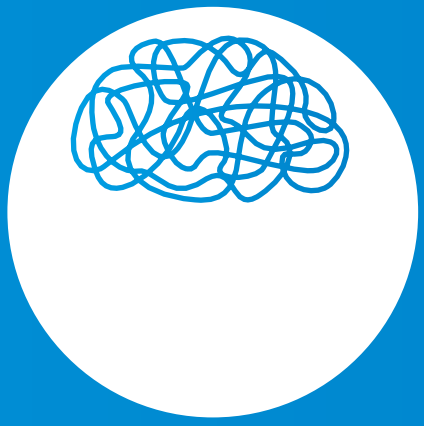

Under the surface

Perioperative pathophysiology of the surgical newborn

Sophie Costerus

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Under the surface

Perioperative pathophysiology of the surgical newborn

Onder het oppervlak
De perioperatieve pathofyiologie van de chirurgische neonaat

Proefschrift

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

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Under the surface

Introduction

1. General introduction
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1
General introduction

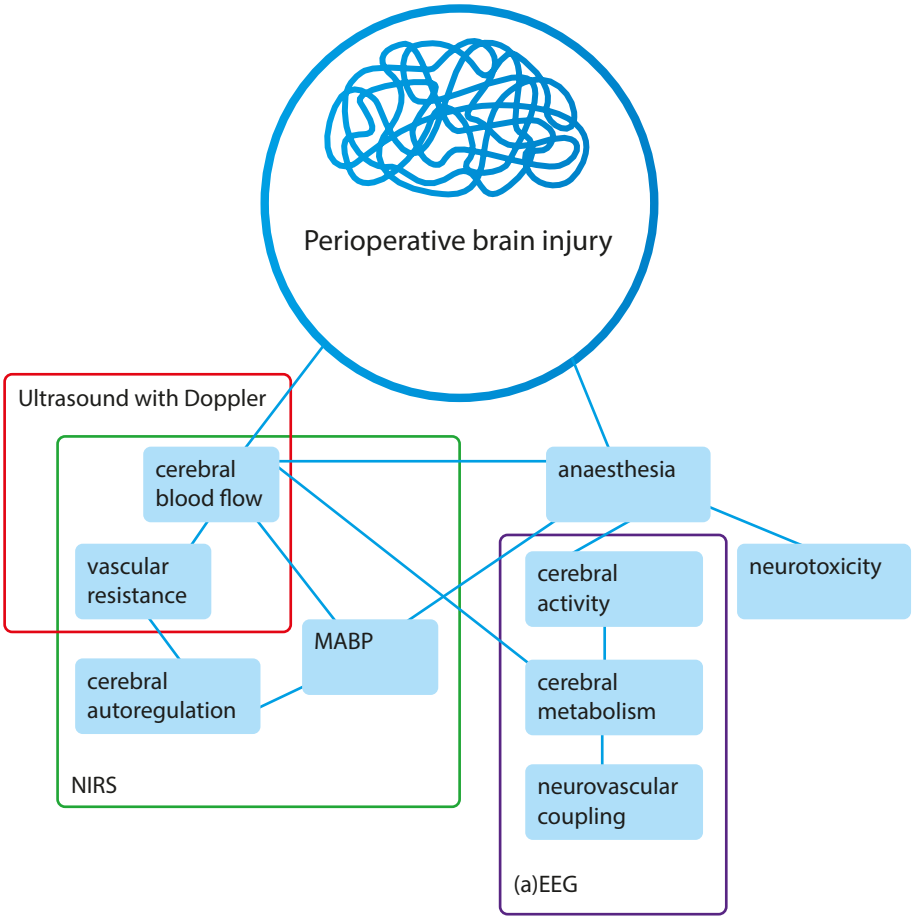

Figure 1. Overview of the parameters which are possibly involved in triggering perioperative brain injury.

1.1. Introduction

In the beginning of this century it became clear that infants who had surgery at neonatal age are at risk of altered neurodevelopment[1]. Since then, multiple studies have reported about the long term follow-up of the non-cardiac surgical newborn and showed impaired long-term neurodevelopmental outcome as well[2,3,4,5,6]. The vast majority of the neonates who are born with a (major) non-cardiac anomaly that requires surgical treatment within the first days of life are born with a normal brain without structural or genetic abnormalities and could

therefore not explain the reported impaired long-term neurodevelopmental outcome.
The possibility that the origin of altered neurodevelopmental outcome could lie in the perioperative period started to be acknowledged after a case series of six infants with severe postoperative encephalopathy[7]. This study showed that neonates can develop severe brain injury in the perioperative period, even during relatively minor surgical procedures[7]. Recently, the striking high incidence - 58% in full-term to 75% in preterm neonates - of brain abnormalities observed on MRI seven days after a broad range of non-cardiac surgical procedures was reported[8]. Another MRI study in teenagers who had surgery during infancy showed broadly distributed, decreased white matter integrity and volume[9]. All of this led to the concept that the surgical newborn is at risk of brain injury during the perioperative period.
Hypotheses about the origin of perioperative brain injury and postoperative encephalopathy were formed, including alterations in perioperative cerebral perfusion[10] as well as neurotoxicity of the anaesthetics itself [11] (figure 1).
Detailed monitoring of the brain is the first step to unravel possible triggers for perioperative brain injury. To date, routine perioperative monitoring includes heart rate, (invasive) blood pressure, oxygen saturation and end-tidal carbon dioxide monitoring. However, they lack sensitivity to detect altered cerebral perfusion.

1.1.1. Cerebral blood flow

Cerebral blood flow is affected by changes in blood pressure and cerebral vascular resistance which are all influences by PaO_2 and $PaCO_2$, and vasoactive/inotropic medication and anaesthetics [10,12,13,14].
The current rule of thumb that is used for reference values of mean arterial blood pressure (MABP) in neonates is: mean arterial blood pressure = gestational age in weeks. MABP monitoring plays an important role in the prevention of on one hand hypoperfusion and subsequently hypoxia of the brain and on the other hand hyperperfusion which may lead to intracranial haemorrhages[15]. The ability of the brain to maintain constant cerebral blood flow during changes in blood pressure is referred to as cerebral autoregulation and is affected by all of the above-mentioned variables[13]. During anaesthesia, a broad range of MABP

values are observed[16]. However, the knowledge whether these values meet the demands of the anesthetized neonatal brain is lacking. Furthermore, anaesthetics mediate vasodilation in the body and the brain[17]. Vasodilatation in the body can be observed by a reduction in MABP, but current monitoring lack the sensitivity to monitor alterations in brain perfusion[18].

Fluctuations in arterial carbon dioxide tension might affect the perfusion of the brain as well. Neonates are prone for respiratory acidosis due to limited cardiopulmonary coping capacity[19,20]. Besides, a popular surgical approach in neonates is thoracoscopic surgery[21]. This approach has potential benefits such as less surgical trauma and faster postoperative recovery. A major disadvantage is the respiratory acidosis as a results of intraoperative carbon dioxide insufflation that is required to create surgical workspace[21]. Yet, the effect of hypocapnia and hypercapnia on cerebral perfusion is virtually unknown in anesthetised neonates[12]. Research with transcranial Doppler ultrasound of the middle cerebral artery during hypercapnia in anesthetized adults showed increased cerebral blood flow velocities and decreased vascular resistance, whereas hypocapnia had the opposite effects[22].

Vasoactive and inotropic medication could mediate changes in vascular resistance in the brain as well. So far, no data about the effect of vasoactive and inotropic medication on cerebral perfusion in neonates have been reported. Nonetheless, a study about memory and attention deficits in 8-year-old survivors of neonatal extracorporeal membrane oxygenation and CDH survivors found that the maximum dose of vasoactive medication was negatively associated with verbal and visuospatial memory[3]. This might suggest that it has effect on the neonatal brain, one way or the other.

Anaesthesia reduces cerebral activity and subsequently cerebral metabolism. As a result, the oxygen consumption of the brain decreases. Cerebral blood flow is triggered by the oxygen demand of the brain[23]. This regulatory mechanism is commonly referred to as neurovascular coupling. In here, cerebral blood flow increases if cerebral oxygen consumption increases to meet the oxygen transport[24]. The most commonly used anaesthetic approach in neonates during surgical procedures is sevoflurane anaesthesiology. Cerebral metabolism is reduced during sevoflurane anaesthesia and a recent study showed that a higher sevoflurane dose significantly correlated with more suppressed background patterns[25]. To date, little is known about the effect of anaesthesia and decreased cerebral activity on neurovascular coupling.

1.1.2. Neurotoxicity

Besides the altered perioperative neonatal physiology, there is a growing concern related to the effect of exposure to anaesthetic agents in young children. In the nineties, the idea was that anaesthetics could be neuroprotective due to a decrease in cerebral metabolism[26]. This is changed towards the hypothesis that anaesthetics in newborns could be neurotoxic. These concerns were raised after the neurotoxic effect of anaesthetics in at least young animals were proven[27,28,29]. Although clinicians found these data clinically difficult to interpret[30,31,32,33,34], the Food and Drug Administration (FDA) Science Board did warn about potential lasting neurotoxic effects of anaesthetic agents[35]. The lack of an obvious phenotype for anaesthetic neurotoxicity and confounding by indication represents a major obstacle to study design and interpretation. In addition, tests for neurodevelopment outcome lack sensitivity to distinguish between the effect of altered neonatal physiology or possible neurotoxic effect of the anaesthetic agent, which made it even harder to investigate[36]. The only clinical trial so far (GAS study, NCT00756600) followed children who had either general anaesthesia or regional anaesthesia for less than 1 hour only for inguinal hernia repair before 60 weeks post-conceptional age. They showed no difference in cognitive development at the age of 2 and 5 years[37,38]. No conclusions can be drawn for children who undergo anaesthesia for more than 1 hour and especially not for neonates/children with cardiopulmonary anomalies/deficits during major high risk surgical procedures[37,38].

1.2. Monitoring

The complex interactions between cerebral oxygenation, activity and perfusion in the perioperative period might play a crucial role in triggering perioperative brain injury[39]. It is therefore of utmost importance to focus on current practice, including perioperative management and monitoring modalities of the brain. Despite state-of-the-art care, anaesthetic monitoring lacks sensitivity to detect altered cerebral perfusion during high-risk neonatal surgery[10]. In the neonatal intensive care, concise brain monitoring is multimodal and includes modalities

that present measures for both brain oxygenation, activity and perfusion (figure 2). This approach might help to create insight in the etiology of the perioperative brain injury. Cerebral oxygenation can be measured with near-infrared spectroscopy (NIRS), cerebral activity can be measured with (amplitude integrated) electroencephalography ((a)EEG) and cerebral perfusion can be measured with transfontanellar ultrasound with Doppler.

1.2.1. NIRS

For brain oxygenation, a user friendly, portable device has been developed, based on the principle of near-infrared spectroscopy (NIRS). Biological tissue is relatively transparent to near-infrared light, which allows the light to penetrate several centimetres into the tissue and illuminate the brain of neonates. This non-invasive technique measures underlying regional cerebral tissue haemoglobin oxygen saturation ($rSCO_2$) using a sensor that is commonly placed on the forehead on the neonate. $rSCO_2$ reflects the oxygenation of the venous (70-80%), capillary (5%) and arterial (20-25%) blood and is therefore mainly used as a surrogate for the measurement of the venous oxygen saturation[40]. Neonatal reference values are generated in the SafeboosC trial, which concluded that these values have a broad range between 55 and 80%[41]. Validated NIRS guided treatment guidelines/ protocols are almost not available, with the exception of its use during cardiac surgery[42].

1.2.2. EEG

Brain activity is generally quantified using electroencephalography (EEG), both in conventional and amplitude-integrated format (aEEG). EEG, an electrophysiological technique, measures the electrical activity of the brain cortex[43]. In the neonatal intensive care unit, aEEG is commonly used to monitor the brain during hypoxic ischemic encephalopathy and therapeutic hypothermia, due to its high prognostic value[44,45]. Therefore, it may also be helpful and informative in infants with encephalopathy of varying etiologies[46,47].

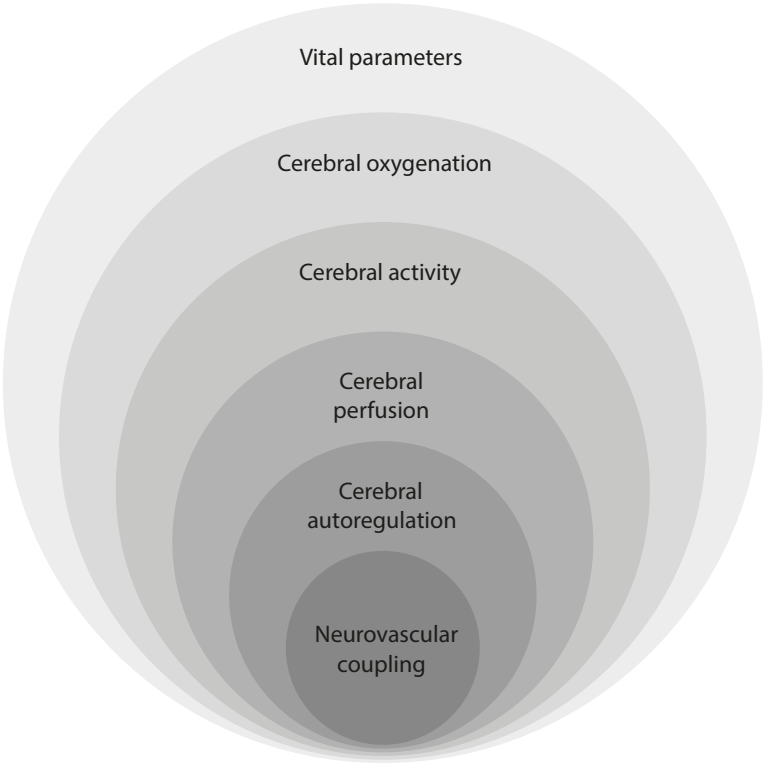

Figure 2. Structure of multimodal/integrative (neuro)monitoring.

1.2.3. Ultrasound with Doppler

Transfontanellar ultrasound with directional power Doppler and pulsed wave Doppler allow imaging real-time cerebral perfusion and quantifying cerebral blood flow velocity (CBFV) in large arteries or veins. This technique is particularly feasible in neonates because of the open anterior fontanel[48], and is frequently used in the neonatal intensive care to screen for intracranial haemorrhages or thrombosis. Five years ago measuring CBFV has been introduced during neonatal cardiac surgery under cardiopulmonary bypass[49,50].
The overall concept underlying this thesis is to create insight in the neonatal physiology and the triggers for perioperative brain injury by implementing these three monitoring modalities, alongside routine perioperative monitoring and

adding mathematical models to compute the cerebral blood flow regulation mechanism (figure 2).

1.3. Aims and outline of this thesis

The aim of this thesis is to provide insight in the altered neonatal physiology in the perioperative period. Firstly, a review about perioperative neonatal neuromonitoring (chapter 2) provides the current knowledge about neonatal neuromonitoring and explores potential additional monitoring modalities. This is followed by, current perioperative and surgical management and its effects on the neonatal physiology (chapter 3, 4 and 5).
The second part is about perioperative neuromonitoring. In here, the feasibility of perioperative cerebral blood flow monitoring is explored (chapter 6) as well as the feasibility to measure cellular oxygenation in neonates (chapter 7). By combining the different monitoring modalities an integrative neuromonitoring approach is created. The different modalities are computationally bundled to provide information about the effect of anaesthetics on the neonatal physiology (chapter 8) and on the autonomic nervous system (chapter 9). On top of this, all parameters and modalities are combined to provide an overview of the neonatal (patho)physiology in the perioperative period (chapter 10). Finally, the results of this study are discussed and placed in a broader perspective (chapter 11).

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2

Towards integrative neuromonitoring of the non-cardiac surgical newborn: a systematic review

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Abstract

Background. The altered neurodevelopment of children operated on in the neonatal period might be due to perioperative changes in the homeostasis of brain perfusion. Monitoring of vital parameters is standard of care, but it usually does not include monitoring of the brain.

Objectives. To evaluate methods with potential and/or suggested additional value towards monitoring of the brain. In addition, we want to clarify if there are specific risk factors resulting in perioperative changes and how this can be evaluated.

Design. Systematic review.

Data sources. A structured literature searchwas performed in MEDLINE in Ovid, Embase, Cochrane CENTRAL, Web of Science and Google Scholar.

Eligibility criteria. Studies in neonates who received perioperative neuromonitoring were eligible for inclusion; studies on neurosurgical procedures or cardiac surgery with cardiopulmonary bypass and/or deep hypothermia cardiac arrest were excluded.

Results. Nineteen of the 24 included studies, totalling 374 infants, reported about the use of near-infrared spectroscopy. Baseline values of cerebral oxygenation greatly varied (mean 53% to 91%) and consequently, no coherent results were found. Two studies found a correlation between cerebral oxygenation and mean arterial blood pressure. Five studies, with in total 388 infants, used (amplitude-integrated) electroencephalography to study perioperative brain activity. Overall, the brain activity decreased during anaesthesia and epileptic activity was more frequent in the perioperative phase. The association between intraoperative cerebral saturation or activity and neuroimaging abnormalities and/or neurodevelopmental outcome was investigated in six studies, but no association was found.

Conclusion. Neuromonitoring with currently used techniques will neither help to better understand the altered neonatal pathophysiology, nor enable early

detection of deviation from the norm. The modalities lack specificity and are not related to clinical (long-term) outcome or prognostics. This led to the inability to draw up a monitoring guideline.

2.1. Introduction

The past decades have seen improved outcomes of the operative treatment and non-operative treatment and care for the surgical newborn with congenital anomalies[1]. Survival rates increased due to changes in resuscitation time, optimization of homeostasis preoperatively, and subsequently better surgical timing and approach[2,3]. Yet, the few studies that investigated long–term outcomes of neonatal surgery show impaired neurodevelopment[4,5,6,7]. Causes of impairment are largely unknown, but a previous study suggested a crucial role for the complex interactions between cerebral oxygenation, activity and perfusion in the perioperative period[8].

Monitoring of vital parameters as a surrogate for end-organ perfusion is standard of care, but it usually does not include monitoring of the brain, except in neonatal cardiac surgery with cardiopulmonary bypass, where, perioperative neuromonitoring is advocated in view of the high risk of brain injury and the existence of abnormal cerebral flow antenatally in some complex cardiac anomalies[9,10]. No valid indications for neuromonitoring of the non-cardiac surgical newborn are reported. However, a recent study also reported a high incidence, 58% in full-term born infants, of anatomical signs of brain injury on MRI after non-cardiac neonatal surgery as well[11]. Hence, surgical newborns may be prone to perioperative brain injury, although it is not clear from previous research whether these injuries occured in the pre-, intra- or postoperative period. Yet, after birth, the biggest changes in the neonatal physiology might occur in the intraoperative period.

The brain can be monitored during surgery and anaesthesia by means of various techniques, such as near-infrared spectroscopy (NIRS), (amplitude-integrated) electroencephalography ((a)EEG), or cerebral Doppler ultrasound (CDU). Measurements with these techniques alongside continuous vital parameter measurements can provide insight into the altered physiology of the surgical

newborn and their brain in the perioperative period. However, a systematic evaluation of indications and treatment algorithms for neuromonitoring is lacking. The aim was to evaluate methods with potential and/or suggested additional value towards monitoring of the brain. In addition, we want to clarify if there are specific risk factors resulting in perioperative changes and how this can be evaluated.

2.2. Methods

2.2.1. Eligibility criteria

We performed a structured literature search to identify clinical studies using perioperative neuromonitoring in neonates, defined as children under 90 days of life or postmenstrual age less than 52 weeks. The search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[12,13]. The studies needed to be originally published in a peer-reviewed journal. Limits were set on human and English-language studies. Studies were excluded if the article did not match the inclusion criteria; if the article was a case report; if the surgical procedure was neurosurgery or cardiac surgery with cardiopulmonary bypass and/or deep hypothermia cardiac arrest; or if the article did not contain original patient data.

2.2.2. Information sources

The search strategy included expanded Medical Subjects Headings (MeSH) terms and predefined search terms (see appendix 2.1). On 11 December 2018, the electronical literature search was performed in MEDLINE in Ovid (PubMed), Embase, Cochrane CENTRAL, Web of Science and Google Scholar.

2.2.3. Search

The following search terms were used for Medline Ovid: (General Surgery/ OR exp "Surgical Procedures, Operative"/ OR (surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*).ab,ti.) AND (electroencephalography monitoring/ OR neuromonitoring/ OR near infrared spectroscopy/ OR cerebral oximeter/ OR electroencephalogram/ OR brain function/ OR (EEG OR aEEG* OR NIRS OR ((near*-infrared*) ADJ (spectro*)) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) ADJ3 (monitor*)) OR ((cerebr* OR brain*) ADJ3 (oximeter* OR oxygenat*)) OR electroencephalogram*).ab,ti.) AND (infant/ OR neonatology/ OR neonatal intensive care unit/ OR pediatric surgery/ OR (infan* OR newborn* OR new*-born* OR baby OR babies OR neonat* OR child* OR NICU).ab,ti.) NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.lg. NOT (exp animals/ NOT humans/). The full search is added as appendix 2.1.

2.2.4. Study selection

After removing the duplicates of the retrieved citations, two authors (SC and CvH) independently screened the titles and abstracts of the remaining citations on relevance, and reviewed the full texts of eligible articles on inclusion criteria (figure 3). All studies were methodological scored (table 5, appendix 2.2).
The following data was extracted: study design, sample size, study patient characteristics, modality, device and period of neuromonitoring, results of neuromonitoring, outcome and – if applicable – the follow-up data.

2.3. Results

2.3.1. Structured literature search

The systematic search retrieved 7963 records (figure 3), of which 24 articles met the inclusion criteria. All studies had a prospective observational design and were methodological scored (table 5, appendix 2.2). The median sample size was 16 (range 5 to 226) and the total number of children studied was 762 (tables 1 and 2). Nineteen studies used NIRS[14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32]. Fourteen of these measured only cerebral oxygenation and five combined cerebral oxygenation with cerebral blood flow or cerebral autoregulation (table 1). Five studies used aEEG – in four to measure cerebral activity[33,34,35,36] and in one, a large cohort study, to detect epileptic activity only[37] (table 2).
Clinical outcome was reported in five studies. Postoperative neuro-imaging was performed in three of these studies[20,35,38], in one of which the findings of the neuro-imaging were combined with neurodevelopmental outcome at the age of 2 years[38]. The two other studies reported about neurodevelopmental outcome[26,29] (table 4).

2.3.2. NIRS - cerebral oxygen saturation

Nineteen of the 24 included studies made use of NIRS (table 1). All but one monitored the patients over time, most commonly starting before surgery and continuing until end of surgery (table 3). The reported mean and median baseline NIRS values range widely (table 3). Results of the four studies that investigated the effect of ligation of (hemodynamic significant) patent ductus arteriosus ((hs) PDA) on cerebral oxygenation conflict: one reported no significant changes after ligation, one a significant decline, and two a significant increase in cerebral oxygenation after ligation[16,17,18,19] (table 3). The other studies concern different types of surgical approach. Four studies investigated NIRS during open abdominal surgery; one during laparoscopic surgery, and two during thoracoscopic surgery. Two studies did not specify the surgical approach. In these studies, measurements at different perioperative moments in the periods where compared with each

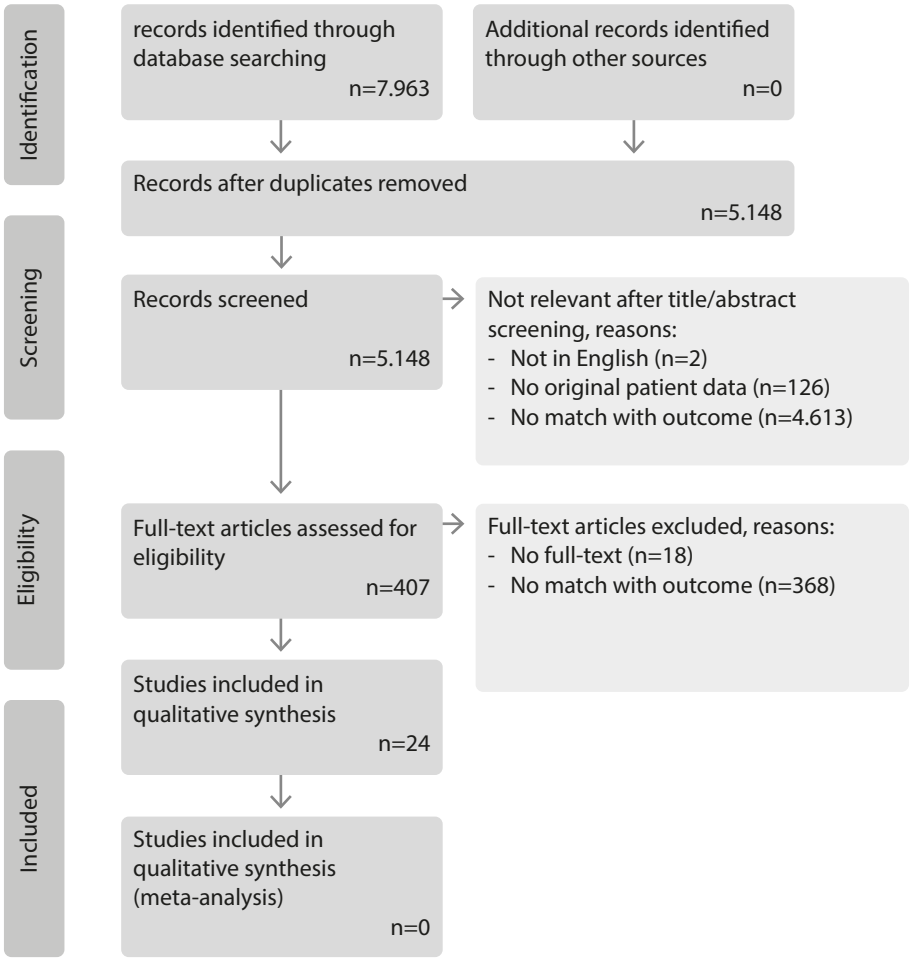

Figure 3. PRISMA flow diagram of manuscript selection.

other; coherent results were not found (table 3). Five studies showed a significant decrease in cerebral oxygenation; four a significant increase; and eight no significant change.

Table 1. Overview of included studies reporting about NIRS as intraoperative neuromonitoring technique

Demographics								Measurement			Results		
Study	N	Device	Pathologies	Surgery	Age at surgery (d)	GA (wk)	BW (kg)	Cerebral oxygenation	Cerebral blood flow	Cerebral autoregulation	Comparison over time	Neuro-imaging	Neuro-development
Fortune et al. 2001 [18]	49	NIRO-300	Acute abdomens	NR	Neonatal age, not specified	26.8-40.0‡	1100-4000‡	X					
Dotta et al. 2005 (19)	25	NIRO-300	CDH	Laparotomy	3.5*±2.5 (2-14)‡.	37.8*±1.8	3057*± 354	X			X		
Zaramella et al. 2006 (20)	16	NIRO-300 + CDU	PDA	Ligation	7-29‡	27.3* (24-34)‡	1036* (680–1740) ‡	X	X		X		
Hüning et al. 2008 (21)	10	NIRO-300	PDA	Ligation	14† (12–22)	24† (23–27)‡	748† (590–1070)‡		X		X		
Vanderhaegen et al. 2008(22)	10	INVOS	PDA	Ligation	33*±30.9 (6–88)‡	27*±2.64 (24–32)‡	987.5*±391 (555–1855) ‡	X			X		
Chock et al. 2011 (23)	12	INVOS	PDA	Ligation	16*±9	26*±1	841*±159	X			X		
Chock et al. 2012 (24)	10	INVOS	PDA	Ligation	NR	26*±1	830*±170		X	X	X	x	
Conforti et al. 2014 (25)	13	INVOS	OA	Laparotomy	NR	33 - 41+5‡	1170-3740‡	X			X		
Michelet et al. 2015 (26)	60	INVOS	Emergency thoracic or abdominal surgery, CVC insertion, urological procedures, imperforate hymen, pharyngeal teratoma and endoscopy	NR	22*±22	37*±4	NR	X			X		
Tytgat et al. 2015 (27)	12	INVOS	HPS	Laparoscopy	38† (15-62)‡	39†(36-41)‡	3500† (2400-4400)‡	X			X		
Conforti et al. 2016 (28)	13	INVOS	CDH	Laparotomy	3† (2-9)‡‡	38† (35-40)‡‡	3055† (2660-3620)‡‡	X			X		
Koch et al. 2016 (29)	21	NIRO-300	CDH, OA, intestinal atresia's, omphalocele, PDA, HPS, circumcision, oophorectomy	NR	12.8*±10.1	35.7*±5.4	2878*±1002	X			X		

Demographics								Measurement			Results		
Study	N	Device	Pathologies	Surgery	Age at surgery (d)	GA (wk)	BW (kg)	Cerebral oxygenation	Cerebral blood flow	Cerebral autoregulation	Comparison over time	Neuro-imaging	Neuro-development
Razlevice et al. 2016 (30)	43	INVOS	General, thoracic or urologic surgery for congenital anomalies or disease	NR	6† (0-70)‡	38† (25–41)‡	3400† (800–5000)‡	X			X		X
Tytgat et al. 2016 (31)	15	INVOS	OA	Thoracoscopy	2†(1-7)‡	39† (36-42)‡	2962† (2155-4490) ‡	X			X		
Beck et al. 2017 (32)	19	INVOS	Gastroschisis, omphalocele, CDH, OA, NEC, neonatal bowel obstruction, abdominal tumour	NR	2† ±5‡‡	38† ±6.1‡‡	2945† ±801‡‡	X	X		X		
Costerus et al. 2017 (33)	10	INVOS	CDH, OA	Thoracoscopy	1.3-4.5‡	34-40.2‡	1941-3338‡	X			X		X
Stolwijk et al. 2017 (34)	5	INVOS	LGOA	Thoracoscopy	4† (2–53)‡	35+3† (33+4 to 39+6)‡	1580-2825	X			X	X	X
Nissen et al. 2017 (35)	12	INVOS	HPS	NR	43† (20-74)‡	38† (35-40)‡	3105† (2380-4000)‡	X			X		
Kuik et al. 2018 (36)	19	INVOS	NEC, SIP	Laparotomy	9† (7–12) ‡‡	27.6† (26.6–31.0) ‡‡	1090† (924–1430) ‡‡	X		X	X		

NR: not reported, CDH: congenital diaphragmatic hernia, OA: oesophageal atresia, LGOA: long gap oesophageal atresia, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, CVC: central venous catheter, SIP: spontaneous intestinal perforation, HPS: hypertrophic pyloric stenosis,

* : mean ± standard deviation, † :median, ‡ :range, ‡‡: IQR,

Table 2. Overview of included studies reporting about (a)EEG as intraoperative neuromonitoring technique

Demographics								Measurement					Results
Study	N	Device	Pathologies	Surgery	Age at surgery (d)	GA (wk)	BW (kg)	Cerebral oxygenation	Cerebral blood flow	Cerebral autoregulation	Comparison over time	Neuro-imaging	Neuro-development
Kohelet et al. 2004 (41)	226	EEG, NR	NEC, PDA	Ligation or laparotomy	NR	>24	Very low birthweight		X				
Kasdorf et al. 2013 (37)	17	Olympic CFM 6000 Infant aEEG Cerebral Function Monitor	PDA	Ligation	24*±13 (8-55)‡	26.6*±3.4 (22.6-35.1)‡	867*±337 (538-1735)‡	X			X		
Leslie et al. 2013 (38)	17	Cerebral Function Monitor aEEG	PDA	Ligation	27† (14–42)‡	25† (23–27) ‡	680† (500–1140) ‡	X			X		
Stolwijk et al. 2017 (39)	111	BrainZ Monitor aEEG	OA, abdominal wall defects, intestinal atresia/ volvulus, anorectal malformation, urogenital malformation	NR	2† (0-32)‡	38.28† (28–42)‡	NR	X	X	X	X	X	
Cornelissen et al. 2018 (40)	17	Waveguard EEG cap & EMU40EX; Natus Medical Incorporated	Elective surgery	NR	2.9† (2.6-3.5) ‡‡ months	NR	NR	X					

NR: not reported, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, OA: oesophageal atresia, *: mean ± standard deviation, †: median, ‡: range, ‡‡: IQR,

Table 3. Studies using NIRS and reporting the changes in rSO_2

Study	Type of surgery	Type of sensor	Baseline values (%)	Comparison between different time points		Significant change rSO_2	Significant change MABP
Dotta et al (2005)	Laparotomy	50mm interoptode separation	NR	Begin surgery	End surgery	↓	NS
Zaramella et al (2006)	Ligation PDA	NR	61.6 (3.8)**	Before ligation	After ligation	↓	NS
Hüning et al (2008)	Ligation PDA		53±15*	Changes during closure		NS	NS
Vanderhaegen et al (2008)	Ligation PDA	40mm interoptode separation (large)	NR	Before ligation	After ligation	↑	NS
Chock et al (2011)	Ligation PDA	Neonatal sensor	63±13*	Before ligation	After ligation	↑	NR
Conforti et al (2014)	Laparotomy	Paediatric sensor	NR	Before surgery	During vs after surgery	NS	NR
Michelet et al (2015)	NR	NR	78±10*	NR	NR	NR	NR
Tytgat et al (2015)	Laparoscopy	Small adult sensor	68±15*	Before insufflation	During and after cessation	NS	↑
Conforti et al (2016)	Laparotomy	Paediatric sensor	HFO 81† (70-98)‡‡	Before surgery	During surgery	↑	NR
			CMV 82† (76-91)‡‡				
Tytgat et al (2016)	Thoracoscopy	Small adult sensor	77±10*	After induction	After CO_2 insufflation	↓	NS
Beck et al (2017)	NR	Neonatal sensor	79.11±9.92*	Changes during surgery		NS	NR
				0 hours postoperative	24 hours postoperative	NS	NR
Costerus et al (2017)	Thoracoscopy	Neonatal sensor	CDH 82*	Before surgery	During surgery	NS	↓ 30 min after insufflation & ↑ after 90 and 120 min insufflation
			OA 91*				NS
Nissen et al (2017)	NR	Neonatal sensor	77.89±5.84*	Before surgery	After surgery	↑	NR
Kuik et al (2018)	Laparotomy	Neonatal sensor	NR	Before surgery	During surgery	NS	NS
				During surgery	After surgery	↑	NS

NR: not reported, NS: not significant, PDA: patent ductus arteriosus, CDH: congenital diaphragmatic hernia, OA: oesophageal atresia, HFO: high frequency oscillation, CMV: conventional mechanical ventilation, * : mean ± standard deviation,** mean (standard error) , † :median, ‡ :range, ‡‡: IQR,

Table 4. Results of neuroimaging and neurodevelopmental outcome

Demographics			Neuroimaging			Neurodevelopmental outcome		
Study	N	Device	Timing/Age	Type	Results	Test	Timing/Age	Results
Razlevice (2016)	43	INVOS, NIRS	NP	NP	NP	Clinically documented neurological function by paediatric neurologist	In-hospital follow-up (range 14 days- 6 months)	Desaturated group: declined in 3 patients Normal group: in normal range
Costerus (2017)	10	INVOS, NIRS	NP	NP	NP	BSID-II, MDI, PDI	24 months	All in normal range
Stolwijk (2017)	5	INVOS, NIRS	Preoperative Postoperative	Ultrasound MRI	2 patients with a small thalamic infarction	Griffith Mental Development Scales and BSID-III	24 months	All in normal range
Chock (2012)	10	INVOS, NIRS	Baseline Before discharge or hospital transfer	Ultrasound and MRI	25% increased abnormalities compared to baseline*	NP	NP	NP
Stolwijk (2017)	111	BrainZ Monitor aEEG	Preoperative Postoperative	Ultrasound MRI	10% intracranial lesions 58% parenchymal lesions and 37% non-parenchymal injury	NP	NP	NP

NP: not performed, NR: not reported, MRI: magnetic resonance imaging, *abnormalities not specified BSID-II or III: Bayley's Scales of Infant Development, MDI: mental developmental index, PDI: psychomotor developmental index

2.3.3. NIRS – correlations with other physiological variables

In the five studies that reported a decrease of cerebral oxygenation, three reported no significant changes in blood pressure[15,16,27] and two did not report blood pressure values[24,28]. In the four studies that reported an increase in cerebral oxygenation, two studies found no significant significant changes in blood pressure[18,32], and the other two studies did not report blood pressure values[19,31] (table 3). Four studies aimed to find associations for cerebral oxygen desaturations and other perioperative monitoring techniques[22,25,26,28]. One of these investigated the applicability of NIRS in neonates undergoing non-cardiac surgery by comparing the event rate of hypoxia (defined as SpO_2<90%,) measured with the conventional peripheral pulse oximeter with the event rate of hypoxia measured with NIRS (defined as >20% decline from rSO_2 baseline or an absolute decline in rSO_2 <40%, lasting for a minimum of 3 min) and found that NIRS events occurred two to three more often than hypoxia measured with the conventional peripheral pulse oximeter. During desaturation, the decline in SpO_2 was similar to that of cerebral oxygen saturation (rSO_2) in pattern and duration. Both SpO_2 and blood pressure were positively correlated with rSO_2 [25]. Other studies found that cerebral oxygen desaturation (defined as delta rSO_2 > 20% from baseline) occurred in almost 20% of the patients and that a decrease in rSO_2 values was associated with a decrease in mean arterial blood pressure[26]. Yet, another of these studies measured perioperative rSO_2 in 60 infants <3 months of age with 960 data points and found cerebral desaturations (defined as delta rSO_2 > 20% from baseline) in 6.1% data points. The data suggests that a decrease in systolic blood pressure of more than 20.5%, or a decrease in mean blood pressure of more than 15.5%, is associated with a decrease in cerebral oxygenation of more than 10%. Furthermore, at the measurement points where delta rSO_2 was > 20% from baseline, the absolute blood pressure was lower (62±15 mmHg) than that at the normally saturated measurement points (71±15 mmHg)[22]. By contrast, the fourth study – with 19 neonates during a variety of surgical procedures – reported intraoperative desaturations (defined as delta rSO_2 > 20% from baseline) in 6 (6.7%) of the measurement points and did not find a correlation between mean arterial blood pressure and cerebral rSO_2 [28]. An overview of physiological variables correlated to NIRS are shown in table 6, appendix 2.3.

2.3.4. NIRS - cerebral autoregulation

Two studies used NIRS to evaluate perioperative cerebrovascular autoregulation[20,32]. Chock et al. compared the effect of different treatments for hsPDA on cerebral autoregulation. Autoregulation impairment was defined as an increase in the pressure passivity index. This is calculated by the concordance between the mean arterial blood pressure (MABP) and rSO_2. Surgical ligation of the hsPDA was associated with an increased risk for impaired cerebral autoregulation in the first 6 hours after ligation compared to neonates who had a conservative treatment[20]. The other study concerned neonates undergoing abdominal surgery; impaired cerebral autoregulation was seen more frequently in the intraoperative period than in the pre- and postoperative periods. Elevated $PaCO_2$ as well as elevated end-tidal sevoflurane levels negatively affected the cerebral autoregulation[32].

2.3.5. NIRS – cerebral blood flow/volume

One study investigated the effect of PDA ligation on the cerebral tissue oxygenation index with NIRS and the cerebral blood volume and cerebral blood flow (CBF) velocity with cerebral Doppler ultrasound in relation to changes in arterial pH [16]. Overall, the cerebral tissue oxygenation index declined after PDA ligation, while the cerebral blood volume remained the same. Furthermore, both a lower pH and an increase in arterial CO_2 were found to be associated with an increase in CBF. In another study, cerebral blood volume changes directly after surgical closure of PDA were measured with NIRS [17]. Total hemoglobin corresponded to cerebral blood volume and was calculated by the sum of oxygentated haemoglobin and deoxygenated haemoglobin. Cerebral oxygenation decreased in the first minutes after ligation (table 3), although not significantly. Cerebral blood volume increased significantly in the first 2 minutes after ligation by a mean (SD) of 0.14 (0.12)ml per 100 grams tissue and returned to baseline within 2–5 minutes.

2.3.6. aEEG – cerebral activity

Interpretation of aEEG is based on pattern recognition of background activity[39]. One study in 111 neonates showed that overall the background pattern regressed two classes during surgery and anaesthesia compared to preoperatively[35]. Postoperatively, the trace returned to continuous normal voltage within 24 hours in 86% of the preterm and 98% of the term neonates. A higher sevoflurane dose was significantly associated with more suppressed background patterns. Furthermore, epileptic activity during surgery was seen in four of the 111 neonates, in one directly after starting sevoflurane induction. Postoperatively, epileptic activity was observed in eight neonates[35]. Another study aimed to determine the incidence of seizures in 6525 very low birthweight infants and to identify perinatal and postnatal factors associated with the occurrence of these seizures. Seizures had occurred in 23/95 (24%) of the infants operated on for PDA versus 10% of the conservatively treated infants and in 21/131 (16%) of the infants operated on for necrotizing enterocolitis versus 12% of the conservatively treated infants[37]. A third study, on age-related changes in EEG traces, showed that in neonates undergoing sevoflurane anaesthesia for elective surgery, slow-delta oscillations were present at all ages, but that theta and alpha oscillations emerged by approximately 4 months; seizures were not investigated[40].
Another study investigated if aEEG could be useful to detect pain during hsPDA ligation in preterm neonates and investigated the relation between vital signs and aEEG during anaesthesia. There was no correlation between vital signs and aEEG voltage; aEEG was suppressed during surgery and remained suppressed during the 2-hours postoperative monitoring; seizures were not investigated[33].
The fifth study investigated aEEG during ligation of hsPDA under fentanyl and rocuronium. During the procedure, the aEEG lower border of the background pattern trace decreased and continuity decreased. Five of the 17 neonates already had a discontinuous background pattern preoperatively and none demonstrated complete recovery of the lower margin 24 hours postoperatively[34].

2.3.7. Neuro-imaging and neurodevelopmental outcome

Neuro-imaging and neurodevelopmental outcome were reported in six studies (table 4). In a study in five children with long-gap oesophageal atresia, two of the children had postoperative intracranial abnormalities on MRI. Signs of changes resulting from altered cerebral perfusion (based on hypotension or hypocarbia) or cerebral oxygenation were absent in these two infants. All five children showed normal cognitive development and motor development at the age of 2 years (assessed with the Bayley Scales of Infant and Toddler Development, Third Edition and the Griffith Mental Development Scales)[38].

Two other studies examined perioperative neuromonitoring in relation to neurodevelopment after neonatal surgery. One examined the relation between cerebral desaturation (defined as at least once delta rSO_2 > 20% from baseline) during anaesthesia and neurologic function during clinical follow-up at 14 days till 6 months. Neurological function had deteriorated in three out of eight infants who had desaturated and in none of the 35 infants who had not desaturated. This deterioration might also be related to other clinical factors than perioperative cerebral desaturation, since all three infants with deteriorated neurological function had received cardiopulmonary resuscitation after birth. Moreover, two of them were born prematurely and had not undergone preoperative imaging. The absolute minimal rSO_2c value in the desaturation group was 66% (41.5–71%), versus 76.5% (60.5–90%) in the group without desaturation[26]. The other study reported NIRS values and neurodevelopmental outcome at the age of 2 years in seven infants after surgery for congenital diaphragmatic hernia and oesophageal atresie neonates. Correlations between intraoperative rSO_2 and neurodevelopmental outcome were not investigated[29].

Chock et al. performed MRI and/or cranial ultrasound in 40 infants after the diagnosis of PDA was made (baseline) and at discharge or hospital transfer, next to perioperative cerebral autoregulation measurements calculated by the pressure passivity index with NIRS as mentioned above. Ten infants showed worsening neuroimaging findings compared to baseline, of whom three were treated with indomethacin alone, four were surgically ligated after failed indomethacin closure, and three received primary surgical ligation. An association between impaired cerebral autoregulation and neuroimaging abnormalities was not found. The neurodevelopmental outcome of these infants was not reported[20].

Another study investigated perioperative aEEG in relation to MRI in 111 various non-cardiac surgical newborns. Preoperatively, 10% of the neonates had brain injury on ultrasound scan; 58% of all neonates had parenchymal lesions and 37% had non-parenchymal injury on the postoperative MRI. An association between MRI-abnormalities and type of aEEG background patterns was not found[35].

2.4. Discussion

This review included 24 articles reporting NIRS, aEEG and cerebral Doppler ultrasound as perioperative neuromonitoring modalities in infants less than 90 days of age undergoing surgery without cardiac bypass. Nineteen studies, with in total 374 infants, reported NIRS. These studies show a large heterogeneity in patient age, pathology, surgical approaches, practical clinical use and measurement timing. Furthermore, baseline values of cerebral oxygenation and definitions of hypoxia greatly varied. Clear associations between changes in cerebral oxygenation and vital parameters were not reported. Treatment algorithms for cerebral oxygenation were not found.
Five studies made use of aEEG studying perioperative brain activity – 388 infants in total. Overall, brain activity decreased and epileptic activity occurred more frequently in the perioperative phase. These studies also show a large heterogeneity in patient characteristics such as gestational age, birth weight and pathology.
Six studies investigated association between intraoperative cerebral saturation or activity and neuroimaging abnormalities and/or outcome. One reported impaired neurodevelopmental outcome after cerebral desaturation episodes[26]. A clear correlation with cerebral desaturation could not be established, however, as these infants had also received cardiopulmonary resuscitation. Another study showed that seizures are associated with a higher mortality rate in very-low-birth-weight neonates[37]. One study combined neuroimaging findings with neurodevelopmental outcome and found no impaired neurodevelopment in infants with intracranial pathology at the age of 2 [38].
Unfortunately, it was not possible to perform statistical analysis on the correlation between neuromonitoring and outcome due to limited data. Overall, there is

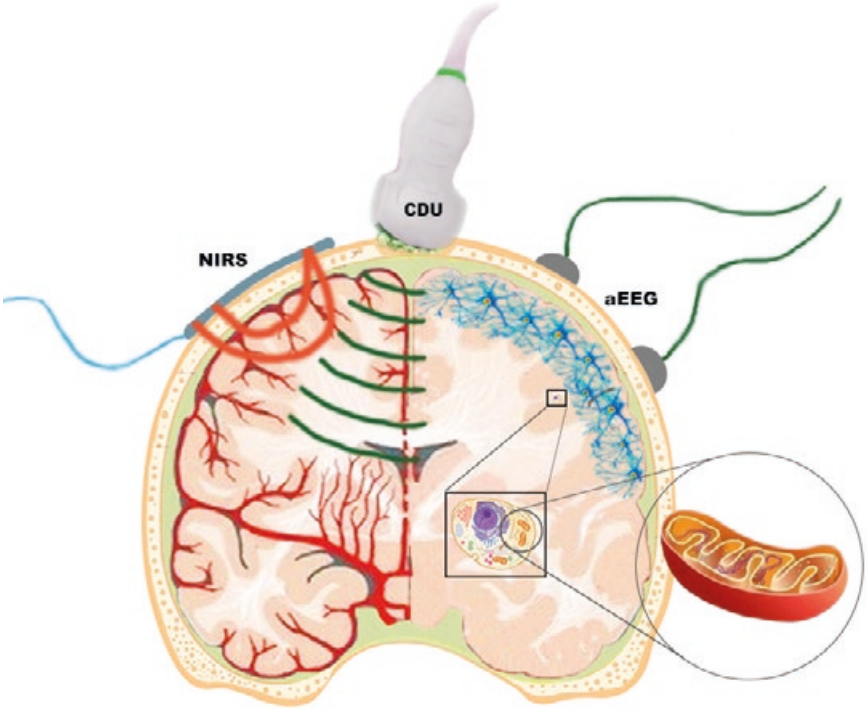

Figure 4. Broad outlines of the different neuromonitoring modalities and its shortcoming to provide information on cellular level.

minimal clinical evidence for using a single neuromonitoring device during non-cardiac surgery in neonates. Yet, a previous systematic review suggests that these neonates have an increased risk on delayed cognitive and motor development at the age of two [5]. It is important to stress that (possible) long term morbidity of neonatal surgery might not been seen before school-age. Motor function, concentration and attention deficits are reported from the age of 8 and later as extensive neuropsychological evaluation is only feasible from that age[41]. Neonatal physiology may be too complex to detect insufficient cerebral perfusion with one device only, but may be better understood when combining different modalities. Therefore, we searched for broader monitoring techniques and new ways of integrated data analysis. We suggest that 'integrative' neuromonitoring might be more beneficial, as visualized in figures 4 and 5. In this context, the term 'integrative' refers to multimodal neuromonitoring which combines multiple modalities for better understanding of the pathophysiology. This starts with

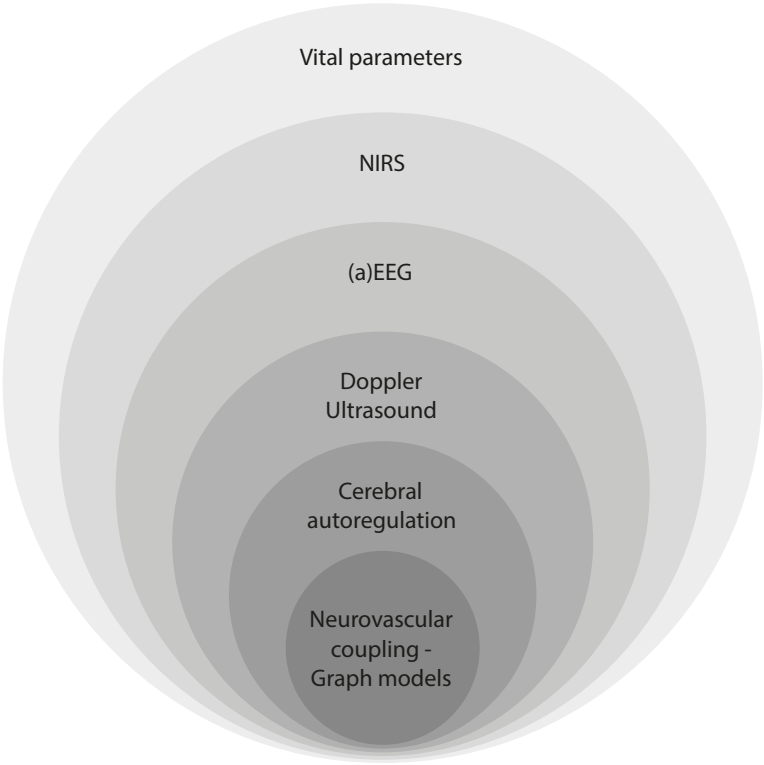

Figure 5. Our proposal of 'integrative' neuromonitoring.

monitoring standard vital parameters which provide information about particular organ systems and reflect end-organ perfusion, but lack specificity for brain perfusion[42,43]. To overcome this, NIRS is increasingly used in neonatal intensive care units. NIRS is based on the relative transparency of biological tissue to light. The technique is limited by inter- and intra-patient variance, because it depents on physiologic variability, the NIRS device and the type of probe that is used for monitoring[44,45,46]. Previous research on liquid phantoms showed device- and sensor-specific hypoxic thresholds[44]. In that study, the NIRO large sensor was associated with a hypoxic threshold of 62%; the INVOS small adult sensor with a hypoxic threshold of 55%; and the INVOS neonatal sensor with a hypoxic thresholds of 63% [47]. In this light, NIRS provides information about changes from an relative arbitrary zero-point, which means that you can only monitor a trend at best[47]. Besides that, cerebral oxygenation varies from 40-56% directly after birth and stabilizes 3 till 6 weeks postnatal between 55%-85% [45]. Changes in

cerebral perfusion due to fluctuations in MABP or end-tidal CO_2 and changes in saturation affects cerebral oxygenation, so it should be stressed that NIRS values can only be interpreted together with standard vital parameter monitoring[47,48]. Anaesthesiologists should use NIRS as a warning signal, needing to check everything else.

