or selective head-cooling, which is performed by fitting a cap filled with cold water to the infant's head. (33) In both instances, oesophageal/rectal temperature is held constant at 33°C to 34°C for 72 hours.
In order to qualify for cooling therapy, neonates must be 36 weeks or more of completed gestation, must arrive for treatment within six hours after birth, and must have experienced a moderate to severe hypoxic-ischaemic insult. Evidence for hypoxic brain injury includes cardiopulmonary resuscitation at delivery, an arterial umbilical blood pH of below 7.00 and/or a base deficit of 16 or lower. (34, 35)

In a study focusing on neonates with suspect asphyxia, who needed resuscitation at birth, had a metabolic acidosis or signs of early encephalopathy, patients underwent head cooling in order to reach a rectal temperature of 34°C to 35°C (mild hypothermia). There was a significant benefit in the subgroup with moderate encephalopathy, but a non-significant result concerning the reduction of survivors with severe disability at 18 months. (36)
Another study showed that moderate hypothermia (cooling of the body to 33.5°C) decreases deaths and disabilities among neonates with hypoxic-ischaemic encephalopathy and increases the number of surviving patients without neurodevelopmental disabilities. (37)

1.7 *Prevention of hypothermia*

There are different possibilities to prevent neonatal hypothermia after birth. Before the 19th century interest in premature infants was little because most births occurred at home and so the mother or (mainly female) family members were responsible for post-delivery care. They used warming methods such as wrapping infants in wool or sheepskin, placing them in a sun-warmed jar of feathers or putting cradles near the fireplace. (38) As the times changed and women increasingly preferred delivering babies in hospitals, new possibilities developed and the focus on preventing newly born infants from hypothermia grew.

The ambient temperature in the delivery room plays a significant role for heart rate, respiratory rate, oxygen consumption and water loss of the neonate. As body temperature and oxygen consumption are inversely related,(39) maintaining a constantly high delivery room temperature is a simple intervention that has a direct impact on heat loss. (40) Referring to the World Health Organization's practical guide of thermal control, the temperature in the delivery room should be 25°C. (10)

Other actions to prevent hypothermia include drying the neonate after birth, putting on a hat, positioning the neonate under a radiant warmer (Figure 2) as well as the use of vinyl bags and incubators especially for preterm neonates (see 1.7.1 and 1.7.2). Physiological options to reduce heat loss are accessible everywhere and

for everyone, i.e. the so-called kangaroo care (see 1.7.3) and breast feeding of the newborn infant. Breast feeding within one hour after delivery provides the neonate with sufficient calories to produce heat. (10)

Figure 2 – Radiant warmer (Ceramotherm, Weyer; personal picture)

1.7.1 Vinyl bags

Vinyl bags are an effective and inexpensive intervention to prevent hypothermia at birth especially in preterm neonates. (41)

Current resuscitation guidelines recommend placing the neonate under a radiant warmer with an environmental temperature between 23°C and 25°C. To reduce heat loss, preterm neonates below 32 weeks of gestation should be immediately put in a vinyl bag without drying. (42) The absence of a competent stratum corneum renders preterm neonates especially vulnerable to transcutaneous water loss,(43) while vinyl bags help preventing heat loss from evaporation and convection.

The non-permeable bags were originally produced for neonates with abdominal wall defects. When using it for hypothermia prevention, the bag gets secured loosely around the neck being fixed with straps. A study compared a group of preterm neonates who were placed in vinyl bags immediately after birth to a control group who received standard care with drying and postnatal care under a

radiant warmer. The use of vinyl bags in the delivery room reduced the incidence of hypothermia significantly and raised the admission temperature by 1.0°C. (41)

1.7.2 Incubator care

Incubators can be traced back to ancient Egyptian methods for hatching eggs. The first-time incubators for human neonatal care were described in the late 1850s by the French physician Jean-Louis-Paul Denuce. The principal behind his invention was a double-walled metal warming tub. Hot water was poured between the inner and the outer layer of the tube and was changed frequently in order to keep the bottom of the tub warm. Incubators relatively similar to the once used nowadays were established in the early 20th century. (44)
The advantage of the closed incubator is that the heat distribution is more homogeneous, than in the open care units. Moreover, the high humidity (80%-95%) reduces the infants water loss, especially in their first days after birth. (9)

In 1957 Silverman and Blanc reported that preterm infants housed in incubators humidified to more than 80% had higher survival rates than the group exposed to less than 60% of humidity. (45)
Later in 1963, Agate and Silverman hypothesized that radiant heat alone could offset heat losses incurred if the convective, conductive or evaporative partitions of thermal protection were compromised. (46) The heat control of the radiant heaters was regulated by servo control in order to maintain a constant skin temperature, measured by a thermistor probe on the abdomen. Comparing radiant heaters and incubators, radiant warmers raise convective and evaporative heat, but also lead to increased water loss. (47) Since then, studies concerning this topic were undertaken, showing a thermal advantage for neonates housed in a radiantly heated closed incubator, facilitated by reducing heat producing metabolic work through the warm and humidity controlled environment. (48, 49)

Figure 3 – Incubator (Giraffe, GE Healthcare; personal picture)

Figure 4 – Incubator (Giraffe, GE Healthcare; personal picture)

1.7.3 Kangaroo care

Kangaroo mother care refers to skin-to-skin contact between the (preterm) infant and one of his/her parents. The name kangaroo care derives from the mimicking of a kangaroo's pouch, because the neonate is usually positioned naked between the mother's breasts or her axillary folds.

