Brain Injury in Infants with Critical Congenital Heart Disease: Insights from Two Clinical Cohorts with Different Practice Approaches

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Objectives To determine prevalence and risk factors for brain injury in infants with critical congenital heart disease (CHD) from 2 sites with different practice approaches who were scanned clinically.

Study design Prospective, longitudinal cohort study (2016-2017) performed at Hospital for Sick Children Toronto (HSC) and Wilhelmina Children's Hospital Utrecht (WKZ), including 124 infants with cardiac surgery ≤60 days (HSC = 77; WKZ = 47). Magnetic resonance imaging was performed per clinical protocol, preoperatively (n = 100) and postoperatively (n = 120). Images were reviewed for multifocal (watershed, white matter injury) and focal ischemic injury (stroke, single white matter lesion).

Results The prevalence of ischemic injury was 69% at HSC and 60% at WKZ ($P = .20$). Preoperative multifocal injury was associated with low cardiac output syndrome (OR, 4.6), which was equally present at HSC and WKZ (20% vs 28%; $P = .38$). Compared with WKZ, HSC had a higher prevalence of balloon-atrioseptostomy in transposition of the great arteries (83% vs 53%; $P = .01$) and more frequent preoperative focal injury (27% vs 6%; $P = .06$). Postoperatively, 30% of new multifocal injury could be attributed to postoperative low cardiac output syndrome, which was equally present at HSC and WKZ (38% vs 28%; $P = .33$). Postoperative focal injury was associated with intraoperative selective cerebral perfusion in CHD with arch obstruction at both sites (OR, 2.7). Compared with HSC, WKZ had more arch obstructions (62% vs 35%; $P < .01$) and a higher prevalence of new focal injury (36% vs 16%; $P = .01$).

Conclusions Brain injury is common in clinical cohorts of infants with critical CHD and related to practice approaches. This study confirms that the high prevalence of brain injury in critical CHD is a clinical concern and does not simply reflect the inclusion criteria of published research studies. *(J Pediatr 2019;215:75-82)*.

Neurologic deficits are among the most common extracardiac morbidities in survivors of early life cardiac surgery for critical congenital heart disease (CHD).[1] Over the last decade, magnetic resonance imaging (MRI) studies of young infants with CHD have provided important insights into the nature and risk factors of acquired brain injury. Infants undergoing cardiac surgery with the use of cardiopulmonary bypass are consistently at greatest risk.[2] We recently showed that brain injury acquired during the first weeks of life, and especially white matter injury, is associated with worse neurodevelopment through school age.[3,4]

Although there is a growing understanding of the spectrum of brain abnormalities in infants with critical CHD, the extent of the problem remains uncertain because of inconsistency in the reported prevalence and differing classification of brain injury across studies.[5] It is unclear whether variability in the reported incidence of brain injury simply reflects disparities in enrollment criteria and MRI protocols for research studies. Alternatively, the variability in the presence of brain injury may reflect important differences in practice approaches across centers. For example, approaches to transition after birth, postnatal nursing, intensive care management and surgical procedures might influence the occurrence of acquired brain injury.[6]

To improve care for young infants with critical CHD and investigate preventive and therapeutic options, consistent clinical information on incidence and risk factors of brain injury is highly important. Previous studies investigating

3D	3-dimensional	SCP	Selective cerebral perfusion
AO	Arch obstruction	SV-AO	Single ventricle physiology with arch obstruction
CHD	Congenital heart disease		
FOV	Field of view	TE	Echo time
HI-WS	Hypoxic-ischemic watershed injury	TGA	Transposition of the great arteries
HSC	The Hospital for Sick Children Toronto	TR	Repetition time
		WKZ	Wilhelmina Children's Hospital Utrecht
LCOS	Low cardiac output syndrome		
MRI	Magnetic resonance imaging		

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brain injury in critical CHD included infants by specific research enrollment criteria and from sites with comparable practice approaches. The aim of our study was to investigate the prevalence of and risk factors for acquired brain injury in a contemporary clinical cohort of infants with critical CHD from 2 sites with different practice approaches to transition after birth, intensive care management, and cardiac surgery. At both sites, infants were scanned clinically and not for research purposes, thereby decreasing the risk of selection bias, providing a more robust and clinically relevant estimate of the incidence of brain injury in this high-risk population.

Methods

This was a prospective, observational cohort study including infants with critical CHD who underwent open heart surgery between January 2016 and December 2017 with the use of cardiopulmonary bypass at ≤60 days of life at The Hospital for Sick Children Toronto (HSC) or Wilhelmina Children's Hospital Utrecht (WKZ). In both centers, MRI of the brain was performed per clinical protocol, preoperatively and postoperatively. A total of 124 infants were enrolled after exclusion of infants with a gestational age of <36 weeks (n = 1), fetal intervention (n = 3), or confirmed genetic disorder or major additional congenital anomaly (n = 12). Cardiac defects included single ventricle physiology with arch obstruction (SV-AO; n = 33), transposition of the great arteries (TGA) with intact ventricular septum (n = 45), TGA with ventricular septal defect (n = 23), TGA with arch obstruction (AO; n = 9), and other biventricular physiology with arch obstruction (AO; n = 14). Ten infants (HSC = 2; WKZ = 8) had cardiac surgery at ≤60 days and MRI of the brain, but were excluded because their cardiac defect was present in <5 infants in the total population, such as Ebstein anomaly, total anomalous pulmonary venous connection, and truncus arteriosus. At both sites, parental informed consent was obtained for the use of clinically obtained data for research purposes.