Adding NIRS, which mainly reflects changes in venous oxygenation[49], enables detecting changes in oxygen delivery to the brain and in oxygen consumption in the brain. These changes are generally quantified using the fractional tissue oxygen extraction parameter[50].

Neuromonitoring with NIRS during sedation is complicated because of changes in oxygen consumption due to changes in cerebral metabolism[51]. Measurements of cerebral oxygenation are therefore often complemented with measurements of cerebral activity by means of aEEG [51]. The EEG is an electrophysiological technique for the recording of electrical activity arising from the brain[52]. EEG can be measured in its conventional format or in an amplitude integrated form (aEEG). At the neonatal intensive care unit, aEEG is most commonly used in hypoxic ischemic encephalopathy and therapeutic hypothermia. Hence, it may also be helpful in infants with encephalopathy of varying etiologies[53,54]. The infants presented in the work by McCann ME et al. all developed new-onset epileptic seizures postoperative within 25 hours of administration of anaesthetics[55]. In here, all patients underwent relative small surgical procedures with an uneventful perioperative course. In this light, perioperative monitoring with aEEG might be useful for early detection of (severe) postoperative encephalopathy and epileptic seizures. To identify the potential value of (a)EEG in the operation threatre, a randomised controlled trial could be performed in which the anaesthesiologists is or is not blinded for aEEG.

Cranial ultrasound with Doppler is still the only way to image and quantify real-time cerebral perfusion and flow velocity[56]. Mathematical approaches to measure the regulation of cerebral blood flow are currently being developed[57]. Cerebral autoregulation is the most extensively studied regulation mechanism in neonates. At its core, cerebral autoregulation maintains a constant cerebral blood flow in a wide range of cerebral perfusion pressures (CPP). Cerebral oxygenation measured by NIRS generally serve as a measure for CBF and MABP as a measure for CPP [58]. A marker for cerebral autoregulation can be obtained by combining CBF and CPP measurements. Note, however, that NIRS measurements are valid surrogates for CBF only in the absence of large variations in arterial saturation and

under the assumption of a constant cerebral metabolism[59]. Besides the partial pressures of arterial blood gases (CO_2 and O_2), the primary controllers of CBF are the cerebral metabolism and the autonomic nervous system, which implies that CBF is mainly determined by neural activity[60]. An increase in neural activity results in a higher oxygen consumption, which, in turn, triggers an increase in CBF, in order to deliver more oxygen to the brain[61]. This regulation mechanism is commonly reffered to as neurovascular coupling[60]. General physiological markers of neurovascular coupling can be obtained by studying the interaction between NIRS and EEG measurements. Multimodal signal processing provides the tools to quantify interaction, coupling between different signals. In practice, signal coupling can be defined using numerous techniques. Popular simple examples include correlation, (wavelet) coherence and transfer function analysis[62]. A straightforward framework to integrate all of the different regulation mechanisms in one model can be constructed using signal interaction graphs[63]. From a clinical point of view, signal interaction graphs allow to capture the dynamic coordinated interactions of organ systems. These interactions are essential to maintain homeastasis; distinct physiological states can be captured using these models. Examples includes the differentiation between sleep and awake states, between consciousness and unconsciousness and the effect of particular medication[64]. More importantly, altered or disrupted organ communications could be detected that, when not managed, might lead to dysfunction of individual systems or to the collapse of the entire organisms, e.g., fever, hypertension, coma, or multiple organ failure[65]. The presently used techniques for perioperative neuromonitoring – NIRS, aEEG, and cerebral Doppler ultrasound – lack specificity, standardized reporting and are not related to clinical (long-term) outcome or prognostics. We narrowed our literature search to neonates up to 90 days old. For this group, the results of this review indicate that neuromonitoring with any of these techniques will neither help to better understand the altered neonatal pathophysiology, nor enable early detection of deviation from the norm. A meta-analysis could not be performed due to the absence of standardized reported results and led to the inability to draw up a clear monitoring guideline.

aEEG monitoring has proved to be useful to detect epilepsy or status epilepticus, but there is no demonstrated additional value of NIRS or cerebral ultrasound with Doppler over standard monitoing of blood pressure, end-tidal CO_2 and SpO_2. The value of these monitoring modalities in the neonate requires further prospective trials with clinical meaningful outcome.

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Appendix 2.1 Structured literature search

The following search terms were used for Embase.com: ('surgery'/exp OR 'peroperative care'/exp OR 'intraoperative monitoring'/exp OR 'perioperative monitoring'/exp OR 'thoracoscopy'/exp OR (surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*):ab,ti) AND ('electroencephalography monitoring'/exp OR 'neuromonitoring'/exp OR 'near infrared spectroscopy'/exp OR 'cerebral oximeter'/exp OR 'electroencephalogram'/exp OR 'brain function'/de OR (EEG OR aEEG* OR NIRS OR ((near*-infrared*) NEXT/1 (spectro*)) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) NEAR/3 (monitor*)) OR ((cerebr* OR brain*) NEAR/3 (oximeter* OR oxygenat*)) OR electroencephalogram*):ab,ti) AND ('infant'/exp OR 'neonatology'/exp OR 'neonatal intensive care unit'/de OR 'pediatric surgery'/exp OR (infan* OR newborn* OR new*-born* OR baby OR babies OR neonat* OR child* OR NICU):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [ENGLISH]/lim NOT ([animals]/lim NOT [humans]/lim)

The following search terms were used for Medline Ovid: (General Surgery/ OR exp "Surgical Procedures, Operative"/ OR (surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*).ab,ti.) AND (electroencephalography monitoring/ OR neuromonitoring/ OR near infrared spectroscopy/ OR cerebral oximeter/ OR electroencephalogram/ OR brain function/ OR (EEG OR aEEG* OR NIRS OR ((near*-infrared*) ADJ (spectro*)) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) ADJ3 (monitor*)) OR ((cerebr* OR brain*) ADJ3 (oximeter* OR oxygenat*)) OR electroencephalogram*).ab,ti.) AND (infant/ OR neonatology/ OR neonatal intensive care unit/ OR pediatric surgery/ OR (infan* OR newborn* OR new*-born* OR baby OR babies OR neonat* OR child* OR NICU).ab,ti.) NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR

chapter* OR dissertation abstract*).pt. AND english.lg. NOT (exp animals/ NOT humans/)

The following search terms were used for Cochrane CENTRAL: ((surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*):ab,ti) AND ((EEG OR aEEG* OR NIRS OR (near* NEXT/1 infrared* NEXT/1 spectro*) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) NEAR/3 (monitor*)) OR ((cerebr* OR brain*) NEAR/3 (oximeter* OR oxygenat*)) OR electroencephalogram*):ab,ti) AND ((infan* OR newborn* OR (new* NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR NICU):ab,ti)

The following search terms were used for Web Of Science: TS=(((surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*)) AND ((EEG OR aEEG* OR NIRS OR (near* NEAR/1 infrared* NEAR/1 spectro*) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) NEAR/2 (monitor*)) OR ((cerebr* OR brain*) NEAR/2 (oximeter* OR oxygenat*)) OR electroencephalogram*)) AND ((infan* OR newborn* OR new*-born* OR baby OR babies OR neonat* OR child* OR NICU)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man))) AND DT=(Article) AND LA=(English)

The following search terms were used for Google Scholar (First 200 references): Surgery|intraoperative|peroperative EEG|NIRS|"near infrared spectroscopy"|neuromonitoring|"cerebral monitoring"|electroencephalography|"cerebral oximeter"|electroencephalogram infants|newborns|"new born|borns"|baby|babies|neonate|neonatology|child|NICU

Table 5. Appendix 2.2. Methodological index for non-randomized studies

Methodological items for non-randomized studies	Fortune (18)	Dotta (19)	Zaramella (20)	Hüning (21)	Vanderhaegen (22)	Chock (23)	Chock (24)	Conforti (25)	Michelet (26)	Tytgat (27)	Conforti (28)	Koch (29)	Razlevice (30)	Tytgat (31)	Beck (32)	Costerus (33)	Stolwijk (34)	Nissen (35)	Kuik (36)	Kohelet (41)	Kasdorf (37)	Leslie (38)	Stolwijk (39)	Cornelissen (40)
A clearly stated aim	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	1	1	2	1	1	1	1	1	1	2	2	1	1	1	1	1	1	2	2	2	2	2	2
Prospective collection of data	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2
Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Unbiased assessment of the study	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Loss to follow up less than 5%	NA	NA	NA	NA	NA	1	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Additional criteria in the case of comparative study																								
An adequate control group	1	NA	NA	NA	NA	2	2	2	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Contemporary groups	2	NA	NA	NA	NA	2	2	2	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Baseline equivalence of groups	2	NA	NA	NA	NA	1	2	1	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Adequate statistical analyses	2	NA	NA	NA	NA	2	2	2	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total score (out of)	17 (22)	9 (14)	9 (14)	10 (14)	8 (14)	17 (22)	19 (22)	16 (22)	18 (22)	9 (14)	10 (14)	10 (14)	9 (14)	9 (14)	9 (14)	9 (14)	9 (14)	8 (14)	10 (14)	10 (14)	11 (14)	10 (14)	11 (14)	10 (14)

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). NA: not applicable.
Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (Minors): Development and validation of a new instrument. ANZ Journal of Surgery2003; doi 10.1046/j.1445-2197.2003.02748.x.

Table 6. Appendix 2.3. Overview of cerebral oxygenation, vital parameters and anaesthesia.

Study	Cerebral oxygenation & Vital parameters					Significance		Induction anaesthesia	Maintenance anaesthesia
Dotta (2005)		Begin surgery	End surgery					Fentanyl 2ug kg^{-1} h^{-1} & pancuronium 0.1mg kg^{-1} h^{-1}	Fentanyl 2ug kg^{-1} h^{-1} & pancuronium 0.1mg kg^{-1} h^{-1}
	rSO_2	Δ -6.05±10.6				↓			
	HR	149.5±9.1*	165.2±14.2*			↑			
	SaO_2	94.1±4.6*	93.4±4.4*			NS			
	FiO_2	0.25±0.05*	0.37±0.14*			↑			
	MABP	54.7±7.7*	55.6±8.1*			NS			
Zaramella (2006)		Before ligation	After ligation					Fentanyl 10-15ug kg^{-1} & Pancuronium 0.05-0.1mg kg^{-1} or Vecuronium bromide 0.08-0.1mg kg^{-1}	Fentanyl 2ug kg^{-1} h^{-1}
	rSO_2	61.6 (3.8)**	55.8 (2.6)**			↓			
	HR	162 (4.29)**	163 (5.1)**			NS			
	SaO_2	95.6 (1.07)**	95.4 (0.93)**			NS			
	MABP	47.25 (2.96)**	45.75 (3.26)**			NS			
Hüning (2008)		Before ligation	+0-2min	+2-5min	+5-10min	NS		Midazolam/Disoprivan & fentanyl/ alfentanil & vecuronium	Fentanyl/alfentanil
	rSO_2	53 (15)*	47 (22)*	48 (21)*	51 (22)*	↓			
	HR	165.4 (18.9)	0.1 (1.0)	0.7 (1.6)	2.0 (2.1)	NS			
	SaO_2	90.4 (8.3)	-2.8 (1.2)	-2.9 (4.3)	-1.3(4.3)	NS			
	MABP	31.9 (9.9)	33.8 (9.7)	31.9 (8.9)	30.9 (9.4)	NS			
Vanderhaegen (2008)		Before surgery vs after surgery (A)	5 min before vs 5 min after clipping (B)			A	B	Fentanyl 10 µg kg^{-1} & ancuronium 0.1 µg kg^{-1}	Fentanyl 3 µg kg^{-1} h^{-1}
	rSO_2	3.1† (-6.8-5.9)‡‡	2.9† (0.49-6.5)‡‡			NS	↑		
	HR	7.9† (-4.4-26.7)‡‡	6.5† (0.82-9.9)‡‡			NS	↑		
	SaO_2	-1.04† (-2.2-0.12)‡‡	0.78† (-0.68-6.08)‡‡			NS	NS		
	MABP	3.9† (1.2-9.1)‡‡	3.3† (-1.3-9.5)‡‡			NS	NS		
Chock (2011)		Before ligation	After ligation					Fentanyl, ketamine, & rocuronium	NR
	rSO_2	63±13*	NNR			↑			
	MABP	35.8±5*	NR			NR			

NR: not reported, NS: not significant, NNR: no numbers reported, MABP: mean arterial blood pressure, HR: heart rate, HFO: high frequency oscillation, CMV: conventional mechanical ventilation, * : mean ± standard deviation,** mean (standard error) , † :median, ‡ :range, ‡‡: IQR,

Study	Cerebral oxygenation & Vital parameters					Significance	Induction anaesthesia	Maintenance anaesthesia
Conforti (2014)		Before surgery	During vs after surgery				NR	NR
	rSO_2	NNR	NNR			NS		
	MABP	NR	NR			NR		
Michelet (2015)		Baseline	NR			NR	Propofol 5–7 mg kg^{-1} & suxamethonium 1.5 mg kg^{-1} & sufentanil 0.2ug kg^{-1} + atracurium 0.5 mg kg^{-1} after intubation OR sevoflurane 6% followed by sufentanil 0.2 ug kg^{-1} & atracurium 0.5 mg kg^{-1}	Sevoflurane 1,5-3% (endtidal expired concentration)
	rSO_2	78±10*	NR			NR		
	MABP	64±13*	NR			NR		
Tytgat (2015)		Before insufflation	Start insufflation	Stop insufflation	After cessation		Sevoflurane (inspired fraction) up to 8%, with a 100% FiO_2 & atracurium	Sevoflurane. Acetaminophen/ paracetamol.
	rSO_2	68±14*	69±15*	69±11*	71±9*	NS		
	HR	141±12*	146±14*	139±15*	136±14*	NS		
	SpO_2	98±2*	97±3*	98±2*	98±2*	NS		
	MABP	35±5*	38±5*	43±9*	41±6*	↑compared to baseline		
Conforti (2016)		Before surgery	During surgery				NR	NR
	rSO_2	81† (70-98)‡‡	61† (52-74)‡‡	HFO group		↓		
	MABP	NR	NR			NR		
	rSO_2	82† (76-91)‡‡	65† (67-93)‡‡	CMV group		↓		
	MABP	NR	NR			NR		
Tytgat (2016)		Baseline	After induction	After insufflation		↓	Sevoflurane 6–8 % (inspired concentration) & atracurium 0.5 mg kg^{-1}	Sevoflurane & sufentanil
	rSO_2	NR	77±10	73±7		↓		
	SaO_2	97±3	NR	90±6		↓		
	MABP	NNR	NNR	NNR		NS		
Beck (2017)		Start surgery	24 hours postoperative				NR	NR
	rSO_2	79.11±9.92*	-0.6±9.1 (IQR)			NS		
	MABP	NR	NR			NR		

NR: not reported, NS: not significant, NNR: no numbers reported, MABP: mean arterial blood pressure, HR: heart rate, HFO: high frequency oscillation, CMV: conventional mechanical ventilation, * : mean ± standard deviation,** mean (standard error) , † :median, ‡ :range, ‡‡: IQR,

Study	Cerebral oxygenation & Vital parameters				Significance	Induction anaesthesia	Maintenance anaesthesia
Costerus (2017)		Before surgery	During Surgery			Propofol 2-3 mg kg^{-1} & sufentanil 0.3 µg kg^{-1} & cisatracurium 0.1 mg kg^{-1}	NR
	rSO_2	82*	Range 81-89	CDH	NS		
	MABP	NNR	NNR		↓ 30 min and ↑ 90 & 120 min after insufflation		
	rSO_2	91*	Range 79-91	OA	NS		
	MABP	NNR	NNR				
Nissen (2017)		Admission	Before surgery	After surgery		NR	NR
	rSO_2	72.74±4.60*	77.89±5.84*	80.79±5.29*	Sign ↑ admission vs after surgery		
	MABP	NR	NR	NR	-		
Kuik (2018)		Before surgery	During surgery	After surgery		Sevoflurane & fentanyl & rocuronium.	Sevoflurane
	rSO_2	64† (53-75)‡	65† (53-73)‡	72† (60-82)‡	Sign ↑ during vs after surgery		
	MABP	35(28-38)	32(30-36)	35(32-41)	NS		

NR: not reported, NS: not significant, NNR: no numbers reported, MABP: mean arterial blood pressure, HR: heart rate, HFO: high frequency oscillation, CMV: conventional mechanical ventilation, * : mean ± standard deviation,** mean (standard error) , † :median, ‡ :range, ‡‡: IQR,

Under the surface

Perioperative/surgical management

3. Thoracoscopic versus open repair of CDH in cardiovascular stable neonates
4. Perioperative Management of Esophageal Atresia/ Tracheo-esophageal Fistula: an analysis of 101 consecutive patients
5. Effects of Neonatal Thoracoscopic Surgery on Tissue Oxygenation: A Pilot Study on (Neuro-) Monitoring and Outcomes

3

Thoracoscopic versus open repair of CDH in cardiovascular stable neonates

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Abstract

Background. Thoracoscopic surgery is an increasingly popular surgical technique to repair congenital diaphragmatic hernia (CDH). However, acidosis during surgery and the higher recurrence rate are considerable risk factors. The aim of this retrospective study is to compare the outcome of open versus thoracoscopic repair of the diaphragm in neonates with CDH with the same degree of cardiovascular and pulmonary illness who meet the criteria for thoracoscopic repair.

Methods. Retrospective analysis of all patients of two large national reference centers for CDH born in the years 2008 through 2012, and meeting the criteria for surgical repair on cardiopulmonary and physiological criteria according to the CDH EURO consortium consensus and meeting the criteria for thoracoscopic repair according to the review by Vijfhuize et al. The surgical technical aspects were comparable in both centers.

Results. 108 patients were included, of whom 75 underwent thoracoscopic repair and 34 underwent open repair. The gestational age and lung-to-head ratio were significantly lower, and stay on the ICU significantly longer in the open-repair group. The operation time was longer (178 vs. 150 minutes, p= .012) and the recurrence rate higher (18.9% vs. 5.9% p= .036) in the thoracoscopic-repair group. The arterial pH, pO_2, pCO_2 and base excess before and after thoracoscopic repair were all significantly different.

Conclusion. After critical selection for thoracoscopic repair of left-sided CDH based on the patient's preoperative condition, the outcomes of open repair were almost identical to those of thoracoscopic repair. A notable exception is the recurrence rate, which was significantly higher in the thoracoscopic-repair group. For the time being, thoracoscopic primary closure seems a safe and effective procedure, but efficacy of thoracoscopic patch repair has not been established.

3.1. Introduction

Over the last decades, survival of neonates operated on for congenital diaphragmatic hernia (CDH) has improved, but management of the condition is still a challenge for pediatricians and pediatric surgeons alike[1,2]. The prognosis is mainly determined by the degrees of pulmonary hypertension, pulmonary hypoplasia and abnormal morphology of the pulmonary vasculature[3,4,5]. Nowadays, only few centers perform thoracoscopic repair if the patient is cardiopulmonary stable. The criteria of stability still differ and have been published in several retrospective studies, but were never investigated prospectively[6].

Early studies reported higher recurrence rates after thoracoscopic repair; i.e. 5-25% versus 0-11% after open repair. This was explained by the effect of the so-called learning curve. However, more recent studies still do not report lower recurrence rates after thoracoscopic repair[6]. Also the reported conversion rate of thoracoscopic surgery to open surgery varies (3.4 to 75.0%), dependent on both technical and ventilatory problems. In these retrospective studies the open approach was associated with higher mortality, possibly due to a higher rate of comorbidities in neonates with large diaphragmatic defects and case selection bias.

All previous studies are retrospective and non-randomized. In these studies the differences in patient characteristics make it hard to compare outcomes of the two types of surgery. A pilot study reported that outcome of thoracoscopic surgery may be more detrimental due to the long-term consequences of hypercapnia and severe acidosis during surgery[7]. In an attempt to better define the risk of recurrence we conducted this 5-year retrospective study in patients with the same degree of cardiovascular and pulmonary illness. Comparability of the two groups allowed studying the effect of type of surgery on ventilation settings, length of stay at the pediatric intensive care unit (PICU) and the arterial blood gas changes.

3.2. Methods

Since January 2008 CDH patients of the Rotterdam Group and the Mannheim Group, both tertiary centers, are being treated according to the CDH-EURO consortium recommendations[4]. This created a standard of care for all of the patients and recommendation for the timing of surgical repair. The surgeons who performed the thoracoscopic CDH surgery, 2 in Mannheim and 4 in Rotterdam, all had more than 2 years experience before the start of this study in 2008 and had been specifically trained for MAS in Pediatric Surgery.
In a previous open review, we provided a decision tree for type of surgery (figure 6)[6]. The recommendations and the decision tree formed the selection criteria for thoracoscopic repair. A shared database was created with details of patients of two large pediatric surgery centers and who met the criteria for thoracoscopic repair in the period January 2008 through December 2012. The choice of surgery was based on surgeon's preferences and logistic possibilities. This way it was possible to compare thoracoscopic repair and open repair without the bias of different patient characteristics, thus reducing case selection bias.
Included in this study were inborn CDH patients with a left-sided congenital diaphragmatic hernia (type Bochdalek) who had been operated upon within 30 days after birth. The diagnosis had been established either antenatally or postnatally. Data on gender, birth weight, gestational age, Apgar scores, prenatal diagnosis, lung-to-head ratio (LHR), liver position, need of ECMO and associated anomalies were obtained from medical records and entered in the shared database. Technical specifications of both types of surgeries were registered, i.e. suture material and patch material.
The following exclusion criteria applied: right-sided or bilateral diaphragmatic hernia, ECMO-treatment before surgery, HFO during surgery, intrathoracic liver position at preoperative ultrasound screening, and major cardiac anomalies.
The primary outcome was the number of recurrences within one year after surgery. The secondary outcomes were duration of surgery, postoperative number of days on ventilator, pCO_2 and pH levels pre- and postoperatively, length of stay in the ICU and total hospital stay, duration until full enteral feeds and survival.

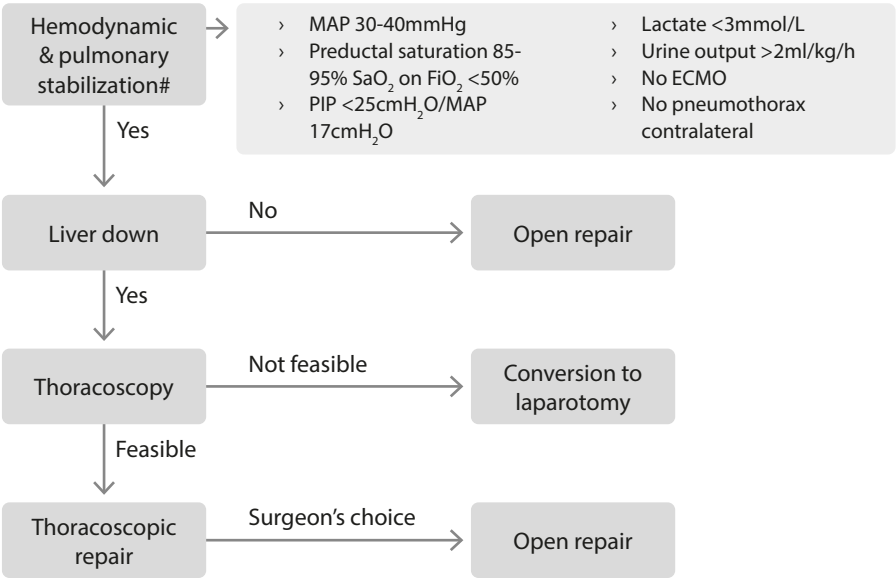

Figure 6. Decision tree for type of surgery.

3.2.1. Statistical analysis

Descriptive and non-paired t-test statistics, as well as Mann-Whitney U tests, were performed with the use of SPSS 22 (SPSS Inc., Chicago, IL). The Fisher exact test was used for analysis of contingency tables. All data are presented as median. A p-value <.05 was considered statistically significant.

3.3. Results

The thoracoscopic group included 75 patients; the open group 34. Characteristics are shown in table 7.

The demographic characteristics of the two groups (see table 7) did not significantly differ except for gestational age and lung-to-head ratio (LHR). The neonates in the open-repair group (OG) also had a lower median birth weight (2538g, range1140-3660) than the neonates in the thoracoscopic-repair group (TG) (2915g, range 2340-3800g), although this difference was not statistically significant.

	Thoracoscopic Group			Open Group			P-value
	25%	Median	75%	25%	Median	75%	
Number of patients		75			34		
Female (n)		34			18		.592
Gestational age (weeks)	37.90	38.28	38.57	36.86	38.00	38.42	.043
Birth weight (g)	2915	3045	3313	2538	2950	3180	.066
Apgar 1 min	5.5	7	8	5	7	7	.147
Apgar 5 min	8	8	9	8	8	8.25	.077
Apgar 10 min	8	9	9	8	8	9	.081
Lung-to-Head Ratio	1.8	1.9	2.4	1.3	1.7	2	.024

Table 7. Demographic Characteristics. Demographic characteristics of the thoracoscopic and open surgery group. The data comparisons are shown in median with the 25 and 75 percentiles.

	Thoracoscopic Group (n=75)			Open Group (n=34)			P-value
	25%	Median	75%	25%	Median	75%	
Heart rate	121	133	147	130	140	150	.418
Mean blood pressure	42.0	48.0	54.0	42.5	47.5	51.0	.776
pH	7.32	7.37	7.42	7.30	7.38	7.43	.826
pO_2(kPa)	11.93	15.48	20.01	12.66	17.34	21.21	.312
pCO_2(kPa)	4.75	5.54	6.53	5.05	5.85	6.50	.343
BE	-2.4	-1.0	2.0	-3.2	-1.2	2.6	.605
Highest pCO_2 (kPa)	6.24	7.02	8.90	6.33	7.45	8.96	.749
Lowest pCO_2 (kPa)	3.20	3.60	4.00	3.42	3.70	3.92	.758
Lactate (mmol/l)	0.8	1.1	1.4	1.0	1.2	1.5	.224
Urine output (ml/2h)	16	25	35	16	23	34	.936

Table 8. Pre-operative Characteristics. Comparison of preoperative characteristics in median with 25 and 75 percentiles. The data are the latest preoperative characteristics. Blood gas samples are preductal. Highest and lowest pCO_2 are between admission PICU and surgical repair.

	TG	OG	P-value
No ventilation (n)	1.4% (1)	0% (0)	.045
CMV (n)	58.1% (43)	79.4% (27)	
HFO (n)	24.3% (18)	5.9% (2)	
PEEP (cm H_2O)	4.50	3.50	.0001
FiO_2 (%)	40	45	.050
NO (n)	5.4% (4)	17.6% (6)	.068

Table 9. Pre-operative Ventilation Settings. Comparison of preoperative ventilation settings. TG= Thoracoscopic group, OG = Open group.

The range of the lung-to-head ratio (LHR) in the TG was 0.90-4.90 and in the OG 1.00-3.00. Two neonates in the TG had a LHR under 1, three between 1-1.4, and 42 above 1.4. For the 28 other neonates in the TG the LHR had not been registered. None of the neonates in the OG had a LHR under 1, five between 1-1.4, and 12 above 1.4. For the other 17 neonates in this group the LHRs had not been registered.

At the preoperative screening the liver was assumed to be intra-abdominal in all neonates. During surgery it appeared that the left liver lobe was in the chest in 8.2% of the TG and 23.5% of the OG. In four cases, two in the TG and two in the OG, the position of the liver was not reported in the operation journal.

Pre-operative characteristics (table 8) did not differ significantly between groups, except the ventilation settings (table 9).

The preoperative positive end expiratory pressure (PEEP) was significantly higher in the TG (range 3-7 mmHg versus 2.5-6 mmHg in the OG). The fraction of inspired oxygen (FiO_2) was higher in the OG, with a large range of 22-75% versus 21-60% in the TG.

The duration of the total operation, including anesthesiological procedures, was significantly longer in the TG (p= .017). Large ranges were found: 58' – 351' in the TG, and 70'- 244' in the OG (table 10). OG patients stayed longer in the ICU than did TG patients. The median difference was 5 days with a mean difference of 10 days.

The recurrence rate in the TG was 9 out of 34 (26.5 %) in the Rotterdam Group and 5 out of 41 (12.2 %) in the Mannheim Group (p= .143), of which 6 and 4, respectively, concerned patch repair (p= 1.0). Both recurrences in the OG (5.9%) had been previously repaired with a patch. Survival in both groups was 100%.

The Rotterdam Group uses always Ethibond or Mersilene, both in open and thoracoscopic surgery. The Mannheim Group used Ethibond in primary closure (open and thoracoscopic) and thoracoscopic patch repair; only in open surgery with patch repair they used Tycron. All sutures are polyester (table 11). All patients in both centers who needed patch-closure, GORE-TEX® soft tissue patches were used.

Small, not clinically relevant changes were found in the comparison of the arterial blood gases before and after surgery. In the TG, the median pH decreased from 7.37 to 7.31; the median of the pCO_2 increased from 5.54 to 5.93; and the median of the base excess decreased from -1.0 to -2.0. Nevertheless, as shown with the paired differences test, preoperative values for the pH, base excess, pCO_2 and pO_2

	Thoracoscopic Group (n=75)			Open Group (n=34)			P-value
	25%	Median	75%	25%	Median	75%	
Age at repair (days)	3	3	4	3	3	5.5	.525
Duration of operation (min)	143	178	219	114	150	192	.012
Primary surgical repair % (n)		41.3% (31)			32.4% (11)		.634
Patch repair % (n)		58.7% (44)			67.6% (23)		.184
Conversion % (n)		20.3% (15)					
Peroperative liver(lobe) intrathoracic % (n)		8.2% (6)			23.5% (8)		.069
Extubation (days)	7	10	14	7	12	20	.265
Stay ICU (days)	11.0	16,5	24.0	14.5	21.0	35.0	.027
Recurrences % (n)		18.9% (14)			5.9% (2)		.036
Survival (%)		100%			100%		1

Table 10. Per- and Post-operative Characteristics. Comparison of the thoracoscopic and open surgery group in median, 25 and 75 percentiles.

were significantly different from the corresponding postoperative values in the TG. In the OG, only base excess and pO_2 were significantly different before and after surgery.

3.4. Discussion

The traditional surgical management of CDH consists of repair through laparotomy. In the last decade, however, minimal access surgery (MAS) has gained wider popularity[6,8]. Both are centers of expertise with respect to congenital diaphragmatic hernia neonates and pediatric surgery. Together they treat approximately 80 CDH neonates per year. The Mannheim Group performed their first MAS in 1993 and performed their first thoracoscopic surgical repair of a CDH neonate is 2008. The Rotterdam Group performed their first MAS in 1998 and operated thoracoscopically on the first CDH neonate in 2006.
Thoracoscopic repair for CDH is potentially associated with fewer postoperative ventilator days and possibly less use of analgesics[9,10]. On the other hand, the artificial pneumoperitoneum (or pneumothorax) needed for MAS negatively affects hemodynamics[11,12,13,14,15,16,17].
Multiple studies show a higher recurrence rate associated with thoracoscopic repair, as is also found in the present study, due to learning curve, limited workspace and the use of a patch[6]. Furthermore the surgical difference between

	Rotterdam Group	Mannheim Group
Primary closure open surgery	Ethibond/Mersilene	Ethibond
Primary closure MAS	Ethibond/Mersilene	Ethibond
Patch closure open surgery	Mersilene	Tycron
Patch closure MAS	Ethibond/Mersilene	Ethibond
Knotting primary closure	Intracorporeal	Intracorporeal
Knotting patch closure	Intracorporeal	Intracorporeal

Table 11. Technical specifications. Comparison of the surgical and technical specifications between the Rotterdam and the Mannheim Group.

open en thoracoscopic repair is that the rim of diaphragm is mostly adhered to the dorsal pleuroperitoneal canal and preparation from thoracic side is challenging. From the abdominal route preparation is much easier and more obvious, while from thoracic route these structures are harder to find
A recent prospective multicenter study showed a lower recurrence rate after open repair with patch than after MAS repair with patch during the first hospital stay[18]. In that study laparoscopy and thoracoscopy were clustered in one MAS group and the patient characteristics were not comparable between the open group and the MAS group. However, the high recurrence rate for the MAS group might be compensated for by the associated benefits mentioned above and by shorter ICU stay.
In the TG, recurrence rate in Rotterdam was 26.5% versus 12.2% in Mannheim. To explain this discrepancy we looked at possible technical differences between both centers. In both centers, however, the surgery was performed only by a small group of surgeons with several years' experience in MAS in neonates and large experience in CDH surgery. Moreover, the same type of sutures was used. Thus, the discrepancy may be due to the type of patch used. Loff et al. from Mannheim showed reduced recurrence rates in open repair with a Dual Mesh cone-shaped patch[19]. In the thoracoscopic repair with patch they also used the Dual Mesh cone-shaped patch, in contrast to the Rotterdam group. Furthermore, the conventional open patch repair is performed using a patch of the size of the defect or with an overlapping border of 1 cm circumferentially and sutured with interrupted non-absorbable material to the rim of the diaphragm[19]. Thoracoscopically the overlapping border is possibly smaller and the patch is sutured at the thoracic side instead of the abdominal side as in open surgery. The advantages of the cone-shaped patch are an increased abdominal capacity and reduction of redundant chest capacity, thereby allowing normal physiological position of the abdominal organs, which in turn prevents gastroesophageal reflux and causes fewer recurrences because of separate fixation of the overlapping border of the cone and less abdominal pressure on the patch[19].

Several articles describe selection criteria for thoracoscopic repair[3,6,8,9,20,21]. The cardiovascular criteria are almost the same in these overviews, i.e. no clinical signs of persistent pulmonary hypertension (PPHN), no need for inhaled nitric oxide (iNO) during surgery, and no need for ECMO. All agree that the patient has to be respiratory stable, but the definition of respiratory stable differs for PIP, PEEP, FiO_2 and the pulse oxymeter oxygen saturation (SpO_2). The ventilation criteria as recommended by the CDH consortium are a PEEP of 2 to 5 cm and in addition FiO_2<50% with a SpO_2 between 85-95%, so that both open and thoracoscopic repair are possible. These recommendations are based on nonanalytic studies, case reports, or expert opinions[4].

In the present study, only the preoperative differences in PEEP (4.5 vs. 3.5) between the TG and the OG suggest cardiopulmonary differences between the two groups. Two neonates in the TG had a LHR < 1.0 versus none in the OG, but data on the observed versus expected LHR were not available. Ten patients, 4 in the TG and 6 in the OG, received a low maintenance dose of iNO before surgery. Patients after open repair stayed longer in the ICU than did patients after thoracoscopic repair. This may suggest that the former group had a worse pulmonary condition, but the median LHR in both groups was >1.4 and the ranges of the PEEP and FiO_2 were not suggestive of worse condition. Still, the open repaired diaphragm defects, especially if patch closure was necessary, may suggest a bigger defect.

The artificial pneumothorax needed for thoracoscopic surgery creates acidosis due to hypercapnia by CO_2 insufflation. This, in combination with higher intra-abdominal pressure, is believed to be related to deficient microcirculation[13,16,22,23]. Splanchnic redistribution of blood flow with altered renal and hepatic function has been demonstrated. Also, testicular damage and reduced strength of (colonic) anastomoses have been reported as negative side effects of pneumoperitoneum[24,25]. Nevertheless, patients with hypercapnia show global hyperperfusion of the cerebral blood flow[26]. The cerebral blood flow and volume depend on the ability of the cerebral arteries to respond to changes in the partial pressure of arterial CO_2 [27].

Bishay et al. recently proved severe arterial blood gas changes during thoracoscopic repair of CDH, but this finding was based on only 5 patients[7]. We also showed a significant difference in pH and pCO_2 values before and after thoracoscopic repair. However, these differences were small and deemed of limited clinical relevance. Due to the acidosis and hypercapnia, High Frequency

Oscillatory Ventilation (HFOV) during neonatal thoracoscopic repair has gained attention in recent years. Mortellaro et al. showed that this allowed good intraoperative exposure in correction of esophageal atresia and CDH, while allowing excellent oxygenation and elimination of carbon dioxide to prevent acidosis[28]. Whether this ventilation technique can truly prevent the changes in acid-base balance associated with capnopneumothorax has yet to be established.
For this study, a selection of left-sided CDH patients meeting the criteria for thoracoscopic repair was made based on their preoperative condition. Some patients who met these criteria underwent open repair. These patients were, as a group, comparable to patients operated on thoracoscopically. The difference in overall recurrence rate that was found cannot be explained by the patient characteristics. Possible explanations are the position of the patch (abdominal vs. thoracic side of the defect) and the level of security with which the patch is sutured because the suture material, the knot tying and the patch material were the same. The only difference between the centers is the use of a cone-shaped patch as mentioned above. But still patch-repair in thoracoscopic surgery is more challenging and many centers convert to open surgery when a patch is needed for closing the diaphragm and only primary closure is performed thoracoscopically.
In both the TG and the OG the pO_2 and the base excess values changed significantly from before to after surgery. In the TG, the pH and the pCO_2 changed significantly as well. This is probably the result of CO_2 insufflation during thoracoscopic surgery.
In addition, the overall time until recovery after surgery was longer for the OG. This does not seem to be due to a higher degree of pulmonary hypoplasia in this group. Perhaps the increased surgical trauma of open repair or maybe inadvertent selection bias may be responsible for this.
The effects of acidosis and hypercapnia on the (long-term) neurological development of the thoracoscopically repaired CDH patients are unknown. Thus there is a strong need for a well-designed study with state-of-the art neurological monitoring during thoracoscopic surgery but also for structured long-term follow up, looking at psychomotor development after this type of surgery. The higher recurrence rate in the thoracoscopically repaired group needs further attention, specifically when a patch is used. For the time being, thoracoscopic primary closure seems a safe and effective procedure, but efficacy of thoracoscopic patch repair has not been established.

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4

Perioperative Management of Esophageal Atresia/ Tracheo-esophageal Fistula: an analysis of 101 consecutive patients

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Abstract

Background. The perioperative management of esophageal atresia/tracheo-esophageal fistula by open or thoracoscopic approach can be complicated by metabolic derangements. Little is known, however, about the severity of derangements of vital and metabolic parameters in the perioperative period.

Aim. The aim of this study is to describe the perioperative courses of vital and metabolic parameters in 101 consecutive neonates undergoing surgical repair of esophageal atresia type C.

Method. In a retrospective cohort study, we extracted all data from the electronic anesthetic and medical charts of patients who underwent esophageal atresia type C repair within 30 days of life (2007- 2017). We distinguished three types of surgery: primary open, primary thoracoscopic, and primary thoracoscopic surgery converted to open surgery. Descriptive analysis was applied.

Results. The charts of 117 patients were reviewed: data of 101 were included. The perioperative anesthetic management was not standardized; various methods and medications were used for anesthesia induction and maintenance. Intraoperative blood gas analysis data of 72 patients were available and showed derangements regardless of type of surgery. The median pH-value decreased to 7.21 [IQR 7.14-7.30] and a pH-value below 7.20 was found in 29 patients; in 4 cases below 7.0, with the lowest value 6.83. The median $PaCO_2$ reached an upper level of 7.5kPa [IQR 5.8-9.2]; in 13 cases above 10.0kPa, with a peak value of 25.8kPa. These high $PaCO_2$ levels fluctuated with lowest measured $PaCO_2$ of median 5.6 [IQR 4.5-6.6], with the lowest value 2.8kPa. The median PaO_2 level reached an upper level of 16.9kPa [IQR 11.8-25.7], in 22 cases above 20.0kPa, with a peak value of 50.0kPa. These high levels fluctuated with lowest measured PaO_2 levels of median 8.3kPa [IQR 6.73-10.5]; the lowest PaO_2 value was 4.7kPa.

Conclusions. Open and thoracoscopic correction of esophageal atresia were associated with periods of severe metabolic derangements. These events need to be taken into account for the evaluation of esophageal atresia (surgical) care and in evaluations of short- and long-term outcomes.

4.1. Introduction

Surgical repair of esophageal atresia (EA) is a challenging procedure which requires close collaboration between the surgical and anesthetic teams. Factors such as prematurity, low birth weight, respiratory problems and associated morbidities, in particular cardiac anomalies, increase the complexity of the procedure[1,2]. The presence of a tracheo-esophageal fistula (TEF) – found in the majority of cases – carries the risk of insufflating the stomach, instigating high intra-abdominal pressures and impeding ventilation.
The EA/TEF repair can be done with either a traditional open or a thoracoscopic approach[3]. The success and progress of the surgery, in particular of the thoracoscopic surgical approach, hinge on effective cooperation between surgeon and anesthesiologists because of the interference of (mostly) the right-sided lung in the working area, which compels adaptation in ventilation[4]. The arguments on the preferred surgical approach mostly relate to the perioperative severity of metabolic derangements, which are largely influenced by the anesthetic (ventilation) technique. Little is known, however, on the relation between type of the surgical approach and this severity. Only one study on this topic has been published so far[5]. This was a randomized (pilot) study comparing a primary thoracoscopic and an open surgical repair in 10 patients with congenital diaphragmatic hernia and 10 patients with EA/TEF. The thoracoscopic approach appeared to be associated with more profound and more prolonged hypercapnia and acidosis than open surgery. Thoracoscopic management is preferred in some hospitals because it provides better visualization of the surgical field, and is associated with less surgical damage and better long-term outcome with expected lower risk of scoliosis[6]. As reported EA survival rates have increased to more than 90% nowadays[7,8] leading to a shift of attention towards possible long-term morbidities[9]. Previous research on developmental outcome after EA/TEF repair showed normal to impaired motor- and mental development. The impairment was associated with the total anesthesia time[10]. Any interrelationships between intraoperative events, type of surgical approach – thoracoscopic or open – and (developmental) outcomes have not yet been elucidated. Comorbidities, intraoperative events like duration of surgery, the occurrence of hypercapnia (and its effect on cerebral autoregulation), acidosis, hypertension, postoperative complications (such as recurrence of the TEF, esophageal stricture formation and gastro-esophageal reflux) may negatively affect the short- and long-term clinical

outcomes[11,12,13,14,15]. It is also not known what surgical technique is associated with the best outcome[12,16].
In this paper we describe the perioperative courses of vital parameters and metabolic derangements as well as the short-term outcome in relation to the type of surgical approach in 101 consecutive neonates undergoing esophageal atresia type C repair.

4.2. Methods

In this retrospective cohort study we made use of the electronic Anesthetic Information Management System (AIMS; Anesthesia Manager, PICIS Clinical Solutions S.A., Barcelona, Spain), Patient Data Management System dedicated to ICU (PDMS, ChipSoft, Amsterdam, The Netherlands), and medical charts (on paper until 2012 and electronically from 2012 onwards) to identify patients who underwent correction of EA/TEF between January 2007- December 2017 at the Erasmus MC-Sophia Children's Hospital, Rotterdam. All pre-, intra- and postoperative data of these patients were gathered as well as annual follow-up data on major health changes and mortality. Data was gathered during the scheduled follow-up at regular intervals (minimum once per year with the surgeon in our hospital) until the age of 18 years old. Data on mortality rates up to and including April 2019 were included. Inclusion criteria were EA type C (as classified by Gross) and surgical correction within the first 30 days of life. Patients with EA types A, B, D and E were excluded to ensure optimal homogeneity of the data[17].
Cardiac malformations were classified as minor or major according to Hoffman[18].
Prematurity was defined as born before 37 weeks postconceptional age.
Standard preoperative care at the intensive care unit following the protocol of the Dutch Association of Pediatric Surgery consisted of (physical) examination for VACTERL association and syndromes, genetics, thoracic- and abdominal x-rays and echographic cardiac examination[19].
During the study period, a thoracoscopic procedure was generally the preferred surgical approach to achieve continuity of the esophagus and closure of the fistula. The surgeon, anesthesiologist and the neonatologist/intensivist together

decided on the type of surgical approach if the neonate had any clinically relevant cardiac or respiratory morbidities. Conversion from thoracoscopic to open surgery was based on either surgical and/or anesthesia related problems.
In 2012, pediatric surgeons and anesthesiologists of the Erasmus MC-Sophia Children's Hospital had issued a recommendation to convert thoracoscopic to open procedure if the pH was below 7.0 (independent of the duration of acidosis).
Anesthetic management during the study period included standard monitoring (saturation, non-invasive blood pressure measurements, ECG, $EtCO_2$) and preferably inserting an arterial line for invasive blood pressure monitoring (considered mandatory for thoracoscopic approach) and arterial blood gas analyses. Placement of the arterial line – either preductal or postductal – had not been recorded. A central venous line was placed only on indication. Capillary, arterial and/or venous blood gas analyses were standardly performed pre- and post-operatively but not standardly during anesthesia. In the data analysis, we did not distinguish between arterial-drawn, capillary-drawn or venous-drawn blood samples since for pH and pCO_2 measurements, capillary-drawn and venous-drawn blood are clinically acceptable alternatives for arterial-drawn blood[20,21].
Acidosis was defined as pH<7.35; severe acidosis as pH<7.20; hypercapnia as $PaCO_2$ >6.40 kPa (Erasmus MC-Sophia reference value); hypocapnia as $PaCO_2$ <4.7 kPa (Erasmus MC-Sophia reference value); hypoxemia as peripheral saturation ≤90% or PaO_2<5.4kPa; severe hypoxia as peripheral saturation <80%; and hyperoxia as PaO_2>12.4kPa [22,23]. Hypotension and hypertension were defined respectively as measurement below the 2SD and above the 2SD range, calculated per patient based on weight and sex according to recently developed reference ranges[24].
Unavailable data are referred to as unknown/missing. Due to the retrospective nature of this study we cannot distinguish between non-registered data (unknown) and missing data.

4.2.1. Statistics

For the evaluation of surgical techniques and their anesthetic management, the cohort was divided into three groups: primary open surgery (POS), primary thoracoscopic surgery (PTS) and converted thoracoscopic to open surgery (COS). Univariate regression analysis and multivariable regression analysis (stepwise

	Total n=101	POS n=34	PTS n=56	COS n=11
Male	63 (63%)	21 (62%)	36 (64%)	7 (64%)
Birth weight	2805 [2169 – 3185]	2240 [1640-3071]	2900 [2530-3240]	2910 [2456-3345]
Gest. Age	37.9 [36.3 – 39.6]	36.6 [33.8 – 38.4]	38.3 [37.0 – 40.0]	38.0 [36.9 – 39.9]
Premature	38 (38%)	17 (50%)	16 (29%)	5 (45%)
Preoperative oxygen	38 (38%)	10 (29%)	22 (39%)	6 (55%)
Preoperative intubation	15 (15%)	13 (38%)	1 (2%)	1 (9%)

Table 12. Patient characteristics. Numbers are presented as n (%) or median [interquartile range].

backward) was performed exploratory, post-hoc to determine the association between the most severe metabolic derangement in pH (lowest pH) and perioperative factors (preoperative intubation, weight at surgery, duration of surgery, gestational age, gender, surgical technique, minor and major cardiac anomalies). The perioperative anesthetic management and pre-, intra- and postoperative variables are presented as frequencies and percentages for categorical variables and median with interquartile range [IQR] for continuous variables. Statistical analysis was performed with a statistical analysis program (SPSS 24.0 for Windows, SPSS, Inc, Chicago, IL, USA).

4.3. Results

4.3.1. Patient characteristics

From January 2007 to December 2017, a hundred and seventeen neonates had undergone surgery for EA/TEF in our hospital. After exclusion of EA type A (n=5), B (n=1), D (n=1) and E (n=8), 102 neonates with EA type C remained. One of those (referred from abroad) had surgery at the age of 68 days and was excluded. Thus, we included data of 101 neonates. Sixty-three percent were boys; 38% were born premature (table 12). Patients in the POS group had lower birth weights and lower gestational ages than those in the PTS group. Surgery was performed at a median of 2 (0 – 9) days after birth (table 12).
Minor cardiac malformations had been diagnosed in 63 patients; major cardiac malformations in 5 patients, of whom only 1 had a cyanotic cardiac malformation

Cardiovascular	n=	Pulmonary	n=	Preoperative intubation?	Chromosomal	n=	Other	n=
ASD	24	Atelectasis	14	2	VACTERL	6	Genitourinary	17
VSD	11	Pneumothorax	8		Trisomy 21	3	Limb	12
ASD+VSD	7	IRDS	5	3	CHARGE	1	Anorectal malformation	12
Dextrocardia	5	Hypoplasia	3	2	Silver Russell	1	Vertebral	9
Valve problems	5	Other pulmonary**	11	8	Pierre Robin	1	Neurological	3
Pulmonary stenosis	1						Duodenal atresia	3
Tetralogy of Fallot	1							
Right descending aorta	1							
DORV	1							
Other cardiovascular*	12							

Table 13. Congenital anomalies diagnosed in the patients. ASD atrial septal defect; VSD ventricular septal defect; DORV double outlet right ventricle; VACTERL Vertebral, Anorectal, Cardiac, TracheoEsophageal, Renal, Limb; CHARGE Coloboma, Heart disease, Atresia choanae, Retarded growth and development, Genital anomalies, Ear anomalies; IRDS Idiopathic Respiratory Distress Syndrome. * Other cardiovascular anomalies include impaired left ventricle function, absent pulmonary artery, enlarged heart, dilated right atrium and ventricle, persistent superior vena cava, overriding aorta, mesocardia. ** Other non-cardiac anomalies include congenital pulmonary airway malformation, wet lung, mediastinum shift, bronchitis. All pulmonary abnormalities were confirmed by chest X-ray.