This easily available method was first implemented in Bogota, Columbia, and then used in the 1980s for non-intubated preterm neonates in colder central European and Scandinavian countries. A study on kangaroo care found a significant reduction in early neonatal mortality and morbidity. (50) Kangaroo care is also associated with improved relationship between mother and infant, better neonatal weight gain and an earlier hospital discharge. Moreover, infants with bronchopulmonary dysplasia have improved oxygenation during kangaroo care with less periodic breathing and reduced rates of apnoea. (34) In a study which focused on respiratory control and thermoregulation during skin-to-skin-contact, the neonates' rectal temperature increased from 36.9°C to 37.3°C over the course of two hours. (51)

As utilization of incubators for preterm care has become the standard in our region, many more recent studies about kangaroo care are published in low-income countries, proving the possibilities and advantages of skin-to-skin neonatal care. It is one of the basic methods to prevent neonatal hypothermia worldwide. (52)

1.8 *Hyperthermia*

Neonatal hyperthermia is mostly caused by inappropriate incubation, which is often connected with high humidity and air temperature. Term infants are at a higher risk of becoming hyperthermic, because they do not cool down as fast as preterm neonates, who commonly need a convection warmed incubator. Referring to this topic, there is even a warning by the American Academy of Pediatrics: "The use of infant radiant warmers poses a hazard of neonatal hyperthermia. Serious overheating can result from mechanical failure of the controls, from dislodgment of

the sensor probe, or from manual operation without careful monitoring. Deaths have been associated with hyperthermia induced by radiant warmers.“ (53)

1.8.1 Definition

Hyperthermia is defined by a rectal temperature of more than 37.5°C. The reasons for hyperthermia can be exogenous or endogenous. The most important exogenous factor is excessive heat supply. Drug therapy with prostaglandin E_1 or erythropoetin and drug withdrawal can also result in hyperthermia. Additionally, hyperthermia can be caused by heat accumulation due to disproportionate clothing or covering. Most important endogenous reasons for hyperthermia are sepsis, infections of the central nervous system, dehydration and disturbances of the cerebral temperature regulation. (9)

Consequences of hyperthermia

Hyperthermia can lead to a loss of fluid, mainly caused by evaporation, an increase in oxygen consumption, apnoea and brain damages. (9) The reason for neurologic injury caused by hyperthermia are thought to be free radicals, cytokines, a strong systemic inflammatory response as well as a release of amino acids. (54)

Hyperthermia is also associated with increased neonatal mortality. (55)

1.8.2 Neonatal Fever

Neonatal fever is defined as a rectal temperature above 37.4°C. (56) It is an infrequent, but highly feared symptom of neonatal sepsis, especially in cases of body temperatures exceeding 38-39°C. Culture proven sepsis, however, is only found in fewer than 10% of febrile neonates. (34) The (patho-)physiological basis of fever is a disturbance in the relationship between central heat conservation and thermal losses, which is mainly caused by prostaglandin E_2 and other immunogenic pyrogens. (34)

Interestingly, maternal fever during pregnancy with a temperature as low as 38.3°C may be associated with an increased risk of neural tube defects in the newborn. (57)

1.9 *Near-infrared spectroscopy*

Near-infrared spectroscopy (NIRS) is a non-invasive method to measure tissue oxygen saturation. While ultraviolet and visible light is mostly absorbed when getting in contact with optical pigments such as melanin, myoglobin or haemoglobin, near-infrared light in the spectrum range from 700 to 1100nm is less susceptible for absorption and, thus, has better tissue penetration. (58)

NIRS measurements are based on detecting changes of tissue concentrations of oxygenated (HbO_2) and deoxygenated haemoglobin (Hb). Changes of the total haemoglobin concentration can also be measured by summation of HbO_2 and Hb. (59) Thus, these measurements allow quantification of oxygen saturation of the examined tissue. (60)

When interpreting NIRS data it is important to know that several demographic parameters such as gestational age, birth weight, body weight, calf diameter and subcutaneous adipose tissue as well as vital parameters (heart rate, peripheral temperature) are associated with peripheral muscle tissue oxygenation index (TOI) in neonates. (61) On the other hand, $crSO_2$ is influenced by oxygen delivery and consumption as well as metabolic factors. Pichler et al. (62) and Baik et al. (63) published percentiles for $crSO_2$ and cerebral TOI in term neonates during immediate postnatal transition.