Preoperative MRI was undertaken in 100 infants (24 missing; 12 had surgery on the first or second day of life, 4 postnatal diagnosis with immediate surgery, 8 hemodynamic instability). Postoperative MRI was performed in 120 infants (4 died ≤14 days after surgery without MRI). In HSC, all subjects were scanned in an Avanto 1.5T Magnetic Resonance (MR) system (Siemens, Erlangen, Germany). The infants were fed and swaddled before imaging and scanned without sedation using a 16-channel Siemens Paediatric Head Coil. Infants were not scanned when on mechanical ventilation. HSC scanning protocol included: volumetric 3D T1-weighted imaging (echo time [TE]/repetition time [TR] of 3/1920 ms, field of view [FOV] of 200 × 200 × 200 mm, matrix size of 256 × 256 mm, slice thickness of 0.8 mm), axial T2-weighted imaging (TE/TR of 210/9970 ms, FOV of 140 × 140 × 114 mm, matrix size of 218 × 320 mm, slice thickness of 4 mm), axial diffusion weighted imaging (b-value = 800, TE/TR of 97/11 000 ms, FOV of 213 × 213 × 213 mm, matrix size of 192 × 192 mm, slice thickness of 4 mm), axial susceptibility-weighted imaging (TE/TR of 40/50 ms, FOV of 200 × 200 × 119 mm, matrix size of 213 × 448 mm, slice thickness of 2 mm). A 3D MR venography was only performed when indicated by the supervising neuroradiologist. In WKZ, all subjects were scanned in a 3.0T MR system (Philips Medical Systems, Best, the Netherlands). Infants were fed, swaddled in a vacuum cushion, and, if necessary, sedated with oral chloral hydrate (50-60 mg/kg) and scanned using a 32-channel Philips SENSE Head Coil. Infants who required mechanical ventilation at the time of MRI also underwent MRI and received continuous sedation (10% of cohort). WKZ scanning protocol included volumetric 3D T1-weighted imaging (TE/TR of 4.7/9.7 ms, FOV of 200 × 200 × 132 mm, matrix size 256 × 220 mm, slice thickness of 1.2 mm), coronal T2-weighted imaging (TE/TR of 150/4851 ms, FOV of 180 × 180 × 132 mm, matrix size of 232 × 202 mm, slice thickness of 1.2 mm), axial diffusion-weighted imaging (b-value = 1000, TE/TR of 66/6500 ms, FOV of 160 × 182 × 132 mm, matrix size of 144 × 138 mm, slice thickness of 2 mm), axial susceptibility-weighted imaging (TE/TR = 30/53 ms, FOV of 160 × 144 × 90, matrix size of 320 × 289 mm, slice thickness of 2 mm). A 3D MR venography (TE/TR of 7.3/20 ms, phase contrast velocity = 5-10 cm/s) was performed in all infants.

All MR images of both sites were scored by ≥2 independent researchers with ≥1 researcher from each site who were blinded to the clinical course and ischemic brain injury, hemorrhagic brain injury, and cerebral sinovenous thrombosis. Ischemic brain injury included (**Figure 1**): hypoxic-ischemic watershed injury (HI-WS), white matter injury with multiple lesions (white matter injury with multiple lesions, classified as mild [≤3 lesions, all ≤2 mm], moderate [4-6 lesions ≤2 mm or 2 lesions >2 mm], severe [>6 lesions or >2 lesions >2 mm or 5% hemisphere involved]), single white matter lesion (>2 mm), and stroke (specific arterial distribution, involving cortical grey matter and/or basal ganglia-thalamus). Multifocal injury was classified as moderate to severe white matter injury with multiple lesions or HI-WS; focal injury was classified as single white matter lesion or stroke. Hemorrhagic brain injury included cerebellar hemorrhage, subdural hemorrhage, intraventricular hemorrhage (grade 1, restricted to germinal matrix or choroid plexus; grade 2, extension into ventricles, with normal sized ventricles; grade 3, extension into dilated ventricles; grade 4, associated intraparenchymal hemorrhage; based on the intraventricular hemorrhage score for preterm infants by Papile et al[7]). Hemorrhages were classified as parenchymal (cerebellar hemorrhage, grade 4 intraventricular hemorrhage) and extraparenchymal (subdural hemorrhage, grades 1-3 intraventricular hemorrhage). Susceptibility-weighted images were used to score hemorrhagic injury. Cerebral sinovenous thrombosis was defined as ultrasound-proven and/or MR venography-proven with T1 correlation. Brain maturity was evaluated using a total maturation scoring system modified by Licht et al.[8,9]

