Brain Injury and Neurodevelopmental Outcomes in Children Undergoing Surgery for Congenital Heart Disease

Inauguraldissertation
zur Erlangung des Grades eines Doktors der Medizin
des Fachbereichs Medizin der Justus-Liebig-Universität Gießen, Deutschland

in Kooperation mit dem Children's National Hospital in Washington, DC, USA

vorgelegt von Justus Gregor Reitz
aus Hadamar

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Aus dem Fachbereich Medizin der Justus-Liebig-Universität Gießen

Zentrum für pränatale Medizin und fetale Therapie
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1 Preface

Results of this study have already been published:

Reitz, J. G., Zurakowski, D., Kuhn, V. A., Murnick, J., Donofrio, M. T., d'Udekem, Y., … Carpenter, J. L. (2023). Brain Injury and Neurodevelopmental Outcomes in Children Undergoing Surgery for Congenital Heart Disease. JTCVS Open, 0(0). https://doi.org/10.1016/J.XJON.2023.11.018 (Reitz et al., 2023)

2 Introduction

2.1 Congenital Heart Disease

Congenital heart disease (CHD) is defined as a structural abnormality of the heart and/or great vessels already present at birth (Wu, He, & Shao, 2020). Worldwide, CHD is prevalent in about 1% of all newborns and therefore the most common congenital disorder (Liu et al., 2019; Van Der Linde et al., 2011). CHD can be divided into several subtypes (Mavroudis & Jacobs, 2000). The morbidity and mortality of the children affected are heterogenous and depend on various factors, including the subtype of CHD.

2.2 Classification of Congenital Heart Disease

CHD can be distinguished into cyanotic (right-to-left shunt) and non-cyanotic (left-to-right shunt) subtypes (Huml, Fremuth, & Jehlička, 2023). In cyanotic CHD, deoxygenated blood bypasses the lungs to varying degrees. It typically becomes symptomatic soon or immediately after birth. The newborns present with a bluish skin-color due to reduced oxygen saturation of the blood in the systemic arterial circulation (Desai, Rabinowitz, & Epstein, 2019). Cyanotic CHD can be subdivided in

right-heart obstructive lesions, such as

- Tetralogy of Fallot (ToF),
- Tricuspid Atresia (TA),
- Pulmonary Atresia (PA) and
- Pulmonary Stenosis (PS),

left-heart obstructive lesions, such as

- Hypoplastic Left Heart Syndrome (HLHS) and
- Interrupted Aortic Arch (IAA)

and mixing lesions, such as

- Transposition of the Great Arteries (TGA)
- Total Anomalous Pulmonary Venous Return (TAPVR) or
- Truncus Arteriosus (TA) (Huml et al., 2023).

The severity of cyanotic CHD strongly depends on the subtype and degree of the individual cardiac defect.

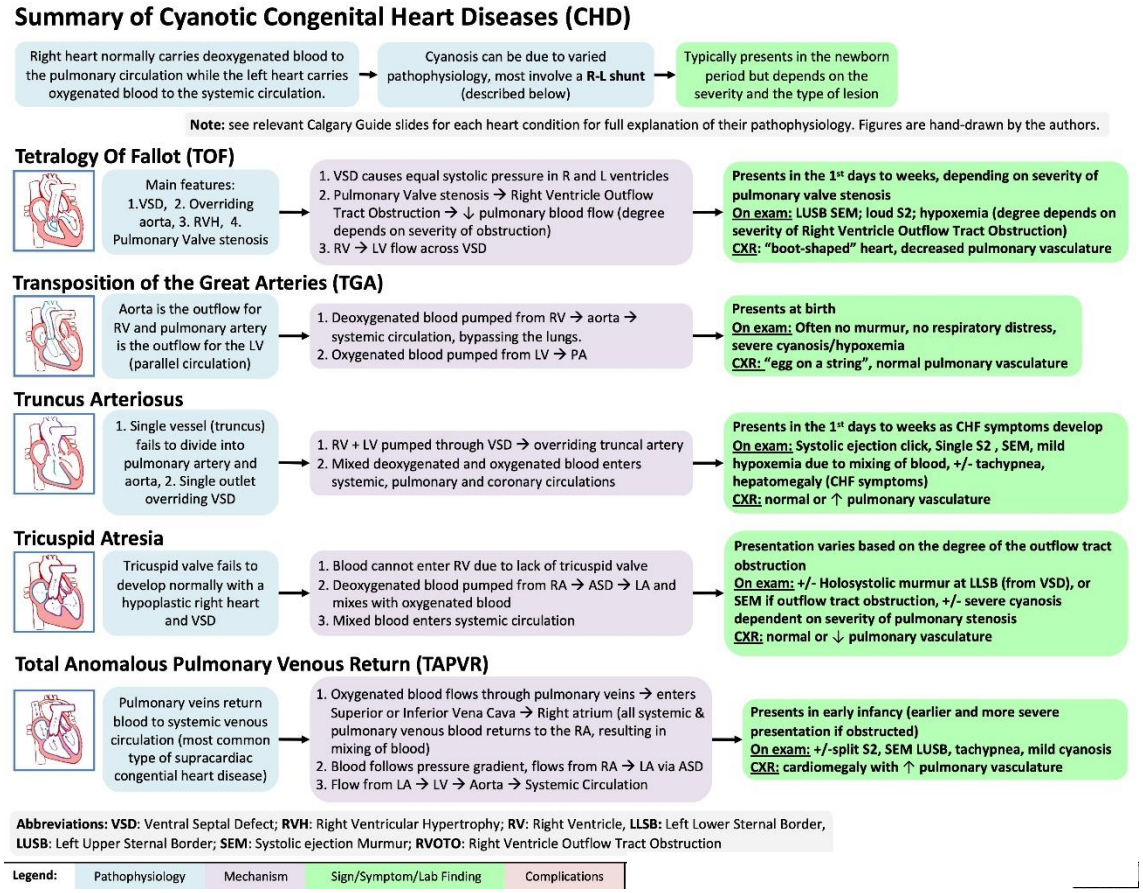


Figure 1 Pathophysiology and forms of Cyanotic Congenital Heart Disease, adapted from The Calgary Guide to Understanding Diseases. ("Summary of Cyanotic Congenital Heart Diseases | Calgary Guide," n.d.).

On the other hand, the severity of non-cyanotic CHD differs greatly. Patients born with e.g., septal defects such as atrial or ventricular septal defects (ASD or VSD) might take months or years to develop symptoms.

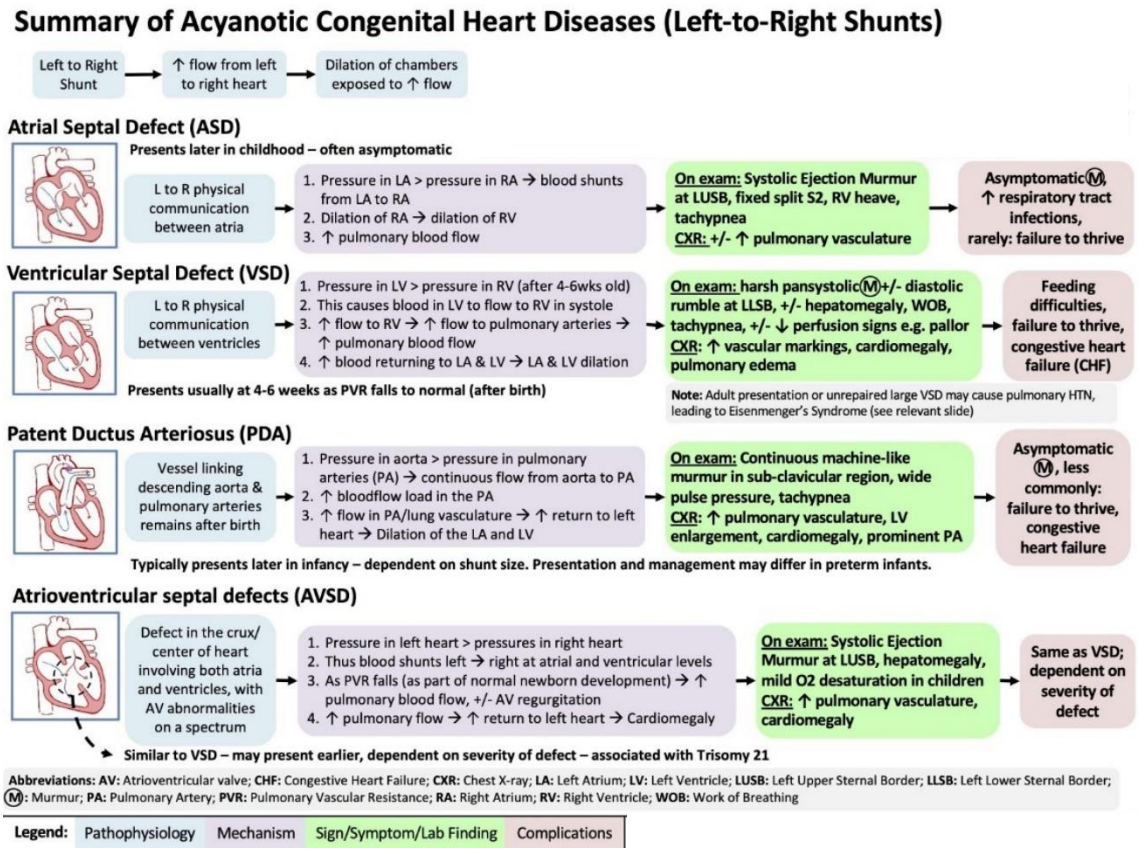


Figure 2 Pathophysiology and Forms of non-cyanotic Congenital Heart Disease, adapted from The Calgary Guide to Understanding Diseases. ("Summary of Acyanotic Congenital Heart Diseases | Calgary Guide," n.d.).

2.3 Therapy of Congenital Heart Disease

2.3.1 Perinatal

Therapeutic options have to be evaluated for each patient individually. Nowadays, many forms of non-cyanotic CHD can be treated sufficiently with catheter interventions. Corrective surgery has to be considered in more complex subtypes (Syamasundar Rao, 2019). The watch and wait strategy, with regular follow up assessments, is an option in many mild cases. Often patients can grow up before interventions or corrective surgery is necessary, if at all (Rao, 2013a).

On the other hand, cyanotic CHD should have already been diagnosed, evaluated and possible therapeutic options discussed prenatally at best (Donofrio et al., 2014; Van Velzen et al., 2016). In most cases of cyanotic CHD, it is crucial to begin therapy immediately after birth (Rao, 2013b). Firstly, cardiac circulation has to be maintained, e.g. by starting Prostaglandin E1 (PGE) infusions to prevent Ductus Arteriosus closure in ductal dependent lesions such as HLHS or balloon arterial septostomy (BAS) in severe forms of TGA. Secondly, in most forms of cyanotic CHD corrective or palliative surgery and/or catheter interventions are typically required soon after birth (Rao, 2019).

2.3.2 Surgical

Surgical therapy of CHD can be distinguished between corrective and palliative surgery (Joffs & Sade, 2000). While corrective surgeries aim to achieve normal physiological circulation, palliative surgery is performed to modify the circulation to relieve the patient's symptoms when corrective surgery is not possible. Still, often corrective surgery can follow palliative surgery e.g., when infants have to reach a certain bodyweight or age or the circulation must be prepared before corrective surgical alternatives can be considered (Yuan & Jing, 2009).

Both palliative and corrective surgery have in common, that at least one cardiac chamber and/or a great vessel is affected and has to be operated on. Therefore, the heart has to be stopped and the function of heart and lung temporarily maintained by cardiopulmonary bypass (CPB). During CPB, the blood is drained via venous cannulas to the pump of a heart-lung machine and pumped through its oxygenator. In the oxygenator blood is oxygenated and carbon dioxide is eliminated as air passes the blood on the other side of the oxygenator's membrane. Usually, a heat exchanger is included in the oxygenator to achieve a set temperature. Finally the blood is returned via an arterial cannula to the

bodies' arterial circulation (Andersen, Meza, & Turek, 2023; Hessel, 2015; Hirata, 2018; Motta & Walker, 2023; Sarkar & Prabhu, 2017).

