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Aspects of neonatal intensive care and anesthesia

Thermal balance and respiratory management

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Abstract

Karlsson, V. 2018. Aspects of neonatal intensive care and anesthesia. Thermal balance and respiratory management. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1475. 46 pp. uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-0375-8.

This thesis is based on four articles originating from three studies conducted in the neonatal intensive care unit and the children's operating deparment at Uppsala University Hospital, Sweden.

The overall aim was to obtain new knowledge about thermal balance and care environment in extremely preterm infants during skin-to-skin care (SSC), evaluate different methods of intraoperative monitoring of carbon dioxide (CO_2), and to investigate how different levels of inhaled oxygen affect infants' oxygenation during anesthesia and surgery. *Study I* investigated infant thermal balance and the physical environment for extremely preterm infants during SSC. *Study II* formed part of a prospective study to assess the performance of non-invasive transcutaneous and end-tidal technique to continuously monitor CO_2 levels in the infants blood during anesthesia. *Study III* was a prospective randomized trial to investigate oxygenation during induction of anesthesia with room air versus high fraction (80%) of oxygen in healthy newborn infants.

The infants maintained normal body temperature during SSC. In comparison to care in an incubator, during SSC ambient humidity was lower and insensible water loss through the skin was higher. Compared to blood gas Pco_2, transcutaneous carbon dioxide monitoring yielded a bias of 0.3 ± 0.7 kPa, and end-tidal technique a bias of -1.9 ± 0.9 kPa. After intubation, saturation measured by pulse oximetry was lower ($p < .05$) in the group breathing room air than in the group with high oxygen ($93\% \pm 6.7$ and $99\% \pm 1.5$). None of the infants spent time below the pre-specified safety oxygen saturation targets to mandate supplemental oxygen.

This thesis provides new knowledge about early initiation of SSC after birth for extremely preterm infants, the results will be useful to guide safe routines for implementation of early SSC. These results suggest that during anesthesia would transcutaneous monitoring of carbon dioxide be beneficial, end-tidal monitoring correlated poorly to blood gas and induction of general anesthesia in newborn infants can be safely performed without the use of high levels of supplemental oxygen. Taken together, this new knowledge has the potential to improve intraoperative respiratory management.

Keywords: Neonatal, anesthesia, kangaroo-mother-care, skin-to-skin care, carbon dioxide

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To all parents who chose to let their infant contribute to these studies without any personal gain, but out of consideration of future newborn sick infants.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Karlsson V., Heinemann A.B., Sjors G., Hedberg Nykvist K., Ågren J. (2012) Early skin-to-skin care in extremely preterm infants: Thermal balance and care environment. *J Pediatr, 161(3):422-6*

II Karlsson V., Sporre B., Ågren J. (2016) Transcutaneous P_{CO_2} monitoring in newborn infants during general anesthesia is technically feasible. *Anesthesia & Analgesia, 123(4):1004-7*

III Karlsson V., Sporre B., Hellstrom-Westas L., Ågren J. (2017) Poor performance of main-stream capnography in newborn infants during general anesthesia. *Paediatr Anaesth, 27:1235-1240*

IV Karlsson V., Sporre B., Fredén F., Ågren J. (2018) Randomized controlled trial of room air vs. 80% oxygen for induction of neonatal anesthesia: Feasibility and safety. *In manuscript*

Contents

Abbreviations

BG	Blood gas
ET	End-tidal
FiO_2	Fraction of inspired oxygen
GA	Gestational age
HIOX	High oxygen
NICU	Neonatal intensive care unit
OR	Operating room
PCA	Postconceptional age
PCO_2	Partial pressure of carbon dioxide
PO_2	Partial pressure of oxygen
RA	Room air
ROS	Reactive oxygen species
SSC	Skin-to-skin care
TC	Transcutaneous

Introduction

The dynamic field of neonatal medicine is steadily evolving. Improvements in both medical and nursing care have contributed to a higher rate of survival, particularly in preterm infants (with a gestational age of less than 37 weeks) (1). Many critically ill newborn infants in need of intensive care are at risk of adverse outcome, and some will be discharged from the hospital with significant challenges (2, 3). In this vulnerable population it is reasonable to assume that *how* the care is provided matters, and efforts to optimize current practice have been shown to improve outcome (4, 5). Significant progress has been made in several areas of neonatal care provision including thermal care (6, 7), parental involvement (8), respiratory management (9), infection prevention (10), and nutritional support (11).

Avoidance of hypothermia and cold stress has long been known to improve the outcomes of preterm infants (12), and this knowledge led to the universal practice of nursing infants in incubators, under radiant warmers, in heated beds, and/or using skin-to-skin care (SSC). Until quite recently SSC was a measure reserved for term or moderately preterm infants (13) but it is now increasingly being applied in less-mature infants to preserve body heat and improve temperature stability (14). SSC also confers other important advantages such as reduced parental and infant stress (15), improved cardiorespiratory stability (7, 16), appropriate sensory stimulation (17), and higher rates of breastfeeding (18). All these factors could be expected to contribute to a better central nervous system growth and development, thereby opening a window for early intervention.

Respiratory distress is a frequent cause of neonatal intensive care, and management of respiration in newborn infants is both critically important and resource consuming. Although basic physiological principles still apply, the use of respiratory support in neonates often requires approaches and methodologies that are different from those used in children and adults. Mechanical ventilation and oxygen therapy are associated with significantly harmful side effects in themselves (19, 20). The avoidance of volume trauma (21), hypocapnia, hypercapnia (22), hypoxia, and hyperoxia (23) during assisted ventilation has been shown to reduce the risk of adverse long-term pulmonary and neurological outcome (24). General anesthesia during surgery is a unique situation when assisted ventilation is almost always required, even in

an otherwise healthy infant without compromised respiratory function. Respiratory support during general anesthesia is complicated by the type of surgery *per se* and the limited visibility and availability of the infant.