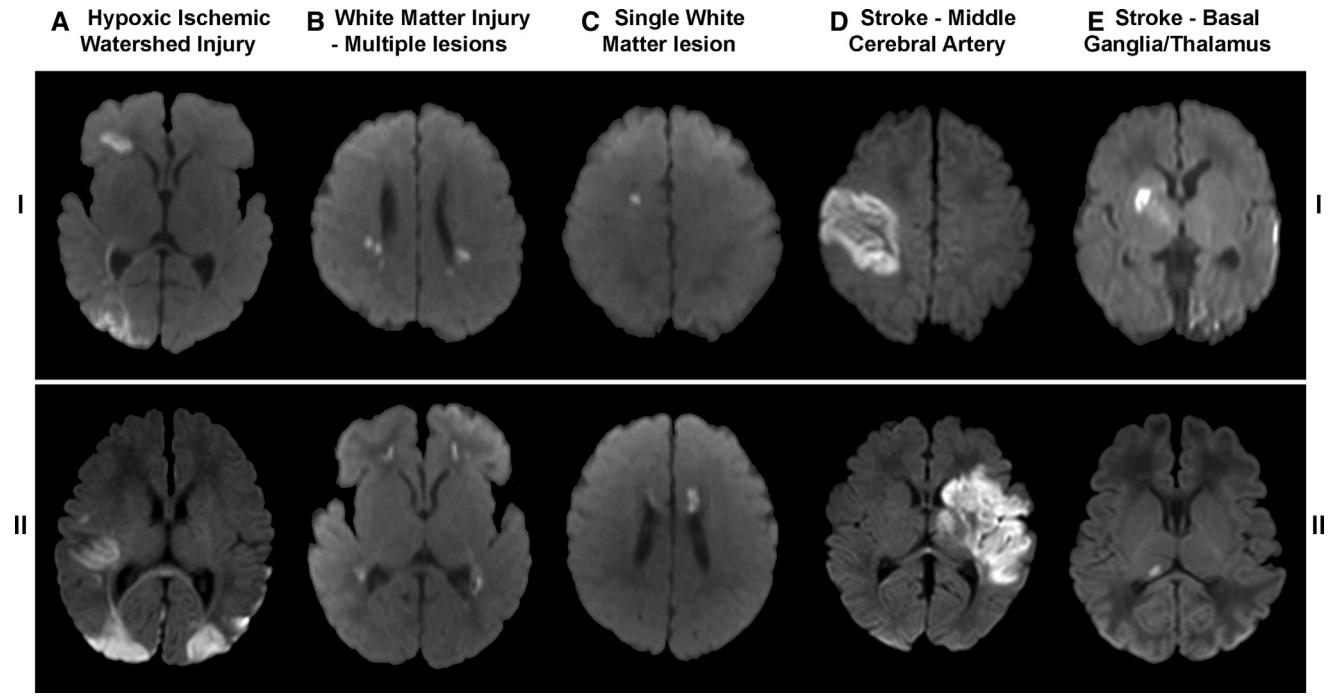

Figure 1. Axial diffusion weighted images different types of ischemic brain injury. HI-WS was characterized by diffuse ischemia in (multiple) border zones between tissues supplied by the anterior, middle, and posterior cerebral arteries. **A-I,** Diffusion restriction in both frontal (middle-anterior artery) and occipital (middle-posterior artery) border region of the right hemisphere. **A-II,** Bilateral watershed injury in multiple border regions of the middle and posterior artery. Moderate-severe multifocal white matter injury (white matter injury with multiple lesions) was characterized by multiple punctate lesions in the white matter (>3 lesions, or ≥2 lesions >2 mm). **B-I,** Multiple, bilateral white matter lesions in the periventricular white matter. **B-II,** Multiple white matter lesions in the periventricular and frontal white matter. Single white matter lesions (single white matter lesion, >2 mm) were classified separately from white matter injury with multiple lesions. **C-I,** Single white matter lesion in centrum semiovale. **C-II,** Single lesion in the frontal white matter with involvement of the corpus callosum. Stroke was defined as ischemic injury after a specific arterial distribution involving the cortical grey matter and/or basal ganglia. **D-I,** Right middle cerebral artery stroke involving both cortical grey matter and white matter, at the level of the centrum semiovale. **D-II,** Left middle cerebral artery stroke (both anterior and posterior branch) involving the cortical grey matter, white matter, and basal ganglia. **E-I,** Stroke in the right lentiform nucleus and thalamus. **E-II,** Stroke in the right thalamus.

Clinical variables were predominantly not normally distributed, therefore nonparametric tests were performed and medians (25th/75th percentiles) were presented for continuous data. Counts (percentage) were presented for categorical data. Missing postoperative MRI data (n = 4) were not missing at random, and therefore were imputed (R, mice package 3.1.0; The R Foundation, Vienna, Austria). The prevalence of preoperative and postoperative brain injury were calculated, and were presented with Poisson 95% CIs. To test the differences in clinical variables between the 2 sites, the Mann-Whitney *U* test was performed for continuous variables and Fisher exact test for discontinuous variables. Multivariable logistic regression models were built for preoperative and new postoperative multifocal and focal brain injuries. Model selection was performed using a best subset model selection approach (R, leaps package 3.0), with site forced into the final model. Tested clinical variables were selected based on the previous literature (and were defined taking into account available recordings at each site), including preoperatively site, CHD category, prenatal diagnosis, cesarean delivery, Apgar score, delivery mode, gestational age, birth weight z-score (according to Dutch reference standards, as the Canadian and Dutch population show similar birth weight curves), balloon atrioseptostomy, preoperative low cardiac output syndrome (LCOS, defined as lactate >4 with pH <7.30, at any time between birth and preoperative MRI), preoperative intensive care time (%), and brain maturity score.[10,11] Postoperatively collected clinical variables were postmenstrual age at surgery, age in days at surgery, duration cardiopulmonary bypass, duration surgery, selective cerebral perfusion (SCP; all antegrade, right side), delayed sternal closure, postoperative infection (culture proven), postoperative arrhythmias (electrocardiogram proven arrhythmias requiring treatment), repeat thoracotomy, postoperative LCOS (defined as lactate >4 with pH <7.30), preoperative brain injury, and brain maturity score. The predicted probability with 95% CI of cumulative and new postoperative ischemic injury was calculated for age at surgery (cohort divided into 9 categories) and presented as graph

(smoothened 4 neighbors to average). A P value of $< .05$ was considered significant. For statistical analysis, R 1.1.423 was used.