In addition, in patients with surgery concerning the aortic arch, cerebral perfusion cannot be maintained for a certain time while operating near the outlets of the cerebral vessels. This is critical since the brain's functions decrease already seconds after blood-flow and consecutive oxygen and nutrient delivery stop (Rossen, Kabat, & Anderson, 1943) and suffers severe permanent damage only a few minutes after perfusion ceases (Sandroni, Cronberg, & Sekhon, 2021). Therefore, to minimize the impact on the brain while operating on the aortic arch, either selective cerebral perfusion through separate arterial cannulas from the heart-lung machine (Asou et al., 1996) or deep hypothermic circulatory arrest (DHCA) with temporary halt of all perfusion after reducing the bodies' temperature to 15°C (degree Celsius) to minimize oxygen consumption (Barratt-Boyes, Simpson, & Neutze, 1971; Das, Dutta, & Roy Chowdhuri, 2021) is used (Elmistekawy & Rubens, 2011; Tian et al., 2013). Thus, operations on the aortic arch of several dozen minutes can be realized (Kornilov et al., 2015; Wypij et al., 2003).

However, the process of establishing CPB, stopping the heart with cardioplegia and reversing it, the blood-flow through the heart-lung machine with a huge foreign surface, possibly circulatory arrest with DHCA or selective cerebral perfusion and the trauma of major surgery altogether result in numerous reactions in the bodies' homeostasis such as inflammatory reactions (systemic inflammatory response syndrome (SIRS)) and require extensive medical therapy (Manrique, Vargas, Palmer, Kelly, & Litchenstein, 2020; Squiccimarro et al., 2019). Postoperative intensive care therapy is mandatory (Miller-Smith, Flint, & Allen, 2021). Postoperative complications are common due to the complexity of the disease (Agarwal, Wolfram, Saville, Donahue, & Bichell, 2014).

The mortality and morbidity after heart surgery for CHD depend largly on the subtype of underlying CHD and wheather corrective surgery was feasible or palliation required (McCracken et al., 2018; Zheng et al., 2021). Children with palliation usually undergo multiple surgeries throughout childhood and still have compromised circulation due to reduced oxygen levels, elevated central venous pressure and/or reduced cardiac function (Yuan & Jing, 2009). Their mortality and morbidity are higher than those of children undergoing corrective cardiac surgery (Spector et al., 2018). However, especially adverse neurodevelopmental outcomes are known to be common in children with corrective cardiac surgery such as arterial switch or even minor surgeries as well (Kosiorek et al.,

2022; Kuhn et al., 2020). Neurodevelopmental delays often take years to become apparent. Still, a connection to CHD and perioperative factors potentially impacting the brain is often likely (Rollins & Newburger, 2019).

2.4 Brain injury and Congenital Heart Disease

Brain injuries on magnetic resonance imaging (MRI) are commonly seen in children with CHD. A wide range of complex and cumulative risk factors are proposed to contribute during different phases of brain development. Starting at mid-gestation, oligodentrocytes (OD) originate from the subventricular zone, migrate, expand and speed up myelation resulting in new connections of neurons (Morton, Ishibashi, & Jonas, 2017). In this period the fetal brain develops from a smooth mass towards its fully grown form with gyri and sulci. This differentiated process is highly susceptible to negative influences such as restricted nutrition and hypoxemia, which are often prevalent in fetuses with CHD. In fetuses with CHD cortical gyrification is reduced and 25% of children with complex CHD are microcephalic at birth (Clouchoux et al., 2013; Miller et al., 2007). In postnatal brain MRIs of newborns with CHD, brain injury is prevalent in 26% (Beca et al., 2013) to 57% (Andropoulos et al., 2010a).

After birth, about 25% of children born with CHD will require surgery or treatment within their first year of life (Huml et al., 2023; Moller, Taubert, Allen, Clark, & Lauer, 1994) – at a time when the brain is especially vulnerable. Within the first year of life, the brain doubles its volume. Synapses – the foundation for neuronal communication regionally and globally throughout the brain to achieve higher-order cognitive functions later in childhood and adolescence - are formed during the fast-progressing maturation of an infant's brain (Morton et al., 2017). The impacts of the multiple stressors like compromised cardiac circulation with resulting restricted nutrition and hypoxemia in children with CHD as well as the consecutive impacts from additional surgeries during childhood can result in severe brain injuries. Postoperative, brain injury on MRI is seen in 35% (McQuillen et al., 2007) to 77% (Andropoulos et al., 2010a; Kuhn et al., 2020) with new postoperative new lesions in about 50% of the patients (Kosiorek et al., 2022; Kuhn et al., 2020).

2.4.1 Subtypes of brain injury

With the increasing role of MRI during the last two decades, timing and differentiation of numerous types of brain injuries have been specified. Several subtypes of brain injuries are known to be common in CHD patients. MRI abnormalities commonly include white matter injury (WMI) and stroke. WMI is the most common and seen in 16% (Andropoulos et al., 2010a; Mahle et al., 2002) to 31% (Andropoulos et al., 2014) preoperatively and 15% (Andropoulos et al., 2014) to 42% (Beca et al., 2013) postoperatively. Stroke is observed in 5% (Beca et al., 2013) to 23% (Andropoulos et al., 2014) before and in 4% (Beca et al., 2013) to 31% (Dimitropoulos et al., 2013) after surgery. Furthermore, intraparenchymal and intraventricular hemorrhage (IPH/IVH), subdural hematoma (SDH) and dural venous sinus thrombosis (DVST) have been described in children with CHD (Kuhn et al., 2020).

2.4.2 Clinical risk factors for brain injury

Several clinical risk factors have been described as being associated with brain injuries. BAS (McQuillen et al., 2007), higher scores for neonatal acute physiology with perinatal extension (SNAP-PE) and lower preoperative oxygen saturation (Dimitropoulos et al., 2013) increase the risk for preoperative brain injury. The risk for postoperative brain injury is increased in single ventricular (SV) patients undergoing the Norwood procedure and in patients with CPB (McQuillen et al., 2007), longer intensive care unit (ICU) length of stay (Kuhn et al., 2020) and lower postoperative systolic & mean blood pressure (BP) (Dimitropoulos et al., 2013). Especially postoperative WMI was associated with preoperative brain injury, low brain maturation, single ventricular physiology (Andropoulos et al., 2010a), longer duration of CPB, 6h postoperative lactate (Beca et al., 2013) and low mean BP on the first postoperative day (McQuillen et al., 2007).

Lower birth weight (BW), preoperative intubation, lower intraoperative hematocrit, higher systolic BP on ICU admission (Chen et al., 2009) and HLHS (Kuhn et al., 2020) increased the risk for postoperative stroke.

Still, the impact of brain injuries on MRI on the long-term neurodevelopmental outcome is controversially discussed.

2.5 Neurodevelopmental outcome in children with Congenital Heart Disease

Nowadays, life expectancy is steadily rising for patients with CHD. The vast majority of children with CHD will reach adulthood (Mazor Dray & Marelli, 2015). Still, children with CHD have worse long-term neurodevelopmental (ND) outcomes compared to healthy controls. Current estimates report ND disorders impact more than 50% of children with severe CHD (Marino et al., 2012). Therefore, efforts to ensure positive long-term neurologic outcomes for patients with CHD are imperative.

2.5.1 Risk factors for impaired neurodevelopmental outcome

A variety of independent risk factors for ND impairment in children with CHD have been reported. When predicting an individual's prognosis, a combination of risk factors needs to be considered. Not only are there significant differences between the many subtypes of CHD, but within each subgroup individual defects vary significantly. Patients with CHD are heterogeneous in their extra-cardiac risk factors as well. Studies have shown elements inherent to the patient (i.e. genetic vulnerabilities (Mussatto et al., 2014), low birth weight), environment (i.e. lower socioeconomic status (SES)) and clinical course (e.g. prolonged mechanical ventilation, longer stay in the ICU (Kuhn et al., 2020)) all have an impact on the ND outcome.

2.5.2 Impact of brain injuries on neurodevelopmental outcome

Despite the extensive evaluation of brain injuries in infants with CHD, there are gaps in our understanding of how these radiographic injuries impact the ND outcome. Some studies have shown brain immaturity, but not brain injury predicts impaired neurodevelopment at 2 years (Beca et al., 2013). While others have demonstrated that new postoperative injury predicts lower cognitive scores (Andropoulos et al., 2014) and yet, others have found moderate to severe WMI to be associated with lower cognitive scores at 2 years and full-scale intelligence quotient (IQ) at 6 years of age (Claessens et al., 2018).

On the other hand, some commonalities exist. For example, length of ICU stay and duration of mechanical ventilation are shown to consistently have a negative association with ND outcome (Kuhn et al., 2020). As such, modifiable determinants of outcome can likely be found in the perioperative care of these patients.

2.6 Aim of the study

In this study, we investigated the timing and subtype of acute brain injury on the risk for poor ND outcome in patients with surgery for CHD during infancy. Clinical biomarkers were also evaluated to identify when a patient is at risk for an unfavorable ND outcome.

We hypothesize that ischemic brain injury acquired during the perioperative course may have an adverse impact on ND outcome. Furthermore, we propose that elevations of serum lactate during the perioperative period may be a useful clinical biomarker for identifying patients at risk for ischemic brain injury.

3 Material and methods

3.1 Cohort

Term infants who underwent congenital cardiac surgery at a single tertiary care center between 2008 and 2019 were retrospectively identified from a cardiac surgery database. Patients with surgery performed within the first 90 days of life and with both a preoperative and postoperative brain MRIs were included in the analysis. Patients born before 37 weeks of gestation and those with multiple congenital malformations or a suspected/confirmed genetic condition were excluded. ND assessments were evaluated as part of clinical care.

The study was approved by the Institutional Review Board of the Children's National Hospital, Washington, DC (Pro00009673) and the Justus-Liebig Universities' Ethics Committee, Giessen (AZ 158/19). Patient consent was waived due to the retrospective design of this study and the use of de-identified data.

3.2 Clinical data

Patient demographics and clinical data were extracted from the database and supplemented by the electronic medical record. Patient characteristics included gestational age (GA), birth weight, birth head circumference (HC) and age at the time of the MRI. Intraoperative data captured included age and weight at the time of surgery, aortic cross-clamp time, duration of DHCA and the procedure performed. Markers of oxygenation and perfusion in the postoperative period were collected and consisted of the highest arterial lactate, highest arterial pCO2, and lowest arterial pH. Peak values were defined as the highest value in the postoperative ICU course after initial surgery and before postoperative MRI. Clinical events recorded included time from surgery to postoperative MRI, duration of intubation, length of stay in the ICU, length of hospital stay, presence of electrographic seizures, cardiac arrest, need for extracorporeal membrane oxygenation (ECMO) support, and subsequent cardiac surgery or catheterization. Outcome variables comprised mortality, ND evaluations, and gastrointestinal tube (G-tube) placement prior to discharge.

3.3 MRI data

3.3.1 MRI imaging

Preoperative brain MRI scans were obtained as soon as the newborn could be safely transported to the MRI scanner as determined by the clinical team. Postoperative studies were performed after the patient's condition stabilized and the pacing wires were removed. MRI scans were acquired as part of clinical care.

Pre- and postoperative MRI studies were performed on either a 1.5 T (Discovery MR450; GE Healthcare, Waukesha, Wisconsin or Siemens Avanto, Erlangen, Germany) or 3.0 T scanner (Discovery MR750; GE Healthcare, Waukesha, Wisconsin). The MRI scans consisted of T1- and T2-weighted images, susceptibility-weighted images, diffusion-weighted imaging, and MR spectroscopy.

3.3.2 MRI analysis

MRI scans were scored for brain injury by either a pediatric neuroradiologist or a pediatric neurologist. Scores were assigned outside of routine clinical care; formal blinding was not performed. Brain injury on preoperative and postoperative brain MRIs was characterized using the brain injury score devised by Andropoulos et al., 2010b, and as previously described (Kosiorek et al., 2022; Kuhn et al., 2021).

Brain injuries are divided into 8 different subcategories: WMI, infarction (ischemic stroke), IPH, punctate lesions (PL), elevated lactate on magnetic resonance spectroscopy (MRS), IVH, SDH and DVST. The severity of each injury was scored depending on the number and size of the abnormality 0 for none, 1 for mild, 2 for moderate and 3 for severe.

