Clinically silent preoperative brain injuries do not worsen with surgery in neonates with congenital heart disease

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Objective: Preoperative brain injury, particularly stroke and white matter injury, is common in neonates with congenital heart disease. The objective of this study was to determine the risk of hemorrhage or extension of preoperative brain injury with cardiac surgery.

Methods: This dual-center prospective cohort study recruited 92 term neonates, 62 with transposition of the great arteries and 30 with single ventricle physiology, from 2 tertiary referral centers. Neonates underwent brain magnetic resonance imaging scans before and after cardiac surgery.

Results: Brain injury was identified in 40 (43%) neonates on the preoperative magnetic resonance imaging scan (median 5 days after birth): stroke in 23, white matter injury in 21, and intraventricular hemorrhage in 7. None of the brain lesions presented clinically with overt signs or seizures. Preoperative brain injury was associated with balloon atrial septostomy ($P = .003$) and lowest arterial oxygen saturation ($P = .007$); in a multivariable model, only the effect of balloon atrial septostomy remained significant when adjusting for lowest arterial oxygen saturation. On postoperative magnetic resonance imaging in 78 neonates (median 21 days after birth), none of the preoperative lesions showed evidence of extension or hemorrhagic transformation (0/40 [95% confidence interval: 0%–7%]). The presence of preoperative brain injury was not a significant risk factor for acquiring new injury on postoperative magnetic resonance imaging ($P = .8$).

Conclusions: Clinically silent brain injuries identified preoperatively in neonates with congenital heart disease, including stroke, have a low risk of progression with surgery and cardiopulmonary bypass and should therefore not delay clinically indicated cardiac surgery. In this multicenter cohort, balloon atrial septostomy remains an important risk factor for preoperative brain injury, particularly stroke. (J Thorac Cardiovasc Surg 2010;140:550-7)

Multiple studies using highly sensitive magnetic resonance imaging (MRI) have identified a high frequency of preoperative brain injury in neonates with congenital heart disease (CHD).¹⁻⁶ In particular, brain injuries such as stroke, white matter injury (WMI), and intraventricular hemorrhage (IVH) are seen in more than one third of term neonates with CHD scanned *before* surgery.^{3,4,7} These lesions are typically clinically silent in the neonatal period and usually

not identified by routine cranial ultrasound scans.^{3,4} It is unknown whether heart surgery with cardiopulmonary bypass (CPB) and perioperative hemodynamic instability might worsen these areas of brain injury. Two studies published to date with preoperative and postoperative MRI noted worsening of a preoperative hemorrhagic lesion² in a single patient and worsening of periventricular leukomalacia in 2 patients.¹ In the latter cases, the authors did not distinguish between extension of existing WMIs or addition of new WMIs. Thus, the identification of these injuries poses a dilemma in the clinical care of these critically ill neonates: should heart surgery be delayed if brain injury is present preoperatively? The answer to this question must balance the need for and timing of life-saving surgery and the risk posed by exposing areas of injured brain to CPB and hemodynamic instability.

Most neonates with severe CHD, such as dextro-transposition of the great arteries (TGA), or single ventricle physiology, including the hypoplastic left heart syndrome, require open cardiac operations with CPB to correct or palliate their heart defect.⁸ Neonates undergoing cardiac surgery are exposed to the risks of intraoperative ischemia, postoperative low cardiac output syndrome,⁹ and anticoagulation required for CPB. Therefore, we hypothesized that preoperative brain injuries will be at significant risk of

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Abbreviations and Acronyms

BAS	= balloon atrial septostomy
CHD	= congenital heart disease
CI	= confidence interval
CPB	= cardiopulmonary bypass
IQR	= interquartile range
IVH	= intraventricular hemorrhage
MRI	= magnetic resonance imaging
OR	= odds ratio
RR	= relative risk
Sao ₂	= arterial oxygen saturation
TGA	= transposition of the great arteries
UBC	= British Columbia Children's Hospital University of British Columbia
UCSF	= University of California San Francisco Children's Hospital
WMI	= white matter injury

progression from the preoperative to the postoperative scan, including hemorrhagic transformation of stroke or extension of WMI.

The objective of this study is to determine the frequency of progression of preoperative brain injuries with cardiac surgery in a prospective dual-center cohort of neonates with TGA and single ventricle physiology. This cohort also provides an opportunity to re-examine clinical risk factors previously identified for preoperative brain injury.

PATIENTS AND METHODS**Subjects**

Between September 2001 and March 2008, this dual-center prospective cohort study enrolled term neonates (>36 weeks' gestation) with CHD delivered at or transferred to the University of California San Francisco Children's Hospital (UCSF) or British Columbia Children's Hospital University of British Columbia (UBC), both tertiary level cardiac referral centers. The research ethics board at each site approved the study protocol. The neonates were recruited and studied with the informed consent of their parents. Subgroups of this cohort were previously reported.^{3-5,7} Term neonates with TGA or single ventricle physiology, including hypoplastic left heart syndrome, were included in this study. They were excluded if they had a congenital infection or genetic malformation syndrome.