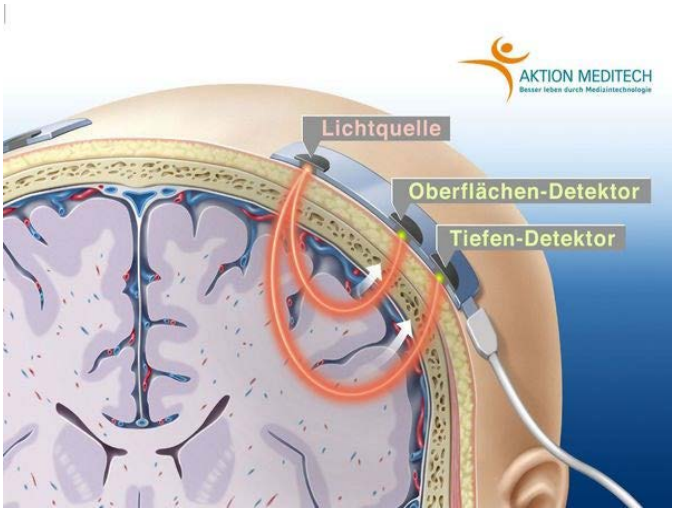

Figure 5 – Cerebral oximetry by near-infrared spectroscopy (64)

1.9.1 Lambert-Beer law

Physics behind NIRS is defined by the Lambert-Beer law, which relates the absorption of light to the material the light is penetrating.(65)

$A = \log(I_o/I) = \alpha \cdot c \cdot d$

A....Absorption

Io....supplied light intensity

I....remaining light intensity

α....extinction coefficient

c....concentration

d....layer thickness

Figure 6 – Lambert-Beer law (65)

Haemoglobin changes absorption features depending on its oxygenation status. Based on this physical characteristic, TOI can be calculated from the relation between HbO_2 and Hb. (66)

2 Materials and methods

2.1 *Study design*

Data were obtained as exploratory parameters of prospective observational studies in preterm and term neonates after delivery by caesarean section. The primary aim of the study was to assess if there is a correlation between rectal temperature and cerebral regional tissue oxygenation saturation ($crSO_2$) during immediate postnatal transition. The secondary objective was to compare rectal temperature and $crSO_2$ between preterm and term neonates.

All prospective observational studies were performed at the Division of Neonatology, Department of Paediatrics, Medical University of Graz, and were approved by the local Ethics Committee. For all patients, informed written consent was obtained from parents prior to study inclusion. Patient data such heart rate, arterial oxygen saturation, non-invasive blood pressure, measures of ventilatory support (ventilation rate, peak inspiratory pressure, positive endexspiratory pressure, inspired oxygen concentration) and $crSO_2$ were saved automatically in a polygraphic data management system (alpha-trace digital MM, BEST Medical Systems, Austria – Figure 7). These data were extracted and saved in a Microsoft Excel database together with prenatal and demographic information. Diagnoses (IVH, periventricular leucomalacia, NEC and bacterial infection) were extracted from electronic medical records (MEDOCS, University Hospital of Graz, Austria).

Figure 7 – Screenshot of alpha-trace digital MM, BEST Medical Systems, Austria

All neonates were placed in supine position under the resuscitation table's (CosyCot™, Fisher & Paykel Healthcare, New Zealand) pre-warmed overhead heater immediately after birth. If the neonate was below 28 weeks of gestation, it was put in a polyethylene bag. During clinical stabilisation of the neonate, a research assistant attached a neonatal NIRS sensor to the neonate's left forehead using an adapted continuous positive airway pressure cap and/or a cohesive conforming bandage. For $crSO_2$ measurements, INVOS 5100C (Somanetics Corporation, Michigan) with a neonatal sensor (Figure 8) was used. $crSO_2$ was measured continuously during the first 15 minutes of life, while body temperature (degrees Celsius = °C) was measured rectally by the use of a temperature probe (IntelliVue MP50 monitor, Philips, The Netherlands) in minute 15 after birth.

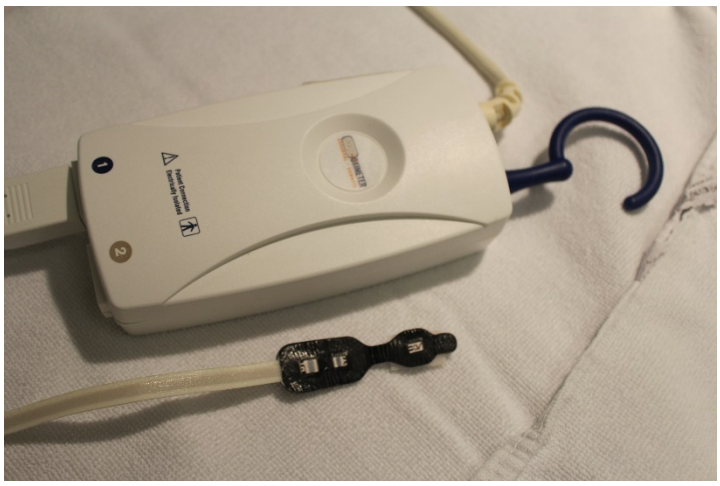

Figure 8 – NIRS sensor (INVOS 5100C, Somanetics Corporation; personal picture)

2.2 *Inclusion and exclusion criteria*

We included preterm and term neonates delivered by caesarean section in whom a) crSO2 was measured continuously during immediate postnatal adaptation and b) rectally measured body temperature was available from 15 minutes after birth. Patients with severe cardiovascular or central nervous malformations and neonates with missing data – as mentioned above – were excluded.

