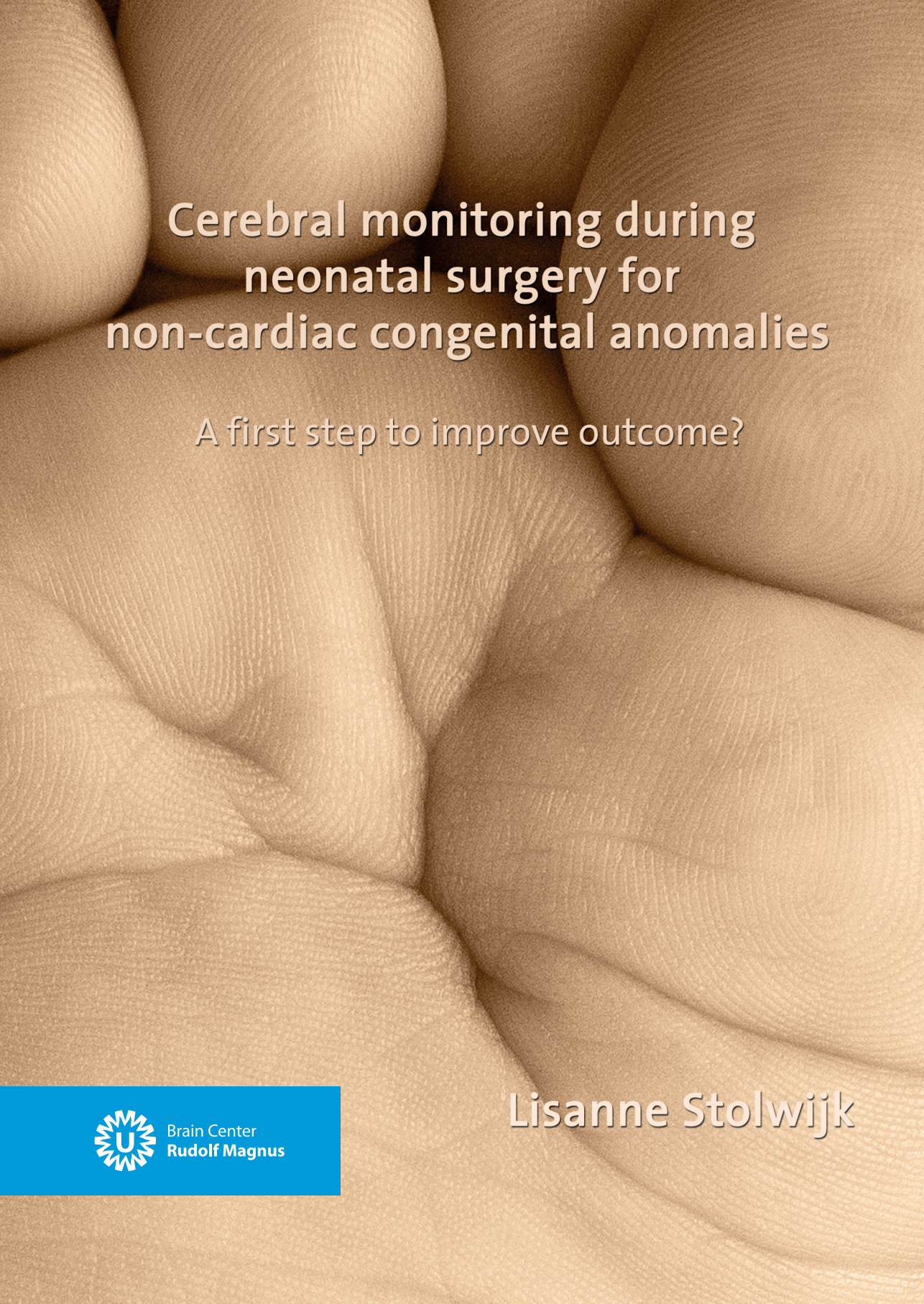

Cerebral monitoring during neonatal surgery for non-cardiac congenital anomalies

A first step to improve outcome?

Lisanne Stolwijk

Brain Center
Rudolf Magnus

Cerebral monitoring during neonatal surgery for non-cardiac congenital anomalies:
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Thesis, Utrecht University, with a summary in Dutch
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Cerebral monitoring during neonatal surgery for non-cardiac congenital anomalies:

a first step to improve outcome?

Neuromonitoring tijdens neonatale chirurgie voor niet-cardiale aangeboren aandoeningen:
een eerste stap naar een betere toekomst?
(met een samenvatting in het Nederlands)

Proefschrift

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in het openbaar te verdedigen
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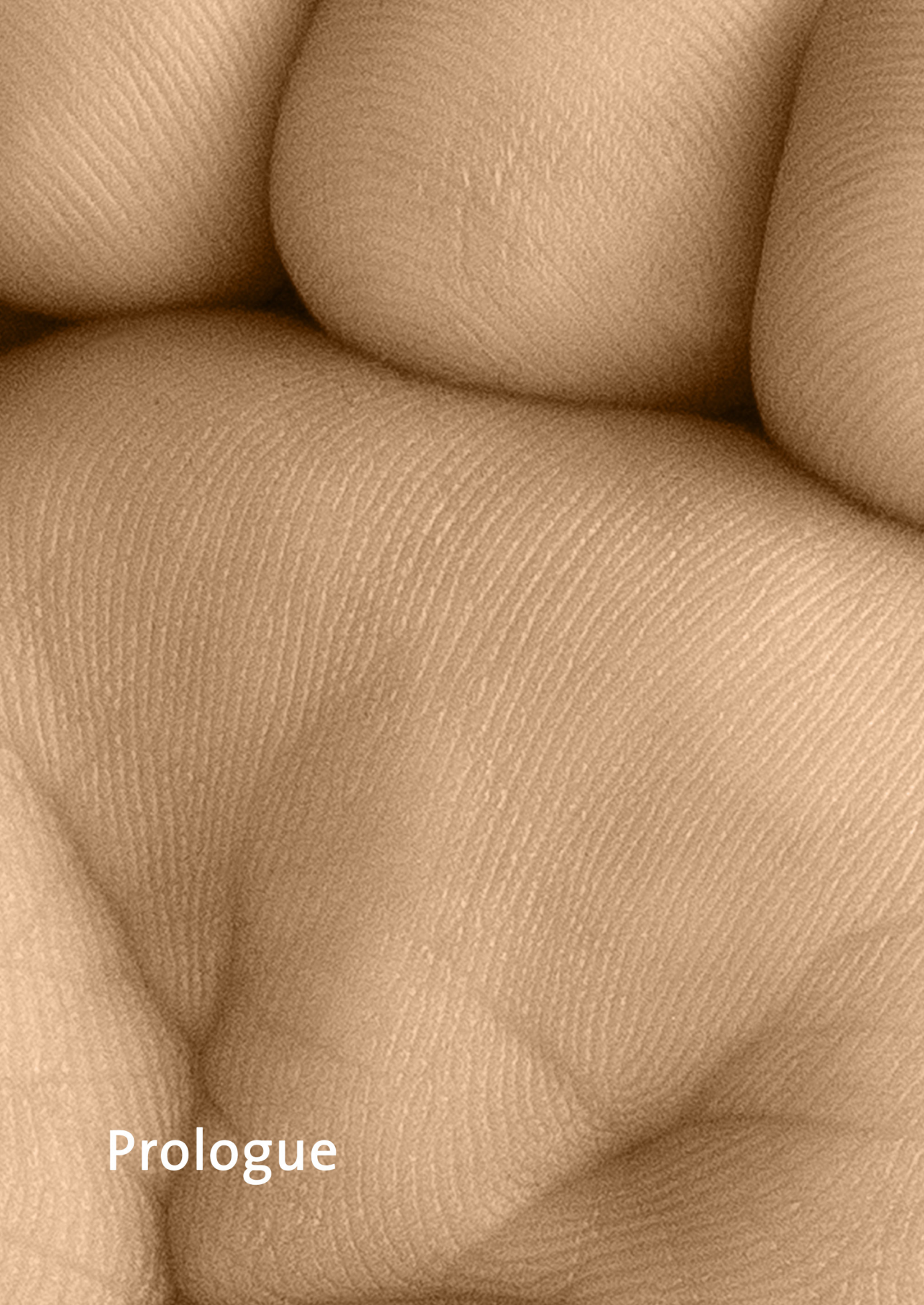

Prologue

Het verhaal van Luuk

Sinds kort is bekend dat kinderen die vlak na de geboorte al moeten worden geopereerd aan een aangeboren aandoening, risico lopen op een ontwikkelingsachterstand. De exacte oorzaak is onduidelijk. Dat was de aanleiding om in het Wilhelmina Kinderziekenhuis uitgebreid onderzoek te starten. Het verhaal van Luuk schetst het onverwachte beloop van één van deze kinderen, verteld door zijn ouders.

"Na een zorgeloze zwangerschap zitten we plots op de Neonatale Intensive Care Unit. Luuk ligt niet in een wiegje, maar in een couveuse, met slangetjes, draadjes en stekkertjes om hem in de gaten te houden. Over een paar uur wordt hij geopereerd, hij is zes dagen oud."

Vlak na zijn geboorte blijkt dat Luuk een fistel heeft, een verbinding tussen zijn slokdarm en luchtpijp. Dit wordt duidelijk op het moment dat hij voeding krijgt en 'maskert', zijn lippen kleuren blauw. Op dat moment liggen ze vanwege de keizersnede nog op de kraamafdeling, Luuk had namelijk een laag geboortegewicht en die dag starten ze met bijvoeding. Dan staat de verpleegkundige plots aan hun bed: na het maskeren wordt Luuk direct meegenomen naar de Neonatologie. Het blijkt dat de zuurstofspanning laag is en artsen denken aan een luchtweginfectie. In Deventer kunnen ze niet voldoende onderzoek bij Luuk doen, waarop hij wordt overgeplaatst naar Utrecht.

Het kan erger
Al snel wordt duidelijk dat de artsen aan een fistel denken, een verbinding tussen de luchtpijp en de slokdarm, en een verklaring voor het verslikken. "Je voelt je heel machteloos, het ging allemaal snel, maar alles duurt te lang. Je wilt dat Luuk prioriteit krijgt. Aan de andere kant werkt het voor ons ook relativerend om op de Intensive Care andere kinderen te zien, we zijn niet de ergste." De operatie volgt direct de volgende dag.

Vooral de narcose was spannend
Tijdens de operatie kruipen de minuten voorbij. Achteraf bleek het drie uur te duren, zoals hen vooraf was verteld. Daarna gaat het snel, de beademingsbuis wordt er dezelfde avond nog uitgehaald en langzaam maar zeker worden de stekkertjes, draadjes en slangetjes uit Luuk gehaald. Dan volgt er een complicatie en moet Luuk opnieuw worden geopereerd. "Je kan alleen maar hopen dat het goed gaat," herinnert moeder zich. "Het was Kerst en iedere keer als hij werd geopereerd werden er kerstliedjes gezongen in de centrale hal, 'O kindje zo klein' en 'Slaap maar zacht'."

“We hadden er zo naar uitgekeken om thuis te zijn, maar toen begon het pas. We misten heel erg de piepjes van de monitor. Bij elke hapering in zijn ademhaling zaten we rechtop.” Drie keer per week gaan ze naar het consultatiebureau om hem te wegen. Gelukkig gaat het al snel prima en Luuk drinkt steeds meer zelf. De hobbel lijkt genomen, het defect is gemaakt en het gaat steeds beter.

Dan komt er onverwacht toch een kink in de kabel. Luuk hoort al op z’n buik te kunnen liggen met z’n hoofd opgericht, krijgen ze op het consultatiebureau te horen. Ligt het misschien aan zijn litteken?

De bevestiging komt op 14 december 2016. Luuk blijkt een ontwikkelingsachterstand te hebben. Op 2-jarige leeftijd heeft hij een ontwikkeling van 13 maanden. Ouders maken zich nog geen echte zorgen. “Luuk is vrolijk, eten en drinken gaat goed. Hij begrijpt alles wat tegen hem wordt gezegd. We zien dat hij zelf stappen aan het maken is. Hij bereikt dezelfde mijlpalen, alleen Luuk is niet zo snel als andere kinderen.”

Vooralsnog is onduidelijk wat de exacte oorzaak van Luuk’s ontwikkelingsachterstand is en of dit blijvend zal zijn. Zijn verhaal maakt duidelijk dat we ons niet alleen op de aangeboren afwijking moeten focussen. Met ons onderzoek richten we ons op de hersenen van deze kinderen, vanaf de operatie tot twee jaar daarna, om te achterhalen of de operatie invloed heeft op de ontwikkeling.

A portrait of Luuk

Recently it became clear children requiring neonatal surgery for correction of a non-cardiac congenital anomaly, have an increased risk for developing a delay in psychomotor development. The exact pathogenesis of this delay is unknown. This was the reason to start a research project in the Wilhelmina Children's Hospital. Luuk's story is illustrative of the unexpected course of one of the children, told by his parents.

"After a carefree pregnancy we found ourselves suddenly sitting at the Neonatal Intensive Care Unit. Instead of Luuk lying in a cot, he was in an incubator with wires, lines and ECG patches to monitor him. In a couple of hours he is having surgery, he is six days old."

Just after birth it became clear Luuk had a fistel, a connection between his oesophagus and trachea. He received feeding after which they saw a bluish discoloration of his lips, he aspirated the milk through the fistula. At that moment mother and Luuk were at the maternity ward, since he had a low birth weight. Before going home Luuk had to proof drinking well and growing. However, all of a sudden the nurse was there to bring Luuk to the department of Neonatology. The oxygen saturation appeared to be too low, the doctors suspected a respiratory infection. However, the diagnosis could not be made in Deventer after which Luuk is transferred to Utrecht.

It could be worse
Soon it becomes clear the doctors think of a fistula, which could be the explanation for his choking. "You feel helpless, it went all very fast, but still everything took too long. You want him to get priority. On the other hand, to see the other babies at the Intensive Care placed our situation in perspective, it could be worse." The surgery followed the next day.

During the surgery the minutes feels like hours. In hindsight it took the predicted three hours. After the correction everything goes fast, the ventilation tube is removed the same night, and line by line Luuk is getting rid of al the wires. Unfortunately, due to a complication Luuk needs another surgery. "The only thing you can do is hope everything goes well," remembers the mother. "It was Christmas and every time Luuk was in surgery Christmas carols were sung in the central hall."

"We had been looking forward to go home, but that turned out to be only the beginning. We missed the beeps of the monitor. With every noise we were upright in bed." Three times a week we went to the consultation bureau to weigh Luuk. Fortunately everything seems well and Luuk is drinking more and more milk independently. The hurdle has been taken, the defect is corrected and everything seems to better.

Suddenly there is an unexpectant hitch. Luuk should be able to lie on his belly with his head lifted upwards, says the consultation bureau. Is his scar preventing him from doing so?

The confirmation follows at December 14th 2016. Luuk has a delay in psychomotor development. At the age of two years he has a development score of 13 months. His parents are not really worried. "We see Luuk being happy, eating and drinking goes well. He understands everything what we tell him. He makes progress. He reaches the same milestones, although Luuk is not as fast in comparison to other children."

To date the exact cause of Luuk's developmental delay is still unclear. The portrait of Luuk illustrates our motivation to focus on long-term development of children with non-cardiac congenital anomalies. With our research project we concentrate on the brain of these children, from before the surgery to two years after, to discover the impact of the surgery on the psychomotor development.

1

CHAPTER

General introduction and outline of the thesis

INTRODUCTION

Survival of the neonate, who requires major surgery in the first month of life, has greatly improved over the last decades.[1] This is also true for newborns with major non-cardiac congenital anomalies. Congenital anomalies occur with a prevalence of 2-3% of all newborns in the Netherlands, including cardiac, central nervous system and chromosomal anomalies.[2-6] In the Wilhelmina Children's Hospital approximately 40 infants with non-cardiac congenital anomalies (NCCA) are admitted each year for surgery in the neonatal period. Examples of these anomalies are esophageal atresia, intestinal atresia, gastroschisis and anorectal malformation.

Mortality rates declined significantly, to less than 5%, and consequently attention has shifted to morbidity and neurodevelopmental outcome.[7-10] Recently, it became clear that infants with non-cardiac congenital anomalies are at risk of adverse neurodevelopmental outcomes.[11, 12] Laing et al. reported for the first time that infants requiring newborn surgery for both cardiac and non-cardiac birth defects have an increased risk of developing an impairment in psychomotor development.[9] In patients with cardiac anomalies a high percentage of cerebral injury is seen before surgery and additional brain lesions are found after operation.[13-19] To date, the etiology of the neurodevelopmental delay in children with *non-cardiac* congenital anomalies is mostly unknown.[12] This lack of knowledge could be due to the fact that these children are structurally excluded from large, longitudinal studies.[20, 21]

Major surgery in the first month of life should be considered as a high-risk procedure for the neonate. The neonatal brain is vulnerable for fluctuations in cerebral perfusion and inflammation, which puts the neonatal brain at risk for developing brain damage.[22-25] These disturbances can be induced by hypoxia, hypocapnia, hypercarbia and hypotension. The developing brain is also highly susceptible to hyperoxia. Due to the immature anti-oxidative defenses, free oxygen radicals cause oxidative stress reactions. In addition, the neonatal brain is vulnerable due to the immature, cerebral autoregulatory ability of the neonate, which makes the cerebral blood flow pressure passive.[26-29] Standard monitoring during surgery, including heart rate, blood pressure and arterial saturation, provides indirect information on the brain. Neuromonitoring, measuring cerebral oxygenation and brain activity, offers direct data on cerebral saturation, sedation and an indication on brain perfusion.[30] Stable cerebral perfusion and saturation is vital for the neonatal brain, to prevent brain damage and to ensure adequate blood and oxygen supply. To date, neuromonitoring during major neonatal surgery is not standard clinical care in most hospitals, but may be of great additional value in an effort to protect the neonatal brain.

The first hospital admission usually entails a long neonatal hospitalization, including the transition phase after birth, major surgery and treatment in the intensive care unit. It is

imperative to identify parameters and risk factors during this period for the long-term outcome of these children.

NON-CARDIAC CONGENITAL ANOMALIES

The major non-cardiac congenital anomalies (NCCA) are subdivided in six categories in the present study, based on the surgical index diagnoses of Ravitch; esophageal atresia, abdominal wall defects, intestinal atresia/intestinal malrotation/volvulus, anorectal malformation, Morbus Hirschsprung, and congenital diaphragmatic hernia, next to urogenital and other malformations.

Esophageal atresia

Esophageal atresia (EA) is one of the most prevalent congenital anomalies, accounting for 2.4 in 10.000 births in The Netherlands.[2] Worldwide a prevalence of 2.44 per 10.000 is reported.[3, 31] This congenital malformation is divided into five subtypes (Figure 1). Esophageal atresia with a distal tracheoesophageal fistula (TEF) is the most common type (Type C, 85%). The long gap esophageal atresia (Type A without fistula) is surgically the most challenging to reconstruct (Figure 1).[32] In the majority of infants, a tracheoesophageal fistula is present, either proximal (Type B), distal (Type C) or both (Type D). Finally, Type E consists solely of a tracheoesophageal fistula.[33, 34] Type F concerns a congenital stenosis of the esophagus. Survival rates are up to 95%, causing morbidity and neurodevelopmental outcome to become more relevant.[35] Up to now, outcome in these patients is mainly defined by short-term and long-term morbidities, such as respiratory and gastrointestinal problems.[36-38]

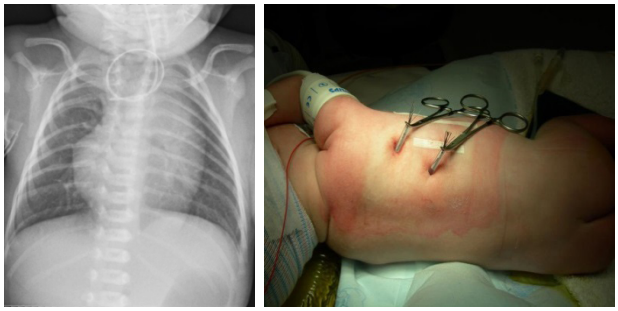

Figure 1. Esophageal atresia 1A. Chest X-ray: Gastric feeding tube curled in the proximal esophageal pouch. 1B. Patient with a long gap esophageal atresia in the neonatal ICU; traction sutures fixed externally with mosquito forceps.

Abdominal wall defects

Abdominal wall defects account for 2.4 per 10.000 live births in the Netherlands,[2] with gastroschisis and omphalocele as most important anomalies. These abnormalities are almost always diagnosed during prenatal evaluation.

Gastroschisis

Gastroschisis is an abdominal wall defect, with herniation of the abdominal content in the amniotic fluid (Figure 2).[39, 40] The intestines are not covered by a membranous sac. A subdivision into isolated gastroschisis and not-isolated (extra-gastrointestinal congenital anomalies) can be made and is prognostic for long-term morbidity.[41] In addition to that, an isolated gastroschisis can be complicated by necrosis of the bowel at birth, or additional atresia, volvulus or perforation, with a higher mortality and a deteriorated outcome.[41] In 5 to 20% of the infants associated anomalies are found postnatally.

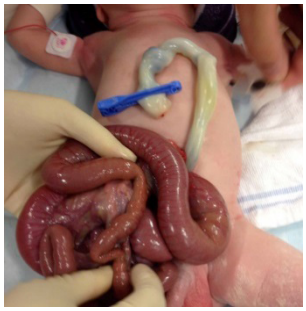

Figure 2. Gastroschisis

Omphalocele

The definition of omphalocele by Ladd and Gross is: *"herniation of viscera into the base of the umbilical cord and covering of these viscera with a membranous sac"*.[33] Important with this anomaly is the increased risk of 45% of associated anomalies or chromosomal abnormalities, with trisomy 13 and trisomy 18 prevailing. This risk varies depending on other factors such as maternal age and gestational age at time of diagnosis.

Intestinal atresia

The incidence of intestinal atresia in the Netherlands is 2 per 10.000 live births.[2] Intestinal atresia means a congenital partial or complete obstruction of the lumen of the duodenum, jejunum, ileum and/or colon (Figure 3).[42] This can either be intrinsic of origin or extrinsic, in case of an annular pancreas for example. The most commonly affected site is the duodenum (60% of the cases), whereas the colon is the least affected (7%).[43] Multiple sites of intestinal atresia occur in 15% of all patients.[33] The rare type 'apple peel atresia' consists of a proximal jejunal atresia with significant loss of intestinal length and a helical configuration around a single vessel.[33] This type of atresia is associated with severe morbidity, like short bowel syndrome.

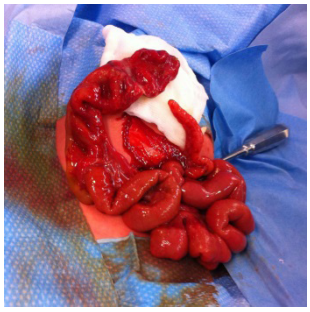

Figure 3. Intestinal atresia

Malrotation and volvulus

Symptomatic gastrointestinal malrotation in the neonate occurs in 1.3 per 10.000 in the Netherlands[2]. Intestinal malrotation is an abnormal rotation of the midgut with a different rotation from the 270° counterclockwise rotation of the intestine around the mesentery root.[33] This results from a failure in the normal embryologic bowel rotation and fixation.[42] Infants

become symptomatic in case of complete obstruction of the lumen. Volvulus is one type of obstruction, where vascular supply is compromised due to rotation of the gut and the mesentery around itself and emergency surgery is indicated to prevent intestinal ischemia.[44]

Anorectal malformation

Malformations of the anorectum occur in 3.3 per 10.000 live births in the Netherlands.[2] Anorectal malformation is defined as the absence of an external anal orifice in the sphincter complex (Figure 4).[45] Most patients lack a communication between the rectum and perineum.[46] In 95% of the infants a fistula is present. The anorectal malformation is classified by the Krickenbeck classification, based on the location of the fistula (perineal, recto-urethral, recto-vesical, vestibular or no fistula)[47], cloacal lesions and anal stenosis. Almost all anorectal malformations are diagnosed postnatally.

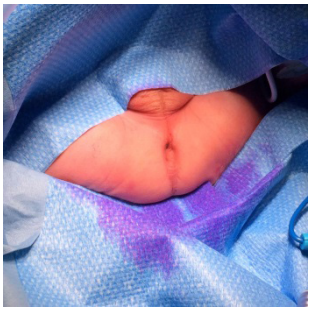

Figure 4. Anorectal malformation

Urogenital malformation

Congenital hydronephrosis

Congenital anomalies of the kidney and urinary tract (CAKUT) are a group of defects, that account for 30 to 50% of the end-stage renal diseases in children. This acronym describes a broad spectrum of disorders, for example multicystic kidney dysplasia, ureteropelvic junction obstruction (UPJ), megaureter and vesicoureteral reflux (VUR). These anomalies cause an obstruction of the urinary tract and possibly dilatation of the renal pelvis, sometimes accompanied by dilatation of the renal calyces, due to obstruction of the urinary tract.[33]

Bladder exstrophy

An extraordinary urogenital malformation is bladder exstrophy, which involves the urinary, reproductive and intestinal tracts, and frequently the musculoskeletal system as well.[33, 48] Anteriorly, the urethra and bladder are open. The size of the bladder varies greatly. Most often this diagnosis is made by prenatal ultrasound, with absence of bladder filling as most important finding. Primary reconstruction in the neonatal period is possible. Important urogenital outcome parameters are bladder storage function and continence.[49]

Others

Morbus Hirschsprung

In Hirschsprung's disease agangliosis of the colon causes a disturbance in motility of the gastrointestinal tract.[50] Failure to pass the first meconium within 48 hours after birth, abdominal distension, constipation and vomiting are important symptoms of Morbus Hirschsprung.[33] The

majority is diagnosed in the neonatal period with a rectal suction biopsy.[51] Surgical intervention with the Duhamel procedure is usually performed after the first month of life, dependent on the extent of the aganglionic segment of the colon.[52] In the rare case (5%) of total agangliosis, earlier intervention is needed. As a result, only one preterm infant was included in our cohort.

Congenital diaphragmatic hernia

One of the major NCCA is congenital diaphragmatic hernia (CDH). This malformation of the diaphragm allows herniation of the abdominal organs into the thoracic cavity.[33] Patients with CDH mainly suffer from respiratory distress directly after birth, due to hypoplasia of the lungs and pulmonary hypertension. These infants are born and treated in dedicated centers with the possibility of extracorporeal membrane oxygenation (ECMO). Consequently, only few patients with CDH are present in our cohort.

Associated syndromes

Down syndrome is diagnosed in 25% of patients with duodenal atresia. In children with trisomy 13 and 18 abdominal wall defects and urogenital anomalies are frequently found.[53]

VACTERL association consists of a group of abnormalities, including vertebral anomalies, anorectal malformation, cardiac malformation, tracheoesophageal fistula and/or esophageal atresia, renal anomalies and limb defects. When three or more abnormalities are found in a patient, then VACTERL association is present. These abnormalities occur together more frequently than can be expected by chance.[53]

SURGERY IN THE NEONATAL PERIOD

Surgery and anesthesia

According to large, retrospective cohort studies, surgery in the neonatal period seems to exert a negative influence on long-term outcome.[9, 12, 39, 54, 55] Multiple surgical interventions in particular affect cognitive and motor development.[56-58] In addition to the surgery, the effect of specific surgical techniques on the neonate, such as the use of CO_2 insufflation during minimally invasive surgery, should be evaluated. Up to now, scientific research mainly focused on preterm patients and infants with cardiac congenital anomalies.[59]

Reports of animal experimental studies suggest a neurotoxic effect of commonly used inhalational anesthetics on the young, neonatal brain.[60-62] Since the newborn brain is still developing an increased neuroapoptosis, impaired neurogenesis and an enhanced inflammation of the neuron can induce destructive effects.[60, 62-64] To prove the clinical consequences of a short exposure to anesthesia during childhood, three long-term clinical trials have been initiated.[65]

Also, early brain activity is vital for the development and growth of the newborn brain.[66] Medication that suppresses neonatal brain activity, such as opioids and sedatives, used during and after surgery, might impact this development as well.

MONITORING THE NEWBORN BRAIN

Near Infrared Spectroscopy

Near Infrared Spectroscopy (NIRS) is a method to measure cerebral oxygenation continuously and non-invasively in the neonate. The technique is based on the transparency of the biological tissue by near-infrared light (700-1000nm) and the absorption of the NIR light by oxygenated and de-oxygenated hemoglobin in the brain tissue.[67] NIRS is a method to monitor cerebral oxygenation, referred to as the regional cerebral oxygen saturation ($rScO_2$) and cerebral fractional tissue oxygen extraction (cFTOE).[68, 69] It estimates the oxygenated hemoglobin in a mixture of venous, arterial and capillary blood (75%/20%/5%).[70] Therefore, it is used as trend monitor to detect substantial changes in regional oxygen saturation. It is a non-invasive monitoring tool that provides data on oxygen delivery, oxygen consumption of the brain tissue and estimates brain perfusion.[71, 72] The Neonatal Intensive Care Unit has extensive experience (>30 years) with monitoring the cerebral oxygenation of preterm and term neonates.[30]

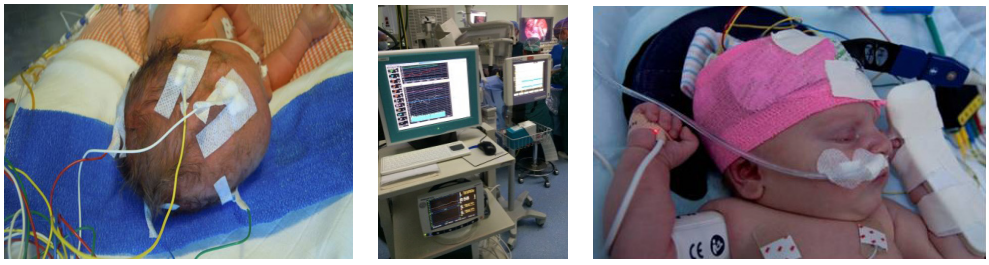

Figure 5. Neuromonitoring *A) Monitoring with amplitude-integrated EEG B) Neuromonitoring during surgery C) NIRS-sensor and aEEG-electrodes are held in place with an elastic band.*

Amplitude-integrated EEG

The amplitude-integrated electro-encephalogram (aEEG) is a technique to monitor neonatal brain activity continuously (Figure 5).[73] The clinical application is mainly in preterm infants, newborns after perinatal asphyxia and infants suspect of having convulsions.[73] In these patient groups the aEEG is prognostic for long-term outcome.[74] Brain activity can be assessed qualitatively, by determining the background pattern or the Burdjalov-score for brain maturation,[73, 75] assessing the presence of Sleep Wake Cycling and epileptic activity or quantitatively by calculating the Spontaneous Activity Transient-rate (SAT-rate) and the InterSATInterval.[66, 76, 77]

Cerebral ultrasound

Cerebral ultrasonography enables a non-invasive, bedside evaluation of large anatomical malformations and brain lesions such as hemorrhages and white matter injury of the neonatal brain.[78] The advantage of this technique is that it is easily accessible and can be performed sequentially and as frequent as indicated.[79, 80] The most commonly used scoring-methods to evaluate the findings at ultrasound are the grading of germinal matrix hemorrhages by Papile et al,[81] leukomalacia by de Vries et al[82] and post-hemorrhagic ventricular dilatation by Levene et al.[83]

MRI

Magnetic Resonance Imaging encompasses advanced imaging to evaluate the development of the newborn brain.[84-87] With the use of conventional images (T1-, T2-Weighted Imaging) even small lesions are detectable. The timing of onset of these lesions is possible with Diffusion Weighted Imaging to detect ischemic lesions and Susceptibility Weighted Imaging to detect hemorrhagic lesions. MRI offers the possibility to predict severe problems in motor development, such as cerebral palsy.[79, 88-90] MR images were systematically scored based on the MRI assessment tools of Kidokoro and Woodward.[89, 90]

Follow-up

Routine clinical follow-up measurements include weight, length and head circumference. For neurodevelopmental follow-up different assessment tools are used. At the age of three months neurodevelopment is evaluated with the Alberta Infant Motor Scale (AIMS),[91] at the age of 9 and 18 months the Griffith Mental Development Scales is used.[92] Finally, the neurodevelopment of the child at the age of 24 months is assessed using the Bayley Scales of Infant and Toddler Development (BSID), Third Version.[93-95] This BSID consists of three developmental scales; the cognitive scale, the language scale and the motor scale. These tests are all norm-referenced, standardized and observational. The BSID Third Version effectively identifies infants requiring early intervention for motor and cognitive development.[96, 97]

AIMS AND OUTLINE OF THIS THESIS

The main aim of this thesis is to study the etiology and underlying mechanisms of the neurodevelopmental delay in patients with non-cardiac congenital anomalies requiring major neonatal surgery. Therefore, a prospective, observational cohort study is performed. All infants with a NCCA, requiring major surgery in the neonatal period, admitted to the NICU or PICU of the Wilhelmina Children's Hospital Utrecht are included.

Part I - Introduction
First, a systematic review and meta-analysis is performed to study the neurodevelopmental outcome of all children with NCCA, requiring major surgery in the neonatal period. The results are described in **chapter 2**.

Part II - Neuromonitoring and neuro-imaging
The second part addresses the findings of the neuromonitoring and neuro-imaging before, during and after neonatal surgery.

In **chapter 3** the neuro-imaging findings of the systematic evaluation of brain injury following neonatal surgery are described. Our aim was to evaluate the incidence of brain lesions visible at the postoperative MRI in a cohort of patients with non-cardiac congenital anomalies.

Chapter 4 reports on the effects of general anesthesia on neonatal brain activity, measured by amplitude-integrated EEG in patients with NCCA during surgery.

Chapter 5 discusses the cerebral autoregulatory ability in term neonates during anesthesia, in comparison to their pre- and postoperative capacity.

In **chapter 6** the predictive value of oxidative stress biomarkers is studied, in relation to brain damage, in patients requiring neonatal surgery.

Part III - Effects of surgical and anesthesiological factors on cerebral hemodynamics
Chapter 7 evaluates the effect of a low- and high-pressure intrathoracic CO_2-insufflation on the cerebral oxygenation and hemodynamics of newborn piglets.

Chapter 8 describes the effect of intrathoracic insufflation of CO_2, during a thoracoscopic esophageal atresia repair, on neonatal cerebral oxygenation. Various hemodynamic parameters and their effect on cerebral oxygenation are evaluated.

In a cohort of patients with long gap esophageal atresia, presented in **chapter 9**, requiring multiple thoracoscopic procedures in the neonatal period, the cerebral oxygenation and hemodynamic parameters before, during and after surgery are evaluated.

In **chapter 10** the results of a survey on the dose of inhalational anesthesia given by anesthesiologists in the Wilhelmina Childrens' Hospital in Utrecht and in the Great Ormond Street Hospital in London, United Kingdom are presented.

Conclusion and future perspectives

In **Chapter 11** the results of the previous chapters are discussed and future perspectives are outlined.

Chapter 12 summarizes the results of the studies in Dutch.

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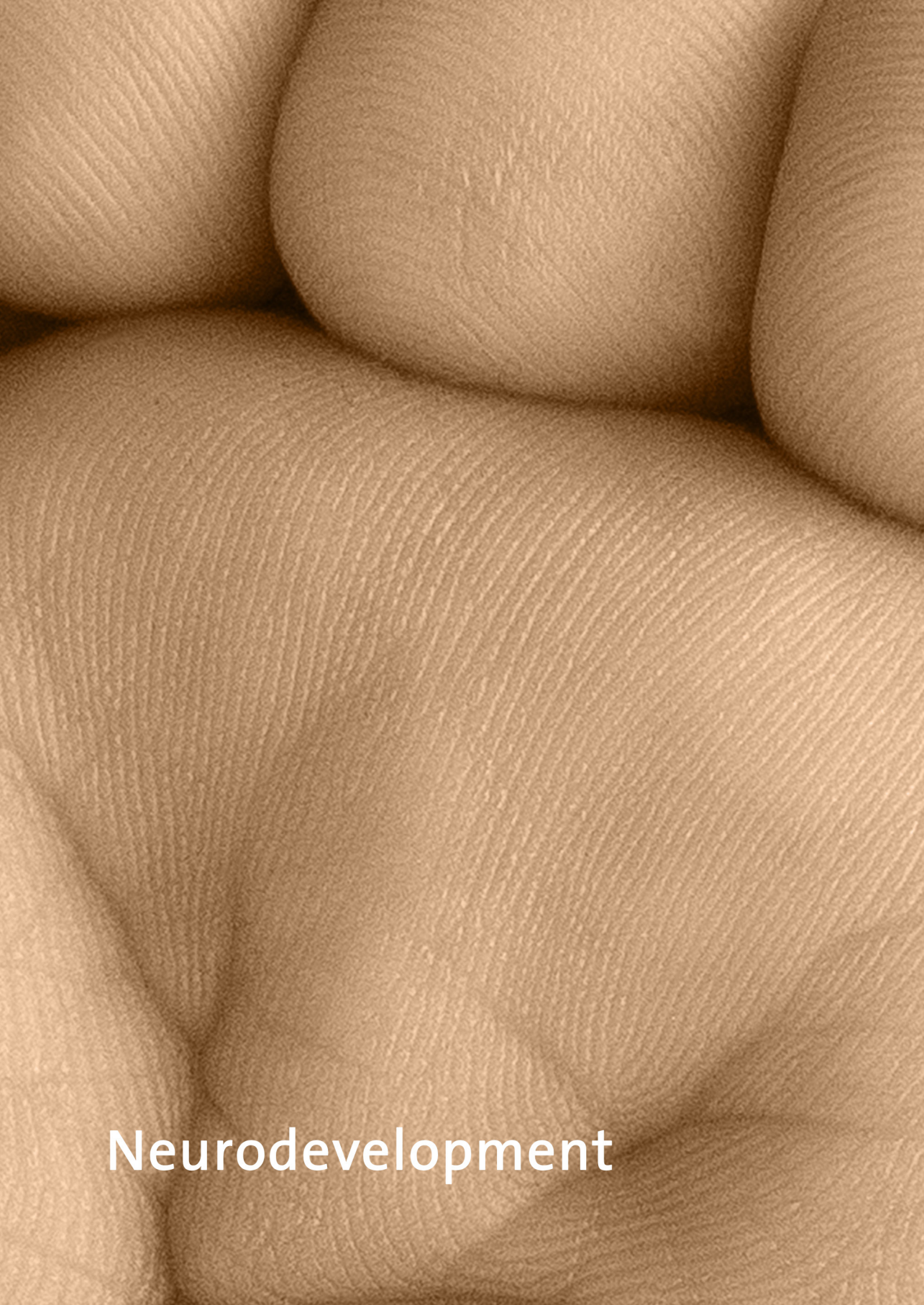
PART 1



Neurodevelopment

2

CHAPTER

Neurodevelopmental outcomes after neonatal surgery for major non-cardiac anomalies

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ABSTRACT

Context: Increasing concerns have been raised about the incidence of neurodevelopmental delay in children with noncardiac congenital anomalies (NCCA) requiring neonatal surgery.

Objective: This study aimed to determine the incidence and potential risk factors for developmental delay after neonatal surgery for major NCCA.

Data sources: A systematic search in PubMed, Embase and the Cochrane Library was performed through March 2015.

Study selection: Original research articles on standardized cognitive or motor skills tests.

Data extraction: Data on neurodevelopmental outcome, the Bayley Scales of Infant Development, and risk factors for delay were extracted.

Results: In total, 23 eligible studies were included, reporting on 895 children. Meta- analysis was performed with data of 511 children, assessed by the Bayley Scales of Infant Development at 12 and 24 months of age. Delay in cognitive development was reported in a median of 23% (3%-56%). Meta-analysis showed a cognitive score of 0.5 SD below the population average (Mental Development Index 92 ± 13, mean ± SD; $P < .001$). Motor development was delayed in 25% (0%-77%). Meta-analysis showed a motor score of 0.6 SD below average (Psychomotor Development Index 91 ± 14; $P < .001$). Several of these studies report risk factors for psychomotor delay, including low birth weight, a higher number of congenital anomalies, duration of hospital admission, and repeated surgery.

Limitations: All data were retrieved from studies with small sample sizes and various congenital anomalies using different neurodevelopmental assessment tools.

Conclusions: Cognitive and motor developmental delay was found in 23% of patients with NCCA. Meta-analysis showed that the mean neurodevelopmental outcome scores were 0.5 SD below the normative score of the healthy population.

INTRODUCTION

Approximately 2% to 3% of all neonates are born with major congenital anomalies[1–4] requiring surgical intervention in the neonatal period. With the reduction in mortality to <5%,[5] attention has shifted to morbidity, which has increasingly become the major concern.

Many studies provide evidence of neurodevelopmental delay and behavioral problems after cardiac surgery in infants. However, for noncardiac congenital anomalies (NCCA), there are limited data regarding the impact on neurodevelopmental outcomes, and results from existing studies are contradictory. Laing et al[6] reported a concerning rate of up to 50% mild to significant neurodevelopmental delay in these children; conversely Gischler et al[7] found no delay in cognitive outcome in this group. The latter did find a significant delay in motor development, however. In a high percentage of the cardiac patients, both preoperative and de novo postoperative brain damage were visible on MRI.[8,9] These lesions could contribute to the risk of adverse neurodevelopmental outcome. The mechanism and factors increasing the risk of neurodevelopmental delay in NCCA remain unknown. In vitro and in vivo experimental studies have demonstrated the neurotoxic effect of general anesthetics on the young, animal brain.[10–13] Large retrospective cohort studies in humans show a significantly higher rate of behavioral problems in children who have undergone multiple surgical procedures at a young age,[14,15] although the causes for this are unclear.[16] In short, data for both incidence and risk factors regarding neurodevelopmental delay are scarce and inconsistent. The aim of this systematic review and meta-analysis is to provide an overview of the current evidence for the incidence of neurodevelopmental delay in children with major NCCA requiring neonatal surgery, and to identify possible associated risk factors.

PATIENTS AND METHOD

Search Strategy

This literature search for human studies provides an update on the current evidence regarding the neurodevelopmental outcome and the incidence of delay after neonatal surgery for major NCCA. The systematic review is conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement.[17] A structured literature search was performed using predefined search terms in PubMed (1960–2015), Embase (1980–2015), and the Cochrane Library (issue 3 of 12, March 2015) until March 2, 2015. For PubMed, the following search terms were used: (neonat*[Title/Abstract] OR infant*[Title/Abstract] OR newborn*[Title/Abstract]) AND (congenital anomal*[Title/Abstract] OR birth defect[Title/ Abstract] OR gastroschisis[Title/Abstract] OR omphalocele[Title/Abstract] OR atresia[Title/ Abstract] OR agenes*[Title/Abstract] OR malformation[Title/Abstract] OR diaphragmatic hernia[Title/Abstract] OR hirschsprung[Title/Abstract] OR choan*[Title/Abstract]

OR abdominal wall defect[Title/Abstract]) AND (surg*[Title/Abstract] OR repair[Title/Abstract] OR correction[Title/Abstract] OR closure[Title/Abstract]) AND (neurodevelopment*[Title/Abstract] OR outcome[Title/Abstract] OR psychomotor[Title/Abstract] OR behavior*[Title/Abstract] OR behavior*[Title/Abstract] OR deficit*[Title/Abstract] OR impairment[Title/ Abstract] OR cognitive[Title/Abstract] OR learning[Title/Abstract] OR iq[Title/Abstract]. We used the same search strategy in Embase, replacing "[Title/Abstract]" by; "ab,ti" and in The Cochrane Library by replacing "[Title/Abstract]" by "ti,ab,kw". Additionally, reference lists of included studies were examined to identify additional studies for inclusion. Search limits were not used in the databases, and language restrictions were not applied.

Assessment of Study Eligibility

Each article was independently assessed for eligibility using the following predefined criteria:
Domain: the study population was neonates ≤44 weeks postmenstrual age.
Determinant: the intervention consisted of neonatal surgery for a major NCCA.
Study outcome: neurodevelopment as measured by the Bayley Scales of Infant Development (BSID)-II and -III,18 the Griffiths Mental Development Scales,[19] the Wechsler Intelligence Scale for Children,[20] Wechsler Preschool and Primary Scale of Intelligence, and the Movement Assessment Battery for Children (M-ABC).[21]
Study design: originally published articles.
Studies were excluded from analysis if the articles did not contain original patient data or did not match the inclusion criteria.

Outcomes of Interest

Studies that were eligible for inclusion reported on NCCA requiring neonatal surgery and described neurodevelopmental outcome in children by a standardized cognitive or motor skills test. Primary outcomes of interest for meta-analysis were cognitive and motor outcomes at 12 and 24 months of age using the BSID. All studies defined neurodevelopmental outcome as mildly delayed if scores on developmental testing deviated between 1 and 2 SD from the normative mean of 100 (70–85) and significantly delayed if scores were <2 SDs below the mean (≤69).
Articles were also examined for evidence of risk factors and their association with poor neurocognitive outcomes. These risk factors consisted of birth weight, gestational age, prematurity, comorbidity, growth delay, occipitofrontal circumference, number of congenital anomalies, number of surgical interventions in first 24 months, age at first surgery, number of days of assisted ventilation and supplemental inspired oxygen, neurologic complications, injury visible with neuroimaging, length of hospital stay, number of hospital admissions, surgical technique, educational level of parents, and sociodemographic characteristics.

Data Extraction

Titles and abstracts as well as full text articles were independently screened by 2 authors (LJS and MH) according to the PRISMA statement.[17] The following data were extracted from all included articles: study population characteristics, study design, assessment tool, duration of follow-up, number of participating subjects, and number followed up. A third author (MvH-L) was consulted in case of discrepancies, and agreement was reached by consensus. Authors of included studies were contacted and provided additional data if necessary.