(table 13). Preoperative pulmonary abnormalities confirmed by chest X-ray had been found in 41 patients (41%) (table 13).

The surgical approach for primary EA/TEF repair was POS in 34 patients, PTS in 56 and COS in 11 patients. Reasons for COS were insufficient overview of the surgical site (n=3); respiratory and/or hemodynamic problems that could not be corrected (n=4); failure to insert an arterial line (n=1); too long gap for thoracoscopic anastomosis (n=2, anastomosis successful after conversion); and a preoperatively unidentified right descending aortic artery (n=1, anastomosis successful after conversion). Surgical procedures for additional congenital abnormalities performed during the same surgical session included gastrostomy (3 POS), colostomy (4 POS, 1 PTS, 1 COS), duodenostomy (1 PTS) and colostomy + duodenostomy (1 COS).

Ten patients underwent a second operation related to the initial EA/TEF repair (excluding esophageal stricture dilatations) within 1 year: delayed planned primary end-to-end anastomosis due to a long gap (n=4); recurrent fistula (n=4); and fundoplication (n=2). For these patients, only the data on the initial surgery was included in this study. Prior to surgery, 38 patients had received non-invasive oxygen supplementation and 15 patients had been mechanically ventilated because of respiratory insufficiency (table 12). Several preoperative blood gas analysis results differed between groups (table 14).

	POS	PTS	COS
Preoperative	n=32	n=54	n=10
Saturation	89 [81-96]	94 [87-98]	89 [83-95]
pH	7.31 [7.26-7.34]	7.34 [7.31-7.39]	7.35 [7.31-7.36]
PaO_2	7.80 [5.75-9.33]	11.2 [7.15-16.6]	6.20 [5.40-10.1]
$PaCO_2$	6.15 [5.73-7.13]	6.30 [5.30-6.95]	5.85 [4.98-6.03]
Intraoperative	n=23	n=39	n=9
Saturation	87 [77-92]	85 [81-89]	84 [69-91]
pH	7.25 [7.17-7.37]	7.28 [7.21-7.35]	7.24 [7.14-7.42]
PaO_2	11.1 [7.5-15.4]	10.5 [8.1-15.2]	8.9 [7.6-15.2]
$PaCO_2$	6.0 [5.0-8.5]	6.4 [5.0-7.2]	5.7 [4.0-9.3]
Postoperative	n=34	n=46	n=11
Saturation	96 [92-99]	98 [92-99]	97 [85-98]
pH	7.32 [7.23-7.41]	7.38 [7.30-7.46]	7.36 [7.31-7.42]
PaO_2	9.4 [7.6-15.0]	11.9 [8.9-19.0]	16.8 [8.8-25.8]
$PaCO_2$	5.2 [4.2-6.8]	4.7 [3.9-6.4]	5.1 [3.8-5.6]

Table 14. Blood gas analysis results. N= number of patients, Median [IQR] of saturation (%), pH, PaO_2 (kPa) and $PaCO_2$ (kPa). Preoperative: last blood gas sample before surgery; Intraoperative: lowest saturation measured; Intraoperative; first pH, PaO_2 and $PaCO_2$ measured; Postoperative; first blood gas sample postoperative. The asterisk (*) represents the sole intraoperative capillary blood gas analysis. All other measured blood gas values are from arterial blood gas samples. Preoperative number of patients with blood bas analysis: POS: arterial 14, venous 1, capillary 18, missing 1. PTS: arterial 20, venous 0, capillary 34, missing 2. COS: arterial 10, venous 0, capillary 7, missing 1. Intraoperative number of patients with blood bas analysis: POS: arterial 23, venous 0, capillary 0, missing 11. PTS: arterial 38, venous 0, capillary 1, missing 17. COS: arterial 9, venous 0, capillary 0, missing 2. Postoperative number of patients with blood bas analysis: POS: arterial 26, venous 0, capillary 8, missing 0. PTS: arterial 43, venous 0, capillary 13, missing 0. COS: arterial 11, venous 0, capillary 0, missing 0.

4.3.2. Intraoperative Phase

For the induction of anesthesia in the 86 patients intubated in the OR (15 patients were already intubated at the ICU), thiopental (n=17), propofol (n=35), sevoflurane (n=30) and unknown/missing (n=4) were used. Muscle relaxation was provided with cisatracurium (n=66), rocuronium (n=8), suxamethonium (n=4) and unknown/missing (n=8). Pain medication consisted of fentanyl (n=61), sufentanil (n=18), remifentanil (n=5) and unknown/missing (n=2). Preoperative tracheoscopy was performed in 42 patients using rigid and/or flexible scopes. The induction time (from arrival at the OR until the incision) was longest for the COS group (75 minutes), followed by the PTS (60 minutes) and POS groups (31 minutes). In the COS group, the mean time from start of thoracoscopic surgery to conversion to open surgery was 51 minutes. The total surgical time for the COS

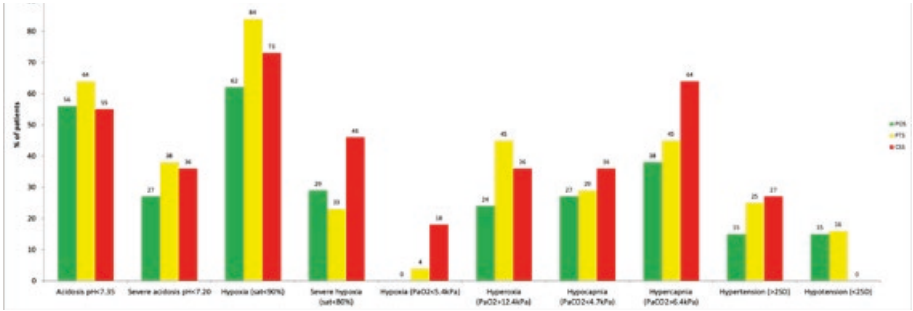

Figure 7. Overview of main measured parameters. This figure shows the incidence of measured values across all surgical approaches. Bars represent percentage of measures values per group. Numbers above bars represent absolute number of patients.

group was 189 minutes; for the POS group 116 minutes; and for the PTS group 152 minutes (table 15).

Preoperative blood gas analysis was done with either capillary (n=59), arterial (n=37) or venous (n=1) blood samples. Intraoperative blood gas analysis was done with either capillary (n=1) or arterial (n=71) blood samples. Intraoperative blood gas analysis results of the 72 patients with intraoperative blood gas measurements were registered in AIMS. The number of analyses was highest in the COS group (median of 4), followed by 2 in the PTS group and 1 in the POS group. Postoperative blood gas analysis was done in all patients, either with capillary (n=21) or arterial (n=80) blood samples.

The mean peak non-invasive blood pressure in the COS group was higher than that in the POS group (figures 7 and 8). The mean invasive blood pressure was highest in the COS group. In total 22 patients had one or more hypertensive events and 14 patients had one or more hypotensive events (figures 7 and 8).

In total 44 patients had received inotropics and vasoactive drugs. Fluid loss (including blood and urine) during the operation was not reported.

None of the patients had been subjected to one-lung ventilation. Eighty-five patients had been placed in the left lateral position (n=85); three in the right lateral position; and for 13 patients the position was missing. The peak ventilation pressures were comparable across all groups (median 6, IQR 5-8), with a highest pressure of 20.0 cmH_2O in all groups. The median highest pressure overall was 24 (IQR 20-28). The highest pressure in the COS group was 47 cmH_2O; 44 cmH_2O in the PTS group; and 36 cmH_2O in the POS group.

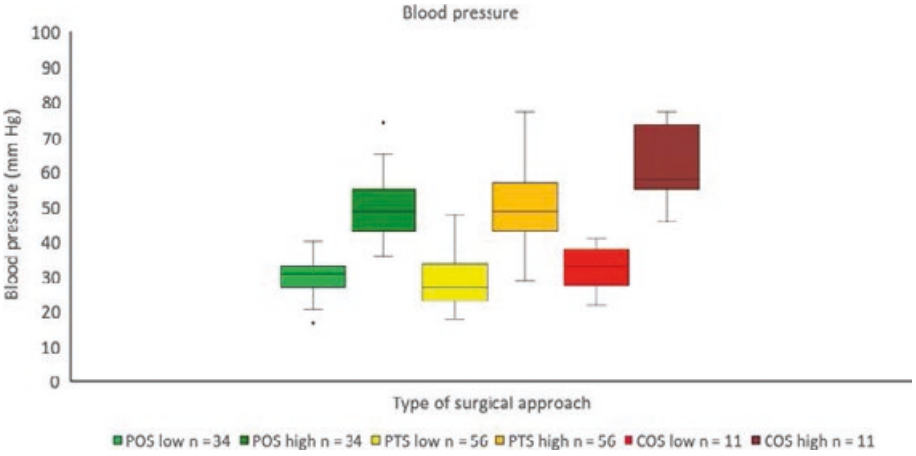

Figure 8. Intraoperative blood pressure measurements. This figure shows the lowest and highest intraoperative mean blood pressure (mmHg, mean, 95% CI) presented per surgical approach. In case of missing invasive blood pressure measurement, non-invasive blood pressure measurement was used.

	Univariate			Multivariable		
Variable	Beta	95%	CI	Beta	95%	CI
Preoperative intubation	-0.107	-0.183	-0.032	-0.079	-0.144	-0.014
Weight at surgery	0.000	-0.037	0.036	-0.006	-0.063	0.050
Surgical approach	-0.017	-0.069	0.036	-0.001	-0.057	0.055
Duration of the surgery	-0.001	-0.002	0.000	-0.001	-0.002	0.000
Gestational age	0.004	-0.012	0.019	0.002	-0.006	0.011
Gender	0.080	0.024	0.137	0.083	0.031	0.134
Minor cardiac	-0.044	-0.107	0.018	-0.047	-0.100	0.005
Major cardiac	0.012	-0.102	0.126	0.012	-0.099	0.123

Table 15. Univariate and multivariable regression analysis of factors associated with lowest intraoperative pH.

Hypoxemic events (peripheral saturation <90%) had been recorded for 75 of the 101 patients, which were severe (sat <80%) in 28 patients. An O_2 saturation below 50% had been recorded for two patients (1 PTS, 1 COS); the lowest value was 42%. measured in the COS group. Blood gas analysis showed hypoxemia in 7 patients. The lowest PaO_2 of 4.70 kPa was measured in the COS group. Hyperoxia was found in 53 patients, with highest PaO_2 of 50.0 kPa in the PTS group, followed by 39.0 kPa in the POS group (figure 7).
Hypocapnic episodes had been reported for 28 patients, with the lowest $PaCO_2$ of 2.8 kPa in the PTS group (table 14). Hypercapnic episodes had been reported for 46 patients; the highest $PaCO_2$ was 25.8 kPa in the PTS group (figure 9). The first

	Total n=101	POS n=34	PTS n=56	COS n=11
Induction anesthesia				
Inhalation (sevoflurane)	30	14 (41%)	13 (23%)	3 (27%)
Intravenous propofol	35	6 (18%)	23 (41%)	6 (55%)
Intravenous thiopental	17	1 (3%)	15 (27%)	1 (9%)
Intubation				
Oral	23	7 (21%)	14 (25%)	2 (18%)
Nasal	57	16 (47%)	33 (59%)	8 (73%)
Tracheoscopy				
Rigid	18	7 (21%)	6 (11%)	5 (46%)
Flexible	6	6 (18%)	0	0
Combination	17	6 (18%)	8 (14%)	3 (27%)
Duration of induction		31 [17-49]	60 [31-75]	75 [51-92]
Duration of surgery		116 [95-154]	152 [124-180]	189 [141-244]
Postoperative ICU stay		12.5 [6-47]	5.0 [3-12]	13.0 [10-19]
Postoperative hospital stay		29.5 [14-84]	14.5 [10-27]	21.0 [13-31]
Postoperative intubation days		2 [1-4]	1 [1-1]	2 [2-3]
Days to oral feeding		8.0 [5-20]	5.0 [3-8]	11.0 [4-18]

Table 16. Anesthetic and perioperative care management. Not all information is known in all patients, induction of anesthesia when performed at NICU is not reported.

measured pH value in the POS group was lower than that in the PTS group (table 14). Intraoperatively, acidosis (pH<7.35) was found in 62 patients; severe acidosis (pH<7.20) in 33 patients, of whom three (2 PTS, 1 POS) had a pH value ≤7.0, with the lowest minimum pH 6.83 in the PTS group (figure 10). The pH values ≤7.0 necessitated breaks from surgery to recover metabolic balances (n=1), clearing of the tube (sputum plug, n=1) and conversion to open surgery (n=1).
The lowest intraoperative pH was associated with longer duration of the surgery, preoperative intubation and male sex in both univariate and multivariable regression analysis. Type of surgery was not associated with lowest intraoperative pH (table 16).
In the period 2007-2012 (before the new recommendation), fewer intraoperative blood gas analyses per patient per surgery had been performed than in the period 2012-2017 (after the new recommendation, median 1 and 3, resp.).
Mean blood gas values did not differ between these periods; the only difference between these periods was a higher incidence of hypoxemic events (saturation <90%) in the POS group after 2012.

4.3.3. Postoperative management

Postoperatively, all patients had been admitted to the pediatric intensive care unit (PICU). Here, patients in the PTS group were extubated within a median of 1 day,

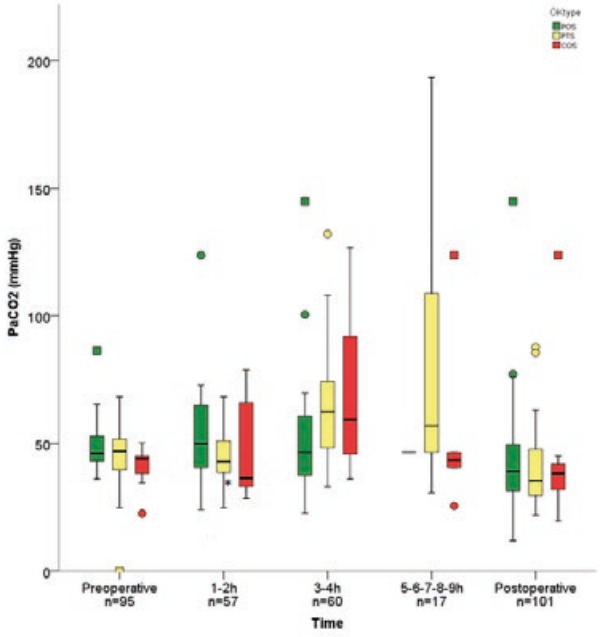

Figure 9. Figure 3A. Pre-, intra- and postoperative $PaCO_2$ measurements. Highest measured $PaCO_2$ in blood gas analysis (median, IQR) preoperative, intraoperative and postoperative. These figures (9 and 10) show the measured values through time: preoperative, intraoperative (per subcategory) and postoperative. It shows acceptable preoperative metabolic values, but derangements increase with length of the procedure. Postoperative values are comparable to preoperative figures. Preoperative number of patients with blood gas analysis: POS: arterial 14, venous 1, capillary 18, missing 1. PTS: arterial 20, venous 0, capillary 34, missing 2. COS: arterial 10, venous 0, capillary 7, missing 1. Intraoperative number of patients with blood gas analysis: POS: arterial 23, venous 0, capillary 0, missing 11. PTS: arterial 38, venous 0, capillary 1, missing 17. COS: arterial 9, venous 0, capillary 0, missing 2. Postoperative number of patients with blood gas analysis: POS: arterial 26, venous 0, capillary 8, missing 0. PTS: arterial 43, venous 0, capillary 13, missing 0. COS: arterial 11, venous 0, capillary 0, missing 0. The asterisk (*) represents the sole intraoperative capillary blood gas analysis. All other measured blood gas values are from arterial blood gas samples.

those in the POS and COS groups within a median of 2 days. Postoperative blood gas analysis results were available for all patients; it appeared that pH, PaO_2 and $PaCO_2$ values had normalized in most patients (table 14).
The total postoperative ICU stay was median 9 days [IQR 4-18]; the total hospital stay was median 18 days [IQR 11-33]. Time to start of oral feeding was median 6 days [IQR 4-13]; time to extubation was 1 day [IQR 1-2] (table 15). The overall mortality was 4% (POS n=0, PTS n=1, COS n=3). None of the patients died in the OR or within 24 hours after surgery. Two patients died during postoperative hospital stay: one in the COS group due to sepsis 14 days postoperatively and one in the PTS group following respiratory failure due to severe edema after cardiac arrest and systemic inflammatory response syndrome 57 days postoperatively.

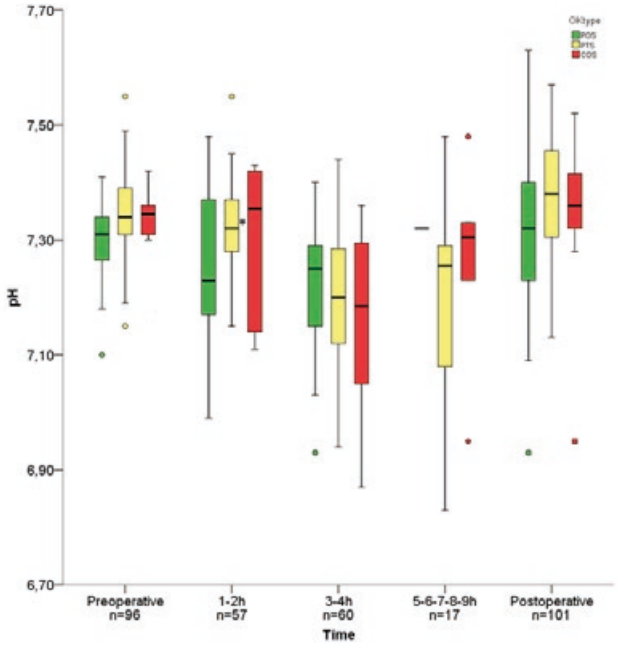

Figure 10. 3B- Pre-, intra- and postoperative pH measurements. Lowest measured pH in blood gas analysis (median, IQR) preoperative, intraoperative stages and postoperative. Also refer to the description for figure 9.

Two patients died after discharge from the hospital, one from refractory epilepsy due to sinus thrombosis, intracerebral hemorrhages and infarctions (COS group, 71 days postoperative) and one from serious cerebral complications related to sepsis (COS group, 225 days postoperative).
Clinically diagnosed postoperative complications during hospitalization had been reported in 50 patients. These included: anastomotic leakage (n=18; 3 POS, 12 PTS, 3 COS); pneumothorax (n=20; all managed with chest tube); respiratory failure (n=9); atelectasis (n=12); infection (n=7); severe acidosis (n=3); recurrent fistula (n=3); and kidney problems (n=2). Various patients had multiple complications (mainly pneumothorax due to an anastomotic leakage in 16 patients) (figure 11).

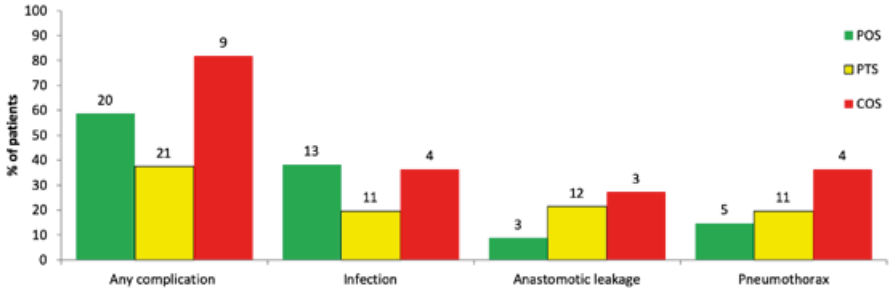

Figure 11. Complications.

4.4. Discussion

We report on the pre-, intra- and postoperative anesthetic management in neonates undergoing type C EA repair and the acute physiological consequences in relation to the type of surgical approach – thoracoscopic, open and thoracoscopic converted to open surgery. The hemodynamic status of most patients was stable during the operation, but many suffered from episodes of acidosis, hypercapnia and hyperoxia, the incidences of which were positively associated with longer duration of the procedure. The severities of metabolic disturbances did not differ between the different surgical approaches. Although a study has suggested that an open surgical approach leads to fewer acidosis, hypercapnia and ventilator problems than does a thoracoscopic approach[3], we found no difference in the occurrence of intraoperative metabolic derangements between both approaches. Therefore, we cannot assert which of the two surgical approaches is superior in this respect.

Sixty-nine percent of the patients had minor and/or major cardiac abnormalities and 41% had pulmonary abnormalities, which percentages correspond with previous reports[25,26,27,28]. Theoretically, cardiac malformations could have a large influence on the perioperative course. However, as only 5 patients had major cardiac abnormalities, of whom 1 had a cyanotic malformation (see supplementary data), and regression analyses did not show major effects of minor and major cardiac malformations on outcome (table 16), we judged it valid to keep their data in the analyses.

More patients were intubated preoperatively in the POS group (38%) than in the PTS group (2%). It seems that preoperative intubation is an important determining factor for primary open surgical approach (table 13). The univariate

and multivariable regression analyses showed associations between lowest intraoperative pH and preoperative intubation and surgery time (table 16).
The clinical preoperative parameters in the PTS group were better than those in the POS group, which might have influenced the postoperative recovery (fewer ventilation days, ICU days, hospital days) in the PTS group. The duration of induction of anesthesia was the longest in the COS group. The duration of the surgical intervention in the PTS group was longer than that in the POS group, as found by others[29,30]. The high occurrence of episodes of acidosis in the present study confirms the findings of Zani et al.[14].
There still is no general consensus on a preferred surgical technique (open vs. thoracoscopic procedure)[5,31]. The medical and surgical management of EA repair are decided in light of comorbidities, type of EA/TEF, experience of the surgeon, distance between the two ends of the esophagus, surgical and anesthesiologist preference and local hospital practice[2,32]. Therefore, the perioperative anesthetic management of EA/TEF in the Erasmus MC-Sophia Children's Hospital was not standardized, which caused a wide variation in care.
Independent of the surgical technique used, periods of severe intraoperative acidosis, hypercapnia, hypocapnia, hyperoxia and hypoxemia, mostly independent of hypo-and hypertension, occurred in the patients this study.
The hypercapnia and acidosis found in this study are most likely caused by compression of the lung (POS and PTS) and absorption of insufflated CO_2 (PTS)[5,14,33,34]. Hypercapnia should be avoided or solved by compensatory increase of the ventilation rate.
The influences of metabolic derangements on the long-term neurodevelopmental outcome in humans are unknown, but preclinical animal research has shown a negative association of metabolic derangements with long-term neurodevelopmental outcome[5,10,13,14,35,36,37,38]. We suggest that non-invasive intraoperative neuromonitoring could be beneficial for optimal registration of brain oxygenation and perfusion during EA repair.
Patients in the PTS group had shorter lengths of stay in the ICU and the hospital than patients in both other groups, in line with previous studies[30,39]. Patients in the COS group, however, had more complications than those in the PTS group. Recurrent fistula were only found in the PTS group. Time to postoperative extubation was longer for the POS group, in line with other studies evaluating this aspect[40,41]. Various explanations have been suggested for this phenomenon; for example, collapse of the lung caused by uniform CO_2 insufflation, resulting

in elimination of retraction trauma and the need of a bigger incision for open surgical approach[40,41]. Unfortunately, during the period of surveillance, intraoperative neuromonitoring and/or routine postoperative ultrasound/MRI and EEGs to detect intraventricular hemorrhage and/or seizures had not been performed. Stolwijk at al suggested that this extra monitoring would be beneficial in this patient population[42].

One of the greatest strengths of this study is the high number of patients included. Since EA is a rare congenital anomaly, most studies regarding EA include small numbers of patients. The 101 patients included in this study give a better representation of all EA patients and their perioperative periods. Several limitations of the study need to be addressed. First, the indication for thoracoscopic surgery might have introduced bias in the findings. Smaller patients with more severe comorbidities were preferably treated with an open procedure, and these characteristics might have influenced the postoperative risk of complications. Second, in the 10-year period covered in this study, changes may have been made in the surgical decision making. Also, the learning curve might have affected the outcome of these patients in time: shorter surgery time and fewer complications are to be expected[43]. Regarding the compliance with the recommendation made in 2012, 15 patients reached a pH < 7.20 but were not converted to an open procedure. Thus, the compliance with the recommendation is low and is not likely to have introduced an important bias. Furthermore, in the data retrieved from AIMS it can be difficult to differentiate patients' actual vital state and artifacts, especially in non-normal values[44]. The storage resolution in AIMS in Erasmus MC was limited and the vital parameters were recorded only every five minutes, so that outliers may have been missed. Fourth, the anesthetic management varied largely with the attending anesthesiologist's preference. Intra-arterial blood pressure measurements and standard interval for blood gas analysis were not standard of care. Therefore, intraoperative (arterial) blood gas results at regular intervals were not available and we were obliged to use all types of blood gas samples interchangeably to evaluate metabolic derangements. Most of the patients included in this study had encountered periods of severe hypoxia, hyperoxia, acidosis, hypercapnia and hypocapnia intraoperatively, regardless of perioperative status and surgical approach. Checking for metabolic changes at regular time intervals during the operation, preferably with arterial blood gas analysis, is recommended.

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5

Effects of Neonatal Thoracoscopic Surgery on Tissue Oxygenation: A Pilot Study on (Neuro-) Monitoring and Outcomes

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Abstract

Introduction. Multiple reports have questioned the feasibility of neonatal thoraco- scopic repair of congenital diaphragmatic hernia (CDH) and esophageal atresia (EA). The aim of this study is to examine the effects of CO_2 pneumothorax on cerebral and renal rSO_2 and to assess the potential predictive value of these data on neurodevelop- mental outcome after neonatal thoracoscopic surgery for CDH or EA.

Methods. A prospective observational pilot study. Cerebral and renal regional tissue oxyhemoglobine saturation (rSO_2) rSO_2 were assessed using near-infrared spectro- scopy (NIRS) during thoracoscopic surgery in neonates with CDH and with EA, in addition to routine anesthesia monitoring. Cerebral and renal rSO_2, linked to repeated arterial blood gas analyses, heart rate, blood pressure, and to structured longitudinal neurodevelopmental follow-up.

Results. Baseline estimated marginal means of cerebral rSO_2 values (CDH: 82%, EA: 91%) did not change significantly during pneumothorax (CDH: 81%, EA 79% [n.s. versus baseline]) despite severe acidosis (lowest pH, CDH: 6.99, EA: 7.1). Neurodevelopmental outcomes at 24 months were normal in all 7 patients who were available for evaluation.

Conclusion. Neonatal thoracoscopic repair of CDH and EA using CO_2-pneumothorax leads to severe acidosis. Cerebral rSO_2 remained within clinical acceptable limits during intraoperative periods of acidosis. Neurodevelopmental outcome was favorable within the first 24 months. The potential of NIRS to further improve perioperative care and long-term outcome in this specific patient group deserves further investigation.

5.1. Introduction

Multiple reports have described and questioned the feasibility of neonatal thoracoscopic repair of congenital diaphragmatic hernia (CDH) and esophageal atresia (EA)[1,2].
Severe acidosis, predominantly due to hypercapnia with application of an artificial CO_2-pneumothorax, is a common feature and regarded as a significant drawback of neonatal thoracoscopy[3,4]. Little is known about the effects of acidosis during neonatal thoracoscopy on cerebral tissue oxygenation and its potential impact on neurodevelopment.
The aim of this pilot study was to determine the changes in regional tissue oxygenation (rSO_2), measured by near infrared spectroscopy (NIRS), that occur during neonatal thoracoscopy with artificial CO_2 pneumothorax. Data from our structured follow-up of neurodevelopmental skills after major neonatal surgery were analysed to gain insight into the intermediate-term effects of the brief period of hypercapnia and acidosis that commonly occurs with CO_2 insufflation, and to investigate a potential predictive value of cerebral and somatic rSO_2 regarding neurodevelopmental outcome in this high-risk patient population.

5.2. Methods

We designed a prospective observational cohort pilot study in neonates with either EA or CDH undergoing neonatal thoracoscopic repair in our national tertiary referral centre that treats approximately 10-15 EA patients and 25-30 CDH patients per annum. Local IRB approval (Erasmus MC, Rotterdam, The Netherlands, MEC-2010-392) and written informed consent of parents or legal guardians of all participants were obtained.

5.2.1. Patients

Neonates (aged 0-28 days) with EA or left-sided CDH, scheduled for thoracoscopic surgery between April 2011 and August 2013 were eligible for inclusion. Criteria for thoracoscopic surgery were: minimal use of vaso-active drugs; absence of relevant hemodynamic compromise due to associated cardiac anomalies; minimal ventilator settings, such as peak inspiratory pressure (PIP) < 25 cm H_2O, FiO_2 < 0.5, pre-ductal saturation > 90%; no pharmacological treatment for pulmonary hypertension; and no contralateral pneumothorax. Patients were admitted to the Paediatric Intensive Care Unit (PICU) directly after birth and treated according to the prevailing international standards of care until surgery[2,5]. Due to the fundamental differences in pathology, patients were divided into two groups (CDH and EA) for data analysis.

5.2.2. Perioperative treatment protocol

5.2.2.1. Anaesthesia

A standardised anaesthesia protocol was used. Patients diagnosed with EA are not routinely on ventilatory support prior to surgery. In these patients general anaesthesia was induced with propofol 2-3 mg kg^{-1} and sufentanil 0.3 µg kg^{-1}. Cis-atracurium 0.1 mg kg^{-1} was given to facilitate endotracheal intubation. In CDH patients, who all received ventilatory support prior to surgery, the anaesthesia protocol started with the maintenance part, which was the same in EA and CDH patients. It consisted of sevoflurane together with remifentanil and a continuous infusion of cis-atracurium.

Pressure controlled mechanical ventilation was applied using a semi-closed anaesthesia circuit system ventilator (Primus, Draeger, Luebeck, Germany). If possible, peak inspiratory pressures lower than 20 mbar were applied, with a positive end expiratory pressure (PEEP) sufficient to avoid complete collapse of the upper lung. In patients who were already on the ventilator on the ICU preoperatively, the initial ventilator settings during the surgical procedure were kept as close as possible to the preoperative course. We strived to ventilate patients to normocapnia, as determined by sequential arterial blood gas analyses (every 30 min.).

All patients had an indwelling arterial catheter enabling continuous monitoring of hemodynamic parameters and the drawing of serial arterial blood samples. Standard departmental guidelines dictate monitoring of heart rate, invasive and non-invasive blood pressure, body temperature and analysis of inspired and expired gases (O_2, CO_2, and sevoflurane).
In case of a deterioration of the patient's cardiorespiratory and/or metabolic condition, it was a shared responsibility of the surgeon and the anaesthetist to decide whether to convert to an open surgical procedure or to take other measures to improve the patient's condition.
After completion of the surgical procedure all anaesthetic agents were discontinued. Prior to return to the PICU an initial bolus of morphine 0.1 mg kg^{-1} was given. All patients were returned to the PICU while still on mechanical ventilatory support.

5.2.2.2. Surgery

Pressures of CO_2 pneumothorax were initially set at 3-4 mmHg. Occasionally CO_2 pressure had to be elevated for a brief period but never exceeded 6 mm Hg. Thoracoscopic repair of left-sided CDH was done using a 3-trocar technique with a 5mm endoscope and 3 mm instruments and with the patient in right lateral decubitus position. Primary repair was performed only when this could be accomplished in a tension-free manner. Otherwise, a dome-shaped patch-repair with Gore-tex® (W. L. Gore & Assoc Inc., Flagstaff, Ariz) was performed with a running braided non-absorbable suture for the posterior rim and interrupted sutures for the medial, lateral and anterior borders. In places where no rim of autologous diaphragm was present, peri-costal sutures were placed. Thoracoscopic repair of EA was also done using a 5 mm endoscope and two 3 mm instruments as described by Rothenberg and Bax[6].

5.2.3. Data collection

Birth weight, gestational age, gender, age at start of operation, duration of anaesthesia, days on the ventilator and number of days in the PICU postoperatively were recorded. Mean arterial blood pressure, peripheral transcutaneous oxygen saturation were continuously recorded during the entire

peri-operative period. Cerebral and renal rSO_2 values were recorded under anaesthetised conditions starting before the application of CO_2-pneumothorax until the end of the surgical procedure. Due to the observational design of the study the screen of the NIRS monitor was obscured.
Arterial blood gas sampling was started approximately 30 minutes before artificial CO_2 pneumothorax (considered as baseline) and repeated every 30 minutes during surgery.

5.2.4. Near infrared Spectroscopy

Near Infrared Spectroscopy (NIRS, INVOS 5100C®, Covidien, Boulder, CO, U.S.A.) is a non-invasive method for in-vivo monitoring of regional haemoglobin oxygen saturation (rSO_2) [7]. The NIRS monitor provides a mainly venous-weighted measure of oxyhaemoglobin, which must not be confused with arterial oxygen saturation. rSO_2 provides information about oxygen demand, oxygen extraction, and oxygen reserve of the underlying tissue. It should always be interpreted in combination with the actual arterial oxygen saturation[8]. Paediatric NIRS optodes were applied to the skin of the forehead and the renal region in accordance with the producer's recommendations for continuous data collection. NIRS recordings were transferred to a personal computer for subsequent analysis using the INVOS™ Monitoring System Analytics Tool software, provided by Covidien.

5.2.5. Longitudinal neurodevelopmental follow-up

As standard of care, patients were offered a structured, longitudinal follow-up program[9]. We collected data on neurological examination by a paediatrician both at 12 and 24 months (corrected for prematurity), neurodevelopmental assessment at 24 months (if applicable), and the number of exposures to general anaesthesia within the first 24 months of life. Neurodevelopmental assessment was performed using the 2nd edition of the Dutch version of the Bayley's Scales of Infant Development (BSID-II-NL)[10]. Developmental psychologists assessed cognitive development (expressed as mental developmental index (MDI)) and paediatric physical therapists assessed motor function (psychomotor developmental index (PDI)). The normalized population mean (±SD) of each composite score is

100(±15). Scores were considered as normal (>-1 SD), mildly delayed (-2< SD< -1) or severely delayed (<-2 SD).

5.2.6. Statistics

Descriptive statistics are presented as median and range for continuous variables and as proportions for dichotomous variables. Cerebral-somatic rSO_2-difference (ΔCR- rSO_2 = rSO_2cerebral - rSO_2renal) was calculated according to the approach previously reported by Bernal et al.[11]. Cerebral and renal fractional tissue oxygen extraction (FTOE = (SaO_2 -rSO_2)/SaO_2) was calculated according to Naulaers et al.[12]. FTOE is a measure of the balance between oxygen delivery and consumption reflecting tissue oxygenation[12].
Linear mixed models[13] were used to estimate the effect of thoracoscopic surgery on tissue perfusion for EA and CDH. This statistical approach is based on the assumption that the data are missing at random, which means that missing values do not depend on unobserved data, given the available outcome data and covariates[14]. Separate models were estimated for pH, BE, PaO_2, $PaCO_2$, mean blood pressure, cerebral rSO_2, renal rSO_2, cerebral and renal FTOE and ΔCR-rSO_2. The independent variable in these models was 'time' combined with the interaction of time and congenital pathology. Time was coded as a categorical variable, with the categories 'baseline', 30, 60, 90 and 120 min after insufflation. A random intercept was included in the models to account for within-subject correlations. The results of the linear mixed models are presented using the estimated marginal means, which are the predicted values of the dependent variable adjusted for covariates in the model. The (two-tailed) level of significance was set to 5%. Statistical analyses were performed using SPSS 22.0 (IBM SPSS Inc., Chicago, IL, USA).

	CDH (n= 4)	EA (n= 6)
Birth weight (g)	3488 (3050-4019)	2850 (1941-3338)
Gestational age (wk)	39.9 (38.5-40.2)	39.0 (34.0-40.0)
Age on day of surgery (d)	2.5 (1.3-4.5)	2.0 (1.8-4.0)
Gender (M/F)	0/4	3/3
Duration of anaesthesia (min.)	128.5 (85-227)	162 (138-235)
Post-operative days on ventilator	4.4 (1.8-6.5)	1.0 (1.0-3.5)
Stay PICU (d)	8 (5-12)	16 (6-21)
Co-morbidity	-	Tetralogy of Fallot (n=1) Kidney dysplasia (n=1) Feingold syndrome (n=1) Intestinal malrotation (n=1)

Table 17. Patient data.

5.3. Results

5.3.1. Patients

During the study period a total of 53 CDH cases and 31 EA cases were treated in our centre.
Written informed consent was obtained in fourteen cases: 6 with CDH, 8 with EA. Two CDH and 2 EA patients were excluded after conversion to open surgery due to surgical difficulties. All other cases that presented during the study period were either not eligible for thoracoscopic repair or could not be included for lack of informed consent or availability of a complete team for all the perioperative measurements. Patient data, duration of surgery, postoperative respiratory support and length of stay in the PICU of the included 10 patients are given in table 17.

5.3.2. NIRS - rSO_2

rSO_2 data were available for analysis from all 10 patients (see figure 12). In the CDH patients estimated marginal means of cerebral rSO_2 values were 82% at baseline, and ranged from 81 to 89% at the intraoperative time-points . In EA patients estimated marginal means of cerebral rSO_2 was 91% at baseline, ranging from 79 to 91% at the intraoperative time-points. Baseline estimated marginal means of renal rSO_2 values were 75% in CDH patients, ranging from 60 to 67%

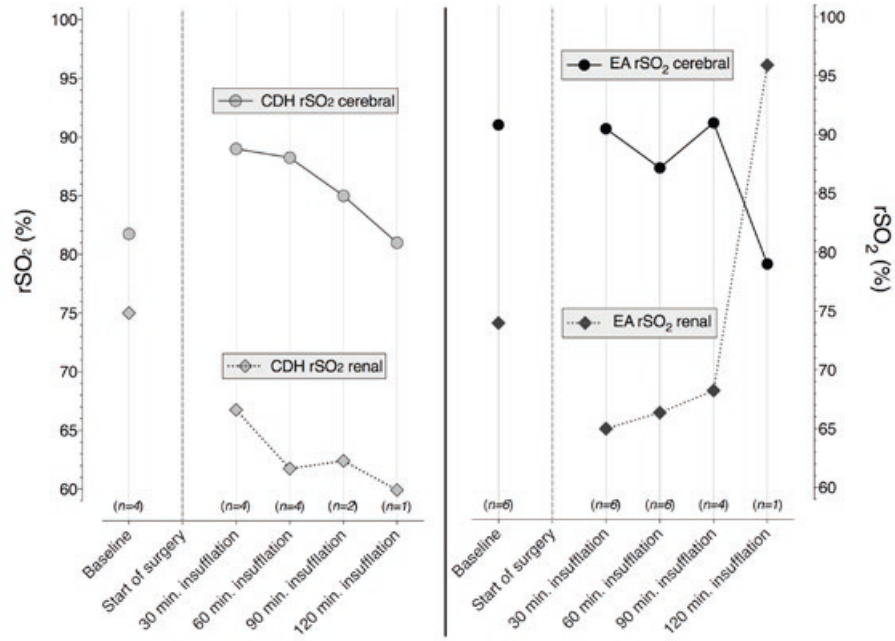

Figure 12. Cerebral and renal rSO_2. Estimated marginal means of cerebral and renal rSO_2 (%) values in patients with congenital diaphragmatic hernia (CDH) and esophageal atresia (EA) at baseline and during artificial CO_2-pneumothorax. No significant differences exist between baseline- and intraoperative values.

at the intraoperative time-points, and 74% in EA patients at baseline, ranging from 65 to 96 % at the intraoperative time-points. Estimated marginal means of cerebral and renal fractional tissue oxygen extraction (FTOE) are given in figure 13. Baseline estimated marginal means of cerebral-somatic rSO_2-differences (ΔCR-rSO_2) were -2.8% in the CDH group and 20% in the EA group. The corresponding estimated marginal means at the intraoperative time points ranged from 22.3 to 26.5% in CDH patients ($p<0.05$ vs. baseline at all time points) and from -16.3 to 28.6% in EA patients ($p=0.006$ vs. baseline at 120 min.).

5.3.3. Arterial blood gas analysis and hemodynamic parameters

Perioperative arterial blood sampling was possible in all 10 patients. For the course of pH, BE, and $PaCO_2$ see figure 14. Intraoperatively, the arterial pH in one CDH-patient dropped to a minimum value of 6.99 after 90 minutes of CO_2-insufflation. The lowest pH in the EA group was 7.10. The highest $PaCO_2$ was 12.9

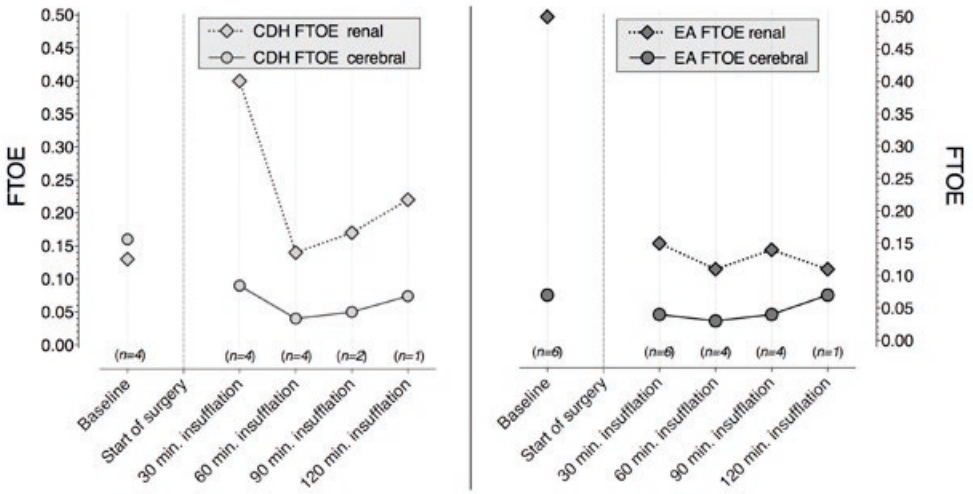

Figure 13. Fractional tissue oxygen extraction (FTOE). Estimated marginal means of cerebral and renal fractional tissue oxygen extraction (FTOE) in patients with congenital diaphragmatic hernia (CDH) and esophageal atresia (EA) at baseline and during artificial CO_2-pneumothorax. Values at 120 min. represent a single patient. No significant differences exist between baseline- and intraoperative values.

kPa in the CDH- and 11.5 kPa in the EA-group. Throughout the observation period, estimated marginal means of PaO_2 ranged from 13.7-18.2 kPa in CDH patients and from 9.9-20.3 kPa in EA patients. Lowest individual PaO_2 values were 7.5 kPa in a CDH patient (after 60 min. of pneumothorax) and 6.0 kPa in an EA patient (after 30 min. of pneumothorax).
The course of estimated marginal means of mean arterial blood pressure (BP) and heart rate (HR) for both CDH and EA is shown in figure 15.

5.3.4. Intermediate term neurodevelopmental outcome

Neurological examination in all 10 patients was normal at 12 months. Neurodevelopment was assessed at 24 months in five EA patients and two CDH patients (all other patients were younger than 24 months). For EA, the median (range) MDI was 93 (78-113), PDI was 87 (83-96). One child who was diagnosed

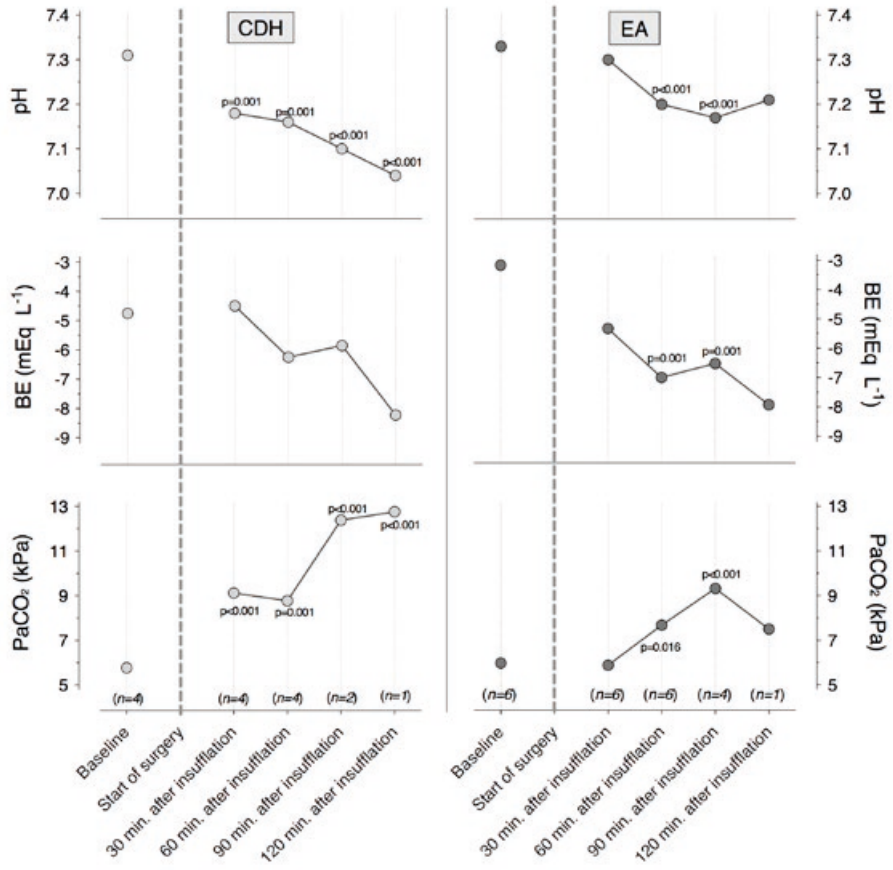

Figure 14. Blood gas analyses. Estimated marginal means of arterial blood gas values pH and $PaCO_2$ (kpA) at baseline and during artificial CO_2-pneumothorax in patients with congenital diaphragmatic hernia (CDH) and esophageal atresia (EA). P-values are for comparisons of the estimated marginal means at each time point with baseline.

with a Feingold syndrome had a mildly delayed mental development. Motor function was slightly delayed in one other EA patient. In CDH, both children that were assessed at 24 months had normal MDI (both 115) and PDI was 87 and 84, respectively. The median (range) number of procedures under general anaesthesia within the first 24 months of life was 2.5 (1-7) in the EA-group and 2 (1-2) in the CDH-group.

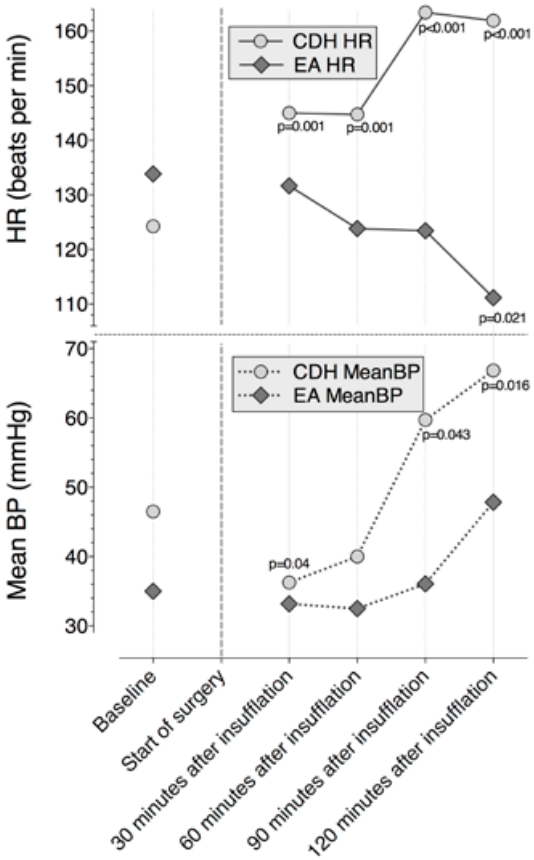

Figure 15. Hemodynamic parameters. Estimated marginal means of hemodynamic parameters heart rate (HR; beats per min.) and mean blood pressure (Mean BP; mmHg) at baseline and during artificial CO_2-pneumothorax in patients with congenital diaphragmatic hernia (CDH) and esophageal atresia (EA). P-values are for comparisons of the estimated marginal means at each time point with baseline.

5.4. Discussion

This pilot study in neonates undergoing thoracoscopic repair of CDH and EA is, to our best knowledge, the first to investigate the impact of CO_2 pneumothorax on cerebral and renal rSO_2, with corresponding intermediate term neurodevelopmental outcome.

Neonatal thoracoscopic surgery is often complicated by substantial hypercapnia as a result of a combination of CO_2 absorption[15] and ventilation-perfusion mismatch[4]. Hypercapnia decreases cerebral vascular resistance, resulting in increased cerebral blood flow[16,17] and may even result in hyperperfusion of the brain[18]. Hypercapnia furthermore results in a decrease of high-energy phosphates leading to a decrease in cellular metabolism, ultimately leading to intra- and extracellular acidosis[16,19]. Acidosis is known to result in activation of a multitude

of enzymes and activation of the transcription of apoptotic genes. This eventually promotes cell death and may lead to neuronal injury[19].

As previously described by Bishay et al[3], patients in our study developed acidosis almost immediately after CO_2 insufflation, which remained during the entire surgical period despite all efforts to more effectively eliminate CO_2 by continuous adjustments of ventilator settings.

