EJA

Eur J Anaesthesiol 2022; **39:**662–672

OPEN

ORIGINAL ARTICLE

Neurocardiovascular coupling in congenital diaphragmatic hernia patients undergoing different types of surgical treatment

Dries Hendrikx*, Sophie A. Costerus *, Katrin Zahn, Alba Perez-Ortiz, Alexander Caicedo Dorado, Sabine Van Huffel, Jurgen de Graaff, René Wijnen, Lucas Wessel, Dick Tibboel and Gunnar Naulaers

BACKGROUND The effect of peri-operative management on the neonatal brain is largely unknown. Triggers for perioperative brain injury might be revealed by studying changes in neonatal physiology peri-operatively.

OBJECTIVE To study neonatal pathophysiology and cerebral blood flow regulation peri-operatively using the neurocardiovascular graph.

DESIGN Observational, prospective cohort study on peri-operative neuromonitoring. Neonates 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 into different groups by type of peri-operative management.

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

MAIN OUTCOME MEASURES The primary endpoint was the difference in neurocardiovascular graph connectivity in the groups over time.

RESULTS Thirty-six patients were included. The intraoperative graph connectivity decreased in all patients operated upon in the operation room (OR) with sevoflurane-based anaesthesia ($P < 0.001$) but remained stable in all patients operated upon in the neonatal intensive care unit (NICU) with midazolam-based anaesthesia. Thoracoscopic surgery in the OR was associated with the largest median connectivity reduction (0.33 to 0.12, $P < 0.001$) 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.

CONCLUSION Neurocardiovascular graphs provided more insight into the effect of the peri-operative management on the pathophysiology of neonates undergoing surgery. 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.

TRIAL REGISTRATION NL6972, URL: https://www.trialregister.nl/trial/6972.

Published online 1 December 2021

* DH and SAC contributed equally as co-first authors.

From the Department of Electrical Engineering, ESAT-STADIUS, KU Leuven, Leuven, Belgium (DH, SVH), Department of Pediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands (SAC, RW, DT), Department of Development and Regeneration, KU Leuven, Leuven, Belgium (GN), Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium (GN), Department of Anaesthesiology, Erasmus MC, Rotterdam, the Netherlands (JdG), Department of Pediatric Surgery (KZ, LW), Neonatal Intensive Care Unit, University Hospital Mannheim, Mannheim, Germany (APO) and Applied Mathematics and Computer Science, School of Engineering, Science and Technology, Universidad del Rosario, Bogotá, Colombia (AC)

Correspondence to Dries Hendrikx, Department of Electrical Engineering, ESAT-STADIUS, KU Leuven, Kasteelpark Arenberg 10, 3001 Leuven, Belgium.
E-mail: dries.hendrikx@esat.kuleuven.be

DOI:10.1097/EJA.0000000000001642

KEY POINTS

- A novel computational model, the neurocardiovascular graph (which focuses on the neonatal brain), unravelled changes in peri-operative neonatal physiology.
- The linical condition of the neonate undergoing surgery as well as the anaesthesia technique utilised and surgical approach might influence the neonatal physiology and homeostasis.
- The network analysis approach using the neurocardiovascular graph could be a potentially useful technique for other researchers.

Introduction

Despite 'state of the art' peri-operative monitoring, the outcome after noncardiac neonatal surgery can be complicated by significant acute and long-term sequelae.[1] Structured analysis revealed a high incidence (48% in full term, 75% in preterm) of brain injury on MRI after noncardiac neonatal surgery.[2] Furthermore, interdisciplinary follow-up studies showed delayed neurodevelopment after neonatal surgery.[3–6] To date, the effect of peri-operative management on the neonatal brain is largely unknown.[2] Triggers for peri-operative brain injury might be revealed by studying peri-operative changes in the neonatal physiology. To this end, a new approach in neuromonitoring is needed, which includes neuromonitoring combined with computational models.

An overview of the co-ordinated 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 into the regulation of cerebral blood flow (CBF), including neurovascular coupling (NVC), cerebrovascular pressure autoregulation (CAR), cerebral oxygen balance and heart rate passivity (HRP).[8–11] Impairment in regulation results in inadequate brain perfusion, which may cause hypoxic ischemic encephalopathy,[12] intraventricular haemor-rhage[13] and periventricular leukomalacia.[14]

An advanced computational approach is needed to capture the status of the CBF regulation mechanisms as 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 peri-operatively to neonates diagnosed with congenital diaphragmatic hernia (CDH). These neonates were stratified into different groups based on different types of peri-operative 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 peri-operatively. 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.