Risk of Bias Assessment

The risk of bias of each article included in the meta-analysis was assessed on the basis of the Cochrane Collaboration's tool and the Newcastle Ottawa Scale.[22]

Statistical Analysis

For the primary outcomes of interest, studies were pooled in a meta-analysis. Data were separated into subgroups: studies reporting on congenital diaphragmatic hernia, abdominal wall defects, and esophageal atresia. Because all included articles were observational cohort studies, there was no control group to perform an Inverse Variance Random Effect weighted metaanalysis. Because the original data of the studies that were used in the analysis were not available, random numbers with the same mean and SD of these studies were generated using SPSS. This procedure was repeated 10 times. Subsequently, these combined numbers were compared using a 1-sample *t* test versus a reference population consisting of a normative healthy population mean (Mental Development Index [MDI] or Psychomotor Development Index [PDI]) of 100 and SD of 15. The results are displayed in forest plots. Since multiple studies have shown that the BSID-III overestimates development in comparison with the BSID-II, we decided to subtract 8 points from results obtained with BSID-III to combine these with BSID-II data.[18,23,24] The value of I2 was used[25] (Higgins et al.) to describe the percentage of total variation across studies, to give a value to the inconsistency of the studies' results, and to quantify the effect of heterogeneity. A regression analysis on the meta-analysis on specific risk factors was not performed due to both the heterogeneity of the studies and the study designs being observational. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement was followed where appropriate.

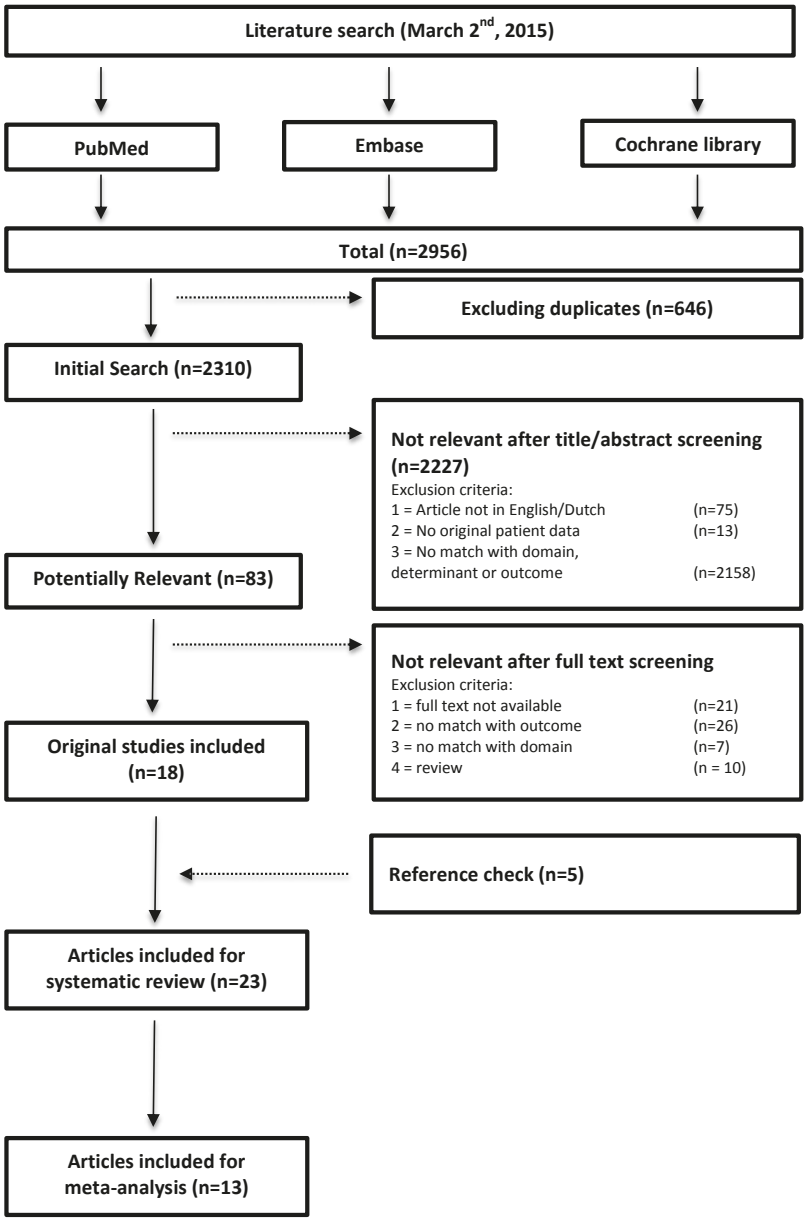


Figure 1. Flow chart illustrating details of the search strategy and the study selection process

RESULTS

The literature search identified 2310 potentially relevant publications. After screening of title/abstract followed by full text, 23 papers[6,7,25–44] reporting on 895 children met our inclusion and exclusion criteria and were selected for systematic review (Table 1). There was a wide range in follow-up duration and time of assessment from 12 months up to 60 months of age. Details of selection and exclusion of studies are specified in Fig 1. Almost all studies (n = 14) used a prospective cohort design (Tables 2 and 3).

Thirteen[6,7,25,26,28,29,31,36–41] of 23 studies were eligible for conducting a meta-analysis. These studies were published between 1995 and 2015 and reported data using BSID from a total of 511 children at 12 or 24 months of age, after excluding syndromal and genetic disorders (Table 3).

Table 1. Clinical Trials Reporting Neurodevelopmental Outcome in Surgical Patients With NCCA

Study	Year	Period of inclusion	Single Anomaly	n	Assessment Tool	Age at Assessment (mo) or Mean ± SD (Range)
Meta-analysis						
d'Agostino et al	1995	1990–1992	CDH	13	BSID-II	12
Ahmad,et al	1999	1985–1994	CDH	11	BSID-II	24
Cortes et al	2005	NR	CDH	16	BSID-II	24
Chen et al	2007	2000–2003	CDH	13	BSID-II	19 (8–40)
South et al	2008	2003–2005	Gastroschisis	17	BSID-II	20 (16–24)
Faugli et al	2009	1999–2002	EA	36	BSID-II	12
Gischler et al	2009	1999–2003	—	69	BSID-II	24
Danzer et al	2010	2004–2007	CDH	27	BSID-III	24, 36, 60
Laing et al	2011	2002–2004	—	45	BSID-III	24.2 ± 4.29 (18–35)
Aite et al	2013	2008–2012	Low-risk EA	30	BSID-III	12
Walker et al	2013	2006–2008	EA	31	BSID-III	12
Wynn et al	2013	2007–2010	CDH	48	BSID-III	24.6 ± 1.3
Bevilacqua et al	2015	2008–2012	—	155	BSID-III	12
Systematic review						
Davenport et al	1992	1983–1989	CDH	23	GMDS	56 (18–94)
Stolar et al	1995	1983–1993	CDH	51	GMDS	31 (2–86)
Somaschini et al	1999	1994–1998	CDH	12	GMDS	12
Buesing et al	2007	2001–2005	CDH	30	BSID-II	3, 6, 12, 24
Cammen-van Zijp et al	2010	1999–2003	—	102	M-ABC	6, 12, 24, 60
Payne et al	2010	1999–2007	Gastroschisis	57	BSID-III	39.1 ± 26.2
Rocha et al	2012	1997–2010	CDH	39	GMDS	3, 6, 9, 12, 18, 24
Gorra et al	2012	2001–2008	Gastroschisis	46	TIPS	24
Benjamin et al	2013	2001–2005	CDH	16	WPPSI-III	59
Van Eijck et al	2013	2004–2007	Omphalocele	8	M-ABC-II	71 (42–141)

EA, esophageal atresia; GMDS, Griffiths' Mental Development Scales; TIPS, Developmental Tracking Infant Progress Statewide; WPPSI, Wechsler Preschool and Primary Scale of Intelligence

Table 2. Risk of Bias Summary Included Studies Meta-Analysis

Study (year)	d'Agostino, et al (1995)	Ahmad, et al (1999)	Cortes, et al (2005)	Chen, et al (2007)	South, et al (2008)	Faugli, et al (2009)	Gischler, et al (2009)	Danzer, et al (2010)	Laing, et al (2011)	Aite, et al (2013)	Walker, et al (2013)	Wynn, et al (2013)	Bevilacqua, et al (2015)
Prospective design	+	-	+	-	+	+	+	+	+	+	+	+	+
Complete report on loss to follow-up	+	+	+	+	+	+	+	+	+	+	+	+	-
Exclusion of genetic/syndromal	NR	-	+	+	-	+	+	+	+	+	+	-	+
Potential other sources of bias	(a)	(a,b,c)	(e)	(c)	(c,d)	-	-	-	-	(f)	(b,c)	-	-

Table 3. Patient Characteristics Meta-Analysis

Study	*n*	Patient Characteristics						Surgery specifications			Follow-up
		Gestational age (weeks)	Birth weight (grams)	Boys n (%)	Apgar score 1 min	Apgar score 5 min	Age at 1st surgery (days)	Surgical interventions 1st 24 months	Assisted ventilation (days)	LOS (days)	Neuro-developmental delay (%)
D'Agostino, et al (1995)	13	38.0 ± 2	3180 ± 460	9 (56%)	4 ± 3	6 ± 3	1-8	NR	29 (4-605)	86.5 (15-605)	46%
Ahmad, et al (1999)	11	38.5 ± 2.4	3170 ± 620	53%	5 (1-8)	7 (2-9)	NR	NR	NR	NR	NS
Cortes, et al (2004)	16	37.4 ± 1	3150 ± 490	13 (81%)	NR	NR	6.4 ± 2.1	3.75	29.6 ± 10	62.1 ± 28.7	57%
Chen, et al (2007)	13	37.6 ± 1.6	3000 ± 500	8 (61.5%)	NR	7 (1-9)	39.1± 2.0*	NR	14 (5-55)	53 (26-295)	77%
South, et al (2008)	17	35.5 ± 1.9	2360 ± 731	6 (35%)	NR	NR	NR	NR	6.5 ± 5.3	33 (21-50)	24%
Faugli, et al (2009)	36	NR	2830 (595-4570)	27 (69%)	NR	NR	2	1 (1-5)	NR	21 (13-270)	11%
Gischler, et al (2009)	88	38.3 (36.8-40.0)	3000 (2500-3300)	47 (53.4%)	8 (7-9)	9 (8-9)	NR	3 (1-4)	NR	30 (21-64)	25%
Danzer, et al (2010)	41	37.2 ± 2.7	2971 ± 508.8	20 (49%)	6 (1-9)	8 (4-9)	6.8 ± 5.8	NR	25.8 ± 32.2	NR	54%
Laing, et al (2011)	45	38.2 ± 1.84	3174 (1852-4215)	32 (71%)	9 (1-9)	9 (3-10)	2 ± 4	1.5 ± 0.94	2.42 ± 4.54	23.3 ± 17.13	43%
Aite, et al (2013)	30	38 (33-42)	2650 (1595-3575)	NR	NR	NR	NR	3 (1-7)	5 (1-30)	22.5 (14-138)	NS
Wynn, et al (2013)	48	38 ± 1.6	0.60 - 1.07#	NR	6±2	8±2	NR	NR	NR	39 (11-211)	48%
Walker, et al (2013)	31	37.6	2718 ± 717	11 (36%)	NR	NR	1 - 2	NR	NR	19 (8-134)	23%
Bevilacqua, et al (2015)	156	38 (36-39)	2870 (2437-3258)	99 (63.9%)	NR	NR	NR	1 (1-2)	4 (0-8)	27 (18.5-49.8)	19%

Cognitive Development

Systematic Review

By reviewing all articles, a delay in cognitive development in all children with NCCA was found to be reported in a median of 23% (range 3%–56%).

Meta-Analysis

Meta-analysis in 498 infants showed a cognitive development score of 0.5 SD below the population reference mean, expressed as MDI score of 92 ± 13 (mean ± SD)[6,7,25,26,28,29,31,36–38,40,41] (Fig 2A), with data from BSID-II and -III at 12 and 24 months of age. One-sample *t* tests demonstrated that the mean MDI was significantly lower than the healthy population mean of 100 ($P < .001$; 95%, confidence interval [CI] 91.7–94.2).

Selecting only data assessed at age 24 months, a similar result was found ($n = 185$, MDI 92 ± 15, $P < .001$; Fig 2B). Including only studies from the past 10 years, the same result was found (MDI 92 ± 13; $P < .001$; 95% CI 91.6–94.1). The heterogeneity of the study results was found to be high. Factors including gestational age, birth weight, prematurity, diagnosis, exclusion of chromosomal and genetic syndromes and correction of the neurodevelopmental score for gestational age could not be identified as possible explanations for this heterogeneity. More patients were lost to follow-up in the older studies (18%–48%) compared with more recent studies (9%–28%).

Motor Development

Systematic Review

Examining all studies, median delay in motor development in all children with NCCA was 25%, ranging from 0% to 77%. In 1 study, the motor development of 102 children with NCCA was investigated with the M-ABC at a mean age of 5.7 years.[30] A delay in motor development (<1SD) was found in 29% of those with NCCA. Most of these patients had CDH or esophageal atresia, and a significant correlation with repeat surgery was found. The motor score correlated negatively with the total number of congenital anomalies.

Meta-Analysis

Thirteen studies contributed data to the quantitative motor outcome analysis.[6,7,25,26,28,29,31,36–41] This meta-analysis in 511 children resulted in a motor development score of 0.6 SD below the population average, indicated by the PDI score of 91 ± 14 (Fig 3A). One-sample *t* tests demonstrated that the mean PDI was significantly lower than the healthy population mean of 100 ($P < .001$; 95% CI 89.8–92.1). Using only data assessed at 24 months of age, a similar result was found ($n = 185$; PDI 90 ± 14; $P < .001$; Fig 3B). Including only studies from the past 10 years, the same result was found (PDI 91 ± 13; $P < .001$; 95% CI 90.1–92.4).

Figure 2a. Cognitive Development
MDI-score of all patients with NCCA at 12 & 24 months of age

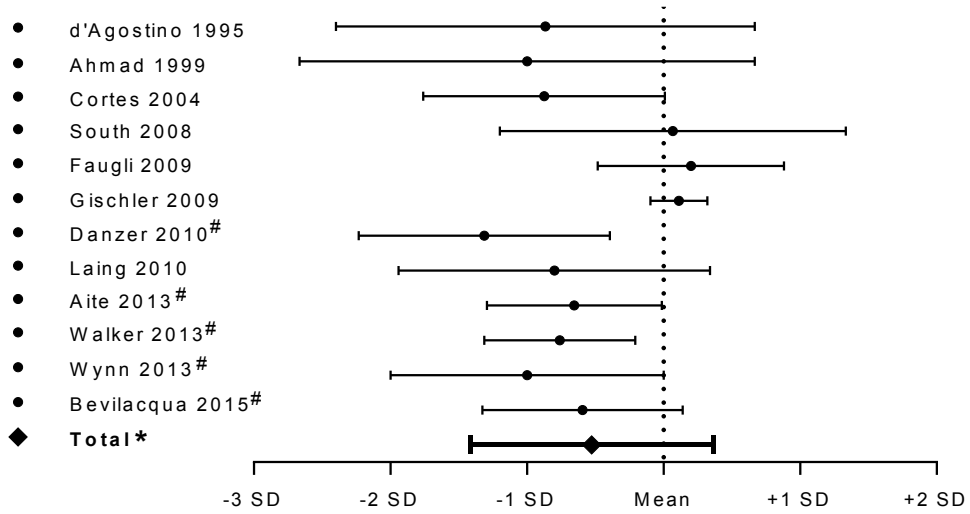


Figure 2b. Cognitive Development
MDI-score of all patients with NCCA at 24 months of age

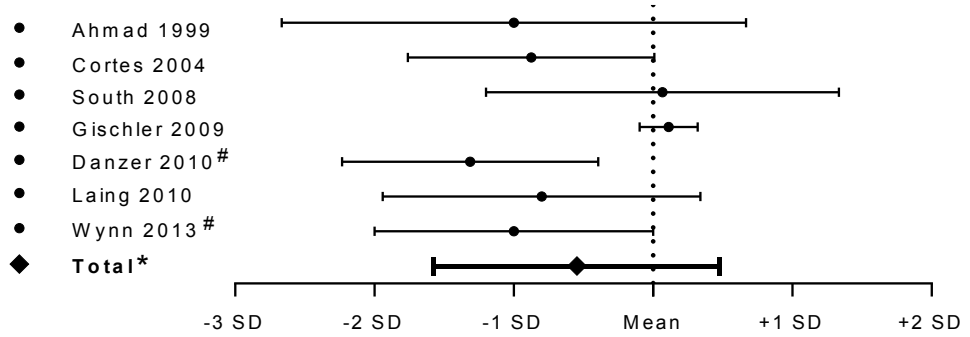
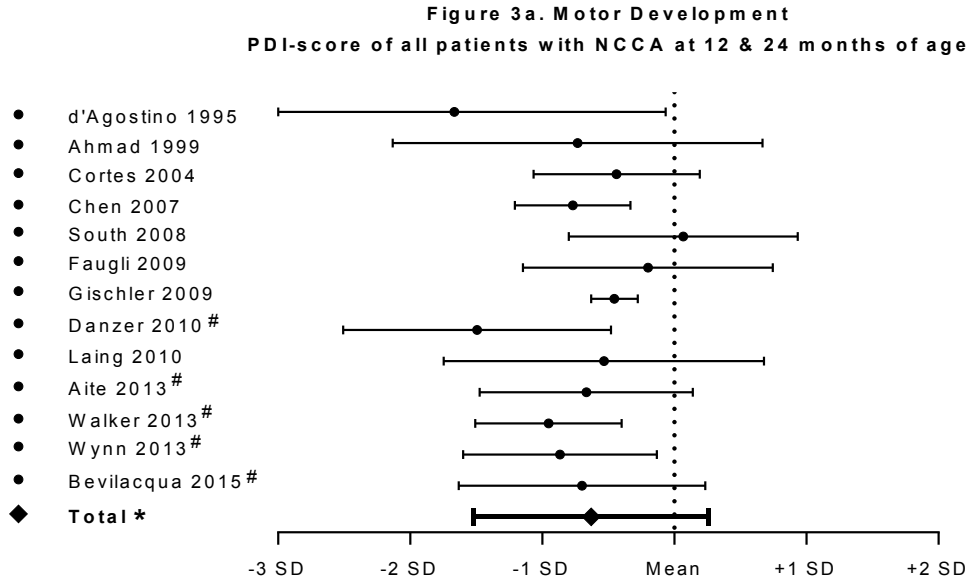


Figure 2a & 2b. Forest plot of meta-analysis of the cognitive developmental outcome in all patients with NCCA, expressed by the MDI-score of the Bayley Scales of Infant and Toddler Development version II and III, at 12 and 24 months of age (2a) and solely at 24 months of age (2b). The scores are displayed in comparison to the reference scores of the healthy population. *One sample t-tests demonstrated that the mean MDI was significantly lower than the population mean of 100 ($p<0.001$). # BSID third version, of which 8 points are subtracted from the mean.



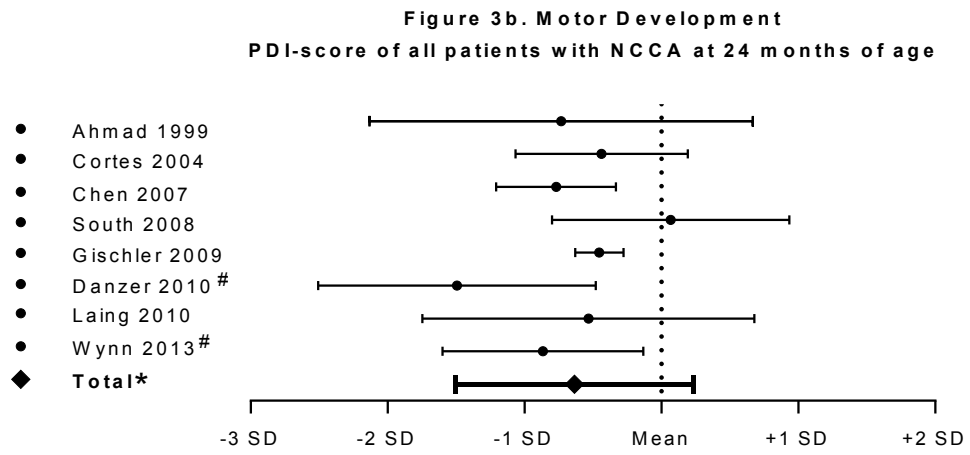


Figure 3a & 3b. Forest plot of meta-analysis of motor outcome in all patients with NCCA, expressed by the PDI-score of the Bayley Scales of Infant and Toddler Development version II and III, at 12 and 24 months of age (3a) and solely at 24 months of age (3b). The scores are displayed in comparison to the reference scores of the healthy population. * One sample t-tests demonstrated that the mean PDI was significantly lower than the population mean of 100 ($p<0.001$). # BSID third version, of which 8 points are subtracted from the mean.

Subgroups

Data were reported separately in 3 NCCAs: congenital diaphragmatic hernia (CDH), abdominal wall defects, and esophageal atresia.

CDH

When systematically reviewing all articles reporting on congenital diaphragmatic hernia, the need for extracorporeal membrane oxygenation (ECMO) was reported as a predictor for worse outcome.[31,38] Neuroimaging with cerebral computed tomography (CT) scanning in patients who had undergone ECMO for CDH revealed abnormalities in 75% of patients with neurodevelopmental delay in 42%.[45]

To evaluate the data on CDH patients quantitatively with a meta-analysis, we divided patients with NCCA into 2 subgroups: studies solely reporting on CDH[26,31,39–41] (*n* = 128, "CDH only") and studies reporting on all other NCCA[6,7,27–29,36–38] (*n* = 383, "Other group"), with a limited percentage of CDH (25% at most). Table 4 shows that the MDI and PDI scores of the subgroup with CDH patients are 1 SD below the population mean, indicating a mild to moderate delay, with low heterogeneity among these studies.

Table 4. Meta-analysis CDH

	All NCCA (n=511)	CDH-only (n=128)	Other NCCA# (n=383)
MDI-score (mean±SD)	92.1 ± 13*	84.5 ± 15*	94.0 ± 12*
PDI-score (mean±SD)	90.6 ± 14*	85.2 ± 15*	91.8 ± 13*

Abdominal Wall Defects

By reviewing all studies reporting on abdominal wall defects, neurodevelopmental delay was reported in 0% to 24% of 128 patients with abdominal wall defects.[28,32,33,46] In 1 study (*n* = 46), neurodevelopment was assessed as part of a state-sponsored follow-up program for all infants discharged from intensive care in the state of Nebraska, United States (the Developmental Tracking Infant Progress Statewide program). No differences were found in delay between patients with simple gastroschisis and matched control subjects.[32] Motor outcome in 8 patients with giant omphalocele, tested with the M-ABC at 6 years of age, was found to be normal.[46]

Esophageal Atresia

Three articles[25,29,36] reported solely on infants with esophageal atresia and their short-term neurodevelopmental outcome at 1 year of age. By systematically reviewing these articles, a delay was reported in 11% to 38%. Meta-analysis (*n* = 100) showed an MDI score and motor score of 0.5 SD below the reference population (MDI 94 ± 13 and PDI 92 ± 14; *P* = .009).

Risk Factors

When reviewing all studies for risk factors, only 5 studies[6,7,28,30,37] were found to report on perinatal risk factors associated with an increased risk of an adverse neurodevelopmental outcome. Two studies found that low birth weight[6] and prematurity[28] were associated with lower PDI scores. A higher number of congenital anomalies also significantly increased the risk of neurodevelopmental delay.[7,30,37]

Neuroimaging with either cerebral ultrasonography, CT, or MRI scanning was reported in 11 studies,[7,26,27,31,34,35,40–42,45,47] and 10 of these articles reported solely on CDH. In 7 studies,[7,34,40–42,45,47] the correlation between brain damage and neurodevelopmental outcome was not explored, and in 4 studies,[26,27,31,35] no significant correlation was found.

Duration of hospital admission was positively correlated with a delay in neurodevelopment.[7,26,28,37,40] A higher number of surgical interventions was found to be correlated with a lower cognitive and motor outcome.[6,7,29,30,37] Duration of mechanical ventilation[29,31,35,37,40,42] and the need for supplemental oxygen at discharge[26] were both reported as risk factors for neurodevelopmental delay.

A delay in growth after neonatal surgery for NCCA during follow-up was reported in 5 studies with an incidence of 13% to 35%[25,26,28,31,40] (Supplemental Table 5). Only 1 study showed neurodevelopmental scores to be significantly lower in children with a delay in growth at 1 year of age.[25] None of the studies reported on nutritional information.

Socioeconomic parameters, such as educational level of the parents, were reported in 7 studies including 383 patients.[6,7,25,29,37,38,43] One study showed a positive correlation of educational level with neurodevelopmental outcome[43] (Supplemental Table 6).

DISCUSSION

Our systematic review and meta-analysis identified >2000 publications by searching the available databases for neurodevelopmental outcomes in children with major NCCA requiring neonatal surgery. Only 23 prospective and retrospective cohort studies that reported neurodevelopmental outcome after neonatal surgery for NCCA could be identified, representing 895 patients. Of these, data from only 13 articles could be pooled in a meta-analysis. The majority of studies on neurodevelopment and NCCA are heterogeneous and lack standardization in follow-up assessment.

In this systematic review, the median reported neurodevelopmental delay was 23% but varied widely (0%–77%) for several reasons. First, in most studies, patient groups were heterogeneous, consisting of various congenital anomalies. As a result of small patient numbers, authors chose to pool different congenital malformations that shared a requirement for neonatal surgery.[6,7,30,37] Second, parameters that may influence neurodevelopmental outcome, such as gestational age,[28] duration of hospital admission,[7,26,28,40] and repeat surgery,[6,7,29,30] varied within and among patient cohorts.

The meta-analysis showed a mean cognitive and motor score (determined by the BSID) of 0.5 to 0.6 SD below the normative score of the healthy population. Interestingly, short outcome scores at 12 months of age did not differ from outcome scores at age 24 months (Figs 2 and 3). Children with NCCA are systematically excluded from longitudinal studies because of their higher risk

of chromosomal disorders and syndromes, influencing neurodevelopment.[7,48] The evidence gathered in this study shows that even after exclusion of syndromal and chromosomal disorders, these children have a 23% risk of an adverse neurodevelopmental outcome. Surprisingly, excluding data from studies of >10 years ago did not influence the neurodevelopmental outcome scores: even though survival has increased, neurodevelopmental outcome remains unchanged. This pattern is similar to that reported in extremely preterm infants. The EPICure studies have shown increased survival of infants born between 22 and 25 weeks' gestation, while their morbidity was not affected.[49] These results stress even further the importance of monitoring neurodevelopmental outcomes in patients with NCCA.

The subgroup with CDH demonstrated a mean cognitive score below −1 SD. These patients generally represent the most severe group of NCCA because they can develop more complications, including prolonged periods of hypoxia and the need for ECMO, due to lung hypoplasia and pulmonary hypertension. The incidence of neurodevelopmental delay in the subgroup of abdominal wall defects is remarkably low. This may be explained by the small sample sizes of these studies[28,32,33,46] (n = 8 and n = 17). Payne et al reported "a generally encouraging outcome of patients with gastroschisis." However, considering the severity of the anomaly, the authors advised close follow-up throughout childhood.

Risk factors that negatively influence neurodevelopment include low birth weight,[6] higher number of congenital anomalies,[7] a longer hospital stay,[7,26,28,40] duration of mechanical ventilation,[29,31,35,40,42] and need for supplemental oxygen at discharge.[26] However, data to evaluate longer-term neurocognitive outcomes associated with these risk factors were limited in the studies that were included in this review.

Neuroimaging after surgery in children with congenital heart disease has revealed brain injury occurring in the perioperative period, possibly contributing to the risk of adverse neurodevelopment.[8] Also, impairment in brain growth and maturation has been described,[50,51] with an increased vulnerability to white matter injury. To date, the prevalence of brain lesions in surgical patients with NCCA is unknown.[12] Several studies in this review have reported on neuroimaging, but none showed a correlation with development. Ultrasound or CT were most frequently used, whereas MRI was not performed routinely in any study, despite it being the most sensitive diagnostic tool for detection of brain injury. Theoretically, comparable to the cardiac group, patients with NCCA are also at risk for developing perioperative brain damage.[14,52] Inflammation is among the known risk factors for developing brain injury.[53,54] Patients with NCCA can be more susceptible to neuronal damage, and preoperative inflammation in patients with gastroschisis can be considerable.[55] The discussion on the neurotoxic effect of inhalational anesthetics on the immature brain is also ongoing.[10] To date, there is no clinical evidence of the adverse effect in the human brain.

A number of limitations need to be considered. First, a limitation of this systematic review is the heterogeneity of the included studies. All data were obtained from studies with small sample sizes and various congenital anomalies using different neurodevelopmental assessment tools. Moreover, the studies described are all observational. Because longitudinal follow-up data are scarce, it is unclear whether these children have delayed longer-term neurodevelopment or grow into their deficits after age 2. Second, different versions of the BSID are used, the BSID-II and the BSID-III. After considering multiple reports about the higher scores of the BSIDIII, we decided to subtract 8 points from the mean of the BSID-III, on the basis of several recent studies, to be able to compare these scores to the BSID-II. Because even larger differences have been reported, we believe this method is reasonable, although consensus in the literature has not yet been reached.[18,23,24]

CONCLUSIONS

Our systematic review and meta-analysis show that patients with NCCA requiring surgery have a higher risk of neurodevelopmental delay. Although it is crucial to identify which parameters increase the risk for delay, data about risk factors are scarce. Future studies are required to perform structured follow-up with specific neurodevelopmental assessment tests and neuroimaging in children with NCCA to elucidate early brain injury as a probable cause of developmental delay.

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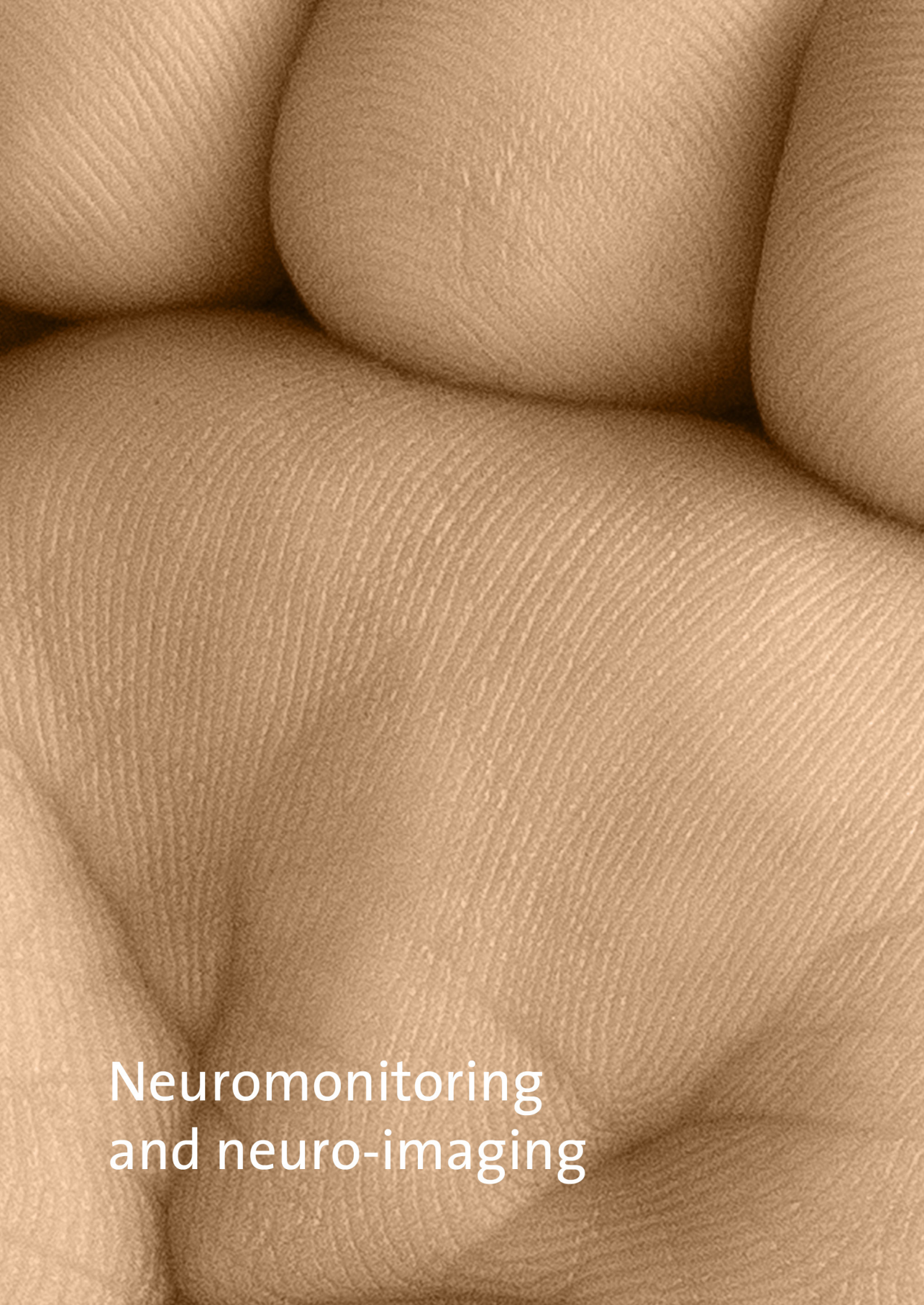
Supplemental table 5. Studies reporting on follow-up

Study	n	Growth delay n (%)	Height delay n (%)	Head circumference delay n (%)
D'Agostino, et al (1995)	16	2 (13%)[a]	2 (13%)[a]	2 (13%)[a]
Cortes, et al (2004)	16	-2.22[b]	-0.6*[b]	-0.35*[b]
South, et al (2008)	17	5 (29%) -0.26±1.46	6 (35%) -0.14±1.59	0 0.36±1.09
Danzer, et al (2010)	41	34.0±29.5[c]	41.9±26.6[c]	61.5±30[c]
Aite, et al (2013)	33	5 (16.7%)[a]	NR	NR

Supplemental table 6

Study	Mother's education						Father's education					
	Mother's age (years)	Primary school n(%)	Secundary school n(%)	High school n(%)	Tertiary or further education n(%)	Bachelor degree or higher n(%)	**Father's age (years)**	Primary school n(%)	Secundary school n(%)	High school n(%)	Tertiary or further education n(%)	Bachelor degree or higher n(%)
Stolar, et al (1995)[a]	NR	NR	22%	26%	24%	29%	NR	NR	NR	NR	NR	NR
Faugli, et al (2009)	31(25-44)[#]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gischler, et al (2009)	31(18-45)[#]	NR	NR	NR	NR	NR	33 (19-50)[#]	NR	NR	NR	NR	NR
Laing, et al (2011)	30.5±6	10(22%)	12(27%)	NR	14(31%)	9(20%)	NR	5(11.4%)	NR	9 (18%)	13 (30%)	18 (41%)
Wynn, et al (2013)	29.5±5.6	NR	NR	25 (41%)	24 (49%)	NR	31.6±6.2	NR	NR	25 (51%)	23 (47%)	NR
Aite, et al (2013)	NR	NR	4 (13.3%)	16(53%)	NR	10(33%)	NR	3(10%)	NR	18 (60%)	NR	9 (30%)
Bevilacqua, et al (2015)	33(30-38)*	0	100(65%)	23(15%)	NR	42(27%)	36 (31-40)*	1(0.6%)	30(19%)	96 (62%)	NR	28 (18%)

PART 2



Neuromonitoring and neuro-imaging

3

CHAPTER

Neonatal Surgery for Noncardiac Congenital Anomalies: Neonates at Risk of Brain Injury

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ABSTRACT

Objective: To evaluate the incidence of brain injury after neonatal surgery for noncardiac congenital anomalies using magnetic resonance imaging (MRI).

Study design: An MRI was obtained in 101 infants at 7 days [range: 1-115] after neonatal surgery for major noncardiac congenital anomalies. Brain injury was assessed using T1, T2, diffusion weighted imaging, and susceptibility weighted imaging.

Results: Thirty-two preterm infants (<37 weeks of gestation) and 69 full-term infants were included. MRI abnormalities were found in 24 (75%) preterm and 40 (58%) full-term infants. Parenchymal lesions were noted in 23 preterm (72%) and 29 full-term infants (42%). These consisted of punctate white matter lesions (n = 45), punctate cerebellar lesions (n = 17), thalamic infarction (n = 5), and periventricular hemorrhagic infarction (n = 4). Nonparenchymal abnormalities were found in 9 (28%) preterm and 26 (38%) full-term infants. These included supra- and infratentorial subdural hemorrhages (n = 30), intraventricular hemorrhage grade II (n = 7), and asymptomatic sinovenous thrombosis (n = 1). A combination of parenchymal lesions was present in 21 infants. Of infants who had an MRI within 10 days after surgery, punctate white matter lesions were visible on diffusion weighted imaging in 22 (61%), suggestive of recent ischemic origin. Type of congenital anomaly and prematurity were most predictive of brain injury.

Conclusions: Infants who have neonatal surgery for noncardiac congenital anomalies are at risk of brain injury, potentially accounting for the neurodevelopmental delay frequently observed in this population. Further research is warranted into potential mechanisms of brain injury and its timing of onset. Long-term neurodevelopmental follow-up is needed in this vulnerable population.

INTRODUCTION

Survival following neonatal surgery for major noncardiac congenital anomalies has improved to more than 95%.[1,2] In recent years, increasing concerns have been raised about the incidence of neurodevelopmental delay in children who underwent neonatal surgery for noncardiac congenital anomalies.[3,4] Although deficits can be ascribed to associated genetic syndromes (eg, Down syndrome) in some children, cognitive and motor problems also occur in up to 45% of children with isolated anomalies.[3]

The etiology of neurodevelopmental impairments is currently unknown, but several potential risk factors have been proposed.[5] Although the General Anaesthesia compared to Spinal Anaesthesia (GAS) study showed that a single episode of general anesthesia was not associated with 2-year neurodevelopmental outcomes,[6] multiple surgical procedures at a young age are associated with a significantly higher rate of behavioral problems in children.[7-9] Experimental studies have demonstrated increased apoptosis because of general anesthetics in the young animal brain.[10] Impaired cerebral autoregulation has been observed in full-term infants receiving anesthesia, increasing the risk for disturbances in cerebral perfusion. Preterm infants may be even more susceptible to cerebral hypoperfusion as a result of limited cerebral autoregulation because of immaturity.[10-13] As many as 73% of infants with critical congenital heart disease display brain lesions after neonatal surgical repair.[14] Severe postoperative brain injury was recently reported in a case series of 6 neonates who had elective surgery. The authors suggested that cerebral hypoperfusion from perioperative hypotension or hypocapnia may have contributed to a predominantly watershed pattern of injury.[15]

To date, there has not been a systemic evaluation of the incidence of brain injury after neonatal surgery for noncardiac congenital anomalies. At our institution, a clinical neuromonitoring program was initiated in 2013, including postoperative neuroimaging and perioperative cranial ultrasonography (cUS) in infants who needed neonatal surgery for noncardiac congenital anomalies. This offered an opportunity to study perioperative brain injury in infants undergoing neonatal surgery. The aim of this study was to evaluate the incidence and pattern of brain injury following neonatal surgery for noncardiac congenital anomalies and to identify perinatal and perioperative risk factors.

METHODS

In January 2013, magnetic resonance imaging (MRI) was implemented as clinical care after neonatal surgery for noncardiac congenital anomalies to evaluate brain injury. To detect recent ischemic injury, neuroimaging was performed, preferably within 10 days after surgery at the discretion of the attending physician in the neonatal intensive care unit. The Institutional Review Board of the University Medical Center Utrecht, The Netherlands, approved the use of

the clinically acquired data for the purpose of the study and waived written parental informed consent. Exclusion criteria consisted of congenital anomalies of the central nervous system and critical congenital heart disease requiring surgical repair in the neonatal period.
cUS was performed upon admission to the neonatal intensive care unit before surgery, and repeated postoperatively. Serial bedside cUS was part of routine clinical care and images were included to assist in the evaluation of timing of injury. The attending neonatologist performed cUS according to a standard clinical protocol using a Toshiba AplioMachine (Toshiba Medical Systems, Zoetermeer, The Netherlands). MRI was performed on a 3.0 Tesla whole-body Achieva system (Philips Medical Systems, Best, The Netherlands).
Infants were sedated per clinical protocol and placed in a vacuum fixation pillow. For hearing protection Minimuffs (NatusMedical Incorporated, San Carlos, California) and Earmuffs (Ems for kids, Brisbane, Australia) were used. A neonatologist or physician assistant monitored the infant throughout the examination. Routine protocol included coronal 3-dimensional (3D) T1-weighted and T2-weighted imaging (3D T1-weighted repetition time [TR] 9.5 ms; echo time [TE] 4.6 ms; slice thickness 1.2 mm and T2-weighted TR 4847 ms; TE 150 ms, slice thickness 1.2 mm), as well as diffusion weighted imaging (DWI) (including a DWI-derived apparent diffusion coefficient map and single-shot echo planar imaging in 3 orthogonal directions; 33 slices; slice thickness 3 mm; TR 5270 ms; TE 108 ms; b-values of 0 and 800 mm2/s, no gap). Additional sequences, including susceptibility weighted imaging (SWI) (3D gradient-echo sequence with flow compensation, multishot echo-planar imaging; TR 52 ms; TE 30 ms, slice thickness 2 mm and echo-planar imaging factor 3), magnetic resonance venography (3D/magnetic resonance venography TR 18.4, TE 6.377, voxel size 0.90 mm, slice/dis 2/1 mm, phase contrast 15 cm/s, slices 130), and magnetic resonance angiography were performed based on imaging findings on the T2-, T1- , and DWI images if considered necessary.

Two neonatologists systematically evaluated and scored the cUS images. Two neonatologists, with more than 10 years of experience in the interpretation of neonatal brain MRI, evaluated all scans. The following abnormalities were systematically scored: parenchymal lesions including punctate white matter lesions defined as <6 or ≥ 6 and described as cluster, linear, or mixed lesion pattern,[16] cerebellar hemorrhage, thalamic, and/or cortical infarction, and periventricular hemorrhagic infarction. Nonparenchymal abnormalities were defined as subarachnoid and subdural hemorrhage, grade I-III intraventricular hemorrhage, classified according to the grading system of Papile et al,[17] and sinovenous thrombosis without associated intracranial lesions.

Anesthesia

All patients were subjected to a standardized anesthesia protocol. For the induction of anesthesia sevoflurane (6%-8% inspired concentration) was used with a 40%-100% fraction of inspired oxygen. Muscle relaxation was applied with atracurium besylate (0.5 mg/kg), rocuronium (0.6 mg/kg), or suxamethonium (1-2 mg/kg), and the patient was intubated. Pain medication consisted of sufentanil, morphine, or bupivacaine by epidural. Dosages varied at the discretion

of the attending pediatric anesthesiologist (**Table I**). Blood samples were taken every 30 minutes as part of routine clinical care. Ventilation settings and depth of anesthesia were adapted to maintain individual values of arterial oxygen saturation, end tidal carbon dioxide (CO_2), heart rate, and mean arterial blood pressure.

Table I. Clinical characteristics

	Total (n=101)	Preterm (n=32)	Full-term (n=69)
Gestational age (weeks)	38.3[30.9-41.9]	34.3[30.9-36.9]	39.1[37.0-41.9]
Birth weight (grams)	2800[1220-4490]	2250[1220-2995]	3060[2155-4490]
Birth weight z-score	-0.65[-3.4-1.3]	-0.53[-2.7-1.2]	-0.89[-3.4-1.3]
Sex (male)	55 (55%)	16 (50%)	39 (56%)
Apgar score (5 minutes)	10 [2-10]	9 [3-10]	10 [2-10]
Syndrome*	5(5%)	1(3%)	4(6%)
Mode of delivery			
Vaginal birth, n(%)	66 (65%)	20 (63%)	46 (67%)
Ventouse extraction, n(%)	10 (10%)	2 (6%)	8 (11%)
Caesarean section, n(%)	25 (25%)	10 (31%)	15 (22%)
Severity of illness			
Culture proven sepsis n(%)			
- *postoperatively prior to MRI*	8 (8%)	2 (6%)	6 (9%)
Preoperative mechanical ventilation, n(%)	25 (25%)	10 (31%)	15 (22%)
Total days of mechanical ventilation	2 [0-145]	3 [0-76]	1 [0-145]
Surgery			
Postnatal age (days)	2 [0-29]	2 [0-29]	2 [0-26]
Corrected GA (weeks)	39.1 [31.9-44.1]	35.2 [31.9-38.3]	39.9 [37.0-45.1]
Duration of anesthesia (minutes)	184 [60-563]	186 [60-490]	182 [63-563]
Duration of surgery (minutes)	108 [15-475]	109 [25-422]	105 [15-475]
Multiple surgeries before MRI, n(%)	17(17%)	6(6%)	11(11%)
MRI			
Time after surgery (days)	7 [1-115]	8 [4-44]	7 [1-115]
Scanned within 10 days, n(%)	87(86%)	26(81%)	61(88%)
Corrected GA (weeks)	40.6 [32.9-53.4]	36.6 [32.9-42.1]	40.9 [38.0-53.4]
Anesthesia			
Type of anesthetic			
Sevoflurane n(%)	100 (99%)	32 (100%)	68 (99%)
Isoflurane n(%)	1 (1%)	0	1 (1%)
Midazolam n(%)	2 (2%)	0	2 (3%)
Propofol n(%)	22 (22%)	4 (13%)	18 (26%)
End tidal sevoflurane concentration (%)	1.26% (0.04-2.5)	1.0%[0.04 – 2.5]	1.46%[0.4 - 2.5]
Type of pain medication			
Sufentanil, n(%)	96 (95%)	30 (94%)	66 (96%)
Bupivacaine, n(%)	29 (29%)	5 (16%)	24 (35%)
Morphine, n(%)	38 (38%)	15 (47%)	23 (33%)
Type of muscle relaxant			
None, n(%)	6 (6%)	1 (3%)	5 (7%)
Atracurium, n(%)	79 (78%)	23 (72%)	56 (81%)
Rocuronium, n(%)	14 (14%)	7 (22%)	7 (10%)
Suxamethonium, n(%)	1 (1%)	0	1 (1%)

All data is presented in median[range], unless specified otherwise
* One patient with Very long-chain acyl-CoA dehydrogenase, one with CHARGE syndrome, three with Down syndrome

Statistical Analyses

Statistical procedures were performed using IBM SPSS Statistics software package v 20 (IBM Corporation, Armonk,New York). Data are presented as mean±SD or as median and range when indicated. First, differences in clinical characteristics between the subgroups, defined as preterm and full-term infants, were tested using the Mann-Whitney *U* test. The two sub cohorts were tested for differences in the incidence of brain lesions with the Fisher exact test. The significance level was set at an alpha *P* value of < .05. The Mann-Whitney *U* test was used to assess the association between findings of brain lesions and several clinical risk factors.