Subcategory	Outcome Significance Multiplier	Score	Definition	Size (total mm, largest diameter, add all lesions)
White matter injury	3	0	none	0
		1	mild: <= 3, < 2mm	1 to 5 mm
		2	moderate: >3, > 2mm	6 to 15 mm
		3	severe: 10% white matter	>15 mm
Infarction (stroke-ischemic)	3	0	none	0
		1	< 1/3 of vascular territory of ACA, MCA, or PCA in one hemisphere	1 to 5 mm
		2	1/3–2/3 vascular territory	6 to 15 mm
		3	> 2/3 vascular territory	>15 mm
IP hemorrhage (stroke-hemorrhagic)	3	0		0
		1		1 to 5 mm
		2		6 to 15 mm
		3		>15 mm
Punctate lesions	2	0	none	0
		1	1–3 lesions	all ≤ 2 mm
		2	4–6 lesions	all ≤ 2 mm
		3	>6 lesions	all ≤ 2 mm
↑Lactate on MRS	2	0	None to Lac/Cr ratio of 0.15	
		1	Lac/Cr ratio of 0.16–0.5	
		2	Lac/Cr 0.5–1	
		3	Lac/Cr >1	
Intra-ventricular hemorrhage (IVH)	1	0	0	
		1	subependymal/germinal matrix hemorrhage/choroid plexus hemorrhage	1 to 5 mm
		2	IVH-isolated	6 to 15 mm
		3	IVH with ventricular dilation	>15 mm
Subdural hemorrhage (SDH)	1	0	subdural blood above tentorium; minimal SDH below tentorium frequently 2° birth process and not considered abnormal	
		1	minimal just above tentorium	
		2	Spread to interhemispheric fissure in occipital area	
		3	Larger hemorrhage; interhemispheric to parietal or frontal area; any mass effect	
Dural Venous Sinus Thrombosis	1	0	Flow voids in dural venous sinuses, confirmed by MR venogram	0
		1		R or L transverse alone
		2		Bilateral R and L
		3		Straight and/or Sagittal sinus

All categories	Multiply score in each of the 9 subcategories with its outcome significance multiplier ↓ Sum all 9 subscores for the total brain injury score (TBIS) ↓ Range TBIS: 0 to 51	TBIS 0	None
		TBIS 1–5	Mild
		TBIS 6–10	Moderate
		TBIS >10	Severe

Table 1 Modified from Andropoulos et al. DWI, diffusion-weighted imaging; ACA/MCA/PCA, anterior/middle/posterior cerebral artery; IP, intraparenchymal; MRS, magnetic resonance spectroscopy; Lac/Cr, lactate-to-creatine ratio; TBIS, total brain injury score.

The scores in each subcategory were multiplied by an outcome significance multiplier (3 for WMI, infarction, or intraparenchymal hemorrhage; 2 for punctate lesions or increased lactate on MRS and 1 for intraventricular hemorrhage, subdural hemorrhage and dural sinus venous thrombosis) and added to a total brain injury score (TBIS). A TBIS of 0 equals no injury; a score of 1 to 5 indicates mild injury, 6 to 10 moderate injury and >10 severe injury.

3.4 Neurodevelopmental outcome assessments

Per institutional routine, patients with CHD and cardiac surgery during the first year of life are referred for outpatient ND evaluation. ND assessments are performed by a pediatric neurologist and/or a developmental psychologist at recommended intervals during childhood. Inpatient assessments were excluded from this study. ND outcome scores were retrospectively assigned using both the Pediatric stroke outcome measure (PSOM) and Glasgow Outcome Scale Extended Pediatric Version (GOS-E).

3.4.1 GOS-E scoring

The GOS-E assesses the outcome after traumatic brain injury (Brown et al., 2001). The extended GOSE-E Pediatric version used in this study was specifically adapted for children up to 17 years of age (Beers et al., 2012). It is divided into 8 different categories:

1) upper good recovery: “No physical or psychical limitations affecting the daily life”

2) lower good recovery “psychological problems occasionally (less than weekly) affecting the interaction with family or friends/ patient participating a bit less in social and leisure activities than before (at least half as often)”
3) lower moderate disability: “Psychological problems frequently affecting the interaction with family or friends”
4) upper moderate disability: “patient participating much less in social and leisure activities than before (less than half as often)”, “reduced capacity for school”
5) lower severe disability: “Patient does not behave age appropriately outside home”
6) upper severe disability: “patient needs frequent help at home”
7) vegetative state: “patient is not able to follow simple commands or communicate”
8) death

Adverse outcome was defined as a GOS-E scores > 2 (lower moderate or worse).

3.4.2 PSOM scoring

The Pediatric Stroke outcome measure (PSOM) is a measure of neurologic deficits focusing especially on motor and adaptive behavior (Cooper et al., 2018; DeVeber, MacGregor, Curtis, & Mayank, 2000). It uses 5 subcategories:

1) sensorimotor function
2) expressive language
3) language comprehension
4) behavior/state regulation
5) cognition

Each subcategory has 4 different scores: 0 for no deficit, 0.5 for mild deficit, 1 for moderate deficit and decreased function, or 2 for severe deficit and missing function.

The total PSOM score was calculated according to the combination of the scores of each subcategory (Felling et al., 2020):

- normal: 0-0.5 in all subscales
- mild: 1 in 1-2 subscales and <1 in all remaining subcategories
- moderate: 1 in ≥3 subscale or 2 in 1 subscale and <2 in all remaining subscales
- severe: 2 in ≥2 subscales

Adverse outcome was defined as a moderate or severe PSOM, comparable to a GOS-E >2.

3.5 Statistical analysis

Outcomes were assigned as early ND outcome (5-24 months) and latest ND outcome (as defined by the most recent ND assessment). For early ND outcome, new postoperative stroke, moderate/severe brain injury (TBIS >5), SV, cardiac arrest, thrombosis, peak lactate during postoperative course, seizure, duration of ventilation, ICU length of stay and DHCA were included in univariate Cox analysis. For latest ND outcome, SV (without HLHS), HLHS, postoperative new stroke, DHCA, peak lactate, duration of ventilation, seizure, thrombosis and subsequent surgery were included in univariate analysis. Variables with $p<0.05$ in univariate analysis were included in multivariable Cox regression analysis. Independent risk factors for poor early and latest ND outcomes were identified with the date of surgery and the date of follow up to determine time-to-event for adverse GOS-E and PSOM. Variables included in multivariable Cox regression analyses were those with $P<0.05$ in univariate Cox analysis. Hazard ratios and 95% confidence intervals were calculated as measures of risk and presented as forest plots. For significant variables in the multivariable Cox regression analysis, the area under the curve (AUC) was calculated and a probability model calculated based on logistic regression. Bootstrap validation with 2,000 bootstrap resamples with replacement was performed to evaluate internal validation of the multivariable predictive outcome models12. Analysis of the data was performed using Stata version 16.1 (StataCorp LLC, College Station, Texas). Two-tailed $P < 0.05$ was considered statistically significant.

4 Results

4.1 Cohort

A total of 204 infants with congenital heart surgery within the first 90 days of life and with both pre- and postoperative brain MRIs during the study period were identified. Of those, 21 were excluded because of preterm birth and 48 were excluded because of genetic malformations or suspected syndromes (7 Trisomy 21, 9 Di-George, 3 Turner, 2 Vaterl, 2 Kabuki, 1 Charge, 1 Noonan, 2 cerebral dysgeneses, 19 others). Thirteen patients were not included in the analysis because of incomplete MRI data. The study cohort comprised 122 patients.

Variable	Total
Cohort, n (%)	122 (100)
Gender male, n (%)	80 (66)
Gestational age at birth, median weeks (IQR)	39 (38-39)
Birth weight, median kg (IQR)	3.23 (2.9-3.5)
Head circumference at birth, median cm (IQR)	34 (33-35)
CHD Class, n (%) I + II = Biventricular (BV)	 55 (41) + 25 (25)
III + IV = Single Ventricle (SV)	13 (11) + 29 (22)
Lowest SpO_2 preop, median % (IQR)	73 (55-87)
Lowest pO_2 preop, median mmHg (IQR)	34 (26-43)
Highest pCO_2 preop, median mmHg (IQR)	48 (43-58)
Lowest pH preop, median (IQR)	7.32 (7.27-7.35)
Highest lactate preop, median (IQR)	2.9 (1.9-4.6)
Lowest SBP preop, median (IQR)	51 (47-57)
Lowest DBP preop, median (IQR)	25 (20-29)
iNO used preop, n (%)	10 (8%)
PGE used, n (%)	112 (92%)
PGE duration, median days (IQR)	5 (3-7)
Mechanical ventilation preop, n (%)	63 (52)
Duration ventilation preop, median days (IQR)	2 (1-5)
Inotropic support used preop, n (%)	23 (19%)

Balloon atrial septostomy, n (%)	33 (27)
Age at cardiac surgery, median days (IQR)	7 (5-10)
Weight at surgery, median kg (IQR)	3.26 (2.96-3.63)
Surgery with/without CPB, n (%)	103 (84)/19 (16)
CPB duration, median min (IQR)	150 (122-180)
Clamp aorta, n (%)	93 (76)
Clamp duration time, median min (IQR)	79 (51-111)
DHCA, n (%)	75 (62)
DHCA duration, median min (IQR)	33 (9-49)
DHCA >=40 min	31 (25)
Lowest temp during surgery in °C, median (IQR)	15 (14-24)
Cardiac index	0.49 (0.46-0.53)
Open chest after surgery, n (%)	72 (59%)
Open chest duration after surgery, median days (IQR)	3 (3-4)
Highest pCO_2 immediately postop, median (IQR)	75 (64-95)
Lowest pH immediately postop, median (IQR)	7.18 (7.09-7.27)
Lowest pH postop later, median (IQR)	7.29 (7.15-7.34)
Highest pCO_2 postop later, median (IQR)	65 (59-74)
Cardiac arrest, n (%) • Between MRIs • Before discharge • Overall	 11 (9) 14 20
Fever (>38,5°C), n (%) • Between MRIs/perioperative • Before discharge	 20 (16) 27 (22)
ECMO, n (%) • Between MRIs • Before discharge • Overall	 7 (6) 7 (6) 10
Venous Thrombosis (initial hospitalization), n (%)	20 (16)
Electrographic seizures, n (%)	16 (13)
Duration of ICU stay, median days (IQR)	17 (13-28)
Duration of hospital stay, median days, (IQR)	26 (18-48)
Duration of mechanical ventilation total, median days (IQR)	7 (4-11)
Duration surgery to postoperative MRI, median days (IQR)	14 (8-29)

Tracheostomy, n (%)	3 (2.5)
G-Tube, n (%)	28 (23)
SpO_2 at discharge, median % (IQR)	95 (83-99)
Need for subsequent cardiac catheters, n (%)	47 (39)
Subsequent cardiac surgery performed, n (%)	60 (49)
Subsequent surgery with CPB, n (%)	55 (45)
Subsequent surgery not palliation, n (%)	29 (24)
Subsequent surgery more than 1 time, n (%)	37 (30)
Early follow up at 5-24 month • n (%) • age (without deaths), median months (SD)	 95 (78) 8 (4.5)
Latest follow up >=5months • n (%) • age (without deaths), median months (SD)	 101 (83) 36 (18-53)
2 Follow up (at 5-24 months AND >24months, at least 12 months apart) • n (%) • time difference months (w/o deaths), median (SD) • PSOM recent follow up (deaths included) worse/better than first follow up, n (%) • GOS-E recent follow up (deaths included) worse/better than first follow up, n (%)	 67 (55) 34 (20.8) 31 (46) / 6 (9) 31 (46) / 11 (16)
Death, n (%) • Age, mean/median in weeks (IQR) • Age, mean/median in years (IQR)	10 (8) 116/66 (35-184) 2.2/1.3 (0.7-3.5)

Table 2 Cohort characteristics. IQR, Interquartile range; CHD, congenital heart disease; SV, single ventricular; BV, biventricular; iNO, inhaled nitric oxide; PGE, prostaglandin; SBP, systolic blood pressure; DBP, diastolic blood pressure; CPB, cardiopulmonary bypass; DHCA, deep hypothermic cardiac arrest; MRI, magnetic resonance imaging; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; SD, standard deviation; PSOM, Pediatric Stroke Outcome Measure; GOS-E, Glasgow Outcome Scale Extended.