During general anesthesia, levels of both carbon dioxide and oxygen need to be monitored to guide the respiratory support. There are several different methods for intermittent measurement and/or continuous tracing of carbon dioxide levels in the infants' blood (25). For any given patient, care culture tradition dictates that these methods are applied differently depending on whether the patient is in the neonatal intensive care unit (NICU) or in the operating room (OR). The evidence base for this difference in practice is largely unknown.

Supplemental oxygen plays an important role in critical care (23), but excessive use is known to be harmful (26). With increasing understanding of the potential negative impact of oxygen on processes such as the regulation of cerebral blood flow (27) and the induction of apoptosis by oxygen stress (28), clearly oxygen should be administered with caution to avoid hyperoxia (29).

Today, care of newborn infants aims beyond survival. Efforts to optimize aspects of critical care that are central to the maintenance of normal physiology could be expected to minimize harm and improve neurocognitive outcomes.

Background

Being newborn

The neonatal period involves a dynamic process of adjustment to the extrauterine environment (30). In a full-term healthy infant, the transition from fetal life usually occurs without complications and with no involvement of neonatal care. The newborn's unique physiology will only be apparent in situations when the infant fails to adapt to extrauterine life due to premature birth, or sickness (31). Transition to extrauterine life is characterized by establishment of air breathing and oxygenation via the lungs, and by changes in the cardiovascular system. The fetus is adapted to the low-oxygen low oxygen environment and produces fetal hemoglobin with a high affinity for oxygen, which is also important in the newborn period to ensure sufficient delivery of oxygen to the tissue. Infants born preterm carry an increased risk of complication in transition from fetal to extrauterine life, due to surfactant deficiency, and increased risk of hypothermia, hypoglycemia.

Body temperature and skin-to-skin care

The establishment and maintenance of a normal body temperature is of vital importance to preterm infants, and improves their chances of survival (12). Measures to provide heat and limit heat loss in infants during intensive care include incubators, radiant warmers, heated beds, and SSC. Care in closed incubators has the advantage that both heat and moisture can be added, thus mitigating the child's fluid and heat loss, but physically separates the child from its parents and often results in a relatively unstable body temperature (32).

SSC has several favorable effects (15, 17, 33-36) in addition to the attainment of thermal balance (32), and the method is increasingly used in modern neonatal care (37). It has been shown to provide comfort, decrease stress response (15), and relieve pain (38). Exposure to repeated pain-related stress in the neonatal period is known to lead to poor neurodevelopment, but medical pain treatment has side effects for the newborn and non-pharmacological interventions are essential. SSC is a safe method of pain relief as well as an opportunity for the parent to comfort their infant. In comparison to incubator

care, SSC has physiological stabilizing effects (32). Early initiation of SSC improves the transition to extrauterine life by stabilizing thermal and cardiorespiratory physiology (39). During SSC the infants sleep longer and are less disturbed than those not offered SSC (34). Sleep allows rest from discomfort, and is essential for brain growth and development.

SSC provides an excellent care environment regarding thermal balance for healthy moderately preterm infants (born at a gestational age of < 32 weeks and > 28 weeks). However, infants born extremely preterm (born at a gestational age of ≤ 27 weeks) are at particular risk for hypothermia, and require a strictly controlled care environment to maintain thermal homeostasis. In these infants, evaporative heat loss because of poor skin barrier function is the dominant mechanism of heat loss early after birth (40). Because the loss of fluid from the skin is inversely related to ambient relative humidity, creating a high relative humidity microenvironment close to the skin will reduce fluid loss and improve thermal balance (41). Furthermore, the high body surface-to-mass ratio and poor capacity for thermogenesis seen in extremely preterm infants implies that these infants need to gain heat from the environment to avoid hypothermia and cold stress (42). In modern neonatal intensive care, such an environment is most often created by maintaining the infants in intensive care incubators with high air temperature leading to convective heat gain (43) in combination with high humidification. The care environment during SSC in extremely preterm infants requiring neonatal intensive care, including respiratory support, has only been studied to a limited extent (14, 44, 45).

Respiratory management

Advances in perinatal care and much of the progress is thanks to improved respiratory management (46). Interventions that have increased the probability of survival without major morbidity include the avoidance of hypocapnia, hypercapnia, hypoxia, and hyperoxia; use of surfactant; non-invasive ventilator support when possible; and use of volume controlled ventilation when intubated (47).

Carbon dioxide

Carbon dioxide is a potent vasoactive substance, and there is a clear relation between the partial pressure of carbon dioxide (PCO_2) and cerebral perfusion. Both hypercapnia (ventilation leading to elevated levels of carbon dioxide) and hypocapnia (ventilation leading to low levels of carbon dioxide) have adverse physiological effects, and can be particularly harmful for the sick newborn and/or premature infant (48).

Hypocapnia reduces cerebral blood (49) flow, which might result in ischemia. Accordingly, hypocapnia has been shown to increase the risk of damage to the central nervous system such as periventricular leukomalacia (22, 50), a condition that is directly related to subsequent sensorimotor disabilities and developmental delay.

In preterm infants, the immature vasculature of the periventricular area is particularly vulnerable to fluctuations in cerebral perfusion, and rapid changes in carbon dioxide levels are also a risk factor for intracranial hemorrhage (51).

Hypercapnia is better tolerated by the infant, but a rapid increase in carbon dioxide leads to a compensatory increase in blood flow to the brain (52). In the immature individual with limited autoregulation of cerebral blood flow (27), the increased blood flow is linked to impaired functioning of the blood brain barrier, cerebral edema, and intracranial hemorrhage.

Thus, the prevention of hypo- and hypercapnia mandates the use of frequent and precise monitoring in all infants requiring assisted ventilation.

Monitoring of carbon dioxide

Blood gas

Arterial blood gas (BG) analysis from intermittent sampling from an indwelling catheter is considered the gold standard in measuring P_{CO_2}. However, this is an invasive procedure and provides only an intermittent estimate of what is frequently a continuously changing value. Placing arterial lines in the tiniest infants is not only painful, but also carries a risk of vascular thrombosis (53).