RESULTS

From January 2013 to December 2015, 114 infants with noncardiac congenital anomalies were admitted to the neonatal intensive care unit for neonatal surgery. Thirteen infants were not eligible for inclusion in this study because no postoperative MRI was available for the following reasons: death (n = 2), metal jaw screws (n = 1), logistic reasons (n = 5), and no parental consent to MRI (n = 5). This resulted in a final sample of 101 infants enrolled in the study (**Tables I**; **Table II; Table III**). Of all patients, 51% were transported from other centers. Inborn or outborn status was not related to the neuroimaging findings (parenchymal injury $\chi 2^2 = 4.464$, $P = .11$; nonparenchymal injury $\chi 2^2 = 1.491$, $P = .47$).

Table II. Incidence major noncardiac congenital anomalies

	Congenital anomaly
Intestinal atresia	22
Esophageal atresia	25
Anorectal malformation	15
Gastroschisis	11
Intestinal duplication cyst	5
Malrotation / Volvulus	5
Obstructive uropathy	5
Extrophia vesicae	4
Long gap esophageal atresia	4
Ovarian cyst	3
Omphalocele	2
Choanal atresia	1
Congenital lobar emphysema	1
Diaphragmatic hernia	1
Morbus Hirschsprung	1
Sacrococcygeal teratoma	1
Tongue cyst	1
Tracheo-esophageal fistula	1

Three patients with multiple anomalies: esophageal atresia and anorectal malformation

The number of postoperative days until MRI acquisition was not statistically different between preterm and full-term infants (**Table I**). Preoperative and postoperative cUS images were available in 99 (98%) and 96 (95%) infants, respectively.

Table III. Abnormalities visible on cUS

	Preoperative cUS	Postoperative cUS	MRI
>6 punctate white matter lesions	9[#]	10[#]	17
Cerebellar lesions	0	3	17
Thalamic infarction	0	4	5
Periventricular hemorrhagic infarction	1	2[*]	4
Extra-axial hemorrhages	0	0	30
Intraventricular hemorrhage grade II	0	0	7
Sinovenous thrombosis	0	1	1

inhomogeneous echogenicity
* 2 postoperative cUS images missing

Neuroimaging Findings

Preoperative cUS showed inhomogeneous echogenicity, suggestive of punctate white matter lesions in 9 infants and a periventricular hemorrhagic infarction in 1 infant. Postoperatively, 10 infants showed inhomogeneous echogenicity, and 1 infant had a dilated superior sagittal sinus, suggestive of a sinovenous thrombosis. None of the grade II intraventricular hemorrhage and subdural hemorrhages that were visible on MRI were identified on cUS. The overlap and differences between cUS and MRI findings are outlined in Table III.

MRI revealed mild to moderate brain abnormalities in 24 (75%) of the preterm and 40 (58%) of the full-term infants (**Table IV**). Several infants displayed a combination of lesions (n = 21, including 6 preterm infants). In 37(37%) infants no brain lesions were present.

Table IV. MRI abnormalities

	Preterm n=32	Full-term n=69
No injury	8(25%)	29(42%)
Parenchymal lesions		
<6 punctate white matter lesions	14(44%)	14[#](20%)
≥6 punctate white matter lesions	9(28%)	8[#](12%)
Punctate cerebellar lesions	6(19%)	11(16%)
Thalamic infarction	2(6%)	3(4%)
Periventricular hemorrhagic infarction	1(3%)	3(4%)
Non-parenchymal abnormalities		
Infra- and supratentorial extra-axial hemorrhages	7(22%)	23(33%)
Intraventricular hemorrhage	4(13%)	3(5%)
Sinovenous thrombosis	0	1(2%)

Fisher's Exact test p<.05 in comparison to preterm incidence. Data is presented in n(%)

Preterm Infants

Parenchymal lesions were observed in 23 (72%) preterm infants. All preterm infants had punctate white matter lesions (<6: n = 14 and ≥6: n = 9). Of the 16 preterm infants who had an MRI within 10 days of surgery, punctate white matter lesions were visible in 11 (69%) on DWI suggestive of an ischemic origin. Four (21%) punctate white matter lesions showed low signal intensity on the SWI and were therefore classified as hemorrhagic. Different patterns of punctate white matter lesions were noted including a cluster appearance in 8 (35%) infants and a mixed appearance in 3 (13%) (**Figure 1**), suggesting an ischemic origin.[16] Punctate lesions in the cerebellum were seen in 6 preterm infants and confirmed to be hemorrhagic in 3 who also had SWI. All cerebellar lesions were accompanied by supratentorial brain lesions: <6 punctate white matter lesions (n = 1); ≥6 punctate white matter lesions (n = 5); thalamic infarction (n = 1), and periventricular hemorrhagic infarction (n = 1). Non-parenchymal abnormalities were present in 9 (28%) preterm infants, including 7 (22%) with extra-axial hemorrhages (**Tables IV** and **V**; **Table VI**).

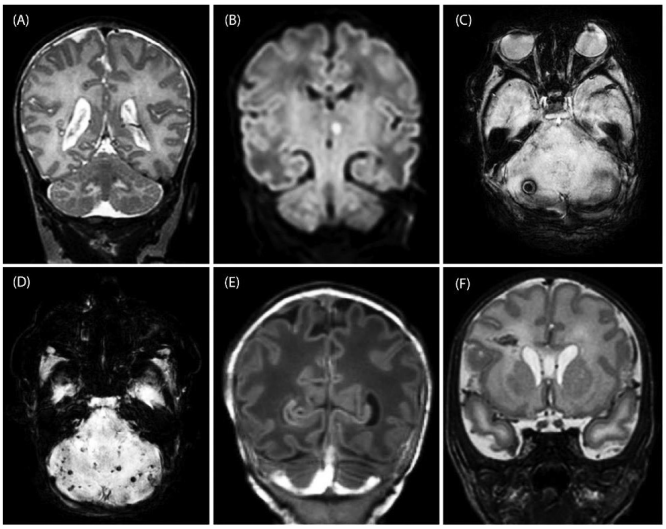

Figure 1. Brain injury visible on MRI in preterm infants. **A,** cT2, 12 days after gastroschisis repair: ≥6 punctate white matter lesions; **B,** cDWI, 6 days after jejunal atresia repair: thalamic infarction; **C,** SWI, 8 days after gastroschisis repair: cerebellar hemorrhage; **D,** SWI, 3 days after urethral valves repair: multiple cerebellar hemorrhages; **E,** cT1, 7 days after duodenal atresia: subdural hemorrhage; and **F,** cT2, 7 days after intestinal atresia repair: periventricular hemorrhagic infarction.

Table V. Extra-axial hemorrhages

	All n=30	Preterm n=7	Full-term n=23
Infratentorial	11 (35%)	1(3%)	10(15%)
Supratentorial	5 (16%)	1(3%)	2(3%)
Infra- and supratentorial	14 (45%)	4(13%)	9(13%)
Subarachnoid	6 (19%)	5*(16%)	4*(6%)

Data are presented in n(%) * Combination subarachnoid and subdural hemorrhages in 4 preterm and 2 full-term infants

Table VI. MRI abnormalities by type of congenital anomaly

	n	Patients with abnormalities	Parenchymal lesions	Nonparenchymal abnormalities
Gastroschisis / omphalocele	15	12(80%)	11(73%)	7(47%)
Intestinal atresia/volvulus/malrotation	32	23(72%)	20(63%)	11(34%)
Urogenital malformation	7	5(71%)	4(57%)	3(43%)
Esophageal atresia	25	13(52%)	9(36%)	6(24%)
Anorectal malformation	12	3(25%)	1(8%)	3(25%)
Other	10	8(80%)	7(70%)	5(50%)

Full-Term Infants

Parenchymal lesions were observed in 29 (42%) of the full term infants. Of 22 full-term infants with punctate white matter lesions, 20 patients were scanned within 10 days after surgery and 11 (55%) of these showed punctate white matter lesions on DWI. In 1 infant, punctate white matter lesions could be classified as hemorrhagic. A cluster appearance was present in 7 (32%), and a mixed appearance was present in 3 (14%), suggesting an ischemic origin.16 Punctate cerebellar lesions were visible on SWI in 7 (78%) scans. All cerebellar lesions, except in 1 infant, were accompanied by supratentorial abnormalities: < 6 punctate white matter lesions (n = 2), ≥6 punctate white matter lesions (n = 4), intraventricular hemorrhage (n = 2), supratentorial subdural hemorrhages (n = 5), and periventricular hemorrhagic infarction (n = 1).

Nonparenchymal abnormalities were visible in 26 (38%) infants (**Tables IV and V**). In 19 patients, a subdural hemorrhage was located in the posterior fossa (**Table V**). Two of these infants were born by vacuum extraction, 2 by cesarean delivery, and 19 infants by an uncomplicated cephalic delivery. An asymptomatic sinovenous thrombosis was found in 1 infant with a gastroschisis who had a complicated postoperative course with cardiorespiratory instability requiring mechanical ventilation with high peak inspiratory pressures and extensive vasopressor support (**Figure 2**). Screening for thrombophilia did not reveal any abnormalities. Therapy with low molecular weight heparin was started and continued for 3 months.

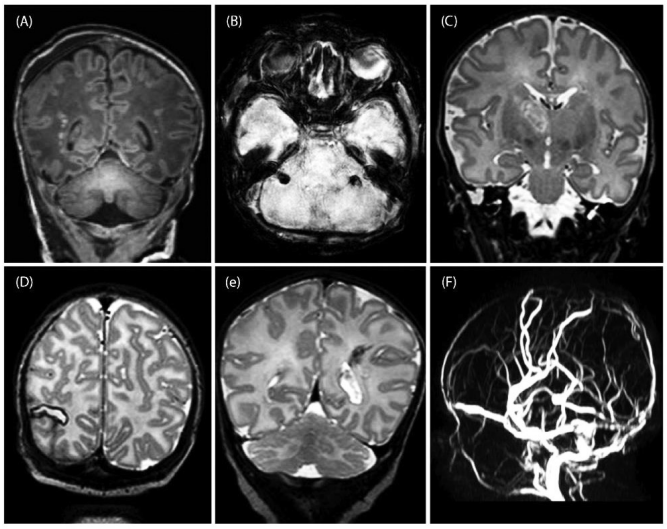

Figure 2. Brain injury visible on MRI in term infants. **A,** cT1, 5 days after gastroschisis repair: ≥ 6 punctate white matter lesions; **B,** SWI, 11 days after esophageal atresia repair: cerebellar hemorrhages; **C,** cT2, 5 days after bilateral megaureter repair: thalamic infarction; **D,** cT2, 6 days after congenital lobar emphysema resection: occipital hemorrhagic infarction; E, cT2, 6 days after tongue cyst repair: periventricular hemorrhagic infarction; and **F,** magnetic resonance venography, 20 days after gastroschisis repair: sinovenous thrombosis.

Risk Factors

Prematurity was significantly associated with parenchymal brain lesions (**Table IV**). Punctate white matter lesions were particularly more prevalent in preterm infants compared with full-term neonates ($P = .04$). In addition, the type of congenital anomaly appeared to be predictive of presence of brain lesions on MRI, with a higher incidence in infants with gastroschisis, intestinal atresia, and esophageal atresia than infants with an anorectal malformation ($P < .01$; **Table VI**;). No other pre-, peri-, or postoperative risk factors could be identified. Several potentially relevant factors in the pathogenesis of or susceptibility to brain injury were investigated, including birth weight, postnatal age at surgery, preoperative respiratory compromise defined as the need for mechanical ventilation before surgery, duration of surgery, signs of hypotension (mean arterial blood pressure < gestational age at the time of surgery) and circulatory failure during and after surgery including vasopressor treatment (fluid bolus or dopamine), hypocarbia (defined as arterial CO_2 <30mmHg, measured every 30 minutes during surgery and whenever indicated before and after surgery), hypoglycemia (glucose < 46.8 mg/ dL), and low arterial pH (<7.35) in the perioperative period, total duration of mechanical ventilation (days), total duration of catheterization using central venous and/or arterial catheters (days), and culture proven sepsis before MRI. None of the children had persistent hypocarbia or hypoglycemia >30 minutes. None of these variables were significantly associated with the presence of parenchymal brain lesions.

DISCUSSION

In a systematic evaluation of the incidence and pattern of brain injury after neonatal surgery for noncardiac congenital anomalies, 52% of the infants demonstrated mild to moderate parenchymal brain lesions, and 35% had nonparenchymal abnormalities including intraventricular hemorrhage and subdural hemorrhages. The type of congenital anomaly seemed to be the best predictor of parenchymal lesions, with up to 73% of infants with gastroschisis displaying lesions, compared with 8% of neonates with an anorectal malformation. Prematurity was also predictive of brain lesions. Predefined perinatal and perioperative risk factors, including signs of cerebral hypoperfusion, hypocarbia, postnatal age at surgery, and prolonged mechanical ventilation, were not significantly related to brain injury.

To date, infants with noncardiac congenital anomalies have not been extensively investigated. These patients are often excluded from large longitudinal studies because their anomalies are frequently associated with chromosomal disorders and genetic syndromes that may affect neurodevelopment. However, even after exclusion of infants with syndromes, children with noncardiac congenital anomalies have been noted to be at risk of neurodevelopmental delay, indicated by a low score (≤1 SD) on the Bayley Scales of Infant and Toddler Development.[3,4] The pathogenesis of neurodevelopmental impairment in these children has not been elucidated, but our study shows that neonatal brain injury may be an important factor.

None of the patients in our cohort displayed visible cortical dysgenesis, such as polymicrogyria or heterotopia. Visible cerebral dysgenesis, thus, is not likely to account for neurodevelopmental deficits as observed in children with noncardiac congenital anomalies. Rather, two predominant patterns of lesions were noted in this study: hypoxic-ischemic white matter lesions and hemorrhagic white matter lesions. The punctate white matter lesions demonstrated in this cohort may result from both hypoxic-ischemic and hemorrhagic processes.[16] In this cohort of infants with noncardiac congenital anomalies, the majority of punctate white matter lesions displayed a mixed or cluster appearance to a linear appearance. The first two are more often associated with ischemic injury, whereas the latter is more frequently related to hemorrhagic injury.[16] When the MRI was obtained within 10 days after surgery, restricted diffusion was present in more than one-half (61%) of the infants, suggesting that timing of onset was most likely in the perioperative phase. Ischemic lesions may be induced by disturbances in cerebral perfusion during surgery. A second risk factor includes an unflammatory state.[18,19] Free oxygen radicals because of high fractions of inspired oxygen also have been suggested to render the neonatal brain susceptible to injury[13,20] and could contribute to these lesions as well.

Hemorrhagic lesions consisted of punctate white matter lesions, periventricular hemorrhagic infarction, punctate cerebellar lesions, and nonparenchymal abnormalities including extra-

axial hemorrhages. Hemorrhagic punctate lesions may arise from fluctuations in cerebral perfusion. Pressure passive cerebral circulation is common in preterm infants as a consequence of immature autoregulatory ability; impaired cerebral autoregulation also has been observed in full-term infants receiving anesthesia. Other factors that may play a role in disturbances in cerebral blood flow include fluctuations in CO_2-levels and inflammation. Increased CO_2-levels during thoracoscopic and laparoscopic procedures as well as hypocarbia because of mechanical hyperventilation may have detrimental effects on brain perfusion that could be particularly more harmful in the absence of adequate autoregulation. Impaired cerebral perfusion may have been of relevance in our population as 45% of infants required vasopressor support during surgery. Nevertheless, vasopressor support was not significantly related to brain injury in our analysis. In this study, the incidence of punctate cerebellar hemorrhages was similar in preterm and full-term infants, in contrast to what has so far been reported in literature with a much higher incidence in preterm infants.[21] Cerebellar hemorrhages have been reported in up to 15% of very preterm infants (<32 weeks of gestational age), with a decreasing incidence with increasing gestational age. These lesions may also be attributed to changes in cerebral circulation[22,23] and often coincide with supratentorial lesions. A notion that is in agreement with our results, concomitant supratentorial abnormalities were present in 92% of preterm infants with cerebellar hemorrhages.

The infants in this study had a high percentage of subdural hemorrhages (30%), mostly in full-term infants and predominantly in the posterior fossa. The presence of hemosiderin and free iron in the extracerebral space surrounding the cerebellum has been related to cerebellar growth impairment.22,24 The prevalence of subdural hemorrhages in asymptomatic full term infants has been reported to range from 8% to 46 %.[25,26] At our institution, neuroimaging is also systematically performed shortly after birth in full-term infants receiving hypothermia because of perinatal asphyxia. Subdural hemorrhages are observed in 19% of asphyxiated infants and, thus, considerably less frequent than in this study, suggesting that the subdural hemorrhages in our cohort may be related to the perioperative period, at least to a certain extent.

Preoperative cUS revealed a periventricular hemorrhagic infarction in 1 infant and inhomogeneous echogenicity suggestive of punctate white matter lesions in 9 infants. Postoperatively, the number of infants with inhomogeneous echogenicity was 10, and 1 infant was suspected of a sinovenous thrombosis. MRI confirmed the periventricular hemorrhagic infarction, the suspected punctate white matter lesions in 10 and the sinovenous thrombosis, but identified another 7 infants with ≥6 punctate white matter lesions, not seen with cUS. Infarcts and periventricular hemorrhagic infarction were mostly seen postoperatively and, therefore, appear to develop in the perioperative period. Punctate cerebellar lesions, small intraventricular hemorrhages, and extra-axial hemorrhages were never identified with cUS and could have been already present

before surgery. The additional value of MRI, especially for the detection of small parenchymal and cerebellar lesions and nonparenchymal abnormalities, is considerable.
To identify risk factors for brain lesions, we evaluated various perinatal characteristics, perioperative risk factors, including vasopressor support during surgery and prolonged mechanical ventilation. In contrast to what one would expect, none of these variables were related to the occurrence of brain injury except for preterm birth and type of anomaly. Other factors that may be related to brain injury include the impact of anesthetics on the developing brain. The effect of sevoflurane during minor surgery was recently investigated and was demonstrated not to exert any negative effect.[6] However, our patient cohort had major surgery at a young age, and factors such as the potential presence of minor genetic defects may underlie a common pathway of the congenital anomaly and altered brain development.

Several limitations need to be addressed when interpreting these results. First, the data did not allow us to accurately time the onset of lesions, as no preoperative MRI was obtained.
Preoperative cUS scans were available in all infants and assisted in the differentiation between preoperative and perioperative lesions.
Second, patients with noncardiac congenital anomalies comprise a heterogeneous group because of the presence of various congenital anomalies and different levels of surgical complexity. Because all anomalies observed in this cohort are rare, we pooled the noncardiac congenital anomalies because they share the requirement of neonatal surgery.
Third, this was a single center study, and future studies in other centers are needed to confirm these findings. Finally, follow-up data are being collected but not yet available for the whole cohort. Relevance of the MRI findings for neurodevelopment needs to be established.

In conclusion, this study provides evidence that infants with noncardiac congenital anomalies undergoing neonatal surgery are at risk of mild to moderate brain lesions. Careful perioperative monitoring of vital signs and cerebral perfusion and function should be mandatory in this vulnerable group of infants. Neuroimaging should be considered in infants with noncardiac congenital anomalies after neonatal surgery, especially in infants suffering from gastroschisis or omphalocele and intestinal atresia. The etiology and timing of onset of these brain lesions remain largely unclear and warrant further investigation. Furthermore, long-term follow-up is required to evaluate the consequences for cognitive development, behavior, and motor performance later in life.

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4
CHAPTER

Effect of general anesthesia on neonatal aEEG

a cohort study of patients with non-cardiac congenital anomalies

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ABSTRACT

Introduction: The aim of the current study was to determine the effect of general anesthesia on neonatal brain activity using amplitude-integrated EEG (aEEG).

Methods: A prospective cohort study of neonates (January 2013-December 2015), who underwent major neonatal surgery for non-cardiac congenital anomalies. Anesthesia was administered at the discretion of the anesthetist. aEEG monitoring was started six hours preoperatively until 24 hours after surgery. Analysis of classes of aEEG background patterns, ranging from continuous normal voltage to flat trace in six classes, and quantitative EEG-measures, using spontaneous activity transients (SATs) and interSATintervals (ISI), was performed.

Results: In total, 111 neonates were included (36 preterm/75 full-term), age at time of surgery was(median (range) 2 (0-32) days. During anesthesia depression of brain activity was seen, with background patterns ranging from flat trace to discontinuous normal voltage. In most patients brain activity was two background pattern classes lower during anesthesia. After cessation of anesthesia, recovery to preoperative brain activity occurred within 24 hours in 86% of the preterm and 96% of the term infants. Gestational age and the dose of sevoflurane were significantly associated with SAT-rate ($F(2,68)=9.288$, $p < 0.001$) and ISI- durations during surgery ($F(3,71)=12.96$, $p < 0.001$). Background pattern and quantitative EEG-values were not associated with brain lesions($\chi 2(4)= 2.086$, ns).

Conclusion: aEEG shows a variable reduction of brain activity in response to anesthesia in neonates with noncardiac congenital anomalies, with fast recovery after cessation of anesthesia. This reduction is related to gestational age and the dose of sevoflurane. The aEEG offers the opportunity to monitor the depth of anesthesia in the neonate.

INTRODUCTION

EEG-derived monitors are most frequently used to investigate the anesthetic depth in children. However, EEG-derived monitors, such as the Bispectral Index Monitor, have only been investigated in a limited number of children and data is limited in infants(1-4). Since EEG characteristics of infants are different from those of older children, a monitoring tool to guide anesthetic depth in neonates is not available(5). A widely used monitoring tool for electrical brain activity in neonates admitted to the neonatology department is the amplitude-integrated EEG (aEEG). It offers continuous long-term monitoring of electrical brain activity, which is suitable to assess the background activity, detect sleep-wake cycling, and screen for seizures.

The cerebral activity is classified by background pattern recognition and voltage criteria(6). Typically, the aEEG is discontinuous in preterm infants and gradually becomes continuous at term. The patterns burst suppression, continuous low voltage and flat trace have a poor prognosis in term infants(7;8). Another prognostic indicator is sleep wake cycling(9), which is present from around 32 weeks of gestation to 44 weeks. This is recognized by sinusoidal variation in amplitude(6). The presence of spontaneous activity transients (SAT) is a sign of brain immaturity and is observed in discontinuous and continuous brain activity. With increasing maturation the frequency of SATs decrease, although SATs are still observed in full-term neonates (10;11).

Neurodevelopmental outcome of patients with major non-cardiac congenital anomalies (NCCA), who require major neonatal surgery, warrants attention(12-14). At two years of age, a cognitive and motor delay of up to 50% has been reported(15). The causal pathway of this neurocognitive delay in children without a genetic syndrome is not completely understood. The clinical impact of inhalational anesthetics in infants and children is currently under investigation in three trials (PANDA, MASK and GAS-study)(16-18). The first results show no differences in IQ-scores in later childhood, after a single and short exposure to anesthesia(16;19). Nevertheless, this is only partly reassuring, since our patient cohort consists of young newborns undergoing major surgery, which might be of greater impact to the brain.

The aim of this study is to 1) evaluate the effect of general anesthesia on brain activity in preterm and term neonates using aEEG and 2) to review the effect of the anesthetic dose, brain injury and epileptic activity on the aEEG during anesthesia .

MATERIALS AND METHODS

Patients

In this prospective cohort study, patients with major non-cardiac congenital anomalies, requiring surgery in the neonatal period, were included between January 2013 to December 2015 at the Wilhelmina's Children Hospital, University Medical Center Utrecht. This study was approved by the Medical Ethical Committee of the University Medical Center Utrecht (Utrecht, The Netherlands) for the use of clinically acquired data and approved the lack of exclusively-written parental or guardian consent. Inclusion criteria consisted of major non-cardiac congenital anomalies, surgery in the neonatal period, a postmenstrual age of 44 weeks or less during surgery. Exclusion criteria consisted of critical congenital heart disease and major congenital anomalies of the central nervous system.

Amplitude-integrated EEG

Patients were monitored with a two-channel EEG, using the BrainZ Monitor (BRM3, version, Natus CA, Seattle, USA). The BRM3 records a two-channel aEEG as well as a raw EEG from two electrodes over each hemisphere (F3-P3, F4-P4, according to the international 10-20 system of electrode placement). The amplitude ranges from 0 to 100 μV and is displayed on a semilogarithmic scale(Fig 1). Monitoring started six hours prior to surgery, continued during surgery and for 24 hours after surgery. Patients with a shorter duration of measurement were not excluded from analyses, when background assessment was feasible.

Neuro-imaging

At hospital admission, cranial ultrasonography (cUS) was performed, in order to detect the presence of pre-surgical brain injury, and repeated postoperatively. A postoperative MRI was performed on a 3.0 Tesla whole-body Achieva system (Philips Medical Systems, Best, Netherlands) as part of routine clinical care(20). The scanning protocol included T1-, T2-, diffusion and susceptibility weighted imaging.

Anesthesia

Anesthesia was administered at the discretion of the anesthetist. For the induction of anesthesia sevoflurane or isoflurane was used with an FiO_2 of 40-100%. Atracurium besylate was used most often as a muscle relaxant, and sufentanil for pain medication.

Data analysis

The aEEG background pattern and raw EEG signals were simultaneously assessed offline by three aEEG experts (M. Toet, L.S. de Vries and L.C. Weeke) using Analyze. Only recordings with an impedance <5 kΩ were analyzed and periods containing artifacts, such as nursing care,

intubation at the operating room, and diathermy were excluded. The aEEG background patterns were classified according to Hellström-Westas et al.(7) as: continuous normal voltage (CNV), discontinuous normal voltage (DNV), burst suppression (BS), continuous low voltage (CLV), and flat trace (FT) (Fig 1).

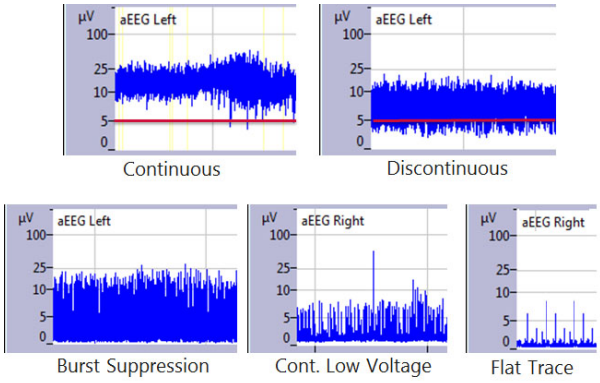

Figure 1. aEEG background patterns

Epileptic activity was defined as evolving rhythmic activity for >10s on the raw EEG in the absence of artifacts and classified as single seizure, repetitive seizures, or status epilepticus(8). Sleep-wake cycling (SWC) was classified as no SWC(no cyclic variation of the aEEG background), imminent SWC and normal SWC(9). The time to return to baseline background activity and to SWC was documented up to 24 hours postoperatively.

For quantitative analyses the cross-cerebral EEG signal (P3-P4) was used. EEG-data were recorded at a sampling rate of 256 Hz. The recorded aEEG were assessed visually to identify marked artifacts, periods of high impedance, and other events (e.g. diathermy, blood sampling, care). Using in house developed software (Signalbase; version 7.8; University Medical Center Utrecht, Utrecht, The Netherlands) NIRS and EEG data were simultaneously analyzed. The following variables were calculated: number of spontaneous activity transients (SAT) per minute (SAT-rate) and the interval in seconds between SATs, the InterSatInterval (ISI).

For analysis, nine epochs of 30 minutes were manually selected: preoperatively, first 30 minutes of surgery, last 30 minutes of surgery, total duration of surgery (variable duration), and 1hr, 6hrs, 12hrs, 18hrs and 24hrs after surgery (Fig 2). Start of surgery was defined as time of surgical incision (first 30 minutes) and end of surgery as time the surgeon finished (last 30 minutes of surgery). Other parameters, including heart rate (HR), arterial saturation, mean arterial blood pressure (MABP), perfusion index (PI), end-tidal carbon dioxide ($etCO_2$), applied fraction of inspired oxygen (FiO_2), respiration rate (RR), and end tidal sevoflurane (etSevo), were also simultaneously analyzed. These parameters were captured by in house developed software (Signalbase) at a sampling frequency of 1dp/sec.

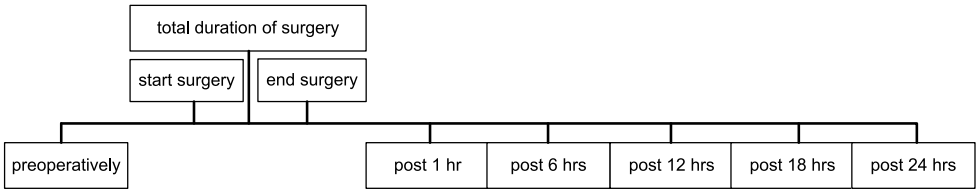

Figure 2. Epochs for analysis

Infants were classified preterm with a postmenstrual age < 37 weeks' gestation at time of surgery. In children who underwent multiple surgical interventions, the first surgical intervention was included.

Statistical analysis

Statistical procedures were performed using IBM SPSS statistics software package (IBM® SPSS® Statistics version 22, IBM Corp. Armonk, NY, USA). Data are presented as mean ± standard deviation (SD) or as median and range when indicated. A multivariable linear regression analysis was used to analyze the relationship during surgery between the SAT-rate or ISI, and postnatal age at surgery, birth weight z-score, dose of sevoflurane, sufentanil, propofol and duration of anesthesia. Correlations were checked using the Spearman correlation test. The Wilcoxon Signed Rank test was used to compare ISI- and SAT-values before, during and after surgery, a post hoc Bonferroni correction was applied to correct for multiple testing. A p-value < .05 was considered statistically significant.

RESULTS

Study population

From January 2013 to December 2015, 114 infants with NCCA were admitted to the NICU for major neonatal surgery. Three infants were not eligible for inclusion in this study, since no perioperative aEEG was available due to logistic reasons. This resulted in a final sample of 111 infants being enrolled in this study (Table 1). Of these, 13 infants underwent multiple surgical interventions in the neonatal period.

Table 1. Demographic and surgical details of included patients

	n=111
Gender (male, %)	59 (53%)
Preterm (n, %)	36 (32%)
Gestational age (weeks)	38.28 (28-42)
Birth weight z-score	-0.50 (-3.12-2.00)
Apgar score	
At 1 minute	9 (2-10)
At 5 minutes	10 (2-10)
At 10 minutes	10 (6-10)
Congenital abnormality, n(%)	
Esophageal atresia	28 (25%)
Gastroschisis / omphalocele	16 (15%)
Intestinal atresia / volvulus	34 (31%)
Anorectal malformation	11 (10%)
Urogenital malformation	8 (7%)
Other	14 (12%)
Surgery	
Postnatal age (days)	2 (0-32)
Duration anesthesia (minutes)	186 (60-563)
Duration surgery (minutes)	119 (15-475)
Multiple surgical interventions (patients) Type of surgery	13(12%)
Laparotomy n(%)	49 (44%)
Laparoscopy n(%)	33 (30%)
Thoracoscopy n(%)	29 (26%)
Laparoscopy and thoracoscopy n(%)	1 (1.6)
Arterial line n(%)	95(86%)

Data are displayed in median[range], unless otherwise indicated

aEEG background patterns

The median duration of aEEG recorded preoperatively was 5 hours and 24 minutes (range 3 minutes to 24 hours), seven patients had no preoperative measurement due to emergency surgery (n=5) and logistic (n=2) reasons. In seven patients sleep wake cycling could not be determined, because the duration of the preoperative measurement was too short (3 to 60 minutes).

Pre-operatively, preterm infants (GA 34.7[28.1-36.9] weeks) had a continuous normal voltage background pattern in 58%, discontinuous normal voltage 37% and burst suppression 5%. During entire duration of surgery brain activity was depressed in all preterm infants. Postoperatively, 86% of the preterm infants returned to their preoperative background pattern within 24 hours, of which 60% within one hour. Sleep-wake cycling returned to preoperative patterns in 69%, and stayed imminent in 11% (Fig 3). Excluding patients who received midazolam postoperatively (n=17), 87% returned to their preoperative background pattern within 24 hours, of which 65% within one hour. Sleep-wake cycling returned to preoperative patterns in 78%.

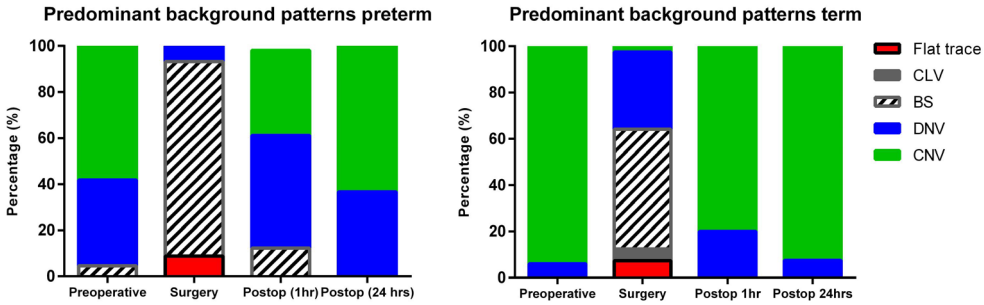

Figure 3. Predominant background pattern before, during and after surgery

Of the term infants (39.1[37.0-41.9 weeks], 94% had a continuous normal voltage and 6% discontinuous normal voltage prior to surgery(Fig 3). In most patients the background pattern regressed two classes in comparison to preoperatively (preterm 67%, term 49%)(Fig 4). Of the two term patients with a predominant flat trace, one was diagnosed with a syndrome and the other had received a high dose of propofol (15 mg). Postoperatively, 98% recovered to continuous normal voltage within 24 hours, of which 78% within one hour (Fig 3). Sleep-wake cycling returned to a normal pattern in 57%, and was imminent in 40%. Postoperatively, no difference in the administered dose of pain medication for the different background patterns and return of sleep-wake cycling was found (Kruskal Wallis, (H(1) = 2.220, p = 0.136)).

Excluding patients who received midazolam postoperatively (n=22), 95% returned to continuous normal voltage within 24 hours, of which 84% within one hour. Sleep-wake cycling returned to a normal pattern in 95%.

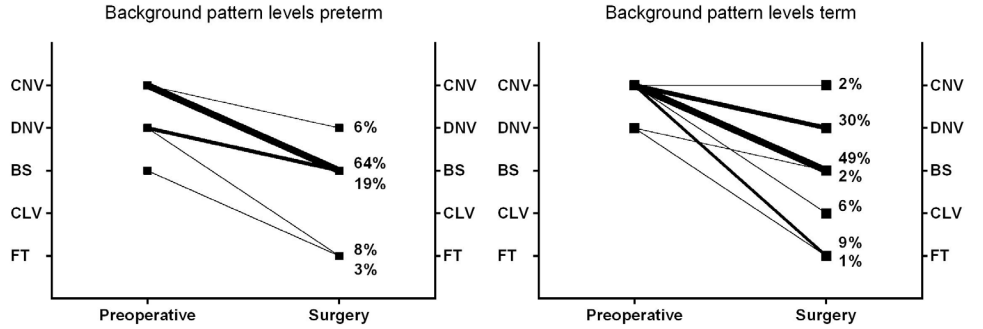

Figure 4. Degree of background pattern depression during surgery

During anesthesia nine term infants had a severe reduction in brain activity, from continuous normal voltage to continuous low voltage or flat trace. Of these, six patients received propofol during surgery (67% versus 19% all infants). No other common explanatory factors were found.

Epileptic activity

Preoperatively, none of the patients had known or suspected seizure activity. In 11 patients epileptic activity was identified. In four infants epileptic activity (2 single seizures, 2 repetitive seizures) occurred during surgery, of which one directly after administration of sevoflurane during the induction of anesthesia (end tidal concentration sevoflurane 2.5-5%). Eight infants had seizures postoperatively (6 single seizure, 2 repetitive seizures). One infant had clinical seizures, and was diagnosed with a thalamic infarction, the other seven had subclinical seizures. No correlation with background pattern or brain injury was found. Four patients were suspected to have a genetic syndrome, one was diagnosed to have Moebius syndrome.

Quantitative EEG analysis

In preterm infants, ISI-durations were significantly longer during surgery (median ISI during total surgery period 33 seconds[3-571]) versus preoperative ISI (4 seconds[1-113]), Wilcoxon's Signed rank test T=29.0, r = - 0.810, p<0.001 (Fig 5). One hour after surgery ISI were not significantly longer (median ISI 1hr: 5 seconds[1-75]) in comparison to preoperative ISI, T=553, r = -0.304, p = 0.055 (Fig 5).

SAT-rates were significantly reduced during surgery (median SAT-rate during total surgery period: 2.23/minute [0.08 – 8.50]) than preoperative SAT-rates (7.94/minute[0.29-10.36]), T=773, r = -0.850, p < 0.001 (Fig 5).

In term infants, ISI-durations were significantly longer during surgery (median ISI during total surgery period 14 seconds[3-253]) versus preoperative ISI (2 seconds[1-16]), Wilcoxon's Signed rank test T=2.0, r = -0.868, p<0.001 (Fig 5). One hour after surgery ISI-durations were significantly longer (median ISI 1hr: 3 seconds[1-81]) in comparison to preoperative ISI, T=1731, r = -0.578, p < 0.001 (Fig 5).

SAT-rates were significantly reduced during surgery (median SAT-rate during total surgery period: 4.30/minute [0.16 – 8.50]) than preoperative SAT-rates (8.45/minute[2.67-11.13]), T=2049, r = -0.844, p < 0.001 (Fig 5).

Table 2. Detailed characteristics of medication administered before, during and after surgery

n=129	Patients n(%)	Absolute dosage	Dosage/kg	Dosage/kg/hr
Preoperative				
Midazolam	9(7%)			0.05[0.04-0.1]
Morphine	29(22%)		0.37[0.23-1.00]	
Surgery				
Anesthetic				
Sevoflurane n(%)	126 (98%)	1.26[0.04-2.49]	NA	NA
Isoflurane n(%)	3(2%)	0.5[0.4-0.6]	NA	NA
Propofol, mg/kg n(%)	24 (19%)	10[2-20]	3.26[0.8-10.17]	1.06[0.23-3.41]
Midazolam n(%)	5(4%)	1.5[0.5-2.75]	0.53[0.15-0.88]	
Pain medication				
None	3(2%)			
Sufentanil	124 (96%)	2.25[0.25-12.50]	0.84[0.09-4.87]	2.47[0-32.45]
Bupivacaine*	31 (24%)	1.75[0.71-3.65]	0.56[0.19-2.37]	0.19[0.06-0.8]
Morphine	51 (40%)**	0.13[0.04-2.75]	0.06[0.02-1.17]	0.19[0.01-0.49]
Muscle relaxant				
None	6(5%)	-	-	-
Atracurium	106(82%)	4.0[1-15.50]	1.39[0.33-4.68]	3.43[0.54-41.91]
Rocuronium	16(12%)	4.5[1-10]	1.63[0.48-3.68]	4.34[1.73-17.05]
Suxamethonium	1(1%)	5.0	1.24	3.69
Postoperative				
Midazolam	38(29%)	-	-	0.05[0.03-0.28]
Morphine	101(78%)	-	0.28[0.22-0.62]	-
Bupivacaine	29(22%)			

Postoperative period was defined as 24 hours after end of surgery.
Sevoflurane in %, propofol mg/kg, midazolam mg/kg, sufentanil ug/kg, morphine g/kg.
*Bupivacaine was administered through epidural at a continuous drip of 0.33mg/kg

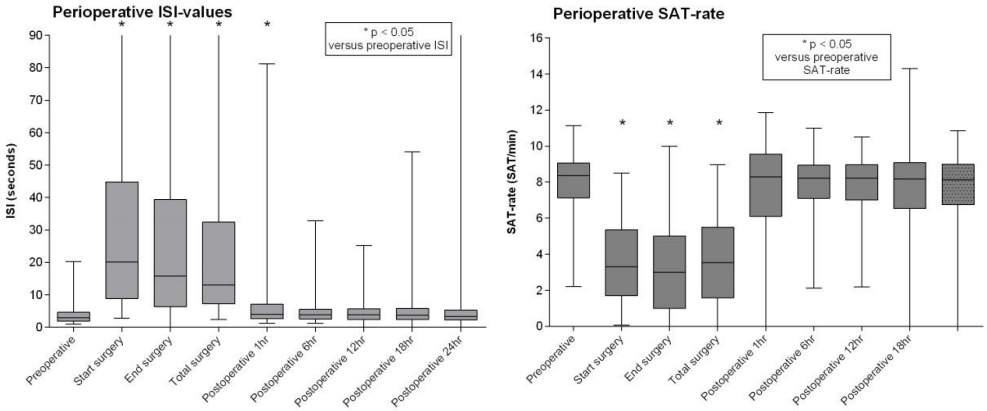

Figure 5. Median ISI-values and SAT-rates of all patients

ISI and background patterns

ISI-values during surgery correlated with the background pattern classification, showing that ISI-values of a continuous normal voltage pattern (median ISI 2.77 seconds[2-4]) were significantly shorter than a discontinuous normal voltage pattern (ISI 4.72 seconds[3-7]), and these were significantly shorter than a burst suppression (ISI 21.21 seconds[11-85]). Values during burst suppression were significantly lower than flat trace (ISI 76.95 seconds[25-215]).

A factor significantly influencing the ISI-values was the type of procedure: ISI-values were significantly longer during a thoracoscopic procedure median 28.4 seconds [3-571]) than during non-thoracoscopic surgery (median 15.3 seconds [3-393]), U 1121.00, $p < .005$, $r = -0.26$, $z = -2.910$.

Multivariable linear regression analysis SAT-rate and ISI during surgery

In the multivariable analysis, correcting for gestational age, the dose of sevoflurane showed a significant linear relation with SAT-rate and ISI during surgery. In particular, sevoflurane was positively related to ISI ($\beta = 0.531$, $F(3,71)=12.96$, $p < 0.001$, $R^2 = 0.364$, $R^2_{adjusted}=0.336$) and negatively associated with SAT-rate ($\beta = -0.420$, $F(2,68)=9.288$, $p < 0.001$, $R^2 = 0.291$, $R^2_{adjusted}=0.259$). Birth weight z-score, postnatal age at time of surgery, duration of anesthesia, the dose of sufentanil and the administration of propofol were not significantly associated to quantitative EEG measures.

aEEG and brain injury

Preoperatively, 11 patients had brain injury on their ultrasound scan: one periventricular hemorrhagic infarction, one cerebellar lesion and nine infants inhomogeneous echogenicity, suggestive of punctate white matter lesions. Of all infants, in 58% parenchymal lesions were present on MRI and in 37% non-parenchymal injury. MRI-abnormalities were not significantly associated with the different background patterns or ISI and SAT-rate during surgery (Fisher-Freeman-Halton Exact Test: $\chi 2(4)= 2.086$, ns).

DISCUSSION

Our study investigated the effects of general anesthesia on brain activity measured by aEEG in a neonatal cohort. The main findings were that the aEEG showed a transient, but very variable reduction of brain activity in neonates with major non-cardiac congenital anomalies. In most patients the background patterns decreased two classes during anesthesia. This depression in brain activity ranged from a flat trace to a discontinuous normal voltage. After cessation of anesthesia, 60% of the preterm and 78% of the term infants recovered within one hour after surgery to their preoperative background pattern. Within 24 hours, the background pattern of

86% of the preterm and 96% of the term infants had recovered. The gestational age and the dose of sevoflurane were significantly associated with the level of reduction in brain activity. Background patterns and quantitative EEG-measures during surgery were not associated with brain lesions and the occurrence of seizures.

There are no previous studies assessing the effect of anesthesia on the aEEG in a cohort of neonates during surgery(21). Reports on EEG-derived measurements during anesthesia are rare in children, and limited in neonates (2;3;5;22-24). In search of a neonatal device, diverse anesthetic depth monitors contain an algorithm based on adult EEG data. Since EEG parameters in neonates differ greatly from older children and adults, these devices cannot be used (3;25;26). Therefore, we decided to investigate the use of the aEEG. The aEEG is commonly used in neonatal practice, and extensive knowledge has been gained on the use of aEEG in neonates. Although quantitative data rather than patterns may be preferred, the described background patterns can assist the pediatrician and anesthesiologist to intervene immediately.

In our quantitative analysis the Spontaneous Activity Transients were used. This endogenous activity is important for brain development(11). These SAT's are decreasing with GA, in number and amplitude approaching term equivalent age and remain detectable at least until week 44(27). In our study the SAT-rate was able to make a distinction between the different background patterns and was therefore considered suitable for further analysis.

The reduction of brain activity, expressed by an increased interSATinterval and a decreased SAT-rate, was inversely related to the dose of sevoflurane. This is as expected, since this anesthetic causes a dose-dependent cortical inhibition by GABA stimulation(28). It is of interest to observe such a large variation in brain activity, given the dose range used in our hospital. One of the guidelines for the appropriate dosage of sevoflurane is the Minimal Alveolar Concentration (MAC), which is 3.3% in the neonatal age group(29). The range of the dose of sevoflurane used in our study was substantially lower: 0.4 to 2.5%. In a study performed by McKeever et al. no changes in aEEG were observed in children between one month and two years of age with a dose between 0.75MAC and 1.25MAC(5), which is in contrast to our results. A possible explanation could be the younger age of our cohort. Furthermore, the reduction was age-dependent, even observable in the small gestational age width of our patient population(30).