4.2 Diagnoses and surgeries performed

Forty-two patients (34%) had SV circulation; 80 patients (66%) had BV circulation. Of the 103 (84%) patients who had surgery with CPB, during 75 surgeries (62%) DHCA was used, and in 31 cases (25%), DHCA was 40 minutes or longer (Table 2).

Variable	Total
Diagnosis, n (%)	
• TGA	37 (30)
• HLHS	24 (20)
• DORV	15 (12)
• Other SV	6 (5)
• CoA	14 (11)
• TOF	10 (8)
• TrA	5 (4)
• VSD	3 (2)
• TAPVR	3 (2)
	5 (4)
Procedure, n (%)	
• Arterial Switch operation	35 (29)
• Norwood operation	27 (22)
• Coarctation of Aorta Repair	14 (12)
• Blalock-Taussing Shunt	13 (11)
• TOF repair	10 (8)
• Truncus repair	5 (4)
• VSD repair	3 (3)
• DORV repair	3 (3)
• TAPVR repair	3 (3)
• Other	9 (7)

Table 3 Diagnoses and procedures performed. TGA, Transposition of the Great Arteries; HLHS, Hypoplastic left Heart Syndrome; DORV, Double Outlet Right Ventricle; SV, single ventricle; CoA, Coarctation of Aorta; TOF, Tetralogy of Fallot; TrA, Truncus Arteriosus; VSD, Ventricular Septal Defect; TAPVR, Total Anomalous Pulmonary Venous Return.

4.3 Brain MRIs

Preoperative brain injury was present in 53% (n=64), and injury was characterized as moderate or severe in 16% (n=19). Injury was noted on the postoperative scan in 74% (n=90) with 33% (n=40) suffering moderate or severe injuries. Fifty-seven percent (n=69) of the injuries identified on the postoperative MRI were defined as new or expanded injuries. The median age (SD) at preoperative MRI was 3 (5.8) days with the scan occurring a median (SD) of 3 (9.2) days before surgery. The median (SD) age at postoperative MRI was 25 (18.3) days, occurring at a median (SD) of 15 (17.1) days after surgery (Table 4).

	Preoperative MRI		**Postoperative MRI**			
median age in days at time of MRI, n (IQR)	3 (2-5)		25 (18.25-36)			
Brain injury present, n (%)	64 (52.5%)		90 (73.8%)			
New Brain injury, n (%)	N/A		69 (56.6%)			
TBIS mean, median (IQR)	2.39, 1 (0-3)		4.40, 3 (1-7)			
Brain injury score	58 normal - 45 mild - 14 moderate - 5 severe		32 normal - 50 mild - 28 moderate - 12 severe			
Brain injury subtype	Brain injury preoperative		Brain injury postoperative		new or worse injury post vs. pre	
WMI	23	18.85%	39	31.97%	25	20.49%
infarction	14	11.48%	23	18.85%	17	13.93%
IPH	6	4.92%	9	7.38%	4	3.28%
SDH	24	19.67%	23	18.85%	14	11.48%
IVH	14	11.48%	19	15.57%	10	8.20%
PL	9	7.38%	39	31.97%	34	27.87%
MRS	10	8.20%	8	6.56%	1	0.82%
DVST	0	0.00%	3	2.46%	3	2.46%

Table 4 Brain MRI findings. MRI, Magnetic resonance imaging; IQR, interquartile range; N/A, not available; TBIS, total brain injury score; WMI, White matter injury; IPH, intraparenchymal hemorrhage; SDH, subdural hemorrhage; IVH, intraventricular hemorrhage; PL, punctate lesions; MRS, magnet resonance spectroscopy; DVST, dural venous sinous thrombosis.

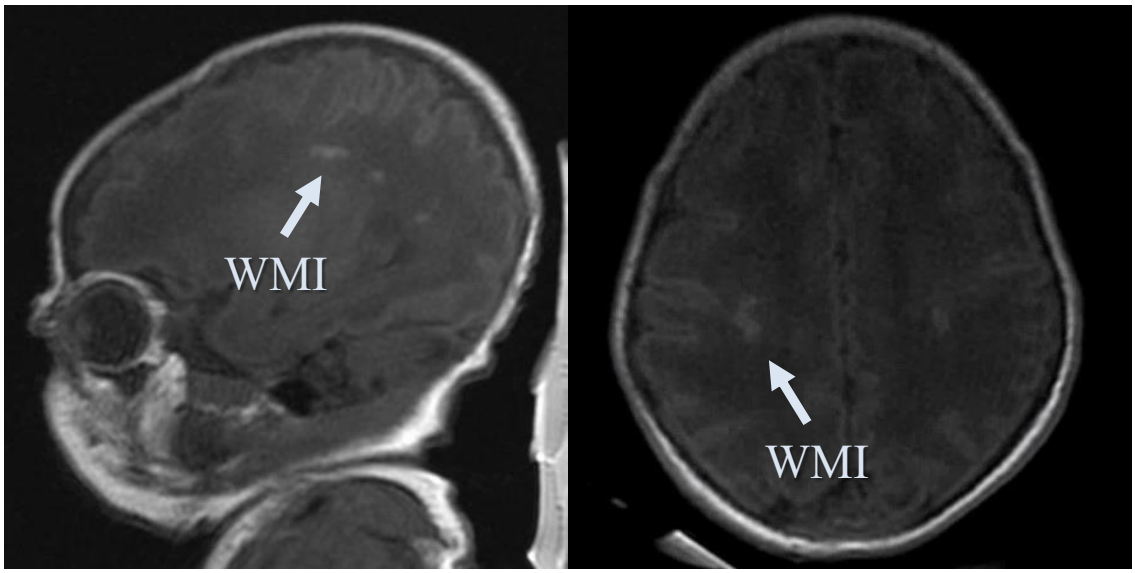


Figure 3 Postoperative WMI. WMI, white matter injury.

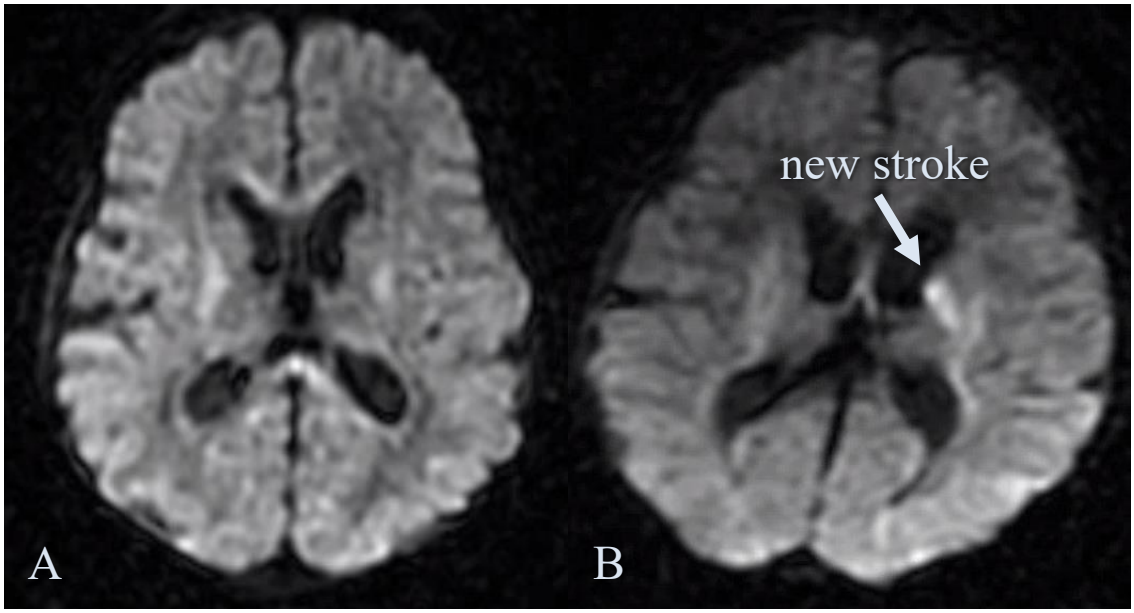


Figure 4 Pre- (A) and postoperative (B) brain MRIs of the same patient with newly acquired stroke.

4.4 Neurodevelopmental outcome assessments

A total of 101 patients (83%) had at least one ND assessment. The median (IQR) age was 36 (19-54) months. Ninety-five children (78%) had an early assessment (at 5-24 months) at a median (SD) age of 8 (4.5) months. Sixty-seven (55%) of the children had two assessments at least 12 months apart. The median (SD) time between the two assessments was 34 (20.8) months.

Of the 122 patients studied, 10 died. Three died before 5 months of age and had no ND assessment. Consequently, those three were not included in the analysis of ND outcomes. All 7 patients who died after 5 months of age had an adverse ND assessment before death.

An early ND outcome assessment was obtained in 95 children. Thirteen (7%) had a poor outcome by PSOM and 21 (22%) had a poor outcome by GOS-E. A poor PSOM score was found on the latest ND assessment in 21 (21%) whereas a poor GOS-E was assigned in 35 (35%) of the latest follow ups. Of the sixty-seven children with two assessments at least 12 months apart, 31 (46%) ND assessments (both PSOM and GOS-E) were worse at the second assessment compared to the first. Alternatively, at the second assessment, 6 children (9%) had better PSOM score and 11 (16%) a better GOS-E score.

An ischemic stroke was present on 14 (11%) of the preoperative MRIs. Twenty-three (19%) of the postoperative MRIs contained an ischemic stroke, of which 17 (14%) were new or expanded ischemic injury. ND assessments were obtained in 12 of the 14 patients with stroke on preoperative MRI and 20 of the 23 patients with stroke on postoperative MRI. 16 of the 17 patients with new stroke on postoperative MRI were assigned an ND outcome score. Adverse ND outcome was only present in the patients with new postoperative stroke (Figure 1).