Results

A total of 124 infants were enrolled (HSC = 77; WKZ = 47; **Table I**). Cardiac procedures performed are provided in **Appendix 1** (available at www.jpeds.com). The prevalence of ischemic brain injury was 65% (95% CI, 57%-74%), 60% at WKZ and 69% at HSC (**Table II**). Brain injury prevalence by heart lesion is presented in **Appendix 2** (available at www.jpeds.com). The clinical pattern of single white matter lesion was more comparable with stroke than with white matter injury with multiple lesions (**Table III**; available at www.jpeds.com). Based on this analysis, moderate to severe white matter injury with multiple lesions and HI-WS were considered multifocal injury, and single white matter lesions and stroke were considered focal injury for further analysis.

Preoperatively, a higher prevalence of focal ischemic injury was seen at HSC than WKZ (24 vs 10%; $P = .05$) with a comparable prevalence of multifocal ischemic injury. Postoperatively, a higher prevalence of new focal ischemic injury was seen at WKZ compared with HSC (36% vs 16%; $P = .01$) with comparable prevalence of new multifocal injury (**Table II**).

Preoperative multifocal injury was associated with preoperative LCOS (OR, 4.6; **Table IV** [available at www.jpeds.com]). Preoperative LCOS was equally present at HSC and WKZ (20% vs 28%, respectively) and more common in infants with postnatal CHD diagnosis (47% had LCOS; $P = .001$). Compared with WKZ, HSC had a higher prevalence of postnatal CHD diagnosis, also within the TGA population (52 vs 26%; $P = .05$). Postnatal diagnosis was not independently associated with preoperative multifocal ischemic injury at both sites ($P = .74$).

Compared with WKZ, HSC had a higher prevalence of balloon atrioseptostomy in the TGA population: 83% at HSC (95% CI, 73-93) and 53% at WKZ (95% CI, 28-77; $P = .01$). In infants with TGA, preoperative focal injury was nonsignificantly more common at HSC than at WKZ (27% vs 6%, respectively; $P = .06$; **Figure 2**). Balloon atrioseptostomy was the single variable selected as a predictor of focal injury in best subset selection analysis (OR, 3.2; **Table IV**). In regard to age at surgery, infants with TGA without balloon atrioseptostomy showed less multifocal brain injury when operated in the first week of life: none of the 7 infants without balloon atrioseptostomy and surgery at ≤7 days of life had multifocal injury; however, in 8 infants without balloon atrioseptostomy and surgery at 8-14 days of life, 4 (50%) had multifocal injury ($P = .06$).

HSC had a higher prevalence of elective cesarean and WKZ had higher prevalence of induced vaginal delivery (**Table I**). At both sites, mode of delivery was not associated with the CHD group ($P > .10$). Comparing infants with induced vaginal delivery or elective cesarean delivery (n = 39), preoperative multifocal injury was present in 23% and 12%, respectively ($P = .37$), and the prevalence of multifocal injury was nonsignificantly higher at WKZ than HSC (24% vs 14%; $P = .35$).

In addition, SV-AO was an independent risk factor for preoperative multifocal ischemic injury in multivariable analysis (OR, 3.5, **Table IV**). Within the SV-AO population (n = 33), the prevalence of preoperative multifocal injury was 25% at HSC and 29% at WKZ ($P = .60$), and of focal injury 17% and 14%, respectively ($P = .64$).

Postoperative LCOS was the main risk factor for new multifocal injury at both sites, and 30% of new postoperative multifocal brain injury could be attributed to postoperative LCOS (OR, 2.7; **Table IV**). Postoperative LCOS was equally present at HSC and WKZ (38% vs 28%; all onset within 12 hours after surgery); however, it was associated with delayed sternal closure and repeat thoracotomy at WKZ ($P < .01$), and postoperative arrhythmias at HSC ($P = .02$). Infants with SV-AO had a higher occurrence of postoperative LCOS than other CHD groups at both HSC and WKZ (71% and 69%, respectively; $P < .001$). At HSC,