Early brain activity is important for neuronal development(31). Anesthesia causes a relatively short depression of brain activity with a rapid recovery postoperatively. Still, Backeljauw et al. found a decreased language comprehension and performance IQ in children exposed to anesthetics before the age of four(32). In our cohort, severe brain lesions were not related to perioperative background patterns, SAT-rate or ISI-values.

Epileptic activity was identified on EEG in 11 neonates. One infant had been diagnosed with clinical seizures during admission. These seizures were not more prevalent in infants with a more depressed background pattern or with a higher prevalence of brain lesions. One child had a single seizure directly after the start of sevoflurane. This epileptiform activity has been described previously, and seems to be related to the speed of induction(33). Rapid induction is associated with a higher incidence of epileptiform discharges in comparison to a gradual induction(33-36). Worldwide, concerns have been raised on the potential harmful effects of general anesthesia on the young infant's brain. Awaiting the results of the clinical trials The Food and Drug Administration and the American Academy of Pediatrics recommended to reduce the overall drug dosage of anesthetics in young children. However, little is known about the immediate and long-term effects of clinical levels of volatile anesthetics on the developing brain. In general, the dose of anesthesia is based on the 'clinical judgment of the anesthetist'(37;38). Monitoring neonatal brain activity during anesthesia could ensure adequate dosing. Anesthetic depth monitors have been shown in adults to reduce the amount of anesthetic drugs used, reduce awareness and shorten recovery(3).

To be able to determine the adequate depth of anesthesia, we have to decide what level of depression in brain activity is sufficient. Do we agree that a discontinuous normal voltage is adequate anesthesia, in case of a continuous pattern preoperatively? Or, do we prefer to avoid any stress in the infant and lower the brain activity to a flat trace? One of the definitions of anesthesia is a loss of consciousness, amnesia, immobility and a reduction in the reflex autonomic responses associated with noxious stimuli(39). The EEG measures cortical brain activity, which gives an indication of consciousness. This is of important additional value to other clinical parameters, such as HR, RR and MABP. Since for example, a movement response to a noxious stimulus is mediated by the subcortical brain(40).

One of the limitations of our study is the lack of a standardized anesthesia protocol. Anesthesia was administered at the discretion of the anesthesiologist, which reflects normal practice. The strength of this study is that the aEEG is commonly used in neonatal practice and our results add to the literature data on describing the clinically used background pattern. The aEEG offers continuous, bedside monitoring and the data can readily be interpreted by pediatricians and anesthesiologists. The study comprises a cohort with a small gestational age width, which is important since we know that cerebral maturation influences the EEG and the neonatal brain is developing fast.

The future perspective is to correlate the background pattern during anesthesia to long-term neurodevelopment. The time to recover to a normal background pattern and the onset of sleep-wake cycling has been proven in patients with hypoxic-ischemic encephalopathy to be important

prognostic factors of outcome. Since the depressed pattern during anesthesia is iatrogenic and recovery after cessation is rapid, the prognostic value may limited. Surgery cannot easily be postponed or avoided, therefore studies on early childhood anesthesia for surgery and the effect on long-term cognitive function are needed.

In conclusion, general anesthesia in neonates causes a variable reduction in brain activity. This reduction is transient and recovery to the preoperative level of brain activity occurs rapidly. The depressant effect of sevoflurane is proportional to the dose, even observed in the small dose range in our study population. The aEEG offers the opportunity to monitor the depth of anesthesia in the neonate. The question remains which depth based on aEEG we aim for during anesthesia.

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5

CHAPTER

Non-invasive monitoring of cerebral oxygenation, autoregulatory ability, and hemodynamics in neonates with non-cardiac congenital anomalies

preliminary data

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ABSTRACT

Objective: Major surgery in the neonatal period is a risk factor for neurodevelopmental outcome. The aim of the present study is to evaluate the presence of cerebral autoregulation (CA) and parameters of influence in preterm and full-term neonates in the perioperative period.

Study design: To study the cerebral autoregulatory ability of patients with non-cardiac congenital anomalies (NCCA) during neonatal surgery, in comparison to pre- and postoperative ability, this prospective, observational cohort study was conducted. Inclusion criteria consisted of patients with major NCCA, requiring surgery in the neonatal period, to a postmenstrual age of 44 weeks or less during surgery. All had continuous monitoring of blood pressure (MABP) and regional cerebral oxygenation ($rScO_2$) was measured by Near Infrared Spectroscopy. CA was assessed by means of correlation (ρ) between the MABP and $rScO_2$, a correlation >0.5 indicates a pressure passive CBF.

Results: 54 infants were included (33% preterm). Medication administered during anesthesia consisted of sevoflurane (98%), propofol (19%), and sufentanil (100%) as pain medication. Of the patients, 29(54%) received the vasopressor dopamine during surgery. The percentage of time that the $\rho > 0.5$, was significantly longer during surgery with 27.5% in comparison to pre- and postoperative durations. Preterm infants experienced a longer period of hypotension during surgery. During surgery, the $rScO_2$ was significantly increased to 75.5% and the MABP decreased to 42 mmHg in comparison to pre- and postoperative periods.

Conclusions: In a patient group with an intact autoregulation before surgery, 28% of the duration of surgery an impairment of autoregulatory ability was observed. Neuromonitoring is important to protect the brain during surgery. The results of the present study demonstrate a promising method for bedside monitoring of cerebral autoregulation in the near future.

INTRODUCTION

Infants with non-cardiac congenital anomalies, undergoing neonatal surgery, are at risk of brain injury.[1] A previous study showed in 63% of the infants mild to moderate parenchymal and non-parenchymal lesions.[2] Since these patients have an increased risk on a neurodevelopmental delay, these lesions may contribute to the long-term outcome.[3]

Neonatal surgery is a risk factor for developing brain injury.[4] Morriss et al. showed that multiple surgical interventions in preterm infants were prognostic for an adverse neurodevelopment at the age of two years.[5]

Disturbances in cerebral hemodynamics can contribute to brain injury. Cerebral hemodynamics consist of cerebral blood flow (CBF), cerebral blood volume, and cerebral blood flow velocity.[6] Maintenance of CBF and stable cerebral perfusion and oxygenation is most critical, since adequate CBF is required for the delivery of nutrients and oxygen to the brain.[7, 8]

An important factor affecting the CBF is the mean arterial blood pressure (MABP).[8] Cerebral autoregulation implies the maintenance of a constant CBF in the face of a changing cerebral perfusion pressure. In neonates we can presume that the perfusion pressure is mainly defined by the changing blood pressure. A pressure passive blood flow means the CBF follows the dynamics of the blood pressure.[9] The autoregulatory plateau is unknown in the neonatal population.[10] The definition of hypotension in newborns is not clear, it can either be the lower boundary in MABP as 30 mmHg or the actual gestational age (GA) in weeks of the neonate.[11] Cerebral autoregulation is studied by the relation between MABP and CBF. This relation shows the ability of the brain to regulate and maintain a stable CBF during variations in MABP. There is discussion whether cerebral autoregulatory ability is immature or even absent in preterm infants. A previously described estimator of autoregulatory ability, is the correlation coefficient between arterial MABP and the non-invasively measured cerebral oxygenation ($rScO_2$).[6]

Anesthesia with sevoflurane can also affect the cerebral autoregulatory ability of the full-term neonate, which is reported by Rhondali et al.[12] Authors presented an association between a significant decrease in MABP and variation in CBF in infants younger than 6 months.

Disturbances in hemodynamics and loss of autoregulatory ability of the CBF due to the anesthetics attributes to the vulnerability of the neonatal brain. The aim of the present study is to evaluate the presence of autoregulation in preterm and full-term neonates in the perioperative period. Parameters influencing the autoregulatory ability are analyzed.

METHOD

Study population

To study the cerebral autoregulatory ability of patients with non-cardiac congenital anomalies (NCCA) during neonatal surgery, in comparison to pre- and postoperative ability, this prospective, observational cohort study was conducted. Inclusion criteria consisted of patients with major NCCA, requiring surgery in the neonatal period, to a postmenstrual age of 44 weeks or less during surgery, between January 2013 to December 2015 at the Wilhelmina's Children Hospital, University Medical Center Utrecht. This study was approved by the Medical Ethical Committee of the University Medical Center Utrecht (Utrecht, The Netherlands) for the use of clinically acquired data. The lack of written parental consent was approved. Exclusion criteria consisted of critical congenital heart disease, major congenital anomalies of the central nervous system and incomplete perioperative monitoring.

Perioperative monitoring

All patients had an indwelling arterial catheter (in the umbilical, tibial or radial artery) for continuous monitoring of the arterial blood pressure. End-tidal CO_2 and end-tidal sevoflurane concentrations were measured continuously during surgery. All variables were monitored and stored with a 1 Hz-sample rate on a personal computer for offline analysis using in-house-developed software (Signalbase; University Medical Center Utrecht, Utrecht, The Netherlands). Artifacts in MABP and $rScO_2$ were removed by an automated script and checked manually. The data is divided into five epochs of 30 minutes: 1. Preoperative period, 2. During surgery, 3. Early postoperative period (within six hours after surgery), 4. Medium postoperative period (six to 20 hours after surgery), 5. Late postoperative period (from 20 hours after surgery).

Near Infrared Spectroscopy

To estimate the cerebral oxygenation the method Near Infrared Spectroscopy (NIRS) is used. NIRS is based on the transparency of biological tissue to light in the near-infrared part of the spectrum (700-1000 nm) and its subsequent absorption by oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb) in the cerebral blood vessels, which are within the near-infrared light beam.[13] The regional cerebral oxygen saturation ($rScO_2$) is calculated, it reflects the venous (70-80%), arterial (20-25%), and capillary (5%) blood. The INVOS 4100-5100 (Somanetics, Troy, USA) is used, with a small adult sensor (SomaSensor SAFB-SM; Somanetics). Normal NIRS values were considered between 55% and 85%.[14]

Cerebral autoregulation

The correlation between MABP and $rScO_2$ was used as an estimator of cerebral autoregulation.[6, 8] The validity of MABP-$rScO_2$ correlation as an estimate of cerebral autoregulatory ability has

been established before.[15] The correlation is expressed as Pearson's correlation coefficient ρ. The correlation coefficient is calculated by dividing the covariance of the MABP and the $rScO_2$ by the product of their standard deviations (Equation 1). The $\overline{x}$ and $\overline{y}$ represents the mean of the x and y respectively.

Equation 1: Correlation coefficient

$$\rho_{xy} = \frac{\sum_{i=1}^{N}(x_i - \overline{x})(y_i - \overline{y})}{\sqrt{\sum_{i=1}^{N}(x_i - \overline{x})^2 \sum_{i=1}^{N}(y_i - \overline{y})^2}}$$

The correlation (ρ_{xy}) between the MABP (x) and the $rScO_2$ (y) is calculated using the Pearson's linear correlation coefficient. The correlation coefficient was corrected for phase shift, using a delay of 10 seconds. These 10 seconds represents the delay between MABP and NIRS measurements due to the cerebrovascular transit time. For calculating the correlation coefficient between MABP and $rScO_2$ the data was divided in epochs of 30 minutes, with an overlapping percentage of 90%. Each epoch was divided in a sub-window of five minutes with an overlapping percentage of 80%. A $\rho > 0.5$ is considered as a lack of cerebral autoregulation. The correlation of each epoch was averaged and the percentage of time that ρ_{xy} was above 0.5 was calculated. Episodes of desaturation ($SaO_2 < 85\%$) before, during and after surgery were marked as artifacts and excluded from analysis.

Hypotension

In literature, several definitions of hypotension are used as treatment thresholds, including MABP (in mmHg) of less than GA in weeks, MABP <30 mmHg, and a MABP below the 5th-10th percentile according to age- and birth weight-specific reference values.[11] In our study, the threshold of 30 mmHg is used to define hypotension. A prolonged period of hypotension was defined as >10% duration of surgery.

Statistical analysis

Statistical procedures were performed using IBM SPSS Statistics software package v 20 (IBM Corporation, Armonk, New York). A descriptive analysis of the population was conducted and data were presented as mean ± SD or as median and range when indicated. The significance level was set at an alpha p-value of < .05. Due to the relatively small sample size and predominantly no normal distribution of the data, non-parametric tests were used. The Wilcoxon Signed Rank test was applied to analyze differences between pre- and postoperative values and during surgery, the post-hoc Bonferoni correction was used to correct for multiple testing. Means of two different groups were compared using the Mann-Whitney *U* test. Differences in duration

of no autoregulation during surgery between groups, subdivided in gender and preterm birth, were tested with the Mann Whitney *U* test. The association between autoregulatory ability and the administration of dopamine and propofol was analyzed with the Spearman's Rho test.

RESULTS

In this study, 54 infants were included (33% preterm). Medication administered during anesthesia consisted of sevoflurane (98%), propofol (19%), and sufentanil (100%) as pain medication (Table 1). Of the patients, 29(54%) received the vasopressor dopamine during surgery. Most infants (52%) underwent either thoracoscopy or laparoscopy, which includes insufflation of CO_2.

Table 1. Clinical characteristics

Variable	all infants n= 54 (100%)	full-term infants n=36 (67%)	preterm infants n=18 (33%)
Gestational age (weeks)	37.78 [30.86 - 41.57]	39.5 [37-41.57]	34.64 [30.86-36.28]
Preterm birth	18 (33.3%)	0 (0%)	18 (100%)
Plurality	3 (6%)	1 (3%)	2 (11%)
Birth weight (grams)	2832.50 [1405 – 4430]	3172.5 [2155-4430]	2152.5 [1405-2995]
Birth weight z-score	-0.43 [-3.12 – 1.85]	-0.43 [-3.12 – 1.85)	-0.34 [-2.11 – 1.28)
Apgar Score (1/5 minute)	9/10 [2-10]	9/10 [2-10]	9/9 [3-10]
Sex (male)	27 (50%)	18 (50%)	9 (50%)
Surgery			
Postnatal age (days)	2 [0-15]	2 [0-15]	2 [0-13]
Corrected GA (weeks)	37.99 [31.86-42.71]	39.71 [37.14-42.71]	34.78 [31.86-36.57]
Thoracoscopic surgery	13 (24%)	10 (28%)	3 (17%)
Laparoscopic surgery	15 (28%)	8 (22%)	7 (39%)
Duration of anesthesia (minutes)	190 [63-563]	201 [63-563]	169 [72-407]
Duration of surgery (minutes)	117 [23-475]	125 [23-475]	109 [28-368]
Postoperative day at MRI	7 [3-115]	7 [3-1915]	7 [4-10]
Medication			
Dopamine	29 (54%)	20 (56%)	9 (50%)
Sevoflurane	53 (98%)	35 (97 %)	18 (100%)
Isoflurane	1 (2%)	1 (3%)	0 (0%)
Sufentanil	54(100%)	36(100%)	18(100%)
Propofol	10 (19%)	8 (22%)	2 (11%)
Bupivacaine	19 (35%)	16 (44%)	3 (17%)
Atracurium	40 (74%)	27 (75%)	13 (72%)
Rocuronium	11 (20%)	6 (17%)	5 (28%)
Morphine	24 (44%)	13 (36%)	11 (61%)

Data are presented in median [range] or n (%), unless indicated otherwise

Perioperative monitoring

The cerebral oxygenation was significantly increased during surgery to a $rScO_2$ of 75.5% in comparison to pre- and early postoperative periods (preoperative: 71.6%, Z = -3.781, p < .001, r = -.57, early postoperative: 71.9%, Z = -3.678, p<.001, r = -.52, medium postoperative: 72.7%, Z = -2.249, ns, late-postoperative: 73.6, Z = 6.557, ns, Figure 1A). The percentage of time the $rScO_2$ was in the normal range (55-85%) was significantly less during surgery with 78.7% of the total duration of surgery in comparison to pre- and early and medium postoperative values (preoperative: 91.4%, Z = -3.641, p<.001, r = -.55, early postoperative: 89.0%, Z = -3.713, p<.001, r = -.53, medium postoperative: 89.6%, Z = -3.094, p<.001, r = -.43, late postoperative: 73.6%, Z = -2.219, ns, Figure 1C).

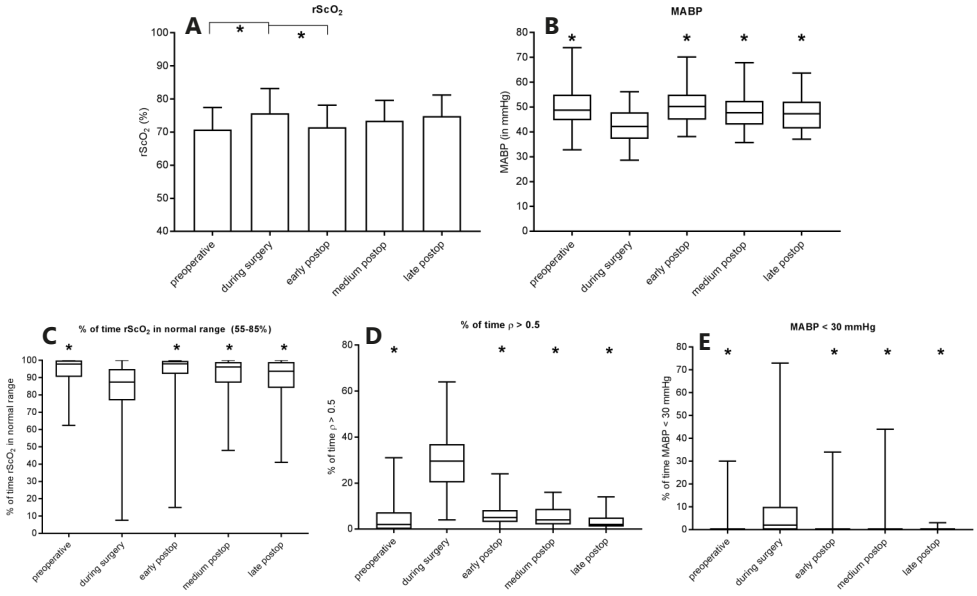

Figure 1. Perioperative monitoring. Asterix indicates significant difference with 'during surgery'. Preoperative period, during surgery, early postoperative period (within six hours after surgery), Medium postoperative period (six to 20 hours after surgery), 5. Late postoperative period (from 20 hours after surgery).ρ > 0.5 indicates absence of autoregulatory ability.

A significant decrease in MABP to 42 mmHg in comparison to pre- and postoperative values was observed during surgery (preoperative: 51 mmHg, Z = -4.352, p<.001, r = -.72, early postoperative: 50 mmHg, Z = 5.079, p<.001, r = -.74, medium postoperative: 47 mmHg, Z = -4.243, p<.001, r = -.61, late postoperative: 47 mmHg, Z = -3.956, p<.001, r = -.59, Figure 1B). Patients showed a significant higher percentage of time MABP < 30 mmHg during surgery of 7.32% in comparison to pre- and postoperative durations (preoperative: 0.88%, Z = -3.886, p<.001, r = -.63, early postoperative: 2.12%, Z = -3.682, p<.001, r = -.54, medium postoperative: 0.73%, Z = -4.190, p<.001, r = -.60, late postoperative: 0.06%, Z = -4.518, p<.001, r = -.67, Figure 1E).

The percentage of time that the correlation between MABP and $rScO_2$, expressed by the correlation coefficient $\rho > 0.5$, was significantly longer during surgery with 27.5% in comparison to pre- and postoperative durations (preoperative: 4.6%, Z = 6.14, p<.001, r = -.81, early postoperative: 6.1%, Z = 6.782, p<.001, r = -.83, medium postoperative: 5.1%, Z = 6.928, p<.001, r = -.85, late postoperative: 3.9%, Z = 6.481, p<.001, r = -.86, Figure 1D).

Parameters influencing cerebral autoregulation

In our study, no differences in % of time $\rho > 0.5$ was found between full-term and preterm birth (U = 235.00, ns, r = -.66) and between females and males (U = 354.00, ns, r = -.02). However, preterm infants had significant more prolonged hypotension during surgery (>10% of the total duration of surgery) in comparison to full-term infants (full-term 14%, preterm 56%; χ_2=10.385, p = .001).

Patients who received dopamine spent a longer duration of time with a $\rho > 0.5$ during surgery (no dopamine: 23.0% vs dopamine: 34.0%, r_s = 352.00, p = 0.02, Figure 4) and no difference was found with administration of propofol (no propofol: 30.0%, propofol: 31.5%r_s = .094, ns).

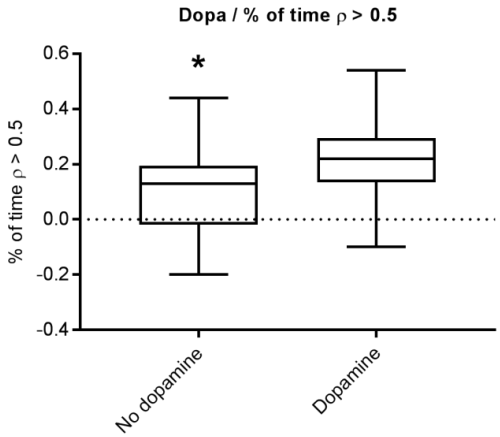

Figure 2. Dopamine administration and % of time $\rho > 0.5$ during surgery

Studying associations between perioperative variables, a reverse correlation between % of time spent $\rho > 0.5$ and level of MABP during surgery was found (r_s= -0.330; p = .015, Figure 3)

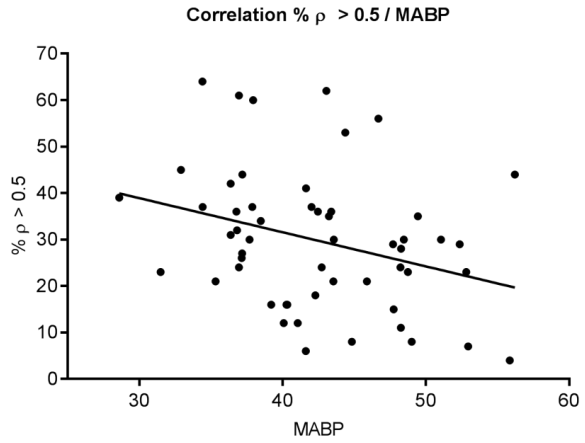

Figure 3. Reverse correlation between % of surgical time spent with ρ > 0.5 and MABP during surgery

The % of time spent ρ > 0.5 during surgery was linearly related with end-tidal CO_2 (r_s = 0.432; p =.001, Figure 4). No correlation between ρ > 0.5 and end-tidal sevoflurane was found (rs = -0.118, ns).

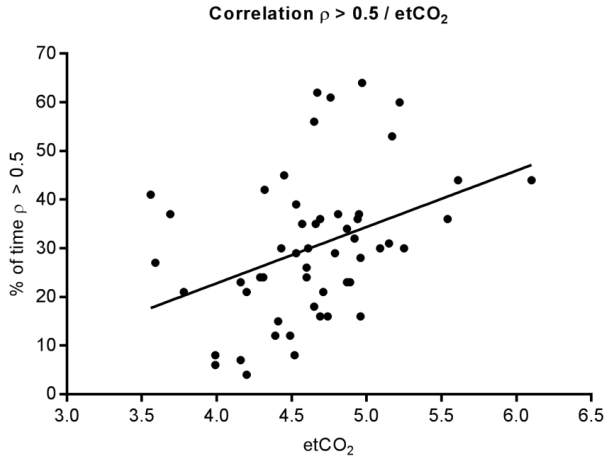

Figure 4. Correlation between % of surgical time spent with ρ > 0.5 (indicating possible cerebral autoregulation impairment) and end-tidal CO_2 levels

DISCUSSION

In this prospective cohort study the presence of autoregulatory ability, measured by the correlation between arterial MABP and non-invasive measured cerebral oxygenation, in preterm and full-term neonates during surgery in comparison to the pre- and postoperative period is investigated. The main finding is that CBF became pressure passive during major surgery. Before and after surgery cerebral autoregulation was predominantly intact, while during anesthesia with sevoflurane cerebral autoregulation was impaired for 28% of the time. An impaired cerebral autoregulation makes the brain vulnerable, which indicates an increased risk for the neonatal brain during surgery. Parameters of influence on the cerebral autoregulation are a decrease in MABP and an increase in end-tidal CO_2 during surgery. Preterm infants experienced a longer period of hypotension during surgery.

Our results confirm the results of Rhondali et al, who found a decrease in CBF during anesthesia with sevoflurane in children under the age of two years. The CBF was measured by Doppler, while a stable end-tidal CO_2 was maintained.[12] They showed effective autoregulation in children older than six months. To date, the lower limit of MABP to maintain cerebral autoregulation during anesthesia with sevoflurane has not been established in term neonates, where in extreme low-birth-weight neonates it is thought to be 30 mmHg.[16, 17] To date, monitoring the cerebral autoregulation in neonates lacks a golden standard.[18]

The results show that the $rScO_2$ was significantly increased during surgery, and the duration of $rScO_2$ between normal limits (55-85%) was significantly decreased. A possible explanation of this finding is the applied fraction of inspired oxygen during anesthesia, which gives a higher oxygen supply. This is of utmost importance, given the harmful effects of oxygen radicals in neonates.[19] Furthermore, concentrations of CO_2 and O_2 and their partial pressures, pCO_2 and pO_2 respectively, are known for their impact on cerebral blood flow. An increase in pO_2 leads to mild vasoconstriction, resulting in a decrease of CBF. Reversely, an increase in pCO_2 gives vasodilatation, resulting in an increase in CBF. Most of the surgeries were performed thoracoscopically or laparoscopically, in which CO_2 was used for inflation of the abdomen or thorax.[20] The results show a correlation between an increase in end-tidal CO_2 and a decrease in autoregulatory ability, even within the normal limits or pCO_2.[21] The increase in pCO_2 might causes MABP to pass the upper limit of the autoregulatory plateau.

The lower limit of MABP < 30 mmHg was used to define hypotension. The rationale for the use of this specific threshold is threefold. First, the association between adverse outcome and hypotension with blood pressures below 30 mmHg is reported.[22] Second, the suggestion that the lowest threshold for intact cerebral autoregulation is a MABP of 30 mmHg in neonates with PMA of more than 30 weeks. Finally, none of the patients in our study had a gestational age below 30 weeks. The results demonstrate a lower mean MABP during surgery in the entire

patient group and a prolonged period of hypotension was observed during surgery. In this study, the correlation (ρ_{xy}) of MABP and $rScO_2$ was significantly different between the periods before, during, and after surgery. Since the autoregulatory system is weakened or blocked during surgery, a high correlation between MABP and CBF was expected.

The strength of this study is the focus on the neonatal age group. Previous studies focused mainly on extremely preterm infants, in which the impairment of cerebral autoregulation is expected. Our analysis show that even in term patients with an intact autoregulation, neonatal brain might be at risk during anesthesia. Whether this is caused by the vasodilatation that moves the patient outside the plateau of the autoregulation curve, or a combined effect of the anesthesia, needs further investigation. Furthermore, the extensive continuous perioperative neuromonitoring with an indwelling peripheral arterial catheter has not been described before in this patient group.

This study has several limitations. First, the cohort consists of a heterogeneous patient group, with different gestational ages and divergent congenital anomalies. Consequently, the surgical procedures differ in duration and technique. The common denominator of the patient group is the neonatal surgery, before 44 weeks of postmenstrual age. Second, the study design was observational, where parameters influencing CBF such as pCO_2, pO_2 and sevoflurane were not kept at a constant level during surgery.

For future perspectives the upper and lower limits of blood pressure to maintain autoregulatory plateau in preterm and term neonates undergoing anesthesia is relevant to determine. Also, the relation between impairment of cerebral autoregulation during surgery and postoperative brain damage will be analyzed. We hypothesize that a longer duration of impairment in cerebral autoregulation is associated with a higher incidence of ischemic lesions. Following that, the correlation with neurodevelopmental outcome at the age of two years will be assessed.

Conclusion

Since the results show in 28% of the duration of surgery an impairment of autoregulatory ability, in a patient group with an intact autoregulation before surgery, neuromonitoring is important to protect the neonatal brain during surgery. The results of the present study demonstrate a promising method for bedside monitoring of cerebral autoregulation in the near future.

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6

CHAPTER

Predictive role of oxidative stress biomarkers for brain damage after neonatal surgery

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Submitted to Disease Markers

ABSTRACT

Objective

Neonates have a high risk of oxidative stress during anaesthestic procedures. The predictive role of oxidative stress biomarkers on the occurrence of brain injury in the perioperative period has not been reported before.

Methods

A prospective cohort study of patients, requiring major surgery in the neonatal period was conducted. Biomarker levels of non-protein bound iron (NPBI) in plasma and F_2-isoprostane in plasma and urine before and after surgical intervention were determined. Brain injury was assessed using postoperative MRI.

Results

In total, 61 neonates were included, median gestational age 39 weeks [range 31–42], weight 3000 grams [1400-4400]. Mild to moderate brain lesions were found in 66%. Logistic regression analysis showed a significant difference between plasma NPBI in patients with non-parenchymal injury versus no brain injury: 1.34 umol/L was identified as correlation threshold for non-parenchymal injury (sensitivity 67%, specificity 91%). In the multivariable analysis, correcting for GA, no other significant relation was found with the oxidative stress biomarkers and risk factors.

Conclusion

Oxidative stress seems to occur during anaesthesia in this cohort of neonates. Plasma non-protein bound iron showed to be associated with non-parenchymal injury after surgery, with values of 1.34 umol/L or higher. Risk factors should be elucidated in a more homogeneous patient group.

INTRODUCTION

The impact of surgery and anaesthesia on the young infants' brain is subject of ongoing debate. Major surgery has been shown to give a higher risk of death or neurodevelopmental impairment in a large, retrospective cohort study in very low-birth-weight infants[1]. Commonly used inhalational anaesthetics are reported to be neurotoxic in experimental studies and induce neuronal apoptosis[2,3]. Studies on the clinical effect of anaesthetics on the developing brain are challenging. Infants with major non-cardiac congenital anomalies requiring neonatal surgery (esophageal atresia, intestinal atresia, anorectal malformation, gastroschisis e.d.) have an increased risk of a neurodevelopmental delay[4]. These patients are at risk of oxidative stress due to the anaesthetic procedure including administration of sevoflurane, the fraction of inspired oxygen and pain, especially since the tendency is to keep them highly saturated during surgery[5]. Fluctuations in blood pressure, arterial CO_2 and duration of anaesthesia pose a risk for the neonatal brain in terms of developing brain injury.[6] In 63% of patients with non-cardiac congenital anomalies in this cohort study, brain lesions were visible in on their postoperative MRI.[7] The exact timing of the brain injury may help to discover the pathogenesis of these lesions. In this process, biomarkers of oxidative stress might provide insight in aetiology and pathogenic factors. To date, very few reported on the role of the anaesthesic procedure in this patient group. In this study, we hypothesize that biomarkers of oxidative stress (i.e. plasma and urinary F_2 isoprostane and plasma Non Protein Bound Iron) are associated with brain injury and aim to clarify the aspects of oxidative stress during anaesthesia. The association between perioperative parameters, such as mean arterial blood pressure, arterial CO_2, administration of opioids and duration of anaesthesia and biomarkers for neuronal injury was investigated.

MATERIAL AND METHODS

Patients

This prospective, cohort study was performed from January 2014 to December 2015 at the Neonatal Intensive Care Unit of the Wilhelmina Children's Hospital Utrecht, Utrecht, The Netherlands. All eligible newborns with non-cardiac congenital anomalies, requiring major neonatal surgery, were enrolled. This study was approved by the Medical Ethical Committee of the University Medical Center Utrecht, parents were asked for written informed consent, in accordance to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

Exclusion criteria consisted of critical cardiac congenital malformations, major congenital anomalies of the central nervous system, and insufficient Dutch language proficiency of the parents.

Methods

Biomarkers

Heparinized blood samples of 1 ml were drawn from the indwelling, peripheral arterial catheter, inserted for clinical purposes. These samples were centrifuged immediately, to obtain platelet-poor plasma, and butylated hydroxytoluene (BHT) 1% w/v in methanol (5µl per ml of plasma) was added to prevent the *in vitro* lipids peroxidation[8]. Urine samples of 4 ml were collected from already inserted urinary catheters or non-invasively from a gauze placed in the infants' diaper. Six time points were chosen; within 24 hours prior to surgery, immediately after surgery, 6, 24 and 72 hours after surgery for measurements of biomarkers of neuronal injury (Figure 1). Blood and urine samples were stored in a refrigerator at -80° Celsius until analysis. Plasma levels of NPBI were detected by high-performance liquid chromatography (HPLC) as described by Paffetti P. et al. 2006[9] using an HPLC system consisted of quaternary pumps, vacuum degassers, thermostated autosampler, DAD detector and fluorimeter detector (Agilent 1100 series). The method is based on preferential chelation of NPBI by a large excess of the low-affinity ligand of nitriloacetic acid (NTA).

Determination of F_2-isoprostanes in plasma and urine was described by Casetta B. et al.[10] The method was centered around an API 4000 Tandem Mass Spectrometer (AB Sciex, Toronto, Canada) equipped with an electrospray ionization (ESI) probe on the Turbo-V source. The chromatographic configuration was an Agilent 1200 stack.

For measurements, the tandem mass spectrometer has been run in multiple reaction monitoring (MRM) with the electrospray source operating in negative ion mode, and by exploiting the transition m/z 353.3 > 193.2 for F_2-isoprostanes and 357.3 > 197.2 for the isotopically-labeled form used as internal standard (d4-8-iso $PGF_{2\alpha}$, Cayman Chemical Co., Ann Arbor, MI, USA).[11]

Neuro-imaging

A postoperative MRI was performed on a 3.0 Tesla whole-body Achieva system (Philips Medical Systems, Best, the Netherlands) as part of routine clinical care. The scanning protocol included T1-, T2-, diffusion and susceptibility weighted images.

Data

Obstetric and neonatal data, perioperative data, as well as details on anaesthetic and surgical management were collected from patient charts.

Statistical analysis

Statistical procedures were performed using IBM SPSS statistics software package (IBM® SPSS® Statistics version 20, IBM Corp. Armonk, NY, USA, and R statistical computing).[12] Data are presented as mean ± standard deviation (SD) or as median and range when indicated. Comparison of biomarker levels before and after surgery was performed using the Wilcoxon

Signed Rank test and the Bonferroni post hoc correction for multiple testing. The Mann Whitney *U* test was performed to compare biomarker levels and presence of brain injury. A multivariable regression analysis was performed using the cumulative concentration of biomarker levels in the first 60 hours after surgery. Parameters investigated were gender, type of congenital anomaly, endoscopic procedure and the occurrence of parenchymal injury, after correcting for gestational age. Receiver operating characteristic curves (ROC) were calculated at different time-points from T1 to T4, in order to detect the best time point correlating with damage.

RESULTS

Of the 84 patients, admitted to the NICU between January 2014 and December 2015 and who underwent major surgery in the neonatal period, parents of 73 neonates were approached and asked for consent of their infant to participate in the study. Exclusion criteria consisted of emergency surgery (n = 4), absence of one of the parents (n=3), insufficient Dutch language proficiency (n =3) or diagnosis made during surgery (n=1). In 61 of these 73 neonates, parental informed consent was given. Clinical data are presented in Table 1 (Supplemental Table 1. Overview of congenital anomalies). Figure 1 shows the time distribution of each sampling point.

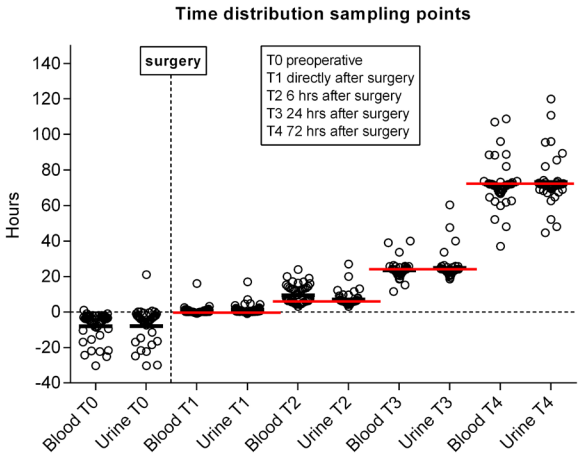


Figure 1. Time distribution sampling points

Table 1. Clinical data

	n=61
Gestational age (weeks)	38.9 [30.9-41.6]
Male, n(%)	36 (59%)
Birth weight (grams)	3000 [1405-4430]
Birth weight z-score	-0.25 [-2.1-1.9]
Small for gestational age, n(%)	2 [3%]
Preterm, n(%)	15 [25%]
Apgar score 1 minute	9 [2 – 10]
Apgar score 5 minutes	10 [2 – 10]
Postnatal age in days at time of surgery	2 [0 – 8]
Postnatal age in hours at time of surgery	39.9 [2 – 184]
Surgery	
Thoracoscopy, n(%)	18 (30%)
Laparoscopy, n(%)	16 (26%)
Laparotomy, n(%)	23 (38%)
Duration surgery (minutes)	115 (23 – 475)
Duration anaesthesia (minutes)	189 (63 – 563)
Medication during anaesthesia	
Sevoflurane, n(%)	60 (98%)
Isoflurane, n(%)	1 (2%)
Sufentanil, n(%)	60 (98%)
Propofol, n(%)	14 (23%)
Morphine, n(%)	17 (28%)
Caudal analgesia, n(%)	13 (21%)
Suxamethonium, n(%)	1 (2%)
Atracurium, n(%)	51 (84%)
Rocuronium, n(%)	9 (15%)

*data displayed in median[range] or indicated otherwise

Oxidative stress biomarkers

Plasma and urinary levels of F_2-isoprostane and plasma NPBI were not significantly different before surgery in comparison to values after surgery (T0 versus T1-T4, Wilcoxon Signed Rank test with post hoc Bonferroni, $p>0.3$ (Figure 2)(Supplemental Table 2. Statistics of Wilcoxon Signed Rank test).

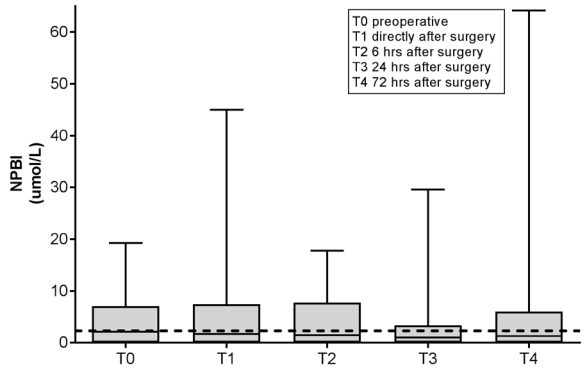
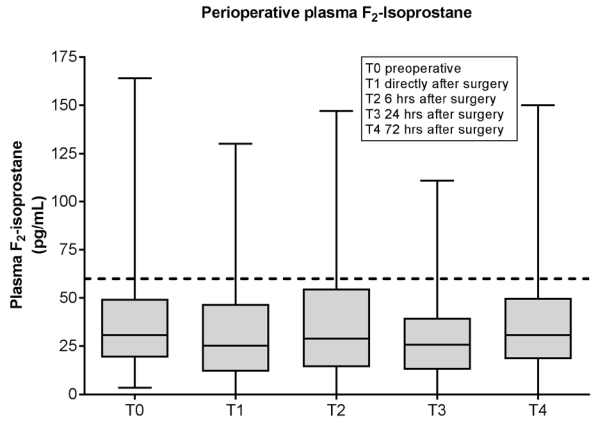
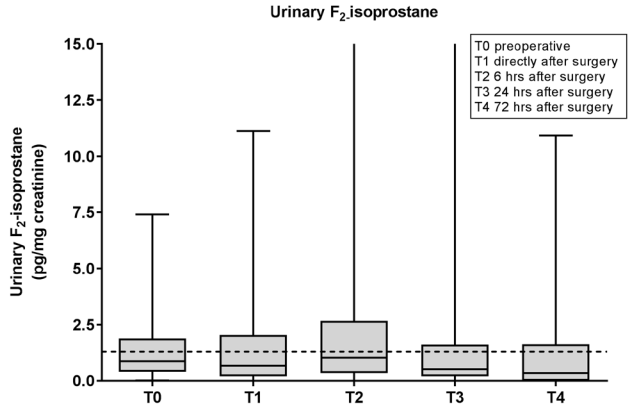


Figure 2. Perioperative data of oxidative stress biomarkers

Legend 2a: Data of plasma NPBI at each time point. Dotted line indicates 2.3 umol/L NPBI, normal values of plasma NPBI are below this cut off value.



Legend 2b: Data of plasma F_2-isoprostane at each time point. Dotted line indicates 60 pg/mL F_2-isoprostane, normal values of plasma F_2-isoprostane are below this cut off value.



Legend 2c: Data of urinary F_2-isoprostane at each time point. Dotted line indicates 1.3 pg/mg creatinine F_2-isoprostane, normal values of urinary F_2-isoprostane are below this cut off value.

Brain lesions

Parenchymal and/or non-parenchymal brain lesions were found in 66% of 58 postoperative MRI-scans (Table 2. Incidence of brain injury and Figure 3. Examples of parenchymal and non-parenchymal brain injury). In 18 neonates a combination of parenchymal and non-parenchymal injury was visible. In 51% of the neonates parenchymal injury was present, 55% of these lesions were visible on the diffusion weighted images (DWI), which indicates timing of the injury to be in the perioperative period. The cumulative concentration of plasma F_2-isoprostane of patients with no brain injury showed significantly lower levels than patients with parenchymal injury (Mann Whitney U, U=11.0, $p<0.01$, $r=-0.70$, Figure 4), indicating higher concentrations of F_2-isoprostane in patients with brain injury.

Table 2. Incidence of brain injury

Brain injury	n*
No injury	20
Parenchymal injury	13
Non-parenchymal injury	7
Parenchymal and non-parenchymal injury	18

* MRI was not available in three patients: one was declined by the parents, one had a preoperative MRI scan only and one patient was diagnosed with Down's syndrome.

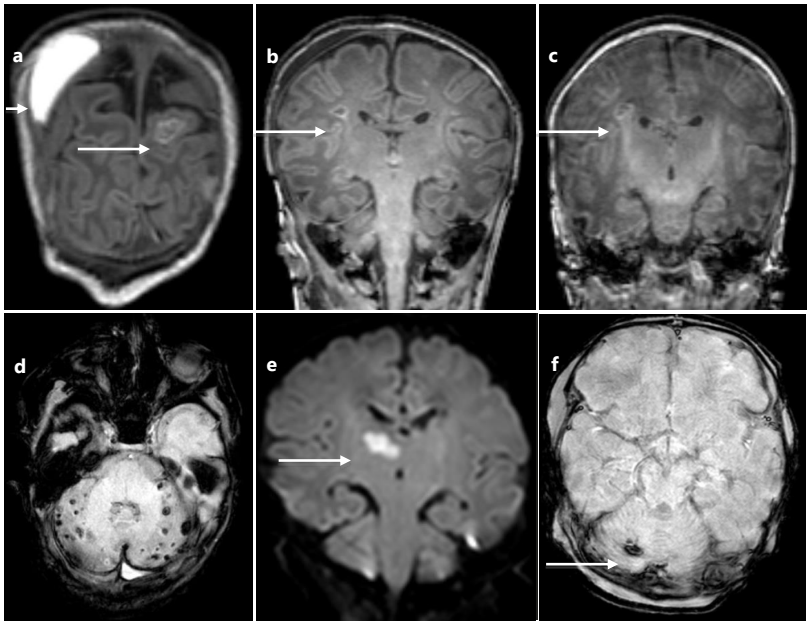


Figure 3. Examples of parenchymal and non-parenchymal brain injury: a) coronal T1-weighted image: cortical infarction and subdural haemorrhage, b) coronal T1-weighted image: white matter lesion, c) coronal T1-weighted image: white matter lesion, d) susceptibility weighted image: multiple punctate cerebellar lesions, e) diffusion weighted image: thalamic infarction, f) susceptibility weighted image: cerebellar haemorrhage.

Multivariable linear regression

In the multivariable analysis using the cumulative concentration starting directly after surgery to 60 hours after surgery for each biomarker, correcting for GA, none of potentially influencing factors showed a significant linear relation with plasma and urinary F_2-isoprostane or plasma NPBI. Parameters investigated consisted of gender, type of congenital anomaly, endoscopic procedure and the occurrence of parenchymal injury (Figure 4. Cumulative concentration). This indicates that after correcting for gestational age, the absence or presence of brain injury did not influence the overall concentrations of the oxidative stress biomarkers in the perioperative period.

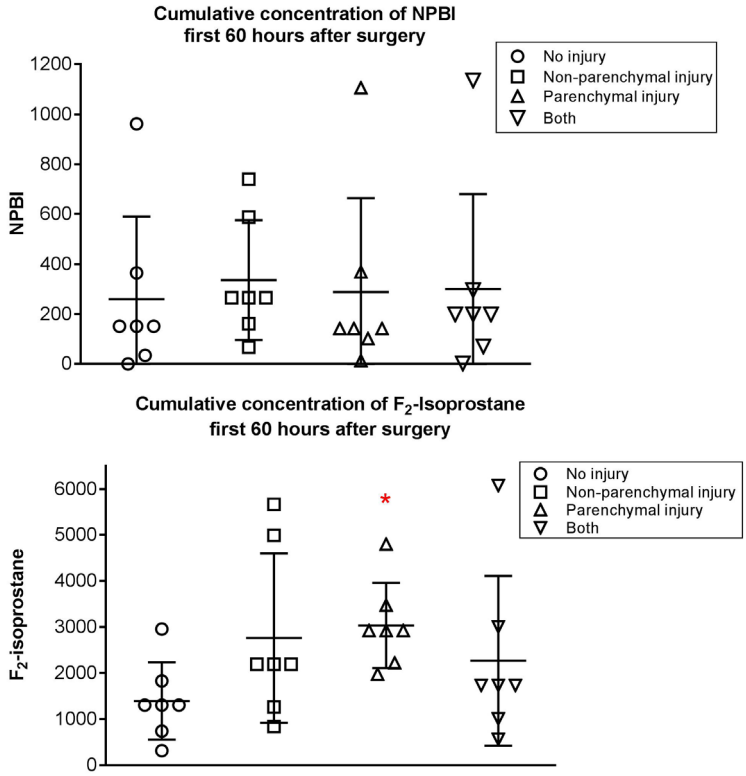


Figure 4. A significant difference in plasma F_2-isoprostane between 'no injury' and 'parenchymal injury' was found using the Mann Whitney U test with post hoc Bonferroni correction (U=11.0, p<0.01, r=-0.70)

ROC curve analysis

A logistic regression was performed for each time point. A significant difference in plasma NPBI was found between patients with non-parenchymal injury (78.5%) and patients with no brain injury after anaesthesia. The results indicate plasma NPBI at 72 hours after surgery, as the best

early predictor for non-parenchymal injury. The determination of NPBI levels at 72 hours after surgery allow to differentiate neonates having non-parenchymal brain injury from no brain injury: AUC 78.5% (95% Confidence Interval: 0.595– 0.975), with 66.7% specificity and 90.9% sensitivity (Figure 5). The threshold 1.34 micromol/l was identified as predictive value for having non-parenchymal injury. A predictive threshold value at one specific time point could not be identified for F_2-isoprostane.