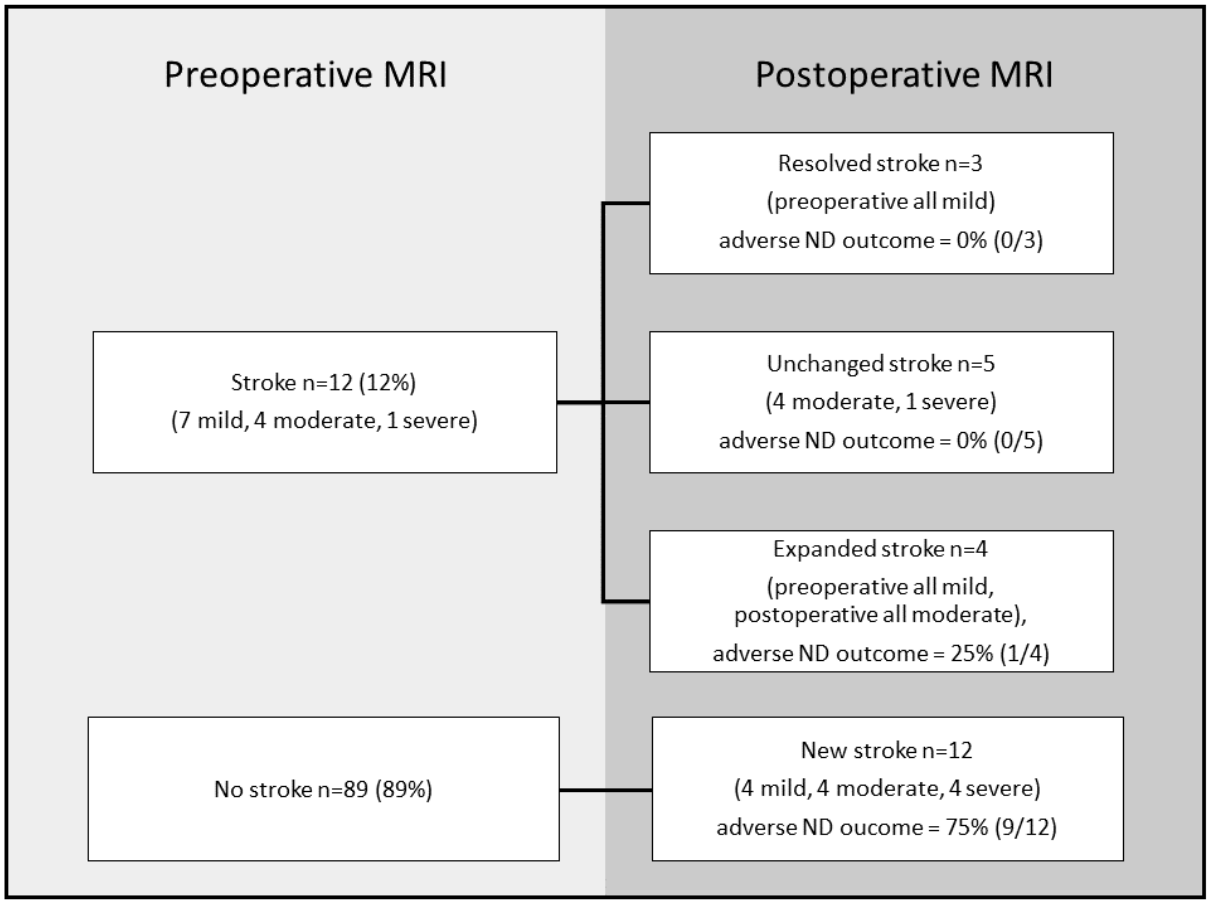


Figure 5 ND outcome by stroke time and severity (includes only patients with ND assessment). Mild: less than 1/3 of vascular territory of anterior/middle/posterior cerebral artery in 1 hemisphere, total size 1 to 5 mm. Moderate: 1/3 to 2/3 of vascular territory, total size 6 to 15 mm. Severe: greater than 2/3 of vascular territory, total size greater than 15 mm. MRI, magnetic resonance imaging; ND, neurodevelopmental.

The individual outcomes of patients with stroke can be seen in Table 5.

stroke preop	stroke postop	patient number	preop stroke	postop stroke	outcome assessment
yes	better	1	mild	none	no assessment
		2	mild	none	normal
		3	mild	none	normal
		4	mild	none	normal
	same	5	moderate	moderate	no assessment
		6	moderate	moderate	normal
		7	moderate	moderate	normal
		8	moderate	moderate	normal
		9	moderate	moderate	normal
		10	severe	severe	normal
	worse	11	mild	moderate	normal
		12	mild	moderate	normal
		13	mild	moderate	normal
		14	mild	moderate	adverse
no	worse	15	none	mild	normal
		16	none	mild	normal
		17	none	mild	adverse
		18	none	mild	died
		19	none	moderate	no assessment
		20	none	moderate	adverse
		21	none	moderate	adverse
		22	none	moderate	adverse
		23	none	moderate	adverse
		24	none	severe	adverse
		25	none	severe	adverse
		26	none	severe	died
		27	none	severe	died

Table 5 Neurodevelopmental outcome by stroke time and severity of the individual patients with stroke.

4.5 Statistical analysis

Multivariable Cox regression of the early (5-24 months) ND outcomes confirmed that perioperative stroke on postoperative MRI and cardiac arrest before initial discharge are significant independent predictors of poor outcome by GOS-E assessment (Table 6, Figure 6). For the GOS-E model, the two independent risk factors (stroke and cardiac arrest) provide an AUC of 0.833 (95% CI: 0.732, 0.934; Table 6). Doing a bootstrap validation with 2,000 bootstrap resamples with replacement, this model demonstrates robust internal model performance with regards to discrimination (bootstrap AUC = 0.833) and calibration (Brier Score = 0.10, Hosmer-Lemeshow goodness-of-fit test P = 0.887).

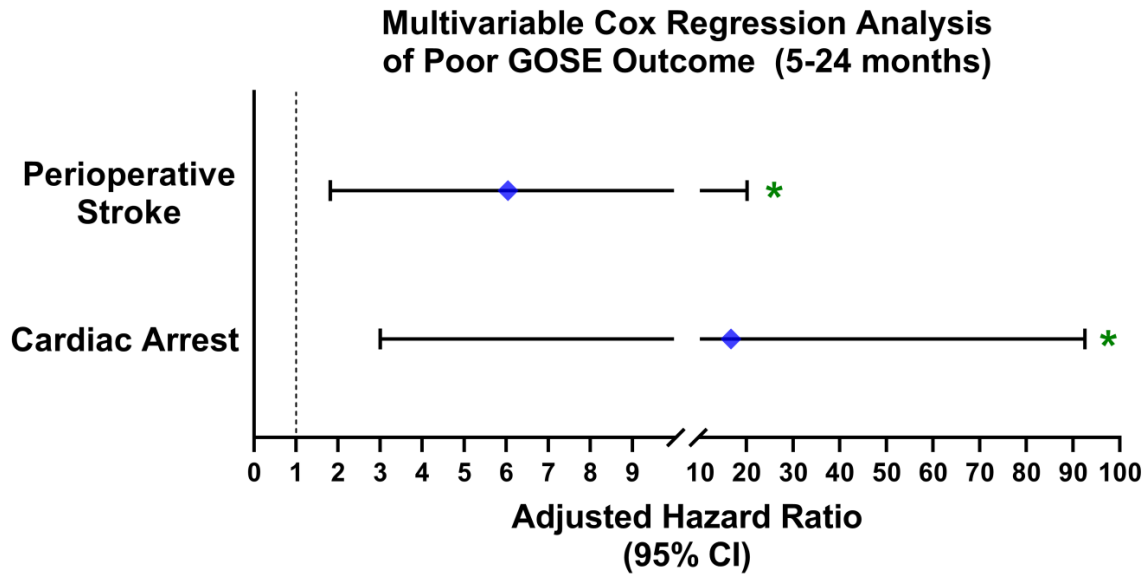


Figure 6 Significant risk factors in multivariable analysis for poor neurodevelopmental outcome (GOS-E) at 5-24 months of age. GOSE, Glasgow Outcome Scale Extended; CI, confidential interval.

Univariate and Multivariable Cox Regression Analysis of poor GOSE Outcome (age 5-24 months)

Variable	Univariate Analysis			Multivariable Analysis		
	HR	**95% CI**	**P value**	**Adjusted HR**	**95% CI**	**P value**
Perioperative Stroke	3.6	(1.51, 8.57)	**0.004***	6.04	(1.81, 20.1)	**0.003***
Moderate/Severe Brain Injury	2.68	(1.12, 6.37)	**0.026***	Omitted due to collinearity		
Single Ventricle	6.02	(2.02, 17.9)	**<0.001***	3.3	(0.94, 11.5)	0.062
Cardiac Arrest	9.26	(3.6, 23.9)	**<0.001***	16.7	(3, 92.5)	**<0.001***
Thrombosis	2.45	(0.99, 6.09)	0.053			
Peak Lactate†	1.21	(1.1, 1.34)	**<0.001***	0.92	(0.8, 1.07)	0.275
Seizure‡	2.65	(1.09, 6.42)	**0.031***	Omitted due to collinearity		
Duration of Ventilation	1.03	(1.02, 1.04)	**<0.001***	1	(0.98, 1.03)	0.736
ICU Length of Stay	1.02	(1.01, 1.03)	**<0.001***	1	(0.99, 1.02)	0.409
DHCA						
No DHCA	Reference	.	.			
1-39 minutes of DHCA	0.65	(0.16, 2.56)	0.537			
40+ minutes of DHCA	1.99	(0.77, 5.15)	0.157			

Table 6 Variables with P<.05 in univariate analysis were included in the multivariable model. HR, Hazard ratio; CI, confidence interval; ICU, intensive care unit; DHCA, deep hypothermic cardiac arrest. *Statistically significant. †Peak lactate after surgery and before postoperative MRI. ‡Clinical seizure confirmed on electroencephalogram.

Stroke on postoperative MRI is the only significant independent predictor of poor PSOM outcome (Table 7, Figure 7). A bootstrap validation with 2,000 bootstrap resamples for stroke on MRI predicts poor PSOM outcome at 5-24 months. Based on the numbers below, the bootstrap validation indicates good discrimination and calibration: bias-corrected AUC = 0.727, bias-corrected Somers' D = 0.45, bias-corrected Brier Score = 0.10.

Notably, postoperative moderate to severe brain injury and stroke on postoperative MRI (a component of the total brain injury score), were colinear in the univariate model and therefore only new stroke on postoperative MRI was included in the multivariable analysis.

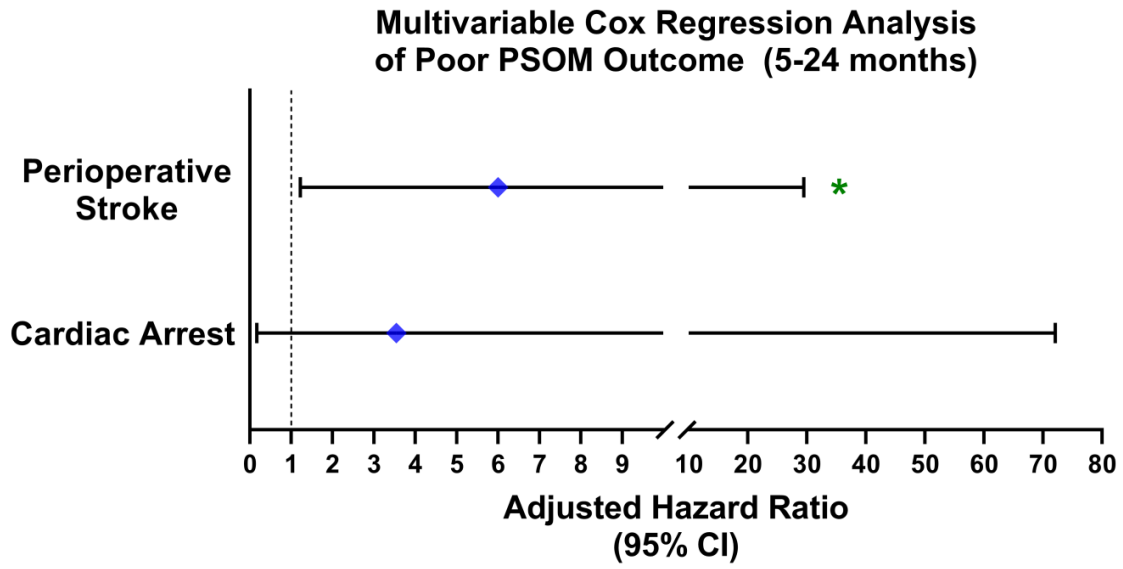


Figure 7 Significant risk factors in multivariable analysis for poor neurodevelopmental outcome (PSOM) at 5-24 months of age. PSOM, Pediatric Stroke Outcome Measure; CI, confidential interval.

Univariate and Multivariable Cox Regression Analysis of poor PSOM outcome (age 5-24 months)

Variable	Univariate Analysis			Multivariable Analysis		
	HR	95% CI	P value	Adjusted HR	95% CI	P value
Perioperative Stroke	5.57	(1.86, 16.6)	**0.002***	6	(1.22, 29.5)	**0.028***
Mod/Sev Brain Injury	4.41	(1.35, 14.4)	**0.014***	Omitted due to collinearity		
Single Ventricle	7.9	(1.75, 35.7)	**0.007***	2.6	(0.45, 14.4)	0.289
Cardiac Arrest	7.43	(2.07, 26.6)	**0.002***	3.54	(0.17, 72.1)	0.411
Thrombosis	2.98	(0.97, 9.16)	0.057			
Peak Lactate†	1.28	(1.12, 1.47)	**<0.001***	1.01	(0.82, 1.23)	0.95
Seizure‡	4.82	(1.61, 14.5)	**0.005***	Omitted due to collinearity		
Duration of Ventilation	1.03	(1.02, 1.04)	**<0.001***	1	(0.98, 1.03)	0.582
ICU Length of Stay	1.02	(1.01, 1.03)	**<0.001***	1.01	(0.99, 1.04)	0.228
DHCA						
No DHCA	Reference	.	.			
< 40 minutes of DHCA	0.81	(0.14, 4.59)	0.816			
≥ 40 minutes of DHCA	2.24	(0.65, 7.69)	0.231			

Table 7 Variables with P<.05 in univariate analysis were included in the multivariable model. HR, Hazard ratio; CI, confidence interval; ICU, intensive care unit; DHCA, deep hypothermic cardiac arrest. *Statistically significant. †Peak lactate after surgery and before postoperative MRI. ‡Clinical seizure confirmed on electroencephalogram.