Transcutaneous technique

In the NICU, continuous carbon dioxide is almost exclusively obtained by transcutaneous (TC) measurements. This is considered to be the standard of care both for absolute measurement and for trend analysis, and TC readings have been found to correlate well with blood P_{CO_2} (54-56) However, the use of TC carbon dioxide monitoring in intraoperative care of neonates is limited, and its accuracy has not been established in this population.

End-tidal technique

End-tidal (ET) monitoring of carbon dioxide (or capnography, as it is more commonly referred to in the OR) is a standard of care in the OR. This technique approximates P_{CO_2} by measuring the carbon dioxide in each exhaled

breath. ET monitoring can broadly be divided into two groups: main-stream (flow-through) devices and side-stream (aspirating) devices. The main-stream technique uses an adapter placed between the y-piece and the endotracheal tube, and carbon dioxide is analyzed with infrared light in the exhaled air flowing through the adapter. In the side-stream method, air is continuously aspirated at approximately 100 ml/min through a thin catheter into an analyzer which again uses infrared light. When applied in small children, the main-stream technique is known to be the more accurate of the two methods (57).

Oxygen

Oxygen, was first discovered in 1772 and introduced into the care of the newborn in 1930; as of today, it is probably the most widely used drug in the neonatal period. Oxygen was soon found to improve survival in patients with lung impairment, but concern was raised regarding side effects such as mental changes in patients breathing 100% oxygen. The toxic nature of oxygen has been of concern in neonatal care since the 1940s, when it was recognized that the use of a high fraction of inspired oxygen (FiO_2) can cause retinopathy of prematurity.

Supplemental oxygen has an important role in neonatal anesthesia and intensive care, but excessive use causes hyperoxia, which is known to increase mortality in neonates (26). In preterm infants, hyperoxia is related to an increase in retinopathy of prematurity (51), bronchopulmonary dysplasia, and brain damage (58). The optimal level of oxygen content in the blood of the preterm newborn infant has not been established (51, 59, 60).

Toxicity of oxygen occurs when more oxygen is administered than needed, thereby inducing hyperoxia and formation of reactive oxygen species (ROS). Under normal physiological conditions, oxygen is metabolized to form H_2O and a small amount of ROS. The production of ROS depends on the balance between the O_2 concentration in the tissue and its antioxidant capacity (61). If the ROS exceeds the antioxidant capacity, free radicals will be formed and cause oxidative stress. Free radicals are aggressive, causing damage to DNA, proteins, and lipids and inducing apoptosis and necrosis (61, 62). It is not known how short an exposure to unnecessary oxygen is needed to trigger the formation of excess ROS. Newborn infants have decreased antioxidant defenses and are highly susceptible to oxidative stress (63). Oxidative stress has been quantified and measured by several methods, including analysis of isoprostanes in blood and/or urine. Isoprostanes have clearly been shown to be the most reliable indicator of oxidative stress *in vivo* (64).

In adults (65) and older children (66), a high FiO_2 during anesthesia induction causes smaller portions of the lung to collapse, a condition known as atelectasis. The degree of atelectasis can be indirectly assessed by measurement of the degree of lung collapse. It is not known whether the oxygen concentration during anesthesia induction also has an impact on the development of atelectasis in newborns.

Within neonatology, the risks of hyperoxia and subsequent oxidative stress are well known. This knowledge has changed clinical practice and the way oxygen is used. At present, it is recommended to use 21% O_2 and avoid supplementary oxygen during resuscitation of newborn infants (67), and the most recent guidelines recommend saturation targets of 90-95% for neonatal infants (47, 68). Clinical practice in anesthesia is still to use a high FiO_2 during induction and maintain at least 30% O_2 in the exhaled air during maintenance, which will most likely induce hyperoxia (23). The rationale for this practice is to create safe margins to avoid hypoxic events.

Monitoring of oxygen

Pulse oximetry

Pulse oximeters became available in the NICU in the 1980s, and today oxygen levels in the blood are routinely monitored with pulse oximetry in all infants in need of assisted ventilation and/or supplementary oxygen (29). The reading from pulse oximetry is of such value that it is referred to as the "fifth vital sign". The monitors are an excellent tool for detecting hypoxemia, but were not designed to display hyperoxia and cannot easily separate normal oxygenation from hyperoxia. Important, with high values (>95%) displayed on the pulse oximeter little information is known about the partial pressure of oxygen (PO_2).

Transcutaneous partial pressure of oxygen

TC electrodes were introduced in the 1970s, and with them the possibility to monitor PO_2 (69). This technique has been less extensively used for this purpose since pulse oximetry became available, but remains a useful non-invasive tool to detect hyperoxia.

Near-infrared spectroscopy

Near-infrared spectroscopy is an alternative method, adapted for clinical use in neonates, for monitoring oxygen content of the tissue (70). It non-invasively measures cerebral oxygen saturation in the tissue (1-2 cm below the sensor) reflecting the average saturation in arterioles, veins, and capillaries. The method provides a reflection of the balance between tissue oxygen supply and demand.

Impetus for this thesis

This research was inspired by questions raised during daily bedside nursing while caring for infants and their parents in the NICU and children's OR.

Increasing evidence of the positive impact of SSC on the newborn infant and their parents, in addition to its ability to promote thermal balance, has led to its becoming an important intervention in neonatal intensive care. This evidence supports initiation of SSC without delay in the moderately preterm infant. However, performing SSC with ventilated extremely preterm infants remains challenging; this, along with a lack of evidence in this group, may inhibit early initiation of SSC for these infants.

Anesthesia and surgery are sometimes a necessary part of the care for infants requiring neonatal intensive care. Strong evidence from animal studies suggest that exposure to anesthetic agents in a period of rapid brain development results in adverse outcome. Some studies suggest that similar problems occur in infants exposed to anesthetic agents, and it has been argued that it is necessary to also consider other factors during the perioperative period that might affect cerebral perfusion and add to the negative effects of anesthesia. Infants in the NICU are a vulnerable group already at risk of adverse outcome.