Table I. Clinical characteristics and practice approaches by site

Postnatal characteristics	HSC (n = 77)	WKZ (n = 47)	*P* value
Male sex	61 (79)	31 (66)	.14
Gestational age, weeks	39.1 (38.1/39.9)	39.4 (38.7/40.4)	.14
Prenatal diagnosis	44 (57)	37 (79)	.02
Heart defect			
TGA-IVS	33 (43)	12 (26)	<.001
TGA-VSD	17 (22)	6 (13)	
TGA-AO	8 (10)	1 (2)	
BV-AO	2 (3)	12 (26)	
SV-AO	17 (22)	16 (34)	
Preoperative factors			
Balloon atrioseptostomy	50 (65)	14 (30)	<.001
Mode of delivery			
Spontaneous vaginal	40 (52)	20 (43)	.01
Induction vaginal	11 (14)	16 (34)	
Elective cesarean	18 (23)	3 (6)	
Secondary cesarean	8 (10)	8 (17)	
ECMO	5 (7)	0 (0)	.09
Preoperative LCOS	15 (20)	13 (28)	.38
Preoperative MRI age, days	4 (2-5)	5 (3-7)	.01
Intensive care time, %	57 (20/100)	83 (39/100)	.61
Perioperative factors			
Age at surgery, days			
≤7	32 (42)	16 (34)	.02
8-14	23 (30)	24 (51)	
15-30	11 (14)	6 (13)	
31-60	11 (14)	1 (2)	
SCP	22 (29)	21 (45)	.05
Delayed sternal closure	41 (53)	20 (43)	.17
ECMO, immediate	5 (7)	3 (6)	.65
Postoperative LCOS	29 (38)	13 (28)	.33
Postoperative arrythmias	34 (44)	15 (32)	.12
Postoperative MRI age, days after surgery	12 (7-18)	7 (7-10)	.03
Intensive care time, days after surgery	7 (3/14)	7 (4/12)	.88

ECMO, extracorporeal membrane oxygenation; *IVS*, intact ventricular septum; *VSD*, ventricular septal defect.
Data are median (25th/75th percentiles) or number (%). The presented *P* values are a result from the comparison between HSC and WKZ using Fisher exact test or Mann-Whitney *U* test.

Table II. Prevalence of ischemic injury, hemorrhagic injury, and sinovenous thrombosis

	Overall	HSC	WKZ	
Cumulative incidence	**n = 124**	**n = 77**	**n = 47**	**Comparison sites *P* value**
Ischemic injury	65 (57-74)	69	60	.20
Multifocal injury	44 (35-52)	43	45	.49
Focal injury	32 (24-41)	30	36	.30
Parenchymal hemorrhagic injury	12 (6-18)	12	13	.47
Sinovenous thrombosis	12 (7-19)	10	15	.21
Preoperative incidence	**n = 100**	**n = 58**	**n = 42**	
Ischemic injury	30 (21-39)	35	24	.18
Multifocal injury	16 (9-23)	14	19	.33
Focal injury	18 (10-26)	24	10	.05
Parenchymal hemorrhagic injury	8 (3-13)	5	11	.06
Extraparenchymal hemorrhagic injury	49 (39-59)	41	60	.06
Sinovenous thrombosis	4 (0-8)	7	0	.08
New postoperative incidence	**n = 124**	**n = 77**	**n = 47**	
Ischemic injury (new)	51 (42-60)	48	55	.27
Multifocal injury	37 (28-46)	36	38	.49
Focal injury	23 (16-31)	16	36	.01
Parenchymal hemorrhagic injury (new or extended)	5 (1-9)	6	2	.05
Extraparenchymal hemorrhagic injury (new or extended)	16 (9-23)	23	7	.02
Sinovenous thrombosis (new or extended)	12 (7-19)	10	15	.21

The first column shows the overall incidences as percentages (with 95% CI); the second and third columns show incidence per site as percentages. In the fourth column, the *P* values for the comparison between HSC and WKZ using the Fisher exact test are shown.