Methods

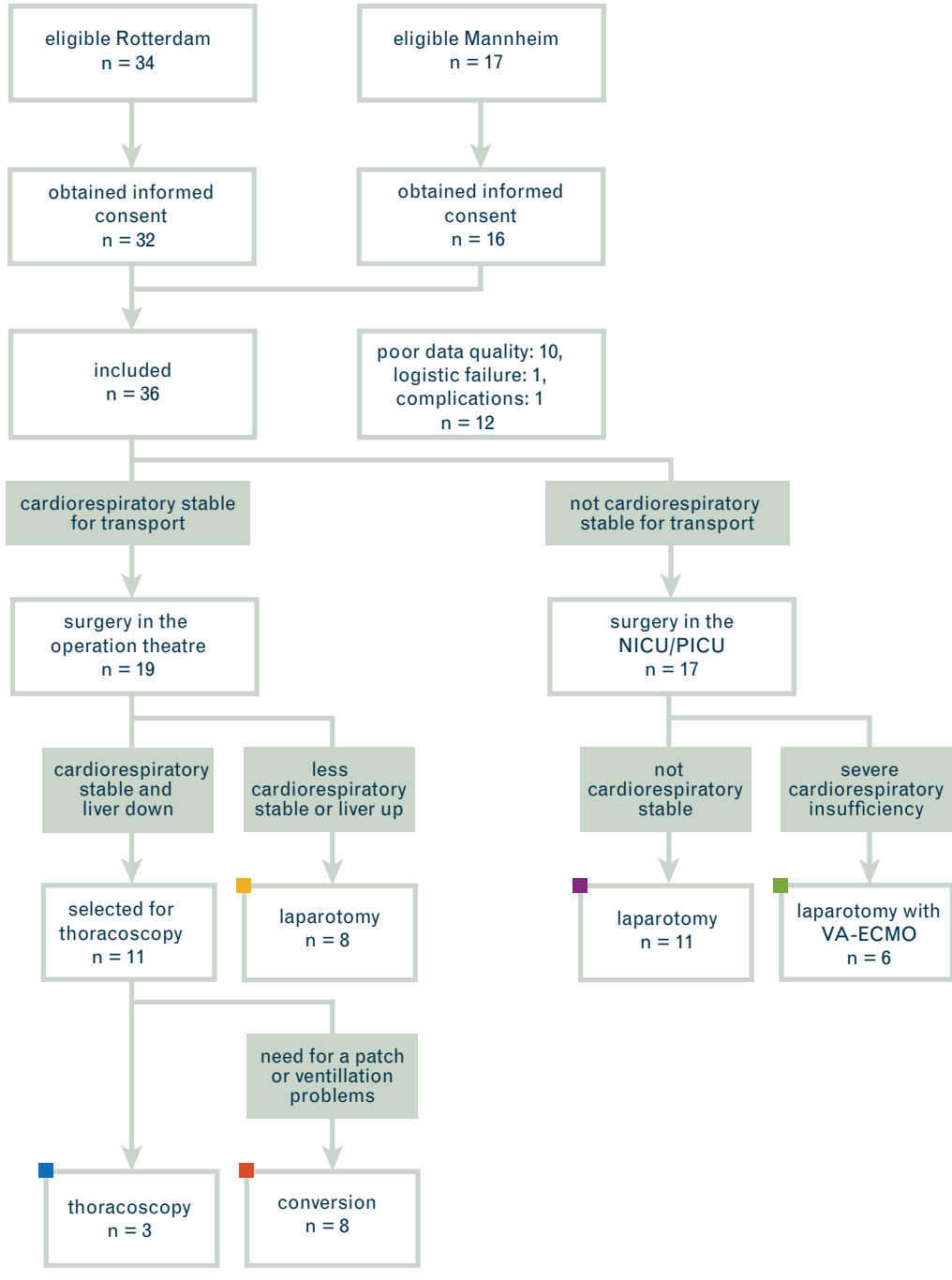
This was a multicentre, observational, prospective study on peri-operative neuromonitoring in neonates with CDH undergoing surgery in one of two tertiary paediatric centres: the Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands), and the Mannheim University Hospital (Mannheim, Germany). 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 Professor HJ Metselaar and Professor HW Tilanus, protocol number MEC 2017–145) and the Medical Ethics Committee of the University of Heidelberg, Mannheim, Germany on 6 July 2018 (Chairperson Professor JP Striebel, protocol number 2018–578N-MA). Trial registration NL6972.

Patients and peri-operative management

Neonates with CDH, a major noncardiac congenital anomaly, were studied as 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) intra-thoracic liver are more prone to develop PPHN. Venoarter-ial 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 peri-operative 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 ICU (PICU) during VA-ECMO. The subjects were stratified into groups based on clinical condition (Fig. 1): thoracoscopic surgery in the OR if the neonate was

Fig. 1 The patients are stratified in five groups based on their clinical conditions.



Five perioperative strategies were compared. These are indicated by the small coloured squares: thoracoscopy in the OR (blue), conversion from thoracoscopy to laparotomy in the OR (orange), laparotomy in the OR (yellow), laparotomy in the NICU (purple), and laparotomy on VA-ECMO in the PICU (green).

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 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).

The location of surgery defined the anaesthesiological approach (Table 1). In the operation room, 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