Overall, the knowledge about the adverse effects of hypo- and hypercapnia and hyperoxia further strengthens the importance of maintaining adequate ventilation during anesthesia. Implementation of knowledge from neonatology into neonatal anesthesia might be of value when deciding the best possible care. Today, there is a gap between the evidence-based care established in the NICU and clinical practice in the OR. Could this gap be eradicated if practice from the NICU is evaluated during anesthesia and surgery? The new knowledge could have the potential to improve quality of care if used to guide the development and implement of practices to prevent hypocapnia and hyperoxia in routine anesthesia.

Overall and specific aims

The aims of this thesis were to obtain new knowledge about thermal balance and care environment in extremely preterm infants during SSC, to evaluate different methods of intraoperative monitoring of carbon dioxide, and to investigate how different levels of inhaled oxygen affect the infants' oxygenation during anesthesia and surgery.

The specific aims of the three studies were:

I To investigate infant thermal balance and the physical environment for extremely preterm infants during SSC.

II To assess the performance of non-invasive TC and ET techniques to continuously monitor carbon dioxide levels in the infants during anesthesia and ongoing surgery.

III To investigate infants' oxygenation during induction of anesthesia with room air (RA) versus high (80%) oxygen (HIOX) in healthy newborn infants undergoing planned surgery.

Materials and methods

These clinical studies were all performed at Uppsala University Hospital, study I in the NICU and II – III in the childrens OR . Study I includes extremely premature infants during their first week of life, study II includes both term and preterm infants, scheduled for surgery and ≤ 44 weeks postconceptional age (PCA) on study day, and study III included term and near term infants (born at a gestational age of < 37 weeks ≥32 weeks) scheduled for surgery, without any prior need of assisted ventilation or supplemental oxygen and being ≤ 44 weeks PCA.

Table 1. Overview of study design, study population, number of participants and analysis

Paper	**I**	**II**	**III**	**IV**
Design	Prospective descriptive study	Prospective descriptive study	Prospective descriptive study	Randomized, descriptive, and comparative study
Study population	Extremely preterm infants (GA < 28w)	Infants ≤ 44 w PCA and scheduled for surgery	Infants ≤ 44 w PCA and scheduled for surgery	Infants ≤ 44 w PCA and scheduled for surgery
Participants	n=26	n=25	n=23	n=35
Analysis	Descriptive comparative statistics	Descriptive comparative statistics	Descriptive comparative statistics	Descriptive comparative statistics

GA: gestational age; PCA: postconceptual age

Study I

Study I was a prospective study of a cohort of extremely premature infants cared for in the NICU. The aim was to investigate the infants' thermal balance and the care environment during SSC.

Setting

This study was conducted in the NICU at Uppsala University Hospital, Uppsala, Sweden. This NICU has three intensive care rooms, each with four care spaces, and every care space is equipped with an adult bed next to the incubator.

Study sample

A consecutive sample of 26 infants with a mean birth weight of 600 g and GA ranging from 22+4 to 26+5 was included (Table 2). The infants had a mean postnatal age of 5 days (range: 2-9 days) on the day of the study.

Table 2. Infant characteristics (n=26) at birth, and at day of study

	At birth	At day of study
Gestational age (weeks)	24 (22-26)	
Postnatal age (days)		5.0 (2-9)
Weight (g)	666 (400-1064)	600 (365-900)
Ventilator (n)	24	11
Nasal CPAP (n)	2	15

Values are given as mean (range). CPAP, continous positive airway pressure; BW, Birth weight

Data collection

Background data on the infants' status, such as weight change and daily fluid intake, was collected from each infant's medical records. Body temperature, transepidermal water loss, ambient temperature and humidity, and physiological variables were measured before, during (Figure 1), and after SSC, allowing individual comparisons of the different modes of care and their effect on thermal homeostasis. Body temperature was measured in °C as both axillary temperature and skin temperature. Skin temperature was continuously measured from the lower back of the infant, and axillary temperature was measured intermittently according to standard clinical care procedures. Evaporimetry was used to determine transepidermal water loss.

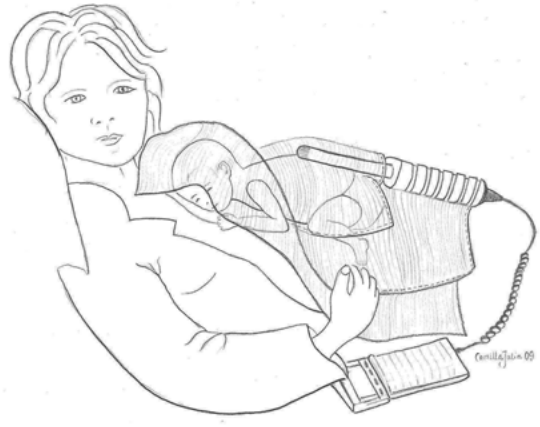

Figure 1. Measurement setup during SSC. The infant is placed skin-to-skin and covered by a vapor-impermeable blanket with a relative humidity and air temperature measurement probe in place.

Data analysis

Student's t-test for paired observations was used to test for statistical significance. Version 20.0 of the SPSS software package was used for the statistical analyses, and a p-value of less than .05 was considered statistically significant.

Study II

Study II was a prospective comparative study with a consecutive sample of infants < 44 weeks postconceptional age (PCA), cared for at the NICU and scheduled for surgery. The study was performed to assess and elucidate the properties of non-invasive methods for continuous monitoring of carbon dioxide.

Setting

The study was performed at the Operating Department for children at Uppsala University Hospital, Uppsala, Sweden. According to the prevailing practices at the department at the time, P_{CO_2} was monitored with ET main-stream capnography and the side-stream technique was used solely for monitoring of anesthetic agents and oxygen.

Study sample

The participants consisted of a consecutive sample of infants with a GA of 23 to 41 weeks. At the time of the study, the infants' weight ranged between 670 and 4110 grams and thirteen infants needed respiratory support prior to anesthesia and surgery. Medical background variables were retrieved from the medical chart.