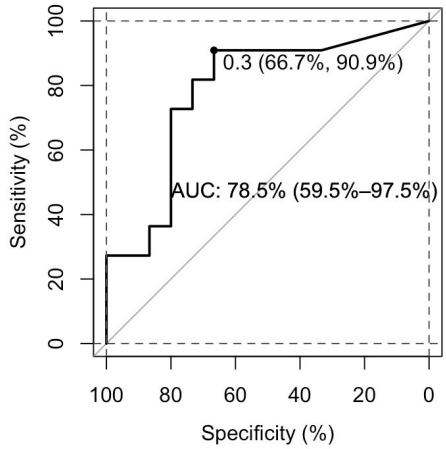


Figure 5. Legend: Receiver operating characteristic (ROC) curve analysis for NPBI at 72 hours after surgery. The area under the curve indicates that NPBI at 72 hours after surgery allows to differentiate neonates with non-parenchymal injury from no injury. The area under the curve was 0.785 (95% Confidence Interval: 0.595–0.975), with 66.7% specificity and 90.9% sensitivity. 1.34 micromol/l or higher was identified as predictive threshold to have non-parenchymal injury.

DISCUSSION

This study investigated oxidative stress biomarkers in neonates undergoing neonatal surgery for non-cardiac congenital anomalies. In this cohort, 66% of the neonates had mild to moderate brain lesions visible on their postoperative MRI. A combination of parenchymal and non-parenchymal injury was found in 30% of the infants. In the total patient cohort, after correcting for gestational age, perioperative biomarker concentrations of F_2-isoprostane and NPBI were not correlated to perioperative brain injury. In the ROC curve analysis, assessing the sub groups no brain injury, parenchymal and non-parenchymal brain injury at each time-point, oxidative stress seems to occur as a consequence of anaesthesia. This was shown by elevated levels of NPBI in plasma and urinary F_2-isoprostane after surgery in patients with parenchymal injury in comparison to patients with no brain injury. In addition to that, the level of 1.34 umol/L plasma NPBI was identified as risk threshold for non-parenchymal injury. Despite the bias related to

heterogeneity, this study points out that these neonates are at risk of oxidative stress during the anaesthetic procedure.

There is no previous literature available on biomarkers in patients with non-cardiac congenital anomalies requiring surgery. This could be explained by the fact that patients with congenital malformations are structurally excluded from trials. However, biomarkers of neuronal injury might be of great value in this vulnerable group of patients.

The hypothesis was to find an increase in biomarker values after surgery in comparison to preoperative values. The basal level of oxidative stress before surgery was reported for the first time. Interestingly, the values of F_2-isoprostane at baseline – before surgery – were low , in comparison to the findings of Comporti et al. Newborns in this study had values between 50-150 pg/ml after birth, blood samples were obtained from the umbilical vein. Our results show a median F_2-isoprostane of 30 pg/ml creatinine at baseline, drawn from the arterial catheter at a median age of two days. Apparently, the oxidative stress at birth caused by the transition from a low oxygen pressure in utero to a relatively high oxygen pressure after birth has resolved[20].

Oxidative stress is a unifying term for the end product of several diseases, which can be produced by free radicals. Biomarkers are defined as indicators of normal processes or measures of pathological processes[13]. Free radicals damage the endothelial cell and cause inflammatory reactions and brain cell damage, which can be evaluated by an increased level of non-protein bound iron. NPBI has been proven to be a predictive biomarker of neonatal brain damage in preterm infants.[14] This biomarker seems to play a pivotal role in identifying neonates at risk of brain damage. F_2-isoprostanes, discovered by Morrow et al, are a product of free radical-induced injury by peroxidation of lipids. This biomarker is formed via non-enzymatic peroxidation of polyunsaturated fatty acids mediated by free radical production.[15] This peroxidation of arachidonic acid is produced by a non-cyclooxygenase mechanism[16] and is a non-invasive method to monitor lipid peroxidation in vivo. An increase of F_2-isoprostane in plasma and urine occurs after hypoxic-ischaemic brain injury and reperfusion[17], and predicts the risk of having brain injury. Previous studies have shown that F_2-isoprostane is a reliable and chemically stable biomarker and thus an oxidative stress marker of cerebral white matter lipid oxidation[18,19]. Importantly, it is previously described that plasma F_2-isoprostane levels are inversely correlated with gestational age[20]. This is also the case in healthy infants, Friel et al. found an increased level of F_2-isoprostane in a cohort of 12 infants at the age of one month.[5] Furthermore, lipid exposure to high concentrations of NPBI also leads to formation of isoprostanes.

Reactive oxygen species (ROS) are known to cause oxidative stress in the newborn infant, leading to damage to cell structures like lipids and membranes[5,21,22]. Free radical oxidative damage in the newborn is involved in diseases like retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis and patent ductus arteriosus.[22] In addition, the developing brain of the neonate, with its high concentration of polyunsaturated fatty acids, is highly susceptible to hypoxia and hyperoxia[23]. These pathological circumstances cause oxidative stress reactions,

in particular in the neonate with their immature anti-oxidant defenses[24]. White matter is selectively injured, since the developing oligodendrocyte is the main target of oxidative stress in hypoxia-ischaemia and systemic inflammation[23,25]. Brain injury has previously been described in the group of patients with cardiac congenital anomalies, undergoing major surgery[26]. Our results show a high incidence of mild to moderate brain lesions in infants with non-cardiac congenital anomalies as well.

The sensitivity of the rapidly developing brain of the neonate undergoing major surgery to brain injury is threefold. First, the developing brain tissue is sensitive to free radicals. ROS cause oxidative stress[21], in particular in newborns with their reduced enzymatic and non-enzymatic anti-oxidant defense[22]. Neonates undergoing surgery are exposed to fluctuating fractions of inspired oxygen. During induction of anaesthesia an increased supply of oxygen is administered, to prevent hypoxia during intubation, which enhances the risk of free oxygen radicals. Secondly, inhalational anaesthetics are thought to cause neurotoxic effects in the developing newborn brain[27-29]. The anaesthetic causes an increase in apoptosis, an impaired neurogenesis and neuroinflammation in animal experimental studies[30]. Third, cerebral perfusion is at risk due to immature cerebral autoregulatory ability in preterm infants or a loss of cerebral autoregulation caused by sevoflurane anaesthesia[31]. Presence or absence of autoregulatory ability can be determined by blood pressure and cerebral oxygenation, measured by Near Infrared Spectroscopy[32]. In case of pressure-passive perfusion, fluctuations in respiratory and cardiovascular parameters pose a risk for cerebral saturation and perfusion. Maintenance of cerebral blood flow is critical to ensure adequate oxygenation of the brain.

This study has several limitations. First, with the use of F_2-isoprostane only a specific type of brain damage was investigated, involving the prostaglandin metabolism. The second limitation is that our cohort consists of a heterogeneous patient group. In order to solve this problem, each patient is used as their own control, with the baseline measurement before surgery. Furthermore, the bias consisted of differences in gestational age, weight, different surgical techniques, differences in administered dose of anaesthesia and pain medication. The strength of this study, however, is that it is the first study to investigate these biomarkers in neonates with non-cardiac congenital anomalies, at multiple time points, in combination with the use of MRI. Also, the clinical use of these biomarkers is investigated in this prospective study where cerebral monitoring is applied in the perioperative period as well. The combination of biomarkers and MRI offers the opportunity to identify neonates at risk of brain injury more precisely, which might be of great value to develop tailored therapy and preventive measures for brain injury in the future.

Conclusion

Despite the bias related to heterogeneity of the study group, our results showed a risk of oxidative stress during anaesthesia in neonates.

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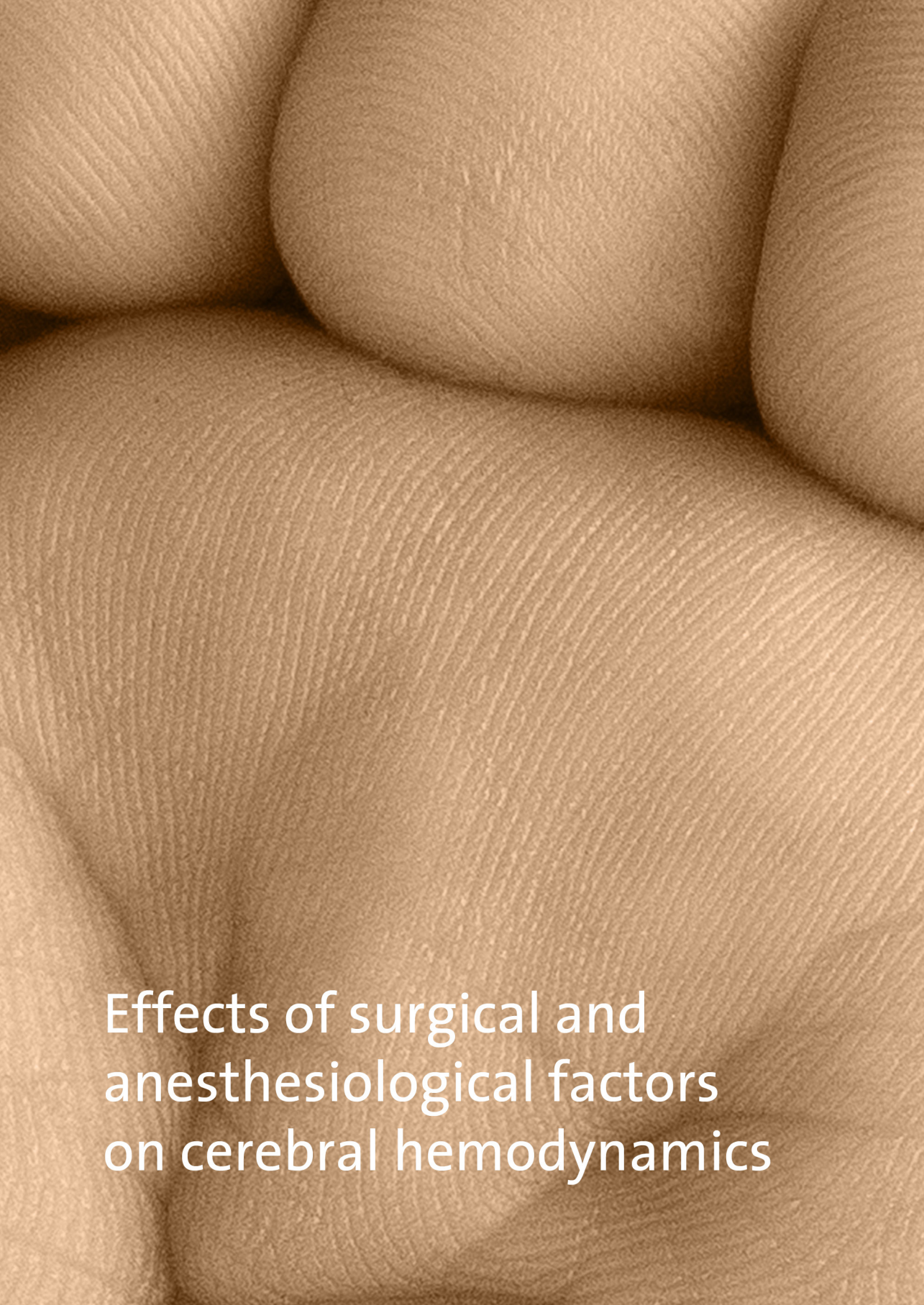
PART 3



Effects of surgical and anesthesiological factors on cerebral hemodynamics


7
CHAPTER

The effects of CO_2-insufflation with 5 and 10 mmHg during thoracoscopy on cerebral oxygenation and hemodynamics in piglets:

an animal experimental study

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ABSTRACT

Objective: To evaluate the effect of CO_2-insufflation with 5 and 10 mmHg on cerebral oxygenation and hemodynamics in neonates.

Background: An increasing percentage of surgical interventions in neonates are performed by minimal invasive techniques. Recently, concerns have been raised regarding a decrease of cerebral oxygenation in neonates during thoracoscopy as a result of CO_2-insufflation.

Methods: This was an animal experimental study. Piglets were anesthetized, intubated, ventilated, and surgically prepared for CO_2-insufflation. Insufflation was done with 5 or 10 mmHg CO_2 during 1 hour. Arterial saturation (SaO_2), heart rate (HR), mean arterial blood pressure (MABP), and cerebral oxygenation ($rScO_2$) were monitored. CFTOE, an estimator of cerebral oxygen extraction ((SaO_2 - $rScO_2$)/SaO_2)), was calculated. Arterial blood gases were drawn every 15 minutes: pre (To), during (T1-T4) and after CO_2-insufflation (T5).

Results: Ten piglets (4 kg) were randomized for 5 (P5) and 10 (P10) mmHg CO_2-insufflation. Two P10 piglets needed resuscitation after insufflation, none P5. Linear mixed-effect modeling of $paCO_2$, pH, and SaO_2 showed that values were dependent on time and time squared (p\0.001) but were not different between the 5 and 10 mmHg groups. Analysis demonstrated significant changes over time in heart rate and MABP between the 5 and 10 mmHg groups, with a significant higher heart rate and lower blood pressure in the 10 mmHg group ($p<0.001$). For $rScO_2$ and cFTOE, no group differences could be demonstrated, but a significant effect of time was found: $rScO_2$ increased and cFTOE decreased ($p<0.001$).

Conclusions: Insufflation of CO_2 during thoracoscopy with 10 mmHg caused more severe hemodynamic instability and seems to be related with a decrease of cerebral perfusion as represented by a higher oxygen extraction. CO_2-insufflation of 5 mmHg for thoracoscopy seems to have no adverse effects on cerebral oxygenation.

INTRODUCTION

Nowadays, an increasing percentage of major surgical interventions in neonates are performed by minimally invasive techniques, such as thoracoscopic repair of esophageal atresia,[1–3] Thoracoscopy enables shorter duration of postoperative-assisted ventilation and less days of sedation use,[4] whereas thoracotomy may be associated with detrimental musculoskeletal outcomes like weakness of the latissimus dorsi musculature, winging of the scapulae, and thoracic scoliosis.[5,6]

The mortality of patients with esophageal atresia decreased to <5 % and attention shifted to morbidity and long-term outcome, with mostly anastomotic stenosis and gastroesophageal reflux.[7] In recent years, however, concerns have been raised regarding impaired neurodevelopmental outcome in these patients. The cause of this neurologic impairment in these patients is currently unknown and most likely multifactorial.[8,9] The neonatal brain is extremely vulnerable for external changes because of an immature autoregulatory system and hemodynamic instability, especially within the first days to weeks after birth in neonates.[10]

Only scarce information is available about the effects of pneumothorax by insufflation of CO_2 on the cerebral oxygenation and perfusion during thoracoscopy in neonates.[11] Where it seems to be safe in adults, recently concerns have been raised about the application in neonates[12, 13] where high intrathoracic pressures up to 10 mmHg have been used. This is in contradiction to our normal clinical practice where a capnothorax in neonates is created using pressures of only 3 to a maximum of 5 mmHg and a flow of 1 L/min which seemingly does not result in the aforementioned disturbing effects.

Near infrared spectroscopy is a non-invasive method to continuously monitor the regional cerebral oxygen saturation ($rScO_2$) and is an estimator of cerebral tissue perfusion. $rScO_2$ is influenced not only by the arterial oxygen saturation but also by other parameters influencing cerebral hemodynamics and oxygenation like mean arterial blood pressure (MABP), mean airway pressure, hemoglobin concentration, and also $paCO_2$. Hypercapnia causes cerebral vasodilatation and increased perfusion, while hypocapnia causes vasoconstriction and decreased perfusion.[14]

This study aimed to test the hypothesis that high-pressure insufflation of CO_2 with 10 mmHg during thoracoscopy in newborn piglets compromises the hemodynamic stability and the regional cerebral oxygen saturation ($rScO_2$) while insufflation with 5 mmHg, used in normal clinical practice in our hospital, will not.

METHODS

This was an animal experimental study to test the difference in effect of creating a pneumothorax with 5 and 10 mmHg CO_2 in newborn piglets. The study protocol was approved by the Animal Experimental Board of the University of Utrecht, the Netherlands. Surgical preparation and veterinary care were given by a veterinary technician in the animal laboratory.

Surgical preparation and anesthesia of the piglets

Ten Dutch store piglets of 10–14 days of age were included.
A standard anesthesia protocol was used for all the piglets. The piglets were given premedication of 0.7 mg/kg midazolam i.m., 13 mg/kg ketamine i.m., and 0.05 mg/kg atropine i.m. Induction of anesthesia was given by administering a bolus of 4 mg/kg intravenous thiopental after an arterial catheter was inserted. For general anesthesia, 0.011 mg/kg/h sufentanil was given, 0.09 mg/kg/h cisatracurium and 1 mg/kg/h midazolam for maintenance. Tracheal intubation was performed after administering pain medication by meloxicam 0.4 mg/kg and lidocain locally. The oxygenation and ventilation were set to maintain a peripheral oxygenation of [90 %, pH 7.40–7.50, and $paCO_2$ 35–50 mmHg.

Monitoring of cerebral oxygenation and oxygen extraction

The $rScO_2$ measured by NIRS was used to monitor changes in the cerebral oxygenation. Although $rScO_2$ is not a robust quantitative measure of cerebral oxygenation, it can be reliably used to detect substantial changes in cerebral oxygenation. The $rScO_2$ reflects oxygen saturation in veins, capillaries, and arteries. The NIRS monitor (INVOS 5100-P Cerebral Oximeter; Covidien, Mansfield, Massachusetts) was used with the small adult sensor (Somanetics SomaSensor_ no. 4100-SSA Adult/Disposable). This is a transducer containing a light emitting diode and two distant sensors that was attached to the frontoparietal side of the piglets head. The rScO2 was calculated from the differential signals obtained from the two sensors.[15]
The fractional cerebral tissue oxygen extraction (cFTOE) represents the balance between oxygen delivery and oxygen consumption. An increase in cFTOE might reflect an increase in oxygen extraction by the brain tissue, and a decrease in cFTOE suggests that there is less utilization of oxygen by brain tissue, in relation to the supply of oxygen.[16,17] The cFTOE is formulated as a ratio by $((SaO_2 - rScO_2)/SaO_2)$.[18]

Experiment

The near infrared sensor was placed right frontoparietal on the shaved head of the piglet, after which premedication was given (Fig. 1). After induction of anesthesia, a 5 mm trocar was inserted in the fifth intercostal space of the right hemithorax. Insufflation was initiated with either 5 or 10 mmHg CO_2 during 1 h with continuous non-invasive NIRS-monitoring. The physiologic

parameters end tidal CO_2 ($etCO_2$), arterial saturation, heart frequency (HF), and mean arterial blood pressure (MABP) were monitored. Arterial blood gases for $paCO_2$ and pH were drawn every 15 min before, during and after insufflation of CO_2 (Fig. 2).

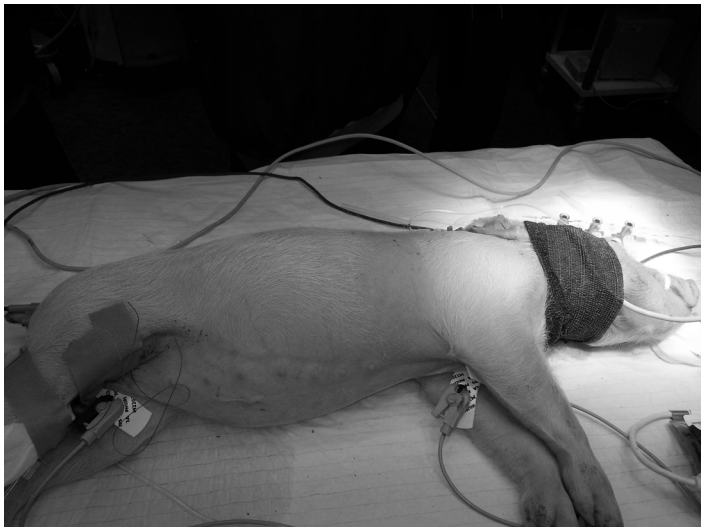

Figure 1. Set-up of experiment

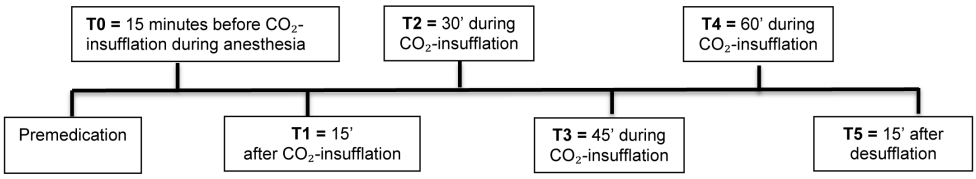

Figure 2. Time-line experiment

Statistical analysis

Data from the monitor were extracted to Excel workbooks. The mean (SD) or median (range) of all parameters was calculated for every 15-min block. Data were analyzed using a linear mixed-effect model (R-software version 2.15.0; package nlme) with time, squared time, and group (5 vs. 10 mmHg) as independent variables, including interactions with time and squared time, and individual pig as a random factor. A p value of 0.05 was considered significant. Models were simplified using Occam's Razor based on Akaike Information Criterion.

RESULTS

Ten piglets (≈4 kg) were included in this study and were randomized into two different pressure groups, either CO_2-insufflation with 5 mmHg (P5) or CO_2-insufflation with 10 mmHg (P10).
At baseline, the vital parameters between P5 and P10 were not different and within normal limits. (Table 1). Also $rScO_2$ and cFTOE were not different between the groups; the $rScO_2$ was 42 % ± 3 with a cFTOE of 0.58 ± 0.02 in P5; and the $rScO_2$ was 37 % ± 8 in P10 with a cFTOE of 0.61 ± 0.06.
The procedure was terminated prematurely in two P10-piglets (piglets 2 and 8) due to the need of resuscitation. Termination of the procedure occurred in none of the P5.
After the experiment, all the piglets, including those in which the procedure was terminated prematurely, were thoracoscopically examined, and in none of the animals, damage or hemorrhages were present.

Table 1. Baseline characteristics of P5 and P10

To	P5	P10	p-value
HR	172 ± 31	152 ± 18	NS
MABP (mmHg)	78 ± 13	84 ± 8	NS
SaO_2 (%)	97.9 ± 0.4	97.4 ± 0.3	NS
$paCO_2$ (mmHg)	36 ± 4	35 ± 5	NS
pH (AU)	7.46 ± 0.03	7.43 ± 0.04	NS
$rScO_2$ (%)	42 ± 3	37 ± 8	NS
cFTOE	0.58 ± 0.02	0.61 ± 0.06	NS

Variables in mean±SD
NS: not significant

Piglets 5 mmHg

The vital parameters of the P5 showed a stable arterial saturation, heart rate, and MABP during CO_2-insufflation and after desufflation and were within normal limits (Fig. 3).
The $paCO_2$ increased, and the pH decreased significantly. The $rScO_2$ (%) increased, and the cFTOE decreased over time.

Piglets 10 mmHg

In 3 piglets in P10, a complete registration was obtained; in two piglets, there were missing monitor results at T4 during the resuscitation in which we stopped the insufflation of CO_2. Consequently, we report the results of the resuscitated piglets in the 10 mmHg group individually.
The vital parameters of three non-resuscitated P10-piglets showed a decrease in arterial saturation. The $rScO_2$ (%) increased, and the cFTOE decreased over time (Fig. 4). The heart rate and $paCO_2$ increased significantly, and the MABP and pH decreased.

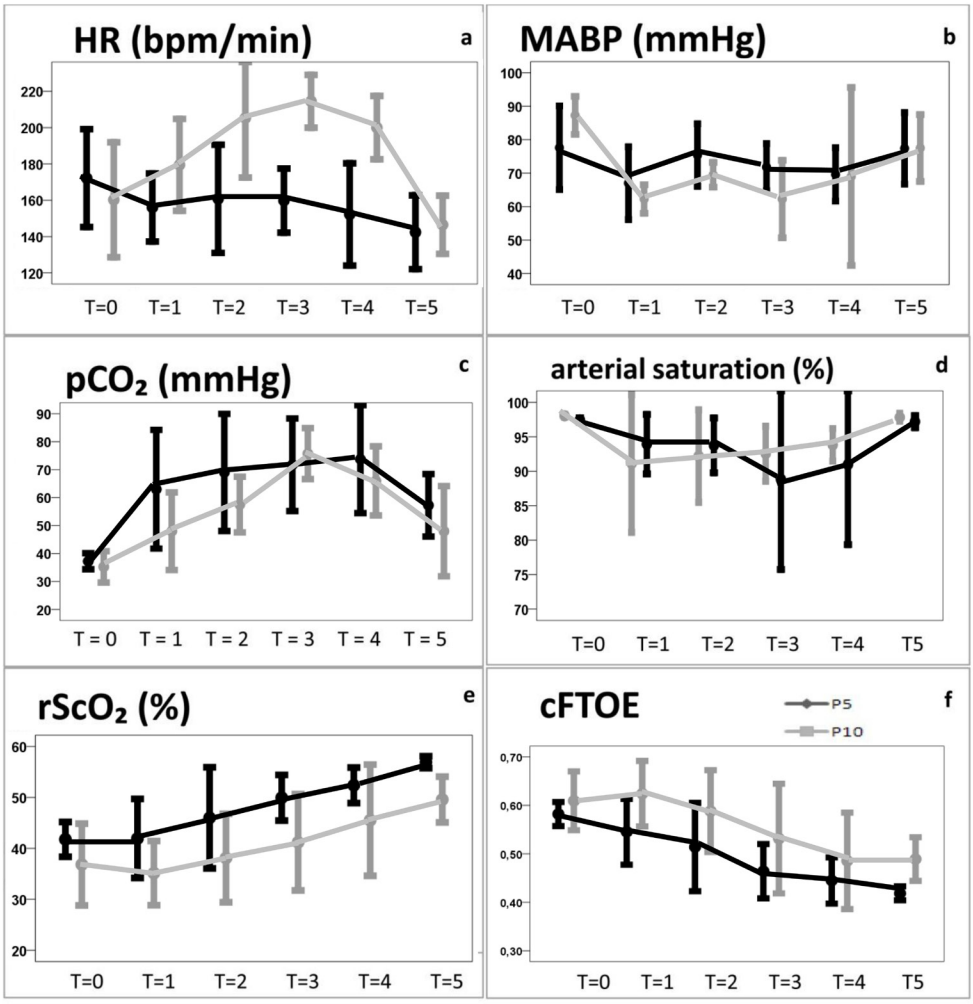

Figure 3. Vital parameters of P5 and P10. Vital parameters of the two groups, 5 mmHg CO_2-insufflation (dark grey line) and 10 mmHg (light grey line). The mean values of heart rate (HR, a), mean arterial blood pressure (MABP, b), arterial CO_2 ($paCO_2$, c), arterial saturation (%, d), regional cerebral oxygen saturation ($rScO_2$, e) and cerebral fractional tissue oxygen extraction (cFTOE, f). At T4 are missing values of piglets 2 and 8.

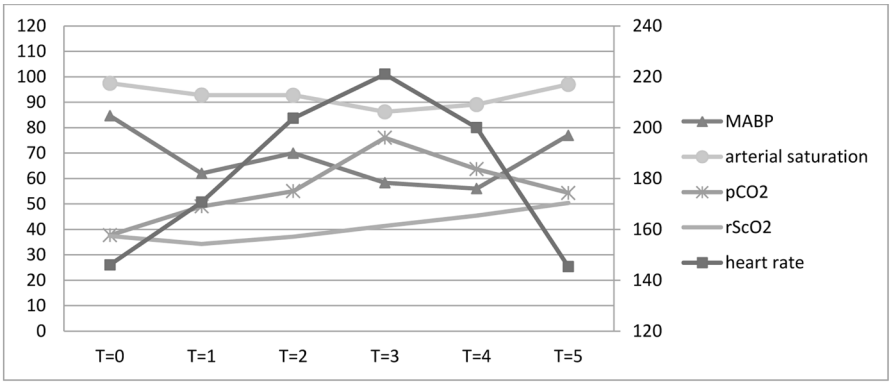

Figure 4. Vital parameters and rScO2 of P10. MABP in mmHg, heart rate beats per minute, arterial saturation (%), $rScO_2$ (%), $paCO_2$ (mmHg). * = $p < 0.05$ vs. baseline within the same group.

In piglet 2, the MABP dropped from 95 to 68 mmHg (Fig. 5), and the heart rate increased to 206 beats per minute after insufflation. The ventilation had to be adjusted frequently. After a new ventilation problem occurred, the CO_2-insufflation had to be stopped and resuscitation started after T3.

The heart rate of piglet 8 increased from 169 beats per minute to 258. The insufflation of CO_2 was stopped prematurely because of the severe decrease in MABP (73–22 mmHg); there were no measurements at T4. The piglet needed resuscitation (Fig. 6).

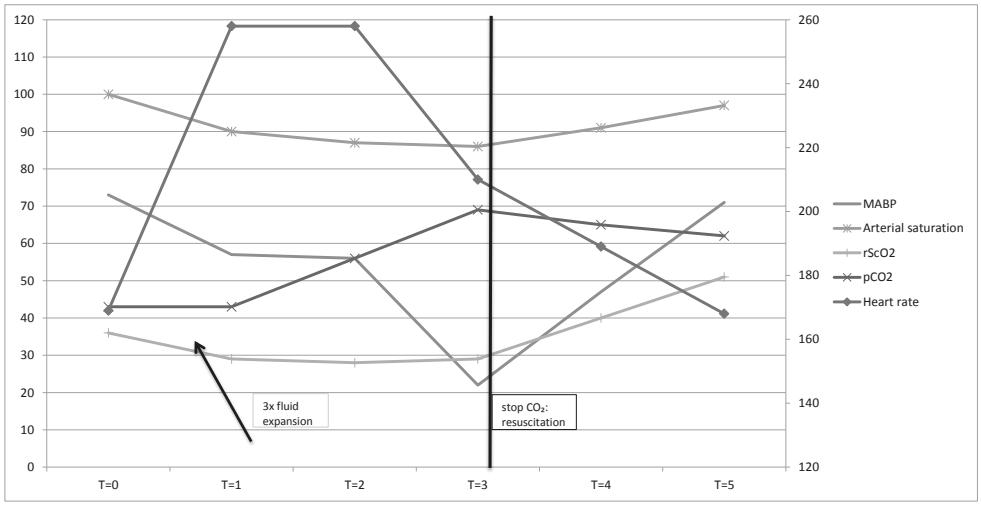

Figure 5. Vital parameters and $rScO_2$ of piglet 2 (10 mmHg). MABP in mmHg , heart rate beats per minute, arterial saturation (%), $rScO_2$ (%), $paCO_2$ (mmHg). After CO_2-insufflation the heart rate increases and the MABP drops. The ventilation had to be adjusted frequently. Due to a ventilation problem the insufflation had to be stopped and the piglet needed resuscitation after T3.

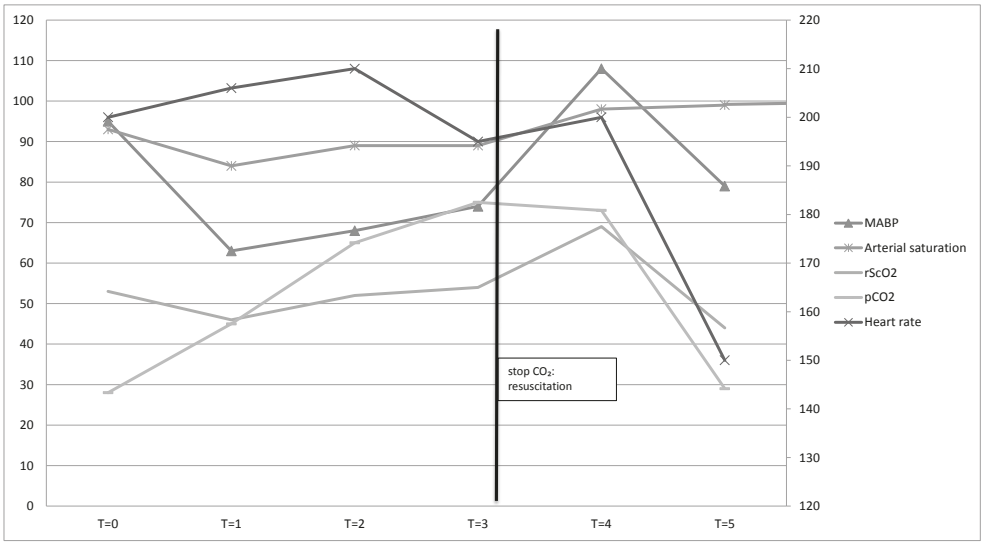

Figure 6. Vital parameters and rScO2 of piglet 8 (10 mmHg). MABP in mmHg , heart rate beats per minute, arterial saturation (%), $rScO_2$ (%), $paCO_2$ (mmHg). The insufflation was stopped prematurely because of the severe drop in blood pressure, the piglet needed resuscitation after T3.

P5 versus P10

Analysis using the mixed-effect model demonstrated significant changes over time in heart rate and MABP between the P5 and P10 groups, with a significant higher heart rate and lower blood pressure in the P10 group ($p<0.001$).

For $rScO_2$ and cFTOE, no group differences could be demonstrated, but a significant effect of time was found: $rScO_2$ increased and cFTOE decreased ($p<0.001$).

Linear mixed-effect modeling of $paCO_2$, pH, and SaO_2 showed that values were dependent on time and time squared ($p<0.001$) but were not different between the P5 and P10 groups.

DISCUSSION

The results of this animal experimental study show that intrathoracic CO_2-insufflation with 10 mmHg causes a severe loss of hemodynamic stability, even resulting in resuscitations in contradiction to stable hemodynamic parameters in piglets insufflated with 5 mmHg. Nevertheless, in this study, we observed a cerebral oxygenation that increased during thoracoscopy with 5 and 10 mmHg CO_2-insufflation. In P10, there was an increased $paCO_2$ up to 70 mmHg observed during procedure with a severe acidosis, where in P5, a milder acidosis was observed, although no significant difference was demonstrated. In both groups, the ventilation was adjusted where needed to maintain normal values.

Two recent publications by Bishay show that thoracoscopy in infants with pressures as high as 10 mmHg is associated with an extended decrease of $rScO_2$, measured by near infrared spectroscopy (NIRS), and hypercapnia with extreme severe acidosis.[12,13]

The devastating results from these studies could not be reproduced in this animal experimental model. The former outcomes could greatly restrain the application of thoracoscopic procedures being performed in neonates, such as esophageal atresia repair. The initial values of cerebral oxygenation in this study were higher than normally observed in humans.[19] We suggest that this discrepancy is caused by a different sensor being used which gives a 10 % higher value or that it is due to a high FiO_2 during the induction of anesthesia.[20] Although in this study, the values always remained within the normal limits, it stresses the importance of starting the neuromonitoring preoperatively at the ward, to assess the normal values of the patient.

Given the advantages of minimal invasive surgery techniques, it is important to emphasize the possibilities of thoracoscopy with pressures up to 5 mmHg. Although in our experiment, suprafysiologic values of $paCO_2$ up to 70 mmHg and in a few cases a pH of 7.10 were observed, they are not near the extreme hypercarbia and hypercapnia of up to 120 reported earlier by Bishay. One should take into account by interpreting these results that the high pressures of up to 10 mmHg and 4 L/min flow were used during those procedures. Because a significant decrease in the $rScO_2$ can be damaging, we gave preference to evaluate the effects of CO_2-insufflation of up to 10 mmHg in this animal experimental model. Previous research showed that a nadir $rScO_2$ of less than 35 %[21] is associated with impairments in neurodevelopment.[8,10]

How can we explain our results? Even though we saw a severe loss of hemodynamic stability in the 10 mmHg group, we observed that cerebral oxygenation increased over time. The decrease in MABP could have been antagonized by the vasodilatating effect of the raised $paCO_2$. Kaiser et al.[22] showed that progressive hypercapnia results in a loss of autoregulation of the brain. We speculate that the difference in hemodynamic stability is caused by exceeding the central venous pressure which results in a decreased venous return and a compromised cardiac output.[7] Higher heart rate and lower mean arterial blood pressure suggest a loss of hemodynamic stability, apart from the necessity of resuscitations with this pressure.

We underline that it is important to be aware of extreme hypercarbia and acidosis during this procedure, by frequently drawing blood gases, also for the maintenance of cerebral autoregulation. In neonates, the end tidal CO_2 is no reliable estimator for arterial CO_2 like it is in adults [23]. In normal practice, the ventilation has to be adjusted after insufflation of CO_2, during this experiment as well, to maintain a normal saturation.

Although the differences were not significant, the cerebral tissue oxygen extraction (cFTOE) was higher in P10 at all time points in comparison to P5, which reflects a higher oxygen extraction in P10. The difference in cFTOE between P5 and P10 might have become significant during an extended procedure. This suggests that, although a high $paCO_2$ causes vasodilatation and thus increased cerebral perfusion, there was a mild and not significant decrease in cerebral perfusion as represented by a higher oxygen extraction in P10. A possible explanation is the exceeding of the central venous pressure with high intrathoracic pressure, which could compromise the cerebral perfusion.

The limitation of this study is the relative small number of piglets in each group. We do believe the harmful effect of CO_2-insufflation with 10 mmHg is so profound that a larger number of piglets will only mark the hemodynamic instability more. In order to draw valid conclusions, we used conservative statistical tests, which all became highly significant. Furthermore, piglets are not the same as neonates, with a lower cerebral oxygenation like we observed according to Kurth et al.[24] and Chien et al.[25] However, we do think these results are representative as the trend of the cerebral oxygenation is more important than the absolute value.[19] There was no continuous registration of all parameters; thus, the relation between blood pressure and $rScO_2$ as an estimator of autoregulatory ability could not be measured.[10,26] In the future, a prospective, human study is required to confirm the effects of CO_2-insufflation with 5 mmHg on cerebral oxygenation hemodynamics and with neurodevelopmental follow-up. Such a study is currently underway in our hospital.

In conclusion, this animal experimental model shows that insufflation of CO_2 during thoracoscopy with a pressure of 10 mmHg caused a severe hemodynamic instability with a decrease in blood pressure and an increased heart rate. Although higher CO_2-levels are related with higher brain perfusion by cerebral vasodilation, insufflation with 10 mmHg seemed to be related with a decrease of cerebral perfusion as represented by a higher oxygen extraction. Special attention should be given to the possible suprafysiologic $paCO_2$ values reached during CO_2-insufflation. CO_2-insufflation of 5 mmHg for thoracoscopy seems to have no adverse effects on cerebral oxygenation in this animal study.

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8

CHAPTER

Neonatal brain oxygenation during thoracoscopic correction of esophageal atresia

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ABSTRACT

Background: Little is known about the effects of carbon dioxide (CO_2) insufflation on cerebral oxygenation during thoracoscopy in neonates. Near-infrared spectroscopy can measure perioperative brain oxygenation [regional cerebral oxygen saturation ($rScO_2$)].

Aims: To evaluate the effects of CO_2 insufflation on $rScO_2$ during thoracoscopic esophageal atresia (EA) repair.

Methods: This is an observational study during thoracoscopic EA repair with 5 mmHg CO_2 insufflation pressure. Mean arterial blood pressure (MABP), arterial oxygen saturation (SaO_2), partial pressure of arterial carbon dioxide ($paCO_2$), pH, and $rScO_2$ were monitored in 15 neonates at seven time points: baseline (T0), after anesthesia induction (T1), after CO_2-insufflation (T2), before CO_2 - exsufflation (T3), and postoperatively at 6 (T4), 12 (T5), and 24 h (T6).

Results: MABP remained stable. SaO_2 decreased from T0 to T2 [97 ± 3–90 ± 6 % ($p < 0.01$)]. $PaCO_2$ increased from T0 to T2 [41 ± 6–54 ± 15 mmHg ($p < 0.01$)]. pH decreased from T0 to T2 [7.33 ± 0.04–7.25 ± 0.11 ($p < 0.05$)]. All parameters recovered during the surgical course. Mean $rScO_2$ was significantly higher at T1 compared to T2 [77 ± 10–73 ± 7 % ($p < 0.05$)]. Mean $rScO_2$ levels never dropped below a safety threshold of 55 %.

Conclusion: The impact of neonatal thoracoscopic repair of EA with insufflation of CO_2 at 5 mmHg was studied. Intrathoracic CO_2 insufflation caused a reversible decrease in SaO_2 and pH and an increase in $paCO_2$. The $rScO_2$ was higher at anesthesia induction but remained stable and within normal limits during and after the CO_2 pneumothorax, which suggest no hampering of cerebral oxygenation by the thoracoscopic intervention. Future studies will focus on the long-term effects of this surgery on the developing brain.

INTRODUCTION

Congenital esophageal atresia (EA) with tracheoesophageal fistula (TEF) is principally corrected in the neonatal phase. Increasingly, the correction of atresia and closing of the fistula is performed via a thoracoscopic approach.[1] A low-pressure carbon dioxide (CO_2) pneumothorax (PT) environment col- lapses the right lung enough to visualize the atresic esophagus and TEF. The procedure is performed under permissive hypercapnic conditions.[2,3] Recent literature addressing thoracoscopic procedures in neonates has specified some concerns regarding the extra CO_2 load of applied PT with decreased venous return under elevated intrathoracic pressure. This may be hazardous to neonatal physiology[4] and the developing central nervous system. In particular, impairment of cerebral oxygenation levels in neonates undergoing thoracoscopic procedures has been reported.[5] During surgical procedures and at the patient bedside, neonatal brain hemodynamics and oxygenation can be assessed by transcranial near-infrared spectroscopy (tcNIRS). This tcNIRS permits continuous noninvasive monitoring over extended periods of time. Until now tcNIRS monitoring was not a standard procedure in most neonatal intensive care units (NICU)'s and in OR's during surgery of newborns. However, in recent years more information has become available concerning the relationship between low cerebral oxygenation monitored by NIRS and the occurrence of brain damage among newborns and young children.[6–8] Currently NIRS monitoring is routinely performed in our NICU and in our OR during thoracoscopic correction of EA. Thus far NIRS findings during thoracoscopic correction of EA of only two patients have been reported.[5] The aim of the present study was to investigate tcNIRS in the perioperative period of neonates elected for minimally invasive EA reconstruction.

METHODS

Guidelines and procedures for this investigation were reviewed and approved by the institutional Medical Ethics Committee of the University Medical Center Utrecht. Parents were informed about the study design and procedures, and informed parental consent was obtained from both parents of each participating neonate. This study was performed in compliance with the principles established in the Helsinki Declaration (version Fortaleza, October 19, 2013). NIRS monitoring is already used as a standard clinical monitoring tool in the NICU of the Wilhelmina Children's Hospital.

Patients

In this single-center prospective observational study, 15 patients diagnosed with EA with TEF (Type C atresia), admitted to the NICU of the Wilhelmina Children's Hospital of the University Medical Center Utrecht were enrolled between January 2012 and September 2014. Preoperative

workup consisted of screening for associated anomalies (VACTERL) including ultrasound of the heart and aorta to exclude right descending aortic involvement. Before surgery arterial and venous lines were placed for monitoring blood pressure, arterial blood sampling, and venous access, respectively. A suction drain was placed in the proximal esophageal pouch to prevent aspiration.

Anesthesia

All patients were subjected to a standardized anesthesia protocol. For the induction of anesthesia sevoflurane (6–8 % inspired concentration) was used with a 40–100% fraction of inspired oxygen (FiO_2). After muscle relaxation with atracurium (0.5 mg/kg), the infants were tracheally intubated. Thoracoscopy was performed with both lungs ventilated. Anesthesia was maintained with sufentanil and an oxygen/air mixture and sevoflurane. During the procedure tcNIRS values and simultaneously monitored heart rate, blood pressure, arterial oxygen saturation (SaO_2), and end tidal CO_2 values were collected and stored in a high frequency rate (0.5 Hz) on a PC (Bedbase software, UMC Utrecht, NL). Every 30 min blood samples (blood gas; Hb) were taken as part of the routine clinical procedure during thoracoscopic neonatal surgery. The aim was to establish stable anesthetic conditions based on the $rScO_2$, SaO_2 values, end tidal CO_2 values and blood gas analysis by adjustment of respiratory settings in frequency, maximum inspiratory pressure (Pmax) and FiO_2. Hypotension was prevented with fluid expansion or inotropes. The CO_2 gas insufflation was temporarily stopped if the applied PT caused insufficient ability to adequately ventilate the patient.

Surgery

All surgery was performed in the same operating theater with a stable room temperature of 22 ± 1 °C. In one patient rigid bronchoscopy was performed prior to surgery to assess possible concomitant tracheomalacia and to locate the TEF. The patients were placed in a left laterally recumbent position on a heated operating table (36 ± 1°C) and tilted 10°–20° reverse Trendelenburg. All thoracoscopic EA repairs were performed through the right thoracic cavity according to earlier described techniques.[9] In short, the PT was created through a 5-mm intercostal camera-trocar placed via an open incisional procedure. An intrathoracic pressure of 5 mmHg was achieved with a flow of 1 L/min insufflation with CO_2. Two trocars were placed through two 3-mm wounds (one caudodorsal and one cranio-anterior from the camera-trocar). If necessary, an extra trocar was placed to manipulate the lung out of sight to maximize the operating field-of-view. The azygos vein was coagulated and transected when it blocked exposure of the TE junction; the TEF was subsequently ligated with a transfixing absorbable 4.0 Vicryl suture close to the trachea. After transection of the distal esophagus, the proximal pouch was opened. Finally, both ends of the esophagus were anastomosed with interrupted 5.0 absorbable Vicryl sutures over a nasogastric feeding tube.