A growing body of evidence suggests that cerebral rSO_2 values are predictive of neurological outcome after cardiac surgery in infants; goal directed intervention strategies according to rSO_2 values have been shown to improve outcome in this patient group[20,21]. No clinically relevant changes in renal or cerebral rSO_2 values were found in our patients, despite significant combined respiratory and metabolic acidosis. In patients with CDH, the course of renal FTOE during the surgical procedure (see figure 13) peaked after 30 minutes of CO_2-pneumothorax, whereas cerebral FTOE remained relatively constant. This initial peak in renal FTOE may be due to a shift of oxygen supply from the kidneys to the brain after initiation of CO_2-pneumothorax, in order to ensure sufficient oxygen supply of the brain in favour of the kidneys. The same applies to the course of ΔCR- rSO_2 in the CDH group, with a negative baseline value (-2.75%) and positive values (22.25-26.25) throughout the procedure.

In patients with EA, cerebral FTOE remained relatively stable throughout the procedure, whereas renal FTOE showed quite a different pattern, starting with a high baseline value (0.5) and rather constant intraoperative values on a lower level (0.03-0.07). In EA patients ΔCR- rSO_2 showed a different pattern, starting high at baseline (20.03) and then developing a variable pattern during surgery with ups and downs between 28.6 and -16.3. We can only speculate on the reasons for these findings. One possible explanation could be that it might be a result of the effects of anaesthesia induction and endotracheal intubation on vascular resistance, blood pressure and cardiac output (which only had to be performed in patients with EA). Additionally, CDH and EA are fundamentally different pathologies, also possibly contributing to these findings.

Our observation of normal values for tissue oxygenation during neonatal thoracoscopic surgery, with concordant normal neurodevelopmental outcome in this study could indicate a predictive value of NIRS with regard to intermediate-term neurological outcome, as previously described in paediatric cardiac patients[20,21]. It could however also be that this apparent lack of change is due to the small number of patients, with only one patient in each group still undergoing

surgery at 120 min. Also, potential compensatory changes resulting from the effects of anaesthetic drugs on the cerebral circulation may play a role. When considering the assumed advantages of minimal access surgery in neonates, i.e. less pain, lower stress response and better cosmetic outcome, these have to be weighed against the risks and side-effects, also considering neurodevelopmental outcomes in the long term[22,23]. In our study, neurodevelopmental outcome within the first 24 months of life was within normal ranges and comparable to previously published data in EA and CDH patients who underwent an open surgical procedure[9]. However, (subtle) neurodevelopmental deficits may be present and problems with school performance may arise at older age[23]. Whether neonatal thoracoscopic surgery carries an additional risk for patients related to acidosis and presumed neuronal damage deserves further research. That research should be performed by experts in the field within the framework of well-designed, sufficiently powered prospective clinical trials with structured neurodevelopmental long-term follow-up until school age. We are aware that such trials are not easy to realise, in view of the low incidence of both CDH and EA and considering that paediatric surgical care is not always centralised. However, our patients and their parents deserve evidence-based answers on questions regarding the benefits and risk of neonatal minimal access surgery.

5.5. Conclusion

Artificial CO_2-pneumothorax, applied during neonatal thoracoscopic surgery for repair of CDH and EA, frequently leads to severe acidosis. In this prospective pilot study, cerebral rSO_2 remained within clinically acceptable limits during periods of acidosis. Neurodevelopmental outcome was favourable within the first 24 months. Our findings suggest that it is worth further investigating the potential of NIRS to improve perioperative care during neonatal thoracoscopic surgery and neurodevelopmental outcome.

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6

Feasibility of Doppler ultrasound for cerebral blood flow velocity monitoring during major non-cardiac surgery of newborns

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Abstract

Background and aim. Newborns needing major surgical intervention are at risk of brain injury and impaired neurodevelopment later in life. Disturbance of cerebral perfusion might be an underlying factor. This study investigates the feasibility of serial transfontanellar ultrasound measurements of the pial arteries during neonatal surgery, and whether perioperative changes in cerebral perfusion can be observed and related to changes in the perioperative management.

Methods. In this prospective, observational feasibility study, neonates with congenital diaphragmatic hernia and oesophageal atresia scheduled for surgical treatment within the first 28 days of life were eligible for inclusion. We performed transfontanellar directional power Doppler and pulsed wave Doppler ultrasound during major high-risk non-cardiac neonatal surgery. Pial arteries were of interest for the measurements. Extracted Doppler ultrasound parameters were: peak systolic velocity, end diastolic velocity, the resistivity index and pulsatility index.

Results. In 10 out of 14 patients it was possible to perform perioperative measurements; the others failed for logistic and technical reasons. In 6 out of 10 patients, it was feasible to perform serial intraoperative transfontanellar ultrasound measurements with directional power Doppler and pulsed wave Doppler of the same pial artery during neonatal surgery. Median peak systolic velocity was ranging between 5.7 and 7.0 cm s^{-1} and end diastolic velocity between 1.9 and 3.2 cm s^{-1}. In patients with a vasEActive-inotropic score below 12 the trend of peak systolic velocity and end diastolic velocity corresponded with the mean arterial blood pressure trend.

Conclusion. Perioperative transfontanellar ultrasound Doppler measurements of the pial arteries are feasible and provide new longitudinal data about perioperative cortical cerebral blood flow velocity.

6.1. Introduction

Newborns requiring major surgical intervention are at risk for brain injury and impaired neurodevelopment later in life[1,2,3]. A review including a meta-analysis showed this applies to all sorts of non-cardiac congenital anomalies[3]. A study in 101 neonates who had an MRI exam seven days after different types of non-cardiac major surgical procedures reported an incidence of brain injury of 75% in preterm and 58% in term neonates[2]. In here, parenchymal lesions (punctate white matter lesions, punctate cerebellar lesions, thalamic infarction, periventricular hemorrhagic infarction) were found in 42% and nonparenchymal lesions (supra- and infratentorial subdural hemorrhages, intraventricular hemorrhage grade II, asymptomatic sinovenous thrombosis) in 38% of the term neonates. A case series (n=6) of infants with severe postoperative encephalopathy showed supratentorial watershed infarction in the border zone between the anterior, middle, and posterior cerebral arteries after relatively moderate surgical procedures[4]. Disturbance of cerebral perfusion might be the underlying factor triggering brain injury[4,5].

Despite state-of-the-art care, anesthetic monitoring lacks sensitivity to detect altered cerebral perfusion during high-risk neonatal surgery[6]. Transfontanellar ultrasound with directional power Doppler (DPD) and pulsed wave Doppler (PWD) allows imaging real-time cerebral perfusion and quantifying cortical cerebral blood flow velocity (CBFV) in large arteries or veins. PWD is used for measuring flow velocities by calculating the Doppler waveform shift, while DPD presents the amount of Doppler energy from the vessel, instead of an alteration in velocity and therefore represents the amount of blood flow (perfusion). Doppler ultrasound is particularly feasible in neonates because of the open anterior fontanel, and is frequently used in the neonatal intensive care to screen for intracranial hemorrhages or thrombosis[7]. Recently measuring cortical CBFV has been introduced during neonatal cardiac surgery under cardiopulmonary bypass[8].

Transfontanellar ultrasound with DPD and PWD might provide insight in the perioperative cerebral cortical blood flow in neonates, which is currently a black box. So far, one study used transfontanellar ultrasound intraoperatively, although they measured the internal carotid artery to predict fluid responsiveness in a specific patient group following cardiac surgery and a mean age of 5 months[9]. In view of the above mentioned brain injuries, we consider the cortical arteries

within the supratentorial watershed area of interest for creating understanding about the trigger for perioperative brain injury.
The aim of this study was to determine the feasibility of perioperative serial transfontanellar ultrasound measurements of the pial artery with DPD and PWD in neonates undergoing high risk non-cardiac surgery. Additionally, we investigate whether inter- and intra-individual perioperative changes in cortical CBFV can be observed with DPD/PWD and can be related to changes in perioperative management which might indicate the additional value of this new technique in comparison to conventional monitoring systems.

6.2. Materials and methods

In this prospective, observational feasibility study, we performed transfontanellar ultrasound with DPD and PWD before, during and after surgical treatment of neonates with 2 major congenital anomalies: congenital diaphragmatic hernia (CDH) or esophageal atresia (EA). Measurements were performed after institutional research board approval and written informed consent from both parents. Ethical approval was provided by the Medical Ethical Committee of Erasmus Medical Centre, Rotterdam, The Netherlands on 13 February 2019 (Chairpersons Professor H.J. Metselaar and Professor H.W. Titanus, protocol number MEC 2017-145, amendment feasibility study). Trial registration NL6972, URL: https://www.trialregister.nl/trial/6972).

6.2.1. Patients

Children born with CDH or EA scheduled for surgical repair between May 2019 and February 2020 were eligible for inclusion, except those with chromosomal anomalies, syndromes associated with major cognitive impairment or complex cardiac anomalies. CDH neonates were managed according to the CDH-EURO consortium protocol[10]. EA neonates breathed spontaneously postnatally and received respiratory support if necessary.

We focused on patients with CDH or EA representing major non-cardiac anomalies that require surgical repair within the first days of life. Patients with CDH are cardiopulmonary unstable due to the lung hypoplasia and pulmonary hypertension, while neonates with an isolated EA are cardiopulmonary stable.

6.2.2. Data collection

Cerebral perfusion is quantified as a volume of flow per unit time and is affected by perioperative management, fluctuations in PaO_2 and $PaCO_2$, vaso-active medication and changes in blood volume[11]. Therefore, the following data were obtained: continuous registration of vital parameters (heart rate, blood pressure, saturation) (Primus, Draeger, Luebeck, Germany), cerebral regional oxygenation (rSO_2) with neonatal sensor, (INVOS 5100C, Covidien, Boulder, Colorado, United States) and continuous transcutaneous carbon dioxide levels (Sentec, Therwil, Switzerland) were registered and analyzed off-line. Continuous transcutaneous pCO_2 measurements were used in combination with intermittent arterial blood gas analyses. Ventilation settings, medication, fluids and arterial blood gas analysis were registered in the electronic patient record (Hix, Chipsoft, Amsterdam, The Netherlands). Patients received general anesthesia with sevoflurane (end expiratory concentration: 1-2%) in the operation theatre or bolus complemented with continuous dosage of midazolam (200 $\mu g\ kg^{-1}\ h^{-1}$) if surgery was performed in the pediatric intensive care unit (PICU). Both groups also received fentanyl (1.5-3$\mu g\ kg^{-1}$) and rocuronium (0.5-1$mg\ kg^{-1}$). After induction of anesthesia, patients with CHD or EA planned for thoracoscopic surgery were positioned laterally and for open surgery in supine position.
The vasoactive-inotropic score (VIS) was calculated to quantify necessity of cardiovascular support[12]. VIS reflects the grade of vasoactive/inotropic pharmaceutical intervention and is calculated: dopamine dosage ($\mu g\ kg^{-1}\ minute^{-1}$) + dobutamine dosage ($\mu g\ kg^{-1}\ minute^{-1}$) + 100x epinephrine dosage ($\mu g\ kg^{-1}\ minute^{-1}$) + 100x norepinephrine dosage ($\mu g\ kg^{-1}\ minute^{-1}$) + 10x milrinone dosage ($\mu g\ kg^{-1}\ minute^{-1}$) + 1000x vasopressin dosage ($U\ kg^{-1}\ minute^{-1}$). Vital parameters and VIS were analyzed off-line from electronic registration obtained during successful ultrasound measurement.
Routine preoperative and postoperative cranial ultrasound scans were performed by an experienced pediatric radiologist to screen for cerebral injury.

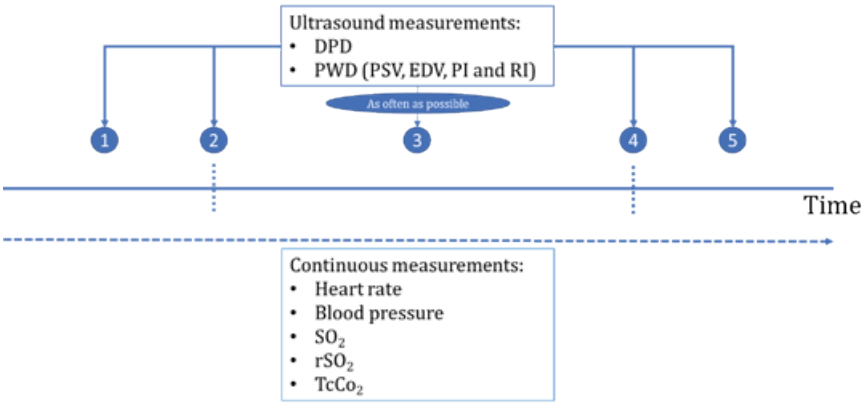

Figure 16. Overview of the measurements. Description of timepoints on the horizontal axes: period 1: at PICU preoperative, 2: after induction of anaesthesia before surgery, 3: during surgical procedure, 4: after completion of the surgery and before transport to PICU, 5: PICU postoperative. SpO_2: oxygen saturation, rSO_2: cerebral oxygenation. PSV: peak systolic velocity, EDV: end diastolic velocity, RI: the resistivity index and PI: pulsatility index.

Preoperative transfontanellar ultrasound with DPD and PWD measurement was obtained in the PICU within the hour before transport to the operation theatre. Serial intraoperative measurements were performed as frequently as possible, without interfering with regular perioperative care. A final measurement was performed within 30 minutes after surgery in the PICU. A schematic overview of all measurements is provided in figure 16.

6.2.3. Ultrasound protocol

A clinical ultrasound machine, Zonare ZS3 (Mindray Medical International, Hoevelaken, Netherlands) with a high frequency linear probe (L20-5) was used for all ultrasound measurements. DPD and PWD are standardly available and commonly used modes on ultrasound machines. The frequency for DPD was 11 MHz with a medium wall filter, the velocity scale was set as low as possible. For PWD, frequency was set to 8 MHz with a low wall filter.
Two researchers (SC, AK) were trained by a brain ultrasound specialist and neonatologist (PG) in performing transfontanellar ultrasound in neonates. For practical reasons and limited space available in the operating theatre, two researchers were needed to perform measurements; one to control the ultrasound machine and one to hold the probe and perform the scan (figure 17). Visual feedback of the scan for this second person was provided by a 9-inch

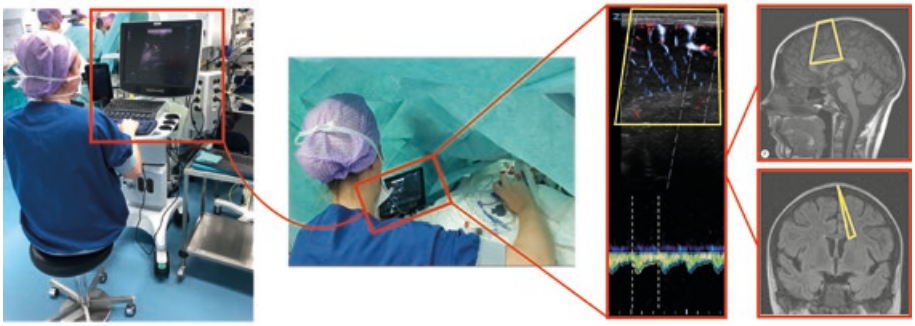

Figure 17. Ultrasound measurement setup. Left panel: One researcher controlled the ultrasound machine outside the workspace of the surgeon and anaesthesiologist. Middle: One researcher held the probe and performed the ultrasound scan with the feedback by an extended screen. Right panel: The cerebral vasculature in the ultrasound plane was visualized with power Doppler. The spectral Doppler gate was placed in a vertically oriented part of this pial artery.

extension screen connected to the ultrasound machine. This way the ultrasound machine was kept out of the workspace of surgeon and anesthesiologist.
Since the area adjacent to the lateral ventricle is one of the border zones prone for watershed injury[3,4], the probe was placed sagittally on the anterior fontanel on the plane adjacent to one of the lateral ventricles. Then, the cerebral vasculature in the ultrasound plane was visualized with DPD. Measured cortical pial arteries were perfused by the anterior cerebral artery. A recognizable pial artery confirmed the plane location for subsequent measurements in the same patient. The spectral Doppler gate was placed vertically in the pial artery (figure 17), and the beam-to-flow angle was corrected. In some patients, both the left and right hemisphere were measured during surgery. In others, it was not possible to find the same pial artery for every measurement. We only used measurements in the same pial artery in the same hemisphere to compare measurements. Peak systolic velocity (PSV) in cm s^{-1}, end diastolic velocity (EDV) in cm s^{-1}, resistivity index (RI) and pulsatility index (PI) values were collected from PWD. RI is an arterial resistivity index which quantifies pulsatile blood flow and reflects resistance of CBF[13,14]. RI is calculated by (PSV–EDV)/PSV. PI is the difference in pulsatile flow velocities divided by time-averaged velocity[15]. PI is calculated by (PSV–EDV)/Vmean in which Vmean is the time-averaged velocity of the PWD in cm s^{-1}. Even though the different parameters are interdependent, they provide complementary information: PSV and EDV reflect absolute flow velocities, while RI and PI reflect intra-beat ratios.

Patient number	Anomaly	Sex	GA (weeks + days)	BW	Age at surgery (d)	Preoperative sedated and ventilated	Anaesthesia intraoperative	Surgical approach	Duration surgery (min)	VIS-score PICU preoperative	Range VIS score intraoperative	VIS-score PICU postoperative
1	CDH	M	38 + 5	3000	12	Yes	Midazolam	Laparotomy	105	5	15	5
2	CDH	F	38 + 2	3260	2	Yes	Sevoflurane	Laparotomy	76	0	1 to 12	3
3	CDH	F	41 + 0	3420	2	No	Sevoflurane	Laparotomy	70	0	3 to 8	8
4	CDH	M	40 + 1	3018	3	No	Sevoflurane	Thoracoscopy, conversion	99	0	6 to 56	8
5	CDH	M	40 + 4	3155	3	Yes	Sevoflurane	Thoracoscopy	128	0	0 to 8	0
6	CDH	M	38 + 4	2700	4	Yes	Sevoflurane	Thoracoscopy	106	27	17-27	15
7	CDH	F	40 + 6	4042	3	Yes	Sevoflurane	Thoracoscopy, conversion	170	0	5 to 20	0
8	OA	M	40 + 2	2970	2	No	Sevoflurane	Thoracoscopy	142	0	0 to 48	0
9	OA	M	34 +1	1950	1	No	Sevoflurane	Thoracotomy	80	0	0	0
10	OA	M	32 + 6	1734	1	No	Sevoflurane	Thoracotomy	108	0	0 to 10	0

Table 18. Patient characteristics. CDH: congenital diaphragmatic hernia, OA: oesophageal atresia, M: male, F: female. GA: Gestational Age, BW: birth weight, Vasoactive-inotropic score (VIS): dopamine + dobutamine +10 x milrinone + 100 x epinephrine + 100 x norepinephrine + 1000x vasopressin, all dosages in microgram per kilogram per minute[37].

6.2.4. Data analysis

Data were collected at multiple time points; in the PICU preoperatively (period 1), after induction of anesthesia, before start of surgery (period 2), during surgical procedure (period 3), after surgical procedure (period 4) and after returning in the PICU postoperatively (period 5). Retrospectively, transfontanellar ultrasound measurements were analyzed off-line for changes in cortical CBFV in the perioperative period and for their relation to perioperative management by studying HR, MABP, oxygen saturation, rSO_2, transcutaneous pCO_2 and VIS in relation to PSV, EDV, RI and PI. We presented visualized measurement series with the most repetitive measurements if the same pial artery was not identified. Data were analyzed in absolute values for each time point. Data and graphs are expressed as medians with inter quartile ranges (IQR) and outliers (MathWorks MATLAB v9.7.0.1190202 (R2019b), Natick, Massachusetts, United States). During surgical procedure, multiple measurements were obtained and presented as the medians of the mean values.

6.3. Results

Informed consent was obtained for 14 neonates. In four patients it was not possible to obtain adequate measurements because of our learning process (n=1), logistic and technical failure due to small operation theatre (n=1), the position of the surgeon near the neonate's head (n=1) and insufficient image quality because of small fontanel size and too much hair (n=1) (figure 18). Data of ten neonates were analyzed. Median gestational age was 39.4 weeks (IQR 38.4 to 40.5), birth weight 3009 grams (IQR 2500 to 3234), age at surgery 2.5 days (IQR 2 to 3) and duration of surgical procedure 106 minutes (IQR 85 to 123). One patient had surgery in the PICU, the other nine patients had surgery in the operation theatre (table 18 and in the appendix, table 19). Five patients were sedated and mechanically ventilated preoperatively. In all patients, routine cranial ultrasound examinations were performed one day before and after surgery and no signs of brain injury were found.

6.3.1. Feasibility

Preoperative measurements were successfully performed in all ten patients. It was possible to perform measurements after induction in seven patients. In five patients it was possible to measure the same pial artery. It was possible to perform measurements in all ten patients during surgery. It was possible to follow up the same pial artery during surgery, although in four patients it was not the same artery as measured preoperatively. There were 4 to 14 successful ultrasound measurements per patient during surgery (figure 19, 20 and 21). It was possible to perform measurements after surgery in five patients in the same pial artery as during surgery. Postoperatively in the PICU, it was possible to perform measurements in nine patients. It was not possible to measure the same pial artery in one patient (appendix, table 20). The research setup (figure 17) with two persons led to efficient good-quality imaging without interfering with the anesthesiologist's or surgeon's workspace.

6.3.2. Perioperative measurements

Perioperative median HR ranged between 111 and 142 bpm with a decrease postoperatively (figure 19). Median MABP ranged between 46 and 59 mmHg increasing postoperatively. Saturation remained above 90% in all patients during surgery and cerebral oxygenation increased after induction with a median up to 95%. Transcutaneous pCO_2 was measured intraoperatively with a median varying between 5.5 to 6.3kPa. There was little need for preoperative hemodynamic support, but support was needed intraoperatively (VIS 0-56, table 18 and in the appendix, table 21). Administered vasoactive and inotropic drugs were norepinephrine, epinephrine, dobutamine and milrinone. The highest VIS during an ultrasound measurement intraoperatively was 40 (appendix 21).
Cortical CBFV changes occurred perioperatively as well. Median PSV ranged between 5.7 and 7.0 cm s^{-1} and EDV between 1.9 and 3.2 cm s^{-1}. Median RI and PI increased over time; RI increased from 0.47 to 0.65 after induction and decreased intraoperatively to 0.53. PI increased from 0.69 to 1.1 after induction, decreased intraoperatively to 0.78 and postoperatively in the PICU to 0.78 (figure 19).

6.3.3. Cerebral ultrasound parameters in relation to perioperative management

For the nine out of ten patients who were operated in the operation theatre and anaesthetized with sevoflurane, postoperative PSV and EDV were higher than intraoperatively. In patients with limited need of hemodynamic support (maximum VIS of 12 or deltas of less than 12), the trend of PSV and EDV corresponded with the MABP trend (patients 2, 3, 5, 9, 10) (figure 20). In these five patients, especially the pattern and fluctuations of EDV were similar to those of MABP. In all patients, fluctuations in PSV were larger than fluctuations in EDV. Differences between PSV and EDV increased intraoperatively over time. A comparable trend between rSO_2 and PSV/EDV was observed in two patients (patient 2, 9). rSO_2 fluctuated more than PSV and EDV. In patients with higher need of hemodynamic support, PSV and EDV trends corresponded less with the MABP trend (patients 1, 4, 6, 7, 8). In these five patients VIS was not only higher (maximum VIS of 56), but also had larger changes in dosages (VIS ranging from 10 to 50) compared to the patients in whom PSV and EDV showed the same trend

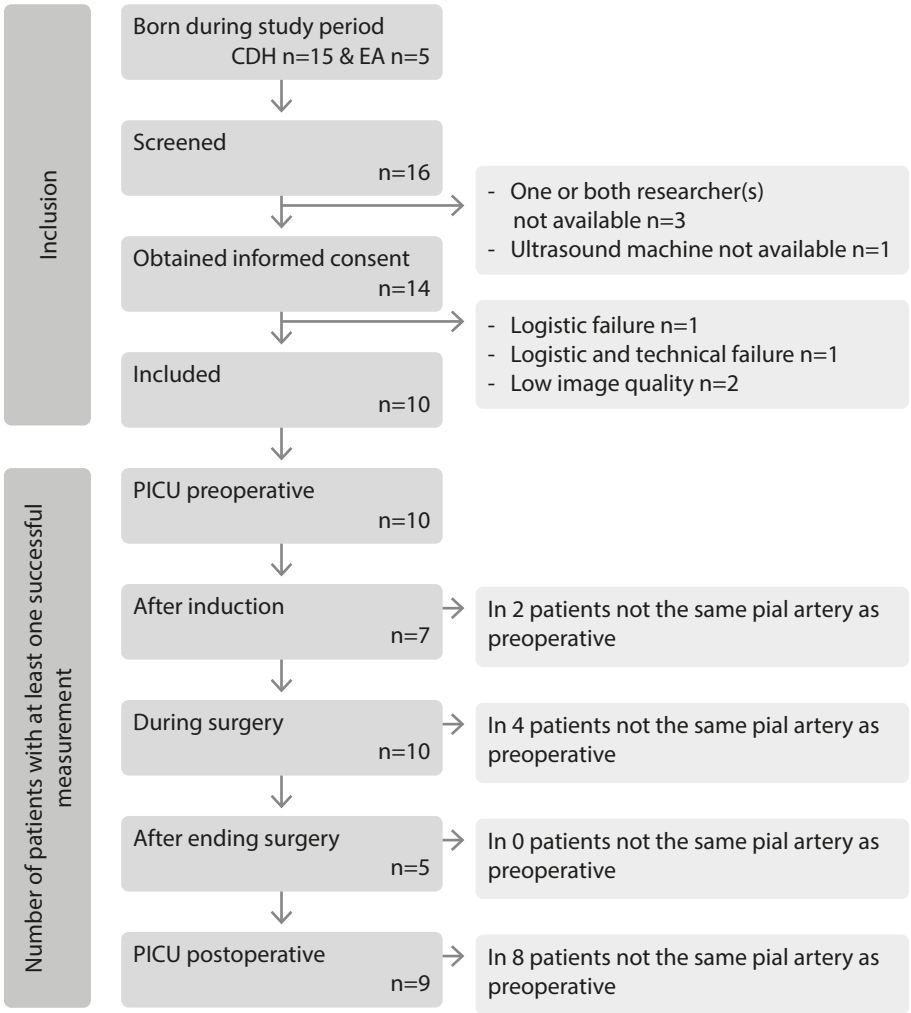

Figure 18. Inclusion and feasibility flowchart.

as MABP (table 18). One patient (patient 7) had an increase in VIS of 20 which was reduced to a VIS of 5 at the start of the surgical procedure (figure 21). No relation between MABP and PSV/EDV could be observed during a VIS of 20. Once VIS decreased and modifications in VIS remained limited, changes in PSV and EDV started showing the same trend as MABP. No comparable trend between rSO_2 and PSV/EDV was observed in these five patients.

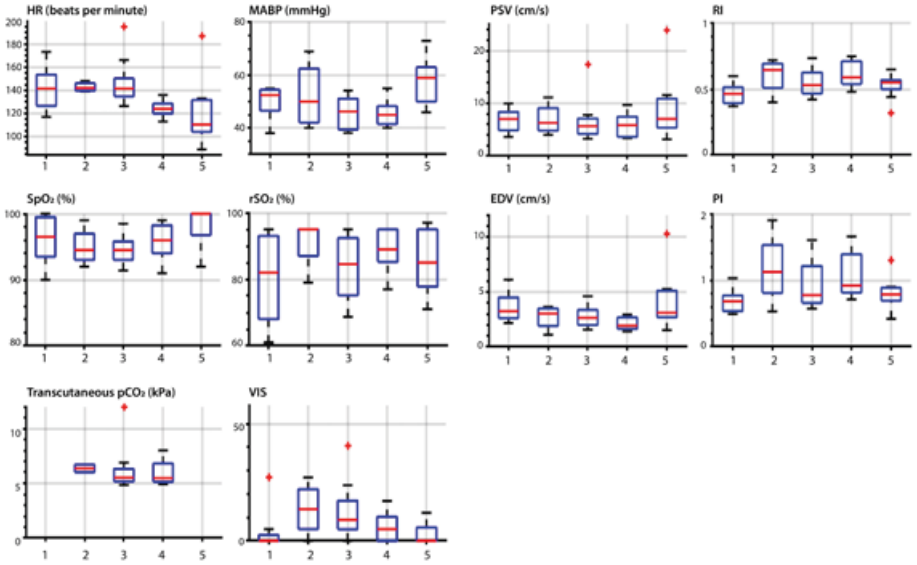

Figure 19. Overview of vital parameters and ultrasound parameters during the perioperative measurements. Description of timepoints on the horizontal axes: 1: at PICU preoperative, 2: after induction of anaesthesia before surgery, 3: during surgical procedure, 4: after completion of the surgery and before transport to PICU, 5: PICU postoperative. HR: heart rate, MABP: mean arterial blood pressure, SpO_2: oxygen saturation, rSO_2: cerebral oxygenation. PSV: peak systolic velocity, EDV: end diastolic velocity, RI: the resistivity index and PI: pulsatility index. The red central mark of the box indicates the median and the bottom and top of the box indicates the interquartile ranges. The whiskers end at the most extreme data points not considered outliers, which are marked with a red +.

6.4. Discussion

This study shows it was feasible to perform serial intraoperative transfontanellar ultrasound measurements of the pial arteries with DPD and PWD during high-risk non-cardiac neonatal surgery. In six out of ten patients, it was possible to perform repetitive measurements to obtain longitudinal perioperative cortical CBFV data. Furthermore, we observed large changes in cortical CBFV perioperatively which were independent of heart rate or measures of cerebral oxygenation, but did correspond with mean arterial blood pressure during limited need for hemodynamic support.

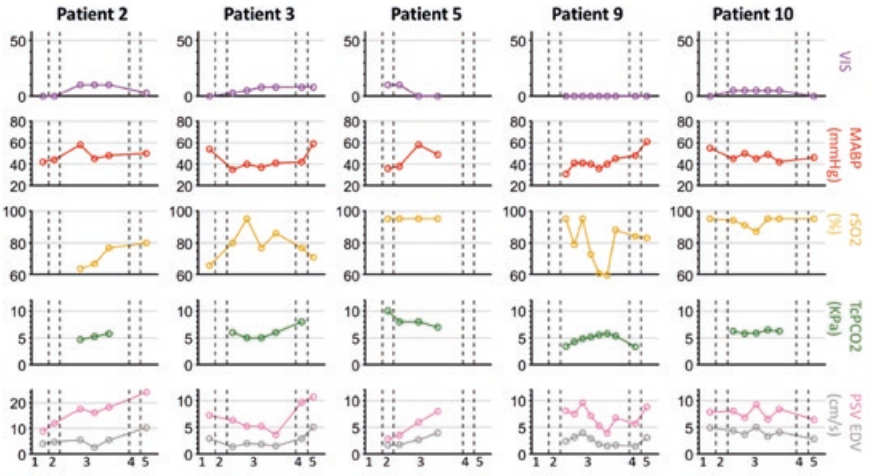

Figure 20. Measurements in patients during stable hemodynamic equilibrium with low VIS. Timepoint 1: at PICU preoperative, 2: after induction of anaesthesia before surgery, 3: during surgical procedure, 4: after completion of the surgery and before transport to PICU, 5: PICU postoperative.

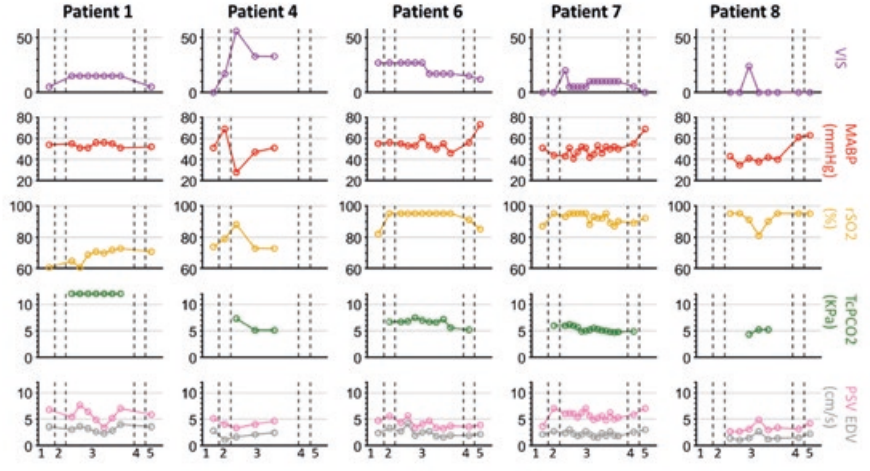

Figure 21. Measurements in patients during less stable hemodynamic equilibrium with high VIS. Timepoint 1: at PICU preoperative, 2: after induction of anaesthesia before surgery, 3: during surgical procedure, 4: after completion of the surgery and before transport to PICU, 5: PICU postoperative.

6.4.1. Feasibility

Adaptability of surgeons and anesthesiologists was crucial in this feasibility study because we had to interfere with their workspaces. The setup (figure 17) with two sonographers enabled us to obtain serial measurements with limited influence on perioperative care. The feasibility of repetitive measurement in the same pial artery in the same plane mainly depended on position of both the patient and the surgeon. When the neonate was positioned laterally for thoracotomy or thoracoscopy, there was very limited maneuvering space. During thoracoscopic repair the surgical workspace is more around the patient's head, making it especially difficult to perform transfontanellar ultrasound measurements without interfering with the surgical procedure.
In four of the 14 patients it was not possible to perform ultrasound measurements or to obtain sufficient image quality. Measurements in the first patient failed because of technical issues, mainly related to our learning process. This was our first attempt to measure intraoperatively and we had to optimize the research set-up. It was challenging to position the ultrasound probe at the neonate's head, since the neonate was placed in the middle of the operation table. Additionally, the extended screen was placed behind the researcher. The lack of visual feedback resulted in insufficient image quality. Another patient was operated in a small operation theatre with minimal space for our research set-up with an ultrasound machine and two researchers. Measurements could not be obtained without interfering with regular care. For one patient, the position of the surgeon was adjacent to the neonate's head, which made ultrasound measurements impossible without hindering the surgical procedure. Even though there were logistic and technical issues in measurements in three patients, only in one patient the measurements failed due to patient characteristics. This neonate had a small fontanel size and too much hair which resulted in insufficient image quality. The amount of successful perioperative measurements varied between 4-14 measurements per patient. The main factors that explained this large variation are the learning curve and operation time. Over time it became easier to find the same pial artery intraoperatively, this resulted in a reduction in time for ultrasound scanning. Furthermore, measurements were obtained as often as possible, without interfering with the perioperative care. In longer surgeries, there were more opportunities for ultrasound scanning. However, (multiple) interventions by the anesthesiologist could be needed if a neonate became

cardiorespiratory instable during the surgical procedure, which led to less available moments for ultrasound measurements.
Successful, repetitive measurements of the same pial artery preoperatively and intraoperatively was possible in 60% of the patients. Intraoperatively, repetitive measurements of the same pial artery were possible in 100% of the patients.
This study shows that cortical CBFV changes intraoperatively, suggesting that monitoring pial artery perfusion provides crucial information about cortical CBFV, whether it is the same pial artery as measured preoperatively or not. Follow-up of the same pial artery perioperatively might be ideal, although one could argue if the preoperative clinical condition of these patients provides representative baseline measurements of cortical CBFV.

6.4.2. Cerebral ultrasound parameters in relation to perioperative management

Our study suggests that cortical CBFV changes in the perioperative period, while changes in the vital parameters remained limited to fluctuation in MABP and changes in PSV and EDV are related to changes in MABP, except when MABP was strongly manipulated with vasoactive and inotropic drugs. Limited fluctuations of hemodynamic support – maximum delta VIS of 12 or maximum VIS of 12 – had no visible effect on the relations between MABP and PSV or EDV. Relations between the ultrasound parameters and rSO_2 were not found.
Current techniques monitoring vital parameters (HR, MABP, SpO_2 and rSO_2) are poor approximations of brain perfusion in the neonate. Transfontanellar ultrasound measurements with DPD and PWD is a sensitive and objective method that might be of additional value in the perioperative period, especially during great need of hemodynamic support. One study proofed it is feasible to predict fluid responsiveness with transfontanellar ultrasound intraoperatively. Although this was measured in the internal carotid artery during cardiac surgery in older patients[9].
An earlier study of our team found that the maximum dose of vasoactive medication was negatively associated with verbal and visuospatial memory in 8-year-old survivors of neonatal extracorporeal membrane oxygenation and CDH survivors[16]. The patients in our current study participate in a structured long-term

follow-up program which could clarify the effect of these VIS fluctuations on brain development later in life.

6.4.3. Regulation of cerebral blood flow

Regulation of CBF in the healthy human brain is complex and multiple regulation systems are involved; cerebral autoregulation, flow-metabolism coupling and neurogenic regulation[17]. Cerebral autoregulation is affected by vasoactive and inotropic medication and PaO_2 and $PaCO_2$ have an effect on cerebral vascular resistance[5,6,18]. Vasoactive and inotropic medication mediate changes in the cerebral vascular resistance by the cerebrovascular adrenergic receptors. In adults, the administration of norepinephrine, which was the most administered inotropic drug in our study, led to unchanged or decreased cortical CBFV, unchanged or increased cortical CBFV and an increased cerebral perfusion pressure[19,20,21,22,23,24]. This may explain our incoherent results in cortical CBFV during changes in vasoactive and inotropic medication.

Neonates are prone to intraoperative hypercapnia[25,26,27]. However, the effect of hypercapnia on cerebral perfusion in anesthetized neonates is virtually unknown[5]. Research with transcranial Doppler ultrasound of the middle cerebral artery during hypercapnia in anesthetized adults showed increased PSV, EDV and decreased RI and PI, whereas hypocapnia had the opposite effects[28]. In our study, the variance of CO_2 was limited and the number of other highly changing parameters was too big to observe an effect of changes in $PaCO_2$.

Additionally, the CBF-metabolism coupling might be affected during anesthesia, when the cerebral activity is reduced[29]. In this study, the PSV and EDV increased postoperatively in all patients anaesthetized with sevoflurane intraoperatively. This suggests that the cerebral oxygen consumption increased postoperatively due to an increase in cerebral activity and metabolism. All of the above-mentioned changes might be determinants of the development of brain injury. Previous research showed that there is a link between fluctuation and extreme values in cortical CBFV and germinal matrix hemorrhages, intraventricular hemorrhages and white matter injury in (preterm) neonates[30,31,32]. However, a correlation between Doppler parameters and structural brain damage has not yet been found, possibly explained by the lack of frequent measurements in previous research[33].

6.4.4. Improvements

A possible improvement to increase continuity could be a probe holder designed for neonatal surgery, making the second sonographer redundant. This would also allow measuring at specific moments or during specific surgical interventions without interfering with the anesthesiology or surgery. A probe holder would solve the technical and logistical issues we encountered and increase the feasibility of the measurements. An example of transfontanellar Doppler ultrasound in neonates is the NeoDoppler probe, which enables measuring cerebral blood flow velocities in a cylindrical shape with a diameter of 1 cm and a depth between 3-35 mm [34]. Another improvement could be made in optimizing vascular imaging. The ultrasound technique used in this study does not provide information about microcirculation in the (sub)cortex. A promising technique is high frame rate ultrasound (>1000 frames per second), which enables more sensitive vascular imaging throughout the imaging plane and facilitates quantification in every vessel[35]. In 2014, Demené et al.[36] used high frame rate ultrasound for neonatal brain scanning for the first time, which resulted in high resolution images of the vascular network with simultaneous quantitative data of the ultrasound plane.

In the future, transfontanellar ultrasound measurements with DPD and PWD could guide clinicians in detecting fluctuations in CBFV. Potentially, this could aid in preventing brain injury by early detection of potential hazardous CBFV evoking protective intervention. Monitoring of the pial arteries could especially lead to a reduction in parenchymal lesions and supratentorial watershed infarction. The combination of DPD and PWD enables to image real-time cerebral perfusion. This allows for visualizing the vessel tree and monitoring CBFV throughout the surgery. Future additions of high frame rate ultrasound and the use of a probe holder would expand the possibilities of this technique.

In conclusion, this study shows that it is possible to perform transfontanellar ultrasound measurements in the pial arteries with DPD and PWD during major high-risk non-cardiac neonatal surgery. Cortical cerebral blood flow does fluctuate perioperatively, which could not be observed with the currently used monitoring techniques, especially not in neonates with higher need of hemodynamic support. Therefore, the next step would be to implement transfontanellar ultrasound with DPD and PWD in a larger group of patients perioperatively.

Acknowledgments

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Patient number	Anomaly	Side	Defect size/type	Liver
1	CDH	Left	C	Down
2	CDH	Left	A	Down
3	CDH	Right	A	Up
4	CDH	Left	A	Down
5	CDH	Left	B	Down
6	CDH	Left	B	Down
7	CDH	Left	C	Down
8	OA		C+TEF	
9	OA		C+TEF	
10	OA		C+TEF	

Table 19. Appendix 1. Additional patient characteristics.

Patient number	Anomaly	PICU preoperative (1)	After induction (2)	During surgery (3)	After ending surgery (4)	PICU postoperative (5)
1	CDH	1 right	-	7 right	1 right	
2	CDH	1 left/1 right	1 left	2 left/3 right		1 left/1 right
3	CDH	1 left/ 1 right	-	4 left	1 left	1 left
4	CDH	1 right	1 right	3 right/2 right different pial artery	-	1 right same different pial artery as during surgery
5	CDH	1 left/1 right	1 right/1 right in a different pial artery	3 right in a different pial artery/2 left	-	1 right
6	CDH	1 right	1 right	7 right	1 right	1 right
7	CDH	1 right	1 right	14 right	1 right	1 right
8	OA	1 left	1 left	1 left/6 left in a different pial artery	-	2 left same different pial artery as during surgery
9	OA	1 left/1 right	-	6 left in a different pial artery	1 left same different pial artery as during surgery	1 left same different pial artery as during surgery
10	OA	1 left	1 left different artery	5 left	-	1 left

Table 20. Appendix 2. Overview of all performed measurements.

Anomaly	Patient	PICU preoperative (1)	After induction (2)	During surgery (3)	After ending surgery (4)	PICU postoperative (5)
CDH	1	Milrinone 0.5γ	Milrinone 0.5γ and start epinephrine 0.05γ and norepinephrine 0.05γ	Milrinone 0.5γ, epinephrine 0.05γ and norepinephrine 0.05γ	Milrinone 0.5γ and epinephrine 0.05γ. Stop norepinephrine 0.05γ	Milrinone 0.5γ
	2	0	Start norepinephrine 0.12γ	↓ norepinephrine to 0.10γ	Norepinephrine 0.10γ	↓ norepinephrine to 0.03γ
	3	0	Start norepinephrine 0.03γ	↑ norepinephrine to 0.08γ	Norepinephrine 0.08γ	Norepinephrine 0.08γ
	4	0	Start norepinephrine 0.17γ	↑ norepinephrine to 0.56γ and ↓ norepinephrine to 0.33γ	↓ norepinephrine 0.11γ	↓ norepinephrine 0.08γ
	5	0	Start dobutamine 5γ and epinephrine 0.05γ	Stop dobutamine 5γ and epinephrine 0.05γ	000	0
	6	Milrinone 0.5γ, norepinephrine 0.12γ, epinephrine 0.1γ	Milrinone 0.5γ, norepinephrine 0.12γ, epinephrine 0.1γ	Milrinone 0.5γ, norepinephrine 0.12γ, stop epinephrine 0.1γ	Milrinone 0.5γ, norepinephrine 0.12γ	Milrinone 0.5γ and ↓ norepinephrine to 0.07γ
	7	0	0	Start norepinephrine 0.2γ and ↓ norepinephrine to 0.05γ and ↑ norepinephrine to 0.1γ	↓ norepinephrine to 0.05γ	Stop norepinephrine 0.05γ
OA	8	0	0	Start norepinephrine 0.48γ and ↓ norepinephrine to 0.24γ and stop norepinephrine	0	0
	9	0	0	0	0	0
	10		Start norepinephrine 0.05γ	Norepinephrine 0.05γ	Stop norepinephrine 0.05γ	0

Table 21. Appendix 3. Overview of administrated vasoactive and inotropic drug in the perioperative period. γ: microgram per kilogram per minute

7

Mitochondrial oxygen monitoring during surgical repair of congenital diaphragmatic hernia or esophageal atresia: a feasibility study

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Abstract

Background. Current monitoring techniques in neonates lack sensitivity for hypoxia at cellular level. The recent introduction of the non-invasive Cellular Oxygen METabolism (COMET) monitor enables measuring in vivo mitochondrial oxygen tension(mitoPO$_2$), based on oxygen-dependent quenching of delayed fluorescence of 5-aminolevulinic acid (ALA)-enhanced protoporphyrin IX. The aim is to determine the feasibility and safety of non-invasive mitoPO$_2$ monitoring in surgical newborns.

Method. MitoPO$_2$ measurements were conducted in a tertiary pediatric center during surgical repair of congenital diaphragmatic hernia or esophageal atresia. Intraoperative mitoPO$_2$ monitoring was performed with a COMET monitor in 11 congenital diaphragmatic hernia and 4 esophageal atresia neonates with the median age at surgery being 2 days(IQR 1.25-5.75). Measurements were done at the skin and oxygen-dependent delayed fluorescence was measurable after at least 4 hours application of an ALA plaster.

Results. Pathophysiological disturbances led to perturbations in mitoPO$_2$ and were not observed with standard monitoring modalities. The technique did not cause damage to the skin, and seemed safe in this respect in all patients, and in twelve cases intraoperative monitoring was successfully completed. Some external and potentially preventable factors – the measurement site being exposed to the disinfectant chlorohexidine, purple skin marker or infrared light - seemed responsible for the inability to detect an adequate delayed fluorescence signal.

Conclusion. In conclusion, this is the first study showing it is possible to measure mitoPO$_2$ in neonates and that the cutaneous administration of ALA to neonates in the described situation can be safely applied. Preliminary data suggests that mitoPO$_2$ in neonates responds to perturbations in physiological status.

7.1. Introduction

Major (non-cardiac) neonatal surgery is challenging for clinicians. The neonatal homeostasis is a frail equilibrium and is highly affected by general anesthesia and surgical manipulation[1,2]. The anesthesiologist aims to monitor the physiology with the help of the heart rate, invasive blood pressure, saturation, end-tidal carbon dioxide, skin perfusion, urine output and serum lactate. These broad range of monitoring modalities are used as surrogate of end-organ perfusion with adequate oxygen transport as a prime goal. To date, the optimal blood pressure in neonates for adequate perfusion of peripheral and cerebral tissue is unknown. Invasive techniques available for effective monitoring of the circulation/cardiovascular system are seldom used due to technical restraints in neonates or are simply not feasible during neonatal surgery[3]. Yet, the incidence of brain injury after (non-cardiac) neonatal surgery is increasingly reported[4,5] as well as altered long–term neurodevelopmental outcomes[6,7,8,9]. Several factors are thought to contribute to the postoperative brain injury, including alterations in the perioperative neonatal hemodynamics.

Adequate oxygen supply to tissues is of pivotal importance. A non-invasive, bedside monitoring modality for cellular oxygenation could provide direct information about oxygen transport. This allows clinician to adjust their management on actual measurements of tissue perfusion and oxygenation instead of systemic circulatory measures. In this light, monitoring of cellular oxygenation has been suggested to be beneficial during neonatal-cardiac surgery due to the highly affected hemodynamics [10]. Yet, major non-cardiac congenital anomalies which requires surgery within the first days causes alterations in the neonatal physiology as well[4,7]. The recent introduction of the non-invasive Cellular Oxygen METabolism (COMET) monitor (Photonics Healthcare B.V., Utrecht, The Netherlands) makes it possible to measure in vivo mitochondrial oxygen tension (mitoPO$_2$). Although mitochondrial oxygen sensing has been recognized as a promising technique for pediatric ICU and anesthesia[11,12], until now reported use has been limited to adults[13,14,15,16]. The present study tests feasibility and safety of intraoperative use of COMET monitoring in infants for the first time.

The COMET monitor measures mitoPO$_2$ by means of oxygen-dependent quenching of delayed fluorescence[17]. Green pulsed laser excitation of protoporphyrin IX (PpIX) leads to a relatively long-lived red-light emission, called "delayed fluorescence". The intensity of the delayed fluorescence decays with an

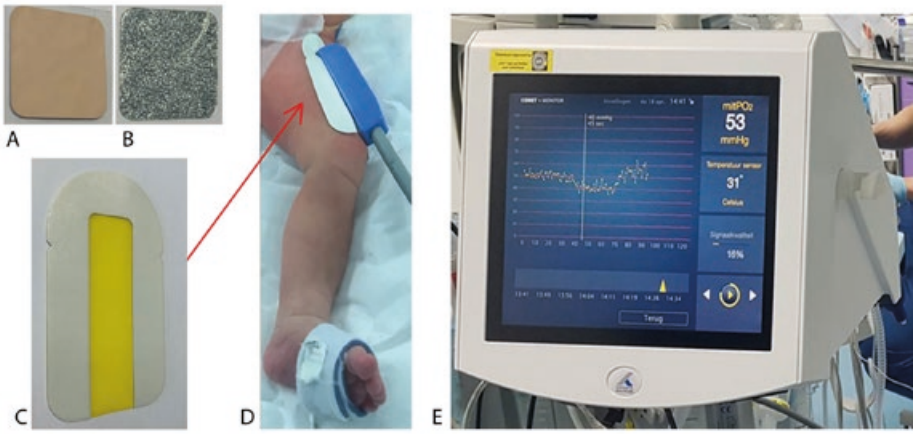

Figure 22. The ALA plaster with the aluminium cover (A) and the ALA side (B), double-sided tape (C) which is used for the application of the COMET-skin sensor (red arrow) on the frontal side of the upper leg (D) and the Cellular Oxygen METabolism (COMET) monitor (E).

oxygen-dependent lifetime, meaning more oxygen results in a shorter lifetime and vice versa. PpIX is the final precursor of heme in the heme-biosynthetic pathway, synthesized inside the mitochondria. Under normal (non-sensitized) conditions PpIX concentrations in human skin are very low and non-detectable with COMET. Administration of 5-aminolevulinic acid (ALA) increases mitochondrial PpIX concentrations and ensures the mitochondrial origin of the delayed fluorescence signal[15]. Therefore, to enable measurements with the COMET monitor, ALA needs to be applied on skin to induce PpIX, the latter acting as mitochondrially located oxygen-sensitive dye[17,18].