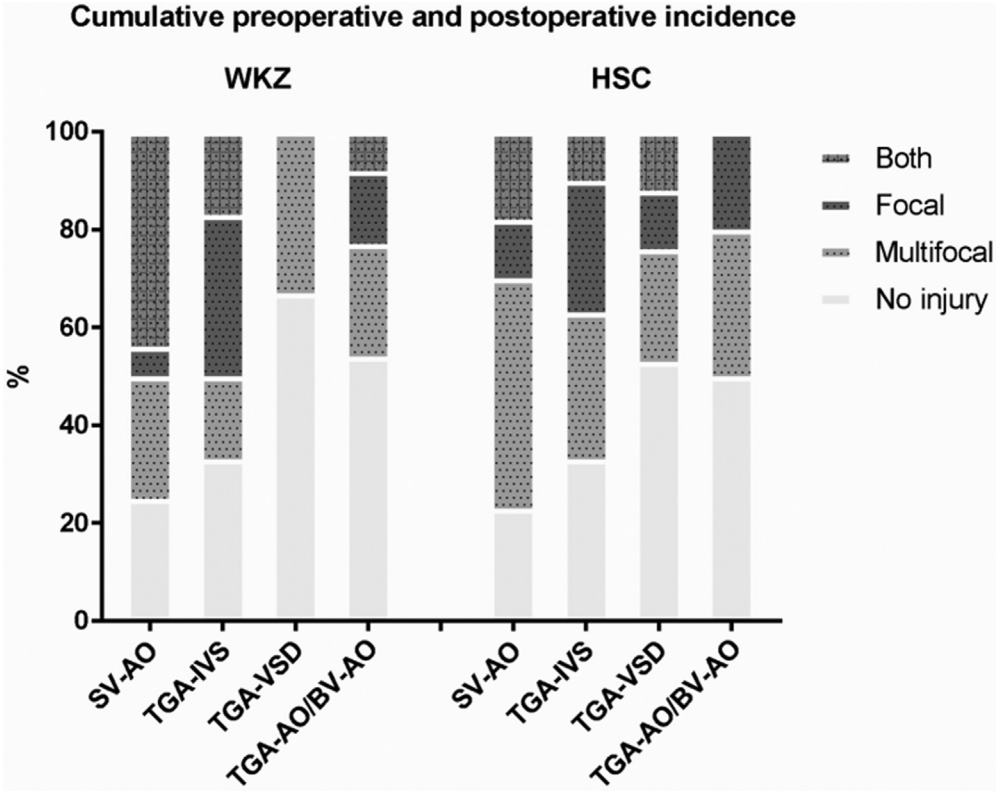

Figure 2. Ischemic brain injury prevalence by congenital heart defect at both sites. Graphs represent cumulative incidence of preoperative and postoperative multifocal injury (*light grey, dotted*), focal injury (*dark grey, dotted*), or both types of injury (*medium grey, striped*): *AO*, arch obstruction; *BV*, biventricular pathology; *CHD*, congenital heart disease; *IVS*, intact ventricular septum; *SV*, single ventricle; *TGA*, transposition of the great arteries; *VSD*, ventricular septal defect.

12 infants with LCOS had new multifocal injury (41%); at WKZ, 7 with LCOS had new multifocal injury (54%; $P = .34$).

SCP was the single risk factor associated with new focal brain injury in multivariable analysis (OR, 2.7; **Table IV**). SCP use in infants with AO was similar at HSC and WKZ (82 vs 72%; $P = .32$). Compared with HSC, WKZ had a higher rate of CHD with AO (**Table I**) and a higher rate of new postoperative focal injury (**Table II**). SCP was not associated with the side of new focal lesions (56% right hemisphere; $P = .60$).

Compared with WKZ, HSC had more surgeries performed after the first 14 days of life (**Table I**). The predicted probability of new postoperative ischemic brain injury in relation to age at surgery in all infants was nonlinear (**Figure 3**; available at www.jpeds.com). Preoperative injury did not increase the risk of new postoperative injury (data not shown). Postoperative age at MRI was older at HSC than WKZ (**Table I**); however, postoperative age at MRI was not associated with the incidence of ischemic brain injury ($P = .22$).

The prevalence of parenchymal hemorrhagic injury was 12% and 13% at HSC and WKZ, respectively (**Table II**). At both HSC and WKZ, preoperative parenchymal hemorrhage was only present in infants born by vaginal delivery and in none born by caesarean section ($P = .08$). The prevalence of vaginal deliveries was higher at WKZ than HSC (**Table I**), and the prevalence of preoperative parenchymal and extraparenchymal hemorrhages was higher at WKZ (**Table II**). New or extended postoperative parenchymal hemorrhage occurred infrequently at both sites (**Table II**).

Before surgery, sinovenous thrombosis was only seen at HSC ($P = .08$; **Table II**). The placement of a preoperative and intraoperative central line in the internal jugular vein was more common at HSC than WKZ (82% vs 13%; $P < .001$). At HSC, all infants with preoperative SVT had a central line in the internal jugular vein. New postoperative sinovenous thrombosis was associated with a central line placed in the internal jugular vein at both sites ($P < .01$). Because HSC only performed imaging to detect sinovenous thrombosis (venography) in case of parenchymal injury, no further comparisons between sites could be performed. At WKZ, 5 of 7 infants (71%) with sinovenous thrombosis had additional parenchymal injury. Infants with new postoperative sinovenous thrombosis were more likely to have a stroke of the basal ganglia in the combined cohort (4 of 12 vs 12 of 112; $P = .04$).

Discussion

In our study, balloon atrioseptostomy was associated with preoperative focal brain lesions, either stroke or single white matter lesion. Balloon atrioseptostomy has been inconsistently reported as risk factor for brain injury in infants with CHD.[12-16] In our study, a practice approach with routine performance of balloon atrioseptostomy in (almost) all infants with TGA predicted an increased prevalence of preoperative focal ischemic lesions, when compared with a practice approach with performance of balloon atrioseptostomy only in those with hemodynamic instability. In addition, the prevalence of multifocal injury was not lower in infants with balloon atrioseptostomy when compared with infants without balloon atrioseptostomy. A previous study showed that preoperative multifocal white matter injury in infants with TGA was associated with a longer time to surgery.[16] This finding is consistent with our findings, suggesting that surgery in the first week of life might decrease the risk of acquiring multifocal white matter injury, especially in those infants without balloon atrioseptostomy. Not performing routine balloon atrioseptostomy does not increase the risk of multifocal white matter injury if surgery is not delayed.