Regional cerebral oxygenation

To measure $rScO_2$, the INVOS 5100c near-infrared spec trometer (Covidien, Mansfield, Ma USA) was used. The NIRS-determined $rScO_2$ was used as an estimator for changes in regional cerebral oxygenation. This measurement provides absolute values, is less sensitive to movement artifacts, and allows for comparison over time. The transducer, containing a light-emitting diode and two distant sensors (i.e., small adult sensor; SAFB-SM, Covidien), was carefully positioned and fixed gently to the frontoparietal surface of the infants head using an elastic band, at the NICU. Differential signals are obtained from these two sensors, and from these signals the $rScO_2$ is calculated. The $rScO_2$ measures the oxygen saturation of the brain tissue. In a mixture of venous (70–80 %), arterial, and capillary blood the oxygenated hemoglobin (Hb)/total Hb (oxygenated Hb + non-oxygenated Hb) is calculated. Although it still cannot be used as a robust quantitative measurement of cerebral oxygenation, it can serve as a trend monitoring device to detect substantial changes in regional tissue oxygen saturation.[10] The $rScO_2$ was monitored during the entire surgical procedure and continued after the patient had returned to the NICU. Detected $rScO_2$ levels are considered within safe reference range in (preterm) neonates when values are between 55 and 85 %.[11–14] When $rScO_2$ values exceeded reference limits, anesthetic interventions were made according to our NICU protocol as described by Pellicer et al. and Naulaers et al.[15–17]

Data acquisition

Intraoperative hemodynamic parameters and data on $rScO_2$, measured by NIRS (INVOS 4100-5100; Covidien, Mansfield, MA, USA), were continuously monitored and stored for offline analysis using locally developed software (BedBase/SignalBase; University Medical Center Utrecht, Utrecht The Netherlands). Data were analyzed during seven intervals that lasted 10 min. These seven time points were as follows: baseline at the NICU ward (T0), directly after anesthesia induction (T1), 30 min after PT CO_2-in- sufflation (T2), 30 min before PT CO_2-exsufflation (T3), and postoperatively at 6 (T4), 12 (T5), and 24 h (T6).

Statistical analysis

Data analysis was performed using IBM SPSS statistics software package (IBM® SPSS® Statistics version 20, IBM Corp. Armonk, NY, USA). Data sets are presented as mean ± SD or as median and range when indicated. The data at different time points was analyzed by related parametric or nonparametric methods as appropriate. When no differences were found in an overall analysis across all seven time points, for clinical reasons, analysis subsequently focused on differences between baseline, anesthesia induction and the initial phases of the surgical procedure. Differences between two time points were analyzed with a Student t test. Differences between time points with a p value < 0.05 were considered statistically significant.

RESULTS

Fifteen patients with type C EA (with distal TEF) had complete data registration and were eligible for analysis. Table 1 presents demographics and clinical characteristics of the patients in this study. Eight patients had associated comorbidities, of which two patients had a right descending aorta and two patients had non-cyanotic cardiac malformations that required surgical correction at a later stage; one patient with dextrocardia and partial anomalous pulmonary venous connection (PAPVC) and one patient with a malaligned ventricular septal defect with overriding aorta. All patients had an overall uneventful thoracoscopic correction of EA. Median time in the OR was 211 [126–387] min, and the median time of PT was 130 [74–260] min.

Table 1. Patient characteristics of 15 patients that had a thoracoscopic correction of an esophageal atresia with tracheoesophageal fistula

Clinical characteristics	$N = 15$
Gender (M:F)	10:5
Gestational age (weeks)	39 [36–42]
Postnatal age at surgery (days)	2 [1–7]
Birth weight (grams)	2962 [2155–4490]
Apgar score	
After 1 min	9 [4–10]
After 5 min	9 [5–10]
Other comorbidity	Cor vitium stable hemodynamics 4
No comorbidity $N = 7$	Cor vitium requiring later surgery 2
One or more associated anomalies $N = 8$	Right descending aorta 2
	Tracheomalacia 2
	Duodenal atresia 1
	Anal atresia 1
	Vertebrae/rib deformity 5
Duration (min)	
Time on OR	211 [126–387]
Surgery	148 [83–274]
Pneumothorax	130 [74–260]

Data are presented as median [range]

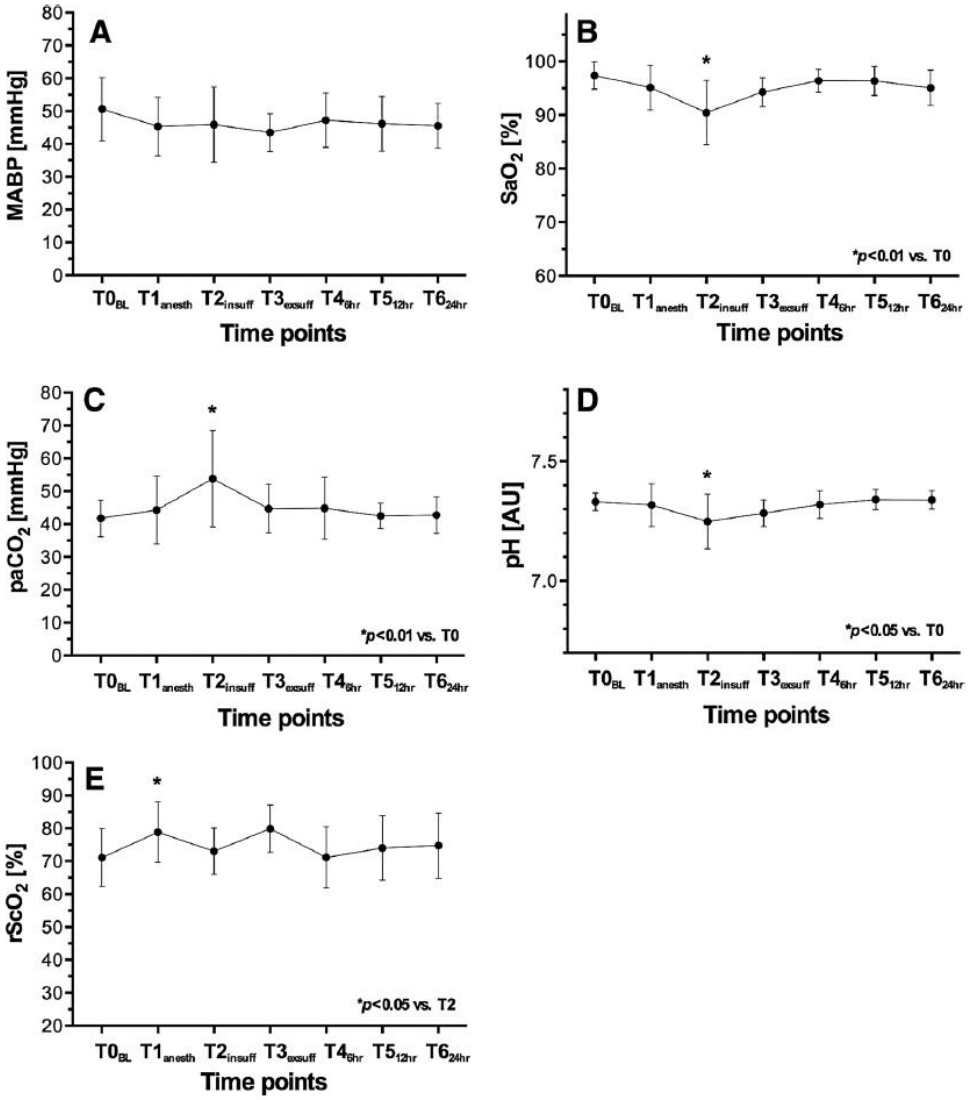

Figure 1. Perioperative physiological parameters and cerebral oxygenation. Perioperative physiological parameters and cerebral oxygenation data at baseline (To), anesthesia induction (T1), 30 min after CO_2-insufflation (T2), 30 min before ending CO_2-insufflation (T3) and in the postoperative phase at 6 (T4), 12 (T5), and 24 h (T6). MABP mean arterial blood pressure (A), SaO_2 saturation of pheripheral oxygen (B), $paCO_2$ partial pressure of arterial carbon dioxide (C), arterial sampled pH (D), $rScO_2$ regional cerebral oxygen saturation (E). Significant differences are marked asterisk and are presented in the figures with Student t test p values.

Intraoperative hemodynamic and cerebral oxygenation parameters

Figure 1 summarizes selected perioperative hemodynamic and cerebral oxygenation parameters. All patients remained normothermic during surgery (data not shown). The applied FiO_2 was 0.68 ± 0.24 at T1 (anesthesia induction), 0.59 ± 0.17 at T2 and 0.49 ± 0.16 at T3 (end of insufflation) ($p < 0.05$). Median inspiratory Pmax [range] was 21 [14–26] cmH2O at T2 and 20 [17–28] cmH2O at T3. Median respiratory frequency was 42 [30–90] at T2 and 40 [28–69] at T3. Changes in MABP were not significant and measurements remained within physiological range (Fig. 1A). Hypotension was prevented by fluid expansion and administration of dopamine in a range of 1–20 mcg/ Kg/ min in 10 of 15 (66 %) patients at T2 and to 12 of 15 (80 %) patients at T3. A significant decrease in SaO_2 was observed at PT application. SaO_2 decreased from 97 ± 3 % at To (baseline) to 90 ± 6 % at T2 (PT application) ($p< 0.01$). SaO_2 recovered to normal ranges during the procedure (Fig. 1B). $PaCO_2$ increased from 41 ± 6 mmHg at To to 54 ± 15 mmHg at T2 ($p < 0.01$) and then recovered to normal ranges during the procedure (Fig. 1C). Arterial sampled pH decreased from 7.33 ± 0.04 at To to 7.25 ± 0.11 at T2 ($p < 0.05$). It then recovered to normal ranges during the procedure (Fig. 1D). Continuous monitoring of cerebral oxygenation was successful in all 15 neonates. Mean $rScO_2$ was significantly higher at T1 compared to T2; 77 ± 10 and 73 ± 7 % respectively ($p < 0.05$). In none of the neonates, the mean $rScO_2$ dropped below the safety threshold of 55 % during or after surgery (Fig. 1E).

DISCUSSION

The aim of this study was to investigate the effects of the installation of a CO_2 PT on the hemodynamics and cerebral oxygenation of neonates receiving thoracoscopic correction of EA. We observed that surgery with an intrathoracic pressure of 5 mmHg can be performed, while the MABP remains within normal limits. Application of the PT initially lowers SaO_2, raises $paCO_2$, and lowers arterial pH levels. These parameters were corrected through the course of surgery by changes in the ventilation. Under these conditions, cerebral saturation remained within the safety range during the whole procedure. Furthermore, in the postoperative phase cerebral oxygenation and all other monitored parameters remained within normal limits. Our results suggest that a thoracoscopic procedure with a CO_2 PT set at a pressure of 5 mmHg and flow of 1 L/min can be performed under conditions that allow for reversible arte- rial blood gas disturbances, with cerebral NIRS values that are elevated during anesthesia induction but that remain stable during and after the PT application.

A large number of pediatric surgical indications can be successfully managed by minimally invasive techniques,[18] especially for cases involving treatment of EA. In an increasing number of pediatric surgical centers, these atresias are managed by thoracoscopic interventions.[19] Although benefits of either open or thoracoscopic approach to EA surgery remain to be proven

in randomized studies,[20] the thoracoscopic approach favors advantages sup- portive of less postoperative pain, shorter hospital stay,[21] less scoliosis caused by rib fusion, decreased respiratory impairment, and improved overall cosmetic result.[3,22,23]

Despite plausible clinical advantages favoring thoraco scopic EA surgery, concerns have been raised regarding the safety of these thoracoscopic interventions in neonates. These concerns focus mostly on the impact of the applied pressurized CO_2 PT on neonatal hemodynamics and organ perfusion.[3,4,20,24,25] Intrathoracic CO_2 insufflation collapses the lung, which adversely affects the O_2 and CO_2 exchange causing hypoxia and hypercarbia. Another factor that causes hypercarbia is the excess systemic CO_2 load that is absorbed from the thoracic cavity during the PT CO_2 gas insufflation.[5] Hypoxia and especially hypercarbia with a lowered pH cause vasodilatation of the cerebral vessels in the neonate.[26–28] When lower arterial oxygen saturation causes lower cerebral oxygen supply, the hypercarbia-induced vasodilatation can compensate for the reduced cerebral oxygen supply if blood pressure remains adequate. Diminished perioperative cerebral oxygen saturation during neonatal cardiothoracic surgery is correlated with poor neurodevelopment outcomes[6,7] and brain magnetic resonance imaging abnormalities at 1 year.[8] Recently, Bishay et al.[5] reported that severe perioperative hypercarbia, acidosis, and decreased cerebral oxygenation were seen in neonates that underwent thoracoscopic surgery for EA and congenital diaphragmatic hernia. It is proclaimed that the reduction in the cerebral oxygenation lingered for up to 24 h postoperatively. However, in the paper by Bishay et al.[5] the $rScO_2$ value at the start of operation of 87% was very high, possibly due to initial hyperoxygenation. It decreased to 75% at the end of operation. Also in the postoperative phase, cerebral oxygenation levels remained within reference range.

Furthermore, in the published series on neonatal thoracoscopic interventions[5,20] that describe the negative impact of CO_2 application, PT pressures of up to 10 mmHg were applied. A recent experimental study in piglets showed that 10 mmHg PT pressures caused severe hemodynamic instability and decreased cerebral perfusion, whereas these conditions remained stable with PT pressures of 5 mmHg.[29] The results from this piglet study suggest that the applied pressure of 5 mmHg, as used routinely in our clinic, has no severe adverse effects and seems safe to use in thoracoscopic procedures.

In response to the concerns about thoracoscopic EA surgery, Conforti et al.[30] concluded that cerebral oxygenation remains stable during open EA correction. The results of our present study show that this conclusion is not exclusively reserved for open EA correction but that it is also possible during thoracoscopic surgery. We believe that close monitoring and a close collaboration between neonatologists, anesthesiologists, and pediatric surgeons is essential for achieving stable physiological conditions with sustained brain oxygenation levels. According to the anesthesia protocol, fluid expansion and inotropes were applied to prevent blood pressure from declining below physiological limits during the thoracoscopic procedure. Moreover, in the present study we observed that in the initial phase of surgery, installation

of the PT caused arterial saturation to drop. To allow adequate ventilation, CO_2 PT insufflation was then stopped until the patient had recovered. If reinstallation of CO_2 PT persisted in causing low oxygen saturation, insufflation pressures were not increased but an additional trocar was introduced to gently move the lung away from the operating field-of-view. Initial hypercarbia and consequent acidosis was alleviated during the operation by continuous adjustment of ventilator settings. Acceptable limits of perioperative CO_2 blood gas values are as yet not known.[2,31] However, to ascertain CO_2 and pH levels stayed within acceptable range, adequacy of ventilation is confirmed by arterial blood gas analysis at 30-min intervals.[20,30]
Whether the initial hypercapnia, which can have strong vasoactive effects[2,26–28] and the acidosis, recorded in our study, could be detrimental for the developing neonatal brain is unknown.[31,32] These blood gas results are comparable though to those seen during open EA surgery. In our study the initial $paCO_2$ during the pneumothorax was 54 mmHg. It was 56 mmHg in a series of patients that were operated via (open) thoracotomy in the study by Bishay et al.[20] Also, the resulting acidosis in our series with a pH of 7.25 is comparable to a pH of 7.26 in the study of Bishay et al.[20] In our study, cerebral oxygenation remained stable and not jeopardized during or after the thoracoscopic procedure. The initial increased cerebral NIRS values prior to the surgical procedure are also described in other studies of open or thoracoscopic neonatal surgery.[5,30] This could be a consequence of an increased supply of oxygen at the phase of anesthesia induction. Also in our study the highest median FiO_2 was recorded at this time (0.68 ± 0.24).
In conclusion, thoracoscopic EA repair can be performed without the need for conversion or extended procedural times with CO_2-insufflation pressures that are sustained around 5 mmHg. Cerebral oxygenation was stable within the normal range during and after the procedure. Close perioperative monitoring of neonatal brain oxygenation and close collaboration between surgeons, anesthesiologists and neonatologists will remain part of our operative protocol for patients undergoing thoracoscopic reconstruction of EA. Future studies in our institution will focus on the long-term effects of these types of surgery in neonates and the aim of understanding and avoiding impact on the neonatal brain with adverse neurodevelopmental outcomes.

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9

CHAPTER

Brain Oxygenation During Thoracoscopic Repair of Long Gap Esophageal Atresia

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ABSTRACT

Background: Elongation and repair of long gap esophageal atresia (LGEA) can be performed thoracoscopically, even directly after birth. The effect of thoracoscopic CO_2-insufflation on cerebral oxygenation ($rScO_2$) during the consecutive thoracoscopic procedures in repair of LGEA was evaluated.

Methods: Prospective case series of five infants, with in total 16 repetitive thoracoscopic procedures. A CO_2-pneumothorax was installed with a pressure of maximum 5 mmHg and flow of 1 L/min. Parameters influencing $rScO_2$ were monitored. For analysis 10 time periods of 10' during surgery and in the perioperative period were selected.

Results: Median gestational age was 35+3 [range 33+4 - 39+6] weeks; postnatal age at time of first procedure 4 [2 - 53] days, and time of insufflation 127 [22 - 425] minutes.
Median $rScO_2$ varied between 55% and 90%. Transient outliers in cerebral oxygenation were observed in three patients. In Patient 2 oxygenation values below 55% occurred during a low MABP and Hb <6mmol/L. The $rScO_2$ increased after erythrocytes transfusion. Patient 5 also showed a $rScO_2$ of 50% with a Hb <6 mmol/L during all procedures, except for a substantial increase during a high $paCO_2$ of 60 mmHg. Patient 4 had a $rScO_2$ > 85% during the first procedure with a concomitant high FiO_2 > 45%. All parameters recovered during the surgical course.

Conclusions: This prospective case series of NIRS during consecutive thoracoscopic repair of LGEA showed that cerebral oxygenation remained stable. Transient outliers in $rScO_2$ occurred during changes in hemodynamic or respiratory parameters and normalized after interventions of the anesthesiologist. This study underlines the importance of perioperative neuromonitoring and the close collaboration between pediatric surgeon, anesthesiologist and neonatologist.

INTRODUCTION

Esophageal atresia (EA) is one of the major congenital anomalies encountered in pediatric surgery, in particular EA with tracheoesophageal fistula (TEF). The repair has always been performed by thoracotomy[1,2]. Since no randomized controlled trial has been done, the debate on the best method to repair the esophageal atresia still continues[3].

Long gap esophageal atresia (LGEA) is a rare form of esophageal atresia. The repair of this defect is still a challenge for the pediatric surgeon[4]. Worldwide different techniques are applied, varying from delayed repair after several months, to elongation or replacement techniques[1,5]. Some authors have stated that an LGEA is a contra-indication for a minimally invasive approach[1]. Scarce and contradictory data is available on the effects of the installation of a low-pressure carbon dioxide (CO_2) pneumothorax (PT) in neonates and in particular on the hemodynamics and cerebral oxygenation[2,6-8].-

Neuromonitoring of the neonatal brain can provide information on neonatal cerebral oxygenation and estimate cerebral perfusion, which can be monitored non-invasively by Near Infrared Spectroscopy (NIRS), measuring the regional cerebral oxygen saturation ($rScO_2$)[9]. The $rScO_2$ is an absolute value that reflects the venous, capillary and arterial oxygen saturation and gives insight in the oxygen delivery and consumption of the brain tissue. Shortly after birth elongation and subsequent repair of the LGEA can be performed thoracoscopically without the need for a gastrostomy. We have described the first thoracoscopic repair in 2007.[10] As these neonates undergo repetitive procedures shortly after birth, maintenance of adequate $rScO_2$ is even more critical. In this study, the effect of the CO_2-insufflation on $rScO_2$ during the consecutive thoracoscopic procedures in repair of LGEA is evaluated.

MATERIALS AND METHODS

This prospective case series was performed, after approval of the institutional Medical Ethical Committee of the University Medical Center Utrecht (Utrecht, The Netherlands). NIRS monitoring is used as a standard, clinical monitoring tool in the NICU of the Wilhelmina Childrens' Hospital, University Medical Center Utrecht.

Patients

Patients with radiologic confirmed LGEA were eligible for this single-center prospective case series, and included between May 2013 and November 2014. LGEA was considered as "any esophageal atresia that has no intra-abdominal air", as was recently defined by a working group within the International Network of esophageal atresia during the 4th International Conference in Sydney in September 2016.

At hospital admission, arterial blood gas analyses were evaluated. Routine preoperative work-up consisted of screening for associated anomalies (VACTERL), including ultrasound of the heart and aorta to exclude right descending aortic involvement. By protocol, a peripheral arterial line - for monitoring blood pressure and regular arterial blood sampling - and venous lines were placed before surgery. A Replogle® suction drain was placed in the proximal esophageal pouch to prevent aspiration. Cranial ultrasound (cUS) was performed upon admission to the NICU prior to surgery, and repeated postoperatively. cUS was performed by the attending neonatologist according to a standard clinical protocol using a Toshiba Aplio Machine (Toshiba Medical Systems, Zoetermeer, The Netherlands). MRI was performed on a 3.0 Tesla whole-body Achieva system (Philips Medical Systems, Best, Netherlands). Neurodevelopment is assessed by the Griffith Mental Development Scales and the Bayley Scales of Infant and Toddler Development Test, Third Edition.

Monitoring of cerebral oxygenation

The regional cerebral oxygen saturation ($rScO_2$) was measured by Near Infrared Spectroscopy (NIRS) to monitor changes in the cerebral oxygenation. The $rScO_2$ reflects the venous (70-80%), capillary and arterial oxygen saturation and can be reliably used as a trend monitor to detect substantial changes in cerebral oxygenation(9). It cannot be used as a robust quantitative measurement, but it can detect substantial changes in cerebral oxygenation within the same patient. The $rScO_2$ is calculated using the oxygenated hemoglobin and the total hemoglobin (oxygenated and non-oxygenated hemoglobin). The NIRS monitor (INVOS 5100-P Cerebral Oximeter; Covidien, Mansfield, Massachusetts) was used with the small adult sensor (SomaSensor® no. 4100-SSA Adult/Disposable). This is a transducer containing a light emitting diode and two distant sensors that was attached to the frontoparietal side of the patients' head. The near infrared sensor was placed at least six hours before surgery to obtain a baseline measurement. Parameters influencing cerebral oxygenation, including end tidal CO_2 ($etCO_2$), arterial oxygen saturation, fraction of inspired oxygen (FiO_2), and mean arterial blood pressure (MABP) were monitored. $paCO_2$, pH and hemoglobin (Hb) were checked in arterial blood gases at least once every 30 minutes and more frequently when deemed necessary by the anesthesiologist.

A clinical treatment guideline with a multidisciplinary team of neonatologists, pediatric surgeons and pediatric anesthesiologists in our hospital is followed to keep cerebral oxygenation stable and within the target range of 55 to 85%, or to avoid fluctuations of >20% from baseline measurement, by adjustments of respiratory and cardiovascular support when necessary(11). The choice for this target range was based on the 95% CI of the cerebral oxygenation in 999 neonates, from Alderliesten et al., using the same sensor(12). It is advised to correct a low $rScO_2$ by correcting the arterial saturation, the Hb and regulating the cerebral blood flow. A low cerebral blood flow can be a consequence of – for instance – a low MAPB (< gestational age in weeks),

a low $paCO_2$ (<30 mmHg) and a high mean airway pressure (MAP). An $rScO_2$>85% reflects an impaired oxygen utilization, an increased oxygen supply or a disturbed cerebral autoregulation. In case the arterial saturation (range 85-95%), FiO_2, $paCO_2$ (30-60 mmHg) and MAP are out of range, these should be adjusted. Hypotension was defined as a mean blood pressure below the gestational age of the patient. Treatment started with the administration of a fluid bolus, followed by vasopressor-inotropes (dopamine) when necessary.

Anesthesia

All patients are subjected to a standardized anesthesia protocol. For the induction of anesthesia sevoflurane (6-8% inspired concentration) was used with a 40-100% FiO_2. After induction of anesthesia rigid tracheobronchoscopy was performed by the pediatric ENT surgeon. Muscle relaxation was applied with atracurium besylate (0.5 mg/kg) and the patient was intubated. Correct placement of the tube was verified by fiberoptic endoscopy. Thoracoscopy was performed with both lungs ventilated. In all procedures sufentanil and an oxygen/air mixture in sevoflurane were used during the maintenance of anesthesia.

Surgical procedure

The technique of the thoracoscopic repair of long gap esophageal atresia has previously been described by Van der Zee et al. (supplemental material)[13].

Data acquisition

All vital parameters and data on $rScO_2$, measured by NIRS, were continuously monitored and stored for offline analysis using locally developed software (Bedbase/Signalbase; University Medical Center Utrecht, Utrecht, The Netherlands). For analysis, 10 representative time periods of 10 minutes before, during and after surgery were selected. The periods in the perioperative period of the three procedures were: baseline at the NICU or PICU (baseline), during induction of anesthesia (induction), last 10 minutes of induction of anesthesia (anesthesia), directly after installation of a carbon dioxide pneumothorax (insufflation 1), last 10 minutes of CO_2-insufflation (insufflation 2), directly after desufflation of CO_2 (desufflation), postoperatively after one hour (post 1 hr), six hours (post 6hrs), 12 hours (post 12hrs), and 24 hours (post 24 hrs). These periods were carefully selected to measure acute changes in hemodynamics or because a steady state was expected to be reached.

RESULTS

Five successive patients are described in this case series with a total of 16 procedures. Patient characteristics are presented in Table 1. None of the infants had major cardiac malformations. One infant had an anorectal malformation as associated major anomaly. All infants were hemodynamically and neurologically stable before surgery. Four infants needed three consecutive surgical procedures for elongation and repair and one infant needed four procedures. The duration of CO_2-insufflation was 127[22-425] minutes (Figure 1, Supplemental Table 1).

Table 1. Demographics of patients with long gap esophageal atresia

Variable	Patient				
	1	2	3	4	5
Gestational age (weeks)	34+0	33+4	35+2	39+2	39+6
Birth weight (grams)	1580	2270	1710	2825	2570
Birth weight z-score	-1.83	0.22	-2.16	-1.76	-2.59
Apgar score (1/5/10)	9/5/8	4/7/8	5/7/8	9/9/10	4/6/9
Associated anomalies	VSD[1] microtia	ARM[2] tracheo malacia			
Surgery					
Postnatal age 1st surgery (days)	9	2	2	4	53#
Procedures (n)	3	4	3	3	3
Dilatations (n)	3	0	8	5	3
Mechanical ventilation (days)	15	76	14	20	13
LOS 1st admission (days)	28	78	38	43	44*
LOS 1st year (days)	42	199	74	48	156*
Lap Thal (y/n)	y	n	y	n	y

LOS Length of hospital stay
1 Perimembranous Ventricular Septum Defect, no treatment necessary 2 Anorectal malformation
need for transportation from another hospital
* Length of hospital stay after transfer from another hospital, where the patient was already admitted for 52 days

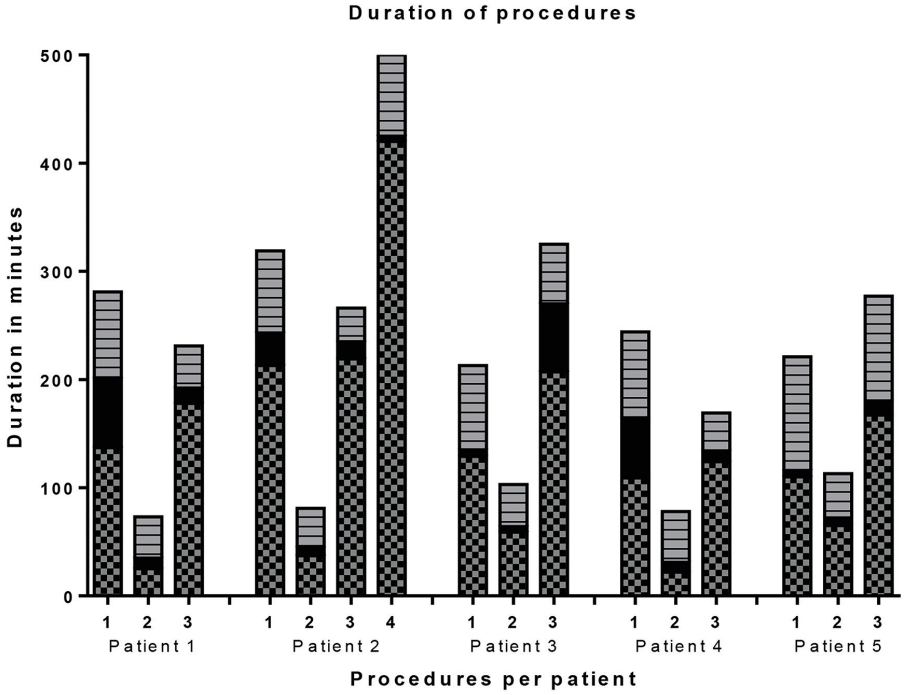

Figure 1. Duration of procedures The entire duration of each procedure is displayed per patient, indicated by the total bar. Of each procedure the grey part with squares indicates the time of insufflation, the black part indicates the duration of surgery without insufflation of CO_2 and the striped grey part the duration of induction and emergence of anesthesia, the time where no surgery is performed.

Supplemental table 1. Perioperative and postoperative course

Variable	Patient				
	1	2	3	4	5
Proximal fistula (y/n)	n	y	n	n	n
Gastrostomy (y/n)	n	y	n	n	y
Gastropexy (y/n)	y	y	y	y	y
Aortapexy	n	n	n	n	y
Complications	Pneumothorax Line sepsis	Perforation by replogle		Fever due to leakage Line sepsis	
Postoperative leakage (n/y)	n	n	n	y	n

Vital parameters

Vital parameters are shown in Figure 2. Low arterial saturations were not observed and a high FiO_2 was applied mainly during the induction of anesthesia. Outliers in $paCO_2$ and MABP are evaluated in the following paragraph. Except for Patient 1, no severely abnormal pH and $paCO_2$ values were observed (Figure 3).

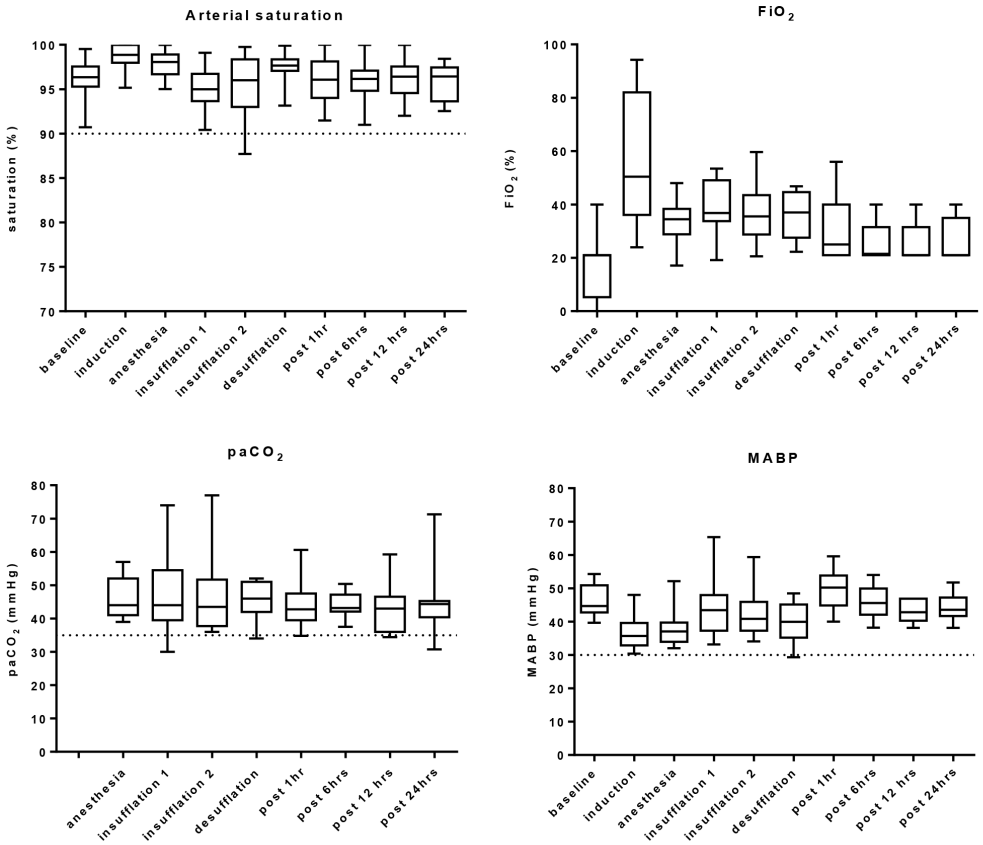

Figure 2. Perioperative vital parameters. Data before, during and after surgery of the vital parameters influencing the cerebral oxygenation: arterial saturation, fraction of inspired oxygen (FiO_2), the arterial CO_2 ($paCO_2$) and the mean arterial blood pressure (MABP). The dotted line indicates the critical limits.

Cerebral oxygenation

Median $rScO_2$ varied between 55% and 90%. In three patients (Patient 2, 4 and 5) transient outliers in the $rScO_2$ (normative range ($rScO_2$ 55 - 85%)) were observed, during all consecutive procedures (Figure 4).

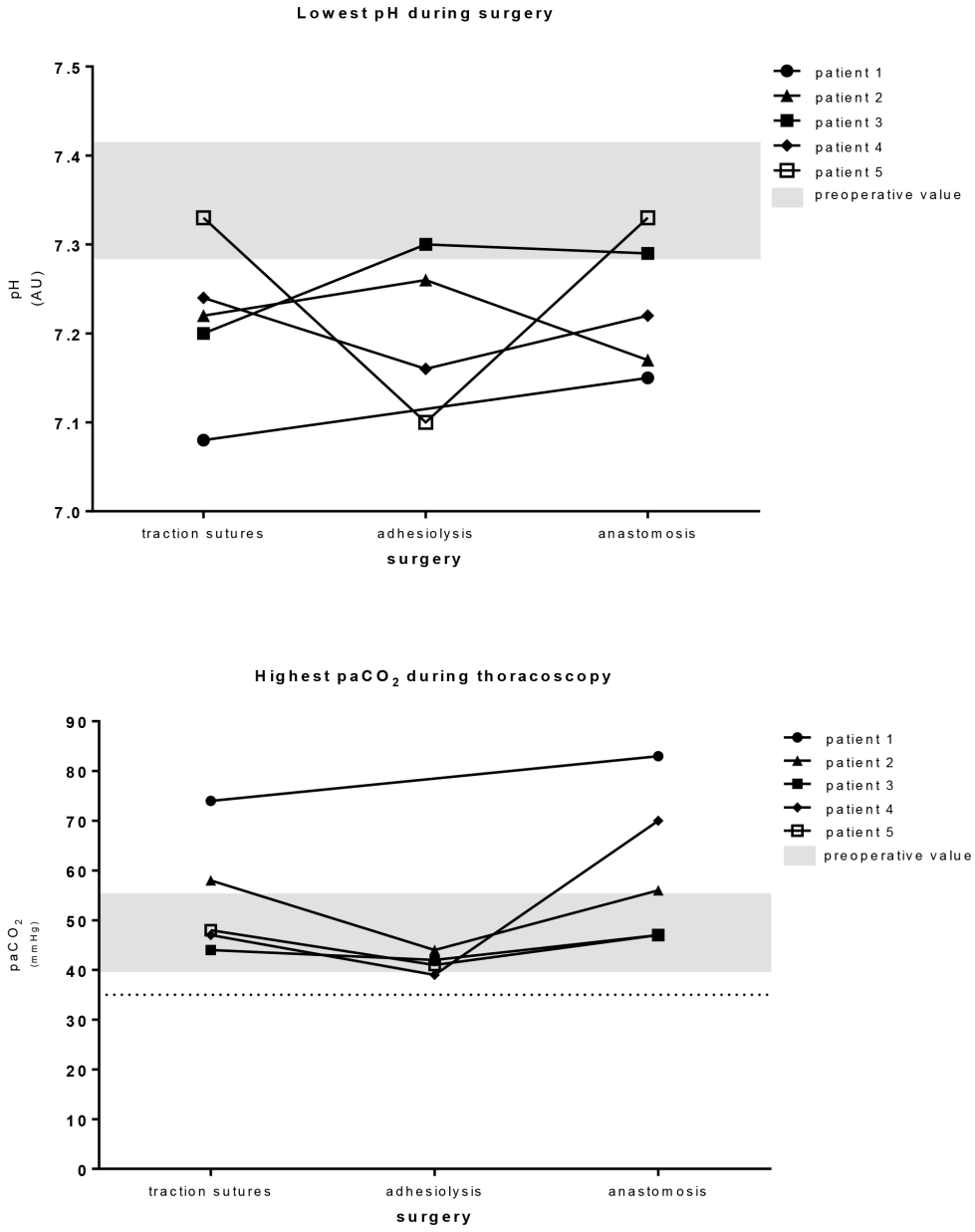

Figure 3. Intraoperative pH and $paCO_2$ Intraoperative lowest pH and highest $paCO_2$ measured during the consecutive procedures of each patient. The preoperative range of all patients is indicated by the grey bar. The dotted line indicates the $paCO_2$ value of 35 mmHg.

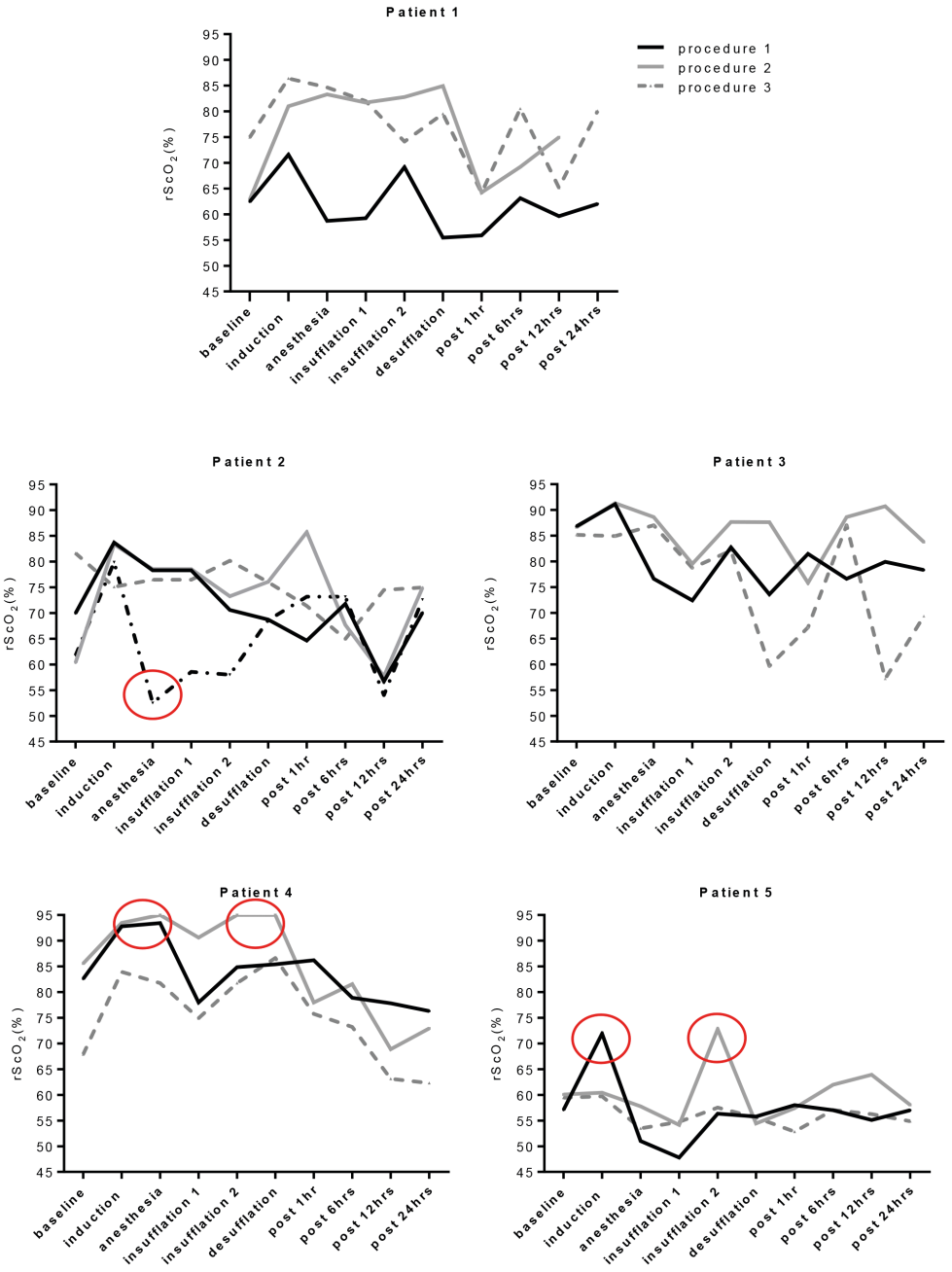

Figure 4. Cerebral oxygenation during consecutive long gap esophageal repair. For each patient the cerebral oxygenation in each procedure is displayed. The black line represents the first procedure, the grey line the second, the dotted grey line the third and the dotted black line the fourth procedure in Patient 2. Data is measured at 10 time periods of 10 minutes. The circles indicate the significant changes in cerebral oxygenation.

Patient 2 had a complicated, surgical course, which has been previously described in detail by Van der Zee et al(13). This patient was operated on four times. The 3rd surgical procedure was performed in a semi-emergency setting due to an iatrogenic perforation of the proximal pouch after repositioning of the Replogle® tube at the ward. During this re-exploration the distance between the two esophagus stumps did not approach sufficiently to perform an anastomosis, after which the traction period was continued. During the 4th procedure anastomosis could only be accomplished by a gastric pull-up. A recorded $rScO_2$ value below 55% at the end of induction of anesthesia during this procedure was related to a low hemoglobin (Hb 5.1 mmol/l) and a MABP of 35 mmHg. The cerebral oxygenation increased after an erythrocytes transfusion and vasopressor support was given.

The cerebral oxygenation of Patient 4 increased above 85% during the first two procedures. This was concomitant with an FiO_2 of 45% (35-75%, during induction of anesthesia, resulting in a paO_2 > 100 mmHg). During the second procedure a transient mild hypercapnia of 55 mmHg occurred as well. All other parameters were within the normal range.

A low hemoglobin (Hb 5.8 mmol/l) was also encountered in Patient 5 during all procedures, with a $rScO_2$ in the lower range (50-60%). His low level of hemoglobin could be explained by normal physiology (seven weeks post term). During induction of anesthesia in the first procedure, prior to intubation, an $rScO_2$ of 73% (sudden increase of 18%) was seen with a concomitant FiO_2 of >90%. A substantial increase in $rScO_2$ to 72% (increase of 19%) was seen at the end of the second procedure with an $etCO_2$ of 60 mmHg.

All patients needed vasopressor support due to hypotension in at least one of the procedures (Supplemental Table 2).

Supplemental table 2. Need of blood pressure support during the surgical procedure

Variable	Patient				
	1	2	3	4	5
1st surgery	dopamine	dopamine	-	dopamine	dopamine
2nd surgery	dopamine	dopamine	fluid expansion	fluid expansion	-
3rd surgery	dopamine	dopamine	dopamine	dopamine	dopamine
4th surgery	NA	dopamine	NA	NA	NA

NA Not applicable

Preoperative cranial ultrasonography did not show brain damage. On postoperative MRI two patients had a small thalamic infarction, and no other signs of brain damage. (Figure 5)During follow-up (the Bayley Scales of Infant and Toddler Development, Third Edition and the Griffith Mental Development Scales) all patients showed a cognitive and motor development in the normal range.

DISCUSSION

This study reports on five infants with thoracoscopic repair of LGEA and the effects that these thoracoscopic procedures have on cerebral oxygenation. In this prospective case series persisting cerebral hypoxia did not occur during the consecutive thoracoscopic procedures. The infrequent transient outliers in cerebral oxygenation could be explained by a low level of hemoglobin, a decrease in MABP, an increase in CO_2 or a high FiO_2. Cerebral oxygenation normalized rapidly after intervention by the anesthesiologist.

The first study using NIRS in neonates that underwent thoracoscopic correction of EA and congenital diaphragmatic hernia, reported a decrease in cerebral oxygenation with severe hypercarbia and acidosis[7]. However, in this study pneumothorax pressures of up to 10 mmHg were applied. An experimental study in piglets showed that these high pressures cause severe hemodynamic instability and that these conditions could remain stable with pressures of maximum 5 mmHg[8]. As was shown in a previous study[2], cerebral oxygenation remained within the safety range (55-85%) during the single thoracoscopic correction of EA type C. The results of this current study show that by intervention of the anesthesiologist, outliers in cerebral oxygenation for the LGEA patients undergoing repetitive thoracoscopic procedures for elongation and anastomosis, can be prevented or normalized quickly.

One of the factors, recognized in this study, of which the importance should be emphasized is the level of hemoglobin. A low $rScO_2$ can be caused by a compromised oxygen delivery and could benefit from an increased hemoglobin[11-14], as was shown in this study. In one of the patients from this study, the low hemoglobin level was not pathological, but due to the physiological anemia of an infant. Nonetheless, this "physiological" lower hemoglobin level may compromise the cerebral saturation during major thoracoscopic surgery. High values of cerebral oxygenation were mostly due to preoxygenation. This was particularly evident in the induction phase of anesthesia, during which an increased supply of oxygen was given in order to prevent a hypoxic event while intubating the patient. This is common practice in pediatric anesthesiology. However, a high supply of oxygen can be hazardous for the neonatal brain[15].