Table 1 Patient characteristics

			Operation theatre			NICU/PICU	
			Thoracoscopy ($n=3$)	Conversion ($n=8$)	Laparotomy ($n=8$)	Laparotomy ($n=11$)	ECMO ($n=6$)
Gestational age	(week + day)		40+4 [30+6 to 40+6]	38+2 [35 to 40+1]	38+1 [36+3 to 41]	37+6 [33+2 to 38+2]	38+1 [36+6 to 41+6]
Age at surgery	(day)		3 [3 to 4]	4 [2 to 5]	3.5 [2 to 4]	6 [4 to 11]	7.5 [6 to 9]
Birth weight	(kg)		3.2 [2.9 to 3.2]	3.0 [2.0 to 3.5]	3.1 [2.3 to 3.5]	2.8 [1.7 to 3.1]	3.1 [2.5 to 3.5]
Antenatal diagnosed			1 (33%)	6 (75%)	7 (88%)	7 (64%)	1 (17%)
Apgar 5 min			9 [9 to 10]	8 [8 to 8]	8 [5 to 8]	8 [7 to 8]	6 [4 to 8]
o/e LHR			41	51 [34–75]	44 [36–74]	40 [32 to 44]	39 [27–57]
Mechanical ventilation		pre to 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 to 128]	120.1 [85 to 170]	72 [61 to 124]	155 ([05 to 202]	101 [81 to 120]
Patch			0 (0%)	5 (63%)	8 (100%)	10 (91%)	6 (100%)
Rocuronium	bolus (mg kg^{-1})	intra-operative	0.74 [0.65 to 0.74]	1.0 [0.6 to 1.0]	0.62 [0.57 to 0.82]	1.0 [1.0 to 1.0]	1.0 [1.0 to 1.0]
Vecuronium	bolus (mg kg^{-1})	induction	–	–	–	0.1 [0.07 to 0.1]	–
	perfusor (mg kg^{-1} h^{-1})	intra-operative	–	–	–	0.2 [0.18 to 0.21]	–
Fentanyl	bolus (µg kg^{-1})	induction	1.3 [0.9 to 1.3]	2.5 [1.7 to 2.9]	2.1 [1.9 to 3.0]	5.0 [4.0 to 7.0]	4.0 [3.1 to 4.0]
	bolus (µg kg^{-1})	intra-operative	5.6 [4.5 to 5.7]	6.3 [5.0 to 16.5]	6.3 [4.0 to 8.7]	11.0 [7.0 to 16.0]	11.3 [3.4 to 25]
	infusion (µg kg^{-1} h^{-1}	intra-operative	–	–	–	4.5 [3.0 to 5.0]	–
Morphine	infusion (µg kg^{-1} h^{-1})	intra-operative	–	–	–	–	13.7 [8.4–18.6]
Sevoflurane	inhalation (MAC expired %)	intra-operative	1.0 [1.0 to 1.9]	1.7 [1.0 to 2.5]	1.5 [1.1–2.4]	–	–
Midazolam	infusion (µg kg^{-1} h^{-1})	pre-operative	84 [50 to 200]	0 [0 to 133]	42 [0 to 133]	40 [30 to 50]	140 [60 to 257]
	infusion (µg kg^{-1} h^{-1})	intra-operative	67 [50 to 179]	0 [0 to 125]	42 [0 to 133]	100 [75 to 100]	134 [75 to 257]
	infusion (µg kg^{-1} h^{-1})	postoperative	67 [25 to 125]	90 [0 to 133]	34 [0 to 133]	50 [20 to 50]	131 [50 to 257]
	bolus (µg kg^{-1})	induction	0 (0%)	0 (0%)	1 (13%)	10 (91%)	4 (67%)
VIS		pre-operative	4.1 [0 to 26]	0 [0 to 16]	8 [0 to 32]	17 [8 to 23]	20 [5 to 61.5]
		intra-operative	8.5 [5 to 18.5]	12.3 [5 to 28]	7.5 [0 to 47]	17 [12 to 32]	7.3 [5 to 25]
		post-operative	1.7 [0 to 9]	1.8 [0 to 39]	1.5 [0 to 30]	14 [7 to 27]	9.5 [5 to 35]
P_aCO_2	(kPa)	intra-operative	6.9 [6.6 to 7.2]	6.1 [5.3 to 7.7]	5.9 [5.3 to 7.4]	5.0 [4.7 to 6.2)	5.5, 7.8
Died			0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (17%)

Data are median [IQR], *n* (%) o/e LHR, observed to expected lung area to head circumference ratio; VIS, vasoactive inotropic score. Data are presented as median [IQR]. Defect size is presented as a score from A (small) to D (very large)[17].

fentanyl and vecuronium (Mannheim), guided by a neonatologist or paediatric intensivist. Neonates on VA-ECMO were operated on 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.

Data collection

Patient demographics were collected in accordance with the standardised reporting about CDH (Table 1).[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, USA). 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 h postoperatively.

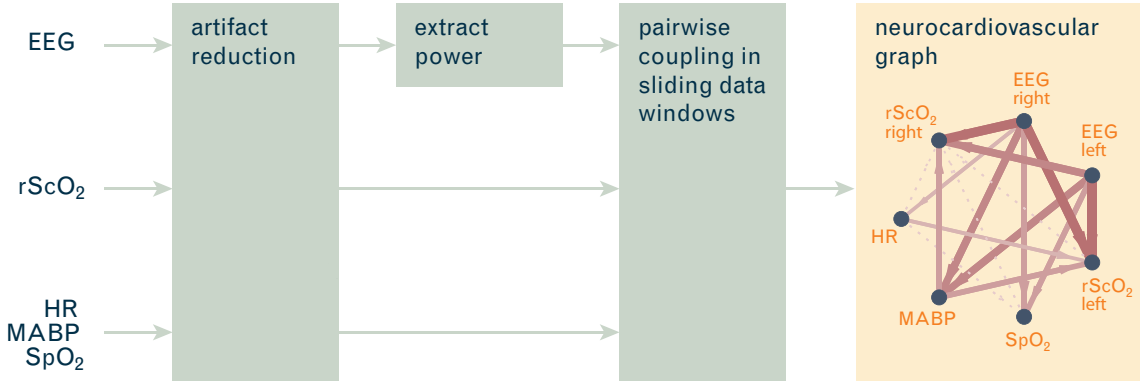
Data processing

After acquisition, the signals were preprocessed to reduce artefacts (Fig. 2). This procedure consisted of filtering the EEG (0.5 to 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 to 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 minimum 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, whereas the links define the coupling between every pair of signals.

Fig. 2 The data processing pipeline to translate the raw measured signals to a signal interaction graph, referred to as the neurocardiovascular graph.