ALA is registered for use in adults, for example for photodynamic therapy in dermatologic pathology[19,20] and to visualize brain tumors during fluorescence-guided surgery[21,22] and was not used in pediatric patients until recently. Research with cutaneous ALA administration up to 354 mg in infants of 5 years and older reported no side effects[23]. Oral administration of 20 mg kg^{-1} ALA in infants of 1 year and older showed a transient increase of alanine aminotransferase[24,25,26]. Rarely, the administration of 5-aminolevulinic acid led to an allergic reaction, in here contact dermatitis are the only reported allergies[27]. Therefore, we assumed the safety on a systemic level of a very low dosage of ALA – 8mg – on the skin of neonates, providing an opportunity to use COMET monitoring in neonates for the first time. Primary outcomes of this study were feasibility and safety, especially

local (photo)toxicity, of cutaneous ALA administration in combination with using the COMET monitor in neonates perioperatively. A secondary outcome was preliminary evaluation of anesthesiologic and surgical procedures influencing mitoPO$_2$.

7.2. Material and Methods

The institutional research board approved a feasibility study of 15 neonates (MEC 2017-145).
After obtained informed consent from both parents, measurements were performed during surgical treatment of neonates with congenital diaphragmatic hernia (CDH) or esophageal atresia (EA). Surgery took place in the operating theater, unless the neonate was on extracorporeal membrane oxygenation (ECMO), in which case the surgery was performed in the pediatric intensive care unit due to logistics.
In this study the feasibility was defined as the possibility of priming the skin with ALA and to measure mitoPO$_2$ in neonates. The safety was defined as (the lack of) any adverse event of the skin after cutaneous administration of ALA and measurement with COMET until 48 hours after the COMET-skin sensor was removed.
An Alacare® plaster has a square format of 2 by 2 cm and contains 2mg per cm2 ALA (Alacare, photonamic, Pinneberg, Germany). The plaster is covered by an aluminum layer to protect the primed skin to light exposure (figure 22)[28]. The plaster was applied in the pediatric intensive care unit (ambient temperature of approximately 22 degrees of Celsius) on the skin on the frontal side of the upper leg for at least 4 hours before starting the measurement. Research in adults showed that a priming time of 4 hours or more was needed to synthesize the suitable concentration of PpIX to enables measurements of mitoPO$_2$ in the skin[15]. The same minimal priming time was maintained in this study.
The COMET-skin sensor has a biocompatible housing of 7 x 2 x 2 cm. The skin sensor was placed on the primed skin and was attached to the skin by a double-sided plaster provided by the COMET manufacturer (figure 22). The influence of light on the primed skin during the application of the COMET-skin sensor was

n=15	Median (IQR)
Male gender, n (%)	8 (53%)
Gestational age, wk	38.1 (37.7 – 40.2)
Birth weight, grams	3000 (2400 – 3340)
Age at surgery, days	2 (2 – 5.5)
Duration of surgery, min	106 (95-116)
Priming time skin, min	465 (413 – 720)
Duration MitoPO_2 measurement	116 (98 – 133)
Surgical approach	
Thoracoscopy, n (%)	5 (33%)
Thoracotomy, n (%)	2 (13%)
Laparotomy, n (%)	8 (53%)
Surgery during ECMO, n (%)	2 (13%)

Table 22. Patient demographics.

minimized by turning off the surgical luminaires/lamps. After the application of the skin sensor, the biocompatible housing was covered with aluminum foil. Continuous registration of routine vital parameters, regional cerebral oxygenation (rSO_2) (INVOSTM 5100C) and mitochondrial saturation (COMET) were obtained and stored for off-line analyses. Sampling rate of the vital parameters was every second, rSO_2 every 6 seconds and mitochondrial oxygen tension (mitoPO_2) every 60 seconds. Intraoperative management was registered in our Patient Data Management System. Patients received general anesthesia with sevoflurane/midazolam, rocuronium and fentanyl. MitoPO_2 measurements started before surgery and continued until after surgery. After completion of the measurement the primed skin was shielded against light with an aluminum plaster for 48 hours. This is based on the pharmacological characteristics of ALA. The mean half-life fluorescence clearance of PpIX is 30 ± 10 hours.

7.3. Results

Informed consent was obtained in 11 CDH and 4 EA patients. Intraoperative measurements were performed in all 15 included neonates. Neonates had a median gestational age of 38 weeks (IQR 37,7 – 40,2), a median birth weight of 3,000 grams (IQR 2,400-3,340) and a median age at surgery of 2 days (IQR 2-5.5). Median duration of the surgical procedure was 106 minutes (IQR 95-116) and two patients received surgical repair of CDH on ECMO in the pediatric intensive

	HR	MABP	Saturation	rSO_2	$MitoPO_2$
Start measurement	133 (113 – 142)	41 (37 – 44)	96 (94 -97)	87 (66 – 93)	58 (51 – 60)
+10 minutes	130 (112 – 146)	48 (40 – 53)	94 (91 – 97)	83 (69 – 92)	57 (55 – 64)
+20 minutes	133 (118 – 140)	49 (40 – 62)	96 (93 – 97)	88 (69 – 93)	54 (53 – 63)
+30 minutes	133 (122 – 151)	47 (44 – 49)	95 (94 – 97)	81 (74 – 93)	53 (49 – 60)
+40 minutes	146 (135 – 160)	42 (35 – 46)	92 (90 – 97)	79 (70 – 88)	53 (52 – 56)
+50 minutes	144 (137 – 156)	41 (35 – 48)	95 (91 – 99)	82 (72 – 89)	50 (48 – 54)
+60 minutes	149 (137 – 164)	43 (39 – 45)	97 (91 – 99)	88 (77 – 95)	51 (49 – 54)
+70 minutes	154 (136 – 166)	45 (40 – 48)	96 (92 – 97)	87 (65 – 94)	52 (49 – 58)
+80 minutes	150 (137 – 168)	45 (35 – 46)	96 (95 – 99)	86 (71 – 95)	52 (47 – 59)
+90 minutes	151 (133 – 168)	42 (37 – 48)	97 (91 – 99)	83 (67 – 94)	53 (52 – 59)
+100 minutes	157 (124 – 163)	42 (39 – 45)	96 (92 – 99)	78 (65 – 91)	51 (50 – 63)
+110 minutes	133 (121 – 168)	46 (42 – 52)	97 (93 – 99)	84 (68 – 91)	53 (50 – 64)
+120 minutes	137 (127 – 171)	42 (37 – 52)	96 (92 – 99)	77 (74 – 91)	48 (45 – 53)

Table 23. Median and IQR values of the 12 successfully obtained measurements.

care unit (table 22). Median skin priming time with ALA was 7h45m (IQR 6h50m – 12h0m). Twelve out of 15 measurements were successful with a median duration of the $MitoPO_2$ measurement of 116 minutes (IQR 98-133) (table 22). The first measurement failed due to the radiant warmer (infra-red light), the second due to pink chlorohexidine-alcohol disinfectants and the third due to purple skin marker on the primed skin.

In the 12 successful measurements (table 23) the $mitoPO_2$ interquartile range at start of the measurement was 51 – 60 mmHg. In all neonates the skin was examined on regular timepoints; after removing the ALA plaster after priming of the skin, directly after removing the COMET-sensor, at 24 hours and 48 hours after removing the COMET-sensor. No adverse events such as erythema or other signs of an irritated skin were observed.

Two cases illustrate fluctuations in $mitoPO_2$ in relation to surgical and anesthetic actions. Case 1 (figure 23A) is a female neonate, gestational age 37 weeks, birth weight 2,500 grams, with CDH requiring veno-arterial ECMO treatment due to therapy-resistant pulmonary hypertension. Surgical treatment was on day 8 of life, during ECMO. Priming of the skin with ALA was 6 hours. During surgery bleeding intercostal arteries caused significant blood loss. Vital parameters and rSO_2 remained unchanged, but $mitoPO_2$ decreased from 62mmHg at start surgery to 36mmHg (a reduction of 42%) during blood loss and partially recovered after supplementation with erythrocyte transfusion with a $mitoPO_2$ up to 53mmHg at the end of the surgery.

Case 2 (figure 23B) is a male neonate, gestational age 34 weeks, birth weight 1,950 grams, with EA type C with a trachea-esophageal fistula. Surgical repair took place on day 1 of life. Skin priming time with ALA was 8 hours. The patient

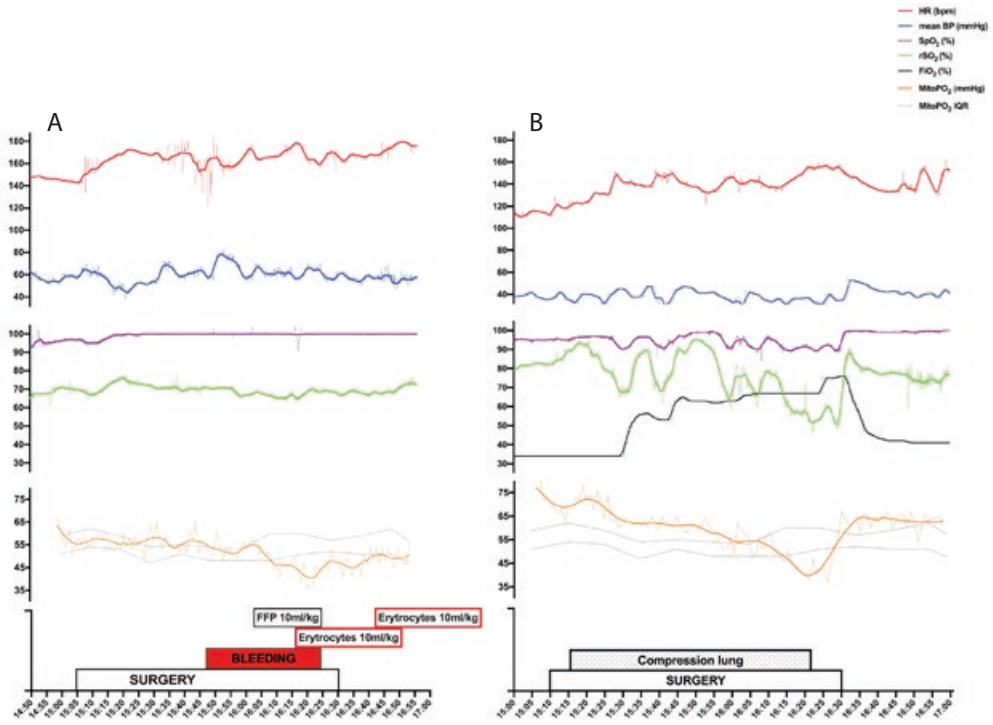

Figure 23. Surgical repair of congenital diaphragmatic hernia during EMCO (A) Surgical repair of esophageal atresia (B).

was positioned on the left side during surgery. Surgical compression of the lung caused hypoxia which required increasing FiO_2 from 35% to 75% to maintain peripheral saturation between 90% and 95%. Blood pressure and heart rate remained stable, rSO_2 responded on the increased FiO_2 firstly, but $mitoPO_2$ decreased soon after the compression started and continues to decrease from 69 mmHg at start surgery to 37 mmHg (a reduction of 47%) and restored within minutes after manipulation of the lung was finished with a $mitoPO_2$ up to 62mmHg at the end of the surgery.

7.4. Discussion

This is the first study showing feasibility of mitoPO$_2$ measurements in neonates, and importantly, in a clinically relevant high-risk perioperative setting. Measurements with the COMET monitor proved feasible and safe in terms of local damage to the skin. Furthermore, pathophysiological disturbances led to perturbations in mitoPO$_2$. In twelve out of fifteen patients mitoPO$_2$ measurements were successful. Failures were caused by external and potentially preventable factors, disabling detection of an adequate delayed fluorescence signal. In one case infrared warming lamp heat or radiation interfered with the priming of the skin with ALA. Aluminum foil is a strong infrared reflector and was successfully used to shield the ALA plaster against infrared radiation during priming of the skin in the following cases. In the two other failed cases colored substances on the skin interfered with measurements, chlorohexidine with pink pigment and skin marker are both significant sources of delayed fluorescence and thereby potent disturbers of the mitochondrial PpIX light emission.

Safety of ALA administration with Alacare plasters was a major concern for the ethics committee due to the off-label use of ALA for measuring mitoPO$_2$ with the COMET. The reaction of the neonatal skin on ALA administration was unknown and consequently we only obtained approval to perform this feasibility and safety study. ALA makes the skin sensitive for light, consequently it is frequently used for photodynamic therapy in different sorts of dermatologic pathology. In children of five years and older, the administration of ALA up to 354 mg, which is over 40 times higher than de 8mg ALA that was applied on the skin in this study, did not have any side effects[23]. Oral administration of 20 mg kg^{-1} ALA in infants of 1 year and older showed a transient increase of alanine aminotransferase[24,25,26]. Systemic effects of topical/local administration of ALA on the skin have not been reported and in this study, we focused on potential local side effects in neonatal skin.

There is a risk for erythema and burns when the skin is exposed to (day)light after the administration of ALA. Therefore, precautionary measures were taken to shield the skin for light for 48 hours after the measurement with the COMET was ended and the skin sensor was removed. In none of the cases local damage or irritation of the skin was observed, so the combination of ALA-plaster and COMET measurements seems safe.

The pharmacokinetic properties of topical ALA administration with Alacare in neonates are unknown, but in adults the reported skin priming time with ALA

takes 4 till 8 hours[13]. In this study, the same priming times were maintained for neonates. In a following efficacy study, the power calculation/sample size will be focused on validating mitoPO$_2$ measurements in neonates and analyzing the ideal priming time of the neonatal skin. This will create insight in the reaction of the skin to the application of ALA in term and preterm neonates.

For this study two major non-cardiac congenital anomalies were included: congenital diaphragmatic hernia (CDH) and esophageal atresia (EA). These congenital anomalies were chosen to be eligible because major surgery is required within the first days of life and postoperative brain injury are reported in children with these congenital anomaly[4,7]. CDH neonates suffer from lung hypoplasia and abnormal morphology of the pulmonary vasculature which results in respiratory insufficiency and severe (therapy-resistant) pulmonary hypertension[29,30]. CDH neonates are a challenge for clinicians to manage due this altered physiology. In EA neonates, the physiology is less affected by the congenital anomaly itself, but requires complex surgery with major intrathoracic manipulation which highly affects the neonatal physiology[31]. In these children, our preliminary results suggest that monitoring mitochondrial oxygenation might register changes in neonatal physiology which could not have been observed using standard monitoring devices. Clearly, further research into the clinical usability of COMET is warranted but seems justified based on this pilot. Although this was only a feasibility and safety study, these results confirm that mitochondrial hypoxia may occur without clear signs of central hypoxia and are in line with previous research in animals and humans[32,33,34,35]. A piglets study demonstrated cutaneous mitoPO$_2$ changed earlier than MABP and lactate during ongoing hemodilution[32]. In a sepsis rat model as well as in rats with induced right ventricular failure due to pulmonary arterial hypertension, mitoPO$_2$ proved an additional parameter monitoring physiological changes[33,34]. The clinical prototype of the COMET was tested in healthy volunteers and showed measuring mitochondrial oxygenation and oxygen consumption in humans[13]. Previous reports demonstrated the intraoperative use of COMET in adults[15] and also demonstrated that mitoPO$_2$ measurements are not limited to the skin[35]. The first study using COMET during upper gastro-intestinal endoscopy showed it is technically feasible and safe[35].

Adequate oxygen supply to tissues is of pivotal importance to sustain mammalian life. Aerobic metabolism is maintained through inhalation of air in the lungs and subsequent transport of the absorbed oxygen to tissues via the circulation. The

flow of hemoglobin-bound oxygen through the macro- and microcirculation and diffusion of molecular oxygen into the tissue cells brings oxygen to the mitochondria. In the mitochondria, oxygen is used in oxidative phosphorylation in order to efficiently produce adenosine triphosphate (ATP) that acts as the energy source for many cellular processes. Furthermore, mitochondria are essential for homeostasis of the cell, they play a major role in (programmed) cell death (apoptosis). Opening of the mitochondrial permeability transition pore, as a result of a stressful stimulus such as calcium or reactive oxygen species overload, leads to loss of the mitochondrial membrane potential[36]. The collapse of the membrane potential results in ATP depletion and necrosis[37], and the release of mitochondrial content such as cytochrome c leads to apoptosis[38]. A correlation to outcome after perturbations in cellular oxygenation have not yet been shown, but it could be used as an early warning sign. Importantly, in both a preclinical[32] and clinical setting[15] mitoPO$_2$ provided different information than hemoglobin saturation-based techniques like near- infrared spectroscopy (NIRS). Although visible light spectroscopy and near-infrared spectroscopy failed to show any response on a perturbation, mitoPO$_2$ clearly dropped. This was observed during hemodilution in piglets, where mitoPO$_2$ was measured simultaneously with tissue oxygen saturation on the thoracic wall. The mitoPO$_2$ decreased after the hemoglobin dropped below a threshold, but tissue oxygen saturation, which was measured with NIRS, did not[32].

We previously published a clinical example in which mitoPO$_2$ showed a different response than microvascular hemoglobin-saturation. During peripheral vasoconstriction, which was induced by the administration of clonidine, microvascular flow and velocity parameters measured with laser-doppler decreased both. The venous-capillary oxygen saturation did not decrease, however, mitoPO$_2$ in the skin measured by COMET decreased along with the decrease in flow and velocity[15]. While mitoPO$_2$ and microvascular flow provided similar information here, we expect additional value of mitoPO$_2$ measurements in clinical situations in which microvascular shunting[39] and loss of hemodynamic coherence occur[40], for example in sepsis and hemodilution. During sepsis microcirculatory dysfunction occurs which causes shunting and loss of the coherence between blood flow and tissue oxygenation. Here microvascular, and ultimately mitochondrial, oxygen measurements can be of additional value[39]. The same holds true during a hyperdynamic circulation due to hemodilution, causing erythrocytes to pass too quickly through the microcirculation. This

phenomenon is referred to as functional shunting and involves the inability of hemoglobin to off-load oxygen fast enough to the tissues as it passes through the microcirculation, causing cellular hypoxia while hemoglobin saturation is normal or increased[40,41].

In this study we found baseline mitoPO$_2$ values in the range of 51-60 mmHg. In a previous study in healthy volunteers we reported mean mitoPO$_2$ to be 44 mmHg, and in a very recently published study in critical care patients mean mitoPO$_2$ was reported to be around 60 mmHg[42]. Such relatively high values match well with other oxygen measurements in skin[43]. The differences between the studies could well be attributed to factors like skin temperature, filling status of the patient, and use of sedation/anesthesia, since such factors are known to influence skin perfusion. Clinical data until now are scarce and normal values for mitoPO$_2$ remain to be determined, as well as the influence of patient factors (such as age) and clinical circumstances. Although we do think mitochondrial oxygen tension is in general higher than anticipated[12], the reader should realize that mitoPO$_2$ in other organs and tissues is likely to differ. Differences in tissue oxygen levels exist between organs, tissues and tissue compartments[43] and metabolic activity (for example muscle contraction) is also of influence.

To date, clinicians are in the dark about the effect of the altered neonatal (patho) physiology during major high-risk surgery on cellular oxygenation. In the past the focus was to optimize macrohemodynamics although the microcirculation has been increasingly recognized as an import variable in the critically ill neonate[44]. To measure tissue oxygenation, a modality based on the principle of near infrared spectroscopy (NIRS) became popular. The optode of the NIRS emits near-infrared light, which easily penetrates biological tissue at a depth of approximately 2 to 3 cm [45,46]. It measures the oxygenation of a combination of 75% venous, 20% arterial and 5% capillary blood, but does not provide information about the oxygen concentration at cellular level. Unfortunately, the clinical use of additional monitoring with NIRS have not been established yet[47]. The COMET allows us to look at oxygen availability at a cellular level. The neonatal skin is an ideal target organ for COMET measurements. It is the biggest organ in neonates and has a relative bigger surface and is more vascularized compared to adults. Skin blood circulation is very sensitive to changes in vascular resistance and blood pressure[48], potentially making the skin a good indicator for the (general) cardiopulmonary status of the neonate.

Compared to interstitial measurements with for example oxygen electrodes COMET has some distinct advantages, such as no need for calibration, non-destructiveness (no need for needle placement), well-defined measurement compartment and very fast response time (no need for signal integration over longer periods of time). A disadvantage of the COMET technique is the necessary priming with ALA. Although previous studies in adults and this study in neonates, show that with some precaution's application of ALA to the skin can be done without harm, it requires planning and currently prevents its use in emergency situations. In elective situations in the operating room and for use in the intensive care this proved not a major issue.
In conclusion, this is the first study showing it is possible to measure mitoPO_2 in neonates and that the cutaneous administration of ALA to neonates in the described situation can be safely applied. Preliminary data suggests that mitoPO_2 in neonates responds to perturbations in physiological status. The added value of mitochondrial measurements for clinical decision making remains to be determined in future studies.

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8

Cerebral oxygenation and activity during surgical repair of neonates with congenital diaphragmatic hernia: a comparative analysis

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Abstract

Objective. In current clinical practice, neonatal brain monitoring is increasingly used due to reports of brain injury perioperatively. Little is known about the effect of sedatives (midazolam) and anesthetics (sevoflurane) on cerebral oxygenation ($rScO_2$) and cerebral activity. This study aims to determine these effects in the perioperative period.

Design. An observational, prospective study.

Setting. Perioperative neuromonitoring in neonates in two high volume pediatric surgical centers.

Patients. Neonates with a congenital diaphragmatic hernia (CDH) who require surgery.

Intervention. All patients received cerebral oxygenation and activity measurements. Patients were stratified based on intraoperatively administrated medication: the sevoflurane group (continuous sevoflurane, bolus fentanyl, bolus rocuronium) and the midazolam group (continuous midazolam, continuous fentanyl, and continuous vecuronium).

Measurements and main results. Intraoperatively, $rScO_2$ was higher in the sevoflurane compared to the midazolam group (84%, IQR 77-95 vs 65%, IQR 59-76, p=<.001), fractional tissue oxygen extraction was lower (14%, IQR 5-21 vs 31%, IQR 29-40, p=<.001), the duration of hypoxia was shorter (2%, IQR 0.4-9.6 vs 38.6%, IQR 4.9-70, p=.023), and cerebral activity decreased more: slow delta: 2.16 versus 4.35 μV^2 (p=.0049), fast delta: 0.73 versus 1.37 μV^2 (p=<.001). In the first 30 min of the surgical procedure, a 3-fold increase in fast delta (10.48 to 31.22 μV^2) and a 5-fold increase in gamma (1.42 to 7.58 μV^2) were observed in the midazolam group.

Conclusion. Sevoflurane-based anesthesia resulted in increased cerebral oxygenation and decreased cerebral activity, suggesting adequate anesthesia. Midazolam-based anesthesia in neonates with a more severe CDH (more liver-up and higher VIS) led to alarmingly low $rScO_2$ values, below hypoxia threshold, and

increased values of EEG power during the first 30 minutes of surgery. This might indicate conscious experience of pain. In the future, integrating population-pharmacokinetic models and multimodal neuromonitoring ware needed for personalized pharmacotherapy in these vulnerable patients.

8.1. Introduction

In current clinical practice, clinicians are increasingly monitoring the neonatal brain during high-risk neonatal surgery, due to the increased number of patients who develop brain injury perioperatively, resulting in impaired neurodevelopmental outcome[1,2,3,4]. For decades, the potential 'protective' effect of agents that reduce cerebral metabolism and consequently reduce cerebral oxygen consumption against ischemia and hypoxia have been raised[5].
A multimodal brain monitoring is needed to monitor the interplay between cerebral oxygenation and activity[6]. Near-infrared spectroscopy (NIRS) presents a continuous, non-invasive measurement of regional cerebral oxygen saturation ($rScO_2$), with reference values between 55% and 85% for awake neonates[7]. Baseline $rScO_2$ can vary as a result of sensor placement[8,9], sensor type, and the measurement device[10,11]. To give a good definition of hypoxia, studies are performed to define the hypoxia threshold for the different sensors[12,13]. Furthermore, it is possible to analyze cerebral oxygen consumption by using the fractional tissue oxygen extraction (FTOE)[14]. Intraoperative use of NIRS has been explored, but no coherent results have been reported in non-cardiac neonatal surgery[6] and NIRS-guided treatment guidelines are only available in pediatric cardiac surgery[15].
The activity of the neonatal brain is generally quantified using electroencephalography (EEG), which measures the overall electrical activity of the cortical pyramidal neurons[16]. Consequently, EEG has a great sensitivity of showing changes in neural functioning[17]. The power of the EEG is computed in different frequency bands. Delta oscillations (δ: 0.5–4Hz) dominate the neonatal EEG and regulate basic homeostatic needs[18]. The delta band can be divided into slow delta (δ_1: 0.5–2Hz) and fast delta (δ_2: 2–4Hz). Noxious-evoked EEG activity can be studied by analyzing gamma oscillations (γ: 32–100Hz) over the

contralateral somatosensory cortex and by analyzing energy in the fast delta band (δ_2)[19]. A strong increase in gamma γ oscillations and an energy increase in the fast delta δ_2 band was shown to reflect nociceptive pain in neonates following heel lance[19].
To date, little is known about the effect of anesthetic approaches on cerebral oxygenation and how $rScO_2$-values should be interpreted during anesthesia[6,20]. In this study, patients with a congenital diaphragmatic hernia (CDH), treated according to a standardized international guideline[21] received two different anesthetic approaches intraoperatively: a sedative-agent (midazolam) with analgesia and muscle relaxation versus an anesthetic-agent (sevoflurane) with analgesia and muscle relaxation. The aim of this study was to determine the effects of midazolam versus sevoflurane on cerebral oxygenation and cerebral activity in the perioperative period.

8.2. Materials & Methods

This is a multicenter, observational, prospective study on perioperative neuromonitoring in neonates with a CDH. All patients underwent surgery in a tertiary pediatric referral center: the Sophia Children's Hospital (Rotterdam, the Netherlands), or the Mannheim University Hospital (Mannheim, Germany), which treat approximately 20 and 60 neonates a year, respectively. Local institutional review board approval (Erasmus MC, Rotterdam, The Netherlands, MEC-2017–145, and Universitätsmedizin Mannheim, Mannheim, Germany 2018-578N-MA) and written informed consent of parents or legal guardians were obtained. The study is registered in the Netherlands trial register (www.trialregister.nl), clinical trial number NL6972, principal investigator Prof R.M.H. Wijnen, date registered 2018-04-15. This manuscript adheres to the applicable CONSORT guidelines.

8.2.1. Patients

The present study focused on neonates with a CDH, a major non-cardiac anomaly, that requires surgical repair within the first days of life. In both expertise centers,

CDH neonates were eligible for inclusion if surgical repair was scheduled between July 2018 and April 2020 within the first 28 days of life, regardless of the type of surgery (open or thoracoscopic surgery), or the need for extracorporeal membrane oxygenation (ECMO) therapy until 24 hours before surgery, for which both centers used the same entry criteria[21]. Neonates were excluded if they had major cardiac or chromosomal anomalies, syndromes associated with altered cerebral perfusion, or syndromes associated with major neurodevelopmental impairment. In addition, neonates on ECMO during the start of the procedure were also excluded. Patients were treated according to the CDH-EURO consortium guidelines[21].

8.2.2. Perioperative management

The neonates enrolled in the present study were stratified in two groups. In Rotterdam, surgery was performed in the operating room (OR) and anesthesia was sevoflurane based (end expired concentration between 1% to 2%), with bolus fentanyl (induction 1-5 ug kg^{-1}) and rocuronium (0.5-1.0 mg kg^{-1}) performed by a pediatric anesthesiologist. In Mannheim, surgery was performed at the neonatal intensive care unit (NICU), and anesthesia was based on continuous midazolam (70-100ug kg^{-1} h^{-1}), fentanyl (2-5 ug kg^{-1} h^{-1}), and vecuronium (0.10-0.30 mg kg^{-1}) and bolus fentanyl (2 – 10ug kg^{-1}), performed by a neonatologist. Repeated administration of analgesia was based on clinical evaluation.
Patients were operated in the OR if transport was possible and at the NICU if transport to the OR was not possible due to cardiorespiratory instability and/or ECMO. Patients operated at the OR underwent thoracoscopic surgery if they were hemodynamically stable and if the liver was not herniated into the thorax.

8.2.3. Data Collection

Patient demographics were collected according to the international consensus about standardized reporting for CDH[22]. Measurements were performed in a continuous fashion, started at least 6 hours before surgery and continued up to 24 hours after surgery. Perioperative management, such as the administration of

medication and the analysis of arterial blood gasses, was recorded in the patient data management system (HiX, Chipsoft BV, Amsterdam, the Netherlands). Heart rate (HR), intra-arterial mean arterial blood pressure (MABP) and peripheral arterial oxygen saturation (SpO_2) were measured at 1 Hz (Primus, Draeger, Luebeck, Germany). The regional cerebral oxygen saturation ($rScO_2$) was measured at a sampling rate of 1 Hz using NIRS (neonatal sensor, INVOS 5100C, Covidien, Boulder, Colorado, United States). The $rScO_2$ hypoxic threshold of this specific device-sensor combination is 63% [13,10]. EEG was recorded using a 4-channel EEG at 256 Hz (Rotterdam: BrainRT, OSG, Rumst, Belgium, Mannheim: Braintrend, Fritz Stephan GMBH, Gackenbach, Germany). The power of the EEG was computed in the slow delta (δ_1: 0.5 – 2 Hz), fast delta (δ_2: 2 – 4 Hz), and gamma (γ: 32 – 100 Hz) frequency bands.

In Rotterdam, the Shell+ RT software Suite of the BrainRT was reprogrammed into a real-time data grabber. In Mannheim, customized software (AnStat, Carepoint, Ede, the Netherlands) for real-time data extraction was used to store all data. In both centers, clinicians were blinded for EEG, but not for $rScO_2$. Partial pressure of carbon dioxide (pCO_2) was measured transcutaneously at 1 Hz in Rotterdam (Sentec, Therwil, Switzerland) and was measured using repeated arterial blood gas sample analysis in Mannheim. The vasoactive-inotropic score (VIS) reflects the need and grade of vasoactive/inotropic pharmaceutical intervention and was calculated to quantify necessity of cardiovascular support[23].

8.2.4. Data processing and statistical analysis

The signal processing pipeline started with three preprocessing steps. First, artefacts were detected and removed. For EEG, segments were excluded from the analysis if the absolute amplitude exceeded 500 μV, which is the maximum voltage that could be detected by the monitor. For the other signals, segments outside of the physiological range, segments containing motion artefacts were removed. Second, the spectral power in the EEG was computed using the continuous wavelet transform and ridge extraction[24]. Three frequency bands of interest were defined: slow delta δ_1 (0.5 – 2 Hz), fast delta δ_2 (2 – 4 Hz) and gamma γ (30 – 100 Hz) frequency bands. Third, FTOE was computed from $rScO_2$ and SpO_2 values as $FTOE = (SpO_2 - rScO_2)/SpO_2$. Since $rScO_2$ mainly reflects the

oxygenation of the venous return from the brain, FTOE defines the amount of oxygen extracted in the brain.
After these processing steps, signal parameters were extracted in four data windows: the preoperative window (Pr: 6 to 3 hours before the start of surgery), the intraoperative window (In: entire surgical procedure), and two postoperative windows (Po3: 3 to 6 hours and Po15: 15 to 18 hours after the end of surgery). These data windows were used to balance the data and to remove transitional effects, such as artefacts of transport, artefacts of care, the effect of intraoperative administered medication.
T-test was used for the comparison of the patient demographics. Generalized least-squares models were used for the statistical analysis of the primary endpoint, since they showed to be the best fit for the data as indicated by the Akaike information criterion[25]. Post hoc comparisons were based on analysis of marginal means, implemented with Tukey's correction for multiple comparisons. All statistical computations were carried out in R, with significance defined as $\alpha<0.05$ [26].

8.2.5. Correlations

Three correlations were studied to determine their effect on our results. Firstly, the correlation between vasoactive and inotropic medication on cerebral oxygenation and oxygen consumption was studied to clarify possible effects of cerebral vasoconstriction on $rScO_2$. Secondly, the correlation between the dosage of anesthesia or sedative and cerebral oxygenation and activity was studied to clarify dosage related changes in $rScO_2$ and EEG-power values. Thirdly, the correlation between cerebral activity and cerebral oxygenation was investigated to study whether the assumption of reduced cerebral activity resulting in increased cerebral oxygenation holds true in this study.

8.2.6. Primary and secondary endpoints

The primary endpoint of this study was the analysis of the differences between anesthesia based on sevoflurane versus midazolam on cerebral oxygenation perioperatively. Secondary endpoints were twofold. First, the analysis of the

	Sevoflurane group	Midazolam group	p-value
n	20	17	
Male	55% (11)	59% (10)	.821
Gestational age (wk)	38+1 (36+5 – 38+5)	37+6 (34+5 – 38+1)	.111
Birth weight (kg)	3.0 (2.7 – 3.3)	2.8 (1.9 – 3.1)	.070
Apgar 5 min	8 (8 – 9)	8 (7 – 8)	.478
o/e LHR	50 (41 – 58)	40 (33 – 54)	.337
Preoperative mechanical ventilation (%)	85% (17)	100%	.101
Preoperative VA-ECMO	0%	29% (5)	.022
Intraoperative VA-ECMO	0%	0%	1.00
Left sided defect (%)	85% (17)	65% (11)	.977
Liver-up	25% (5)	71% (12)	.005
Age at surgery (d)	3 (2-4)	6 (3-12)	.008
Thoracoscopy/laparotomy	40/60% (8/12)	23/77% (4/13)	.026
Conversion	100% (8)	0%	.002
Duration of surgery (min)	95 (70 – 125)	182 (114 – 203)	.000
Defect size (n)	6A, 8B, 5C, 1D	1A, 9B, 6C,1D	.185
Patch (%)	60% (12)	88% (15)	.056
VIS-score preoperative	0 (0-5)$	17 (10 – 25)$	.000
VIS-score intraoperative	9 (5-17)$	17 (12 – 35)$	.010
VIS-score postoperative (ug kg^{-1})	2 (0-11)$	17 (10 – 28)$	.001
Rocuronium bolus dosage intraoperative (mg kg^{-1})	0.8 (0.6 – 1.0)	-	
Vecoronium bolus dosage during induction (mg kg^{-1})	-	0.2 (0.15 – 0.21)	
Vecoronium perfusor dosage intraoperative (mg kg^{-1} h^{-1})	-	0.09 (0.05 – 0.10)	
Fentanyl bolus dosages during induction (ug kg^{-1})	2.3 (1.7 – 2.9)	5 (4-7)	.000
Cumulative fentanyl bolus dosages intraoperative (ug kg^{-1} h^{-1})	6.2 (4.1 – 11.5)	10 (7 – 17)	.119
Fentanyl perfusor dosages intraoperative (ug kg^{-1} h^{-1})	-	4 (3 – 5)	
Sevoflurane concentration (end expired concentration (%))	1.5 (1.1 – 1.9)*	-	-
Midazolam perfusor dosage preoperative (ug kg^{-1} h^{-1})	47 (0 – 92)	40 (30 – 50)	.735
Midazolam perfusor dosage intraoperative (ug kg^{-1} h^{-1})	47 (0 – 67)	100 (68 – 100)	.003
Midazolam perfusor dosage postoperative (ug kg^{-1} h^{-1})	39 (26 – 99)	50 (20 – 50)	.647
Midazolam bolus intraoperative (%)	5% (1)	59% (10)	.000

Table 24. Patient characteristics sevoflurane and midazolam group. Data presented as median (IQR) or (range)$, *: range of the mean values.

differences between the administration of sevoflurane versus the administration of midazolam on cerebral activity and the vital parameters. Second, the changes of the parameters over time, defined using data windows in the preoperative, intraoperative and postoperative period per group, that is, the sevoflurane versus the midazolam neonates.

8.3. Results

8.3.1. Demographics

Informed consent was obtained in 49 CDH neonates, 37 neonates could be analyzed: 20 neonates in the sevoflurane group, 17 neonates in the midazolam group (figure 29, appendix 1). In the midazolam group, 5 neonates received VA-ECMO treatment until one day before surgery. The demographics of both groups were comparable (table 24), except for a lower amount of herniated livers (5 (25%) vs. 12 (71%), p= .005), a lower VIS preoperatively (0, IQR 0 – 5 vs 17, IQR 10 – 25, p= <.001), a lower postnatal age on the day of surgery (3 days, IQR 2 – 4 vs. 6 days, IQR 3 – 12, p= .008), more thoracoscopic surgery (40% vs. 23%, p= .026), and a shorter surgery (95 min, IQR 70 – 125 vs. 182 min, IQR 114 – 203, p= <.001) in the sevoflurane group compared to the midazolam group. Eight patients who underwent thoracoscopic surgery were converted to an open approach because of the need for a patch.

8.3.2. Anesthesia

Preoperatively, in the sevoflurane group, 5 neonates were not sedated while on mechanical ventilation, 2 neonates received continuous administration of morphine, 7 neonates received continuous administration of midazolam and 6 neonates received continuous administration of both midazolam and morphine (figure 24). In the midazolam group, all neonates received continuous midazolam, supplemented with continuous administration of fentanyl (figure 24) and were intubated multiple days before surgery. The patients in the sevoflurane group that were intubated and sedated before start of surgery received comparable dosages of midazolam (47 ug kg^{-1} h^{-1}, IQR 0 – 92 and 40 ug kg^{-1} h^{-1}, IQR 30 – 50, p = .735, respectively, table 24) compared to the midazolam group.
Intraoperatively, the end expired sevoflurane concentration was 1.5% (IQR 1.1 – 1.9). Time between the start of administration of sevoflurane and start of the surgical procedure was 66 min (IQR 45 – 76.6). In six neonates, the preoperative continuous midazolam administration was continued intraoperatively and in two

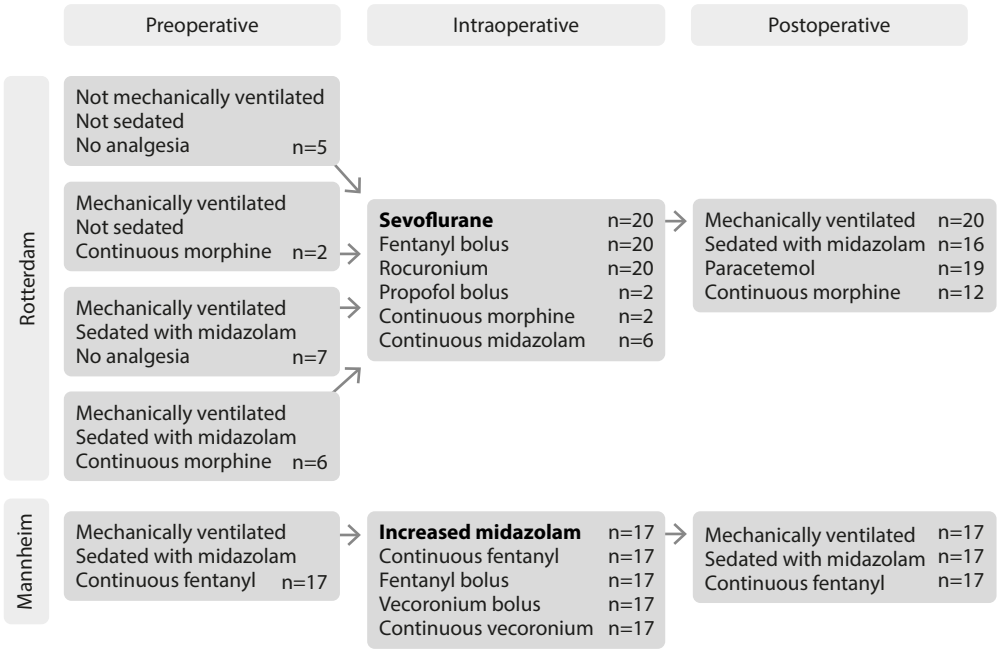

Figure 24. Overview of administrated medication in the perioperative period

neonates the preoperative continuous morphine administration was continued intraoperatively during sevoflurane anesthesia (figure 24). Three neonates received a bolus of propofol (2.9, 3.7 and 7.3 mg kg^{-1} for endotracheal intubation). In the midazolam group, the midazolam dosage was 100 ug kg^{-1} h^{-1} (IQR 68 – 100). The time between the administration of midazolam and the start of the surgical procedure was 21 min (IQR 1 – 30). The midazolam dosage in the sevoflurane group of those in whom the midazolam was continued from PICU (n = 6) was significantly lower (47 ug kg^{-1} h^{-1}, IQR 0 – 67, p = .003) compared to the midazolam group (100 ug kg^{-1} h^{-1}, IQR 68 – 100) (table 24). The fentanyl bolus dosage during the induction of anesthesia was lower in the sevoflurane group compared to the midazolam group (2 ug kg^{-1}, IQR 2-3 vs. 5 ug kg^{-1}, IQR 4-7 vs p=<.001), although the cumulative fentanyl bolus dosages that were administrated intraoperatively did not differ (10 ug kg^{-1}, IQR 7 – 17 vs. 6 ug kg^{-1}, IQR 4 – 12, p = .119). Yet, the midazolam group received additional continuous administration of fentanyl (4 ug kg^{-1} h^{-1}, IQR 3 – 5), whereas the sevoflurane group did not.
Postoperatively, the midazolam dosages did not differ significantly between the sevoflurane (39 ug kg^{-1} h^{-1}, IQR 26 – 99) and the midazolam group (48 ug kg^{-1} h^{-1}, IQR 20 – 50) (table 24 and figure 24).

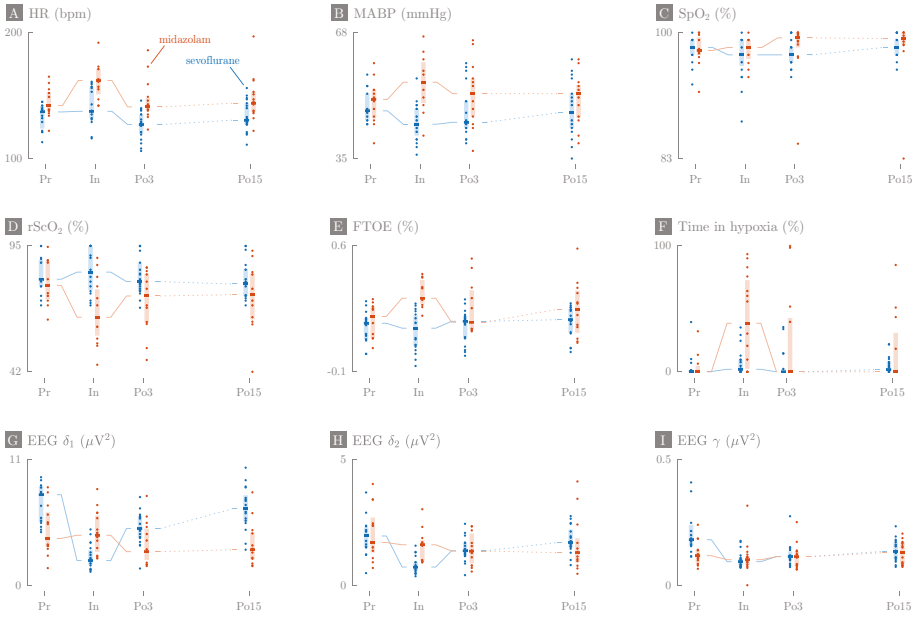

Figure 25. Longitudinal overview of the perioperative changes in cerebral oxygenation (A), oxygen consumption (B), time in hypoxia (C), cerebral activity (slow delta (D), fast delta (E), gamma (F)), HR (G), MABP (H) and SpO_2 (I).

8.3.3. Vital parameters

Preoperatively, HR was significantly lower in the sevoflurane group (137bpm, IQR 126 - 141) compared to the midazolam group (142bpm, IQR 138 – 152) (table 25, appendix 2). MABP did not differ, although the VIS was significantly lower in the sevoflurane group (0, IQR 0 – 5) than in the midazolam group (17, IQR 10-25). Intraoperatively, HR and MABP significantly dropped in sevoflurane group (HR: 138bpm, IQR 132 – 156 and MABP: 44 mmHg, IQR42 – 48) compared to the midazolam group (HR: 162bpm, IQR 153 – 171and 55 mmHg, IQR 50-60). Intraoperatively, the VIS score was again significantly lower in the sevoflurane group (9, IQR 5 – 17) than in the midazolam group (17, IQR 12 – 35).
Three until six hours postoperatively, HR remained significantly lower in the sevoflurane group (127bpm, IQR 120 – 135) compared to the midazolam group (141bpm, IQR 139 – 148). VIS was still significantly lower in the sevoflurane group (2, IQR 0 – 11) compared to the midazolam group (17, IQR 10 – 28).
Fifteen until eighteen hours postoperatively, HR remained significantly lower in the sevoflurane group (131bpm, IQR 127 – 135) compared to the midazolam group (144bpm, IQR 137 – 153).

SpO_2 and $PaCO_2$ did not differ between the group perioperatively.

8.3.4. Cerebral oxygenation

Preoperatively, $rScO_2$, FTOE and duration of cerebral hypoxia did not differ significantly between the groups (figure 25).
Intraoperatively, the $rScO_2$ values were significantly higher in the sevoflurane group (84%, IQR 77 – 95) compared to the midazolam group (65%, IQR 59 – 76, p < .001). The opposite was true for FTOE, which was lower in the sevoflurane group (14%, IQR 5 – 21) compared to the midazolam group (31%, IQR 29 – 40, p <.001). The duration of hypoxia was significantly shorter in the sevoflurane group (2%, IQR 0.4 – 9.6) compared to the midazolam group (38.6%, IQR 4.9 – 70, p = .023). Three until six hours and fifteen until eighteen hours postoperatively, $rScO_2$, FTOE and the duration of cerebral hypoxia did not differ between the groups.

8.3.5. Cerebral activity

Preoperatively, power in the EEG slow delta δ_1 and gamma γ frequency bands was significantly higher in the sevoflurane group (7.9 μV^2, IQR 5.5 – 8.6; 0.19 μV^2, IQR 0.16 – 0.28) compared to the midazolam group (4.1 μV^2, IQR 3.4 – 6.2, p = .009 vs. 0.12 μV^2, IQR 0.09 – 0.14, p = .0017), but not for the fast delta δ_2 frequency (2.0 μV^2, IQR 1.5 – 2.3 vs. 1.7 μV^2, IQR 1.4 – 2.5) (figure 25).
Intraoperatively, slow delta δ_1,fast delta δ_2 and gamma γ power decreased in the sevoflurane group and remained decreased during the entire intraoperative period. In the midazolam group a 3-fold increase of fast delta δ_2 power was observed in the first 30 minutes of the surgical procedure, which decreased later on. A comparable increase was observed for the gamma γ frequency, which was characterized by a 5-fold increase (figure 26). The intraoperative median values of slow delta δ_1 and fast delta δ_2 power decreased significantly in the sevoflurane group (2.2 μV^2, IQR 1.9 – 3.0, 0.73 μV^2, IQR 0.59 – 0.91) compared to the midazolam group (4.4 μV^2, IQR 3.1 – 6.0, p = .0002, 1.6 μV^2, IQR 1.0 – 1.7, p = <.001), but not for gamma γ power (0.09 μV^2, IQR 0.08 – 0.10, 0.10 μV^2, IQR 0.08 – 0.11).
Higher maximal sevoflurane concentration (end expired concentration) was not associated with lower cerebral activity (figure 27). Higher maximum dosages of

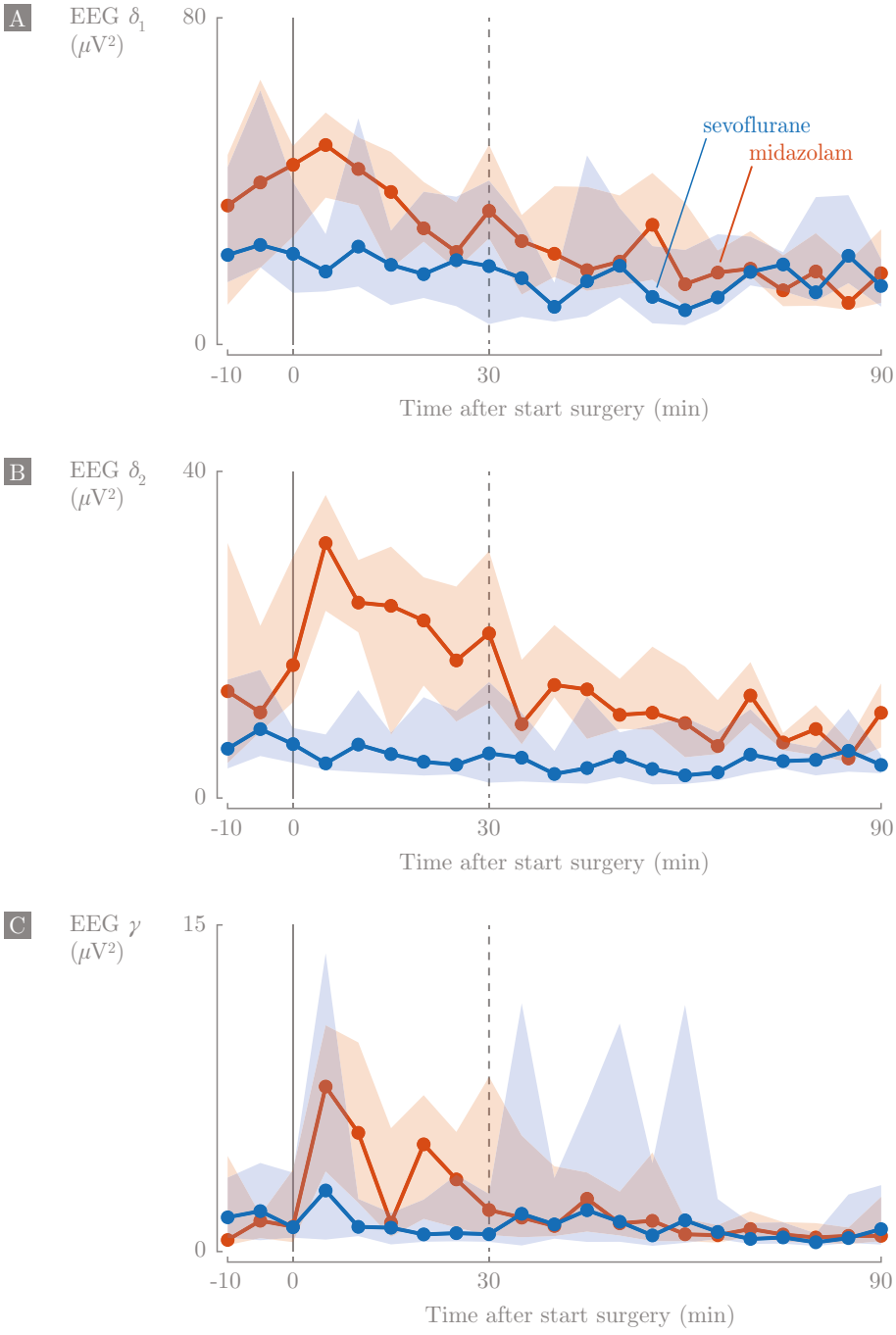

Figure 26. Intraoperative cerebral activity; slow delta (A), fast delta (B), gamma (C) power. Blue: sevoflurane group, red: midazolam group. 0: start surgical procedure.