2.3 *Statistical analysis*

Data are given as median (range) based on distribution. They were analysed with IBM SPSS Statistics 22. To investigate potential differences between groups, we used non-parametric methods (Mann-Whitney-U test). For correlation analyses, we correlated body temperature and $crSO_2$ in minute 15 after birth using Spearman´s correlation. A p-value of <0.05 was considered statistically significant.

3 Results

3.1 *Study population*

A total of 586 neonates (164 preterm and 422 term newborns) were analysed for this study. Of these, 280 (47.8%) were females and 306 (52.2%) were males. The median gestational age was 38.6 weeks, with a minimum of 23.8 and a maximum of 41.4 weeks. The birth weight ranged from 466 grams to 5190 grams (median 2892.9 grams). Median body length was 48.7cm (28.0-61.0cm) and head circumferences varied between a minimum of 22.5cm and a maximum of 67cm (median 34.1cm).

Apgar scores were obtained at one, five and ten minutes after delivery. Apgar score at one minute showed a range between 1 and 10 points with a median of 8.5. Median Apgar score after five and ten minutes was 10 (5-10) and 10 (6-10). Arterial pH of umbilical cord blood was between 7.05 and 7.41 (median 7.30).

Of the 586 patients, 195 patients (33.3%) needed non-invasive respiratory support with oxygen supply and/or mask ventilation. An additional 12 neonates (2.0%) had to be intubated during postnatal adaptation.

All demographic data are summarized in Table 2.

	n	Minimum	Maximum	Median
Female	280			
Male	306			
Gestational age [weeks]	586	23.8	41.4	38.6
Weight [grams]	575	466	5190	2892.9
Body length [cm]	521	28	61	48.7
Head circumference [cm]	510	22.5	67	34.1
Apgar 1	580	1	10	8.5
Apgar 5	580	5	10	9.5
Apgar 10	580	6	10	10
Rectal temperature in °C	586	35	39,9	36.8
$crSO_2$	586	15.9	95.0	78.8
Non-invasive respiratory support (oxygen and/or mask ventilation)	195 (33.3%)	-	-	-
Intubation after birth	12 (2.0%)	-	-	-

Table 2 – Demographic data

Median body temperature was 36.8°C (35.0-39.9) for the whole cohort. A total of 461 neonates (78.7%) were normothermic with a body temperature between 36.5 and 37.5°C (Figure 9). 49 preterm and 51 term neonates were hypothermic, while 5 preterm and 21 term neonates had body temperatures above 37.5°C. Body temperature was significantly lower in preterm neonates (mean difference 0.1°C, p=0.003) compared to term neonates (Figure 10).

Median $crSO_2$ was 78.8% (15.9-95.0) 15 minutes after birth for all patients. In preterm and term neonates, median $crSO_2$ was 78.9% (15.9-95.0%) and 78.8% (22.9-95.0%), respectively. There was no difference in $crSO_2$ between preterm and term neonates (p=0.689; Figure 11).

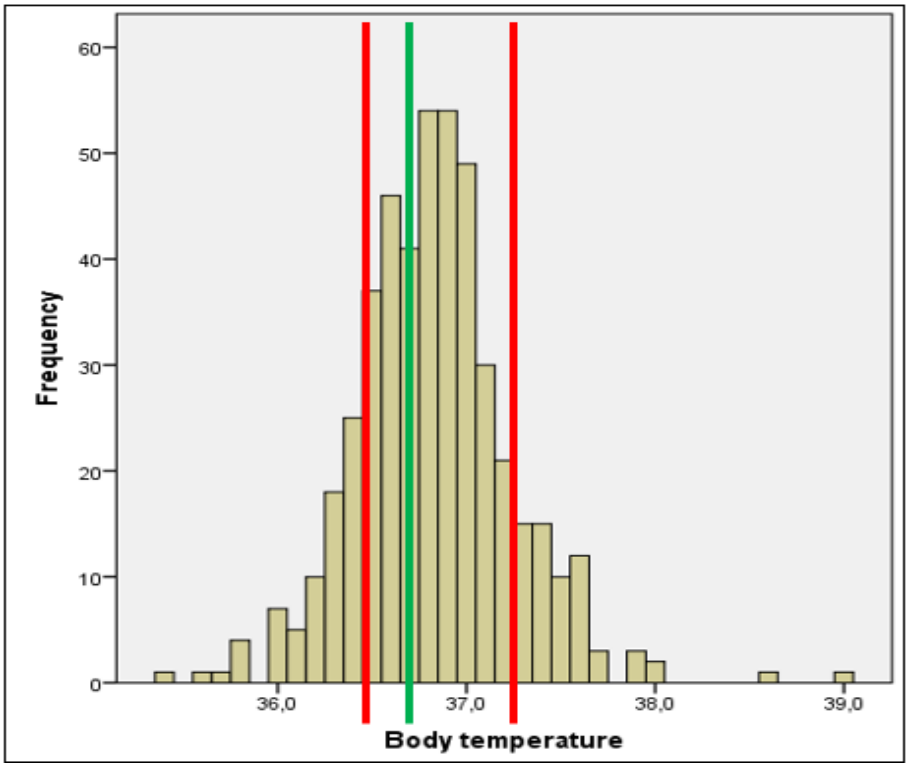

Figure 9 – Body temperature (whole cohort)