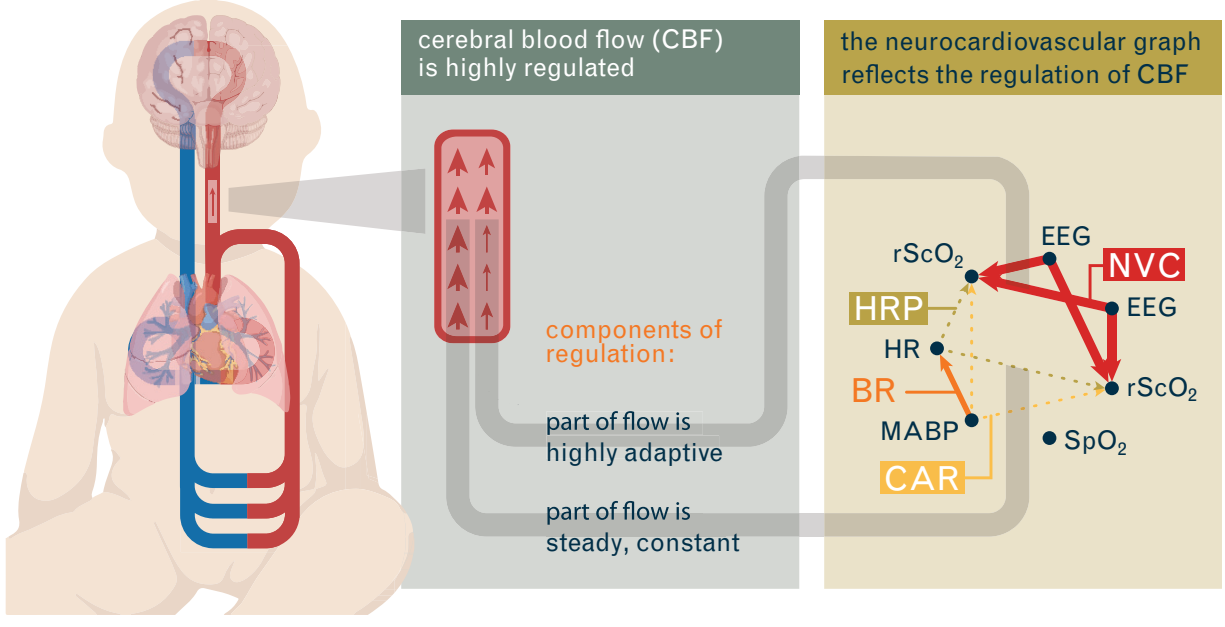


EEG, electroencephalogram; HR, heart rate; MABP, mean arterial blood pressure; $rScO_2$, cerebral tissue oxygenation; SpO_2, peripheral oxygen saturation.

Transfer entropy was used as a measure of coupling.[7] Transfer entropy is a nonlinear, effective measure, which can detect the direction of the interaction. In the transfer entropy 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 its own present. The practical implementation used binning and nonuniform embedding.[20] Finally, the transfer entropy values were normalised as 0 (no coupling) to 1 (perfect coupling) following a procedure previously outlined.[21]

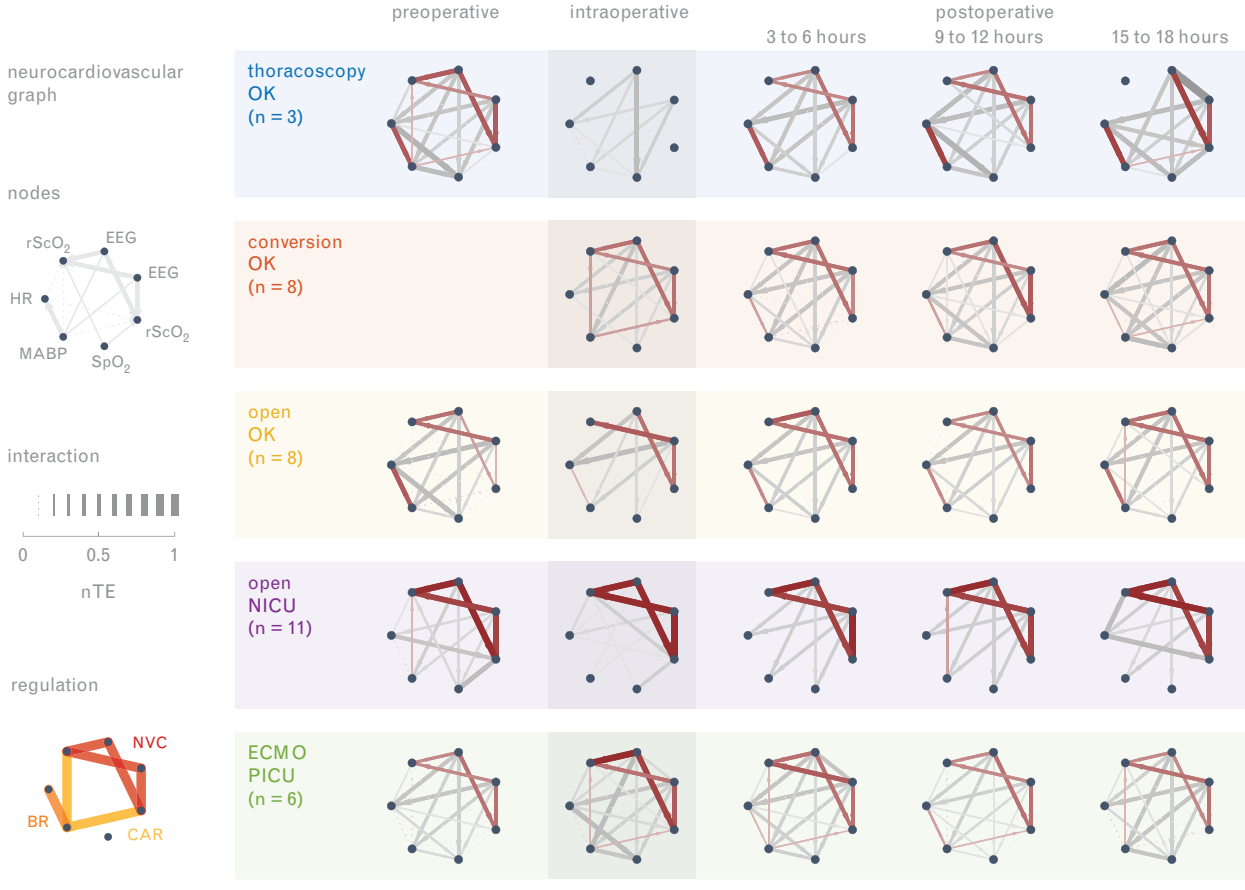
The signal interaction graph used in this study is referred to as the neurocardiovascular graph as it captures the status of the regulation mechanisms affecting CBF (Fig. 3). The coupling between HR and MABP in which HR reacts to changes in MABP, presents a measure for baroreceptor reflexes.[22] As the barorecep-tor reflexes couple HR and MABP, large interaction values are expected. CAR is defined as the coupling between MABP and $rScO_2$. As 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 associated with poor outcome, low interaction values are expected. Lastly, 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

Fig. 3 The neurocardiovascular graph translates the complex regulation of cerebral blood flow into one straightforward model.