Data collection

PCO_2 (kPa) was continuously measured by use of the TC and ET techniques, and recorded at 1-minute intervals. BG analysis was performed using capillary blood samples obtained from the infant's warmed foot and analyzed for PCO_2.

Data analysis

Transcutaneous technique

A mean was calculated from the last five TC PCO_2 values prior to BG sampling. The agreement between TC PCO_2 and BG was evaluated using Bland-Altman plotting (47). To avoid bias from repeated measurements, the Bland-Altman analysis was performed using one (the first) sample pair per infant. Any association between the TC-BG difference and selected infant parameters was evaluated using Spearman's test and compared using Student's paired t-test.

End-tidal technique

Bland-Altman plotting (47) was used to evaluate the agreement between ET PCO_2 and BG. To avoid bias from repeated measurements, the Bland-Altman analysis was performed using one (the first) sample pair per infant. Pearson's correlation coefficient was calculated to evaluate whether need of respiratory support prior to anesthesia was associated with the ET-BG difference.

Version 20.0 of the SPSS software package was used for the statistical analyses, and a p-value of less than .05 was considered statistically significant.

Study III

Study IV was a prospective randomized trial of a cohort of 35 newborn infants (PCA < 44w) scheduled for surgery. The aim was to investigate how different fractions of inhaled oxygen affected the infants' saturation/oxygenation during anesthesia induction. This article is a first report

from the ANOXneo study (ANesthesia-OXygen-neo) registered in ClinicalTrials.gov (study ID: NCT02698020). The primary outcomes of ANOXneo are the occurrence of hyperoxia and differences in biomarkers of oxidative stress in infants managed with RA versus HIOX throughout the anesthesia.

Settings

This study was performed at the Operating Department for children at Uppsala University Hospital, Uppsala, Sweden.

Study sample

The participants comprised 35 infants. The inclusion criteria were:
$\leq$ 44 PCA, being scheduled for surgery, and having no need of assisted ventilation or supplemental oxygen prior to anesthesia and surgery. After parental consent, each infant was randomized to either the RA intervention group or the HIOX control group.

Data collection

Background data on the infants were obtained from the infants' medical records. Oxygenation was continuously measured by pulse oximetry (SpO_2), TC PO_2, and regional cerebral oxygen saturation ($rScO_2$).

Prior to induction of anesthesia, all infants breathed spontaneously in RA. Anesthesia was induced with inhalational anesthesia in combination with intravenous muscle relaxant. At start of induction, all infants were ventilated with sevoflurane and either RA (FiO_2 23%) or HIOX using pressure control mode for three minutes via the anesthesia delivery ventilator (Figure 2).

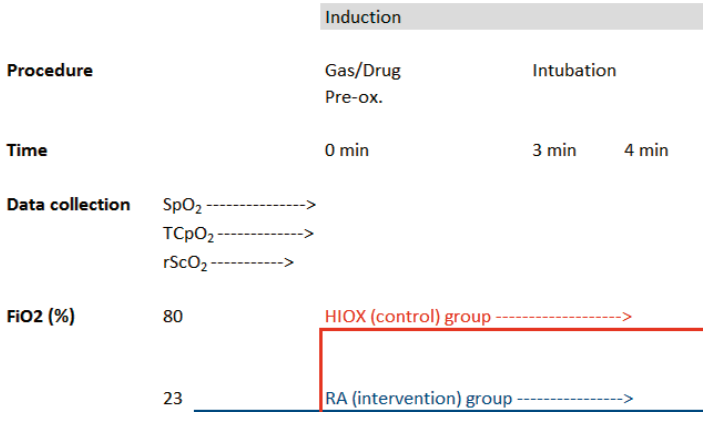

Figure 2. Flowchart of anesthesia induction

All procedures were guided by a timer and documented with a camcorder to allow real-time guidance of every step of the procedure and for detailed subsequent timing and recording of monitoring data.

Data analysis

Data were analyzed using descriptive and comparative statistics. Descriptive statistics were used to delineate how SpO_2, $rScO_2$, and TC PO_2 were affected, and comparative statistics were applied for comparison within groups and between groups. We did not assume the oxygenation to be normally distributed, and accordingly the Mann-Whitney U test was used for these comparisons while Student's t-test was used for comparison of infant characteristics.

A p-value of less than .05 was considered statistically significant. All data were analyzed using version 24.0 of the SPSS software package (IBM Corp, Armonk, NY, USA).

Ethical considerations

The studies were approved by the Regional Research and Ethics Committee of Uppsala. All infants were included after informed parental consent, and parents could withdraw participation at any time. Invasive procedures needed for the studies were either coordinated with otherwise prescribed blood sampling or performed during anesthesia. All methods evaluated in the studies were all approved and implemented in the care of newborns, but in settings different from how they were applied in the current investigations.

Studies I-II, included prospectively collected observational data obtained during routine care to evaluate existing practice (Study I) and/or the perfor-

mance of additional monitoring techniques (Study II). While applying a more extensive monitoring than routinely used, the measurements and the data obtained did not impact patient management.

The practice of early skin-to-skin care of extremely preterm infants were at the time of Study I already an established practice in our unit, but had not been previously evaluated. Further, while transcutaneous carbon dioxide monitoring of respiration is a methodology widely applied in neonatal care, its application during anesthesia in Study II was an effort to evaluate its performance in the OR setting where previous data were scarce. The lack of performance data on intra-operative end-tidal carbon dioxide monitoring in neonates was one basis for Study II. The randomized controlled trial in Study III included an intervention that reflects the more restrictive approach to supplemental oxygen that is indeed evidence-based standard in neonatal care. While acknowledging that induction of anesthesia with room-air represents a novel approach that deviates from current practice at our institution, it was accompanied by rigorous monitoring and safety measures. Further, the existing practice of uniformly exposing neonates to high fractions of inspired oxygen in the OR cannot be considered to rely on a solid evidence-base and may be questioned.

Summary of findings

Paper I

Measurements were performed for a mean SSC duration of 95 minutes (range: 60-180 minutes) at a mean postnatal age of 5 days (range: 2-9 days).