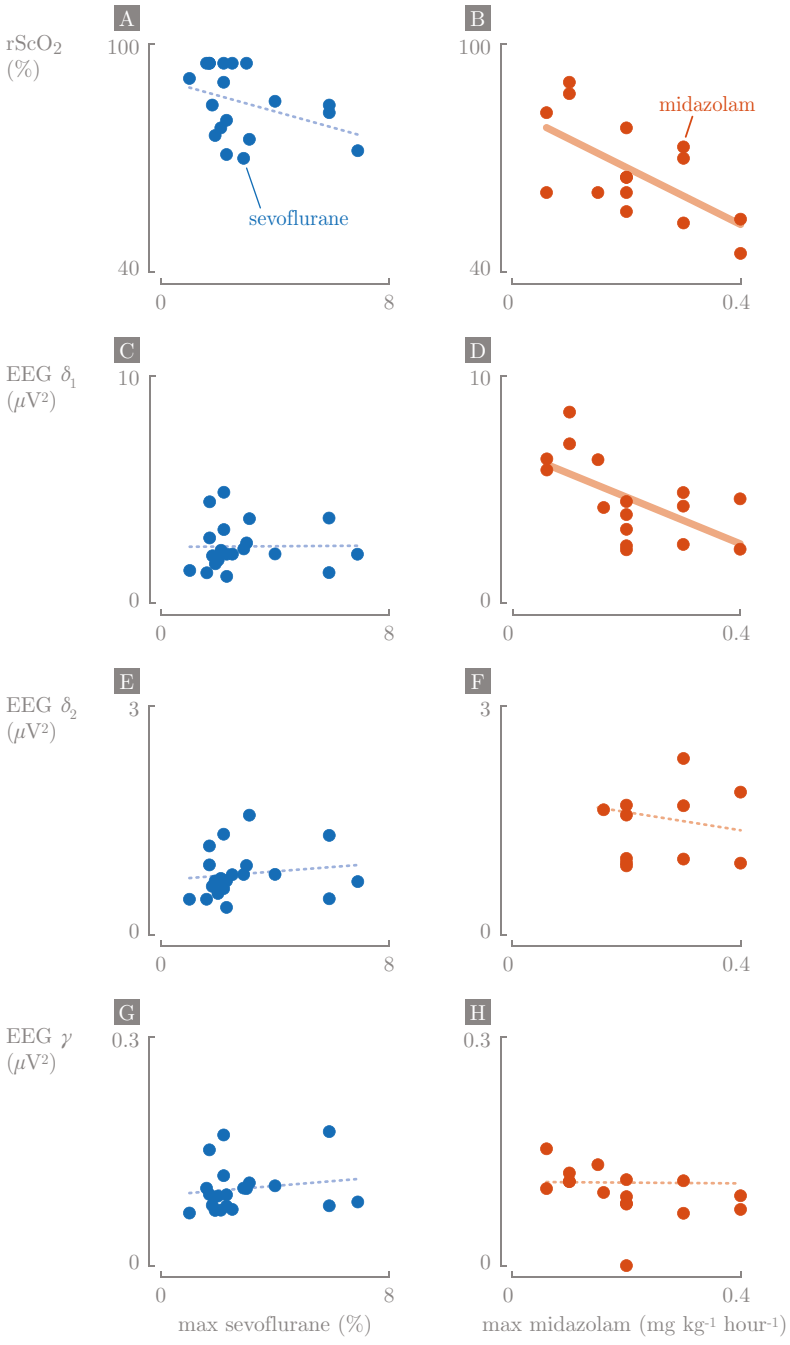

Figure 27. Correlation between the maximum sevoflurane concentration or maximum dosages of midazolam cerebral oxygenation (A,B) and cerebral activity: slow delta (C,D), fast delta (E,F), gamma (G,H) power. Blue: sevoflurane group, red: midazolam group, fat line; significant correlation

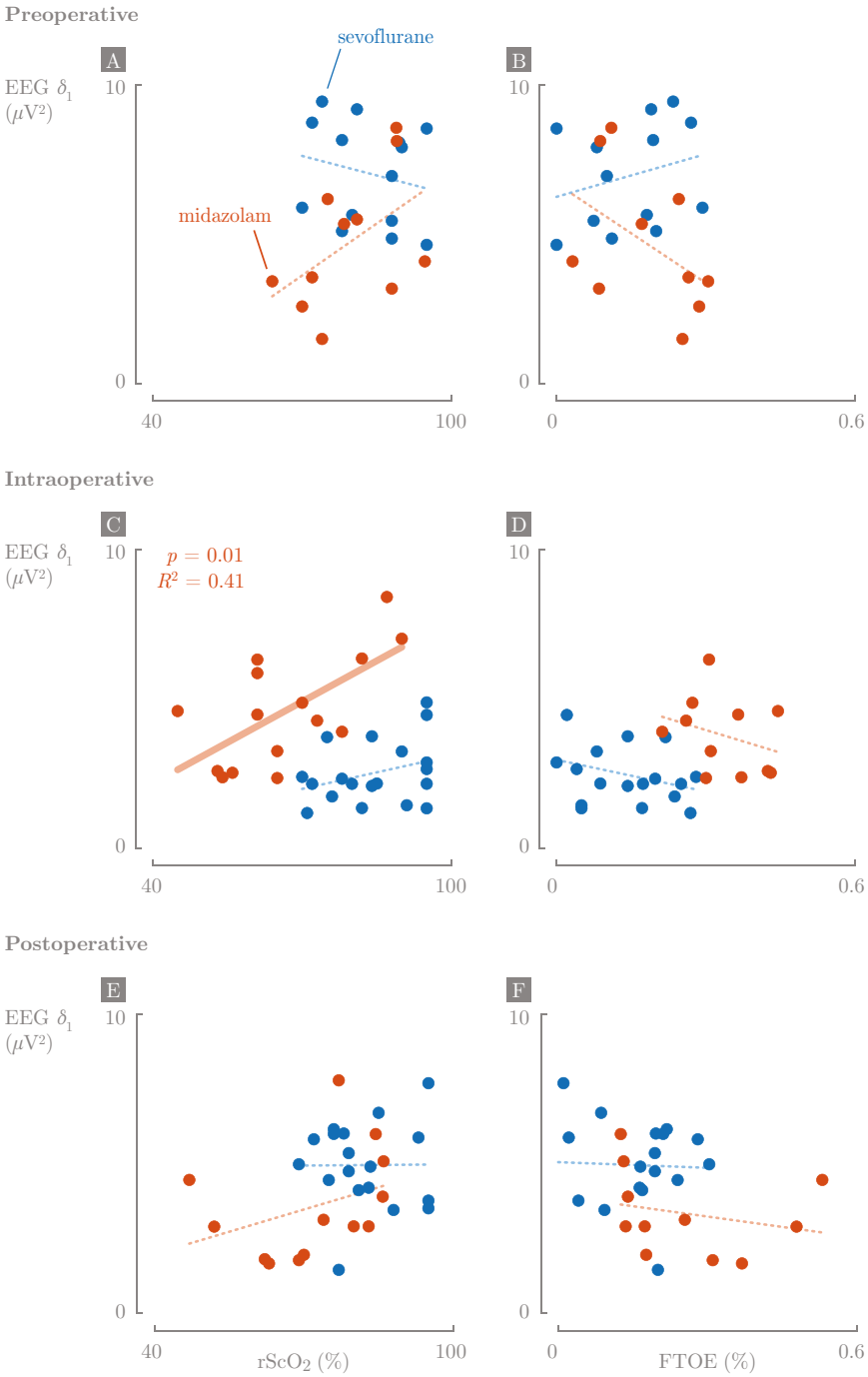

Figure 28. Correlation between the cerebral activity and cerebral oxygenation and oxygen consumption preoperative (A,B), intraoperative (C,D) and postoperative (E,F). Blue: sevoflurane group, red: midazolam group, fat line; significant correlation.

midazolam were associated with lower cerebral activity (p = .023) (figure 28).
The neonates who received a bolus of propofol had EEG delta frequency power (2.15 - 2.16 μV^2) comparable to the other neonates in the sevoflurane group. Three until six hours postoperatively, the EEG slow delta δ_1, fast delta δ_2 and gamma γ frequencies increased again in the sevoflurane group (5.0 μV^2, IQR 4.2 – 6.0, 1.4 μV^2, IQR 1.2 – 1.7, 0.11 μV^2, IQR 0.10 – 0.13), decreased in the midazolam group (2.9 μV^2, IQR 2.4 – 4.8, 1.36 μV^2, IQR 0.95 – 1.93, 0.11 μV^2, IQR 0.08 – 0.13) compared to the intraoperative period.
Fifteen until eighteen hours postoperatively, the EEG slow delta δ_1, fast delta δ_2 and gamma γ frequencies increased further in the sevoflurane group (6.7 μV^2, IQR 5.6 – 7.6, 1.7 μV^2, IQR 1.5 – 2.4, 0.14 μV^2, IQR 0.10 – 0.17), increased in the midazolam group (3.1 μV^2, IQR 2.4 – 4.8, 1.31 μV^2, IQR 0.98 – 2.23, 0.13 μV^2, IQR 0.08 – 0.17) compared to the intraoperative period.

8.3.6. Correlations

Preoperative, no correlation between $rScO_2$ or FTOE and cerebral activity was observed (figure 28).
Intraoperatively, a significantly (p = 0.01) positive correlation between $rScO_2$ and cerebral activity in the midazolam group was found (figure 28). In contrast, there was no correlation between FTOE and cerebral activity. Higher maximum dosages of midazolam resulted in a significant decrease in $rScO_2$ and slow delta EEG power (figure 27). The same trend was observed for maximum sevoflurane concentration, although not significant. In the sevoflurane group, $rScO_2$ was negatively correlated with VIS (R2=0.23, p=.0.04) and positively correlated with FTOE (R2=0.21, p=.04). These correlations were not found in the midazolam group.
Postoperatively, $rScO_2$ was negatively correlated with VIS (R2=0.35, p=.0.01) and FTOE positively correlated with VIS (R2=0.32, p=.001) in the sevoflurane group, and not in the midazolam group.

8.4. Discussion

This is the first analysis that describes the effects of two different, widely used anesthetic approaches on cerebral oxygenation and activity in CDH neonates perioperatively. Surgery during sevoflurane-based anesthesia resulted in stable cerebral oxygenation, decreased oxygen consumption and decreased cerebral activity. The EEG power did not indicate pain stimuli awareness. Surgery during midazolam-based anesthesia resulted in low $rScO_2$, increased cerebral oxygen consumption and increased cerebral activity throughout the first 30 minutes. Inhere, increased EEG power of the fast delta and the gamma band indicated conscious pain perception.

8.4.1. Cerebral oxygenation

Intraoperatively, $rScO_2$ values were observed to be significantly higher in the sevoflurane group compared to the midazolam group, which reached alarmingly low $rScO_2$ values (figure 25). In the sevoflurane group, brain activity decreased significantly intraoperatively, which resulted in stable $rScO_2$ and decreased FTOE, despite a reduction in MABP (figure 25). This is in line with a study in children between 0 and 2 years [27]. In the midazolam group, changes in EEG were accompanied by a decrease in $rScO_2$, an increase in FTOE, despite an increase in MABP and HR (figure 25).
Partial pressures of carbon dioxide ($PaCO_2$), as well as vasoactive and inotropic medication affect cerebral resistance and subsequently cerebral perfusion[28,29]. In both groups, $PaCO_2$ levels were comparable, stable and within clinical range. In the sevoflurane group, increased VIS was associated with lower $rScO_2$ values and higher FTOE intra- and postoperatively. Hemodynamic support, mostly with norepinephrine, was highest in the midazolam group (table 24) without affecting $rScO_2$ or FTOE. A recent study signals that norepinephrine elevates MABP, while, paradoxically, reducing cerebral perfusion in adults[30].

8.4.2. Cerebral activity

Slow delta δ_1, fast delta δ_2, and gamma γ power significantly decreased during sevoflurane administration, independently of the maximum sevoflurane concentration. Overall, EEG power didn't decrease during midazolam-based anesthesia, while increased midazolam dose was found to be associated with a decrease in activity. During the first 30 minutes of surgery, a threefold increase in δ_2 and a sixfold increase in gamma γ were observed, suggesting that nociceptive stimuli were registered by the brain (figure 26) [19]. After 30 minutes, power in the different bands stabilized to lower values (figure 26). The median time between bolus administration or increased continues dosages of midazolam and start of surgical procedure was 21 minutes. This might reflect that midazolam increase requires 30 minutes to reach a new steady state concentration, since higher dosages of midazolam lowered EEG power, or that surgery started too soon after administering midazolam and analgesia, since cerebral activity decreased after 30 minutes. A loading dose helps to induce the effect quicker, although this was given in 59% of the neonates in the midazolam group.

8.4.3. Pharmacological approaches

A recent study showed that higher sevoflurane doses significantly correlated with more suppressed background patterns[31]. This correlation was not observed in our study, but this could be due to the relatively small range in sevoflurane concentrations that were administered (figure 27).
Patients in the midazolam group received midazolam preoperatively for multiple days and had a median midazolam dosage of 0.1 mg $kg^{-1}h^{-1}$ intraoperatively. This is substantially higher than the dosing advice of 0.06 mg $kg^{-1}h^{-1}$ for sedation with midazolam in neonates with a gestational age above 32 weeks [32], although this was already questioned by our research group[33].
A steady-state concentration is reached 24 hours after start of continuous administration. The elimination half-life of midazolam is approximately six hours in the first week of life in full-term neonates[34], although severity of disease and inflammation may also affect the elimination of midazolam in critically ill neonates[35]. A recent Cochrane review concluded that midazolam was an effective sedative in neonates[36]. Although, transient cerebral hypoperfusion

was observed after a bolus of midazolam, as well as significant higher rates of adverse neurological events in neonates treated with midazolam compared to morphine[37,38].
In this study, neonates in the midazolam group all received continuous administration of fentanyl. Single use of fentanyl dosages of 50-100 ug kg^{-1} is a commonly used anesthetic approach during congenital cardiac surgery, and if the neonate has limited hemodynamic reserve[39]. A randomized trial in 1987 already proved the additional value of fentanyl in the stress response of neonates intraoperatively[40]. Another study compared the effect of fentanyl with midazolam combined with fentanyl on stress response during neonatal cardiac surgery, and concluded that intraoperative administration of midazolam in addition to fentanyl did not reduce stress response compared to single use of fentanyl[39]. In combination with our results, this suggests that single administration of high doses of fentanyl might be a better anesthetic approach than midazolam with lower dosages of fentanyl in neonates intraoperatively.

8.4.4. Strengths and limitations

Strengths: both centers have long-lasting experience treating high-risk CDH patients and have acted as 'founding fathers' for well-established international guidelines. Neither treatment modalities, nor composition of the treatment teams changed during the study period. Additionally, both centers used validated pain assessment instruments (Comfort-B) as pharmacodynamic endpoint to evaluate and treat pain.
Limitations: exposure to medication was compared based on dosages instead of its plasma concentrations. Neonates in the midazolam group were more critically ill (more liver-up, higher VIS, longer duration of surgery) than neonates in the sevoflurane group. Furthermore, this is a center comparison study and not a randomized controlled trial.

8.5. Conclusion

This comparison of two anesthetic approaches for CDH surgery showed that sevoflurane-based anesthesia resulted in increased cerebral oxygenation and decreased cerebral activity, suggesting adequate anesthesia. Midazolam-based anesthesia in neonates with a more severe CDH (more liver-up and higher VIS) led to alarmingly low $rScO_2$ values, below hypoxia threshold, and increased values of EEG power during the first 30 minutes of surgery. This might indicate conscious experience of pain.
Following the limitations of midazolam, we argue that current perioperative medication strategies with midazolam and analgesia are not sufficient for perioperative anesthesia. These results stimulate the integration of population-pharmacokinetic models in combination with multimodal neuromonitoring to reach evidence-based perioperative pharmacotherapy in these vulnerable patients.

Acknowledgments

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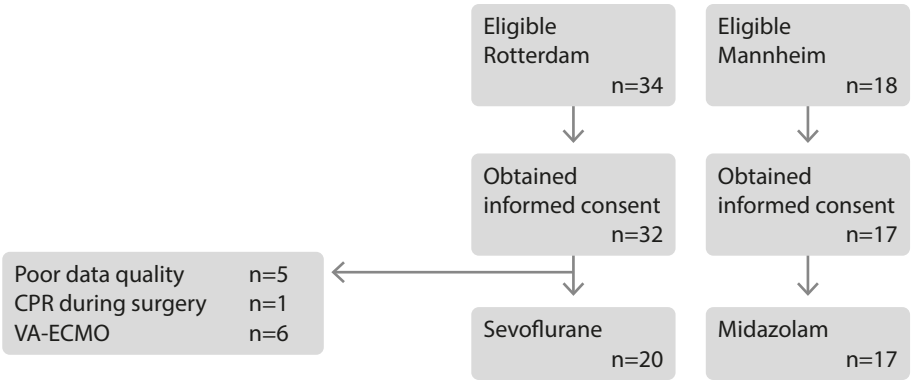

Figure 29. Appendix 1. Flowchart of the included patients.

Table 25. Appendix 2. Overview of exact values Pr, In, Po3.

	Sevoflurane group (N = 20)				Midazolam group (N = 17)			
	Pr	In	Po3	Po15	Pr	In	Po3	Po15
HR (bpm)	137 126 – 141	138 132 – 156	127 120 – 135	131 127 - 144	144 138 – 150	163 154 – 173	141 139 – 149	145 138 - 153
MABP (mmHg)	48 45 – 51	44 42 – 48	45 43 – 50	47 43 – 52	50 46 – 53	52 49 – 58	52 47 – 59	52 45 - 53
SpO_2 (%)	98 97 – 99	97 96 – 99	97 96 – 98	98 97 – 99	98 96 – 99	98 97 – 99	99 97 – 100	99 98 – 100
$rScO_2$ (%)	81 78 – 89	84 77 – 95	80 76 – 87	79 74 - 85	76 71 – 86	65 61 – 77	74 65 – 80	73 67 – 78
FTOE (%)	17 9 – 20	14 5 – 21	18 9 – 21	19 12 - 25	0 0 – 12	30 2 – 60	0 0 – 43	0 0 – 44
Time in hypoxia (%)	0 0 – 1	2 0 – 10	0 0 – 2	2 0 – 8	25 11 – 29	31 26 – 36	22 15 - 32	25 16 - 32
EEG δ_1 (μV^2)	7.9 5.5 – 8.6	2.2 1.9 – 3.0	5.0 4.2 – 6.0	6.7 5.6 – 7.6	4.3 3.5 – 5.7	4.3 3.3 – 5.8	3.4 2.9 – 5.2	3.4 2.6 – 5.9
δ_2	2.0 1.5 – 2.3	0.7 0.6 – 0.9	1.4 1.2 – 1.7	1.7 1.5 – 2.4	1.5 1.3 – 2.4	1.4 1.0 – 1.7	1.3 1 – 1.8	1.3 1.0 – 1.8
γ	0.2 0.2 – 0.3	0.1 0.1 – 0.1	0.1 0.1 – 0.1	0.1 0.1 – 0.2	0.1 0.1 – 0.1	0.1 0.1 – 0.1	0.1 0.1 – 0.2	0.1 0.1 – 0.2
VIS	0 0 – 5	9 5 – 17	2 0 – 11		17 10 – 25	17 12 – 35	17 10 – 28	
$PaCO_2$ (kPa)		6.5 5.9 – 7.6				5.5 4.7 – 6.7		

9

Heart rate variability during non-cardiac-major neonatal surgery

Dries Hendrikx*, Sophie Costerus*, Sabine Van Huffel, Jurgen de Graaff, René Wijnen, Alexander Caicedo, Dick Tibboel, Gunnar Naulaers

* Authors contributed equally

Abstract

Introduction. Anesthesia, surgery and critical illness lead to a varied degree of physiological stress that alters the autonomic nervous system (ANS). In adults, most anesthetics interfere with sympathetic neural activity and cardiovascular control. In neonates, the effect of sedatives and anesthetics on the ANS is still unknown. The primary endpoint of this study was the evaluation of the intraoperative effect of sevoflurane anesthesia on heart rate variability intraoperatively.

Methods. This study focused on neonates with esophageal atresia (EA) and congenital diaphragmatic hernia (CDH), which are two major non-cardiac anomalies that require surgical repair within the first days of life. Numerous features were derived from the tachogram in order to capture heart rate variability (HRV), including the mean RR interval, the standard deviation of the NN intervals (SDNN), the absolute power in the very low frequency (VLF), low frequency (LF), and high frequency (HF) bands, and the sample entropy.

Results. 33 patients were eligible for inclusion, of which 7 patients had to be removed as a result of bad data quality. Over the transition from awake to anesthesia, we observed a significant decrease in SDNN ($p = .047$), in absolute power in the VLF ($p = .016$), LF ($p = .031$) and HF ($p = .047$) frequency band, in LF/HF ($p = .031$) and in relative power in the LF band ($p = .031$). The relative power in the HF frequency band increased significantly ($p = .031$). During surgery, diagnosis (EA or CDH), type of surgery (thoracoscopy, conversion or open), gestational age (GA), the end-expired sevoflurane concentration and the vasoactive inotropic score were found to significantly alter the HRV scores.

Discussion/Conclusion. Sevoflurane-based anesthesia did not affect heart rate, but significantly suppressed the ANS, as indicated by a decrease in all HRV metrics, except entropy. Furthermore, the type of congenital anomaly, GA, the administrated sevoflurane concentration and the vasoactive or inotropic medication affected HRV in neonates intraoperatively. In awake neonates, a suppressed HRV is associated with adverse outcome. During anesthesia, a lowered HRV indicates adequate anesthesia and analgesia. It remains unknown

whether induced decreased HRV due to anesthetics is related to adverse outcome since triggers for postoperative brain injury are still largely unknown.

9.1. Introduction

The surgical newborn is at risk for brain injury, since fluctuations in perioperative cerebral perfusion could trigger the development of brain injury[1,2]. Cerebral blood flow is regulated by vasomotor, chemical, metabolic, and neurogenic mechanisms, of which the autonomic nervous system (ANS) is an important factor. Anesthesia, surgery and critical illness lead to a varied degree of physiological stress that alters the ANS. In adults, most anesthetics interfere with sympathetic neural activity and cardiovascular control[3]. In contrast to adults, the effect of sedatives and anesthetics on the neonatal ANS is still unknown.
The ANS is the regulatory system that controls most of the organ systems and homeostatic mechanisms[4,5]. In general, the ANS consists of two components: the sympathetic (SNS) and the parasympathetic nervous system (PNS). The SNS prepares the body for the Fight-or-Flight response by increasing cardiac output and blood flow. The PNS is responsible for relaxation and moderating control over the active sympathetic system[4,5]. Heart rate is controlled by an interplay between SNS and PNS. Neonates have a higher heart rate which is related to cardiac-linked SNS predominance and decreased vagal tone[6]. The contribution of the PNS increases with postnatal age[7,8]. Hence, the development of the cardiac autonomic innervation is not complete after birth[5]. The understanding of ANS maturation in healthy term neonates is limited[9].
The functional state of the ANS can be studied using heart rate variability (HRV) analysis, derived from the electrocardiogram (ECG)[10]. In HRV analysis, one evaluates the sympathovagal balance at the cardiac sinoatrial level by analyzing the fluctuations of the RR interval between consecutive sinus heartbeats. This reflects the dynamic interactions that exist between the heart and the ANS[11,12]. HRV provides information about the cardiac chronotropic regulation and adaption postnatally[8], since the maturation of the ANS is accompanied by increasing HRV and a pronounced increase of parasympathetic activity[11]. Large HRV is associated with being healthy, while reduced HRV indicates

Demographics	Gender	male: 12, female: 14
	Gestational age (weeks)	38+3 (36+3 – 40+1)
	Age at surgery (days)	2 (2-3)
	Birth weight (g)	2985 (2280 – 3230)
Diagnosis		EA: 12, CDH:14
Surgery	Type	open: 8, conversion: 8, thoracoscopy: 10
	Duration (hh:mm)	01:48 (01:15 - 02:34)
Medication	Sevoflurane (end-expired, %)	1.7 (1.3 - 2.0)
	Midazolam (ug kg^{-1} h^{-1})	57.0 (0.0 – 103.8)
	Fentanyl (ug kg^{-1})	3.5 (0.0 – 8.8)
	VIS	7.2 (4.5 – 12.6)

Table 26. Patient demographics, diagnosis, surgery and medication. Data is presented as median (IQR). Sevoflurane dose, midazolam dose and vasoactive inotropic scores (VIS) are presented as a mean over the intraoperative period, while fentanyl dose is presented as a sum of different boluses administered to the neonate.

impaired cardiovascular autonomic control. Reduced HRV is associated with a compromised cardiovascular system[13,14,15,16], hypoxic-ischemic encephalopathy[17], intraventricular hemorrhage in preterm neonates[18], infection and sepsis[19]. During surgery, one of the most commonly used anesthetics is sevoflurane. Sevoflurane is known to induce deep sleep in the neonate, characterized by a significant decrease in cerebral activity[20]. So far, the functional state of the ANS of the sick neonate has not been studied during surgery-induced deep sleep. In children, the autonomic balance was observed to shift during deep sleep, with more pronounced influences of the PNS[21]. In healthy term neonates, the sleep state was observed to affect various HRV parameters: in quiet sleep, HRV was lower and the influence of the PNS branch increased[22]. The aim of this study is to quantify the effect of sevoflurane anesthesia on heart rate variability in neonates undergoing major non-cardiac surgery.

9.2. Materials and Methods

9.2.1. Patients

This study focused on neonates with esophageal atresia (EA) and congenital diaphragmatic hernia (CDH), which are two major non-cardiac anomalies that

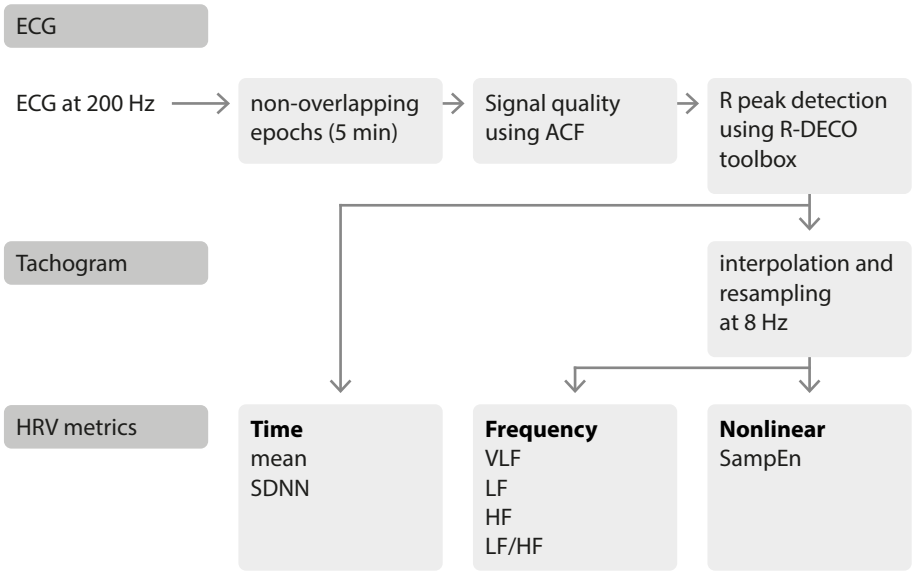

Figure 30. Data processing pipeline used to translate ECG to tachogram to HRV metrics.

require surgical repair within the first days of life. All patients underwent surgery in the Sophia's Children Hospital, Erasmus MC, Rotterdam, the Netherlands. CDH and EA neonates were eligible for inclusion if surgical repair was scheduled between July 2018 and July 2020 and within the first 28 days of life, regardless of the type of surgery (open or minimal access). Neonates were excluded when major cardiac or chromosomal anomalies, syndromes associated with altered cerebral perfusion, or syndromes associated with major neurodevelopmental impairment were present or if the patient needed extracorporeal membrane oxygenation treatment. EA patients were treated according to the protocol of the Dutch Consortium Esophageal Atresia. CDH patients were treated according to the revised CDH-EURO consortium guidelines[23]. Local institutional review board approval (MEC-2017–145, Trial NL6972) and written informed consent were obtained.

9.2.2. Perioperative management

Surgery was performed in the operating room and anesthesia was sevoflurane based (end expired concentration between 1% and 3%), with bolus fentanyl (induction: 1-5 μg kg^{-1}) and rocuronium (0.5-1.0 mg kg^{-1}), performed by a pediatric

anesthesiologist. Repeated administration of analgesia was based on clinical evaluation. CDH neonates received continuous midazolam preoperatively, while EA neonates did not (table 26). Perioperative management, including physiological parameters and pharmacologic therapy, was recorded in the electronic patient data management system (HiX, Chipsoft BV, Amsterdam, the Netherlands). The vasoactive inotropic scores (VIS) were computed manually.

9.2.3. Data collection and processing

ECG was measured at 200 Hz during surgery (Primus, Draeger, Luebeck, Germany). The tachogram was derived in four steps (figure 30). First, the ECG was segmented into non-overlapping epochs of 5 minutes[24]. Second, the epoch signal quality was quantified to detect flatline and overly noisy epochs[25]. Only artifact-free epochs were considered. If no clean epochs were found, the patient was completely discarded from the analysis. Third, R peaks were located[26]. Last, HRV metrics were computed. To compute the frequency-domain and nonlinear metrics, the RR time series was interpolated linearly and resampled at 8 Hz [27].

9.2.4. HRV metrics

Time-domain, frequency-domain and nonlinear metrics (features) were derived to describe the autonomic nervous system in the intraoperative period.
Time-domain metrics included the mean and the standard deviation (SDNN), which measures the variability of all frequency components, since the variance is equal to the total power of the spectral analysis. Time-domain features are expressed in milliseconds (ms).
The sympathovagal activity was assessed using different frequency bands: the very low frequency (VLF; 0 – 0.08 Hz), the low frequency (LF; 0.08 – 0.2 Hz) and the high frequency (HF; 0.2 – 3.0 Hz), computed using the continuous wavelet transform[28,29]. The CWT spectrogram was compressed by summing over frequencies and taking the median in each 5-min epoch. Calculation of VLF, LF and HF power was done in absolute (ms^2) and normalized units: LF (n.u.)=LF/(LF+HF) and HF (n.u.)=HF/(LF+HF). The representation in normalized units emphasizes the controlled and balanced behavior of the two branches of the

autonomic nervous system and minimizes the effect of changes in total power. Finally, LF/HF was computed to define the autonomic balance.
Nonlinear measurements define the unpredictability of a time series, which results from the complexity of the HRV regulation mechanisms. In order to quantify complexity, sample entropy was used, due to its robustness on short time series[30,31].

9.2.5. Statistical analysis

Data are presented as median (interquartile range). The HRV metrics were analyzed using linear mixed effects models. The temporal analysis of the HRV metrics was done using the Wilcoxon signed-rank test, due to the small sample size. Overall, significance level was defined as $\alpha = 0.05$.

9.2.6. Primary endpoint

The primary endpoint of this study was the analysis of the effect of sevoflurane anesthesia on heart rate variability intraoperatively.

9.3. Results

9.3.1. Demographics

33 patients were eligible for inclusion, of which 1 patient was removed as a result of overly noisy data and 6 patients were removed as a result of flatline data. The patient demographics of the resulting 26 patients were collected (table 26).

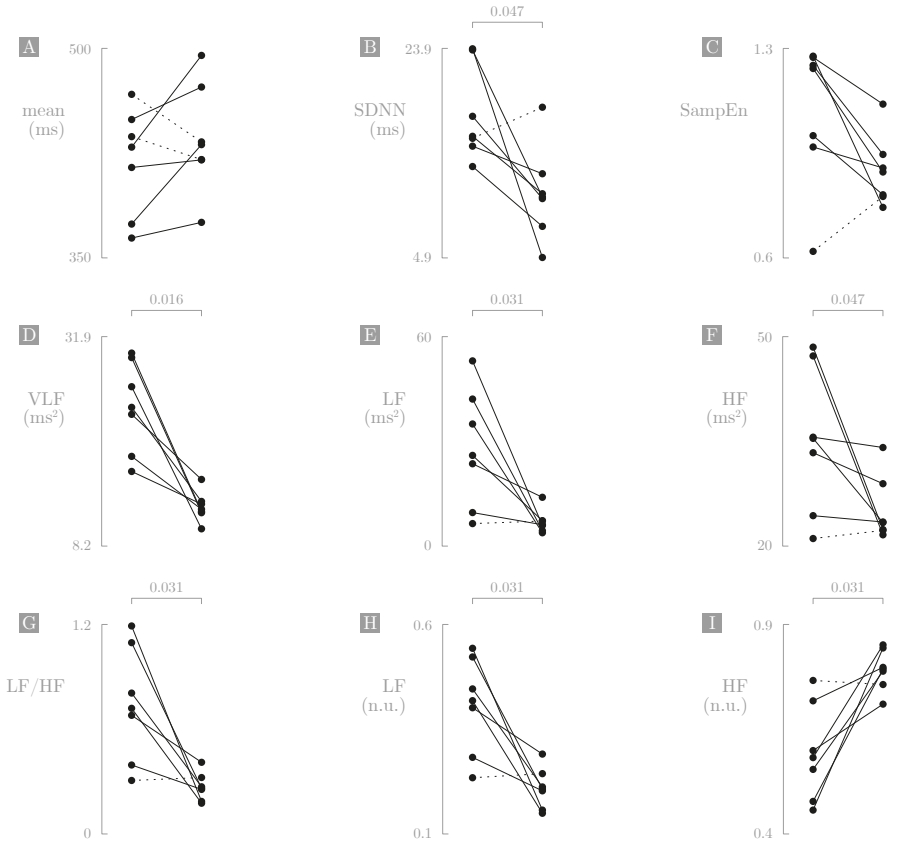

Figure 31. HRV metrics in a cohort with baseline data (7 neonates) changed significantly when transitioning from awake to sevoflurane-based anaesthesia. The majority trend is indicated by solid lines.

9.3.2. Baseline

For 7 neonates, data was available when they were still awake before surgery started (4 EA and 3 CDH) (figure 31). Over the transition from awake to anesthesia, we observed a significant decrease in SDNN ($p = .047$), in absolute power in the VLF ($p = .016$), LF ($p = .031$) and HF ($p = .047$) frequency band, in LF/HF ($p = .031$) and in relative power in the LF band ($p = .031$). The relative power in the HF frequency band increased significantly ($p = .031$). The mean RR and the sample entropy did not show a significant trend.

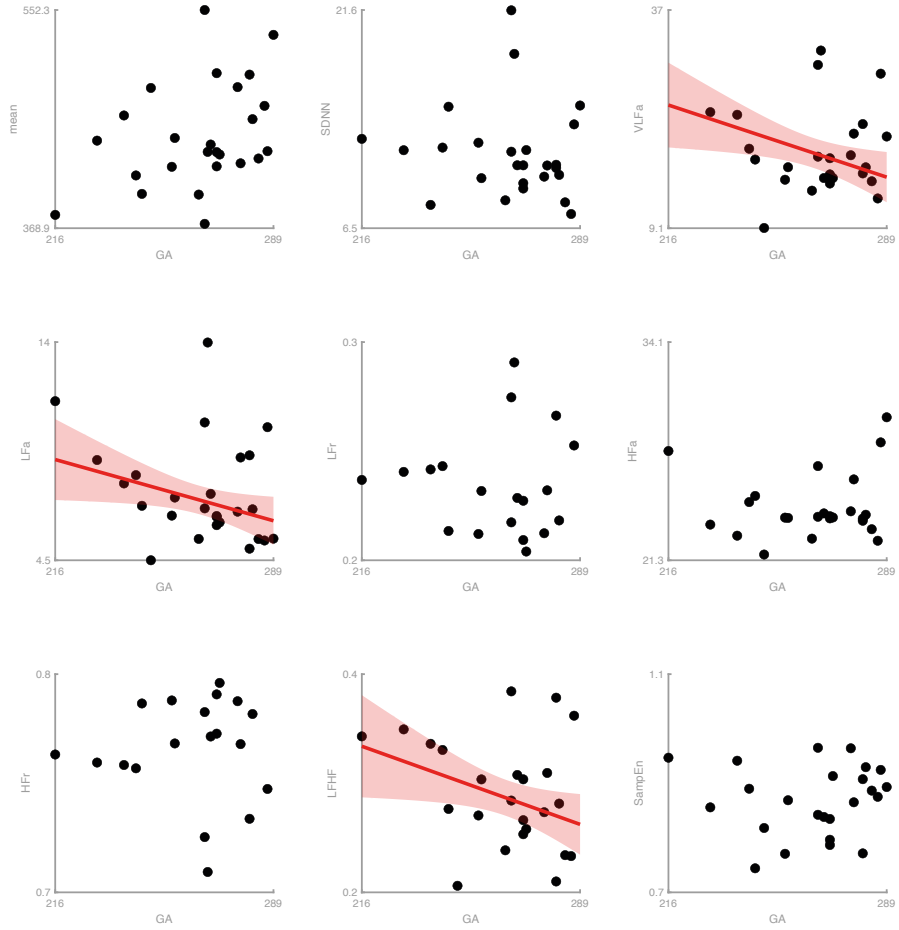

Figure 32. Scatter plots gestational age.

9.3.3. Linear mixed-effects model

For each of the HRV metrics, a linear mixed-effects model was fitted. Gender, postnatal age, birth weight, intraoperative midazolam dose and intraoperative fentanyl dose were removed as fixed effects from the final model, as they did not contribute significantly to any of the models. The remaining fixed effects included diagnosis (EA or CDH), surgery type (thoracoscopy, conversion or open), gestational age (GA), end-expired sevoflurane concentration and VIS, for which the p values are presented in table 27.

The diagnosis was observed to influence both SDNN ($p = .006$) and the absolute power in the HF band ($p < .001$). Both parameters were larger for CDH compared

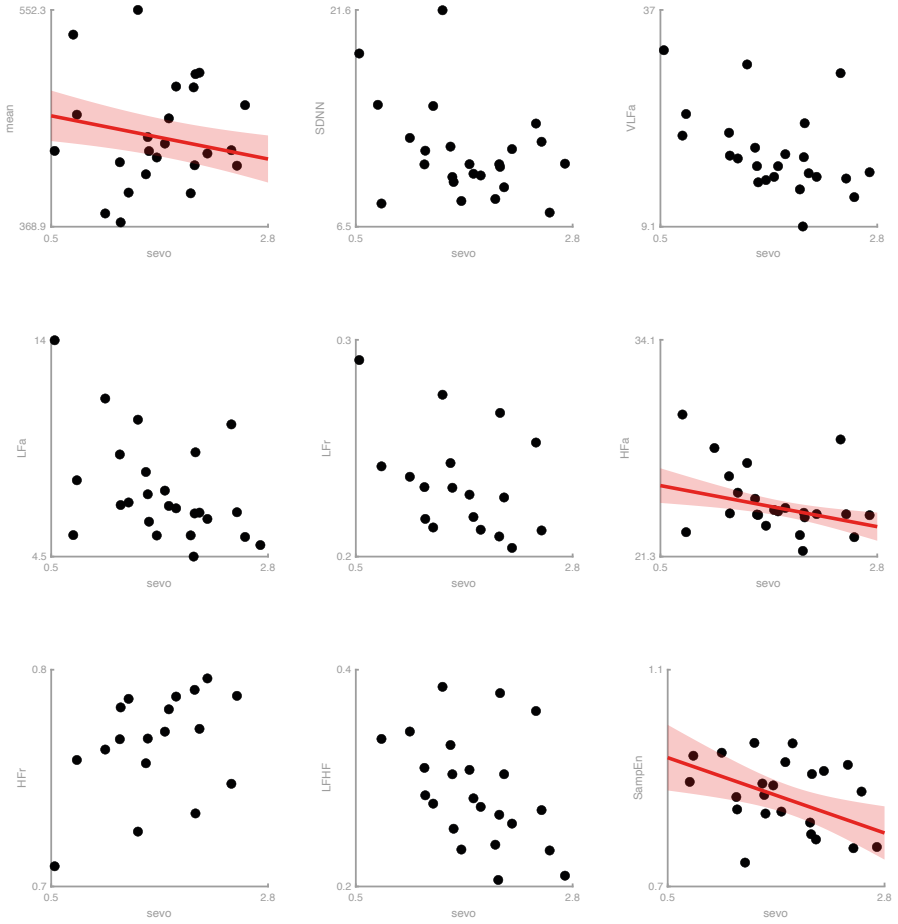

Figure 33. Scatter plots sevoflurane.

to EA. The type of surgery also impacted the absolute power in the HF band ($p = .006$), which increased from conversion to open to thoracoscopic surgery. Changes in GA were associated with changes in absolute power in the VLF ($p = .019$) and LF band ($p = .036$), as well as the LF/HF ratio ($p = .034$) (figure 33). All three parameters decreased with a higher GA. The end-expired sevoflurane concentration was observed to alter the mean RR interval ($p = .006$), the absolute power in the HF band ($p = .004$) and the sample entropy ($p = .005$) (figure 34). All three parameters decreased with increasing sevoflurane concentration. The VIS impacted the mean RR interval ($p < .001$), the absolute power in the VLF band ($p = .039$) and the sample entropy ($p = .046$) (figure 35). All three parameters decreased with increasing VIS.

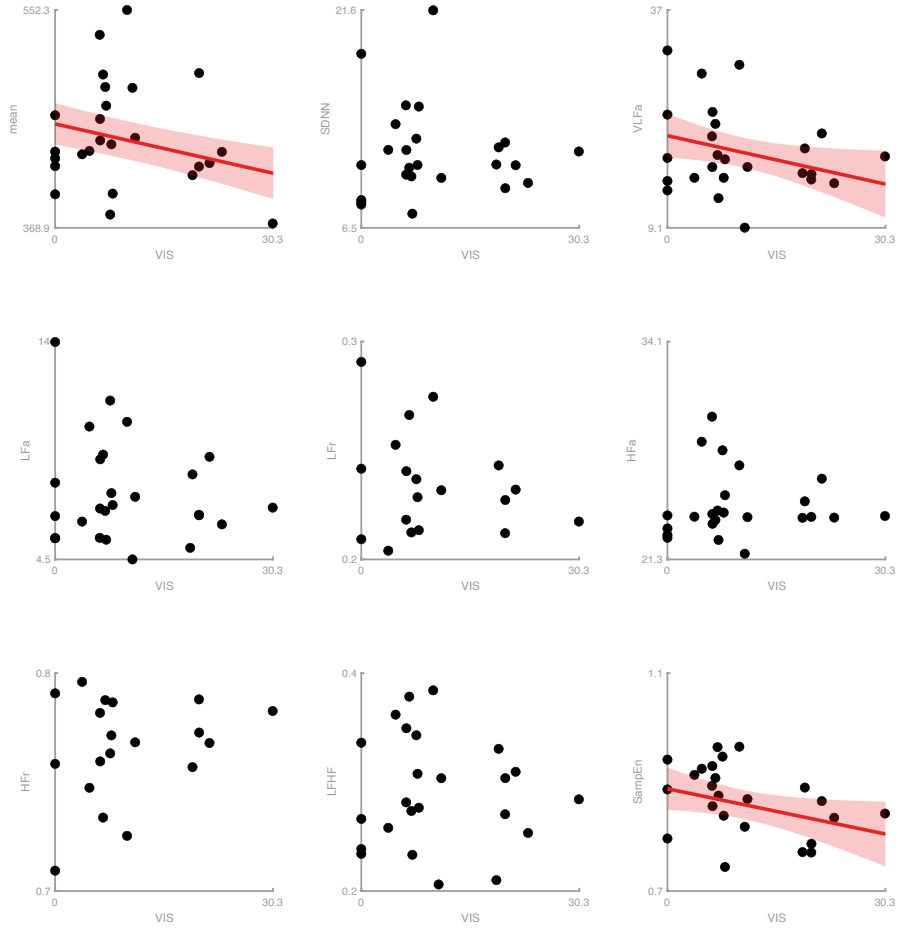

Figure 34. Scatter plots VIS.

9.4. Discussion/Conclusion

9.4.1. Baseline

In seven patients, the ECG included baseline epochs, measured before sevoflurane administration. These epochs showed that the HRV metrics drastically changed when the neonate underwent anesthesia (figure 31). Despite the small subcohort size, the trends were clear and statistically significant. Furthermore, these trends

are in line with a study in healthy newborns[22] and numerous studies in adults[32]. First, in the transition from awake to anesthesia, we observed a decrease in total HRV, indicated by the decrease in SDNN and the decrease in absolute VLF, LF and HF power. The values found in this study are lower compared to reference neonatal HRV metrics reported in literature[9]. In awake neonates, a lowered HRV might point towards a compromised cardiovascular system[13,14,15,16]. During anesthesia, a lowered HRV might be used as an indicator for adequate analgesia and anesthesia, since anesthesia aims to blunt the natural stress response of the surgical trauma, which translates into a reduction in HRV. It is hard to take apart these two effects in our data (a lowered HRV following a comprised cardiovascular system or adequate anesthesia) as literature about HRV in anesthetized neonates is lacking. The decrease in HF might result from an altered respiration, since the neonates transition from spontaneous breathing to mechanical ventilation at a fixed rate. Since the HF band includes the respiratory sinus arrythmia, it could change as a result of a change in respiration pattern. Second, no clear trends were observed in mean HR (mean RR interval) nor in complexity (sample entropy). The amplitude of the HR signal doesn't change significantly, but its dynamics change vastly under anesthesia. Third, a shift in autonomic balance was observed in the transition from awake to anesthesia: LF/HF decreased and relative power in the LF and HF band decreased and increased, respectively, indicating that the influence of the sympathetic branch reduces, while the influence of the parasympathetic branch increases. This reflects the desired effect of anesthesia, which is reducing stress.

9.4.2. Diagnosis

We observed a significantly lower SDNN and power in the HF band for the EA group compared to the CDH group (table 27). SDNN measures total HRV, since it measures the combined power of all frequency components. The difference in SDNN reflects the difference in absolute power in the HF band, since the absolute power in the VLF and LF band were comparable among the groups. Since HF correlates with PNS, this could suggest that the PNS is already more mature in the CDH group compared to the EA group.

		diagnosis	surgery	GA	sevoflurane	VIS
Time domain	mean	.52	.72	.08	.006	< .001
	SDNN	.006	.15	.46	.77	.83
Frequency domain	VLF	.06	.06	.019	.41	.039
	LF (absolute)	.19	.12	.036	.26	.24
	LF (normalized)	.81	.21	.06	.46	.49
	HF (absolute)	< .001	.006	.87	.004	.14
	HF (normalized)	.81	.21	.06	.46	.49
	LF $h^{-1}F$	.78	.27	.034	.55	.36
Nonlinear	SampEn	.67	.91	.71	.005	.046

Table 27. Statistical significance of fixed effects in linear mixed effects analysis. Gender, postnatal age, birth weight, intraoperative midazolam dose and intraoperative fentanyl dose were removed from the final model, as they did not contribute significantly to any of the models. The remaining fixed effects included diagnosis (EA or CDH), surgery type (thoracoscopy, conversion or open), gestational age (GA), end-expired sevoflurane concentration and vasoactive inotropic score (VIS), for which the p values are listed in this table.

9.4.3. Maturation

Postnatal adaption and maturation of the ANS have a significant effect on the HRV parameters. The vagal tone increases with increasing GA, but the development of the LF and VLF is faster than the vagal increase[33,34]. This is confirmed by our data, which showed a decreased power in the VLF and the LF band and a shift in autonomic balance with increasing GA (figure 32). A good maturation of the ANS requires at least a GA of 37 weeks[35]. In addition, the ANS continues to develop in the first weeks postnatally. Therefore, we initially included PNA as a confounder in our models, but we observed no significant effect of PNA. The PNS reaches maturity within a few days after birth, while the SNS reaches maturity by early infancy. In this period, the ANS is vulnerable to adverse environmental and physiologic influences[36].

9.4.4. Surgery

Absolute power in the HF frequency band increased from conversion to open to thoracoscopic surgery. Minimally invasive surgery is generally recognized as an improvement in the field of surgery, due to benefits including a shorter operating and recovery time, minimizing stress and pain due to smaller incisions, and even improving mortality. Our results seem to confirm a smaller stress response in the neonates on thoracoscopic repair, as indicated by the increased power in the HF band, which correlates with the parasympathetic branch of the ANS.