[green line: median; red lines: normothermic range]

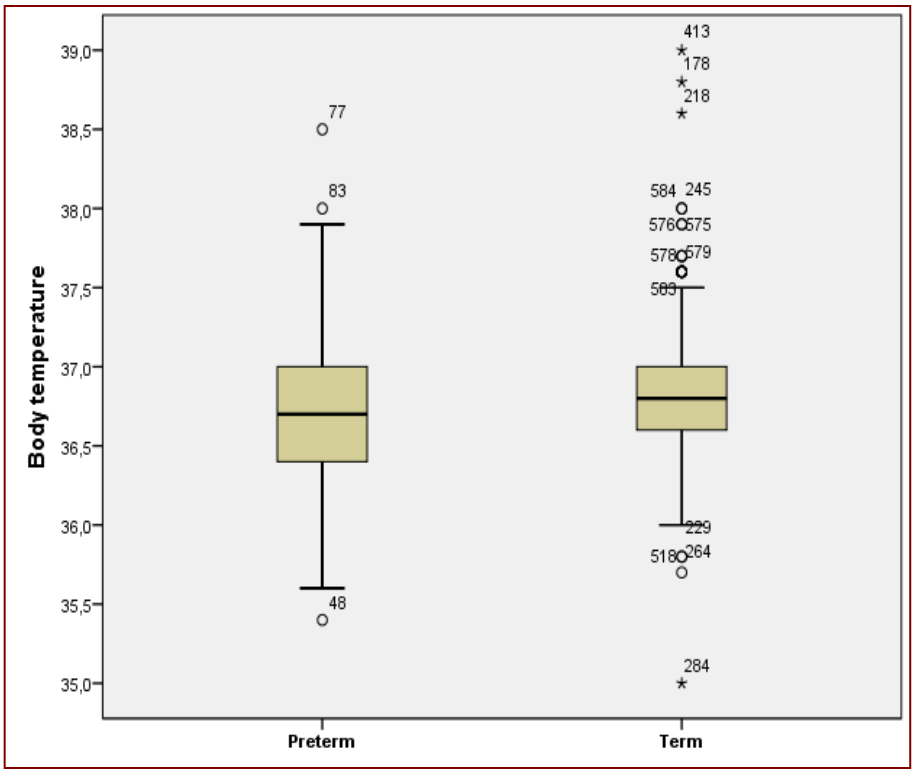

Figure 10 – Body temperature in preterm and term neonates

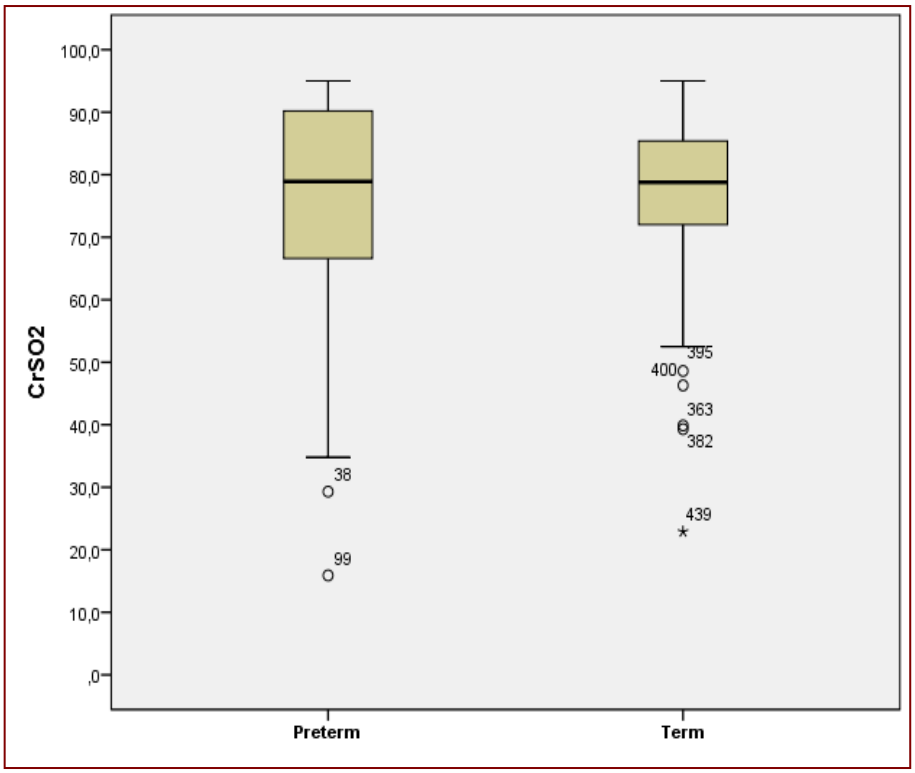

Figure 11 – $crSO_2$ (%) in preterm and term neonates

3.2 *Body temperature and $crSO_2$*

There was no significant correlation between body temperature and $crSO_2$ neither for the whole group (ρ=0.011, p=0.816) nor for preterm (ρ=-0.071, p=0.446) or term neonates (ρ=0.054, p=0.316). Results of correlation analyses are displayed in Figures 12, 13 and 14.