Infant temperature

There was a slight drop in axillary temperature from pretest (36.8 ± 0.0) to posttest (36.7 ± 0.1). The infants maintained a normal body temperature during SSC. Transfer to and from SSC was associated with a drop in skin temperature which then reversed itself during SSC.

Care environment

The care environment during SSC differs from that in the incubator, with a lower relative humidity (42% vs. 68%; $P < .001$). Ambient air temperature was 32.1 °C during SSC and 32.9 °C during incubator care ($p = .11$).

Insensible water loss through the skin

In line with the lower relative humidity outside the incubator, estimated insensible water loss through the skin was higher for SSC than for incubator care ($p < .001$).

Paper II

Study II included BG and TC P_{CO_2} data from 25 infants, obtained during anesthesia and surgery.

All infants

The difference between TC and BG was 0.3 ± 0.7 kPa (mean ± standard deviation), giving a precision of 1.47 kPa (Figure 3). Of the 25 sample pairs, 19 (76%) displayed a difference of <1 kPa (99% confidence interval: 48%–92%; $p = .016$).

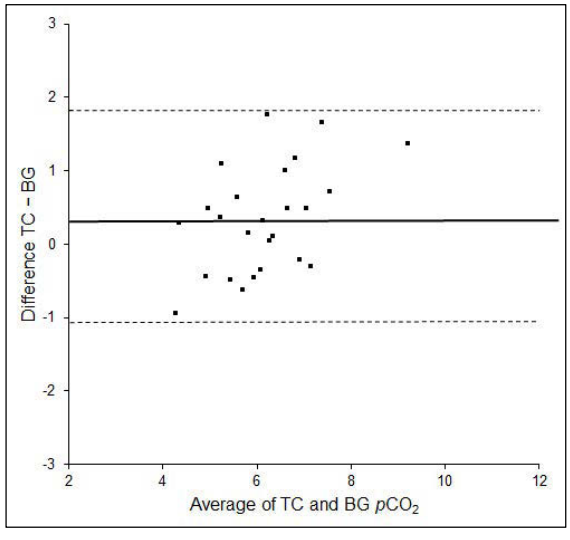

Figure 3. Bland–Altman plot of the difference between transcutaneous (TC) and blood gas (BG) Pco_2 (n = 25) vs. the average of the 2. The lines represent the TC to BG bias (solid line) and the precision (±2.10 × SD; broken lines).

Subgroup analysis

The BG to TC PCO_2 difference was 0.1 ± 0.7 kPa in infants with a postnatal age < 1 week, and 0.1 ± 0.7 kPa in infants born at term (GA: > 37w).

Paper III

Data for ET PCO_2 and BG PCO_2 were obtained from 23 infants, 14 of whom needed respiratory support (mechanical ventilation and/or continuous positive airway pressure with supplemental) prior to anesthesia.

All infants

ET PCO_2 was consistently lower than the corresponding BG values in all sample sets. The difference between ET and BG was -1.7 ± 0.9 kPa (mean ± standard deviation) and the precision being -1.9 kPa (Figure 4).

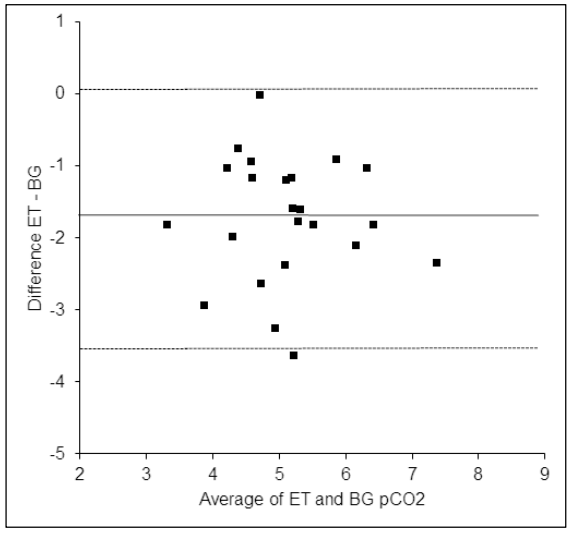

Figure 4. Bland-Altman plot of the difference between endtidal (ET) and blood gas (BG) carbon dioxide Pco_2; kPa at the induction of anesthesia (n = 23) vs. the average of the two. The lines represent the ET to BG bias (solid line) and the precision (±2.1 SD; broken lines)

Subgroup analysis: Relation to pulmonary disease

In the 14 infants who needed respiratory support prior to anesthesia, the ET to BG P_{CO_2} difference was -1,9 ± 0,8 kPa as compared with -1,5±1 kPa in the infants (n = 9) without need for respiratory support

Paper IV

Of the 35 infants enrolled, 17 were randomized to the RA intervention group and 18 to the HIOX control group. There were no differences in background characteristics between the groups (GA: 39 w).

Pattern of oxygenation

After intubation, saturation measured by pulse oximetry was lower ($p < .05$) in the group breathing RA than in the HIOX group (93% ± 6.7 and 99% ± 1.5, respectively). In the HIOX group, TC P_{O_2} increased ($p < .05$) from start of induction (8.2 ± 2.3 kPa) to end of induction (18.3 ± 9.7 kPa). Regional cerebral oxygen saturation was within the normal range at all times, and not statistically different between the groups.

Time and values outside the target SpO_2 range

None of the infants spent enough time below the pre-specified safety oxygen saturation targets to mandate supplemental (or increased) oxygen. In the RA group, 6 of 17 infants desaturated below 90% on one or more occasions, while none of the 18 infants in the HIOX group had SpO_2 below 90%.

Discussion

Paper I

We present detailed data on thermal balance and physical care environment during early postnatal SSC of extremely preterm infants receiving neonatal intensive care, including mechanical ventilation. After SSC, the infants maintained their axillary temperature within the normal range. Transfer of the infant to and from SSC resulted in a drop in skin temperature, but this reversed itself during SSC. Drop in skin temperature during transfer to/from SSC has also been reported by other researchers (14). Optimizing routines for this transfer might further improve the performance of SSC. The physical environment during SSC is characterized by a lower relative humidity than during incubator care, and the magnitude and direction of heat flux differ between different care environments and modes of care.