Looking at the latest follow up, in a multivariable model, peak lactate (adjusted HR = 1.22 per mmol/dL; 95% CI: 1.1, 1.34; P < 0.001) and subsequent surgery (adjusted HR = 4.32; 95% CI: 1.22, 15.3; P = 0.023) are significant independent predictors of poor GOS-E (Table 8).

Univariate and Multivariable Cox Regression Analysis of Poor GOS-E Outcome at latest assessment (median age 36 months)

Variable	Univariate Analysis			Multivariable Analysis		
	HR	95% CI	P value	Adjusted HR	95% CI	P value
Diagnosis						
BV	Reference	.	.	Reference	.	.
SV (not HLHS)	1.79	(0.66, 4.86)	0.255	0.83	(0.23, 2.93)	0.769
HLHS	2.51	(1.14, 5.49)	**0.022***	0.32	(0.08, 1.22)	0.096
Perioperative Stroke	1.42	(0.66, 3.09)	0.373			
DHCA						
No DHCA	Reference	.	.	Reference	.	.
1-39 minutes of DHCA	1.56	(0.58, 4.19)	0.375	2.11	(0.7, 6.35)	0.184
40+ minutes of DHCA	2.51	(1.09, 5.81)	**0.031***	2.62	(0.86, 7.98)	0.089
Peak Lactate†	1.21	(1.11, 1.31)	**<0.001***	1.22	(1.1, 1.34)	**<0.001***
Duration of Ventilation	1.01	(0.99, 1.02)	0.159			
Seizure‡	1.23	(0.59, 2.56)	0.587			
Thrombosis	1.04	(0.48, 2.25)	0.927			
Subsequent Surgery	4.04	(1.41, 11.6)	**0.009***	4.32	(1.22, 15.3)	**0.023***

Table 8 Variables with P<.05 in univariate analysis were included in the multivariable model. HR, Hazard ratio; CI, confidence interval; BV, biventricular; SV, single ventricle; HLHS, hypoplastic left heart syndrome; DHCA, deep hypothermic cardiac arrest. *Statistically significant. †Peak lactate after surgery and before postoperative MRI. ‡Clinical seizure confirmed on electroencephalogram.

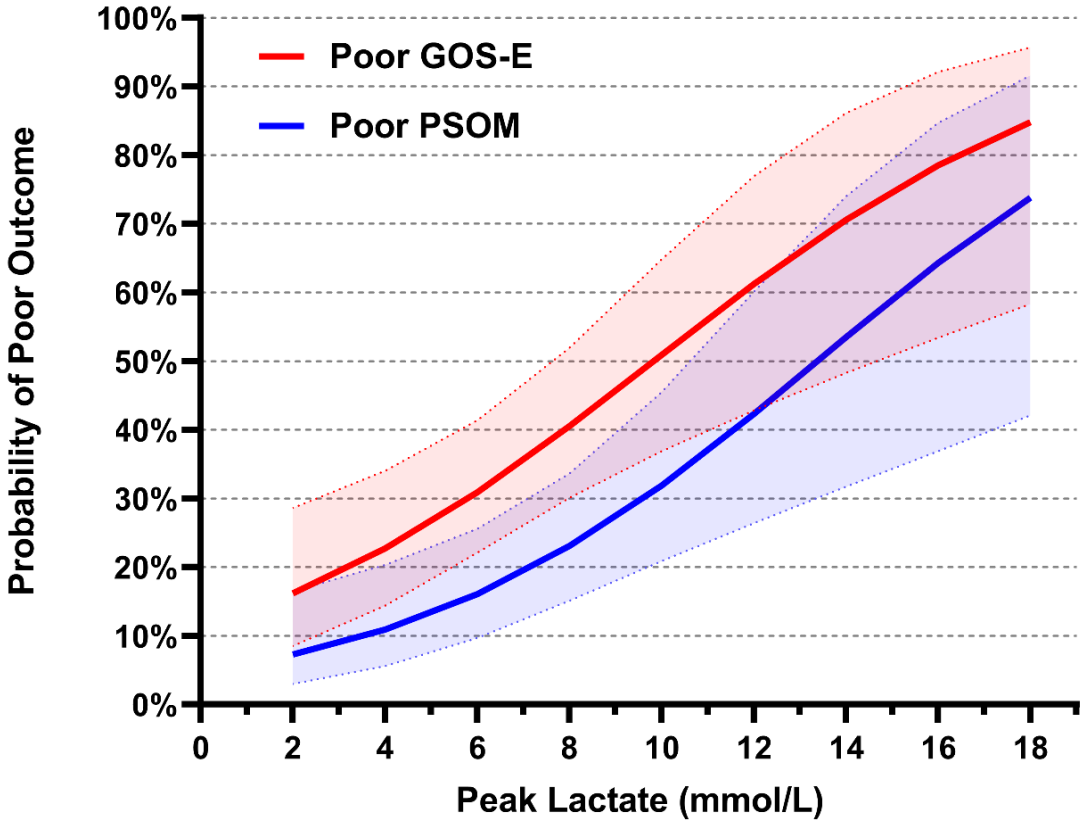
Peak lactate (adjusted HR = 1.17 per mmol/dL; 95% CI: 1.02, 1.34; P = 0.024) was the only significant independent predictor of poor PSOM (Table 9).

Univariate and Multivariable Cox Regression Analysis of poor PSOM outcome at latest assessment (median age 36 months)

Variable	Univariate Analysis			Multivariable Analysis		
	HR	95% CI	P value	Adjusted HR	95% CI	P value
Diagnosis						
BV	Reference	.	.	Reference	.	.
SV (not HLHS)	3.32	(0.91, 12)	0.067	1.5	(0.3, 7.5)	0.622
HLHS	4.07	(1.38, 11.9)	**0.01***	0.91	(0.22, 3.77)	0.892
Perioperative Stroke	2.09	(0.83, 5.26)	0.119			
DHCA						
No DHCA	Reference	.	.		.	.
1-39 minutes of DHCA	1.24	(0.37, 4.2)	0.727			
40+ minutes of DHCA	2.1	(0.74, 5.94)	0.162			
Peak Lactate†	1.21	(1.1, 1.34)	**<0.001***	1.17	(1.02, 1.34)	**0.024***
Duration of Ventilation	1.01	(1.01, 1.03)	**0.021***	1	(0.99, 1.02)	0.646
Seizure‡	2.15	(0.88, 5.23)	0.092			
Thrombosis	2.26	(0.93, 5.46)	0.071			
Subsequent Surgery	5.81	(1.34, 25.2)	**0.019***	3.59	(0.58, 22.2)	0.17

Table 9 Variables with P<.05 in univariate analysis were included in the multivariable model. HR, Hazard ratio; CI, confidence interval; BV, biventricular; SV, single ventricle; HLHS, hypoplastic left heart syndrome; DHCA, deep hypothermic cardiac arrest. *Statistically significant. †Peak lactate after surgery and before postoperative MRI. ‡Clinical seizure confirmed on electroencephalogram.

Peak lactate demonstrated good prognostic accuracy in identifying children with poor outcome assessed by PSOM (AUC = 0.728, 95% CI: 0.618-0.875, P<0.001) and poor outcome assessed by GOS-E (AUC = 0.728, 95% CI: 0.625-0.876; Table 4). Figure 8 shows the probability curves for poor outcome according to peak lactate level based on logistic regression, depicting a steadily increasing risk of poor outcome for both PSOM and GOS-E. Specific probabilities of poor outcome according to peak lactate and corresponding 95% confidence intervals are presented in Table 10.



Predicted Probability of Poor Neurological Outcome based on Peak Lactate

Peak Lactate (mmol/L)	Probability of poor GOS-E	95% CI	Probability of poor PSOM	95% CI
2	16.2%	(8.5%, 28.6%)	7.3%	(3%, 16.5%)
4	22.7%	(14.4%, 34%)	10.9%	(5.6%, 20.3%)
6	30.9%	(22.1%, 41.4%)	16.1%	(9.7%, 25.6%)
8	40.5%	(30.1%, 51.9%)	23.1%	(15.1%, 33.6%)
10	50.9%	(36.9%, 64.8%)	31.9%	(20.9%, 45.5%)
12	61.2%	(42.8%, 76.9%)	42.3%	(26.4%, 60.1%)
14	70.6%	(48.3%, 86.1%)	53.5%	(31.7%, 74%)
16	78.5%	(53.4%, 92.1%)	64.3%	(36.9%, 84.7%)
18	84.8%	(58.3%, 95.7%)	73.8%	(42.1%, 91.6%)

Figure 8 (upper part) / Table 10 (lower part) Predicted probability of poor neurological outcome at latest assessment (median age 36 months) based on peak lactate; PSOM, pediatric stroke outcome measure; GOS-E, Glasgow Outcome scale extended pediatric version; CI, confidential interval.

5 Discussion

To my knowledge, this is the largest single center cohort of patients with cardiac surgery in infancy and with both pre- and postoperative brain MRIs as well as ND follow up.

First Author	Year	n	Age surgery	Main Diagnoses	CPB (%)	DHCA (%)	MRI										
							Preoperative					Postoperative					
							n (%)	any injury		WMI (%)	Stroke (%)	age (days)	n (%)	any injury		WMI (%)	Stroke (%)	comment
								n	(%)					n	(%)			
Mahle	2002	24	<1m	13 SV, 8 HLHS		88	79	7	37	16	8	5 to 12	88	14	67	42	19	postop new injuries; third scan at 3-6 months
McQuillen	2007	62		18 SV	91	23	100		39	18	21		85	19	35	26	9	
Chen	2009	122	<6m		100	62						3 to 14					10	
Andropoulos	2010	68	<30d	36 SV, 35 HLHS	100	50	99	38	57	16	18	7 to 10	82	43	77	15	22	6 had resolution of mild WMI betw. scans; third scan at 3-6 months
Dimitropoulos	2013	120	<3m	71 TGA, 36 SV	?	?	100	49	41	21	19	median 10	87	75	72	38	31	23 (19%) stroke preop, 10 (10%) new postop
Beca	2013	153	<8w	62 SV, 34 Norwood	84	39	96	38	26	20	5	7	88	59	44	42	4	postop new injuries; third scan at 3 months
Andropoulos	2014	59	<30d	28 SV, 20 TGA	100		66	18	46	31	23	0 to 7	66	28	72	36	26	postop new injuries
Classens	2018	34	<4m	all arch obstruction	100	51	100	-	-	47	-	mean 10	-	-	-	79	-	
Peyvandi	2019	104	?	84 TGA, 20 SV	100	?	100	Did not differentiate between pre and post in the manuscript				?	100	56	54	38	26	Total injury rates, did not differentiate between pre and post
Kuhn	2020	53	<1m	29 TGA, 24 HLHS	100	94	100	29	55	22	11	mean 25	100	41	77	35	20	
Kosiorek	2022	42	<10 w	13 SV	57	0	100	21	50	19	17	mean 33	100	28	67	36	14	
Reitz	2023	122	<90d	37 TGA, 42 SV	84	62	100	64	52	23	14	median 25	100	90	74	32	19	

Table 11 Summary of studies in children with infant surgery for Congenital Heart Disease and pre- and postoperative brain MRIs as well as neurodevelopmental outcome assessments