This regulation includes baroreflex (BR, highly coupled), cerebral pressure autoregulation (CAR, weakly coupled), heart rate passivity (HRP, weakly coupled), and neurovascular coupling (NVC, highly coupled). EEG, electroencephalogram; HR, heart rate; MABP, mean arterial blood pressure; $rScO_2$, cerebral tissue oxygenation; SpO_2, peripheral oxygen saturation.

Fig. 4 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 whereas all other graph connections are presented in grey. EEG, electroencephalogram; HR, heart rate; MABP, mean arterial blood pressure; $rScO_2$, cerebral tissue oxygenation; SpO_2, peripheral oxygen saturation.

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 intrao-peratively administered medication, the graphs were computed in five time windows: the preoperative window (6 to 3 h before surgery), the surgical period and three postoperative windows: 3 to 6, 9 to 12 and 15 to 18 h after surgery, respectively.

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. Data re presented as median [IQR] and *n* (%). The coefficient of determination (R2) was also calculated. Statistical computations were carried out in R.[23] Data are presented a median [IQR] and number (%).

Results

Patient characteristics

Forty-eight neonates were enrolled in the study, of whom 11 neonates were excluded following the absence of multiple signals because of data transfer and storage problems. One neonate was excluded because of cardiopulmonary resuscitation intraopera-tively, leaving 36 patients included (Fig. 1). Preopera-tively, data of the thoracoscopic repair and conversion groups were merged in later analysis (Fig. 4) as they included the most stable patients with similar characteristics (Table 1).

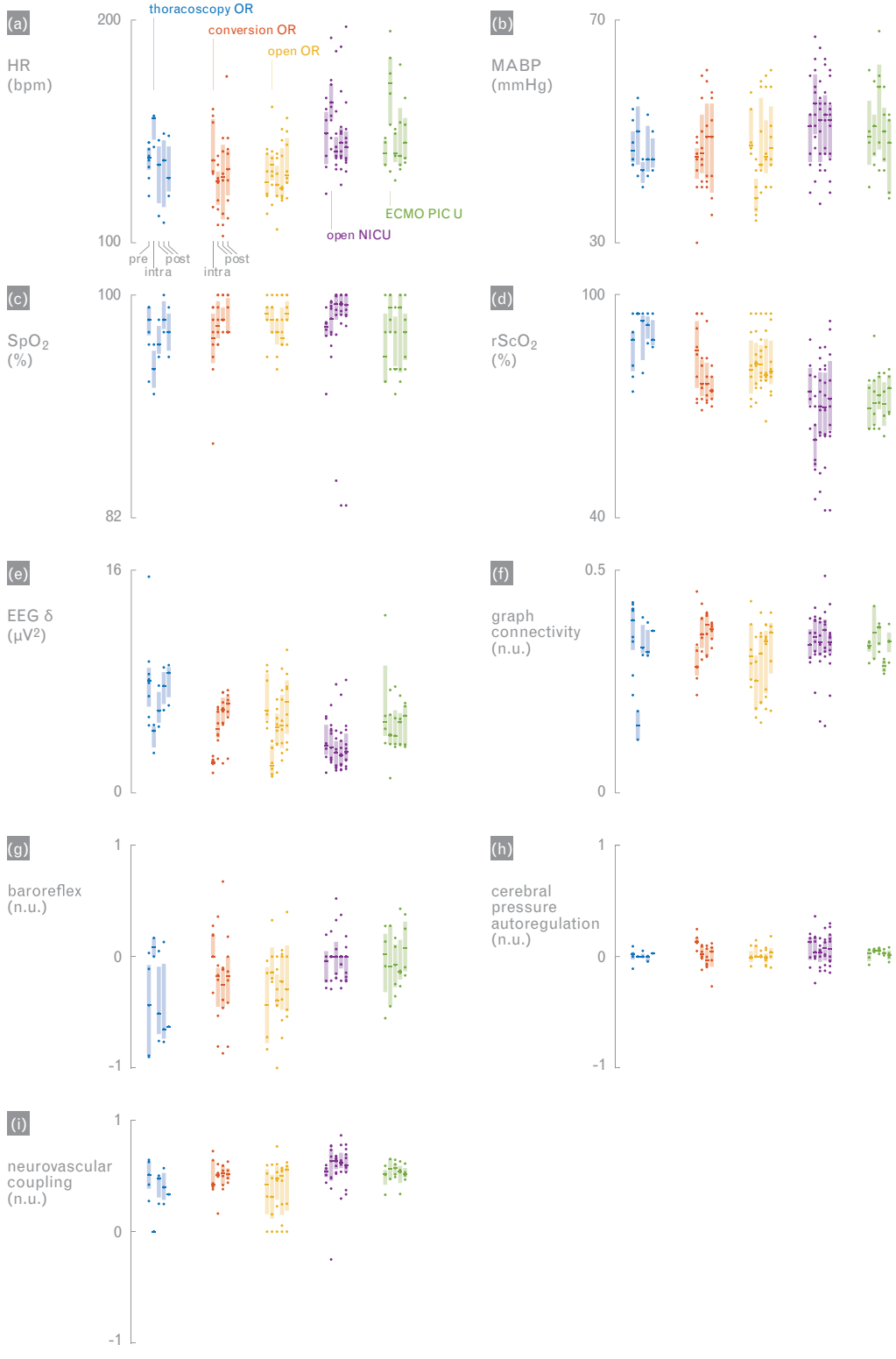
Graphs

The connectivity of the graphs was not affected by gestational age, birth weight, sex, position of the liver, and the size of the diaphragmatic defect, whereas the clinical time window and the clinical group influenced the graph connectivity (both $P < 0.001$).