9.4.5. Medication

We studied various administered drugs to explain the differences in HRV metrics: sevoflurane, midazolam, fentanyl and the combined action of vasoactive and inotropic medication (VIS). The anesthetic effect of sevoflurane is predominantly mediated by the alfa-1-subunit of the GABAA receptor[37,38]. We observed a decrease in mean RR interval (a higher heart rate), in absolute power in the HF band and in sample entropy with increasing end-expired sevoflurane (figure 34). Sevoflurane mediates a decrease in myocardial contractility and mean arterial blood pressure, which can be compensated for by an increase in heart rate[39]. Midazolam is a short-acting benzodiazepine which acts by binding to the benzodiazepine receptor at the intersection between alfa and gamma subunits of the GABAA receptor in the central nervous system[40,41].Midazolam was administrated in 6 of the patients, but did not have an effect on HRV. Fentanyl was administrated in all of the patients and did not affect the HRV. VIS reflects the grade of vasoactive and inotropic pharmaceutical intervention and quantifies the necessity for cardiovascular support. Increasing VIS was associated with a decrease in mean RR interval (increase in heart rate), a decrease in absolute power in the VLF band and a decrease in sample entropy (figure 35). This can be explained by association between the VLF band and hormonal regulation. The administration of vasoactive or inotropic medication causes an increase in stress hormone levels which affects the hormonal regulation, reflected by a decrease in VLF.

9.4.6. Conclusion

In conclusion, we found that sevoflurane-based anesthesia doesn't affect heart rate, but significantly suppresses the ANS, as indicated by a decrease in all HRV metrics, except entropy. Total HRV decreases during sevoflurane anesthesia. Furthermore, the type of congenital anomaly, GA, the administrated sevoflurane concentration as well as the vasoactive and inotropic medication affected the HRV in neonates intraoperatively. In awake neonates, a suppressed HRV is associated with adverse outcome. During anesthesia, a lowered HRV indicates adequate anesthesia and analgesia. It remains unknown whether induced

decreased HRV due to anesthetics is related to adverse outcome since triggers for postoperative brain injury are still largely unknown.

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Appendix: Interpretation of HRV metrics

Neonates present an immature cardiovascular control and ANS, which manifests with an extremely low vagal tone at rest, reflected by a very high heart rate. The immaturity manifests also itself as a weaker blood-pressure control and chemoregulation and a reduced baroreflex sensitivity. Numerous studies confirm that the weak parasympathetic tone is accompanied by a predominant LF tone[33,34,29]. The heart rate evolves while the brain and the ANS mature. The most relevant changes are the decrease of the cardiac frequency with the infants' development and the increase of HRV.

In order to capture all aspects of the ANS, this study uses a combination of time-domain, frequency-domain and nonlinear HRV metrics. The frequency-domain analysis allows to decompose the ANS into the sympathetic and parasympathetic branch[42]. In order to interpret the contributions of the different autonomic branches, one often computes the relative power in the LF and the HF band (expressed in normalized units, n.u.) and the LF/HF ratio. For interpretation, the relative power of LF represents the sympathetic branch of the ANS, while the relative power of the HF represents the parasympathetic branch of the ANS. LF/HF represents the sympathovagal balance. A third component that can be derived from the spectral analysis is the VLF frequency band. The VLF values represent sympathovagal balance and is fundamental to health[43]. In non-anesthetized neonates, a decrease in VLF is more strongly associated with all-cause mortality than HF and LF [9,24].

10

Neurocardiovascular coupling in CDH patients undergoing different types of surgical treatment

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Abstract

Background. The effect of perioperative management on the neonatal brain is largely unknown. Triggers for perioperative brain injury could be revealed by studying changes in neonatal physiology perioperatively.

Objective. Study neonatal pathophysiology and cerebral blood flow regulation perioperatively using the neurocardiovascular graph.

Design. Observational, prospective cohort study on perioperative neuromonitoring. Subjects were included between July 2018 and April 2020.

Setting. Multicentre study in two high-volume tertiary university hospitals.

Patients. Neonates with congenital diaphragmatic hernia were eligible if they received surgical treatment within the first 28 days of life. Exclusion criteria were major cardiac or chromosomal anomalies, or syndromes associated with altered cerebral perfusion or major neurodevelopmental impairment. The neonates were stratified in different groups by type of perioperative management.

Intervention. Each patient was monitored using near-infrared spectroscopy and EEG in addition to the routine perioperative monitoring. Neurocardiovascular graphs were computed off-line.

Main outcome measures. The primary endpoint was the difference in neurocardiovascular graph connectivity, per group over time.
Results: Thirty-six patients were included. The intraoperative graph connectivity decreased in all patients operated in the operation room (OR) with sevoflurane-based anaesthesia ($P < .001$) but remained stable in all patients operated in the NICU with midazolam-based anaesthesia. Thoracoscopic surgery in the OR was associated with the largest connectivity reduction (0.33 to 0.12 to 0.24, $P < .001$) and a loss of baroreflex and neurovascular coupling. During open surgery in the OR, all regulation mechanisms remained intact. Open surgery in the NICU was associated with the highest neurovascular coupling values.

Conclusions. Neurocardiovascular graphs provided more insight in the effect of the perioperative management on the pathophysiology of surgical neonates. The neonate's clinical condition as well as the surgical and the anaesthesiological approach affected the neonatal physiology and CBF regulation mechanisms at different levels.

10.1. Introduction

Despite state-of-the art perioperative monitoring, the outcome after non-cardiac neonatal surgery can be complicated by significant acute and long-term sequelae[1]. Structured analysis revealed high incidence (48% in full term, 75% in preterm) of brain injury on magnetic resonance imaging after non-cardiac neonatal surgery[2]. Furthermore, interdisciplinary follow-up studies showed delayed neurodevelopment after neonatal surgery[3,4,5,6]. To date, the effect of perioperative management on the neonatal brain is largely unknown[2]. Triggers for perioperative brain injury could be revealed by studying changes in the neonatal physiology perioperatively. To this end, a new direction in neuromonitoring is needed which includes neuromonitoring combined with computational models. An overview of the coordinated interaction between the brain and the cardiovascular and cardiopulmonary systems can be created by extending standard monitoring with measurements of cerebral tissue oxygenation ($rScO_2$) and cerebral activity (EEG)[7]. This provides insight in the regulation of cerebral blood flow (CBF), including neurovascular coupling (NVC), cerebral pressure autoregulation (CAR), cerebral oxygen balance, and heart rate passivity (HRP)[8,9,10,11]. Impairment in regulation results in inadequate brain perfusion, which may cause hypoxic ischemic encephalopathy[12], intraventricular hemorrhage[13], and periventricular leukomalacia[14].

An advanced computational approach is needed to capture the status of the CBF regulation mechanisms, since numerous multimodal signals need to be included[7]. To achieve this, we used a model based on signal interaction graphs[15,16]. We applied the signal interaction graph framework perioperatively to neonates diagnosed with congenital diaphragmatic hernia (CDH). These neonates were stratified in different groups based on different types of

perioperative management. The aim was to determine whether the resulting graphs, referred to as neurocardiovascular graphs, provided crucial information about the neonatal pathophysiology and the CBF regulation mechanisms perioperatively. More specifically, the primary endpoint of this study was the difference in neurocardiovascular graph connectivity, per group over time. Secondary endpoints included the coupling between the vital parameters and the interactions corresponding to CBF regulation, per group over time.

10.2. Methods

This is a multicentre, observational, prospective study on perioperative neuromonitoring in neonates with CDH undergoing surgery in one of two tertiary paediatric expertise centres: the Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands), and the Mannheim University Hospital (Mannheim, Germany). The neonates were managed according to the revised 2016 CDH-EURO consortium guidelines[17]. Measurements were performed after institutional research board approval and written informed consent from both parents. Approval was provided by the Medical Ethics Committee of the Erasmus University Medical Center, Rotterdam, The Netherlands on 14 August 2017 (Chairpersons Prof. H.J. Metselaar and Prof. H.W. Tilanus, protocol number MEC 2017-145) and the Medical Ethics Committee of the University of Heidelberg, Mannheim, Germany on 6 July 2018 (Chairperson Prof. J.P. Striebel, protocol number 2018-578N-MA). Trial registration NL6972.

10.2.1. Patients and perioperative management

Neonates with CDH, a major non-cardiac congenital anomaly, were studied since they present a unique profile of clinical needs. Neonates with CDH show pulmonary hypoplasia and abnormal morphology of the pulmonary vasculature, resulting in severe respiratory insufficiency and an increased risk of developing persistent pulmonary hypertension (PPHN). A larger diaphragmatic defect leads to more severe pulmonary hypoplasia, and neonates with a (partial) intrathoracic

liver are more prone to develop PPHN. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) treatment is imperative when therapy-resistant PPHN occurs[18]. CDH neonates were eligible for inclusion between July 2018 and April 2020 if scheduled to receive surgical treatment within the first 28 days of life. Exclusion criteria were a major cardiac or chromosomal anomaly, or a syndrome associated with altered cerebral perfusion or major neurodevelopmental impairment.

Five perioperative settings were compared: thoracoscopic surgery in the operation room (OR), conversion from thoracoscopy to laparotomy in the OR, laparotomy in the OR, laparotomy in the neonatal intensive care unit (NICU) and laparotomy in the paediatric intensive care unit (PICU) during VA-ECMO. The subjects were stratified into groups based on clinical condition (figure 36): Thoracoscopic surgery in the OR if the neonate was cardiopulmonary stable and did not have a herniated liver. Laparotomy in the OR if the patient was cardiopulmonary stable and had a herniated liver. Surgery was performed in the ICU if the patient was not cardiopulmonary stable. Reasons for conversion were the need for a patch in case of a large diaphragmatic, or a ventilation problem (hypoxia or hypercapnia). Preoperatively, data of the thoracoscopic repair and conversion groups was merged, as they included the most stable patients with similar demographics (table 28).

The location of surgery defined the anaesthesiological approach (table 28). In the OR, general anaesthesia was performed by continuous administration of inhaled sevoflurane with a bolus of fentanyl and rocuronium, performed by a paediatric anaesthesiologist. In the NICU, neonates received continuous midazolam, bolus of fentanyl and rocuronium (Rotterdam) or continuous fentanyl and vecuronium (Mannheim), guided by a neonatologist or paediatric intensivist. Neonates on VA-ECMO were operated in the PICU and received continuous midazolam and morphine with a bolus of fentanyl and rocuronium, guided by a paediatric intensivist.

On the days before and after the day of surgery, each patient received a cranial ultrasound, performed by an experienced paediatric radiologist or neonatologist, to screen for intracranial abnormalities and brain injury.

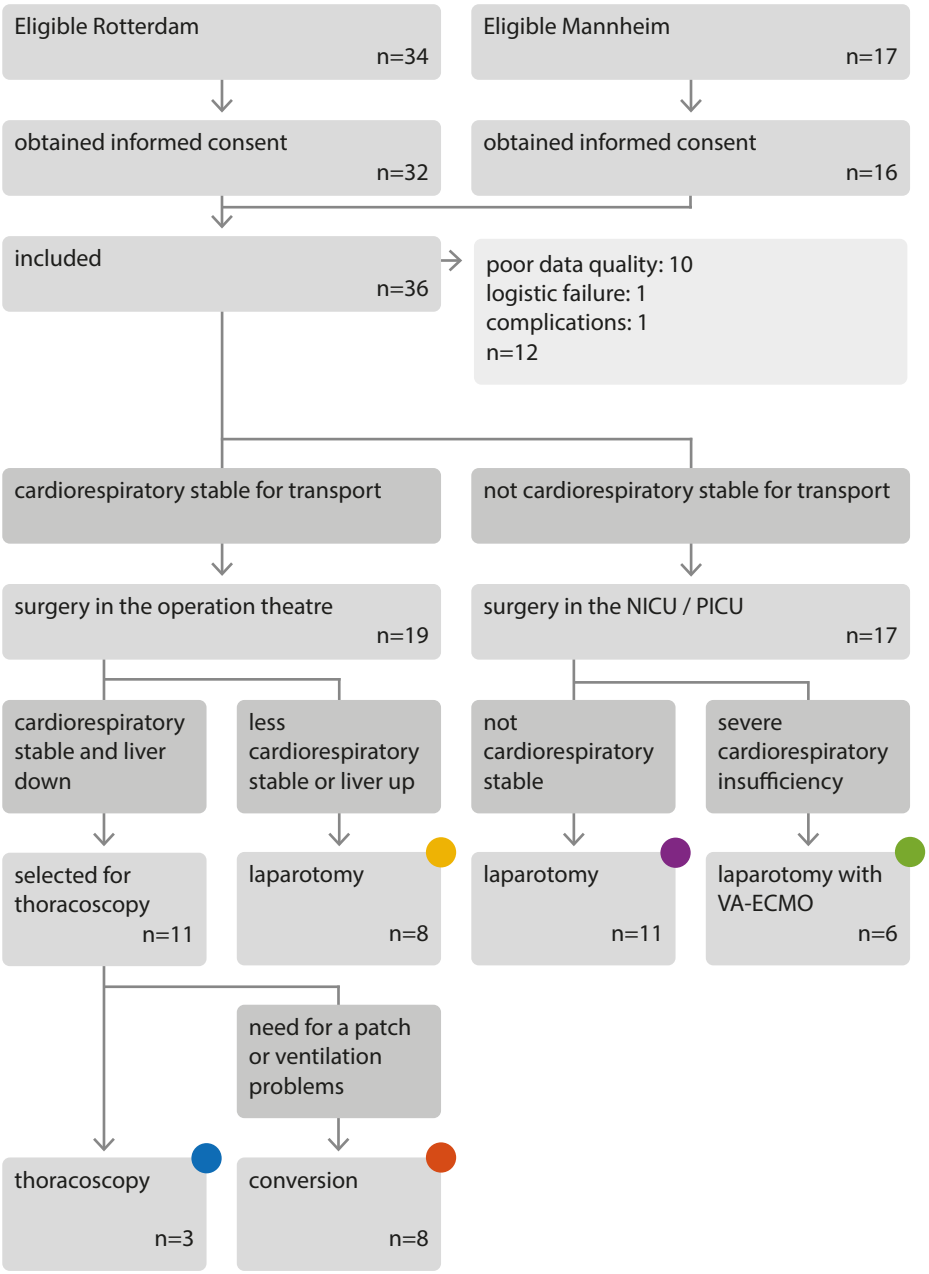


Figure 35. The patients are stratified in five groups based on their clinical conditions.

10.2.2. Data collection

Patient demographics were collected in accordance with the standardized reporting about CDH (table 28)[17]. For each patient, seven signals were measured. Heart rate (HR), mean arterial blood pressure (MABP) (indwelling arterial catheter), and peripheral oxygen saturation (SpO_2) were measured at 1 Hz (Primus, Draeger, Luebeck, Germany). Two frontal $rScO_2$ channels, measured using near-infrared spectroscopy (NIRS), were recorded at 1 Hz (neonatal sensor, INVOS 5100C, Covidien, Boulder, Colorado, United States). Two EEG channels, left (C3-P3) and right (C4-P4), were measured at 256 Hz (Rotterdam: BrainRT, OSG, Rumst, Belgium. Mannheim: Braintrend, Fritz Stephan GMBH, Gackenbach, Germany). Measurements started the day before surgery and continued until 24 hours postoperatively.

10.2.3. Data processing

After acquisition, the signals were preprocessed to reduce artefacts (figure 37). This procedure consisted of filtering the EEG (0.5-32 Hz), removing amplitudes outside of the physiologic range (negative values and saturation above 100), and detecting motion artefacts, defined as epochs in which the moving standard deviation exceeds 3.
To match the temporal scale of the rapidly changing EEG with the hemodynamic signals, the EEG was processed as a running estimate of the power in the delta frequency band (0.5-4 Hz) [19]. The delta oscillations regulate basic homeostatic needs, such as blood flow circulation and normotension enforcement.
Signal interaction graphs were computed in a sliding window of 15 min, which was found to be the minimal length required to estimate signal interaction in a robust way. In each window, the signal interaction was assessed between every pair of signals. This corresponds to the computation of a signal interaction graph. In such a graph, the signals define the nodes, while the links define the coupling between every pair of signals.
Transfer entropy (TE) was used as a measure of coupling[7]. TE is a nonlinear, effective measure, which can detect the direction of the interaction. In the TE framework, a signal X interacts with a signal Y if the past of X facilitates the prediction of the present of Y, to a better extent than the past of Y predicts

Table 28. Patient data. LHR: lung area to head circumference ratio; VIS: vasoactive inotropic score.

			Operation theatre			NICU/PICU	
			Thoracoscopy (n=3)	Conversion (n=8)	Laparotomy (n=8)	Laparotomy (n=11)	ECMO (n=6)
gestational age	(week)		40+4 (30+6 – 40.6)	38+2 (35 – 40+1)	38+1 (36+3 – 41)	37+6 (33+2 – 38+2)	38+1 (36+6 – 41+6)
age at surgery	(day)		3 (3-4)	4 (2-5)	3.5 (2-4)	6 (4-11)	7.5 (6-9)
birth weight	(kg)		3.2 (2.9 – 3.2)	3.0 (2.0 – 3.5)	3.1 (2.3 – 3.5)	2.8 (1.7 – 3.1)	3.1 (2.5 – 3.5)
antenatal diagnosed			1 (33%)	6 (75%)	7 (88%)	7 (64%)	1 (17%)
Apgar 5 min			9 (9-10)	8 (8-8)	8 (5-8)	8 (7-8)	6 (4-8)
o/e LHR			41	51 (34 – 75)	44 (36 – 74)	40 (32-44)	39 (27 – 57)
mechanical ventilation		pre-operative	2 (67%)	2 (25%)	8 (100%)	11 (100%)	6 (100%)
left-sided defect			3 (100%)	8 (100%)	5 (63%)	9 (82%)	1 (17%)
liver-up			0 (0%)	0 (0%)	5 (63%)	8 (73%)	5 (83%)
defect size	(A, B, C, D)		2A, 1B	2A, 3B, 2C, 1D	2A, 3B, 3C	1A, 4B, 5C, 1D	2B, 1C, 3D
surgery duration	(min)		118 (42-128)	120.1 (85-170)	72 (61-124)	155 (105-202)	101 (81-120)
patch			0 (0%)	5 (63%)	8 (100%)	10 (91%)	6 (100%)
rocuronium	bolus (mg kg^{-1})	intra-operative	0.74 (0.65-0.74)	1.0 (0.6-1.0)	0.62 (0.57-0.82)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
vecuronium	bolus (mg kg^{-1})	induction	-	-	-	0.1 (0.07-0.1)	-
	perfusor (mg kg^{-1} h^{-1})	intra-operative	-	-	-	0.2 (0.18-0.21)	-
fentanyl	bolus (µg kg^{-1})	induction	1.3 (0.9-1.3)	2.5 (1.7-2.9)	2.1 (1.9-3.0)	5.0 (4.0-7.0)	4.0 (3.1-4.0)
	bolus (µg kg^{-1})	intra-operative	5.6 (4.5-5.7)	6.3 (5.0-16.5)	6.3 (4.0-8.7)	11.0 (7.0-16.0)	11.3 (3.4-25)
	perfusor (µg kg^{-1} h^{-1})	intra-operative	-	-	-	4.5 (3.0-5.0)	-
morphine	perfusor (µg kg^{-1} h^{-1})	intra-operative	-	-	-	-	13.7 (8.4 – 18.6)
sevoflurane	perfusor (MAC expired %)	intra-operative	1.0 (1.0-1.9)	1.7 (1.0-2.5)	1.5 (1.1 – 2.4)	-	-
midazolam	perfusor (µg kg^{-1} h^{-1})	pre-operative	84 (50-200)	0 (0-133)	42 (0-133)	40 (30-50)	140 (60-257)
	perfusor (µg kg^{-1} h^{-1})	intra-operative	67 (50-179)	0 (0-125)	42 (0-133)	100 (75-100)	134 (75-257)
	perfusor (µg kg^{-1} h^{-1})	postoperative	67 (25-125)	90 (0-133)	34 (0-133)	50 (20-50)	131 (50-257)
	bolus (µg kg^{-1})	induction	0 (0%)	0 (0%)	1 (13%)	10 (91%)	4 (67%)
VIS		pre-operative	4.1 (0-26)	0 (0-16)	8 (0-32)	17 (8-23)	20 (5-61.5)
		intra-operative	8.5 (5-18.5)	12.3 (5-28)	7.5 (0-47)	17 (12-32)	7.3 (5-25)
		post-operative	1.7 (0-9)	1.8 (0-39)	1.5 (0-30)	14 (7-27)	9.5 (5-35)
$PaCO_2$	(kPa)	intra-operative	6.9 (6.6-7.2)	6.1 (5.3-7.7)	5.9 (5.3-7.4)	5.0 (4.7-6.2)	5.5, 7.8
died			0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (17%)

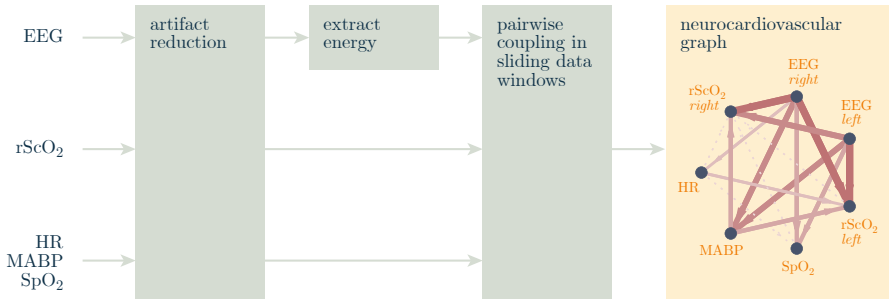


Figure 36. The data processing pipeline to translate the raw measured signals to a signal interaction graph, referred to as the neurocardiovascular graph.

its own present. The practical implementation used binning and nonuniform embedding[20]. Finally, the TE values were normalized as 0 (no coupling) to 1 (perfect coupling) following a procedure outlined in[21].

The signal interaction graph used in this study is referred to as the neurocardiovascular graph, as it captures the status of the regulation mechanisms affecting CBF (figure 38). The coupling between HR and MABP, in which HR reacts on changes in MABP, presents a measure for baroreceptor reflex (BR) [22]. Since BR couples HR and MABP, large values of interaction are expected. CAR is defined as the coupling between MABP and $rScO_2$. Since CBF should be independent of cerebral perfusion pressure, baseline coupling between MABP and $rScO_2$ is low. HRP was recently defined as the coupling between HR and $rScO_2$ [11]. As high values of HRP have been found associated with poor outcome, low interaction values are expected. Last, the coupling between EEG and $rScO_2$ presents a measure for NVC, which is properly functioning if cerebral oxygenation and cerebral activity are highly coupled[7]. The overall connectivity of the neurocardiovascular graph was quantified as the average over all graph links (average degree).

To balance data and remove transitional effects, such as artefacts of transport and care and the effect of intraoperatively administered medication, the graphs were computed in five time windows: the preoperative window (6 to 3 hours before surgery), the surgical period, and three postoperative windows: 3 to 6 hours, 9 to 12 hours, and 15 to 18 hours after surgery, respectively.

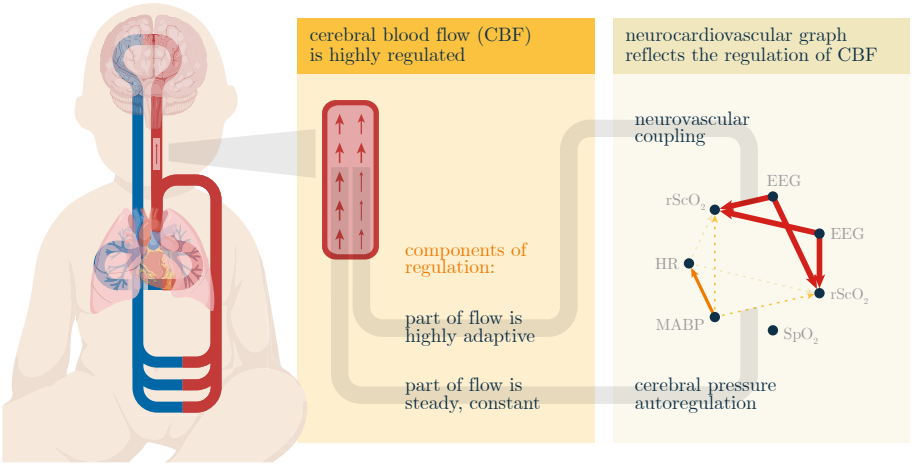


Figure 37. The neurocardiovascular graph translates the complex regulation of cerebral blood flow into one straightforward model. This regulation includes baroreflex (in orange, highly coupled), cerebral pressure autoregulation (in yellow, weakly coupled), heart rate passivity (in greed, weakly coupled) and neurovascular coupling (in red, highly coupled).

10.2.4. Statistical analysis

Linear mixed effects models were used to test the primary endpoint. Post-hoc analysis was done using estimated marginal means with Tukey correction. Statistical computations were carried out in R [23].

10.3. Results

10.3.1. Patient characteristics

Forty-eight neonates were enrolled in the study, of whom 11 neonates were excluded following the absence of multiple signals due to data transfer and storage problems. One neonate was excluded due to cardiopulmonary resuscitation intraoperatively, leaving 36 patients included (figure 36).

10.3.2. Graphs

The connectivity of the graphs was not affected by gestational age, birth weight, sex, position of the liver, and the diaphragmatic defect size of the defect was found on, whereas the clinical time window and the clinical group influenced the graph connectivity (both $P < .001$).

10.3.3. Thoracoscopic repair group

Neonates selected for thoracoscopic repair had the largest connectivity of 0.33 (IQR 0.26 – 0.37) preoperatively (figure 40F). During surgery, the connectivity of the neurocardiovascular graph dropped, reaching values of 0.12 (IQR 0.08 – 0.15) ($P < .001$), which increased again to 0.24 (IQR 0.23 – 0.33) ($P < .001$), 0.26 (IQR 0.25 – 0.36) and 0.32 (IQR 0.32 – 0.32) postoperatively.
Preoperatively and postoperatively, there was intact and strong interaction between the vital parameters and a functioning BR (figure 40G), CAR (figure 40H) and NVC (figure 40I, table 29). During surgery, CAR remained intact, while both BR and NVC disappeared.
Main finding: The largest reduction in connectivity was observed in the thoracoscopic repair group (figure 39, table 29).

10.3.4. Conversion group

During surgery, graph connectivity slightly decreased to 0.31 (IQR 0.24 – 0.34). After surgery, connectivity further decreased to 0.27 (IQR 0.23 – 0.31) ($P < .001$), after which it increased again to 0.33 (IQR 0.26 – 0.34) and 0.32 (IQR 0.30 – 0.34) ($P = .014$) (figures 39 and 40).
The interaction between the vital parameters dropped intraoperatively, after which it steadily increased postoperatively (table 29). CAR and NVC remained intact over the perioperative period. BR dropped intraoperatively but restored again after surgery.
Main finding: The connectivity in the conversion group is larger than that in the open repair OR group.

	Surgical approach	Intraoperative medication strategy	Clinical centre	BR	CAR	NVC	Main results
OR	Thoracoscopy	Sevoflurane	Rotterdam	-	+	-	largest reduction in overall connectivity
	Conversion from thoracoscopy to laparotomy	Sevoflurane	Rotterdam	-	+	+	larger intraoperative connectivity compared with the open repair OR group
	Laparotomy	Sevoflurane	Rotterdam	+	+	+	the only group in which all regulation mechanisms remained intact
ICU	Laparotomy	Midazolam	Mannheim	-	+	+	largest values of neurovascular coupling
	Laparotomy with VA-ECMO	Midazolam	Rotterdam	-	+	+	high interaction among vital parameters

Table 29. Main findings. A '+' and '–' indicate the presence and absence of a particular cerebral blood flow regulation mechanism, respectively. BR, baroreflex; CAR, cerebral pressure autoregulation; NVC, neurovascular coupling; OR, operation room; ICU, intensive care unit, VA-ECMO, venoarterial extracorporeal membrane oxygenation.

10.3.5. Open repair OR group

In the open repair OR group, the connectivity was 0.28 (IQR 0.20 - 0.36) preoperatively, then slightly dropped to 0.25 (IQR 0.12 – 0.28) intraoperatively ($P < .001$), and increased to 0.25 (IQR 0.15 - 0.31) ($P = .037$), 0.27 (IQR 0.12 - 0.30), and 0.30 (IQR 0.18 - 0.32) postoperatively.
The interaction among the vital parameters was strong preoperatively, dropped intraoperatively, and reached baseline values again postoperatively (table 29). CAR remained intact over the perioperative period. The same holds true for BR and NVC, although they were associated with slightly lowered values during surgery.
Main finding: The open repair OR group is the only group in which BR, CAR and NVC remained intact over the perioperative period.

10.3.6. Open repair NICU group

The graph connectivity remained stable for neonates on open surgery in the NICU, reaching values of 0.30 (IQR 0.23 - 0.34), 0.34 (IQR 0.26 – 0.38), 0.26 (IQR 0.22 - 0.33), 0.32 (IQR 0.24 - 0.37), and 0.28 (IQR 0.27 - 0.36) for the five consecutive time windows, respectively.
Interaction among the vital parameters, including BR, was absent over the entire perioperative period (table 29). CAR was intact over the entire perioperative period, as was NVC, had the largest values compared with all other groups over all time windows.
Main finding: NVC had the largest values in the open repair NICU group.

10.3.7. ECMO group

Neonates on VA-ECMO had the lowest connectivity before surgery; i.e. 0.27 (IQR 0.23 - 0.30). The connectivity increased to 0.34 (IQR 0.28 – 0.41) during surgery. Postoperatively, the connectivity was 0.30 (IQR 0.30 - 0.32), 0.21 (IQR 0.20 - 0.23) ($P < .001$) and 0.28 (IQR 0.26 - 0.31) ($P < .001$).
Strong interaction among the vital parameters, intact CAR, and NVC was observed throughout the perioperative period (table 29). CAR values only increased slightly intraoperatively, and in the first hours after. BR was absent, especially in the preoperative period, as well as in the postoperative windows of 9 to 12 hours and 15 to 18 hours after surgery.
Main finding: Strong interaction among vital parameters was observed in the ECMO group.

10.3.8. Correlations

During sevoflurane anaesthesia, increased sevoflurane concentration correlated with increased BR ($R2 = 0.34$) and decreased HRP ($R2 = 0.32$); increased fentanyl dose correlated with increased HRP ($R2 = 0.60$), increased CAR ($R2 = 0.41$) and decreased EEG to MABP coupling ($R2 = 0.42$); and increased partial pressure of CO_2 ($PaCO_2$) correlated with increased HRP ($R2 = 0.33$).
During midazolam sedation, increased midazolam dosage correlated with increased CAR ($R2 = 0.47$) and increased interaction between MABP and the two EEG signals ($R2 = 0.39$ for the left channel, and $R2 = 0.34$ for the right channel); and increased fentanyl dosage correlated with increased MABP to EEG coupling ($R2 = 0.33$ for the left channel and $R2 = 0.37$ for the right channel).
Increased $PaCO_2$ correlated with decreased BR during both sevoflurane and midazolam anaesthesia.

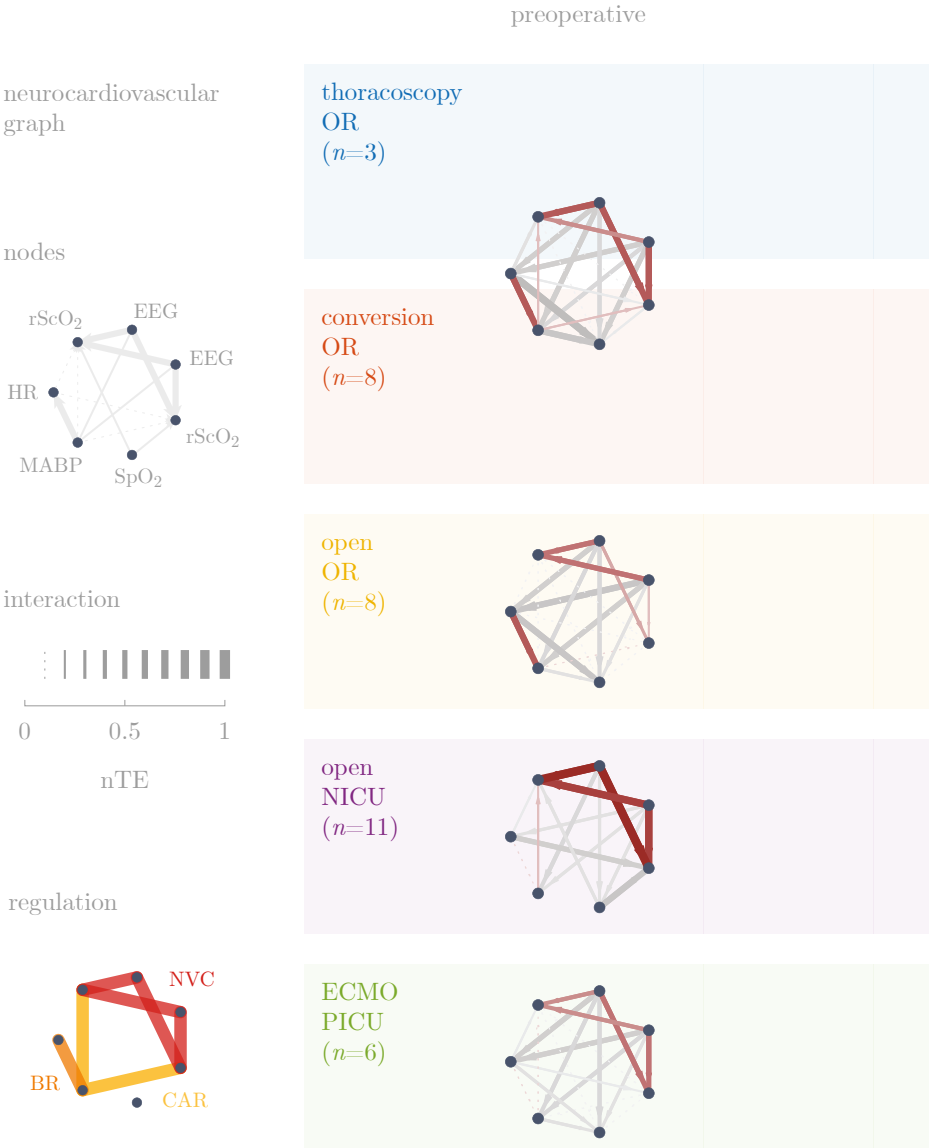
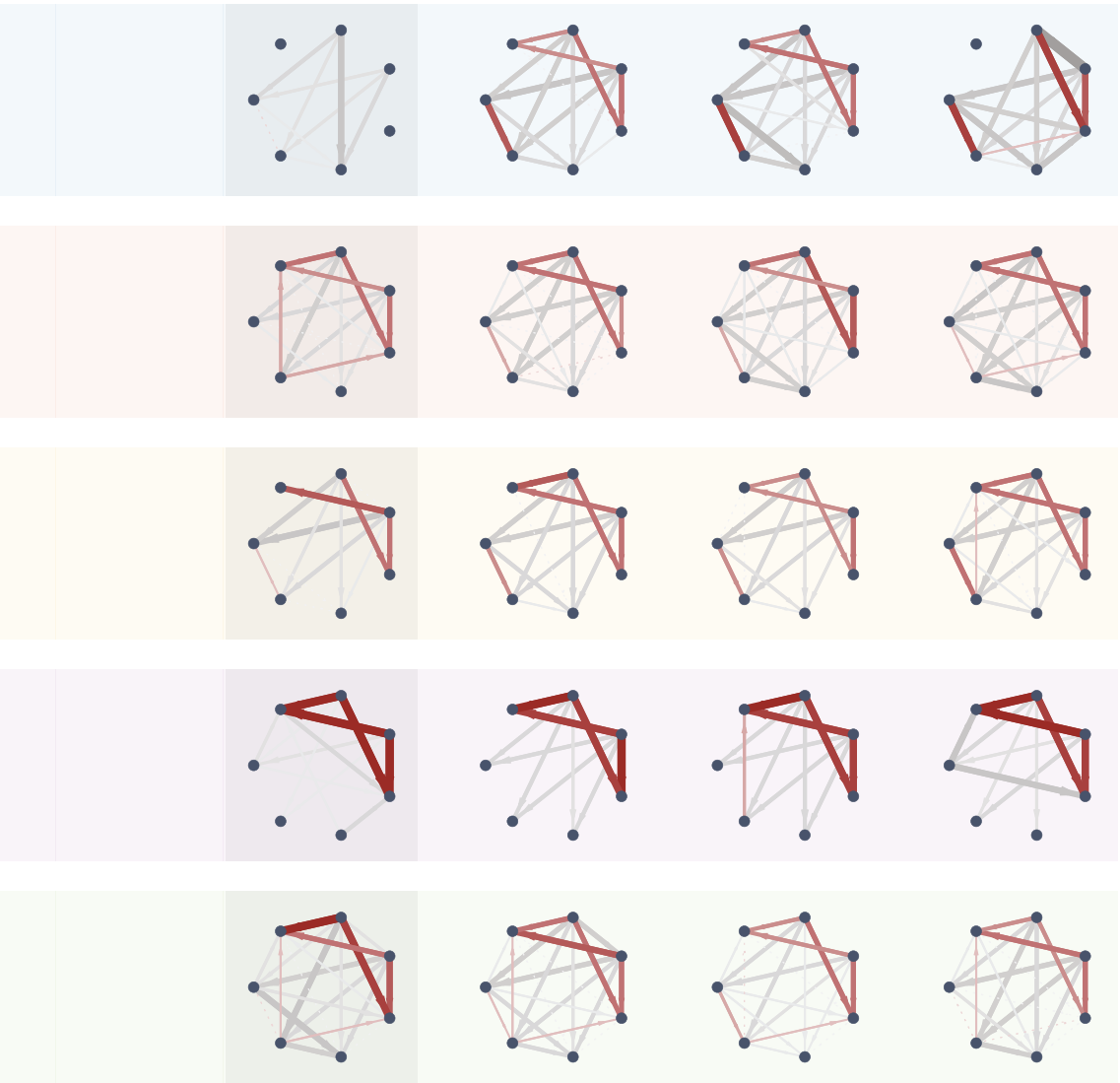
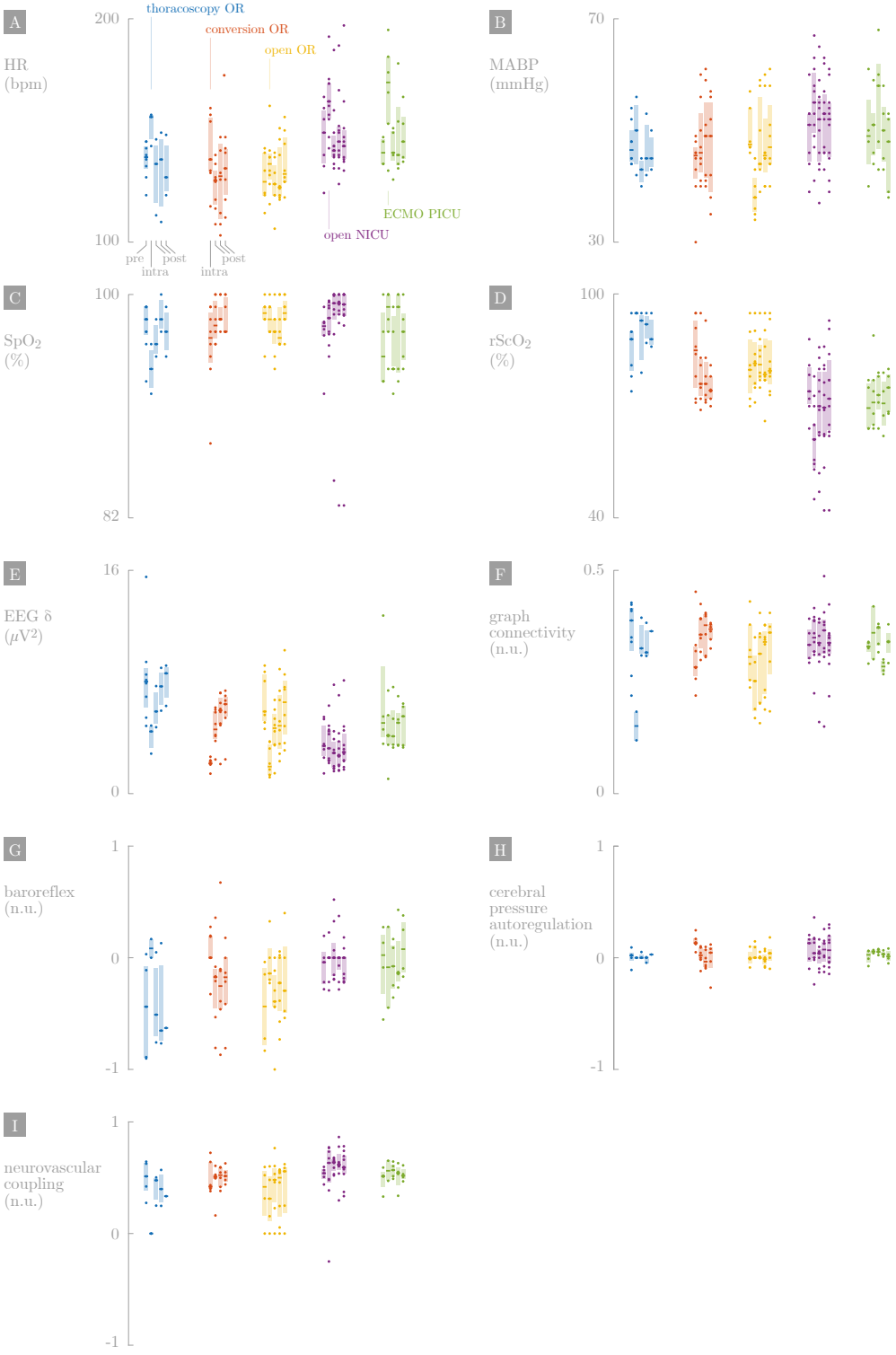


Figure 38. The neurocardiovascular graph is strongly influenced by both the patient group (rows) and the clinical time window (columns). Graphs are presented as a median over all patients in a group. The regulation mechanisms are highlighted in red, while all other graph connections are presented in gray.

intraoperative postoperative




A
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MABP
(mmHg)
70
30
C
SpO2
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82
D
rScO2
(%)
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EEG δ
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16
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graph
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Figure 39. (left page) Overview of heart rate (A), mean arterial blood pressure (B), peripheral oxygen saturation (C), regional cerebral oxygen saturation (D), EEG (E), graph connectivity (F), baroreflex (G), cerebral pressure autoregulation (H) and neurovascular coupling (I). Each dot represents a patient mean in the corresponding time window.

10.4. Discussion

Both the anaesthesiological and the surgical approach highly influenced the connectivity of the neurocardiovascular graph (figure 39). Despite the small sample size and the novelty of the applied methodology, some observations can be made, which will have to be validated in future studies. The largest reduction in connectivity was observed during thoracoscopic surgery, which included an absence of BR and NVC (table 29). This was striking, as neonates selected for thoracoscopic repair were the most cardiopulmonary stable patients (table 28). The conversion group was characterized by a larger connectivity compared with the open repair OR group, most likely because the neonates in the conversion group were clinically more stable (table 28). Yet, the open repair OR group was the only group in which all CBF regulation mechanisms remained intact. Of all groups, the open repair NICU group had the largest NVC values, while the ECMO group had a significantly larger interaction among the vital parameters intraoperatively. CAR remained stable in all groups (table 29). NVC remained functioning in all groups, except during thoracoscopic surgery.

10.4.1. Anaesthesia

The majority of the drugs used at NICUs are unlicensed or off-label[24,25]. Intravenous midazolam for sedation has been used for decades in the NICUs[26]. Nonetheless, a recent Cochrane review raised concerns about the safety of midazolam in neonates[27]. An included study reported statistically significant higher rates of adverse neurological events (death, grade III or IV intraventricular haemorrhage, periventricular leukomalacia) in neonates treated with midazolam compared to morphine[28]. Two studies observed a (transient) decrease in middle cerebral artery blood flow velocity and transient cerebral hypoperfusion after a bolus of midazolam in preterm neonates[29,30]. Our data showed a more impaired CAR with increasing midazolam dose.
In general, literature reports a negative effect of general anaesthesia on the neonatal physiology[31]. In the present study, we observed a stronger BR and less HRP with increasing sevoflurane dose during sevoflurane anaesthesia, which

might indicate that a higher sevoflurane dosage does not adversely affect regulation. Sevoflurane mediates a decrease in myocardial contractility and mean arterial blood pressure[32]. In the brain, sevoflurane mediates vasodilation, suppresses somatosensory-evoked potentials and reduces cerebral metabolism[33].

Increasing fentanyl dosage during induction, however, was associated with a more pronounced HRP, a more impaired CAR and a stronger, directed coupling between EEG and MABP in the intraoperative period, which aspects are all associated with adverse outcome in neonates[11,34,35].

10.4.2. Surgery

Thoracoscopic surgery is popular due to its potential benefits, including fewer postoperative ventilator days, lesser need for analgesics and a shorter hospital stay[36,37,38,39]. A drawback is that an artificial CO_2-pneumothorax is needed to create surgical workspace, which use results in hypercapnia and acidosis[40]. Signal interaction was highly affected during thoracoscopic surgery, which might be due to increased CO_2 or the increased intrathoracic pressure which affects venous return. An increase in $PaCO_2$ correlated with a less functioning BR, and a more pronounced HRP. The observed increase in HR might indicate a comprised venous return, although MABP did not decrease (figure 40). Open surgery gives fewer oxygenation and ventilation problems for the anaesthesiologist to deal with, but our data showed that graph connectivity decreased anyway. Although ECMO is associated with (intracranial) haemorrhagic and thrombotic complications, our results suggest that ECMO might help to preserve the signal interactions intraoperatively.

10.4.3. Importance

Perioperative management, including ICU management, anaesthesia and surgery, could cause undesirable changes in the neonatal physiology, which might trigger perioperative brain injury[2,3,4]. So far, most of the studies on this subject have focused on the analysis of one of the CBF regulation mechanisms, and lack information about other physiology parameters. Advanced computational

approaches need to be developed to quantify and understand the impact of perioperative management on the neonatal physiology[7]. In this study, we applied a computational framework (with visual and graphic feedback) that allowed to handle multiple concomitant signals, and thereby to study all major regulation mechanisms in one straightforward model.

As numerous signals are measured from the same physiological system, a strong, coordinated interaction should exist between them.16 The neurocardiovascular graph captures continuous information about the ability of the autonomic nervous system to react on changes in MABP (BR), and about the ability of the brain to regulate CBF, independently of fluctuations in MABP (CAR) and dependently of the cerebral metabolism (NVC). Therefore, it provides insights in cerebral perfusion. As HR, MABP and SpO_2 are included, the coordinated interactions between the brain and the cardiopulmonary systems can also be analysed.

Clinical decisions should be based on precise, qualified, and selected information. Information overload in perioperative medicine is a major concern[41]. New monitoring strategies which integrate different information sources in one straightforward, visual model could help to reduce information overload. The neurocardiovascular graphs provided new information on how the neonatal physiology and the CBF regulation mechanisms are affected by the actions of the clinicians, even in the most cardiorespiratory stable patients. Therefore, this approach could assist clinicians in making timely decisions about the optimal surgical and anaesthesiological approach, thereby making clinical practice more patient-specific and potentially preventing brain injury[7].

10.4.4. Limitations

The framework was applied in a very specific pathology during major, high-risk surgery. This approach needs further validation in other pathologies as well as in cardiorespiratory healthy neonates with and without anaesthesia.

The severity of the critical illness also differed between the groups, in addition to the surgical and the anaesthesiological approach.

Exposure to medication was compared based on dosages instead of its plasma concentrations.

10.5. Conclusions

We showed that neurocardiovascular graphs provide new and crucial information about the effect of the perioperative management on the pathophysiology of surgical neonates. The neonate's clinical condition and the surgical and anaesthesiological approach affected the neonatal physiology and CBF regulation mechanisms at different levels. This new direction could assist clinicians in making patient-specific decisions about the optimal perioperative management, aiming to prevent brain injury and possibly impaired neurodevelopmental outcome. At this stage, however, given the patient numbers in each group and the novelty of our approach, it is still too early to couple our results directly to changes in clinical management.

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Under the surface

Discussion and summary

11
General discussion

Monitor (verb): 'to watch and check a situation carefully for a period of time in order to discover something about it'.

By Cambridge English Dictionary

11.1. Background

Two major non-cardiac congenital abnormalities require high-risk surgical treatment in the first days of life and are at risk for impaired long-term neurodevelopment outcome. Firstly, neonates with congenital diaphragmatic hernia (CDH). These neonates are considered to be high-risk patients with uncertain prognosis, as even today mortality still remains around 25% worldwide[1].
CDH, mostly a left sided posterolateral defect in the diaphragm, comes with a complex pathophysiology due to lung hypoplasia and abnormal morphology of the pulmonary vasculature. In the majority of cases this results in severe respiratory insufficiency shortly after birth and an increased risk of developing persistent pulmonary hypertension (PPHN)[2]. Veno-arterial ECMO treatment can be imperative if therapy resistant PPHN occurs[3]. The CDH Euro-consortium created guidelines for postnatal management, ICU management and the timing of surgical repair[2,4].
Secondly, neonates with an oesophageal atresia (OA), defined as a disconnection between the oesophagus and the stomach, in the majority of the cases combined with a tracheo-esophageal fistula (TEF) and tracheomalacia[5]. Prematurity, dysmaturity and associated morbidities, in particular cardiac anomalies, increase the complexity of the postnatal and perioperative care[6].
For both congenital anomalies altered long-term neurodevelopmental outcome have been reported[6,7,8,9,10,11,12,13].