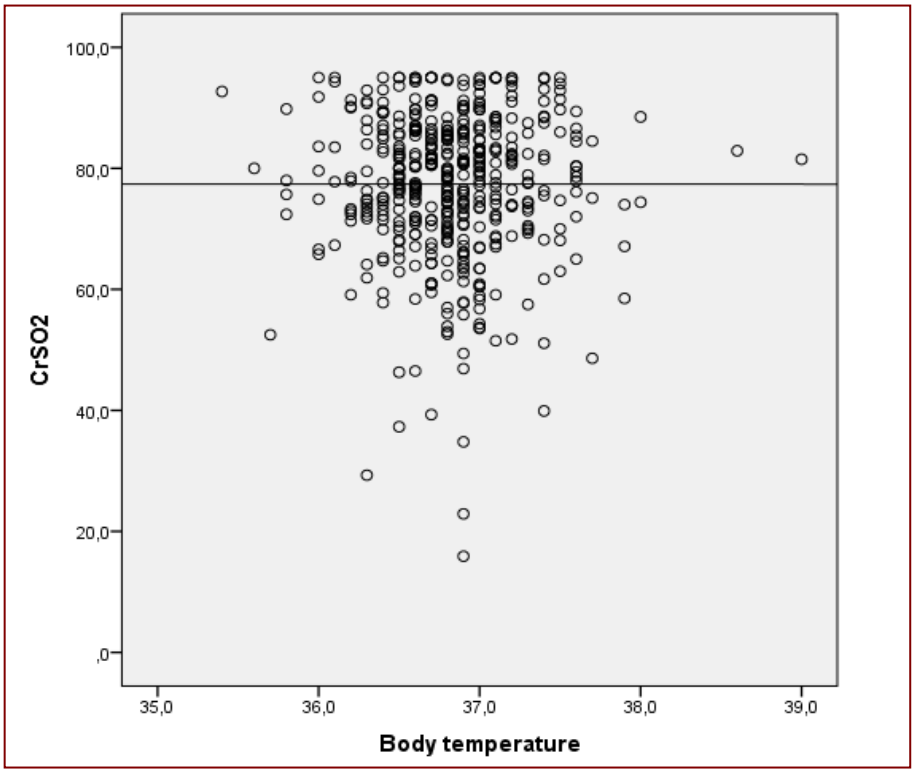

Figure 12 – Correlation between body temperature and $crSO_2$ (whole cohort)

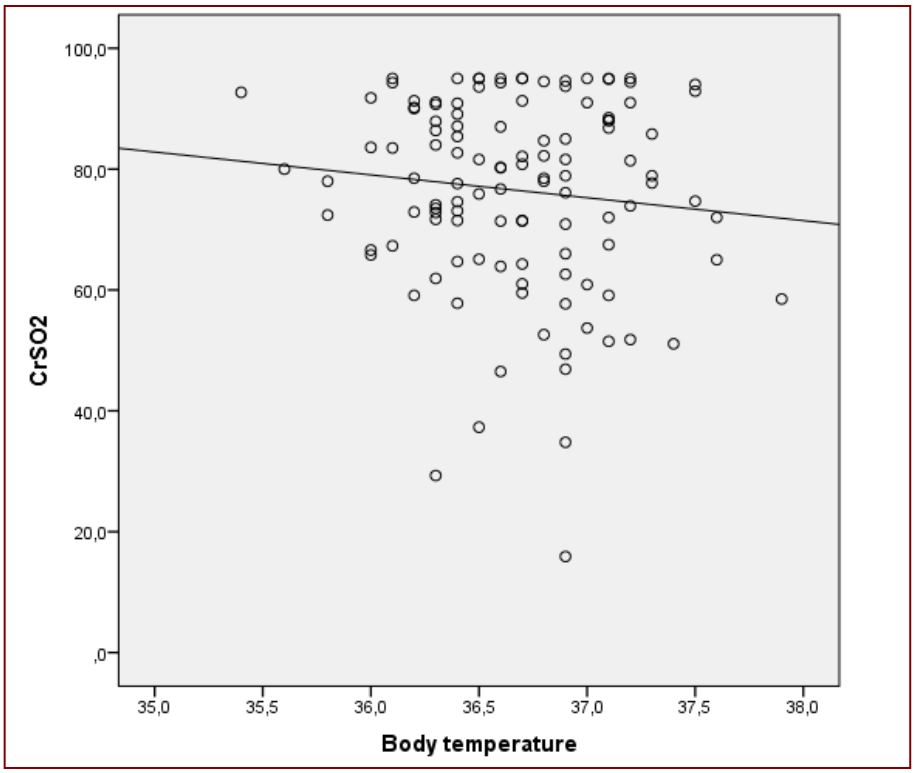

Figure 13 – Correlation between body temperature and $crSO_2$ (preterm neonates)