Thoracoscopic repair group

Neonates selected for thoracoscopic repair had the largest connectivity of 0.33 [0.26 to 0.37] preoperatively (Figs. 4 and 5f). During surgery, the connectivity of the neurocardiovascular graph dropped, reaching values of 0.12 [0.08 to 0.15], $P < 0.001$, which increased again to 0.24 [0.23 to 0.33], $P < 0.001$, 0.26 [0.25 to 0.36] and 0.32 [0.32 to 0.32] postoperatively.

Fig. 5 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 surgical setting is represented by a different colour, as indicated in (a). Each subfigure (a to h) contains five columns, which correspond to the five monitoring periods: pre-operative, intra-operative, 3 to 6, 9 to 12 and 15 to 18 h postoperative. In each column, a dot represents the mean value for one patient. The bar and the shaded area represent the median and interquartile range, respectively. n.u., normalised units between 0 and 1.

Table 2 Main findings

	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

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

Preoperatively and postoperatively, there was intact and strong interaction between the vital parameters and a functioning baroreceptor reflex (Fig. 5 g), CAR (Fig. 5 h) and NVC (Fig. 5i) and (Table 2). During surgery, CAR remained intact whereas both baroreceptor reflex and NVC disappeared.

The main finding was that largest reduction in connectivity was observed in the thoracoscopic repair group (Fig. 4 and Table 2).

Conversion group

During surgery, graph connectivity slightly decreased to 0.31 [0.24 to 0.34]. After surgery, connectivity further decreased to 0.27 [0.23 to 0.31], $P < 0.001$, after which it increased again to 0.33 [0.26 to 0.34] and 0.32 [0.30 to 0.34], $P = 0.014$ (Figs. 4 and 5f).

The interaction between the vital parameters dropped intraoperatively, after which it steadily increased postoperatively (Table 2). CAR and NVC remained intact over the peri-operative period. Baroreceptor reflex dropped intraoperatively but restored again after surgery.

The main finding here was that the connectivity in the conversion group was larger than that in the open repair operation room group.

Open repair operation room group

In the open repair operation room group, the connectivity was 0.28 [0.20 to 0.36] preoperatively, then slightly dropped intraoperatively to 0.25 [0.12 to 0.28], $P < 0.001$, and increased to 0.25 [0.15 to 0.31], $P = 0.037$, 0.27 [0.12 to 0.30], and 0.30 [0.18 to 0.32] postoperatively (Figs. 4 and 5f).

The interaction among the vital parameters was strong preoperatively, dropped intraoperatively, and reached baseline values again postoperatively (Table 2). CAR remained intact over the peri-operative period. The same holds true for baroreceptor reflex and NVC, although they were associated with slightly lowered values during surgery.

The main finding here was that the open repair OR group is the only group in which baroreceptor reflex, CAR and NVC remained intact over the peri-operative period.

Open repair neonatal intensive care unit group

The graph connectivity remained stable for neonates on open surgery in the NICU, reaching values of 0.30 [0.23 to 0.34], 0.34 [0.26 to 0.38], 0.26 [0.22 to 0.33], 0.32 [0.24 to 0.37] and 0.28 [0.27 to 0.36] for the five consecutive time windows, respectively (Figs. 4 and 5f).

Interaction among the vital parameters, including baroreceptor reflex, was absent over the entire peri-operative period (Table 2). CAR was intact over the entire perioperative period, as was NVC, and had the largest values compared with all other groups over all time windows.

The main finding here was that NVC had the largest values in the open repair NICU group.

ECMO group

Neonates on VA-ECMO had the lowest connectivity before surgery; that is, 0.27 [0.23 to 0.30]. The connectivity increased to 0.34 [0.28 to 0.41] during surgery. Postoperatively, the connectivity was 0.30 [0.30 to 0.32], 0.21 [0.20 to 0.23], $P < 0.001$) and 0.28 [0.26 to 0.31], $P < 0.001$ (Figs. 4 and 5f).

Strong interaction among the vital parameters, intact CAR, and NVC was observed throughout the peri-operative period (Table 2). CAR values only increased slightly intraoperatively, and in the first hours after. The baroreceptor reflex was absent, especially in the preop-erative period, as well as in the postoperative windows of 9 to 12 and 15 to 18 h after surgery.

The main finding here was that a strong interaction among vital parameters was observed in the ECMO group.

Correlations

During sevoflurane anaesthesia, increased sevoflurane concentration correlated with increased BR ($R^2 = 0.34$)

and decreased HRP ($R^2 = 0.32$); increased fentanyl dose correlated with increased HRP ($R^2 = 0.60$), increased CAR ($R^2 = 0.41$) and decreased EEG to MABP coupling ($R^2 = 0.42$) and increased partial pressure of CO_2 (P_aCO_2) correlated with increased HRP ($R^2 = 0.33$).

During midazolam sedation, increased midazolam dose correlated with increased CAR ($R^2 = 0.47$) and increased interaction between MABP and the two EEG signals ($R^2 = 0.39$ for the left channel, and $R^2 = 0.34$ for the right channel); and increased fentanyl dose correlated with increased MABP to EEG coupling ($R^2 = 0.33$ for the left channel and $R^2 = 0.37$ for the right channel).

Increased P_aCO_2 correlated with decreased baroreceptor reflex during both sevoflurane and midazolam anaesthesia.

Discussion

Both the anaesthesiological and the surgical approaches highly influenced the connectivity of the neurocardiovascular graph (Fig. 4). Despite the small sample size and the novelty of the methodology used, some observations can be made, which will have to be validated in future studies. The largest reduction in connectivity, which included an absence of baroreceptor reflex and NVC, was observed during thoracoscopic surgery (Table 2). This was striking, as neonates selected for thoracoscopic repair were the most cardiopulmonary stable patients (Table 1). The conversion group was characterised by a larger connectivity compared with the open repair operation room group, most likely as the neonates in the conversion group were clinically more stable (Table 1). Yet, the open repair operation 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 whereas the ECMO group had a significantly larger interaction among the vital parameters intraoperatively. CAR remained stable in all groups (Table 2). NVC remained functioning in all groups, except during thoracoscopic surgery.