Neurodevelopmental Assessments				**key findings**
scoring	age	percentage	score	
NA				• Established high frequency of asymptomatic ischemic lesions on pre- and postop brain MRI in neonates with surgery for CHD • at third scan resolution of early lesions in 8 and mild cerebral atrophy in 2
NA				• BAS increased the risk for preoperative brain injury • Low mean BP on POD#1 increases the risk for postoperative WMI • Risk for postoperative brain injury was increased in 1) SV with a Norwood and 2) CBP w/ RCP
NA				Inc stroke risk with lower BW, preop intubation, lower intraop HCT, higher SBP on CICU admission
NA				• Risk factors for preop injury was low brain maturity score, for postop WMI: preop injury, low brain maturation & SV; • at third scan 27% incidence of new minor lesions, but 58% of previous lesions partially or completely resolved
NA				• Higher SNAP-PE, lower preop O2 sat, lowest post op BP mean, and BAS (in TGA) predicted higher preoperative BIS. • New postop BIS was assoc. with lower postop systolic & mean BP
Bayley	2 years	?	cognitive 94±15, language 94±16, motor 97±12	• New postop WMI predicted by longer duration of CPB, 6h postop lactate, brain maturity & preop WMI • Brain immaturity, but not brain injury predicted impaired neurodevelopment at 2 years • MRI at three months: WMI resolved at 3 months in 75% percent, no new WMI, stroke, or hemorrhage
Bayley-III	1 year	71%	cognitive 102.1±13.3, language 87.8±12.5, motor 89.6±14.1; initially 93 enrolled	New postop MRI injury, higher VAA exposure and increased ICU LOS each predicted lower cognitive scores
Bayley / Wechsler	2 years / 6 years	86% / 81%	initially 37 patients enrolled	• Mod-severe WMI was assoc. with lower cognitive scores at 2 yrs. and full-scale IQ at 6 years • Grey matter, focal infarctions did not impact outcome (n = 9, 26%) - pre vs. post not distinguished in the manuscript)
Bayley-III	12 month / 30 month	67% / 46%	initially 165 patients enrolled	• At 12 months, only clinical variables associated with outcome. • At 30 months, subjects with moderate-severe WMI had significantly lower psychomotor development index score. • Stroke (total pre- and postoperative) was not associated with outcome at 30 months.
PSOM and GOS-E	10 month	85%	82% of the HLHS patients and 17% of the d-TGA patients had adverse outcome	• BAS no assoc. with inc'd preop injury or stroke • HLHS inc'd risk for postop stroke in mod-severe range • ICU duration inc'd risk for postop injury in mod-severe range
PSOM and GOS-E	28 month	69%	45% had adverse GOS-E outcome	Adverse outcome associated with longer ICU stay, mechanical ventilation, MBT shunt procedure and postop seizures. Total BIS did not predict outcome. Post infarction and/or IPH were associated with worse outcome
PSOM and GOS-E	8 month / 36 month	78% / 83%	adverse outcome: PSOM 7% and GOSE 21% / PSOM 21% GOS-E 35%	• New or expanded ischemic stroke on postop brain MRI is predictive of poor early outcome, mainly defined by poor motor outcomes, did not improve on repeat assessment • Elevated lactate in the postoperative period is a predictor of adverse ND outcome in childhood

The aim of this study was to evaluate brain injury subtypes and timing of the injury as potential clinical biomarkers to signal an elevated risk for poor ND outcome in patients with surgery for CHD during infancy.

The statistical analyses revealed two novel clinical biomarkers for predicting ND outcome in children with surgery for CHD in infancy. First, new ischemic stroke on postoperative MRI increases the risk for early ND disability. Second, elevated lactate peak during the postoperative course is a predictor for poor ND outcome in childhood.

5.1 Perioperative brain injuries and neurodevelopmental outcome

Radiographic evidence of brain injury in infants with CHD is well documented, with multiple studies describing the incidence and subtypes of injury in cohorts with pre- and postoperative MRI (Andropoulos et al., 2010a; Beca et al., 2013; Peyvandi et al., 2018). White matter injury is the subtype studied in the greatest detail in those studies. Some studies have described an association of white matter (WM) lesions on MRI in infancy and cognitive impairment when assessed after 3 years of age (Claessens et al., 2018; Peyvandi et al., 2018) while others have not (Beca et al., 2013). Especially associations between perioperative brain injury and ND outcome are not well understood, in part due to the fact that only a few studies include brain imaging before and after surgery and ND outcome (Beca et al., 2013; Peyvandi et al., 2018). Those were limited to small numbers of patients. In combination with the inherent variability amongst CHD patients as well as slight differences in surgical techniques and levels of experience of different centers this might explain inconsistent findings in studies linking infant brain injury to ND outcomes as well. In addition, within the body of literature, outcomes are measured at a variety of ages, using different tools and thresholds for poor outcome. The timing of the ND assessment appears to be particularly important when considering the impact of specific brain injury subtypes, as earlier assessments have more of an emphasis on motor skills and later assessments on social/emotional and cognitive skills (Peyvandi et al., 2018). Finally, the timing (e.g. perinatal vs perioperative) and location of the brain injury may alter the impact of the brain injury subtypes on outcome (Wernovsky & Licht, 2016).

However, ND disabilities are commonly present in patients with CHD prior to 3 years of age and thus we aimed to explore brain injury subtypes predictive of poor early outcome. While WMI appears to have a deleterious effect on long term outcome, multiple studies have shown no significant impact on early ND outcome assessments (Beca et al., 2013; Peyvandi et al., 2018). Ischemic infarction is also common in this population and yet, less

is known about the impact of stroke on outcome. Similar to other studies (see Table 11), our patients had high rates of ischemic infarction before (11%) and after surgery (total 19%, new 14%).

Hereby, timing of postoperative MRI has to be taken into consideration. In other studies postoperative MRIs were obtained closer to the operative date, and thus medically unstable patients were excluded. An example of this can be seen in the study of Beca et al., 2013. They analyzed in a multicenter study a cohort similar to ours, but their rate of stroke is lower than in this study (stroke preoperative Beca 5%, this study 14%; new postoperative stroke Beca 4%, this study 14%). In their study 12% of the patients (n=18) didn't have a postoperative scan due to ECMO (n=9), no preoperative scan (n=3) or other reasons (n=6). In contrast, in our cohort all patients had postoperative MRI scans. 7 of our patients had ECMO support between pre- and postoperative MRIs, 6 (86%) of those showing moderate or severe brain injury on the postoperative MRI and 3 (43%) new or worse stroke. Consequently, stroke as well as other brain injuries might have been underestimated in other studies with different timings of the MRIs.

Furthermore, this study shows, that perinatally acquired and perioperative acquired strokes on MRI have a completely different impact on ND outcome. In our cohort, all 8 patients with stroke on preoperative MRI and no progression of stroke on postoperative MRI and ND outcome assessments had good ND outcome, including one with a stroke characterized as severe (Figure 5). In contrast, 10 of 16 patients (63%) with new or expanded stroke on the postoperative MRI and ND outcome assessments had adverse ND outcome. These patients accounted for more than half (7/13, 54%) of all the patients with adverse PSOM scores on early assessment. New or expanded stroke was a significant predictor for adverse outcome at early ND assessments (Table 6 and Table 7).

While new or expanded stroke was not a predictor of outcome for the group at large at the latest ND assessment, deficits were persistent. For all 7 children with new or expanded stroke by postoperative MRI and poor early ND outcome, outcome assessment remained poor on the latest assessment (mean interval of repeat testing was 4 years).

The prevalence of a poor outcome increased more broadly when considering the latest ND assessment. Adverse GOS-E/PSOM scores were noted in 22%/14% of early outcomes, while 35%/21% of children had impaired ND outcome at the latest assessment. Sixty-seven children had two ND assessments at least 12 months apart. In 31 (46%), both

PSOM and GOS-E were worse at the second assessment compared to the first. In comparison, only 9%/16% had better PSOM/GOS-E scores at the second assessment. Similarly, Peyvandi et al. also demonstrated a decline in ND assessment in children with CHD and perioperative brain injury when measures were obtained at 12 and 30 months of age (Peyvandi et al., 2018).

The reasoning for this perceived deterioration is inherent to children's development; the testing and skills evolve with age. Early assessments are heavily weighted towards motor skills whereas later assessments have a greater emphasis on cognition and language. Of the five subcategories of PSOM (motor, cognitive, language comprehension, language production, behavior), the highest percentage of limitations in the early assessments was in the motor subcategory. At the latest ND assessment, the rate of impairments in the motor subcategory remained the same (25%), whereas the prevalence of cognitive impairment increased from 7% to 32%.

Interestingly, brain injury was not the only factor predictive of poor outcome. Other clinical variables were also found to be correlated with outcome. Cardiac arrest was an independent predictor of poor early outcome in our multivariable model (Table 6 and 7). This is plausible, since cardiac arrest is known to put children at risk for brain injuries with consecutive adverse ND outcome. Subsequent surgery and postoperative peak lactate were associated with poor outcome when the latest assessment was studied (Table 8 and 9).

5.2 Hyperlactatemia and neurodevelopmental outcome

Lactic acidosis is a clinical measure of metabolic failure and in some cases a surrogate marker for hypoxia and hypoperfusion (Maillet et al., 2003; Minton & Sidebotham, 2017; O'Conor & Fraser, 2012). Lactate is an appealing clinical biomarker due to its common availability, rapid turnaround time and broad application. Also, unlike MR imaging, lactate levels can be obtained frequently and in patients who are clinically unstable. There are numerous articles that describe goal directed therapies based on elevated lactate levels, especially in adult cardiac surgery (Hajjar et al., 2013). In pediatric cardiac surgery, investigations of its association with morbidity and mortality have produced inconsistent results. Hatherill et al. found no correlation between peak lactate and mortality (Hatherill et al., 1997) whereas Siegel et al. found the opposite (Siegel et al., 1996). Charpie et al. described a correlation between peak lactate and early outcome after pediatric cardiac surgery (Charpie et al., 2000). One possible explanation for these

incongruent results might be that most studies relied only on a single lactate measurement early after arrival on the ICU, whereas recent studies showed in patients with cardiogenic shock, that lactate after eight hours is superior in mortality prediction in comparison with baseline lactate and lactate clearance (Fuernau et al., 2020). Focusing on the impact of lactate on ND outcome, there is only one study investigating the predictive value of cerebral Tissue Oxygenation Index (cTOI) on ND outcome, that includes lactate as additional marker. Lactate values were gathered prospectively at different timepoints up to 24 hours postoperative (Aly et al., 2017). Adding 24 hour lactate values to the cTOI model improved predictive accuracy on ND outcome at assessments up to 21 months of age. In addition, Beca et al. were able to show higher serum lactate 6h after surgery was a significant independent predictor for new WMI in postoperative MRIs (Beca et al., 2013).

In our cohort, we captured all lactate values from an arterial source during the postoperative ICU course. For most patients, lactate was mildly elevated immediately after surgery and declined within hours. In patients with complicated postoperative course, a second lactate peak could be observed. We found elevated lactate (peak value) during the postoperative course was a strong predictor for adverse latest ND outcome in our multivariable model. A probability model of poor ND outcome based on lactate values is presented in Figure 8. The higher the peak lactate value, the greater the expected risk of poor ND outcomes.

While the association needs to be explored further, it seems reasonable to consider modifying therapies in real time when lactate values are climbing in order to reduce the risk of exposure to hypoperfusion and hypoxia. Furthermore, identifying lactate elevations early may have downstream effects on clinical variables consistently identified to impact ND outcome such as length of ICU stay and duration of mechanical ventilation (Andropoulos et al., 2014; Kuhn et al., 2020).

5.3 Study limitations

This study has several limitations. The cohort includes a mixture of patients with different CHD subtypes and due to small sample sizes, it was not feasible in this study to look within each subtype to assess patterns of vulnerability regarding poor ND outcomes during follow up. Studies with larger sample sizes in each subcategory of CHD are required.

This study is a retrospective study including only patients with pre- and postoperative MRIs. As a result, especially very sick neonates might have been excluded because they were not stable enough for MRIs or died before a postoperative MRI could be obtained. In addition, over the study period of 10 years, the MRI sequences used as part of clinical care as well as their quality might have developed, resulting in inconsistencies of the sensitivity and specificity for brain injuries on the MRI scans over the study period.

In order to focus on perioperative factors for adverse ND outcome in childhood, we excluded premature newborns as well as ones with syndromes or genetic abnormalities know to impact ND outcome. Therefore, our results might not be applicable to all CHD patients with surgery in infancy.