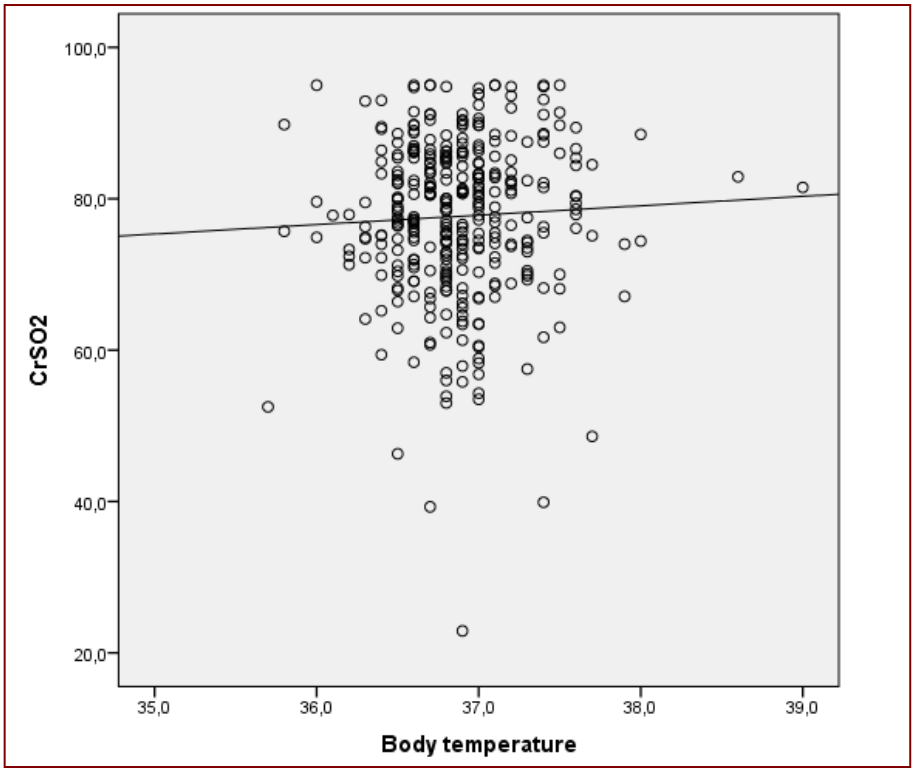

Figure 14 – Correlation between body temperature and $crSO_2$ (term neonates)

3.3 *Neonatal morbidity and body temperature*

Of the 586 neonates, 35 (6.0%) had an early or late bacterial infection, 13 (2.2%) were diagnosed with grade one IVH, five (0.9%) developed periventricular leukomalacia and one patient (0.2%) had a NEC. There was no difference in body temperature between neonates with one of the abovementioned adverse outcomes neither when testing for the combined endpoint (p=0.238) nor for individual testing.

4 Discussion

In this chapter, the motivation to perform this study will be discussed. Furthermore, most relevant results are going to be summarized and important data will be compared with other studies on this topic.

The primary goal of this thesis was to examine if there is a correlation between body temperature and cerebral oxygenation in neonates during immediate postnatal transition. While temperature measurement is an easily available diagnostic tool and has become standard of care during neonatal resuscitation, measurement of $crSO_2$ requires both equipment and experience. If there had been an association between these two vital parameters, $crSO_2$ could have been modulated in cases of hypo- or hyperthermia by proper temperature management. An association between body temperature and $crSO_2$ would have also explained the increased risk of hypothermic neonates. Therefore, this topic certainly is of interest, as it may influence practice of resuscitation and support of neonatal transition at birth.

Over the course of eight years, $crSO_2$ and rectal temperature during the first 15 minutes of life were measured in 586 neonates and analysed. The studied population included 28% preterm neonates. We found that there was no significant correlation between body temperature and cerebral oxygenation, neither for preterm nor for term neonates. However, comparing postnatal body temperature of term and preterm neonates, it turned out that preterm neonates had significantly lower body temperature, while there was no difference in $crSO_2$ between the groups. According to a literature search in electronic databases, no other study has compared $crSO_2$ and body temperature during postnatal transition so far.

4.1 *Body temperature in preterm and term neonates*

The whole study population had a median body temperature of 36.8°C. Considering that normothermia is defined as a body temperature between 36.5°C and 37.5°C, the median temperature of 36.8°C illustrates that temperatures were

mainly in the lower ranges. Still, 78.7% of neonates were normothermic per definition.

When splitting the whole cohort into preterm and term neonates, differences could be observed in body temperature. The preterm group had a median body temperature of 36.5°C, which is on the very low edge of recommended body temperature. Median body temperature in the term group was 36.8°C, which is a median difference of 0.3°C (mean: 0.1°C) compared to the preterm group. However, it has to be taken into account that 72% of studied patients were term neonates, rendering direct comparability difficult. Still, neonates were more vulnerable to hypothermia in our study, which is supported by results of published studies. (17, 22)

Factors contributing to hypothermia and associated increased morbidity and mortality in preterm neonates have been summarized in chapters 1.1 and 1.4, including poorer postnatal adaptation as well as reduced shivering thermogenesis and metabolic gain in cells.

4.2 *Correlation between body temperature and $crSO_2$*

In our analysis, no correlation between postnatal body temperature and $crSO_2$ could be found. The median $crSO_2$ of preterm neonates was 78.9% (15.9%-95.0%) compared to the median of 78.8% (22.9%-95.0%) for term neonates, each in minute 15 after birth.