In the present study, time periods with expected variation in vital parameters and cerebral oxygenation were analyzed. Firstly, the induction of anesthesia, with FiO_2 between 40 and 100%, which often causes an increase in cerebral oxygenation. This increase to a maximum of 95% was observed in Patient 4. At the end of induction of anesthesia a steady state in oxygenation is expected and hypotension due to anesthetics can be observed, right before surgery is commenced. Patient 2 had a low cerebral oxygenation (52%), which could have been caused either by hypotension or low hemoglobin (Hb 5.1 mmol/l). Instillation of a CO_2-pneumothorax can cause transient decrease in arterial saturation and hypercapnia. At the end of insufflation, either a steady state in ventilation or outliers in $etCO_2$, in case of ventilation problems may be expected. In patient 5, we observed hypercapnia, with an $etCO_2$ of 60 mmHg and a sudden increase in

$rScO_2$ to 73%, since carbon dioxide causes an increase in cerebral perfusion by vasodilatation[16;17]. This could have been prevented by increasing the ventilation frequency settings adequately.

Directly after desufflation of the pneumothorax, a higher positive expiratory end-pressure is applied to maximally expand the lung, leading to extra oxygen in the patient, which can cause an increase in $rScO_2$. Desufflation in our population, however, resulted in variable changes in cerebral oxygenation. In Patient 2 an increase in both arterial saturation and MABP led to an increase in $rScO_2$. Patient 1 and 3 had a small decrease in $etCO_2$ with a decrease in $rScO_2$. However, the exact opposite occurred in Patient 4 and 5. Significant differences in cerebral oxygenation during the different procedures within one patient were only seen in Patient 2. He had the first three procedures in the first week of life and the gastric pull-up procedure after four weeks. As this study shows, important parameters influencing the cerebral oxygenation and perfusion are arterial oxygen saturation, CO_2, MABP, FiO_2, and hemoglobin.

Outliers in cerebral oxygenation may pose a risk for brain injury in the developing neonatal brain[18]. From cardiac patients, undergoing major neonatal surgery, it is known that in a high percentage de novo brain injury is visible postoperatively on MRI[19]. In this study, two small thalamic infarctions were found, for which no long-term consequences are expected. Since these abnormalities were not visible at the preoperative ultrasound, they most likely originated in the perioperative period. However, these two patients did not show periods of hypoperfusion of the brain, due to hypotension, hypocarbia or a low cerebral oxygenation. In other words, the etiology of these thalamic infarcts remains unclear. To date, the prevalence of cerebral damage in patients with long gap esophageal atresia and neonatal non-cardiac surgery in general is unknown. The incidence of cerebral injury may be considerable, since a delay in neurodevelopment in patients with esophageal atresia has been reported in several studies [20;21], which could not be explained by their primary anomaly or a genetic syndrome. In the current study, neurodevelopmental follow-up will be performed at the age of two years with the Bayley Scales of Infant and Toddler Development.

A limitation of this case series of LGEA is the small sample size of five cases. This is ofcourse due to the fact that LGEA is a rare congenital anomaly. Patients were born at different gestational ages, both preterm and full-term, which makes their degree of vulnerability diverse. Furthermore, one of the patients underwent the thoracoscopic LGEA correction after the neonatal phase (at 58 days postnatal age) due to transfer from another hospital. For these reasons we decided to describe these patients in a case series, without applying statistics. Stressing risk factors and important time periods of fluctuations in vital parameters was the main goal of this study. This case series is the first description of cerebral oxygenation and perfusion in the thoracoscopic, repetitive procedure of LGEA, and further studies are recommended to ensure our findings. Since NIRS monitoring is part of standard clinical care in our hospital, this was a prospective study where we aimed to keep the cerebral oxygenation within the normal range. In case of outliers the anesthesiologist intervened directly and results of intervention could be ascertained instantaneous.

Thoracoscopic elongation and anastomosis of long gap esophageal atresia is feasible and makes treatment in the neonatal period possible. Consequently, the need for a gastrostomy is avoided, as is an extended hospitalization. Since these patients are at risk of developing fluctuations in vital parameters and cerebral oxygenation during surgery, they should be monitored closely. We emphasize the importance of structural neuroimaging perioperatively, to assess acute brain injury and to compare surgical methods using this outcome. Acknowledging specific time periods of risk regarding hemodynamics and cerebral oxygenation of the neonate and ensuring a close collaboration between neonatologists, anesthesiologists and pediatric surgeons is essential and makes successive thoracoscopic procedures with stable physiologic conditions and cerebral oxygenation feasible.

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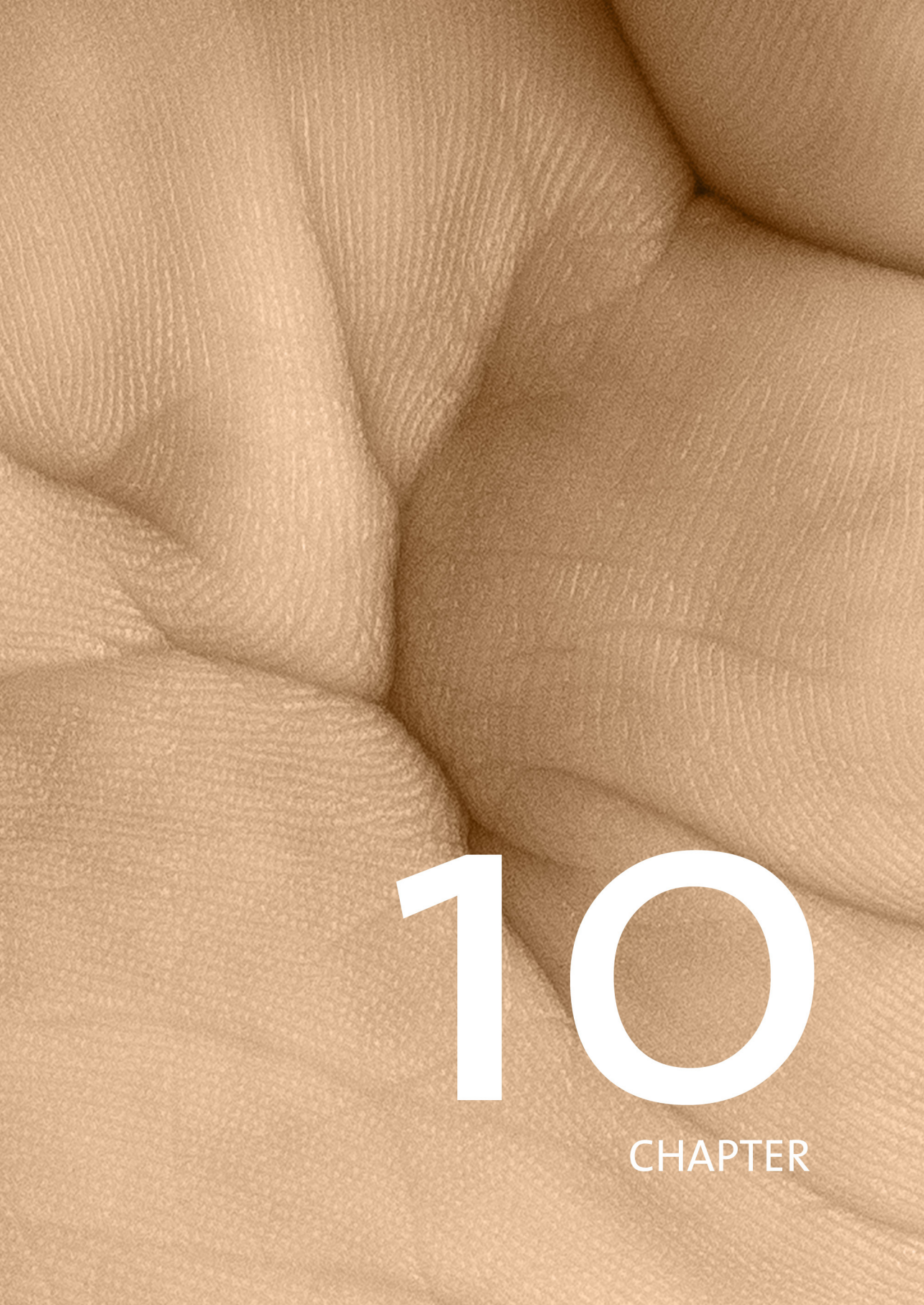

10

CHAPTER

A survey of the dose of inhalational agents used to maintain anaesthesia in infants

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ABSTRACT

Background: Various animal studies suggest that currently used anaesthetics are toxic to the developing brain. Many reviews advise that the total anaesthetic drug exposure should be reduced but the dose usually used in clinical practice has not been clearly elucidated.

Objectives: To provide an overview of the dose ranges currently used in clinical practice during the maintenance phase of anaesthesia in infants undergoing anaesthesia for noncardiac surgery and diagnostic procedures.

Design & Setting: A two-centre mixed prospective (London) and retrospective (Utrecht) observational cohort study. Two independent tertiary paediatric referral centres in March and November 2013; Great Ormond Street Hospital (GOSH), London, United Kingdom and Wilhelmina Children's Hospital, University Medical Center Utrecht (UMCU), The Netherlands.

Patients: A total of 76 infants were included in the analysis, 38 infants from each hospital.

Methods: Patients from GOSH were matched by pro- cedure, age and weight with patients from the UMCU. The end-tidal concentrations of the inhalational agents were investigated from anaesthetic charts during the maintenance phase and corrected for the age-specific minimal alveolar concentration (MAC), expressed as a percentage from the MAC (%MAC).

Results: Three different types of inhalational anaesthetics were used: sevoflurane, desflurane, isoflurane. The mean %MAC was 0.85. No significant differences in %MAC were found between GOSH and the UMCU (P ¼ 0.329); the mean %MAC in GOSH was 0.87 and in the UMCU was 0.82. There was a significant increase in the %MAC in relation to age (slope ¼ 0.036 MAC month-1, P < 0.001). Of all patients, 75% had an end-tidal concentration lower than 1 MAC. There was no significant effect of the use of analgesia on the end-tidal concentration of inhalational anaesthetics (P ¼ 0.366).

Conclusion: The concentration of inhalational anaesthetics in %MAC increased with age and as lowest in neonates. Most young infants received inhalational anaesthetics at a concentration below 1 MAC, which accords with current guidance to minimise anaesthetic drug exposure but may have unintended consequences.

INTRODUCTION

Animal experiments have shown that inhalational anaesthetics used in daily clinical practice have adverse consequences on the developing brain in young animals.[1–3] This anaesthetic-induced brain injury causes an increase in apoptosis, impaired neurogenesis and neuroinflammation.[1–3] Infants with cardiac and noncardiac congenital anomalies requiring surgery have a higher risk of adverse neurodevelopmental outcomes.[4,5] It is not yet certain what the influence of inhalational anaesthetics is on neurodevelopmental outcome in young children. The clinical studies are inconclusive and mainly based on retrospective cohort database analyses.[1–3,6–8] Therefore, three ongoing clinical trials [the Pediatric Anesthesia & Neurodevelopment Assessment (PANDA) project, the Mayo Anesthesia Safety in Kids study and the General Anaesthesia compared to Spinal anaesthesia (GAS) study] are trying to gain more insight into the risks of inhalational anaesthetics in infants.[1,3,8,9] Results of the PANDA study, a sibling-matched cohort study investigating cognitive function after a single exposure to anaesthesia before the age of 36 months, showed no differences in intelligence quotient scores in later childhood.[10] The recently published secondary outcomes of the GAS study showed strong evidence that general anaesthesia does not increase the risk of adverse neurodevelopmental outcome in infants at the age of 2 years.[11] However, the primary outcome results in terms of neurodevelopmental assessments at age 5 years will not be available until 2018. Whilst awaiting these results, it has been suggested that it would be good practice to keep anaesthesia and surgery as short as possible to reduce the overall anaesthetic drug exposure.[1,12,13]

Anaesthetic requirements are usually expressed as a proportion of the minimal alveolar concentration (MAC)[14,15] which is defined as the alveolar (or end-expiratory) concentration at which 50% of patients will not show a motor response to a standardised surgical incision. Age, opioids and local anaesthetics may influence MAC. The range of doses of inhalational anaesthetics currently used in clinical practice in infants is virtually unknown, and this impairs our ability to quantify the potential effect of anaesthetic neurotoxicity. Therefore, the aim of this study is to document the range of doses of inhalational anaesthetics used in clinical practice for maintenance of anaesthesia in infants.

METHODS

Patient selection

In this two-centre prospective [Great Ormond Street Hospital (GOSH), London, United Kingdom] and retropective [Wilhelmina Children's Hospital, University Medical Center Utrecht (UMCU), The Netherlands] observational cohort study, patients younger than 1 year undergoing

anaesthesia for noncardiac surgery and diagnostic procedures in March and November 2013 were studied. The institutional Review Board of the UMCU, The Netherlands, and GOSH, United Kingdom, approved the use of the clinically acquired data for the purpose of the study and waived written parental informed consent. The manuscript was reported in accordance with the reporting of observational studies in epidemiology statement checklist.[16] The study started with a prospective cohort study in GOSH. All infants undergoing inhalational anaesthesia involving mechanical ventilation for at least 15 min were investigated for practical reasons in two study periods of 1 month, March and November 2013. Subsequently, to validate the results, we matched patients from the GOSH retrospectively with patients from the UMCU who were anaesthetised during the same period. Patients from GOSH were individually matched by procedure, age and weight to patients selected from the database of the Anaesthesia Information Management System (AIMS), Anstat (Carepoint, Ede, The Netherlands) from the UMCU in a 1 : 1 fashion who were operated in the same period (March and November 2013).

The primary endpoint was the mean end-tidal concentration of the inhalational anaesthetic used during the maintenance phase of anaesthesia corrected for the age-specific MAC. We calculated the mean end-tidal concentration during the maintenance phase and divided this by the associated MAC from Table 1 (expressed as %MAC).[17–19] This enabled us to compare different anaesthetic agents at different ages. The end-tidal anaesthetic concentration in GOSH was measured by Philips IntelliVue patient monitors (IntelliVue G1 Anesthetic Gas Module, Eindhoven, The Netherlands) and registered by a researcher present in the operating room (LJS or PP). Manual recording by a researcher was required as the automatic recording system was not available in GOSH. Inspired and end-tidal concentrations were assessed every 5 min. The end-tidal anaesthetic concentration in the UMCU was measured by the ventilator (Aestiva 7900 Ventilator, GE Healthcare, Wauwatosa, Wisconsin, USA) and automatically registered every minute in AIMS. In GOSH and in the UMCU, the end-tidal anaesthetic concentrations were sampled at the bacterial filter and/or moisturiser. In both centres, the mean of the end-tidal concentration of the maintenance phase was defined from start to end of surgery or diagnostic intervention. Demographic characteristics of the patients were collected from the anaesthetic article (GOSH) and electronic (UMCU: EZIS, Chipsoft, Amsterdam, The Netherlands) charts.

Table 1. Minimal alveolar concentration by age for types of inhaled anaesthetics

	Age (months) 0-1	Age (months) 1-6	Age (months) 6-12	Age (months) 12
Sevoflurane[a] %	3.30	3.20	2.50	2.30
Isoflurane[b] %	1.67	1.87	1.80	-
Desflurane[c] %	9.16	9.42	9.92	-

[a]Lerman 1994[19], [b]Cameron 1984[17], [c]Taylor 1991[18]

Statistical analysis

The differences in the dose ranges used in the maintenance phase of standard anaesthesia between the two specialised paediatric centres were evaluated. Differences in patient characteristics from GOSH and the UMCU were evaluated with the two-sample t test, Mann–Whitney U test and chi-square test. The relation between anaesthetic concentration and age was analysed through linear regression. The effect of the use of local anaesthetics (e.g. caudal or epidural block) and opioids on the %MAC was evaluated by the two-sample t test. One-way analysis of variance (ANOVA) was used to compare the anaesthetic end-tidal concentration in the four different subgroups of analgesia; no analgesia, opioids, local anaesthetics and opioids combined with local anaesthetics. A P value less than 0.05 was considered statistically significant; all tests were two-sided. The data were analysed using IBM SPSS statistics software pack- age (IBM SPSS Statistics version 21, IBM Corp., Armonk, New York, USA), except for the determination of 95% confidence intervals (95% CIs) for percentages that were calculated according to the method of Agresti–Coull (http://epitools.ausvet.com.au/content.php?page=CIPro portion).

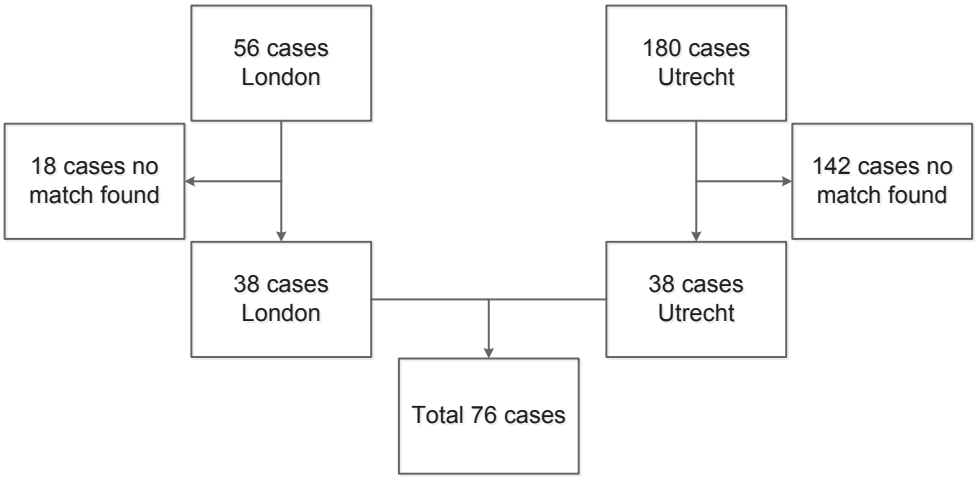

Figure 1. Flow chart: patient enrolment

RESULTS

In total, 56 infants were included in the GOSH database and matched with 180 infants from the retrospectively collected UMCU database. In total, 38 infants enrolled from the UMCU database were useful matches with 38 infants from the GOSH database (Fig. 1). During the study period, 38 different anaesthesiologists participated, 22 from GOSH and 16 from the UMCU.

Table 2. Characteristics of all infants

Clinical characteristics	GOSH (n=38)	UMCU (n=38)	*p*
Age (days)	165 [86-270]	122 [66-244]	0.464
Male, n(%)	12 (31)	13 (34)	0.807
Weight (kg)	7 [5-8]	7 [5-8]	0.947
Gestation (weeks)	40 [37-40]	40 [38-40]	0.450
Preterm, n(%)	8 (21)	6 (16)	0.554
Duration maintenance phase (min)	58 [29-91]	44 [27-72]	0.183
Analgesia, n(%)			0.246
No analgesia	6 (16)	1 (3)	
Opioids	18 (47)	20 (53)	
Local anaesthetics	6 (16)	6 (16)	
Local anaesthetics and opioids	8 (21)	11 (29)	
Anaesthetic used			0.0001
Sevoflurane	25 (66)	38 (100)	
Desflurane	12 (32)		
Isoflurane	1 (2)		
Procedures, n(%)			0.987
Abdominal	21 (55)	21 (55)	
Thoracic	1 (3)	1 (3)	
Orofacial	11 (29)	10 (26)	
Other	5 (13)	6 (16)	
ASA score, n(%)			0.0001
I	11 (29)	29 (76)	
II	12 (32)	7 (18)	
III	10 (26)	1 (3)	
IV	0	1 (3)	
Missing	5 (13)	0	
Airway management [n (%)]			0.0001
Endotracheal tube	37(97)	21(55)	
Laryngeal mask	0	17(45)	
Missing	1(3)	0	

All data are presented in median [interquartile range] or n (%) when indicated. ASA; American Society of Anaesthesiologists physical status classification system; CI confidence interval; GOSH Great Ormond Street Hospital *(2.6 to 3%, 95% CI 0.7 to 14%)

Patient characteristics were similar in both centres, except for the different types of inhalation anaesthetics used (P < 0.0001), types of airway management employed (P < 0.0001) and the American Society of Anesthesiologists physical status classification system (ASA) class (P < 0.0001, Table 2). There were no significant differences in the use of local anaesthetics or opioids between the centres. Abdominal surgery was the main procedure in both centres. The relation between the mean of the end-tidal concentration during the maintenance phase and age irrespec tive of the MAC is shown in Fig. 2. The mean %MAC in GOSH (%MAC, 0.87) was not significantly different from the UMCU (%MAC, 0.82) (P ¼ 0.329). When both groups were combined, the mean %MAC in the total group was 0.85. There was a significant increase in the %MAC in relation to age in the total group (slope ¼ 0.036 MAC month-1, P ¼ 0.0001, Fig. 3). In 57 of the 76 infants [75% (95% CI, 64 to 83%)], the anaesthetic end-tidal concentration was below

1 MAC. There were no significant differences in %MAC between the groups with and without tracheal intubation [mean difference, -0.057 (95% CI, -0.179 to 0.66); P ¼ 0.357]. Furthermore, there were no significant differences in %MAC between the groups receiving local anaesthesia or not [mean difference, -0.088 (95% CI, -0.20 to 0.019); P ¼ 0.105] nor between the groups receiving opioids or none [mean difference, 0.056 (95% CI, -0.67 to 0.179); P ¼ 0.367]. There was no significant effect of the use of analgesia on the end-tidal concentration (P ¼ 0.366).

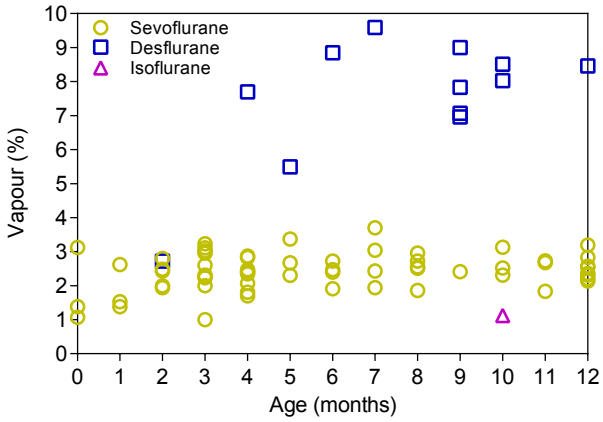

Figure 2. The relationship between the end-tidal concentration of inhalational anaesthetic during maintenance by age and different types of anaesthetics

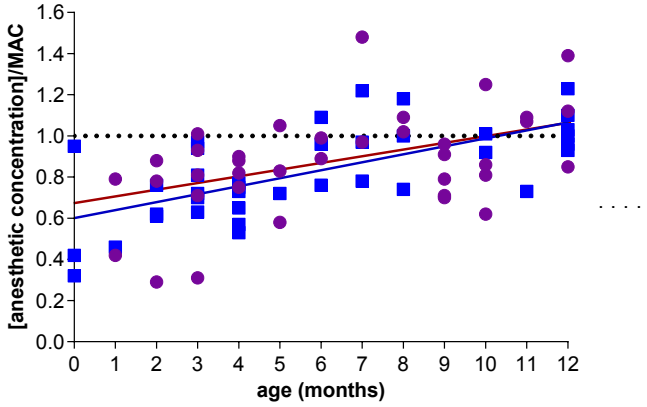

Figure 3. The relationship between the anaesthetic concentration divided by the minimal alveolar concentration during maintenance by age and centre.
The green line represents Great Ormond Street Hospital [slope¼0.033 minimal alveolar concentration per month (95% confidence interval, 0.012 to 0.054), r2¼0.22, P¼0.003]. The blue line represents the University Medical Center Utrecht [slope¼0.038 minimal alveolar concentration per month (95% confidence interval, 0.024 to 0.053), r2¼0.44, P¼0.0001]. There were no significant differences between Great Ormond Street Hospital and the University Medical Center Utrecht (P¼0.329). The orange line represents the total group [slope¼0.036 minimal alveolar concentration per month (95% confidence interval, 0.024 to 0.048), r2¼0.32, P¼0.0001]. The dotted black line indicates one minimal alveolar concentration.

DISCUSSION

The results of our study demonstrate that anaesthetic end-tidal concentrations administered for maintenance of anaesthesia increase with age and that 75% of infants were given an anaesthetic end-tidal concentration below 1 MAC. Furthermore, this study also shows that there were no significant differences in the dose of inhalational anaesthetics used for maintenance of anaesthesia in two distinct institutions from different countries. Contrary to expectations, the use of opioids and the use of local anaesthetics had no significant effect on the dose of inhalational anaesthesia administered.

The Food and Drug Administration, SmartTots and the American Academy of Pediatrics published a consensus Statement recommending a reduction in the exposure to general anaesthesia drugs in infants. Furthermore, most of the anaesthetic agents used in daily clinical practice have not been tested thoroughly for their safety in infants.[13]

MAC is a reference value at which 50% of patients do not move in response to a painful stimulus.[14,15,20] This study showed that the youngest infants received the lowest anaesthetic concentrations and that 75% of the infants received an anaesthetic concentration below 1 MAC, which might imply that anaesthesiologists are already being cautious with dosing of anaesthetic drugs to infants. It could be argued that the MAC value of sevoflurane, desflurane and isoflurane in infants is not employed as a useful dosage guide in clinical practice. This study shows for the first time that anaesthesiologists titrate inhala- tional anaesthetics to a lower concentration target when based on clinical parameters (e.g. heart rate).[17–19] The differences in anaesthetic agents used in this study were based on experience and normal clinical practice, the choice of the anaesthetic being entirely at the discretion of the anaesthesiologist. To correct for the differences in practice, the end-tidal concentrations were corrected for age-specific MAC. Therefore, the present variation clearly illustrates the differences in clinical practice. In any future study, it would be interesting to investigate which physiological parameters are used to target and titrate the dose of anaesthetic drug delivered It is possible that most of the infants in our study received too little anaesthesia with the risk of inadequate sedation and awareness during surgery.21 Animal studies have shown that exposure to painful stimuli causes an increased rate of neuronal cell death.8,22 Previous studies have proven that premature infants experiencing painful procedures encountered stress that can affect outcome.1 If the dose of anaesthesia is minimised, one should be aware of the risks of inadequate anaesthesia as well.[23]

Almost all infants in this study received analgesia. Infants who received no analgesia still had a mean end-tidal concentration of inhalational anaesthetics below 1 MAC. Previous studies have observed that the use of opioids and the use of local anaesthetics reduced the required dose of

inhaled anaesthetics,[8,14] but we did not find this in our study. This rather contradictory result may be due to the fact that we did not take into account the dose of opioids and local anaesthetics due to the small sample size, and so pain medication was studied as a dichotomous measure instead of a continuous variable. Therefore, infants who received one dose of opioids were in the same group as infants who received multiple doses of opioids. Morphine was only given at the end of surgery as pain medication and did not influence the administered dose of anaesthesia.

Although the present study showed comparable results in two centres in two countries, we studied a relatively small group of infants, and so the generalisability of the present results is limited. It might be valuable to perform a similar study in a larger multicentre and multinational population. Furthermore, there were differences in patient characteristics between the two groups, especially for ASA class. However, patients were matched for age, weight and type of procedure, as these factors are more relevant for the primary outcome of the study. There may have been observer bias in the prospective cohort study in GOSH as the researchers were present during surgery that may have influenced the anaesthesiologists in reducing the anaesthetic dosage. This study investigated only the maintenance phase of standard anaesthesia during surgery to try to minimise the number of confounding factors in the anaesthetic technique.

In conclusion, the results of the present study suggest that most young infants received inhalational anaesthetics at a concentration below 1 MAC, which accords with current guidance to minimise anaesthetic drug exposure but may have unintended consequences. Human experience is perhaps a better surrogate of the “true” anaesthetic needs, and MAC might needs to be re-evaluated. However, this would require a larger multi-centre study. Multiple reviews and agencies recommend the reduction of the dose of anaesthesia in infants, nevertheless this study might indicate that the dose used by anaesthesiologists is already in decline.

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11

CHAPTER

Summarizing discussion, conclusions and directions for future research

SUMMARY

Neonates with non-cardiac congenital anomalies (NCCA), requiring major surgery in the neonatal period, are at risk of neurodevelopmental delay.[1-17] The studies presented in this thesis report on the potential factors of influence; patient characteristics, brain injury, reduction and suppression of brain activity during anesthesia, presence or absence of autoregulatory ability and the effects on the cerebral oxygenation and cerebral perfusion.[18, 19]

A general introduction of patients with NCCA, requiring major neonatal surgery, is described in **chapter one**. The various sub groups of congenital anomalies included in the study cohort are described: esophageal atresia, abdominal wall defects, intestinal atresia, intestinal malrotation and volvulus and urogenital malformations. The psychomotor development of these patients, possible risk factors during surgery and anesthesia, and the different techniques to monitor and evaluate the neonatal brain, comprising Near Infrared Spectroscopy (NIRS), amplitude-integrated EEG (aEEG), cerebral ultrasound (cUS) and MRI, are introduced. In this chapter, the aims of the different studies in this thesis are presented as well.

This thesis reports on the results of our prospective, cohort study including all newborns with NCCA, requiring major neonatal surgery, and admitted at the NICU or PICU of the Wilhelmina Children's Hospital. This study attempted to identify risk factors in the perioperative period that are associated with developing a neurodevelopmental delay in this patient group.

PART I INTRODUCTION

Although several studies have already reported on the increased risk of a neurodevelopmental delay in patients with congenital anomalies, results seemed to be contradictory.[2, 4, 8] Our systematic review and meta-analysis on the neurodevelopmental outcome of patients with NCCA, requiring neonatal surgery, is outlined in **chapter two**. All studies reporting on neurodevelopmental outcome and the incidence of delay after neonatal surgery for major NCCA were searched. For the meta-analysis studies using the Bayley Scales of Infant and Toddler Development (BSID) at the age of one or two years were selected. In total, 23 eligible studies are included in the systematic review. Of these, 13 were eligible for conducting a meta-analysis, reporting on 511 children. Of all patients, the reported neurodevelopmental delay was 23% (median) with a wide range of 0 to 77%. The meta-analysis shows a mean cognitive and motor score of 0.5 and 0.6 SD below the normative score of the healthy population respectively, measured with the BSID, Second or Third Version, at 12 and 24 months of age. The meta-analysis shows that patients with esophageal atresia (EA) have a cognitive and motor score of 0.5 SD below the reference population.

Interestingly, the meta-analysis shows that outcome scores at the age of 12 months, representing short term outcome, does not differ from outcome scores measured at the age of 24 months. Furthermore, we report that neurodevelopmental outcome became a concern, since mortality decreased.[20, 21] Consequently, studies published more than 10 years ago could differ compared to more recent publications. Excluding these studies, however, did not influence the neurodevelopmental outcome scores. Even though survival has increased in the last years, the neurodevelopment remained unchanged. Factors that seems to negatively influence neurodevelopmental scores, are low birth weight, prematurity and multiple congenital anomalies.[2, 4, 7, 13, 22] An increased length of hospital admission, a higher number of surgical interventions, a longer duration of mechanical ventilation and the need for supplemental oxygen at discharge are all risk factors for neurodevelopment.[1, 2, 4-8, 12, 17, 22-25] The majority of the studies included in this systematic review consist of heterogeneous patient groups, comprising different congenital anomalies. One remark on the use of two versions of the BSID must be made. The Third Version has been reported to provide higher scores in comparison to the Second Version of the BSID.[26, 27] Therefore, we attempted to correct the scores of the Third Version, according to multiple reports in literature, by subtracting eight points of the outcome score. The findings in this systematic review emphasize the need for structural neurodevelopmental follow-up in NCCA patients.

PART II NEUROMONITORING AND NEUROIMAGING

Chapter three describes the results of our systematic evaluation of the incidence and pattern of brain injury after neonatal surgery for NCCA using the postoperative MRI of 101 patients. Mild to moderate brain lesions were present in 63% of patients on the postoperative MRI. Parenchymal brain lesions were present in 52% of the infants and non-parenchymal abnormalities, including intraventricular hemorrhage (IVH) and subdural hemorrhage, in 35% of the patients. Predisposing factors consist of prematurity and the type of congenital anomaly, with significant differences in the incidence of MRI-abnormalities. The prevalence of brain lesions was the highest in infants with gastroschisis and the lowest in infants with an anorectal malformation. Other risk factors for brain injury before, during and after surgery could not be identified in this study.

Although the high incidence of brain lesions in this patient group is of considerable concern, accurate timing of the onset of lesions is vital. cUS showed none of the moderate to severe cerebral lesions preoperatively. With the Diffusion Weigted Image (DWI) it was possible to determine the timing of onset of the lesions in 86% of the patients, in these patients a DWI was made within 10 days after surgery. Of these, in 61% restricted diffusion was present, which suggests onset in the perioperative period. Still, the most important remark of this study is the

absence of a preoperative MRI, which would permit us to time the lesions even more accurately. Apart from that, this study demonstrates for the first time in a systematic evaluation that neonates with NCCA undergoing surgery are at risk for mild to moderate brain lesions.

Worldwide, increasing concerns have been raised on the potential neurotoxic effects of inhalational anesthetics on the young infants brain.[28] Therefore, anesthetics could be a contributing factor to the observed neurodevelopmental delay in our patient group. The effect of general anesthesia on neonatal brain activity is investigated in **chapter four** by analyzing the perioperative aEEG. The background pattern, epileptic activity and quantitative measures were assessed in the preterm and term NCCA patients. In 98% of the patients sevoflurane was used and sufentanil for analgesia. Results show that a variable degree of reduction in brain activity occurred, which was dose- and gestational age(GA)-dependent. A higher dosage of sevoflurane correlates to lower brain activity during anesthesia. A lower GA correlates to more severe reduction in background pattern. Once sevoflurane was ceased, recovery of the brain activity occurred rapidly, in 60% of the preterm and 78% of the term patients within one hour. This study illustrates the uncertainties existing on the desired effect of anesthetics on the brain activity. Anesthesia can be defined as the triad 'loss of consciousness, retrograde amnesia and immobility', tested by the response to a painful stimulus.[29] The degree of consciousness required in the neonate has yet to be determined. Most patients decreased two 'classes' in background patterns. Seizure activity could not consequently be explained by brain injury, administered drugs or background pattern. Epileptiform discharge was observed after a rapid induction with sevoflurane, as previously described in literature.[30] The presence of severe brain lesion was not related to perioperative patterns of brain activity. Limitations of this study consist of the lack of a standardized anesthesia protocol – anesthetics were administered at the discretion of the anesthesiologist – and the GA of the patients, including preterm and term infants. Although this study is the first to report the effect of general anesthesia on EEG-measured brain activity in a cohort of neonates, the study-design could be more standardized. The aEEG is a suitable device to measure depth of anesthesia, however, the desired depression of brain activity in neonates has yet to be determined.

Disturbances in cerebral hemodynamics contribute to brain injury. Cerebral autoregulation maintains a stable cerebral perfusion during changing blood pressures.[31] The cerebral autoregulatory ability is suspected to be immature or even absent in preterm infants.[32] Anesthesia with sevoflurane can also affect the cerebral autoregulatory ability of the neonate.[33] Disturbances in hemodynamics and loss of autoregulatory ability of the cerebral blood flow (CBF), possibly due to the anesthetics, attributes to the vulnerability of the neonatal brain. To date, monitoring the cerebral autoregulation (CA) lacks a golden standard. We studied the cerebral autoregulation in 54 neonates before, during and after surgery and present the results

in **chapter five**. To determine autoregulatory ability the correlation was used. A correlation of ρ > 0.5 implies pressure passivity. Of our cohort, the time spent ρ > 0.5 during surgery was 28%, indicating an impairment in cerebral autoregulation. Concluding from our results, cerebral blood flow became pressure passive during major surgery. Before and after surgery CA was intact, during anesthesia with sevoflurane cerebral autoregulation was impaired 28% of the time. This indicates an increased risk for the neonatal brain during surgery, stressing the importance of stable parameters influencing cerebral perfusion. This method is promising for bedside monitoring of cerebral autoregulation in the near future.

A method that could assist in determining the exact timing of the onset of brain lesions, and to reveal the exact etiology of the brain injury, are oxidative stress biomarkers.[34] The predictive value of oxidative stress markers for brain damage after neonatal surgery is outlined in **chapter six.** Neonates, diagnosed with NCCA requiring neonatal surgery, were enrolled in this study preoperatively. Plasma and urine were collected before and after surgery to measure F_2-isoprostane and Non-Protein Bound Iron (NPBI). Patients with non-parenchymal injury could be differentiated from patients with no brain injury using the NPBI. In a multivariable analysis, correcting for GA, no relation was found with other risk factor and the biomarkers. This might imply that oxidative stress occurs during anesthesia.

PART III EFFECTS OF SURGICAL AND ANESTHESIOLOGICAL FACTORS ON CEREBRAL HEMODYNAMICS

Surgical interventions in the neonate are increasingly performed by using minimally invasive techniques, for example thoracoscopy in esophageal atresia. Advantages of a minimally invasive approach in comparison to an open procedure include less postoperative pain, shorter duration of postoperative ventilation and an improved cosmetic outcome.[35] It is important to evaluate the effect and the safety of these surgical methods on the neonate as well. In a series of studies, we investigated the effect of intrathoracic CO_2-insufflation on the cerebral oxygenation in neonates.

First, the hypothesis a high-pressure intrathoracic insufflation of CO_2 would cause a deterioration in cerebral oxygenation was tested in an animal experimental study, which is described in **chapter seven**. Ten newborn piglets were randomized into two different pressure groups, either CO_2-insufflation with 5 mmHg or with 10 mmHg. The results show that intrathoracic CO_2-insufflation with 10 mmHg cause severe hemodynamic instability in newborn piglets. Of the five piglets, in two the procedure was terminated prematurely because these piglets needed resuscitation. In contrast, the piglets receiving insufflation with 5 mmHg showed stable hemodynamic parameters. Significant differences were observed between the two pressure groups. In the

group with 10 mmHg heart rate was significantly higher and MABP lower. Interestingly, in both groups the cerebral oxygenation increased during thoracoscopy. This could have been the result of the vasodilatating effect of an increased arterial CO_2, which was particularly present in the group with 10 mmHg. Nevertheless, in the group with an insufflation pressure of 10 mmHg the cerebral tissue oxygen extraction was higher in comparison to 5 mmHg, suggesting that cerebral perfusion was decreased. In this study only a small number of piglets were included, which makes it difficult to draw strong conclusions. However, the differences are very distinct, which also result in highly significant results. To compare results with other hospitals in order to evaluate the safety of surgery techniques, it is important to verify these results.

To confirm the effects of CO_2-insufflation with a maximum of 5 mmHg on the hemodynamic parameters and the cerebral oxygenation a prospective cohort study of 15 neonates with esophageal atresia is performed and presented in **chapter eight**. Newborns underwent thoracoscopic repair in the first days of life. A significant increase in cerebral oxygenation right after the start of CO_2-insufflation was observed, still within the normal range. This was concomitant with an initial decrease in arterial saturation, an increase in $paCO_2$ and a mild acidosis, all parameters recovered to normal values during the procedure. An important remark is the prospective aspect of the study: the anesthesiologist changed ventilation settings during the procedure, after which hemodynamic parameters normalized. Following that, we could conclude that it is feasible to keep hemodynamic parameters and cerebral oxygenation values within normal limits. A close collaboration between surgeons, anesthesiologists and neonatologists together with perioperative neuromonitoring is needed to maintain safe values of the neonatal brain oxygenation.

The thoracoscopic repair of long gap esophageal atresia remains a challenge for the pediatric surgeon.[36, 37] It requires multiple procedures, including one or two procedures for elongation of the proximal and distal esophageal stumps with traction sutures, after which a delayed primary anastomosis can be performed.[38] The effect of the thoracoscopic repair of long gap esophageal atresia on the cerebral oxygenation was investigated in a case series of five patients. The results are reported in **chapter nine**. A total of 16 procedures were performed in this patient cohort. Parameters significantly influencing the cerebral oxygenation during this procedure were identified. A low level of hemoglobin and a decrease in MABP lowered the cerebral oxygenation significantly in this patient cohort. An increase in arterial CO_2 and a high fraction of inspired oxygen were observed to be important factors for an increase in cerebral saturation. Outliers in cerebral oxygenation - outside the normal range of 55-85% - did occur. However, interventions of the anesthesiologist normalized the cerebral oxygenation during the thoracoscopic procedure.

A high fraction of inspired oxygen frequently occurs during the induction phase of anesthesia. This is common practice in pediatric anesthesiology, in order to prevent a hypoxic event during the tracheal intubation of the patient. However, a high supply of oxygen can cause damage in the young, developing brain, due to oxidative stress.[39, 40] Since NIRS-monitoring is standard clinical care in our hospital, all studies were performed prospectively. It might be valuable to confirm our findings preferably in a study with blinded study-design, to evaluate the effect of CO_2-insufflation on the cerebral oxygenation in these young infants.

One of the potential parameters to influence the long-term outcome is the administration of inhalational anesthetics in the neonatal period.[41] Experimental studies showed detrimental effects of a prolonged, high dose of anesthetics used in normal practice on the brain; an increase in neuroapoptosis, an impaired neurogenesis and an induced neuroinflammation.[19, 41, 42] Therefore, it is advised to minimize the overall anesthetic drug dosage used in young children.[43] However, the current guidelines are vague and not directive, based on the minimal alveolar concentration (MAC). Consequently, the dose used in clinical practice is not clear. Therefore, a two-center observational cohort study was performed in the Great Ormond Street Hospital and the Wilhelmina Children's Hospital, outlined in **chapter ten**. The anesthetic dosages during the maintenance phase of anesthesia of 76 infants during surgery were determined. Of all infants, 75% had a concentration below the current guideline of one MAC, and this increased with age. The influence of administering analgesia, in order to reduce the required anesthetic dose, could not be affirmed in this study. At present, anesthesiologists titrate the dose of the anesthetic drug on clinical experience and physiological parameters, such as heart rate and blood pressure.[44] Apparently, the concentration nowadays used in young infants is in accordance to the current guideline to minimize anesthetic drug exposure.[43, 45] These results offer the opportunity to compare clinical practice and to determine formulate a recommended dose.

GENERAL DISCUSSION

Preliminary results neurodevelopmental outcome

The primary aim of this prospective cohort study was to identify risk factors for long-term neurodevelopmental delay. To determine this delay, results of the neurodevelopmental assessment tests are needed. All patients are assessed at the age of two years using the Bayley Scales of Infant and Toddler Development, Third Version.[46]

In this cohort of NCCA, 59 of 120 patients were assessed using the BSID. Three patients died, 13 were diagnosed with a genetic syndrome affecting their cognitive and motor development, ten were lost to follow-up and 35 patients still need to be assessed.

Assessment with the Bayley Scales of Infant and Toddler Development

The BSID was performed at a mean age of 24 months and 15 days with a standard deviation (SD) of one month and nine days. After excluding infants with genetic syndromes, the median MDI was 101 (range 68-134), PDI 98 (64-127). Regarding the MDI, 9 infants scored <85 and 6 infants >115. For the PDI, 6 infants had a score <85 and 5 >115.

Overall, including patients with genetic syndromes, 22 of 85 infants were diagnosed with a neurodevelopmental delay. Of these, 13 infants were diagnosed of having a genetic syndrome explanatory for their cognitive and/or psychomotor impairment. To date, we are awaiting the results of the last 35 patients.

For now, parenchymal injury, non-parenchymal injury or a combination of both did not result in a lower MDI or PDI-score. Concluding, the results of the postoperative MRI could not be correlated to the neurodevelopmental outcome scores. To comment on the results of the BSID, taking into account the distribution of a normal population, one would expect 10 infants to score above and below 1 SD (15.8% each side), in accordance to our results. However, the Third Version of the BSID was used, which has been reported to have higher outcome scores in comparison to the Second Version.[26, 27] Thus, this might imply that patients with a possible delay in development are missed. Therefore, it is important to follow these children through school age.

General remarks on our prospective cohort study is firstly the heterogeneity of the study cohort. Patients with NCCA consist of various congenital anomalies which require different surgical procedures, varying in duration, technique and complexity. Also, influencing the heterogeneity, was that the range in GA was wide comprising preterm and term neonates. Since all anomalies observed in our study are rare, we decided to pool the non-cardiac congenital anomalies, in accordance with reports in literature, with the requirement of neonatal surgery as common denominator. With a cohort of 120 patients and bias due to differences in gestational age, weight, duration and type of surgical procedure, it is hard to identify common risk factors. Second, the absence of a preoperative MRI did not allow us to accurately time the onset of lesions and assign specific brain injury to the surgical procedure. Third, due to the prospective study design we were not able to investigate the protective value of neuromonitoring against brain injury. Therefore, it would be of great additional value to repeat the study in a randomized, blinded study.

Conclusions

The following conclusions can be drawn from this thesis:

- Patients with non-cardiac congenital anomalies requiring surgery in the neonatal period have an increased risk on a neurodevelopmental delay. At the age of one and two years, the Mental Developmental Index, measured with the Bayley Scales of Infant and Toddler Development, is 0.5 SD lower in comparison to the reference population. The Psychomotor Developmental Index is 0.6 SD lower than the reference population (chapter 2).

- In a cohort of 101 patients with non-cardiac congenital anomalies, who underwent neonatal surgery, 63% had brain abnormalities on the postoperative MRI (chapter 3).

- Anesthesia causes a variable reduction in brain activity in neonates, dependent on gestational age and dose of anesthesia (chapter 4).

- Patients had less cerebral autoregulatory ability during surgery in comparison to pre- and postoperative periods (chapter 5).

- The oxidative stress biomarker Non-Protein Bounded Iron is related with non-parenchymal brain lesions postoperatively in a cohort of patients with non-cardiac congenital anomalies requiring neonatal surgery (chapter 6).