Nowadays, the concept that the surgical new-born is at risk of perioperative brain injury is commonly accepted, although the origin of these brain injuries is still unknown. This might be triggered by alterations in the complex

interactions between cerebral oxygenation, activity and perfusion, which cannot be monitored with current routine perioperative monitoring such as heart rate (HR), mean arterial blood pressure (MABP), peripheral oxygen saturation (SpO_2), respiration, and end-tidal CO_2. Additional neuromonitoring could provide information about the brain. Although, the single use of a monitoring technique neither helps to understand the perioperative neonatal (patho)physiology, nor enable early detection of deviation from the norm, as described in chapter 2. Near-infrared spectroscopy (NIRS) is commonly used to measure cerebral oxygenation, nonetheless we found no coherent results perioperatively. Electroencephalography is used to measure cerebral activity and showed the activity to be decreased during anaesthesia. No association between intra-operative cerebral saturation or cerebral activity and neuro-imaging abnormalities and/or neurodevelopmental outcome was found.
Insights in the neonatal physiology and the triggers for perioperative brain injury might be gained by implementing multiple (neuro-) monitoring modalities alongside routine perioperative monitoring and by adding mathematical models to compute the cerebral blood flow regulatory mechanisms.

11.1.1. Perioperative management

There are two surgical approaches to treat CDH and EA neonates: minimal access surgery (thoracoscopic) and the conventional open technique[14]. Thoracoscopic repair of neonates with CDH is feasible if the surgical new-born is cardiorespiratory stable without a herniated liver, as described in chapter 3. Thoracoscopic repair is potentially associated with fewer postoperative ventilator days, less use of analgesics due to less surgical access trauma, and shorter hospital stay[15,16,17,18]. On the other hand, the insufflation of carbon dioxide and the artificial pneumothorax that is created during thoracoscopic surgery result in (severe) respiratory acidosis[19,20,21]. The anaesthesiologist aims to compensate this acidosis by adapting the ventilation with increased tidal volume and/or frequency of ventilation. This might results in a higher mean airway pressure associated with a compromised venous return with decreased right ventricle preload[22]. The retrospective comparison of thoracoscopic surgery with open surgery in CDH patients who all met the criteria for thoracoscopic surgery, was a good first attempt in comparing thoracoscopic surgery with open surgery in comparable

patient groups without the bias of clinically better patients in the thoracoscopic group (chapter 3). Although all CDH neonates were carefully selected to be equally cardiovascular stable, the open group had a lower gestational age and prenatal lung-to-head ratio compared to the thoracoscopic group. This study lacked intraoperative data and arterial blood gas (ABG) sampling. Furthermore, a higher recurrence rate was observed in the thoracoscopic group (19% in the thoracoscopic group vs. 6% in the open group) and the neonates in the open group were admitted longer at the ICU postoperatively. The increased recurrence rates after thoracoscopic surgery in CDH neonates is reported in multiple other studies as well[16,17,23,24,25,26]. Every surgical procedure comes with (specific) risks and potential triggers for brain injury. Therefore, a redundant second surgical procedure should be avoided.
Overall, these results suggest that thoracoscopic surgery is safe in cardiorespiratory stable patients, although intraoperative blood gas analysis is needed to verify this. Additionally, research must be conducted about the effects of (severe) respiratory acidosis on long-term neurodevelopmental outcome.

To date, it is unknown whether the advantages of thoracoscopic surgery outweigh the disadvantages. The potential benefits of thoracoscopic surgery for CDH are still under discussion between paediatric surgeons and are based on personal experience, skills and infrastructure. Data about long-term neurodevelopmental outcome is hard to correlate with the surgical approach and the associated (patho)physiological changes/impairments. Neonates who underwent thoracoscopic surgery are the 'better' (more cardiorespiratory stable) patients, which makes it impossible to compare the long-term follow-up results of these neonates with the neonates who underwent open surgery. Especially neonatal CDH ECMO survivors are at risk for adverse neuro-psychological development and school failure[27]. In addition to this, the surgical new-born is admitted in the ICU, sedated and mechanically ventilated for days till weeks. In the course of these events, multiple potential events can trigger brain injury and consequently alter the neurodevelopmental outcome. Research from our group also showed that neuropsychological impairment may represent a 'growing into deficit' phenomenon, which makes it even harder to correlate neurodevelopmental outcome with the events in the neonatal period[27].The best way to prove the superiority of one of the two surgical techniques would be a randomized controlled trial with neonates who all meet the criteria for

thoracoscopic surgery. Randomized controlled studies are lacking and almost impossible to perform due to the required large patient number. Another possibility is retrospective case selection. This would be the second-best option to compare thoracoscopic surgery with open surgery. By using our current perioperative data grabber system, more information can be obtained compared to our retrospective comparison.

We found that the surgical new-born is prone to intraoperative hypercapnia, regardless the type of surgery, as described in chapter 4 and 5. Detailed information about intraoperative blood gas analysis was obtained during surgical treatment of neonates born with OA in chapter 4. In this study, we found severe respiratory acidosis and hypoxia intraoperatively, regardless the perioperative status, or the surgical approach. The intraoperative hypercapnia is probably caused by limited cardiorespiratory coping capacity of neonates and the limited possibilities of the anaesthesiologist to correct this.
Not much is known about the effect of hypercapnia on cerebral perfusion in anesthetized neonates and currently used routine monitoring lack sensitivity to detect alterations in cerebral blood flow due fluctuations in pCO_2 values[28]. Carbon dioxide is one of the primary controllers of cerebral blood flow. An increase or a decrease in CO_2 from normocapnia affects cerebral blood flow to a lesser extent than large fluctuations from hypocapnia to hypercapnia or form hypercapnia to hypocapnia. Therefore, it is of the utmost importance to monitor CO_2 levels perioperatively. Currently, there are three methods to measure CO_2 levels perioperatively: end-tidal CO_2 on the mechanical ventilation system, arterial blood gas (ABG) sampling, and transcutaneous CO_2 measurements. Intraoperative end-tidal CO_2 measurements are not reliable due to leakage, therefor repetitive ABG analyses are performed. Yet, there is a need for continuous CO_2 registration as an alternative for end-tidal CO_2 measurements. Transcutaneous CO_2 measurements could be a good alternative, although perioperative validation of this technique in neonates is needed.

Lessons learned

› Thoracoscopic surgery is safe in cardiorespiratory stable neonates. Neonates with an EA or CDH are both prone for intraoperative acidosis, regardless the type of surgery.

Perspectives

› The effect of (severe) acidosis on the neonatal brain and the neurodevelopmental outcome is still unknown. A multimodal neuromonitoring study could be a first step in understanding the effect of (severe) acidosis on the neonatal (patho)physiology and the brain.

11.1.2. Towards integrative neuromonitoring

A popular technique to measure regional cerebral oxygenation saturation ($rScO_2$) is near-infrared spectroscopy (NIRS). Reference values in awake neonates are between 55% and 85% [29]. Interpretation of $rScO_2$ is hard, since baseline $rScO_2$ can vary as a result of sensor placement[30,31] sensor type, and the measurement device[32,33]. Therefore, clinical use of $rScO_2$ mainly represents trends in oxygenation[34]. Intraoperative use of NIRS has been explored over the last decades, but no coherent results have been reported in non-cardiac surgical patients[35] and NIRS-guided treatment guidelines are only available in paediatric cardiac surgery patients[36]. To date, studies with $rScO_2$ values as primary outcome or in relation to neurodevelopmental outcome are lacking. Furthermore, NIRS can be used as an estimate for cerebral perfusion, although this only holds true during unchanged cerebral metabolism and oxygen saturation, which makes this method hard to use in sedated or anesthetized neonates[37]. In our pilot study with single use of NIRS, as described in chapter 5, we did not find clinically significant changes in cerebral oxygenation during thoracoscopic surgery in CDH and EA neonates. Cerebral tissue oxygenation did not change significantly during the artificial CO_2 pneumothorax that was created during thoracoscopic surgery, although (severe) respiratory acidosis was observed during the artificial CO_2 pneumothorax. Nonetheless, cerebral oxygenation decreased slightly over time intraoperatively. We hypothesized that cerebral metabolism would decrease during sevoflurane anaesthesia, and hypercapnia would be observed in all neonates. Hypercapnia led to increased cerebral blood flow and subsequently would have resulted in higher cerebral oxygenation values. The fractional tissue oxygen extraction (FTOE) increased in CDH neonates, suggesting that the brain was consuming more oxygen followed by a decrease in cerebral oxygenation. Again, this was the opposite of what was expected, since sevoflurane anaesthesia and hypercapnia decrease cerebral activity/metabolism, resulting in decreased

FTOE and increased cerebral oxygenation. No information about cerebral activity or cerebral metabolism was obtained in this pilot study.
At this point, it was clear that single use of NIRS intraoperatively would not provide sufficient additional information about cerebral perfusion and that additional modalities were needed.
Nonetheless, this is commonly overlooked by clinicians, and during my research I would often hear clinicians say: 'the NIRS is high, so the perfusion of the brain is okay'. This conclusion can only be drawn when the clinician has information about the cerebral activity and subsequently the cerebral metabolism, in combination with MABP and SpO_2. This led to the conclusion that the single use of NIRS was not of additional value and should be used in a multimodal neuromonitoring setting. This was the start of the study named: 'Neuromonitoring during surgical treatment of congenital diaphragmatic hernia or esophageal atresia study' (NeMo CDH/EA study).
Before the NeMo CDH/EA study started, there was neither consensus about the need for neuromonitoring, nor how to interpret neuromonitoring modalities, nor the need, timing or frequency of ABG sampling. During the NeMo CDH/EA study, all neonates with CDH or EA received additional perioperative monitoring with NIRS, aEEG, $tcCO_2$ in combination with intraoperative ABG sampling every 30 minutes. In addition, with the NeMo CDH/EA study, set conversion criteria for thoracoscopic and open surgery were created to prevent severe acidosis and unnecessarily long surgical procedures. By starting the NeMo CDH/EA study, the awareness about the effect of a high-risk surgical procedure on the neonatal physiology was increased and led to a clear Hawthorne-effect.

Lessons learned

- Single use of NIRS does not help to understand the effect of (severe) acidosis on the neonatal brain. An integrative multimodal neuromonitoring approach with at least a combination of cerebral oxygenation and cerebral activity in addition to routine perioperative monitoring is needed to understand the effect of perioperative management on the neonatal (patho) physiology perioperatively.

Perspectives

- NeMo CDH/EA study is a multimodal neuromonitoring study and provide the opportunity to create insight in the neonatal (patho)physiology by

combining standard perioperative monitoring (heart rate, blood pressure, saturation, end tidal CO_2) with cerebral oxygenation (NIRS), cerebral activity (aEEG) and continuous CO_2 measurements ($tcCO_2$).

11.1.3. New (neuro)monitoring techniques

Single use of a neuromonitoring modality such as NIRS and (a)EEG does not help to understand the perioperative neonatal pathophysiology, as described in chapter 2. Therefore, other (neuro)monitoring techniques or a combination of techniques were explored. We investigated the feasibility of perioperative cortical cerebral blood flow monitoring using transfontanellar directional power Doppler and pulsed wave Doppler ultrasound of the pial arteries during CDH and EA surgical treatment in chapter 6. We found that it was possible to perform perioperative measurements and that it was possible to repeat measurements in the same pail artery.
Transfontanellar directional power Doppler and pulsed wave Doppler ultrasound was performed in a so called 'low frame rate' setting of 25 frames per second. This ultrasound technique does however not provide information every vessel. A promising technique is high frame rate (HFR) ultrasound of >1000 frames per second, which enables more sensitive vascular imaging throughout the imaging plane and facilitates quantification in every vessel[38]. In 2014, Demené et al. used high frame rate ultrasound for neonatal brain scanning for the first time, which resulted in high resolution images of the vascular network, simultaneously providing quantitative data of the ultrasound plane[39].
Transfontanellar power Doppler, pulsed wave Doppler ultrasound and HFR measurements are challenging to perform perioperatively. During this study we performed the measurements manually, which made it easy to adapt to changes in position of the patient. With the help of power Doppler, it was possible to find the same pial artery multiple times before, during, and after the surgery in the same patient. The HFR measurements require repetitive measurements in exactly the same field and not only the same pial artery. During these measurements there is no visual feedback which makes it even harder to stay in the same field, while the surgeon is still operating (and the neonate is moving) due to the manipulation of the surgeon. Even the slightest manoeuvre could lead to loss of contact and subsequently loss of signal. Technical improvements

for both transfontanellar power Doppler and pulsed wave Doppler ultrasound and HFR measurements could improve the quality and the repetitiveness of the measurement. A solution could be a probe holder attached to the head of the neonate or a cap with an integrated probe holder. The quality of the HFR measurements would probably also improve with real-time visual feedback.
This was the first study with perioperative longitudinal data of cortical cerebral blood flow. We became interested in the cortical cerebral blood flow due to the location of perioperative brain injuries reported in the study of Stolwijk et al.[7] and case series of McCann et al.[40]. Stolwijk et al. investigated 101 neonates who had an MRI exam seven days after different types of non-cardiac major surgical procedures. Parenchymal lesions were observed in 23 preterm (72%) and 29 full-term neonates (42%), including punctate white matter lesions (n = 45), punctate cerebellar lesions (n = 17), thalamic infarction (n = 5), and periventricular haemorrhagic infarction (n = 4). The case series (n = 6) of neonates with severe postoperative encephalopathy in the report of McCann showed supratentorial watershed infarction in the border zone between the anterior, middle, and posterior cerebral arteries after relatively moderate surgical procedures[40] which are highly suggestive for perfusion disorders in the perioperative phase.
So far, information about cortical perfusion in neonates perioperatively was lacking. We did not know if the cortical perfusion changed during anaesthesia and whether macro-perfusion parameters (MABP, rSO_2, SpO_2) represented the cortical perfusion. As described in chapter 6, we did observe changes in cortical cerebral blood perioperatively. Furthermore, in patients with a vasoactive-inotropic score below 12, the trend of peak systolic velocity and end diastolic velocity corresponded with the MABP trend. This phenomenon was not found in patients with a vasoactive-inotropic score above 12 or a delta above 12. An earlier study of our team found that the maximum dose of vasoactive medication was negatively associated with verbal and visuospatial memory in 8-year-old survivors of neonatal extracorporeal membrane oxygenation and CDH survivors[13]. The patients in our current study participate in a structured long-term follow-up program which could clarify the effect of these VIS fluctuations on brain development later in life.
Preliminary data, not presented in this thesis, of the HFR analysis of the same measurements of this study showed that the tissue perfusion decreases during the administration of norepinephrine. The results of the high transfontanellar directional power Doppler and pulsed wave Doppler ultrasound measurements

and the preliminary data of the HFR measurements suggest that the (cortical) cerebral blood flow is highly affected by the perioperative care/management. This invites to implement transfontanellar ultrasound with directional power and pulsed wave Doppler perioperatively. Yet, reference values of peak systolic velocity and end diastolic velocity in the pial artery in neonates are lacking. To obtain reference values, measurements in non-anesthetized and anesthetized cardiorespiratory healthy term neonates are needed. The measurements in the awake neonates can serve as reference values in a brain of intact cerebral blood flow regulation mechanisms. The perioperative measurements in cardiorespiratory healthy term neonates, meaning measuring neonates with normal cardiorespiratory coping capacity without need for hemodynamic support, could provide information about the cerebral blood flow regulation mechanisms in a brain that has been put to sleep with anaesthetics. It is important to distinguish between non-anesthetized and anesthetized cerebral blood flow due to the possible alterations in cerebral blood flow regulation mechanisms. Two important cerebral blood flow regulation mechanism are cerebral autoregulation and neurovascular coupling. Cerebral autoregulation is the most extensively studied regulation mechanism in neonates. At its core, cerebral autoregulation maintains a constant cerebral blood flow in a wide range of cerebral perfusion pressures (CPP)[41]. Neurovascular coupling reflects the ability of the brain to adapt its cerebral blood flow to the cerebral oxygen consumption/ demand. An increase in neural activity results in a higher oxygen consumption, which, in turn, triggers an increase in CBF, in order to deliver more oxygen to the brain. Impairment in regulation would lead to hypoperfusion of the brain, which causes hypoxic ischemic encephalopathy[42], intraventricular haemorrhage[43], and periventricular leukomalacia[44].

During decreased cerebral activity, the oxygen consumption is less and subsequently the oxygen demand is less, which triggers a decrease in CBF[37]. It is important to learn about the differences in cerebral perfusion in awake and anesthetized neonates because, it is unknown whether aiming for awake reference values of cerebral blood flow in an anesthetized neonate would lead to optimal cerebral perfusion. On the one hand, it could be that this would led to hyperperfusion of the brain and that clinicians should aim for deceased CBF. On the other hand, aiming for decreased CBF could result in a decreased microcirculation which could led to less oxygen transport into the cells.

A monitoring technique that can measure the oxygen tension at a cellular level is the non-invasive Cellular Oxygen METabolism (COMET). We tested the feasibility of measuring mitochondrial oxygen tension (mitoPO$_2$) on the skin in neonates intraoperatively with this technique (chapter 7). To be able to measure mitoPO$_2$ cutaneous administration of 5-aminolevulinic acid (ALA) is needed, which has never been done before in neonates.

ALA is registered for use in adults, for example for photodynamic therapy in dermatologic pathology[45,46] and to visualize brain tumours during fluorescence-guided surgery[47,48] and was not used in paediatric patients until recently. Research with cutaneous ALA administration up to 354 mg in infants of 5 years and older reported no side effects[49]. Oral administration of 20 mg kg^{-1} ALA in infants of 1 year and older showed a transient increase of alanine aminotransferase[50,51,52]. Rarely did the administration of 5-aminolevulinic acid lead to an allergic reaction, with contact dermatitis the only reported allergy[53]. Therefore, we assumed the safety on a systemic level of a very low dosage of ALA – 8 mg – on the skin of neonates, providing an opportunity to use COMET monitoring in neonates for the first time. Yet, we did not know whether neonatal skin would react in the same way as adult skin to ALA application. We found that it was possible to measure mitoPO$_2$ with the help of ALA in neonates. Furthermore, we found that pathophysiological disturbances led to perturbations in mitoPO$_2$ that were not observed with standard monitoring modalities. The administration of ALA and the COMET monitoring technique did not cause damage to the skin, and seemed safe in this respect in all patients.

This study was an important step in measuring the mitochondrial oxygen tension at a cellular level in neonates. The aim of every clinician is to optimize cellular oxygenation. Clinicians can influence the mitochondrial oxygen tension by increasing the oxygen transport to the cells. There are two ways to accomplish this: one is by increasing the oxygen saturation, the other is by increasing the perfusion. Perfusion can be increased by increasing MABP. MABP reflects the macro-circulation and not the microcirculation, while microcirculation represents the oxygen transport into the cells. So far, the COMET is only suitable for measuring mitochondrial oxygen tension in the skin and bowel mucosa. Nonetheless, we observed perturbations in mitoPO$_2$ that were either only later detected by routine monitoring modalities, or not at all. This makes the COMET a promising technique to optimize (cerebral) perfusion in neonates.

Lessons learned

- It is feasible to perform transfontanellar directional power Doppler and pulsed wave Doppler ultrasound measurements perioperatively. Furthermore, repeated measurements in the same pail artery provides longitudinal data about cerebral perfusion during surgery.
- Measurement of mitoPO$_2$ with the help of ALA in neonates and the COMET technique turned out to be safe in neonates. Perturbations in mitoPO$_2$ were observed that were either only later detected by routine monitoring modalities, or not at all.

Perspectives

- A probe holder designed for neonatal surgery might improve the repetitiveness of the transfontanellar ultrasound measurements. Measurements with high frame rate ultrasound will provide more detailed information about the tissue perfusion in the brain and could be the ultimate technique for real-time cerebral perfusion measurements.
- After obtaining reference values of mitochondrial oxygen tension in the skin of neonates, the COMET could be an important monitoring technique to optimize cellular oxygenation in these vulnerable patients.

11.1.4. Integrative neuromonitoring

By combining the different monitoring modalities an integrative (neuro) monitoring approach is created, as described in chapter 8. Routine monitoring was complemented with NIRS and EEG to obtain information about the effects of different anaesthesiologic approaches – sevoflurane versus midazolam - on the neonatal physiology. The administration of sevoflurane resulted in adequate anaesthesia and analgesia with increased cerebral oxygenation and decreased oxygen consumption, as expected. Administration of midazolam in neonates led to rScO$_2$ values below the hypoxia threshold. At first, we were not able this explain this phenomenon. But by studying the different frequency bands of the EEG more information could be obtained. Delta oscillations (δ: 0.5 – 4Hz) dominate the neonatal EEG, since its spectrum is centred around 1 Hz. In addition, delta frequencies were shown to regulate basic homeostatic needs, such as the circulation and normotension enforcement[54]. The delta band can be further

divided into slow delta (δ_1: 0.5 – 2 Hz) and fast delta (δ_2: 2 – 4 Hz). Noxious-evoked EEG activity can be studied by analyzing gamma oscillations (γ: 32 – 100 Hz) over the contralateral somatosensory cortex and by analyzing energy in the fast delta band (δ_2)(55). A pronounced, strong increase in gamma γ oscillations and an energy increase in the fast delta δ_2 band was shown to reflect nociceptive pain in neonates following heel lance at least[55]. Intraoperatively, in the midazolam group a 3-fold increase of fast delta δ_2 power was observed in the first 30 minutes of the surgical procedure, which decreased later on. A comparable increase was observed for the gamma γ frequency, which was characterized by a 5-fold increase. These increases in fast delta δ_2 power and the gamma γ frequency suggests that these neonates were in pain in the first 30 minutes of the surgical procedure. Yet, the patients in the midazolam group received significantly more fentanyl perioperatively (continuously and bolus administration), but still they experienced pain. This confirm the addition value of combining different neuromonitoring modalities and taught us that multimodal neuromonitoring can also help in developing population-pharmacokinetic models in these vulnerable patients.

The autonomic nervous system (ANS) is an important factor in the regulation of cerebral blood flow. In awake neonates, a suppressed HRV is associated with adverse outcome. To date, there is no literature about the effect of decreased HRV due to anesthesia and the risk of postoperative brain injury or altered neurodevelopmental outcome. The effect of sevoflurane anaesthesia on the ANS is analysed using heart rate variability, as described in chapter 9. We found that sevoflurane-based anesthesia doesn't affect heart rate, but significantly suppresses the ANS, as indicated by a decrease in all HRV metrics, except entropy. Total HRV decreases during sevoflurane anesthesia. Furthermore, the type of congenital anomaly, the gestational age, the administrated sevoflurane concentration as well as the vasoactive and inotropic medication affected the HRV in neonates intraoperatively.

Finally, all parameters and modalities (HR, SpO_2, MABP, $rScO_2$ and EEG) were combined to provide an overview of the (patho) physiology of CDH neonates in the perioperative period during five different clinical setting, as described in chapter 10. This is an innovative, integrative neuromonitoring approach, based on signal interaction graphs. Neurocardiovascular graphs allow to study the

coordinated interactions of organ systems and the (patho)physiology of neonates perioperatively[56]. Altered or disrupted organ communication can be detected that could lead to dysfunction of individual systems or entire organisms[57]. Furthermore, neurocardiovascular graphs provide insights in cerebral perfusion by capturing information about the baroreflex, cerebral autoregulation and neurovascular coupling. As HR, MABP and SpO_2 are included, the coordinated interactions between the brain and the cardiorespiratory systems can also be analysed. Though, clinicians are not trained to interpreted and handle all these continuously highly-changing concomitant signals. This computational approach with visual, graphic feedback allows clinicians to handle multiple highly-changing concomitant signals. The signals are presented as nodes, and the links define the extent and direction of the coupling between two signals. Signals are said to be coupled if they react in response to each other[37,58]. Coupling was quantified using normalized transfer entropy, which ranges from 0 (no coupling) to 1 (complete coupling)[59].

We found that the neonatal physiology altered in the perioperative period, as described in chapter 10. Patient were divided based on the surgical approach (thoracoscopic or open) and the location of the surgery (operation room or NICU/PICU). Each patient group was affected differently, and showed different signal interactions in the graphs. The biggest reduction in connectivity was observed during thoracoscopic surgery, which included a complete loss of baroreflex and neurovascular coupling. Neonates selected for thoracoscopic repair were the most cardiorespiratory stable patients and yet, the physiology is highly affected. Although thoracoscopic surgery has potential benefits, the effect of the altered neonatal physiology on long term neurodevelopmental outcome are still unknown.

Cerebral autoregulation remained stable in all groups. Neurovascular coupling remained functioning in all groups, except during thoracoscopic surgery. The neurovascular coupling was close to 1 in the neonates that underwent surgery in the NICU. These are the same patients who had an alarmingly low cerebral oxygenation intraoperatively and who experienced pain in the first 30 minutes of the surgical procedure. It is unknown whether a coupling/connectivity of 1 is normal or pathologically. A high connectivity between cerebral oxygenation and cerebral activity is needed to adapt cerebral blood flow-based on the oxygen consumption of the brain. Yet, if the patient experience pain, the connectivity becomes higher compared to patients without pain. This could be explained by

the increased oxygen consumption of the brain during the experience of pain due to increased cerebral activity, and suggest that a neurovascular coupling close to 1 might reflect a pathophysiological change. Altogether, this shows that both the surgical and the anaesthesiologic approaches are of influence on the neonatal physiology.

Lessons learned

› The neonatal (patho)physiology is highly affected by the surgical and/or the anaesthesiologic approach perioperative. The graph framework provided visualized insights in the neonatal (patho)physiology in different clinical settings perioperatively.

Perspectives

› Multimodal neuromonitoring together with computational approaches with visual, graphic feedback allows to handle multiple concomitant signals and could help clinicians to understand the neonatal (patho)physiology. This combined approach could be helpful in multiple different clinical setting such as in neonates who are at risk for brain injury due to complex congenital heart disease and/or neonates during VV/VA- ECMO treatment.

11.1.5. Pharmacological approaches

The neonatal physiology is affected by the anaesthesiologic approach. In this thesis we focused on the differences between intraoperatively administrated medication: sevoflurane in the operation room (continuous sevoflurane, bolus fentanyl, bolus rocuronium) and midazolam in the NICU/PICU (continuous midazolam, continuous fentanyl, and continuous vecuronium). It is difficult to administrate sevoflurane outside the operation theatre. Sevoflurane is a polyfluorinated methyl isopropyl ether inhalation anaesthetic, which requires special (mechanical ventilation) equipment.
Sevoflurane is commonly used in clinical practice, particularly in paediatric patients, due to its minimal airway reactivity on the one hand and its low blood-gas partition coefficient on the other hand, which implies that the anaesthetic is rapidly taken up and eliminated (60). The alveolar equilibration of sevoflurane is rapid, 85% complete within 30 minutes[60].

Sevoflurane mediates a decrease in myocardial contractility and mean arterial blood pressure[60]. A reduction in MABP after the start of sevoflurane anaesthesia was indeed observed in chapter 8. In the brain, sevoflurane mediates vasodilation, suppresses somatosensory-evoked potentials and facilitates preservation of cerebral blood flow responsiveness to changes in arterial carbon dioxide tension. Cerebral metabolism is reduced during sevoflurane anaesthesia and a recent study showed that a higher sevoflurane dose significantly correlated with more suppressed background patterns[61]. This is, however, not observed in our data, as described in chapter 8, where no correlation was observed between sevoflurane concentration and EEG power. This could be due to the relatively low sevoflurane concentrations that were administered. The decreased cerebral metabolism could however explain the increase in $rScO_2$ that we observed in our data.

Midazolam is a short-acting benzodiazepine and has anxiolytic, sedative, muscle relaxing and anticonvulsant activity. It acts by binding to the benzodiazepine receptor at the intersection between alfa and gamma subunits of the GABAA receptor in the CNS[62,63]. The elimination half-life of midazolam is approximately 6 hours in the first week of life in full-term neonates[64], although severity of disease and inflammation may affect the elimination of midazolam in critically ill neonates[65]. A steady state concentration is reached 24 hours after start of continuous administration. This also implies that it takes up to 24 hours to completely eliminate midazolam after the administration is terminated.

A recent dosing advise for sedation with midazolam in neonates with a GA above 32 weeks is 0.06 mg kg^{-1} h^{-1} for sedation with midazolam[66]. This dosing advise was already questioned by our own department of neonatology due to lack of reliable pharmacokinetic and effect data[67].

Patients in the midazolam group received midazolam preoperatively for multiple days and had a median midazolam dosage of 0.1 mg kg^{-1} h^{-1} (IQR 0.068 – 0.100) during surgery. This is substantially higher than the advised dosages for sedation. The median time between the administration of the additional midazolam bolus or increased midazolam perfusor and the start of the surgical procedure was 21 min (IQR 0 - 34.5). EEG power was only observed to decrease 30 min after the start of surgery, and stayed low afterwards. This might suggest that the time frame between administration of midazolam and start of surgery was too short for adequate sedation. Nonetheless, sedation or anaesthesia is not an analgesia. All neonates in the midazolam group in chapter 8 received continuous administration of fentanyl and still the results suggest nociceptive

pain experience. One could argue whether the administration of midazolam is of any importance perioperatively. High dosages of opioids can be individually used to perform anaesthesia and might be a better approach. Fentanyl dosages of 50–100 ug kg^{-1} is commonly used in neonates during congenital cardiac surgery and if the neonate has limited hemodynamic reserve[68]. A randomized trial in 1987 already proved the additional value of fentanyl in the stress response of neonates intraoperatively[69]. Another study compared the effect of fentanyl versus fentanyl and midazolam on stress response during neonatal cardiac surgery. They concluded that intraoperative administration of midazolam in addition to fentanyl did not reduce stress response compared to single use of fentanyl[68]. This, in combination with our results (chapter 8), suggests that single administration of high dose of fentanyl might be a better anaesthetic approach than midazolam with lower dosages of fentanyl in neonates intraoperatively.

Furthermore, a recent Cochrane review concluded that midazolam was effective in providing sedation in neonates, but had also significant disadvantages[63]. An included study reported statistically significant higher rates of adverse neurological events (death, grade III or IV intraventricular haemorrhage, periventricular leukomalacia) in neonates treated with midazolam compared to morphine[70]. Two studies observed a (transient) decrease in middle cerebral artery blood flow velocity and transient cerebral hypoperfusion after a bolus of midazolam in preterm neonates[71,72]. Midazolam exposure was also associated with macro- and microstructural alterations in hippocampal development due to binding to the glutamatergic N-methyl-D-aspartate (NMDA) receptors in the brain[73,74]. Following these limitations of midazolam, one could argue whether there is a place for midazolam in current perioperative medication strategy in the NICU or PICU.

Our current integrative neuromonitoring approach and the neurocardiovascular graphs allows to study dosage related changes in cerebral activity and cerebral oxygen extraction to optimize analgesia and anaesthesia/sedation in neonates perioperatively. If there is a lack of reliable pharmacokinetic knowledge of a certain administrated analgesic, anaesthetic or sedative in neonates, the integrative neuromonitoring approach provide real-time information about the effect of the administrated medication and can help to improve perioperative medication strategy. To date, neurocardiovascular graphs are computed afterwards offline and do not provide real-time feedback.

Lessons learned

› The comparison of two different perioperative medication strategies – sevoflurane vs midazolam - showed that sevoflurane-based anaesthesia led to adequate perioperative anaesthesia while midazolam-based anaesthesia with analgesia did not led to sufficient for perioperative anaesthesia.

Perspectives

› Multimodal neuromonitoring will be used to reach evidence-based perioperative pharmacotherapy in vulnerable patients such as critically ill neonates or neonates during major high-risk surgery.

11.1.6. Neurodevelopmental outcome

The ultimate goal would be to correlate the results of the integrative neuromonitoring approach and the neurocardiovascular graphs to perioperative brain injury and long-term neurodevelopmental outcome. As mentioned above, the surgical new born is admitted in the ICU directly postnatally, and might already have experienced a hypoxic event. After admission in the ICU, the neonate will be sedated and mechanically ventilated for days till weeks, and will receive surgical treatment. In the course of these events, multiple potential events can trigger brain injury. This makes it impossible to determine the effect of every single event. Therefore, neuro-imaging and neurocognitive evaluation is essential in addition to integrative neuromonitoring approach.
Transfontanellar cerebral ultrasound could be a good non-invasive technique to screen for brain injury. Yet, this only holds true when the ultrasound is performed by a highly trained specialist. Another imaging technique could be MRI, which is a very sensitive technique to detect brain injury. High sensitivity for detecting brain injury is important in these children because even subtle brain injuries at the neonatal age can become functionally evident later in life when demands on cognitive functioning increases. This is known as the 'growing into deficit' phenomenon[9].
The best intervention strategy to reduce brain injury in neonates during this vulnerable period of life can only be found when the integrative neuromonitoring approach is combined with neuro-imaging and neurocognitive evaluation.

11.1.7. Conclusions & perspectives

This thesis showed the need of (neuro)monitoring neonates during major high-risk surgical procedures. We showed that:

- it is feasible to use transfontanellar ultrasound measurements perioperatively to measure cerebral blood flow velocity
- that the COMET can measure MitoPO_2 in neonates
- that an integrative (neuro)monitoring approach is needed to understand the neonatal (patho)physiology
- that the graph framework provided visualized insights in the neonatal (patho)physiology in different clinical settings perioperatively.

The studies in this thesis represents a proof of concept for different neuromonitoring modalities and integrative approaches. So far, these neuromonitoring modalities and integrative approaches demonstrated to be relevant in two congenital anomalies (CDH and EA) and in one well-controlled clinical setting (24h perioperatively). Neonates with CDH are critically ill neonates who are born with an altered cardiorespiratory system and very challenging for every clinician.
The ultimate goal would be to extend these approaches to all vulnerable patients who are at risk for brain injury, such as neonates with complex congenital heart disease and/or neonates during ECMO treatment. To achieve this, two things should be done before ICU and perioperative management could be optimized with the help of neuromonitoring modalities and integrative approaches. Firstly, to start with integrative neuromonitoring in healthy neonates who need a relatively small elective procedure such as inguinal hernia surgery. This allows us to obtain data in cardiorespiratory healthy neonates who are not admitted to an ICU and do not need hemodynamic support, which all might have consequences for neurodevelopmental outcome. These measurements could serve as reference values and could help to validate the neuromonitoring modalities and integrating the data in more complex neonates perioperatively.
Secondly, the current monitoring period might need to be extended to start monitoring directly postnatally until discharge from the ICU. We realize that it is very difficult to couple the effect of events in the perioperative period directly to long-term neurodevelopmental outcome. By extending the measurement period it will not be easier to correlate events in the neonatal period with

neurodevelopment later in life, but it will be possible to register all events during this period using a big data-based approach. Yet, by computational handling big data sets (that are created with integrative neuromonitoring) in a large number of patients it might be possible to find correlations that would otherwise not be possible to find.
In conclusion, surgical new-born 'deserves' state of the art multimodal neuromonitoring to detect deviations from the norm and to prevent impaired neurodevelopmental outcome both in the short and long run.

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12
Summary

The research presented is this thesis concerns the altered physiology of the surgical newborn in the perioperative period.
Firstly, we studied the effect of perioperative (anesthesiologic and surgical) management on the neonatal physiology by analyzing routine monitoring modalities.
Secondly, we added new monitoring modalities and introduced an integrative (neuro-)monitoring approach aiming to create insight in the neonatal (patho)physiology perioperatively. To this end, the NeMo CDH/EA study (Neuromonitoring during surgical treatment of congenital diaphragmatic hernia or esophageal atresia, NL6972, URL: https://www.trialregister.nl/trial/6972) was initiated. During these research projects, the NeMo CDH/EA study has grown into an international, multicenter, prospective, observational study.

The care for the surgical newborn (defined as a neonate born with a congenital anomaly requiring surgery within the first days of life) is one of the most challenging tasks for a clinician. Despite current state-of-the-art care, these neonates are at risk of perioperative brain injury and subsequently impaired neurodevelopmental outcome. Even subtle brain injuries at the neonatal age can become functionally evident later in life when demands on cognitive functioning increases. This is referred to as the 'growing into deficit' phenomenon.
Our review taught us that currently used (neuro)monitoring techniques neither helps to understand the perioperative neonatal (patho)physiology, nor enable early detection of deviation from the norm (chapter 2). Focusing on surgical management, we found that thoracoscopic surgery in cardiovascular stable CDH neonates (n=109) might by safe, although a higher recurrence rate was observed (chapter 3). Intraoperatively severe respiratory acidosis and hypoxia was observed, regardless the perioperative status or the surgical approach in EA neonates (n=101) (chapter 4).

Consequently, a first step towards neuromonitoring with near infrared spectroscopy (NIRS) was made. Cerebral tissue oxygenation did not change significantly during thoracoscopic surgery with an artificial CO_2-pneumothorax in CDH and EA (n=10) intraoperatively. And again, severe acidosis was observed (chapter 5).

Therefore, the feasibility of other monitoring modalities was tested. We found that it was possible to perform perioperative measurements of cerebral blood flow using transfontanellar directional power Doppler and pulsed wave Doppler ultrasound of the pial arteries during CDH and EA (n=14) surgical treatment and that changes in cerebral cortical blood flow could be observed (chapter 6). Furthermore, is was feasible and safe to measure mitochondrial oxygen tension (mitoPO$_2$) with the non-invasive Cellular Oxygen METabolism (COMET) monitor in CDH and EA (n=15) neonates intraoperatively. Pathophysiological disturbances in the neonates led to perturbations in mitoPO$_2$, but were not observed with standard monitoring modalities (chapter 7).

By combining the different monitoring modalities an integrative (neuro) monitoring approach was created. Routine monitoring (HR, SpO$_2$, MABP) was complemented with two NIRS signals and two EEG signals during surgical treatment of neonates with CDH (n=37). We found that surgery during the administration of sevoflurane resulted in adequate anesthesia and analgesia with expected increased cerebral oxygenation and decreased oxygen consumption. However, surgery during the administration of midazolam resulted in cerebral hypoxia. Furthermore, increased values of EEG power during the first 30 minutes of surgery were observed suggesting conscious experience of pain (chapter 8). Analysing heart rate variability, during surgical treatment of CDH and EA (n=26), provided information about the effect of sevoflurane anaesthesia on the autonomic nervous system (ANS). Sevoflurane-based anesthesia did not affect heart rate, but significantly suppressed the ANS, as indicated by a decreased HRV metrics, except entropy (chapter 9).

As already mentioned, currently used neuromonitoring techniques do not provide additional insights in the neonatal (patho)physiology perioperatively. Therefore, a computational approach with signal interaction graphs to study the (patho)physiology perioperatively could be of help.
We presented an innovative, integrative neuromonitoring approach, based on signal interaction graphs. This allowed us to study coordinated interactions of organ systems and cerebral blood flow regulation.
We found that it was feasible to study the neonatal (patho)physiology in CDH patients in the perioperative period using signal interaction graphs (n=37).

The graphs showed that both the surgical and the anesthesiologic approaches highly affects the neonatal physiology, even in the most cardiopulmonary stable CDH neonates (chapter 10).

The general discussion (chapter 11) addresses the main findings, compares them with current literature and makes recommendations for future research to improve the perioperative care for neonates undergoing major non-cardiac surgery.

The main recommendations are:

- Implementation of multimodal neuromonitoring together with computational approaches in multiple different clinical setting, such as in neonates who are at risk for brain injury due to complex congenital heart disease and/or neonates during VV/VA- ECMO treatment, could be helpful for clinicians to understand the neonatal (patho)physiology.
- Multimodal neuromonitoring could be used to reach evidence-based perioperative pharmacotherapy in vulnerable patients such as critically ill neonates or neonates during major high-risk surgery.

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Dutch Summary

Het onderzoek beschreven in dit proefschrift gaat over de veranderde fysiologie van de chirurgische neonaat in de perioperatieve periode. Als eerste is aan de hand van de huidige routine monitoring modaliteiten het effect van het perioperatieve beleid (anesthesiologisch en chirurgisch) op de neonatale fysiologie onderzocht. Vervolgens zijn er nieuwe monitoring modaliteiten toegevoegd en is er een integrale (neuro-)monitoring benadering gecreëerd. Dit is gedaan met als doel om nieuwe inzichten te verkrijgen in de neonatale (patho)fysiologie in de perioperatieve periode. Zodoende is de NeMo CDH/EA studie (Neuromonitoring during surgical treatment of congenital diaphragmatic hernia or esophageal atresia, NL6972, URL: https://www.trialregister.nl/trial/6972) opgezet. De NeMo studie is inmiddels uitgegroeid tot een internationale, multicenter, prospectieve, observationele studie.

De zorg voor de chirurgische neonaat (gedefinieerd als een neonaat met een aangeboren afwijking die chirurgische behandeld dient te worden in de eerste dagen van het leven/na de geboorte) kent een hoop uitdagingen voor een arts. Ondanks state-of-the-art zorg lopen deze kinderen risico op het ontwikkelen van hersenschade in de perioperatieve periode en de daaropvolgende gestoorde neurologische ontwikkeling. Zelfs kleine, subtiele hersenbeschadigingen op neonatale leeftijd kan op latere leeftijd voor functionele beperkingen leiden, zeker wanneer er cognitief meer gevraagd wordt van een kind. Dit noemen we het 'growing into deficit' fenomeen. Ons review heeft duidelijk gemaakt dat de huidige (neuro)monitoring technieken noch bijdragen aan het begrijpen van de perioperatieve neonatale (patho)fysiologie, noch bijdragen aan het detecteren van afwijkingen (hoofdstuk 2). Focussend op het chirurgisch beleid, werd duidelijk dat thoracoscopische chirurgie in de hemodynamisch stabiele neonaat met een congenitale hernia diafragmatica (CHD) mogelijk veilig is (n=109). Echter werd er wel een hoger aantal recidieven waargenomen in de thoracoscopische groep (hoofdstuk 3). Intra-operatief werd in neonaten met een oesofagus atresie (OA) ernstige respiratoire acidose en hypoxie geobserveerd, ongeacht de perioperatieve conditie of de chirurgische benadering (n=101)(hoofdstuk 4). Deze resultaten leidden tot een eerste stap richting neuromonitoring met near infrared spectroscopy (NIRS) voor het meten van de cerebrale weefsel oxygenatie. Intra-operatief veranderde de cerebrale weefsel oxygenatie niet significant gedurende thoracoscopische chirurgie in neonaten met CDH of OA (n=10). Ook hier werd opnieuw ernstige respiratoire acidose geobserveerd (hoofdstuk 5). Zodoende

werd de mogelijkheid en de haalbaarheid onderzocht van andere monitoring modaliteiten. Het bleek mogelijk te zijn om voor, tijdens en na een operatie cerebrale bloedflow metingen te verrichten van piale arteriën door middel van power Doppler en pulsed wave Doppler echografie door de grote fontanel. Dit deden we in neonaten met CHD en OA (n=14)(hoofdstuk 6). Daarnaast bleek het mogelijk te zijn om mitochondriale zuurstofspanning (mitoPO$_2$) te meten met de non-invasive Cellular Oxygen METabolism (COMET) monitor in neonaten met CHD en OA (n=15) intra-operatief (hoofdstuk 7).

Door het combineren van verschillende monitoring ontstond er een integrale (neuro-)monitoring aanpak. Routine monitoring (HR, SpO$_2$, MABP) werd aangevuld met 2 NIRS-signalen en 2 EEG-signalen tijdens de chirurgische behandeling van neonaten met een CHD (n=37). Chirurgie tijdens sevofluraan anesthesie leek te resulteren in adequate anesthesie en analgesie. Hierbij werd een verwachte stijging van cerebrale weefsel oxygenatie en een daling van de zuurstof consumptie. Echter, chirurgie tijdens op midazolam gebaseerde anesthesie resulteerde in cerebrale hypoxie. Daarnaast werd een toename van cerebrale activiteit waargenomen gedurende de eerste 30 minuten van de operatie. Dit suggereert het waarnemen van pijn (hoofdstuk 8).
Door de heart rate variability (HRV) te analyseren tijdens de chirurgische behandeling van neonaten met een CHD of OA (n=26) wordt het effect van sevofluraan anesthesie op het autonoom zenuwstelsel duidelijk. Sevofluraan anesthesie had geen effect op de hartslag, maar wel een significant negatief effect op het autonoom zenuwstelsel. Alle HRV metrics daalden, behalve de entropy (hoofdstuk 9).
Zoals hierboven al benoemd, dragen de huidige neuromonitoring modaliteiten niet bij aan het creëren van inzicht in de perioperatieve neonatale (patho) fysiologie. Een wiskundige benadering middels signaal interactie graphen werd onderzocht. Een innovatieve, integrale neuromonitoring benadering, gebaseerd op signaal interactie graphen maakte het mogelijk om gecoördineerde interacties van orgaansystemen en cerebrale bloedflow regulatie. Het bleek mogelijk te zijn om de perioperatieve neonatale (patho)fysiologie in neonaten met een CHD te bestuderen (n=37). De graphen toonden dat de neonatale (patho)fysiologie door zowel de chirurgische als de anesthesiologische benadering sterk beïnvloed wordt, zelf in de meest cardiopulmonale stabiele neonaten met een CHD (hoofdstuk 10).

De discussie (hoofdstuk 11) richt zich op de hoofdbevindingen, vergelijkt deze met de huidige literatuur en doet aanbevelingen voor toekomstig onderzoek om de perioperatieve zorg voor neonaten die grote niet-cardiologische chirurgie ondergaan.

De belangrijkste aanbevelingen zijn:

- Implementeren van multimodale neuromonitoring in combinatie met een wiskundige benadering in verschillende klinische setting waarbij neonaten risico lopen op het ontwikkelen van hersenschade. Dit zou bijvoorbeeld kunnen helpen om neonatale (patho)fysiologie te begrijpen bij neonaten met complexe aangeboren hartafwijkingen en/of neonaten tijdens VV/VA-ECMO-behandeling.
- Multimodale neuromonitoring kan helpen bij het ontwikkelen van perioperatieve evidence-based farmacotherapie in kwetsbare patiënten zoals ernstig zieke neonaten of neonaten tijden grote, hoge risico operaties.

Under the surface

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Appendices

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PhD portfolio

PhD student	Sophie Costerus
Erasmus MC Department	Paediatric surgery
PhD period	2016 - 2020
Promotors	Prof. dr. D. Tibboel
	Prof. dr. R.M.H. Wijnen
Supervisor	Dr. J.C. de Graaff

	Year	Workload (ECTS)
Courses		
Wetenschappelijke integriteit	2018	0.3
Basis course Rules and Organisation for Clinical researchers (BROK)	2018	1.5
CPO-course: Patient Oriented Research	2018	0.3
Scientific writing English	2019	2.5
R course	2019	1.8
Photoshop and Illustrator CC	2019	0.3
Presentations		
CHD2020	2020	3.0
Sophia Research day	2020	0.3
ESPA	2019	1.5
Wetenschapsdag anesthesiology	2019	0.3
CDH workshop Liverpool	2017	1.5

	Year	Workload (ECTS)
Symposia/Seminars and workshops		
ICT & Health	2020	0.3
TULIPS PhD dag	2019	1.0
Perinatale en neonatale farmacologie symposium	2019	0.3
Newborn brain symposium	2018	2.0
Symposium Prof Tibboel	2018	0.3
Research meetings		
Research meeting paediatric anaesthesiology	2018/20	2.0
Research meeting Neonatology KU Leuven	2018/20	1.0
Research meeting Mannheim	2018/20	1.0
Research meeting farmacology	2018/20	1.0
Research meeting ICK	2018/20	1.0
Other		
Ultrasound training	2018	3.0
Fundamental Critical Care Support	2016	4.0
Communicatie rondom donatie	2016	0.3

About the author

Sophie Anne Costerus was born on the seventeenth of March 1988 in Alkmaar, the Netherlands. After obtaining three secondary school diploma's she decided to study Medical Physics at the VU in Amsterdam. This study made her realize that she wanted to become a doctor, so the next year she started her medical training at the Erasmus Medical Centre in Rotterdam.

As a fourth-year medical student, she did retrospective research at the department of paediatric surgery of Sophia children's hospital in collaboration with the department of paediatric surgery in Mannheim. This research project resulted in a publication and was, in retrospect, the start of her PhD project. She never considered herself a geek, and it took some time before she started to enjoy doing research. After obtaining her medical degree in 2015 she started writing the Neuromonitoring during surgical repair of CDH study (NeMo CDH study) under supervision of Professor Wijnen and Professor Tibboel, her promotors in this thesis.

In the meantime, she also worked as a resident in the Surgical department of Franciscus Gasthuis in Rotterdam and a year later at the Intensive Care Unit of Reinier de Graaf Gasthuis in Delft. In 2018 she became a full-time PhD-student at the department of paediatric surgery of Sophia children's hospital with the NeMo CDH study as her PhD project.

Sophie currently lives in Schiedam with her partner, son and two cats.

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List of abbreviations

AIMS	Anesthetic Information Management System
aEEG	Assisted elektro-encefalogram
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CDH	Congenital Diaphragmatic Hernia
CDU	Cerebral doppler ultrasound
CMV	Conventional Mechanical Ventilation
CPP	Cerebral perfusion pressures
COS	Converted thoracoscopic to open surgery
EA	Esophageal atresia
ECMO	Extra Corporeal Membrane Oxygenation
ECG	Elektrocardiogram
EEG	Elektro-encefalogram
FiO_2	Fraction inspired oxygen
FDA	Food and Drug Administration
HFO	High Frequency Oscillation
HFOV	High Frequency Oscillatory Ventilation
hsPDA	Hemodynamic significant patent ductus arteriosus
iNO	Inhaled Nitric oxide
ICU	intensive care unit
IQR	Inter-quartile ranges
LHR	Lung-to-Head Ratio
LOS	Length of stay

MAS	Minimal Access Surgery
MABP	Mean Arterial Blood Pressure
MRI	Magnetic Resonance Imaging
NIRS	Near-infrared spectroscopy
NICU	Neonatal intensive care unit
OG	Open-repaired group
PDA	Patent ductus arteriosus
PDMS	Patient Data Management System
PEEP	Positive End Expiratory Pressure
PICU	Pediatric Intensive care unit
PIP	Peak Inspiratory Pressure
PPHN	Persistent Pulmonary Hypertension
POS	Primary open surgery
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTS	Primary thoracoscopic surgery
$rSCO_2$	Regional cerebral tissue oxygen saturation
SD	Standard deviation
QLI	Quantitative Lung Index
SEM	Standard Error of the Mean
TG	Thoracoscopically-repaired group
TEF	Tracheo-esophageal fistula

Under the Surface

Perioperative pathophysiology of the surgical newborn

Sophie Costerus

This thesis studies the altered physiology of the surgical newborn in the perioperative period and presents an integrative (neuro) monitoring approach that was created by combining different monitoring modalities.