The optimal timing of surgery to prevent brain injury warrants further attention. A longer time to surgery has previously been reported as a predictor of both preoperative and postoperative ischemic brain injury in infants with CHD.[16,17] Our results suggest, however, that the relationship between the timing of surgery and the probability of new postoperative ischemic brain injury is nonlinear. A practice approach toward surgery in first weeks of life in all infants with critical CHD did not increase the incidence of multifocal brain injury. As suggested by previous studies, surgery within the first week of life might prevent infants with CHD from acquiring ischemic brain injury and other comorbidities.[16,18,19]

The distinct etiologies of focal and multifocal brain injury are highlighted by the different risk factors for focal injury (interventions: balloon atrioseptostomy, SCP) and multifocal injury (LCOS). Balloon atrioseptostomy and SCP might be the origin of thromboembolic events causing acute ischemia in focal regions, mainly in the territory of the middle cerebral artery.[20] Multifocal white matter injury and HI-WS injury both showed a diffuse pattern of ischemia, not related to artery territory. Our results support the hypothesis that white matter injury with multiple lesions and HI-WS are the result of (acute) brain hypoperfusion and decreased cerebral blood flow.[21,22] Critically ill infants with CHD are at risk of impaired cerebral autoregulation, making cerebral hypoxia-ischemia less well-tolerated during periods of low cardiac output.[23] In addition, brain immaturity might even further decrease autoregulatory capacities in these infants, because white matter injury is associated with brain immaturity in previous studies using advanced imaging.[14,24] Brain maturity scores in this study were similar at both sites and on average lower than reported in infants without CHD of comparable postmenstrual age.[8,9] The brain maturity score was not found as an independent risk factor for either focal or multifocal injury in our study.

Over the last years, single white matter lesions have been defined as stroke by some studies and as white matter injury by others. In our study, single white matter lesions were not associated with lower gestational age and birth weight, but were associated with balloon atrioseptostomy. In contrast,

white matter injury with multiple lesions was associated with lower gestational age and birth weight. This finding suggests that single white matter lesions, or at least a substantial part of them, have the same underlying etiology as stroke. In the prediction of neurodevelopmental outcome, tools to help identify brain ischemic lesions based on etiology instead of imaging pattern would be useful. In recent studies, we showed that white matter injury was associated with school age cognitive and behavioral outcome in children with critical CHD, where focal infarction was not.[3,4] We hypothesize that white matter injury might be a sign of overall affected white matter, where a focal lesion owing to a thromboembolic event can be seen as a static lesion. As in the preterm neonate with diffuse white matter injury, we hypothesize that the overall damaged white matter might lead to impaired neurodevelopment, rather than the visible white matter lesion itself.[25] Our findings highlight the importance of uniform and, ideally, etiology-based brain injury definitions.

New or extended postoperative parenchymal hemorrhage occurred at a very low rate in both cohorts, despite the use of heparin and blood products. Preoperative hemorrhage was in most cases extraparenchymal and related to mode of delivery at birth, with a higher prevalence of preoperative hemorrhagic injury at the site with a practice preference for vaginal delivery instead of cesarean. Extraparenchymal hemorrhage is also present in the healthy term-born population.[26]

The presence of sinovenous thrombosis was associated with an internal jugular vein central line, and sinovenous thrombosis occurred at a higher prevalence preoperatively in the cohort with routine internal jugular vein central line placement. This finding confirms our recent study, showing the association of sinovenous thrombosis with internal jugular vein catheters in infants with critical CHD, and the association with focal basal ganglia infarctions.[27,28] At WKZ (with routine performance of venography in all infants), 29% of infants with sinovenous thrombosis had no signs of additional parenchymal lesions. This suggests that around one-third of infants with sinovenous thrombosis will be missed when venography is only performed in indicated cases with parenchymal lesions. This difference in routine and nonroutine performance of venography is likely to be the underlying cause of the difference in the sinovenous thrombosis rate between HSC and WKZ.

This study shows that collaborative studies between sites with different practice approaches contribute to the understanding of the timing and etiology of brain injury in infants undergoing complex cardiac surgery for critical CHD. This study also has several limitations. The sites used different MRI scanning protocols and different scanners (1.5T vs 3T; 16-channel vs 32-channel head coil; slice thickness), which might influence the reported incidence of brain lesions. However, all MRI scans were reviewed by 1 researcher from each site with the aim to reduce the effect of site differences on MRI scoring. The numbers were too small for comparison of all CHD groups separately and rare CHD defects were excluded. In the present study, preoperative and postoperative variables were identified by chart review. New artificial intelligence approaches to continuous physiological data now recorded and stored routinely in the cardiac intensive care unit should enable a more specific assessment of the hemodynamic measures to modify to prevent brain injury in the infant with CHD. For this study, we included infants born in 2016-2017 to examine a contemporary cohort. The timing of this study excluded the possibility to examine long-term neurodevelopmental outcome. ■