Our data clearly demonstrate that SSC results in higher evaporative heat losses due to lower relative humidity compared with incubator care. However, despite the higher evaporative and convective heat losses, the conductive heat transfer to the infant during SSC is apparently sufficient to result in a net heat gain. Approximately one-third of the infant's skin surface would be exposed to the lower relative humidity during SSC, resulting in an increased water loss through the skin (1g/kg) during SSC. This small increase in water loss through the skin should not affect the infant's fluid balance if SSC is limited to a few hours per day during the first days of life.

Paper II and III

Monitoring of PCO_2 during assisted ventilation is of vital importance in the newborn infant. In Studies I and II we evaluated different methods for non-invasive continuous monitoring of PCO_2 during anesthesia and surgery. We found TC monitoring to be feasible during surgery and ET monitoring to be imprecise. Continuous monitoring of PCO_2 during the different phases of anesthesia and surgery could be expected to positively impact on the intra-operative respiratory management of the newborn.

Transcutaneous monitoring of carbon dioxide

The present relatively small investigation does not demonstrate that TC measurements accurately reflect P_{CO_2} in newborn infants during general anesthesia. Although the TC P_{CO_2} determination in 76% of the infants was within our acceptable range of ±1 kPa of the concurrent BG P_{CO_2}, this did not reach statistical significance at $p < .01$.

The recognition that extremes of P_{CO_2} even for brief periods of time are associated with long term neonatal morbidity emphasizes the need for reliable and continuous monitoring of P_{CO_2} during general anesthesia. Arterial BG analysis from intermittent sampling via an indwelling catheter is considered the gold standard in measuring P_{CO_2}. However, the dynamics of neonatal anesthetic management mandate the use of continuous measurements.

It could be argued that management of a newborn in the NICU is distinct from that in the OR, where access to the small patient is limited by sterile draping and the requirement to maintain thermal stability. To measure TC P_{CO_2} the electrode needs to be calibrated, heated, and repositioned at regular intervals. However, in our study these procedures did not form a barrier to the performance of measurements, and we believe that TC P_{CO_2} monitoring could be applied after a minimum of staff training.

The small size of our study prevented us from demonstrating that TC monitoring of P_{CO_2} in the OR is sufficiently accurate for clinical use. However, previous research (25) has concluded that TC is superior to ET and should be used in NICU settings for noninvasive trend monitoring of P_{CO_2}, particularly in infants with pulmonary disease. We believe that TC P_{CO_2} is a valuable and under-utilized tool even for intra-operative monitoring of carbon dioxide, and that routine application of TC P_{CO_2} might improve the management of newborn infants during general anesthesia.

End-tidal monitoring of carbon dioxide

Our results indicate that ET monitoring of CO_2 with main-stream capnography during anesthesia and surgery in small infants might be imprecise. The large bias and poor correlation between ET and BG P_{CO_2} render the method a limited clinical value. Hypercapnia (BG $P_{CO_2} > 6$kPa) increased the discrepancy between ET and BG values. Importantly, infants with pulmonary disease needing respiratory support prior to anesthesia demonstrated an even larger bias between ET and BG P_{CO_2}. In our investigation, the ET values obtained from infants requiring respiratory support prior to anesthesia were essentially unrelated to their true CO_2.

This study is the first to include newborn infants with pulmonary disease and undergoing thoracic and upper abdominal surgery. We found no correlation between ET and BG P_{CO_2} for the infants who needed respiratory support prior to anesthesia. This is in accordance with previous published data from studies performed in NICU settings (54, 71) suggesting that the degree of pulmonary disease has a negative impact on ET CO_2 performance.

The importance of maintaining respiratory homeostasis during mechanical ventilation cannot be overemphasized. ET CO_2 monitoring in the OR serves its purpose well in children and adults, and its use is also widespread in smaller infants, since it is well established and easy to apply. However, its performance in this patient group remains uncertain and might be influenced by a number of factors. Our results imply that ET P_{CO_2} measurements in fact correlate poorly to BG. We conclude that monitoring of P_{CO_2} to guide mechanical ventilation during general anesthesia should not rely solely on ET measurements.

Paper IV

This randomized controlled trial has for the first time investigated induction of neonatal anesthesia with RA versus standard practice using a high FiO_2. The data demonstrate that, at least in our hands, anesthesia of otherwise healthy neonates can be safely managed without the use of supplemental oxygen. It is also evident that current standard practice using high levels of oxygen for pre-oxygenation rapidly and uniformly results in significant hyperoxia.

The optimal oxygen saturation and safety target limits for neonatal anesthesia are not known. Attempts have been made to define acceptable variations in SpO_2, regional cerebral saturation, and the relation between these quantities, and our data allow interesting comparisons to be made with this previous work. Our regional cerebral oxygen measurements consistently followed the same pattern in both groups. From baseline, cerebral saturation decreased by a mean of 15% during the few minutes of anesthesia induction, corresponding to what has been previously suggested (72) as a mild reduction (11–20% below baseline). It is noteworthy that this decrease was independent of FiO_2 and most likely reflects a pharmacological effect of the inducing agents on blood pressure and/or perfusion. It has also been demonstrated (72) that mild cerebral desaturation occurs frequently during anesthesia in infants, and that even more severe desaturation episodes (SpO2 <70% for >3 minutes) are associated with only mild cerebral desaturation. In this context our observed changes in oxygenation seem mild at most, with an incidence comparable to studies using pre-oxygenation (73).

Maintaining physiology in as normal a state as possible during neonatal anesthesia is most likely beneficial (74), and may enable prevention of adverse neurologic outcome (75). Accordingly, attention should be given to every physiological aspect, and the aim should be not only to prevent hypoxia but also to avoid too liberal use of oxygen.