Anaesthesia

The majority of the drugs used in NICUs are unlicensed or off-label.[24,25] Intravenous midazolam for sedation has been used for decades in NICUs.[26] Nonetheless, a recent Cochrane review raised concerns about the safety of midazolam in neonates.[27] One 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 with 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, the literature reports a negative effect of general anaesthesia on neonatal physiology.[31] In the present study, we observed a stronger baroreceptor reflex and less HRP with increasing sevoflurane concentration during sevoflurane anaesthesia, which might indicate that a higher sevoflurane concentration 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 the fentanyl dose 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, aspects, which are all associated with adverse outcomes in neonates. [11,34,35]

Surgery

Thoracoscopic surgery is popular because of its potential benefits, including fewer postoperative ventilator days, a reduced requirement for analgesics and a shorter hospital stay.[36–39] A drawback is that an artificial CO_2-pneumothorax is needed to create a surgical workspace and this results in hypercapnia and acidosis.[40] Signal interaction was highly affected during thoracoscopic surgery, which might be because of increased CO_2 or the increased intrathoracic pressure the latter affects venous return. An increase in P_aCO_2 correlated with a less functional baroreceptor reflex, and a more pronounced HRP. The observed increase in HR might indicate a compromised venous return, although MABP did not decrease (Fig. 5). Open surgery leads to 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.

Importance

Peri-operative management, including ICU management, anaesthesia and surgery, could cause undesirable changes in the neonatal physiology, which might trigger peri-operative brain injury.[2–4] 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 peri-operative management on neonatal physiology.[7] In this study, we applied a computational framework (with visual and graphical feedback) that permitted handling of multiple concomitant signals, and thereby enabled the 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 to changes in MABP (baroreceptor reflex), and about the ability of the brain to regulate CBF independently of fluctuations in MABP (CAR) but dependently on cerebral metabolism (NVC). Therefore, neurocardiovascular graph provides insights about 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 peri-operative 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]

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 their plasma concentrations.

Conclusion

We showed that neurocardiovascular graphs provide new and important information about the effect of the peri-operative management on the pathophysiology of neonates undergoing surgery. The neonate's clinical condition and the surgical and anaesthesiological approach affected neonatal physiology and CBF regulation mechanisms at different levels. This new approach may assist clinicians in making patient-specific decisions about the optimal peri-operative management, aiming to prevent brain injury and possibly impaired neurodeve-lopmental outcomes. At this stage, however, given the limited 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.

Acknowledgements relating to this article

Assistance with the study: none.

Financial support and sponsorship: research supported by Bijzonder Onderzoeksfonds KU Leuven (BOF): C24/15/036 'The effect of perinatal stress on the later outcome in preterm babies', EU: H2020 MSCA-ITN-2018: 'Integrating Functional Assessment measures for Neonatal Safeguard (INFANS)', funded by the European Commission under Grant Agreement #813483. This research received funding from the Flemish Government (AI Research Program). Sabine Van Huffel and Dries Hendrikx are affiliated to Leuven. AI to the KU Leuven institute for Artificial Intelligence, B-3000, Leuven, Belgium. DH is a SB Ph.D. fellow at Fonds voor Wetenschappelijk Onderzoek (FWO), Vlaanderen, supported by the Flemish government. This project was performed by three centres participating in ERNICA, the European Reference Network for rare Inherited and Congenital Anomalies.

Conflicts of interest: none.

Presentation: none.

References

1 Moran MM, Gunn-Charlton JK, Walsh JM, *et al.* Associations of neonatal noncardiac surgery with brain structure and neurodevelopment: a prospective case-control study. *J Pediatr* 2019; **212**:93e2–101e2.
2 Stolwijk LJ, Keunen K, de Vries LS, *et al.* Neonatal surgery for noncardiac congenital anomalies: neonates at risk of brain injury. *J Pediatr* 2017; **182**:335e1–341e1.
3 Stolwijk LJ, Lemmers PMA, Harmsen M, *et al.* Neurodevelopmental outcomes after neonatal surgery for major noncardiac anomalies. *Pediatrics* 2016; **137**:e20151728.
4 Leeuwen L, Schiller RM, Rietman AB, *et al.* Risk factors of impaired neuropsychologic outcome in school-aged survivors of neonatal critical illness. *Crit Care Med* 2018; **46**:401–410.
5 Danzer E, Gerdes M, D'Agostino JA, *et al.* Longitudinal neurodevelopmental and neuromotor outcome in congenital diaphragmatic hernia patients in the first 3 years of life. *J Perinatol* 2013; **33**:893–898.
6 Schiller R, IJsselstijn H, Hoskote A, *et al.* Memory deficits following neonatal critical illness: a common neurodevelopmental pathway. *Lancet Child Adolesc Heal* 2018; **2**:281–289.
7 Hendrikx D, Smits A, Lavanga M, *et al.* Measurement of neurovascular coupling in neonates. *Front Physiol* 2019; **10**:65.
8 Phillips AA, Chan FH, Zheng MMZ, *et al.* Neurovascular coupling in humans: physiology, methodological advances and clinical implications. *J Cereb Blood Flow Metab* 2015; **36**:647–664.
9 Rhee CJ, da Costa CS, Austin T, *et al.* Neonatal cerebrovascular autoregulation. *Pediatr Res* 2018; **84**:602–610.
10 Smits A, Thewissen L, Dereymaeker A, *et al.* The use of hemodynamic and cerebral monitoring to study pharmacodynamics in neonates. *Curr Pharm Des* 2018; **23**:5955–5963.
11 Mitra S, Czosnyka M, Smielewski P, *et al.* Heart rate passivity of cerebral tissue oxygenation is associated with predictors of poor outcome in preterm infants. *Acta Paediatr* 2014; **103**:e374–e382.
12 Chalak LF, Tian F, Adams-Huet B, *et al.* Novel wavelet real time analysis of neurovascular coupling in neonatal encephalopathy. *Sci Rep* 2017; **7**:45958.
13 Mahmoudzadeh M, Dehaene-Lambertz G, Kongolo G, *et al.* Consequence of intraventricular hemorrhage on neurovascular coupling evoked by speech syllables in preterm neonates. *Dev Cogn Neurosci* 2018; **30**:60–69.
14 Volpe JJ, Zipurksy A. Neurobiology of periventricular leukomalacia in the premature infant. *Pediatr Res* 2001; **50**:553–562.
15 Hendrikx D, Thewissen L, Smits A, *et al.* Using graph theory to assess the interaction between cerebral function, brain hemodynamics, and systemic variables in premature infants. *Complexity* 2018; **2018**:6504039.
16 Bartsch RP, Liu KKL, Bashan A, *et al.* Network physiology: how organ systems dynamically interact. *PLoS One* 2015; **10**:e0142143.
17 Lally KP, Lasky RE, Lally PA, *et al. Standardized reporting for congenital diaphragmatic hernia - an international consensus J Pediatr Surg;* 2013; **48**:2408–2415.
18 Snoek KG, Reiss IKM, Greenough A, *et al.* CDH EURO Consortium. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium Consensus -2015 Update. *Neonatology* 2016; **110**:66–74.