- A high insufflation pressure of 10 mmHg, to install a CO_2-pneumothorax during thoracoscopy, causes severe hemodynamic instability contrary to an insufflation pressure of 5 mmHg. The high pressure decreases the cerebral perfusion as well, since cerebral oxygen extraction increased (chapter 7).

- Maintaining a stable cerebral oxygenation during the thoracoscopic procedure of patients with esophageal atresia is possible. Outliers in cerebral oxygenation, arterial saturation and arterial CO_2 can be corrected during the procedure by adjusting ventilation settings (chapter 8).

- During consecutive thoracoscopic procedures in the neonatal period, for the correction of long gap esophageal atresia, it is possible to keep cerebral oxygenation within normal limits (chapter 9).

- The dose of inhalational anesthetics, currently used in clinical practice in the Wilhelmina Children's Hospital Utrecht and the Great Ormond Street Hospital London, administered

during the maintenance phase of anesthesia in infants undergoing surgery is below the current guidelines of one Minimal Alveolar Concentration (chapter 10).

FUTURE PERSPECTIVES

A systematically excluded patient group

As mentioned earlier, patients with congenital anomalies are structurally excluded from large longitudinal trials. This may have been contributed to the fact that the increased risk on a neurodevelopmental delay in this patient group became clear only recently.[2] Therefore, structural neurodevelopmental follow-up in this patient group is warranted and should be continued. The relevance of the MRI findings and the neuromonitoring measurements for neurodevelopment needs to be established, once all follow-up data is collected completely.

The neonatal brain during surgery

The results of our study stress the need for close monitoring of the neonatal brain during major neonatal surgery. This implies neuroimaging, neuromonitoring and monitoring of vital parameters, for example continuous blood pressure monitoring. The use of a peripheral artery line during neonatal surgery is not standard clinical care in many hospitals, although it offers valuable information on the influence of general anesthesia and effect of surgery. It offers the opportunity to monitor the blood pressure continuously and draw blood gases frequently. Since hemodynamic fluctuations put the neonatal brain at risk for brain injury, this monitoring tool might be an important protective measure for the brain and should be strongly advised.[47]

Reference values

The limitation in monitoring the neonate, is the absence of reference values of several hemodynamic parameters. Debate continues on the preferred blood pressure range in newborns, ranging from the corrected gestational age to set values.[48] Especially the blood pressure threshold below which cerebral autoregulation fails, is vital to establish for each neonate.

A preoperative MRI could give additional information on the effect of neonatal surgery on the newborn brain. Importantly, advanced MR imaging techniques could assist in early identification of infants at risk.[49] For example, DTI studies revealed the neuronal network,[50] describing the functional brain network. Using automatic segmentation the brain is quantitatively analyzed, calculating brain volumes, which could serve as early biomarker for neurodevelopmental outcome.[51] This can be performed with the use of the T1- and T2-weighted images, which are obtained standardly.[52, 53] It would be interesting to evaluate the maturation of the newborn with NCCA, since it is recognized that brain development of infants with congenital heart disease is

immature.[54-56] At the same time, the Wilhelmina Childrens' Hospital will start with collecting cerebral MR images of the healthy newborn, which will provide information on the 'normal' neonatal brain for the first time. In the future, comparing the findings of this healthy cohort to the results of our study could provide answers to the effect of the surgical procedure on the neonatal brain.

Currently the absence of reference values of cerebral oxygenation of term infants is a limitation. Let alone reference values of the cerebral oxygenation of neonates during anesthesia.[48, 57] The same is true for the EEG during anesthesia in the neonatal period. Proceeding the research of the neonatal EEG to titrate the minimal required and still sufficient dose of anesthesia will minimize the possible harmful effects on the brain. Studying the effect of the corrected gestational age, postnatal age and sevoflurane concentration on EEG-activity using power spectral analysis in our cohort of neonates will be the next step.[58] Other risk factors for brain development consist of suppression of brain activity in the neonatal period, stress and the need for enteral tube or parenteral feeding. Nutrition impacts early brain growth, which might be suboptimal in the perioperative period.[59]

Postoperative encephalopathy

More and more cases become known of children with encephalopathy following surgery.[18, 60] Most patients underwent relatively small procedures in a non-emergency setting, such as the revision of a stoma. In order to evaluate all cases objectively and retrieve and implement lessons learned in new guidelines a Taskforce 'Postoperative Encephalopathy in Patients at a Young Age' was installed in The Netherlands.[60] It is of utmost importance to continue to report the cases of severe encephalopathy following surgery in the first year of life.

For a future study we would suggest including a preoperative MRI, a postoperative MRI to detect acute injury and three months after surgery to evaluate development. Since for some anomalies a preoperative MRI is not feasible, for example in patients with gastroschisis, a prenatal MRI could be considered. In such a study, close monitoring of vital parameters and neuromonitoring would continue. To perform this study in a randomized, blinded study would be of additional value. Therefore collaboration with other hospitals is important, in which neuromonitoring has not been performed so far in this specific patient group and neuromonitoring could be blinded. However, the Taskforce wrote a directive in which neuromonitoring with NIRS and an arterial line is strongly adviced. Randomization to either normal procedure or care with close neuromonitoring could provide evidence on the protective value of this monitoring, however, it is questionable whether this is ethical to perform.

Furthermore, monitoring of parameters influencing brain development, such as administration of pain and sedative medication, oxygen and CO_2, nutrition, stress in the perioperative period, discomfort of the child, separation from the parents, repeated hospital admissions in addition to the separate congenital anomalies are important to investigate.

Finally, a long term neurodevelopmental follow-up program of these patients is mandatory to gain more insight in the neurodevelopment of these children and to evaluate long-term effects on the developing brain.

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12

CHAPTER

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Pasgeborenen met niet-cardiale aangeboren afwijkingen, die in de eerste levensmaand een grote operatie ondergaan, hebben een verhoogd risico op problemen van de psychomotorische ontwikkeling. De onderzoeken, beschreven in dit proefschrift, rapporteren over de potentiële risicofactoren die van invloed kunnen zijn op de ontwikkeling; de zuurstofsaturatie en perfusie van de hersenen, de aan- of afwezigheid van autoregulatie van de circulatie van de hersenen, de verminderde en onderdrukte hersenactiviteit tijdens de narcose en hersenschade, gerelateerd aan de aangeboren afwijkingen en bijbehorende operatie.

In dit proefschrift worden de resultaten van onze prospectieve cohortstudie beschreven, waarin alle pasgeborenen met een niet-cardiale aangeboren aandoening, die een grote operatie moeten ondergaan in de eerste levensmaand, en die zijn opgenomen op de neonatale en kinder-intensive care van het Wilhelmina Kinderziekenhuis, zijn geïncludeerd. Ons onderzoek heeft gepoogd om risicofactoren in de periode rondom de operatie te achterhalen, die in verband kunnen worden gebracht met een ontwikkelingsachterstand in deze patiëntengroep.

DEEL I INTRODUCTIE

In de literatuur bleken resultaten over de ontwikkeling van patiënten met aangeboren aandoeningen conflicterend, waarbij een aantal studies een verhoogd risico rapporteerden. Daarom hebben we een systematische review en meta-analyse uitgevoerd van de ontwikkeling van patiënten met niet-cardiale aangeboren aandoeningen. Deze wordt beschreven in hoofdstuk 2. Alle geïncludeerde studies rapporteerden de psychomotorische ontwikkeling en de incidentie van een ontwikkelingsachterstand, na een operatie in de eerste levensmaand voor een niet-cardiale aangeboren aandoening. Alle resultaten van de Bayley Scales of Infant and Toddler Development (BSID) op de leeftijd van één en twee jaar werden geselecteerd. In totaal includeerden we 23 studies voor de systematische review. Daarvan bleken er 13 geschikt voor de meta-analyse, waarin in totaal 511 kinderen waren geïncludeerd. Van alle patiënten had 23% (mediaan) een ontwikkelingsachterstand met een brede spreiding van 0 tot 77%. Met de meta-analyse vonden we een cognitieve en motorische ontwikkelingsscore, die 0,5 en 0,6 standaarddeviatie (SD) onder de gemiddelde score van de gezonde populatie lag, welke was getest met de BSID op de leeftijd van 12 en 24 maanden. Patiënten met een congenitale hernia diafragmatica (CHD) bleken 1,0 standaarddeviatie onder de gezonde populatie te scoren. Dit betekent dat deze patiënten een milde tot matige achterstand hebben. Daarnaast liet de meta-analyse zien dat patiënten met een slokdarmafsluiting ook een psychomotorische ontwikkelingsscore hadden van 0,5 SD onder de gezonde populatie.

Opvallend is dat de meta-analyse toont dat de ontwikkelingsuitkomst op de leeftijd van 12 maanden hetzelfde is als op de leeftijd van 24 maanden. Daarbij komt dat ontwikkeling tegenwoordig meer aandacht krijgt, aangezien de overlevingskansen sterk zijn verbeterd in de laatste jaren. Daarom hebben we ook gekeken naar studies die enkel in de laatste 10 jaar zijn gepubliceerd. Echter, bleek dit geen verschil in uitkomst te geven. Factoren die de ontwikkeling benadeelden waren niet statistisch te toetsen, maar een laag geboortegewicht, prematuriteit en meerdere aangeboren aandoeningen werden in de studies genoemd als risicofactoren. Ook een verlengde ziekenhuisopname, meer operaties, een langere duur van de ademhalingsondersteuning en zuurstofbehoefte bij ontslag naar huis werden genoemd als risicofactoren op een ontwikkelingsachterstand. De meeste studies waren niet gestandaardiseerd in het bepalen van de ontwikkeling en bevatten een heterogene patiëntengroep, met verschillende typen aangeboren aandoeningen. Verder is aan te merken dat er twee verschillende versies van de BSID zijn gebruikt, versie twee en drie. In de literatuur is genoemd dat versie drie een hogere score geeft dan de tweede. In een poging hiervoor te corrigeren is de score verminderd met acht punten, zoals wordt voorgesteld in verschillende wetenschappelijke artikelen. De bevindingen in deze systematische review benadrukken de behoefte aan structurele psychomotorische follow-up van patiënten met een niet-cardiale aangeboren aandoening.

DEEL II HERSENBEWAKING EN BEELDVORMING

In hoofdstuk drie worden de resultaten van onze systematische evaluatie van hersenschade na de operatie in de neonatale periode bij 101 kinderen met niet-cardiale aangeboren aandoeningen beschreven. In 63% van de patiënten werd milde tot matige hersenschade op de postoperatieve MRI gezien. Schade van het hersenparenchym was bij 52% van de kinderen zichtbaar en bij 35% werden afwijkingen buiten het parenchym gezien, zoals intraventriculaire en subdurale bloedingen. Het bleek dat de MRI van aanvullende waarde was in het diagnosticeren van hersenschade, in vergelijking met de craniale echo. Voorspellende factoren voor een hogere incidentie van afwijkingen op de MRI, waren prematuriteit en het type aangeboren afwijking. De prevalentie van hersenlaesies was het hoogst bij pasgeborenen met een gastroschisis en het laagst bij kinderen met een anorectale malformatie. Andere risicofactoren voor hersenschade voor, tijdens en na de operatie konden niet worden vastgesteld.

De hoge incidentie van hersenlaesies in deze patiëntengroep is zorgwekkend en nauwkeurige vaststelling wanneer deze schade ontstaat is belangrijk. De grotere afwijkingen werden voor de operatie niet met de craniale echo gezien. De Diffusion Weighted Images (DWI) geven informatie over het moment van ontstaan van de laesies. Bij 86% was een DWI gemaakt binnen 10 dagen na de operatie, daarvan had 61% positieve laesies die suggereren dat ze zijn ontstaan in de periode

rondom de operatie. De belangrijkste aanmerking van dit onderzoek is de afwezigheid van een preoperatieve MRI van de hersenen. Echter, laat deze studie voor het eerst op een systematische wijze zien dat pasgeborenen met niet-cardiale aangeboren aandoeningen, die een operatie ondergaan, risico lopen op hersenschade.

Wereldwijd zijn er in toenemende mate zorgen over de potentieel neurotoxische effecten van narcosemiddelen, die worden gebruikt bij jonge kinderen. Het wordt gesuggereerd dat anesthetica bijdragen aan de psychomotorische ontwikkelingsachterstand in onze patiëntengroep. Daarom werd het effect van algehele anesthesie op de hersenactiviteit onderzocht met gebruik van het amplitude-geïntegreerd EEG (aEEG). Het achtergrondpatroon van de hersenactiviteit, de epileptische activiteit en kwantitatieve maten werden onderzocht bij premature en voldragen pasgeborenen met niet-cardiale aangeboren aandoeningen. Bij 98% van de kinderen was het narcosemiddel sevofluraan gebruikt en sufentanil als pijnstiller. Resultaten laten zien dat er een variabele vermindering van de hersenactiviteit is, welke afhankelijk bleek van de dosis anesthesie en de zwangerschapsduur. Een hogere dosis sevofluraan was gecorreleerd aan een lagere hersenactiviteit tijdens de narcose. Een lagere zwangerschapsduur was gecorreleerd aan minder hersenactiviteit. Na het stoppen van de sevofluraan was er herstel van de hersenactiviteit bij 60% van de prematuren en bij 78% van de voldragen patiënten binnen één uur. Deze studie laat de variabele effecten van de anesthesie zien bij neonaten en laat met name zien dat er aanhoudend onduidelijkheid is over de gewenste effecten van anesthetica op de hersenactiviteit. Narcose kan worden gedefinieerd als verlies van bewustzijn, retrograde amnesie en niet kunnen bewegen, wat wordt getest door de reactie op een pijnprikkel. De mate van bewusteloosheid die nodig is bij een neonaat moet worden bepaald. In onze studie verlaagde de anesthesie de achtergrondpatronen met gemiddeld twee klassen. Epileptische activiteit kon niet consequent worden verklaard door hersenschade, de toegediende medicatie of het achtergrondpatroon. Bij een inleiding met hoge dosis sevofluraan werd epileptische activiteit geobserveerd, zoals eerder beschreven in de literatuur. Hersenschade was niet gerelateerd aan de hersenactiviteit voor-, tijdens of na de operatie. Beperkingen van deze studie bestonden uit het ontbreken van een gestandaardiseerd anesthesieprotocol, het beleid werd bepaald door de anesthesioloog. Daarnaast is er een brede spreiding van zwangerschapsduur, namelijk prematuren en a term geboren kinderen. Echter, dit is de eerste studie die de effecten van algehele narcose op de hersenactiviteit, gemeten met het aEEG, in een cohort van neonaten heeft onderzocht. Het aEEG is een geschikte methode om de diepte van anesthesie te meten, waarbij de gewenste reductie in hersenactiviteit moet worden vastgesteld.

Verstoringen in de hemodynamiek van de hersenen dragen bij aan hersenschade. Cerebrale autoregulatie impliceert een stabiele perfusie van de hersenen tijdens wisselende bloeddrukken. Het vermogen om te autoreguleren is onderontwikkeld in prematuur geboren kinderen.

Narcose met sevofluraan kan dit vermogen ook beïnvloeden in de neonaat. Verstoringen van hemodynamiek en het verlies van autoregulerend vermogen van de cerebrale doorbloeding, mogelijk door anesthetica, dragen op die manier bij aan de kwetsbaarheid van het neonatale brein. Tot op heden is er geen gouden standaard om de cerebrale autoregulatie te monitoren. In onze studie hebben we de cerebrale autoregulatie van 54 neonaten voor, tijdens en na de operatie onderzocht, waarvan de resultaten zijn gepresenteerd in hoofdstuk vijf. Om het autoregulerend vermogen te bepalen, werd de correlatie gebruikt. Een correlatie > 0.5 impliceert een gebrek aan autoregulatie. Gedurende 28% van de operatietijd was er een gebrek aan cerebrale autoregulatie. Concluderend, de cerebrale perfusie is tijdens de narcose afhankelijk van de bloeddruk. Voor en na de operatie was de cerebrale autoregulatie intact. Dit geeft een verhoogd risico voor het neonatale brein om hersenschade op te lopen, waarmee het belang van stabiele parameters, die de cerebrale perfusie beïnvloeden, wordt benadrukt. Deze methode is veelbelovend om de cerebrale autoregulatie te bewaken.

Een andere methode om het exacte moment van het ontstaan van hersenlaesies te bepalen, en om de etiologie van de hersenschade te achterhalen, is met biomarkers voor oxidatieve stress. De voorspellende waarde van deze biomarkers voor hersenschade wordt gepresenteerd in hoofdstuk zes. Pasgeborenen met een niet-cardiale aangeboren aandoening, die een operatie ondergaan in de eerste levensmaand, werden preoperatief geïncludeerd. Plasma en urine werd voor en na de operatie verzameld om F_2-isoprostane en Non-Protein Bound Iron (NPBI) te bepalen. Met NPBI kon er een onderscheid worden gemaakt tussen patiënten met niet-parenchymale hersenschade en zonder hersenschade. In een multivariate analyse, gecorrigeerd voor zwangerschapsduur, werd geen relatie gevonden met andere risicofactoren. Deze resultaten impliceren dat er oxidatieve stress is tijdens de narcose.

DEEL III EFFECTEN VAN CHIRURGISCHE EN ANESTHESIOLOGISCHE FACTOREN OP DE CEREBRALE HEMODYNAMIEK

Chirurgische interventies bij pasgeborenen worden steeds vaker met minimaal invasieve technieken gedaan, zoals bijvoorbeeld thoracoscopie voor het corrigeren van een slokdarmafsluiting. Voordelen van een minimaal invasieve benadering zijn minder postoperatieve pijn, een kortere duur van postoperatieve ademhalingsondersteuning en een mooier cosmetisch resultaat. Daarbij is het van groot belang om ook het effect op en de veiligheid voor de pasgeborene te toetsen. We hebben het effect van het intrathoracaal inblazen van koolstofdioxide op de cerebrale saturatie van neonaten onderzocht.

Eerst is de hypothese dat een hoge druk om koolstofdioxide in de thorax te blazen de cerebrale saturatie nadelig beïnvloed getoetst in een dierexperimentele studie, beschreven in hoofdstuk zeven. De biggen werden gerandomiseerd over twee verschillende drukgroepen, met een insufflatiedruk van 5 mmHg of 10 mmHg. De resultaten laten zien dat een intrathoracale CO_2-insufflatiedruk van 10 mmHg een ernstige verstoring van de hemodynamiek in biggen veroorzaakt. Van de vijf biggen moest bij twee de procedure voortijdig worden beëindigd om de biggen te reanimeren. Dit in tegenstelling tot het gebruik van een lage druk van 5 mmHg, waarbij er stabiele hemodynamische waarden werden gezien. Er werden significante verschillen tussen de twee groepen gevonden. In de groep met 10 mmHg steeg de hartslag significant en daalde de MABP. Echter, in beide groepen steeg de cerebrale saturatie significant gedurende de thoracoscopische procedure. Wellicht was dit het resultaat van de vasodilatatie, die wordt veroorzaakt door een verhoogd arterieel CO_2, wat voornamelijk in de groep met 10 mmHg werd gezien. Echter, in de groep met 10 mmHg was de zuurstofextractie in het hersenweefsel hoger in vergelijking met de groep met 5 mmHg. Dit impliceert dat de perfusie van de hersenen verminderd is. In deze studie werd slechts een klein aantal biggen geïncludeerd, waardoor overtuigende conclusies lastig te trekken zijn. Echter, de verschillen tussen de beide drukgroepen waren zo uitgesproken en de resultaten daarmee sterk significant. Om de resultaten van een thoracoscopische ingreep met andere ziekenhuizen te vergelijken en daarmee de veiligheid van de techniek te evalueren, is het belangrijk om de invloed van de insufflatiedruk verder te onderzoeken.

Om de resultaten van een CO_2-insufflatie van maximaal 5 mmHg op de hemodynamische waarden en de cerebrale zuurstofsaturatie te onderzoeken, werd een prospectieve cohortstudie met 15 neonaten met een slokdarmafsluiting uitgevoerd en gepresenteerd in hoofdstuk acht. Pasgeborenen ondergingen een thoracoscopische correctie in de eerste levensdagen. Een significante stijging van de cerebrale zuurstofsaturatie direct na de start van CO_2-insufflatie werd geobserveerd, nog binnen de normale spreiding. Gelijktijdig steeg de arteriële saturatie initieel, steeg de arteriële CO_2 en was een milde acidose zichtbaar. Alle waarden normaliseerden gedurende de procedure. Een belangrijke aanmerking is dat deze studie prospectief en niet geblindeerd was; de anesthesioloog paste de ventilatie-instellingen tijdens de procedure aan, waarna de waarden herstelde binnen normale grenzen. Daarmee concludeerden we dat het mogelijk is om de hemodynamische parameters en de cerebrale zuurstofsaturatie binnen normale waarden te houden. Een hechte samenwerking tussen de chirurgen, anesthesiologen en neonatologen in combinatie met perioperatieve hersenbewaking is nodig om veilige waarden van de neonatale cerebrale saturatie te behouden.

De thoracoscopische correctie van een oesofagusatresie met een grote ruimte tussen het bovenste en onderste deel van de slokdarm, blijft een uitdaging voor de kinderchirurg. Het vereist meerdere procedures, om de slokdarm op te rekken met tractiehechtingen, waarna er een

anastomose kan worden gemaakt. Het effect van een thoracoscopische correctie bij kinderen met een dergelijke oesofagusatresie op de cerebrale zuurstofsaturatie werd onderzocht in een reeks met vijf patiënten. De resultaten worden beschreven in hoofdstuk negen. Een totaal van 16 procedures werd uitgevoerd in dit patiëntencohort. Parameters die de cerebrale zuurstofsaturatie significant verlaagden, waren een laag hemoglobine en een daling van de MABP. Bij een stijging van het arteriële CO_2 en een hoge fractie van toegediende zuurstof werd een stijging van de cerebrale zuurstofsaturatie gezien. Uitschieters in cerebrale zuurstofsaturatie – buiten de normale waarden van 55 tot 85% - kwamen voor. Met interventies van de anesthesioloog normaliseerde de cerebrale zuurstofsaturatie gedurende de thoracoscopische ingreep.

Een hoge fractie van geïnspireerd zuurstof wordt vaak gebruikt tijdens de inleiding van de anesthesie. Dit is normale zorg bij de kinderanesthesiologie, om te voorkomen dat de patiënt desatureert tijdens de intubatie. Echter, een hoog aanbod van zuurstof kan schade veroorzaken in het jonge, ontwikkelende brein, vanwege oxidatieve stress. Aangezien bewaking met NIRS standaard, klinische zorg is in ons ziekenhuis, werden alle studies niet-geblindeerd uitgevoerd. Het zou daarom van waarde zijn om onze bevindingen te bevestigen in een geblindeerde studie, om de effecten van de insufflatie met CO_2 op de cerebrale zuurstofsaturatie van deze jonge kinderen te onderzoeken.

Eén van de potentiële factoren die de ontwikkeling op de lange termijn beïnvloeden, is de toediening van inhalatie-anesthetica in de neonatale periode. Dierexperimentele studies laten schadelijke effecten zien van een langdurige, hoge dosis anesthetica, die in de praktijk worden gebruikt, op het brein. Het geeft een verhoogde neuroapoptose, een verstoorde neurogenese en een opwekking van neuroinflammatie. Daarom wordt geadviseerd om de totale dosis anesthetica voor jonge kinderen te minimaliseren. Echter, de huidige richtlijnen zijn onduidelijk en niet directief, gebaseerd op de minimale alveolaire concentratie (MAC). Daaruit voortvloeiend is de dosis die momenteel wordt gebruikt in de klinische praktijk niet duidelijk. Om die reden voerden we een observationele cohortstudie uit in the Great Ormond Street Hospital en het Wilhelmina Kinderziekenhuis, beschreven in hoofdstuk tien.

De dosis anesthetica tijdens de stabiele fase van 76 zuigelingen tijdens de operatie werd bepaald. Van alle zuigelingen, had 75% een dosis lager dan de huidige richtlijn van één MAC. Dat de toediening van pijnstilling de vereiste dosis narcose verlaagt, kon niet worden bevestigd in onze studie. Op dit moment titreert de anesthesioloog de dosis van de anesthetica op basis van klinische ervaring en fysiologische parameters, zoals hartslag en bloeddruk. Blijkbaar is de concentratie die tegenwoordig wordt gebruikt bij jonge kinderen in overeenstemming met de huidige richtlijn om de blootstelling aan anesthetica zoveel mogelijk tot een minimum te beperken. Deze resultaten geven de mogelijkheid om ziekenhuizen met elkaar te vergelijken en een aanbevolen dosis te formuleren.

ALGEMENE DISCUSSIE

Voorlopige resultaten ontwikkelingsonderzoek

Het voornaamste doel van onze prospectieve cohortstudie was om risicofactoren voor een ontwikkelingsachterstand te identificeren. Om een dergelijke achterstand vast te stellen, zijn de resultaten van het psychomotore ontwikkelingsonderzoek nodig. Alle patiënten uit het cohort worden op de leeftijd van twee jaar getest met de Bayley Scales of Infant and Toddler Development, Versie Drie.

Op dit moment zijn van ons cohort met patiënten met niet-cardiale aangeboren aandoeningem, 59 van de 120 patiënten getest met de BSID. Drie patiënten zijn overleden, 13 patiënten zijn gediagnosticeerd met een genetisch syndroom die hun cognitieve en/of motorische ontwikkeling beïnvloed, tien zijn uitgevallen in het vervolgonderzoek en 35 patiënten moeten nog worden getest.

Beoordeling met de Bayley Scales of Infant and Toddler Development

De BSID werd gedaan op de leeftijd van 24 maanden en 15 dagen (gemiddelde) met een SD van 39 dagen. De mediane Mean Development Index (MDI) was 101 (spreiding 68-134) en de Psychomotor Development Index (PDI) 98 (64-127).

Met betrekking tot de MDI scoorden negen kinderen <85 en zes kinderen >115. Wat betreft de PDI hadden zes kinderen een score < 85 en vijf > 115.

In totaal hadden 22 van de 85 kinderen een ontwikkelingsachterstand. Van deze kinderen waren 13 kinderen gediagnosticeerd met een genetisch syndroom, die verklarend is voor de achterstand. Op dit moment wachten we de score van de laatste 35 patiënten nog af.

Vooralsnog geeft de hersenschade geen lagere MDI- of PDI-score. Concluderend zijn de resultaten van de postoperatieve MRI niet te correleren aan de ontwikkelingsuitkomst op de leeftijd van twee jaar.

Wat betreft de resultaten van de BSID, rekening houdend met de verdeling van een normale populatie, komt het daarmee overeen. Echter, zoals eerder benoemd, is gerapporteerd dat BSID Versie Drie een hogere score geeft in vergelijking met Versie Twee. Dat impliceert dat patiënten met een mogelijke achterstand in ontwikkeling nu worden gemist. Ook om die reden is het belangrijk de kinderen tot schoolleeftijd te volgen.

Algemene aanmerkingen op onze prospectieve cohortstudie is allereerst het heterogene patiëntencohort. Patiënten met niet-cardiale aangeboren aandoeningen bevatten verscheidene congenitale defecten, die verschillende soorten chirurgische ingrepen behoeven, variërend in duur, techniek en complexiteit. Daarnaast beïnvloedt de spreiding in zwangerschapsduur ook de heterogeniteit en zijn er premature en a terme pasgeborenen geïncludeerd. Aangezien alle aandoeningen in ons cohort zeldzaam zijn, is er voor gekozen de niet-cardiale aangeboren

aandoeningen te bundelen, net als wordt beschreven in de literatuur, met de noodzaak voor neonatale chirurgie als gemene deler. Met een cohort van 120 patiënten en vertekening door verschillen in zwangerschapsduur, gewicht, duur en type chirurgische ingreep, is het lastig om gemeenschappelijke risicofactoren te identificeren. Daarnaast zorgde de afwezigheid van een preoperatieve MRI er voor dat we niet zeer nauwkeurig het moment van ontstaan van de hersenschade konden bepalen. Als derde maakte het niet-geblindeerde studiedesign het onmogelijk om de exacte waarde van de neuromonitoring als wapen tegen hersenschade te bepalen. Om die reden is het van grote toegevoegde waarde om de studie te herhalen met een gerandomiseerd, geblindeerd design.

Conclusies

De volgende samenvattende conclusies kunnen worden getrokken:

- Patiënten met een niet-cardiale aangeboren aandoening, die een chirurgische ingreep in de neonatale periode moeten ondergaan, hebben een verhoogd risico op een ontwikkelingsachterstand. Op de leeftijd van één of twee jaar hebben zij een ontwikkelingsscore, gemeten met de Bayley Scales of Infant and Toddler Development, die 0,5 SD lager is in vergelijking met de gezonde populatie (Hoofdstuk 2).

- In een cohort van 101 patiënten met niet-cardiale aangeboren aandoeningen, die een neonatale operatie hebben ondergaan, had 63% hersenafwijkingen op de postoperatieve MRI (Hoofdstuk 3).

- Narcose zorgt voor een variabele verlaging van de hersenactiviteit bij neonaten, deze reductie is afhankelijk van zwangerschapsduur en de dosis van de anesthetica (Hoofdstuk 4).

- Patiënten hebben minder cerebrale autoregulatie tijdens de operatie in vergelijking met pre- en postoperatieve periodes (Hoofdstuk 5).

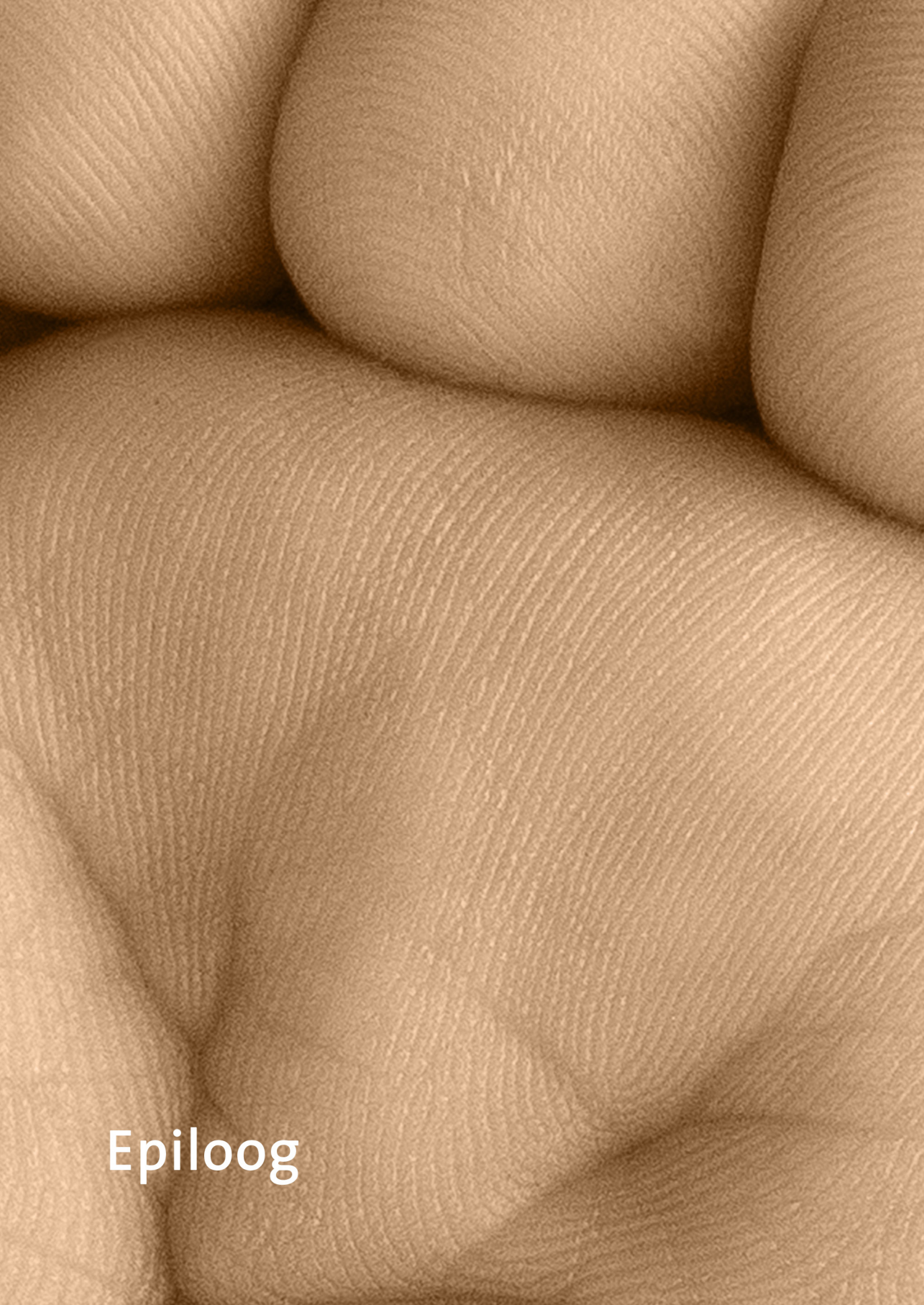
- Oxidatieve stress biomarker Non-Protein Bound Iron is gerelateerd aan postoperatieve, niet-parenchymateuze hersenschade in een cohort van patiënten met niet-cardiale aangeboren aandoeningen, die neonatale chirurgie ondergaan (Hoofdstuk 6).

- Een hoge insufflatiedruk van 10 mmHg, om een pneumothorax met CO_2 te installeren, veroorzaakt ernstige hemodynamische instabiliteit in vergelijking met een insufflatiedruk van 5 mmHg. De hoge druk verlaagt de cerebrale perfusie, gezien de zuurstofextractie in de hersenen stijgt (Hoofdstuk 7).

- Het behouden van een stabiele cerebrale zuurstofsaturatie tijdens de thoracoscopische ingreep van patiënten met een oesofagusatresie is mogelijk. Uitschieters in cerebrale zuurstofsaturatie, arteriële saturatie en arterieel CO_2 kunnen tijdens de procedure worden gecorrigeerd met het aanpassen van de ventilatie-instellingen. (Hoofdstuk 8)

- Tijdens opeenvolgende thoracoscopische procedures in de neonatale periode, om een long gap oesofagusatresie te corrigeren, is het mogelijk om een stabiele cerebrale zuurstofsaturatie te behouden (Hoofdstuk 9).

- De dosis van inhalatie-anesthetica, die momenteel wordt toegepast in de klinische praktijk in het Wilhelmina Kinderziekenhuis en the Great Ormond Street Hospital, tijdens de onderhoudsfase van de narcose bij zuigelingen is lager dan de huidige richtlijn van één Minimale Alveolaire Concentratie voorschrijft (Hoofdstuk 10).



Epiloog

"...op 63% van de postoperatieve MRI's was milde tot matige hersenschade zichtbaar."

Vijftig handen schieten de lucht in. Ik sta voor een zaal met ouders en kinderen met een slokdarmafsluiting de resultaten van ons onderzoek te presenteren. Op congressen is bovenstaande een 'interessante bevinding', hier is het schokeffect groot. Wat is het effect van de operatie? En van de operaties na de eerste operatie? Is de anesthesie schadelijk voor de hersenen? Wat is het gevolg voor mijn kind? Vragen die er toe doen voor ouders en hun kinderen.

Gedurende mijn promotietraject werd duidelijk hoe schaars de informatie is over de psychomotorische ontwikkeling op de lange termijn van deze patiëntengroep. Zijn we met ons onderzoek op de goede weg? Een relevante vraag om te stellen aan de patiënten zelf. Om die reden zocht ik contact met de patiëntenverenigingen om onze onderzoeksresultaten voor te leggen.

Hersenschade
Het percentage postoperatieve hersenschade vinden de woordvoerders schokkend, één van hen heeft het om die reden zelfs niet doorgestuurd naar de ouders. Al staan ouders er ook nuchter in: "Het is vooral van belang wat je met de resultaten kunt." Reacties geven ook weer dat een aantal ouders zich niet kan voorstellen dat er kans is op hersenschade na een operatie en dat ze het een 'eng' idee vinden.

Hersenbewaking
De reacties op de hersenbewaking zijn positief. Het geeft wel weer extra snoertjes, bij een kind met al '10.000 dingen aan het lijf'. "Het hoort erbij en je went eraan," aldus een moeder. Het is vooral belangrijk dat het doel duidelijk is. Als het doel goed wordt onderbouwd, zijn ouders voor om tijdens de operatie de hersenen te bewaken.

Ontwikkeling
Een ontwikkelingsachterstand herkennen de woordvoerders niet direct als ze naar patiënten van de patiëntenvereniging kijken. Wel zien zij dat meer kinderen naar speciaal onderwijs gaan, dat er gedragsproblemen voorkomen en dat kinderen een lagere verwerkingssnelheid lijken te hebben. De kanttekening die zij hierbij maken: welke afspiegeling van patiënten geeft een patiëntenvereniging? De ernstige patiënten, de milde of een combinatie?

Onderzoek
"Het is een angst van ons als ouder wat het effect is van zo'n grote operatie, alle medicatie en de ziekenhuisopname op de ontwikkeling van onze dochter. Je hebt geen keuze, dus dan is het prettig dat de zorg die gegeven wordt goed onderbouwd is." "*Het doen van wetenschappelijk*

onderzoek is heel dubbel." De woordvoerders zijn tegelijkertijd ook ouder of ervaringsdeskundige, zij gaven aan voorstander te zijn van onderzoek, totdat het jouw eigen kind betreft. Ouders geven verrassend vaak aan dat het niet erg is dat het onderzoek niet direct bijdragend is voor hun eigen kind, maar voor kinderen op de lange termijn. Het gaat om zeldzame aandoeningen, dus alle extra informatie draagt bij. De meest gehoorde suggestie voor vervolgonderzoek is de ontwikkeling op lange termijn, aandacht voor het gedragsmatige stuk en de psychologische kant van het kind.

Het contact met patiënten houd je scherp om voor ogen te houden wat daadwerkelijk van belang is voor het kind zelf. Meerdere keren hoor ik dat voor kinderen belangrijk is dat er niet zwaar en beladen met hun aandoening wordt omgegaan, dat ze zo min mogelijk een stempel krijgen en dat er van hun aandoening geen '*big deal*' wordt gemaakt. Op een patiëntendag vraag ik aan een jongen van 10 jaar of vriendjes op school weten dat hij een aangeboren aandoening heeft. Verbaasd kijkt hij mij aan: "De hele school weet het!" Vervolgens laat hij mij zien hoe hij zichzelf heeft aangeleerd zijn brood met grote slokken water snel weg te krijgen, ondanks zijn slokdarmaandoening, om tijdens overblijven niet achter te blijven. De impact van de aandoening op ouder en kind is wisselend, de ernst van de aandoening verschilt en ook de omgang en invloed op het dagelijks leven. De belangrijkste conclusie van alle patiëntenverenigingen: "Belangrijk dat wij er bij betrokken worden."

Zoals één van de ouders zei: "Deze resultaten moeten aanleiding geven tot vervolgonderzoek." De eerste stap is gezet, op naar een betere toekomst voor kinderen zoals **Luuk**.

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LIST OF ABBREVIATIONS

aEEG	amplitude-integrated electroencephalogram
AIMS	Alberta Infant Motor Scale
AUC	area under the curve
BSID	Bayley Scales of Infant and Toddler Development
BS	burst suppression
BHT	butylated hydroxytoluene
CO_2	carbon dioxide
CAKUT	congenital anomalies of the kidney and urinary tract
CA	cerebral autoregulation
CBF	cerebral blood flow
CDH	congenital diaphragmatic hernia
CLV	continuous low voltage
CNV	continuous normal voltage
CI	confidence interval
CT	computed tomography
cUS	cranial ultrasonography
DNV	discontinuous normal voltage
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
EA	esophageal atresia
ECMO	extracorporeal membrane oxygenation
$etCO_2$	end-tidal carbon dioxide
etSevo	end tidal sevoflurane
FiO_2	fraction of inspired oxygen
FT	flat trace
FTOE	cerebral fractional tissue oxygen extraction
GA	gestational age
GABA	gamma-Aminobutyric acid
HHb	deoxygenated hemoglobin
HR	heart rate
IBI	interburst interval
ISI	inter SAT interval
IVH	intraventricular haemorrhage
FiO_2	applied fraction of inspired oxygen
LGEA	long gap esophageal atresia
M-ABC	Movement Assessment Battery for Children

MABP	Mean Arterial Blood Pressure
MAC	Minimal Alveolar Concentration
MAP	Mean Airway Pressure
MDI	Mental Development Index
MRI	Magnetic Resonance Imaging
NA	not applicable
NCCA	non-cardiac congenital anomalies
NICU	Neonatal Intensive Care Unit
NIRS	Near Infrared Spectroscopy
NPBI	non-protein bound iron
NR	not relevant
NS	not significant
O2Hb	oxygenated hemoglobin
OR	operating room
PDI	Psychomotor Development Index
PI	perfusion index
PICU	Paediatric Intensive Care Unit
PMA	postmenstrual age
PT	pneumothorax
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PWML	punctate white matter lesions
ROC	receiver operating characteristic curves
RR	respiration rate
ROS	reactive oxygen species
$rScO_2$	regional cerebral oxygen saturation
SaO_2	arterial saturation
SAT	Spontaneous Activity Transient
SD	Standard Deviation
SWC	sleep-wake cycling
SWI	susceptibility weighted imaging
TEF	tracheo-esophageal fistula
UPJ	ureteropelvic junction obstruction
VACTERL	vertebral, anorectal, cardiovascular, tracheoesophageal, esophageal, renal and/or radial, limb anomalies
VUR	vesicoureteral reflux
ρ	correlation

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CURRICULUM VITAE

Lisanne Stolwijk was born on April 22nd 1987 in Utrecht, The Netherlands and grew up in De Meern. After graduating secondary school at the Christelijk Gymnasium Utrecht she started medical school in 2006 at the University of Amsterdam. In 2010 she did an internship at the editorial office of Medisch Contact, medical journalism for doctors, after which she continued writing about her experiences during her internships in a blog for Arts in Spe. Her first acquaintance with medical research was during her internship in Haemophilia Centre, Royal Brisbane and Women's Hospital, with dr. John Rowell in Australia. During medical school she started doing research at the department of Neonatology and Paediatric Surgery under the supervision of dr. Roel Bakx and dr. Wes Onland. In 2013 she did a clinical elective in the Great Ormond Street Hospital in London, at the department of Paediatric Anesthesiology under supervision of dr. Mike Sury. Directly after graduating medical school she started her PhD position at the department of Paediatric Surgery and Neonatology of the University Medical Center (UMC) Utrecht, supervised by prof. dr. D.C. van der Zee, prof. dr. M.J.N.L. Benders, Dr. P.M.A. Lemmers and Dr. M.Y.A. van Herwaarden-Lindeboom. She completed her thesis early 2017 and has since started working as a resident in paediatrics at Flevoziekenhuis, Almere.

CURRICULUM VITAE

Lisanne Stolwijk is geboren op 22 april 1987 te Utrecht en opgegroeid in De Meern. Na haar middelbare school (Christelijk Gymnasium Utrecht) begon zij in 2006 met de studie Geneeskunde aan de Universiteit van Amsterdam. In 2010 heeft zij een stage bij Medisch Contact gedaan, waarna ze het schrijven voortzette door haar belevenissen bij te houden in een blog voor Arts in Spe. Haar eerste kennismaking met onderzoek was gedurende haar wetenschappelijke stage in Haemophilia Centre, Royal Brisbane and Womens Hospital, bij dr. John Rowell in Australië. Tijdens haar studie deed zij onderzoek op de afdeling neonatologie en kinderchirurgie van het AMC en het Vumc naar necrotiserende enterocolitis, onder begeleiding van dr. Roel Bakx en dr. Wes Onland. Ook deed zij een clinical elective bij de kinderanesthesiologie in the Great Ormond Street Hospital in Londen en haar oudste co-schap kindergeneeskunde in het Flevoziekenhuis, Almere. Direct na haar afstuderen startte zij het promotietraject op de afdeling kinderchirurgie en neonatologie in het Wilhelmina Kinderziekenhuis onder begeleiding van prof. dr. D.C. van der Zee, prof. dr. M.J.N.L. Benders, Dr. P.M.A. Lemmers en Dr. M.Y.A. van Herwaarden-Lindeboom. In februari 2017 is Lisanne gestart als arts-assistent kindergeneeskunde in het Flevoziekenhuis.

DANKWOORD

Het verlossende telefoontje kwam terwijl ik de afwas*shift* draaide op Wimbledon. Met mijn armen diep in een gigantische pan met aangekoekte *'scrambled egg's'* ging de telefoon en ik zag dat het een nummer uit Utrecht was. Ik mocht promotieonderzoek doen, de start van een nieuw avontuur. Ik dacht dat mijn werk op het beroemde Londense tennistoernooi een prachtige ervaring was. Nooit had ik verwacht dat een promotietraject zo bijzonder is en zoveel onvergetelijke momenten zou geven. Het doen van onderzoek en het schrijven van wetenschappelijke artikelen is kenmerkend aan een promotietraject. Mijn eigen grenzen verleggen, de vele bijzondere ontmoetingen met nieuwe mensen, het omgaan met teleurstellingen en nog zoveel meer zijn echter ook onlosmakelijk met mijn promotietraject verbonden. Mede door het multidisciplinaire karakter van mijn onderzoek heb ik de kans gehad op ongelooflijk veel (buitenlandse) congrespodia te presenteren. De spil zijn van drie verschillende disciplines maakte de discussie en vragen op ieder platform interessant. In onze poging aandacht te creëren voor deze kwetsbare patiëntengroep zijn er veel mensen voorbijgekomen, die ik nu wil bedanken.

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Faith is taking the first step even when you don't see the whole staircase.

- Martin Luther King, Jr. -

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Dear Mike Sury, my first acquaintance with clinical research was during my clinical elective in the Great Ormond Street Hospital. Each day you gave me homework 'to think about'. With illustrative articles you showed me what research is, like an RCT for jumping out of a plane with or without a parachute. We started small with our survey in infants and what a great result we achieved by publishing our article. I really appreciate that you will be present during my thesis defence.

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"It always seems impossible until it's done."

- Nelson Mandela -

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A dream doesn't become reality through magic; it takes sweat, determination and hard work.

Colin Powell

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