The generalizability of our investigation is limited by the rigorous study setting, and so the results might not be applicable to all situations and/or institutions. Ventilation was at all times controlled using positive end expiratory pressure, and the procedure was performed by experienced staff including the same pediatric anesthesiologist for all patients. It should also be pointed out that while we considered all anesthesia procedures to be uneventful, and had a relatively short time required for intubation, it is evident that the oxygen reserve in some infants is small enough that desaturation can occur in less than a minute.

Conclusions, clinical implications, and future studies

This thesis has evaluated selected practices used in the care of newborn infants, and examined whether and how they can be applied in a slightly different setting.

The thermal stability and physical environment was investigated during SSC in extremely preterm infants early after birth. SSC was found to provide an adequate thermal environment even for the tiniest babies early after birth. It also became clear that the increase in water loss associated with care outside the incubator is not large enough to warrant any concern. With adequate guidelines and implementation, these findings could be expected to promote earlier institution of SSC, thermal stability, and parental involvement.

Several questions arise. Can other important aspects of the experience of SSC be investigated, such as stress measurements, cortisol, and parents' experience? How can we best support parents to cope with the demanding situation of providing SSC in the NICU for months? It is known from more moderately preterm infants that SSC and parental involvement in care results in fewer painful interventions for the infants. Is this also applicable to the smallest, most vulnerable infants? Can SSC "protect" them from painful/stressful interventions?

The thesis also evaluated two different methods for carbon dioxide monitoring during neonatal anesthesia in the OR, motivated by the desire to bridge discrepancies in management that may have arisen from different treatment traditions in the fields of neonatology and pediatric anesthesia. Continuous monitoring of carbon dioxide by TC methodology was shown to be feasible also in the OR, and although the small sample size limits firm conclusions, the precision of the method is most likely similar to when used in the NICU. A larger study should be performed to address this question. Further, monitoring of carbon dioxide by capnography was shown to correlate poorly to BG values. Caution should be exercised before relying on ET measurements to guide mechanical ventilation in the OR.

The findings suggest that maximal advantage will likely be achieved when the two methods for carbon dioxide monitoring are used to complement, rather than exclude, one another. TC is important for continuous monitoring of carbon dioxide, while the ET capnogram provides valuable information about the endotracheal tube placement, chest wall movements, blood circulation, changing airway pressure, and when/if surgical events limit delivery of tidal volumes. Since both methods have their advantages and disadvantages, TC monitoring should have a more permanent role in guiding ventilation in the OR.

Finally, the thesis deals with the concept of using RA during neonatal general anesthesia. We have shown that in our hands, RA induction of general anesthesia is feasible and safe, and avoids hyperoxia. These results are an important step towards eliminating indiscriminate use of supplemental oxygen in the OR. To further address the issue of oxygen toxicity, an ongoing investigation aims to analyze biomarkers for oxidative stress in blood and urine samples from infants randomized to the two different regimes of supplemental oxygen during anesthesia.

Sammanfattning på svenska

Avhandlingsarbetes övergripande syfte var att få ny kunskap om den fysiska miljön som skapas kring det extremt underburna barnet och deras förmåga att bibehålla sin kroppstemperatur vid vård hud-mot-hud, att utvärdera olika icke-invasiva metoder för monitorering av koldioxid i barnets blod vid assisterad andning under anestesi samt att undersöka hur olika mängd inandad syrgas påverkar barnets syresättning under anestesiinduktion.

I studie I undersöktes 26 stycken extremt underburna barn när de vårdades hud-mot-hud vid ett tillfälle under deras första levnadsvecka. Deras förmåga att bibehålla kroppstemperaturen, hur mycket vätska de förlorar genom huden och omgivningsluftens fuktighet och temperatur mättes vid hud-mot-hud vård och jämfördes med vård i kuvös. Vid hud-mot-hud vård håller barnen en normal kroppstemperatur, de förlorar något mera fukt genom huden och luftfuktigheten var som väntat lägre än i kuvösen.

I studie II och III utvärderade om transkutan mätning av koldioxid i barnets blod är en användbar och tillförlitlig metod under anestesi och pågående kirurgi och om rådande praxis inom anestesi, end-tidal koldioxid mätning är tillförlitlig för nyfödda barn. För de 25 inkluderade barnen var skillnaden vid jämförelse med blod mot transkutan mätning 0.3 ± 0.7 kPa och för end-tidal mätning -1.9 ± 0.9 kPa.

Studie IV var en randomiserad kontrollerad studie där lungfriska, nyfödda barn som skulle opereras lottades till att andas rumsluft heller hög (80 %) koncentration syrgas under anestesiinduktionen. Barnen (n=17) som randomiserats till rumsluft hade efter induktionen lägre ($p < .05$) syremättnad i blodet jämfört med gruppen som andades hög koncentration syrgas (93 % ± 6.7 respektive 99 % ± 1.5). Barnen bibehöll sin syresättning under induktionen i den utsträckningen att extra syrgas inte behövde tillföras. De barn (n=18) som lottats till hög koncentration syrgas hade signifikant högre transkutant uppmätt partialtryck av syrgas i blodet i jämförelse med gruppen som andats rumsluft (18.7 ± 9.9 vs 8.6 ± 2.3; $p < .05$).

Sammanfattningsvis visades att vid hud-mot-hud vård av extremt underburna barn under deras första levnads vecka så bibehåller barnen en normal kroppstemperatur, detta trots att luftfuktigheten var lägre. De ökade vätske-

förlusterna via huden beräknades vara försumbara för barnets vätskebalans. Resultaten av utvärderingen av de olika metoderna för att monitorera koldioxid i barnets blod under anestesi visar att transkutan mätning är en värdefull teknik för att intraoperativt guida ventilationen och att end-tidal mätning stämmer mindre bra och ska användas med försiktighet för att styra ventilationen. Anestesiinduktion med endast rumsluft och utan att tillföra hög koncentration av syrgas är säkert vid anestesi av nyfödda lungfriska barn. Eventuella fördelar med att undvika att inducera hyperoxi i samband med neonatalanestesi behöver undersökas ytterligare.

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"I don't know where I'm going from here, but I promise it won't be boring."

David Bowie

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