19 Blanco S, Figliola A, Quiroga RQ, *et al.* Time-frequency analysis of electroencephalogram series. III. Wavelet packets and information cost function. *Phys Rev E Stat Physics, Plasmas, Fluids, Relat Interdiscip Top* 1998; **57**:932–940.
20 Faes L, Nollo G, Porta A. Nonuniform multivariate embedding to assess the information transfer in cardiovascular and cardiorespiratory variability series. *Comput Biol Med* 2012; **42**:290–297.
21 Gourévitch B, Eggermont JJ. Evaluating information transfer between auditory cortical neurons. *J Neurophysiol* 2007; **97**:2533–2543.
22 Mazursky JE, Birkett CL, Bedell KA, *et al.* Development of baroreflex influences on heart rate variability in preterm infants. *Early Hum Dev* 1998; **53**:37–52.
23 Team RC. *R: a language and environment for statistical computing* 2020.
24 Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. *Arch Dis Child Fetal Neonatal Ed* 1999; **80**:F142–F144.
25 Jong G, Van Der Linden P, Bakker E, *et al.* Unlicensed and off-label drug use in a paediatric ward of a general hospital in the Netherlands. *Eur J Clin Pharmacol* 2002; **58**:293–297.
26 Pacifici GM. Clinical pharmacology of midazolam in neonates and children: effect of disease—a review. *Int J Pediatr* 2014; **2014**:309342.
27 Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database Syst Rev* 2012; **1**:CD002052.
28 Anand KJS, McIntosh N, Lagercrantz H, *et al.* Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. *Arch Pediatr Adolesc Med* 1999; **153**:331–338.
29 Harte GJ, Gray PH, Lee TC, *et al.* Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. *J Paediatr Child Health* 1997; **33**:335–338.
30 van Straaten HLM, Rademaker CMA, de Vries LS. Comparison of the effect of midazolam or vecuronium on blood pressure and cerebral blood flow velocity in the premature newborn. *Dev Pharmacol Ther* 1992; **19**:191–195.
31 Martin LD, Dissen GA, McPike MJ, *et al.* Effects of anesthesia with isoflurane, ketamine or propofol on physiologic parameters in neonatal rhesus macaques (Macaca mulatta). *J Am Assoc Lab Anim Sci* 2014; **53**:290–300.
32 Patel SS, Goa KL, Sevoflurane. A review of its pharmacodynamic and pharmacokinetic properties and its clinical use in general anaesthesia. *Drugs* 1996; **51**:658–700.
33 Stolwijk LJ, Weeke LC, De Vries LS, *et al.* Effect of general anesthesia on neonatal aEEG — a cohort study of patients with noncardiac congenital anomalies. *PLoS One* 2017; **12**:e0183581.
34 Semenova O, Lightbody G, O'Toole JM, *et al.* Coupling between mean blood pressure and EEG in preterm neonates is associated with reduced illness severity scores. *PLoS One* 2018; **13**:e0199587.
35 Armstead WM. Cerebral blood flow autoregulation and dysautoregulation. *Anesthesiol Clin* 2016; **34**:465–477.
36 Costerus S, Zahn K, van de Ven K, *et al.* Thoracoscopic versus open repair of CDH in cardiovascular stable neonates. *Surg Endosc* 2016; **30**:2818–2824.
37 Gourlay DM, Cassidy LD, Sato TT, *et al.* Beyond feasibility: a comparison of newborns undergoing thoracoscopic and open repair of congenital diaphragmatic hernias. *JPediatr Surg* 2009; **44**:1702–1707.
38 Vijfhuize S, Deden AC, Costerus SA, *et al.* Minimal access surgery for repair of congenital diaphragmatic hernia: is it advantageous? - an open review. *Eur J Pediatr Surg* 2012; **22**:364–373.
39 Tsao KJ, Lally PA, Lally KP. Congenital Diaphragmatic Hernia Study Group. Minimally invasive repair ofcongenital diaphragmatic hernia. *J Pediatr Surg* 2011; **46**:1158–1164.
40 Bishay M, Giacomello L, Retrosi G, *et al.* Hypercapnia and acidosis during open and thoracoscopic repair of congenital diaphragmatic hernia and esophageal atresia: Results of a pilot randomized controlled trial. *Ann Surg* 2013; **258**:895–900.
41 Sbaffi L, Walton J, Blenkinsopp J, *et al.* Information overload in emergency medicine physicians: a multisite case study exploring the causes, impact, and solutions in Four North England national health service trusts. *J Med Internet Res* 2020; **22**:e19126.