The question now arises, why body temperature and $crSO_2$ do not correlate with each other. Hypothermia leads to vasoconstriction of the peripheral blood vessels, reducing the blood flow to the extremities. Consequently, heat loss over the extremities decreases, allowing the core of the body including the brain to maintain a higher temperature. Additionally, a left-shift of the oxygen binding curve happens whenever the body temperature drops below 36.5°C. This leads to a drop-in oxygen partial pressure and to a lower diffusion pressure, which is further aggravated by development of an acidosis.

In the situation of hypothermia, one could expect redistribution of blood flow from the extremities to vital organs such as the heart and brain, resulting in improved

oxygen supply of cerebral tissue and, thus, higher $crSO_2$. Despite these physiological assumptions, body temperature was not at all associated with $crSO_2$ in our study, even in a large study cohort with 586 neonates.

4.2.1 Parameters influencing cerebral oxygenation

Cerebral oxygenation is influenced by several factors.

The study from Poppernitsch et al. (67) showed for their collective of 14 term and 46 preterm neonates that maternal preeclampsia was associated with a higher $crSO_2$ in the first days of life (87% versus 77%). Parameters such as gestational age, time of rupture of the membranes, CTG anomalies, multiple births, delivery mode, and type of anaesthesia (general anaesthesia or spinal anaesthesia) did not influence $crSO_2$. In preterm neonates, however, $crSO_2$ was significantly correlated with gestational age, body length, head circumference, and haematocrit, respectively. In addition, they found that patients who got supplemental oxygen had a lower $crSO_2$ (76±8%) than those not requiring respiratory support, who had a $crSO_2$ of 83±7%.

The study ”Cerebral and peripheral regional oxygen saturation during postnatal transition in preterm neonates“ from Binder et al. (68) highlights the decreased cerebral oxygen saturation in preterm neonates receiving respiratory support. The authors hypothesized that the reason may be the increased cerebral fractional tissue oxygen extraction in the respiratory support group, which may represent the compensation for impaired oxygen delivery.

Urlesberger et al. (69) showed in a cohort of 63 neonates no differences in $crSO_2$ during the first 10 minutes after birth between vaginal delivery and elective caesarean section, emphasizing the finding by Poppernitsch et al. (67)

In a prospective cohort study from Pichler et al. (61) including 116 neonates, they found no correlation between core temperature and TOI. However, parameters that were associated with TOI were gestational age, birth weight, age, actual weight, diameter calf, subcutaneous adipose tissue, heart rate, partial pressure of carbon dioxide (pCO_2) and peripheral temperature.

Another study with 60 patients reported that neonates of mothers who smoked during pregnancy had a lower cerebral oxygen saturation. These neonates also

had a higher oxygen extraction during the first two days after delivery compared to the neonates without prenatal nicotine exposure. (70)

4.3 *Correlation between hypothermia and morbidity*

Besides the results discussed above, we also wanted to know if there is a correlation between hypothermia and neonatal comorbidities including sepsis, IVH, periventricular leukomalacia and NEC. There was no such association of low body temperature during immediate postnatal transition and later development of above-mentioned diseases in our cohort. This, however, is contrary to many other study reports.

Referring to a study from 2014 with a cohort of 635 neonates, admission hypothermia was significantly correlated with an increased risk of IVH (grades 3 and 4) and mortality. 17.2% developed a late-onset sepsis (>72 hours after birth), 4.9% of these patients suffered from NEC and 8.8% of the patients died. (71) All of these numbers are significantly higher when compared to our patient outcomes, which may explain different findings.

In the study from Audeh et al. (72) among a group of 271 very low birth weight infants below 33 weeks of gestation, a rectally measured admission temperature below 35°C was significantly associated with development of IVH (grades 3-4).

An association between mild/moderate hypothermia and mortality was found in the study “Temperature on admission among cases of neonatal sepsis and association with mortality“. (73) Of 374 patients, 33 neonates with early-onset sepsis (<72 hours) had mild and 45 had even moderate hypothermia. The mortality rate was increased among cases with hypothermia compared with normothermic neonates.

Two further observational studies indicated a correlation between hypothermia after birth and late-onset sepsis (32, 74), whereas another study could not find any association after multivariate analysis. (75)

4.4 *Limitations*

Retrospective data analyses such as our study depend on the quality of documentation and the number of available patients. Furthermore, it is not possible to correct data for potentially confounding factors. These limitations have to be acknowledged and we cannot rule out documentation-related inconsistencies or data errors completely.

Another limitation of our study is the low number of neonatal morbidities, rendering analysis of short-term outcome difficult.

5 Conclusion

We did not find a correlation between body temperature and $crSO_2$ during the immediate postnatal transition phase. 78.8% of included patients had a body temperature within the recommended range; yet, it was not possible in nearly a quarter of our patients to keep them normothermic immediately after birth, emphasizing that special attention should be paid on heat preservation including drying the infant, placing it under a radiant warmer, employing higher environmental temperature and using skin-to-skin care whenever possible. $crSO_2$ was similar in preterm and term neonates. Patients who developed bacterial infection, IVH, periventricular leukomalacia or NEC did not have different postnatal body temperatures.

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