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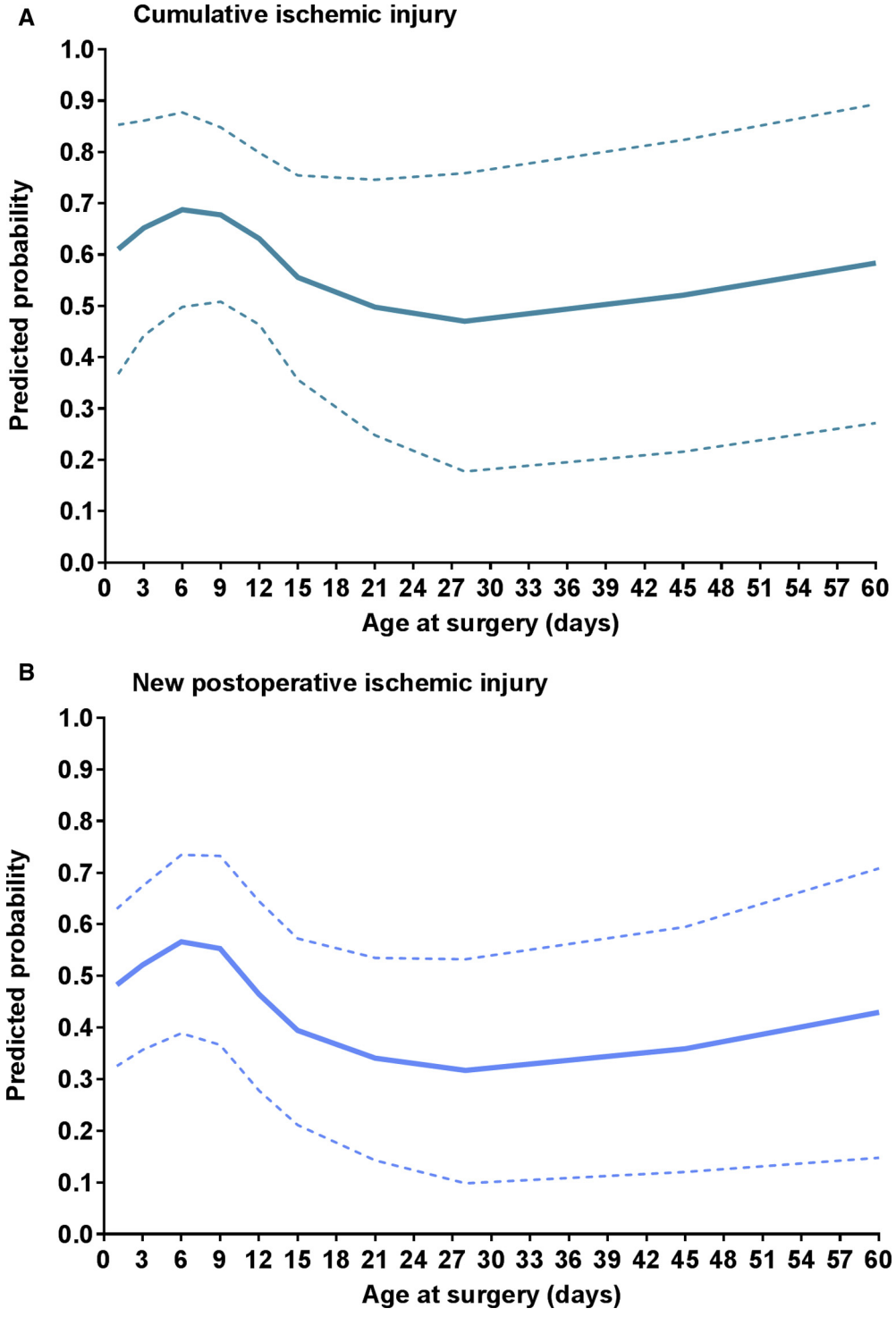

Figure 3. Predicted probability ischemic brain injury by age at surgery. **A,** Calculated relationship between the probability of cumulative ischemic brain injury and age at surgery in days (*continuous line*), presented with lower and upper 95% confidence levels (*dotted lines*). **B,** Calculated relationship between the probability of new postoperative brain injury and age at surgery in days.

Table III. Comparison baseline characteristics between different patterns of preoperative ischemic injury

Characteristics	No injury (n = 70)	White matter injury with multiple lesions (n = 8)	Single white matter lesion (n = 7)	Stroke (n = 5)
Gestational age	39.3 (38.4/40.1)	38.2 (38.0/38.5)*	39.1 (38.0/40.1)	39.3 (36.6/39.4)
Birth weight, z-score	0.0 (−0.6/0.7)	−0.5 (−1.3/0.4)	0.2 (−0.9/0.8)	0.3 (−0.2/1.5)
Prenatal diagnosis	69	88	71	60
Balloon atrioseptostomy	44	38	86*	60

Clinical variables were compared between infants with no preoperative ischemic brain injury at all, with white matter injury with multiple lesions (and absence of other ischemic lesions), infants with single white matter lesion (and absence of other ischemic lesions) and infants with stroke (and absence of other ischemic lesions). Ten infants with multiple forms of preoperative ischemic brain injury were excluded from this analysis.
Data are median (25th/75th percentile) or percentages.
*Significantly different from infants without preoperative ischemic brain injury using Fisher-exact test/Mann-Whitney *U* test.

Table IV. Best multivariable logistic regression model for preoperative and new postoperative multifocal and focal brain injury

Multifocal injuries			Focal injuries		
	OR (95% CI)	*P* value		OR (95% CI)	*P* value
Preoperative multivariable model (n = 100)					
Site*		.93	Site*		.24
SV-AO	3.5 (1.1-12.0)	.04	Balloon atrioseptostomy	3.2 (1.1-9.7)	.04
LCOS†	4.6 (1.4-15.4)	.01			
Postoperative multivariable model (n = 124)					
Site*		.38	Site*		.03
LCOS‡	2.7 (1.2-6.1)	.01	SCP	2.7 (1.2-6.6)	.03

Balloon atrioseptostomy indicates balloon atrioseptostomy.
Variables were selected based on previous literature. Additionally, tested variables can be found in the Methods section.
*Site was forced into final model.
†Preoperative LCOS was associated with postnatal diagnosis.
‡Postoperative LCOS was associated with SV-AO, delayed sternal closure, repeat thoracotomy, and postoperative arrhythmias.