In this study we had a follow up rate of 80%. This is well within the range of comparable studies (Table 10). Still, the absence of ND follow up in 17% of our cohort as well as the wide range of ages at follow up can impact outcome analysis. We used Cox regression analysis to address the varying ages at follow up in the statistical analysis but acknowledge, that a prospective longitudinal study design with predetermined assessment intervals would allow for a more precise temporal analysis.

Due to the retrospective design, we were not able to use the Bayley Score of Infant Development, a more substantive tool than the PSOM and GOS-E scores used in this study. In addition, SES is not included in our analysis even though it is known to have an impact on developmental outcome in children. Still, we believe we have compensated for the limitations of the retrospective assessments by using both GOS-E and PSOM as complementary scores with one emphasizing functional outcome and the latter focusing on neurological assessments.

5.4 Conclusion

New or expanded ischemic stroke on postoperative MRI is predictive of poor early outcome in patients with CHD surgery in infancy. Stroke deficits were primarily defined by motor impairments and did not improve on repeat clinical assessments. Therefore, children with new stroke after infant heart surgery are at risk for adverse neurodevelopmental outcome early in childhood and may benefit from screening for neurodevelopmental disability between 5 and 24 months of age.

High peak lactate levels in the postoperative period are a predictor of adverse ND outcome in childhood. They might be a useful clinical biomarker to identify patients at risk for ischemic brain injury with an impact on ND outcome. In children with rising lactate values, therapeutic options should be discussed for improving perfusion and oxygenation.

Further studies are needed to explore the potential utility of lactate as a predictive biomarker for poor ND outcome and opportunities for intervention.

6 Summary

Background: Brain injury is commonly seen on magnetic resonance imaging in infants with complex congenital heart disease. The impact of perioperative brain injury on neurodevelopmental outcomes is not well understood. This study evaluates the association of brain injury and other markers on neurodevelopmental outcomes in patients undergoing surgery for congenital heart disease during infancy.

Methods: Term newborns with cardiac surgery performed between 2008 and 2019 at a single tertiary center were identified from a clinical database. Patients who underwent both pre- and postoperative brain magnetic resonance imaging were included. Those with underlying genetic conditions were excluded. Brain injury was characterized using an MRI scoring system described by Andropoulos et al. Neurodevelopmental outcomes were assigned using the Pediatric Stroke Outcome Measure (PSOM) and Glasgow Outcome Scale Extended Pediatric Version (GOS-E). Independent risk factors for poor neurodevelopmental outcomes were determined by multivariable Cox regression.

Results: A total of 122 patients were included in this study (n=42 with single ventricle physiology). Surgery was performed using CPB in 103 (84%) patients. New or progressive brain injury was noted on postoperative MRI in 69 patients (57%). A total of 101 patients (83%) had at least one neurodevelopmental assessment (median age 36, interquartile range 19-54 months) with an early neurodevelopmental assessment (5 - 24 months) performed in 95 children. Multivariable Cox regression analysis of early neurodevelopmental outcomes identified new stroke on postoperative MRI as an independent predictor of poor neurodevelopmental outcome. Postoperative peak lactate was an independent predictor of poor outcome assessed by PSOM and GOS-E at the most recent neurodevelopmental follow up.

Conclusion: This study reveals that evidence of new stroke on MRI after congenital heart surgery is a predictor of poor neurodevelopmental outcomes in early childhood. Postoperative lactic acidosis is associated with poor neurodevelopmental outcome and may be a surrogate biomarker for ischemic brain injury.

7 Zusammenfassung

Hintergrund: Bei Kindern mit schwerer angeborener Herzerkrankung werden in MRT-Untersuchungen häufig Gehirnschädigungen festgestellt. Der Einfluss von perioperativ erworbenen Gehirnschädigungen auf die neurologische Entwicklung dieser Kinder ist jedoch noch nicht hinreichend verstanden. Diese Arbeit untersucht daher die Zusammenhänge zwischen Gehirnschädigungen und anderen klinischen Parametern auf die neurologische Entwicklung bei Säuglingen mit herzchirurgischen Operationen.

Methodik: Neugeborene mit herzchirurgischen Eingriffen innerhalb der ersten 90 Lebenstage am Children's National Hospital in Washington, DC zwischen 2008 und 2019 wurden anhand einer herzchirurgischen Datenbank erfasst. Patienten mit prä- und postoperativen Gehirn-MRT-Untersuchungen wurden in die Studie eingeschlossen. Frühgeborene oder Säuglinge mit syndromalen Erkrankungen wurden ausgeschlossen. Die Gehirnschädigungen wurden anhand eines von Andropoulos et al. beschriebenen Bewertungsschemas klassifiziert. Die neurologische Entwicklung wurde mittels des Pediatric Stroke Outcome Measure (PSOM) und der Glasgow Outcome Scale Extended Pediatric Version (GOS-E) beurteilt. Unabhängige Risikofaktoren für Einschränkungen in der Entwicklung wurden mittels multivariater Cox-Regressionsanalyse ermittelt.

Ergebnisse: 122 Patienten wurden in die Studie eingeschlossen, davon 42 mit univentrikulärem Herzen. Die Operation erfolgte bei 103 (84%) unter Verwendung einer Herz-Lungen-Maschine. Bei 69 Patienten (57%) zeigte sich postoperativ im MRT eine neue oder größere Gehirnschädigung. Neurologische Folgeuntersuchungen erfolgten bei 101 Patienten (83%, Altersmedian 36 Monate, Interquartilstreuung 19-54 Monate). 95 Kinder (78%) hatten eine neurologische Folgeuntersuchung zwischen 5 und 24 Monaten Lebensalter. Die multivariable Analyse im frühen Folgeuntersuchungszeitraum zeigte postoperativ neue Schlaganfälle in der MRT-Bildgebung als unabhängigen Prädiktor für Einschränkungen der Entwicklung auf. Bei Verwendung der jeweils am kürzesten zurückliegenden Folgeuntersuchung zeigten sich in der multivariablen Analyse hohe Laktat-Spitzenwerte im postoperativen Verlauf als ein unabhängiger Prädiktor für Einschränkungen der Entwicklung.

Schlussfolgerung: Diese Studie zeigt, dass ein postoperativ neuer Schlaganfall in der MRT-Bildgebung ein Prädiktor für neurologische Einschränkungen im frühen Kindesalter ist. Postoperative Laktat-Spitzenwerte korrelieren ebenfalls mit Entwicklungseinschränkungen.

8 Glossary of abbreviations

ACA	anterior cerebral artery
ASD	atrial septal defect
AUC	area under curve
BAS	balloon atrial septostomy
Bayley	Bayley Scales of Infant Development
BT-Shunt	Blalock-Taussig shunt
BV	biventricular
BW	birth weight
CHD	Congenital Heart Disease
CI	confidence interval
CoA	Coarctation of Aorta
CPB	cardiopulmonary bypass
cTOI	cerebral Tissue Oxygenation Index
DBP	diastolic blood pressure
DHCA	deep hypothermic cardiac arrest
DORV	Double Outlet Right Ventricle
DVST	dural sinus venous thrombosis
e.g.	example given
ECMO	Extra-corporal Membrane Oxygenation
EEG	electroencephalography
Fig.	Figure
GA	gestational age
GOS-E	Glasgow Outcome Scale Extended Pediatric Version
G-tube	gastrointestinal tube
HC	head circumference
HLHS	Hypoplastic Left Heart Syndrome
HR	hazard ratio
i.e.	in example
IAA	Interrupted Aortic Arch
ICU	intensive care unit
iNO	inhalative nitric oxygen
IPH	intraparenchymal hemorrhage
IQ	intelligence quotient

IQR	interquartile range
IVH	intraventricular hemorrhage
Lac/Cr	lactate-to-creatine ratio
MCA	middle cerebral artery
MR	magnetic resonance
MRI	magnet resonance imaging
MRS	magnetic resonance spectroscopy
ND	neurodevelopmental
OD	oligodentrocytes
OR	odds ratio
PA	Pulmonary Atresia
PCA	posterior cerebral artery
PDA	patent Ductus Arteriosus
PGE	prostaglandin
PL	punctate lesions
PS	pulmonary stenosis
PSOM	Pediatric Stroke Outcome Measure
SBP	systolic blood pressure
SD	standard deviation
SDH	subdural hematoma
SES	socioeconomic status
SIRS	systemic inflammatory response syndrome
SNAP-PE	scores for neonatal acute physiology with perinatal extension
SV	single ventricular
TA	Tricuspid Atresia
TrA	Truncus Arteriosus
Tab.	Table
TAPVR	Total Anomalous Pulmonary Venous Return
TBIS	total brain injury score
TGA	Transposition of the Great Arteries
ToF	Tetralogy of Fallot
VSD	Ventricular Septal Defect
Wechsler	Wechsler Adult Intelligence Scale
WMI	white matter injury

9 List of tables

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11 References

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12 Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nichtveröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten sowie ethische, datenschutzrechtliche und tierschutzrechtliche Grundsätze befolgt. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt und indirekt an der Entstehung der vorliegenden Arbeit beteiligt waren. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.

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Ort, Datum Unterschrift

13 Publication list

13.1 Congress contributions

13.1.1 Poster presentations

- 30. Kongress der Deutschen Gesellschaft für Perinatale Medizin, November 2021, Berlin
  "Two-dimensional Speckle Tracking Echocardiography in fetuses with critical aortic stenosis before and after intrauterine aortic valvuloplasty"
- 20th World Congress in Fetal Medicine, June 2022, Crete/ Greece
  "2D Speckle Tracking Echocardiography in fetuses with critical aortic stenosis before and after intrauterine aortic valvuloplasty"
- 8th World Congress of Pediatric Cardiology and Cardiac Surgery, August 2023, Washington, DC
  "Brain injury and neurodevelopmental outcomes in children undergoing surgery for congenital heart disease"

13.1.2 Oral presentations

- 7. Gießener Symposium Pränatale Medizin & Fetale Therapie, February 2020, Frankfurt
  "Brain injury scores and neurodevelopment of children with complex congenital heart disease"
- Versammlung Arbeitskreis Fetale Echokardiographie, October 2021, online
  „2D Speckle Tracking bei Feten mit intrauteriner Aortenvalvuloplastie"
- 31st World Congress on Ultrasound in Obstetrics and Gynecology, October 2021, online
  "2D Speckle Tracking in fetuses with fetal aortic valvuloplasty"
- 8. Gießener Symposium Pränatale Medizin & Fetale Therapie, March 2022, Marburg
  „2D Speckle Tracking bei Feten mit intrauteriner Aortenvalvuloplastie"
- 9. Gießener Symposium Pränatale Medizin & Fetale Therapie, March 2023, Gießen
  "2D Speckle Tracking Echocardiography in fetuses with critical aortic stenosis before and after intrauterine aortic valvuloplasty"

13.2 Publications

13.2.1 First author

Reitz, J. G., Zurakowski, D., Kuhn, V. A., Murnick, J., Donofrio, M. T., d'Udekem, Y., … Carpenter, J. L. (2023). Brain Injury and Neurodevelopmental Outcomes in Children Undergoing Surgery for Congenital Heart Disease. JTCVS Open, 0(0). https://doi.org/10.1016/J.XJON.2023.11.018

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13.2.2 Co-author

Mamalis M, Bedei I, Schoennagel B, Kording F, Reitz JG, Wolter A, Schenk J, Axt-Fliedner R. The Evolution and Developing Importance of Fetal Magnetic Resonance Imaging in the Diagnosis of Congenital Cardiac Anomalies: A Systematic Review. J Clin Med. 2022 Nov 28;11(23):7027. doi: 10.3390/jcm11237027. PMID: 36498602; PMCID: PMC9738414.

Harrar DB, Goss M, Donofrio MT, Murnick J, Reitz JG, Zhang A, Diab Y, Meldau J, Sinha P, Yerebakan C, Carpenter JL. Cerebral Sinus Venous Thrombosis in Infants after Surgery for Congenital Heart Disease. J Pediatr. 2022 Sep;248:59-65.e3. doi: 10.1016/j.jpeds.2022.05.056. Epub 2022 Jun 3. PMID: 35667448.

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