Clinical data thought to be potential predictors of brain injury or neurodevelopmental outcome were collected from the medical records at both sites as described previously.^{3-5,7} Specifically, the lowest preoperative arterial oxygen saturation (Sao₂) was obtained from the intensive care unit nursing record. Inasmuch as this was an observational study, the neonates received routine clinical care for their cardiac lesions, including surgery, irrespective of the MRI findings. However, at UCSF the operations on the first 2 neonates were delayed empirically for 1 week after preoperative brain injury was found on the MRI scan.

MRI Studies

MRI studies were performed as soon as the neonates were sufficiently stable to be transported to the scanner by trained personnel and with the use of a specialized MRI-compatible isolette and a dedicated neonatal

head coil.^{10,11} The transport team is composed of 2 intensive care nurses and a critical care physician at UCSF and of an intensive care nurse and a respiratory therapist at UBC. No adverse events occurred at either center with this scanning protocol. Neonates were examined by a pediatric neurologist, blinded to the MRI findings, within 24 hours of the MRI scan.

At UCSF, most subjects received pharmacologic sedation with pentobarbital (1–2 mg/kg per dose up to a total of 6 mg/kg) and/or morphine sulfate (0.05 mg/kg per dose up to a total of 0.2 mg/kg), according to the institution's sedation guidelines. MRI studies were carried out on a 1.5-tesla Signa Echo-Speed system (GE Medical Systems, Waukesha, Wis) as described previously³⁻⁵ and included (TR/TE/FieldOfView/SliceThickness/Gap): (1) T1-weighted sagittal spin echo images (600/8/20 cm/3 mm/1 mm), (2) dual-echo T2-weighted spin echo (3000/60/120/8 × 13.5 cm/4 mm/2 mm), (3) coronal volumetric 3-dimensional gradient echo images with radiofrequency spoiling images (36/3.5/22 cm/1 mm/0), and (4) average diffusivity maps echo-planar acquisition (8000/150/36 × 27 cm/5 mm/0).

At UBC, MRI studies were carried out without pharmacologic sedation on a Siemens 1.5-tesla Avanto system using VB 13A software and included comparable imaging to that obtained at UCSF (TR/TE/FieldOfView/SliceThickness/Gap): (1) 3-dimensional coronal volumetric T1-weighted images (36/9.2/200 mm/1 mm/0) and (2) axial fast spin echo T2-weighted images (4610/107/160 mm/4 mm/0.2 mm). Average diffusivity maps were generated from diffusion tensor imaging acquired with a multirepetition, single-shot echo planar sequence with 12 gradient directions (4900/104/160 mm/3 mm/0), b = 0, 600 and 700 s/mm², and an in-plane resolution of 1.3 mm.

The MRI scans were reviewed by a neuroradiologist independently at each site (UCSF: A.J.B.; UBC: K.J.P.) blinded to the neonate's clinical condition except for gestational age. As previously described, the neuroradiologists scored each MRI scan for acquired injury (focal, multifocal, or global) or developmental brain abnormalities.⁴ The severity of stroke, WMI, or IVH was recorded using previous scoring systems.⁴ Single lesions in the white matter that measured 3 mm or less were classified as WMI, whereas larger lesions were considered stroke. The differentiation of these lesions is conceptual, with stroke resulting from occlusion of a vessel and being more likely to hemorrhage whereas WMI follows hypoxia-ischemia.¹² However, it is not clear that the two can be differentiated by MRI, and sensitivity analyses for the main findings were performed by reclassifying all lesions as either stroke or WMI. A single neuroradiologist (K.J.P.) reviewed all preoperative and postoperative MRI scans in neonates with preoperative injury, blinded to the original scores. In the 4 cases of discrepancy (all solitary white matter lesions), the size definition was applied and consensus reached in all cases. "Progression" from the preoperative to postoperative scans was defined as enlargement of the size of the injury, regardless of the presence of hemorrhage.

Anesthetic and CPB Management

Neonates in this cohort underwent anesthesia and CPB according to a uniform clinical practice at each institution. At UCSF, anesthesia consisted of fentanyl (25–150 mg/kg total dose), midazolam (0.25–3 mg/kg total dose), sevoflurane (up to 4% end-tidal concentration before and after CPB), and isoflurane (up to 3% in the bypass sweep gas during CPB). Pancuronium was used for neuromuscular blockade. CPB was established with aortic and bicaval cannulation. Patients were cooled by alpha-stat pH management to a minimum nasopharyngeal temperature of 28°C for full-flow bypass or 18°C for regional cerebral perfusion. The CPB prime included Normosol electrolyte solution, methylprednisolone, cefazolin, and albumin. Fresh whole blood or packed red blood cells and fresh frozen plasma were added to the prime to maintain hematocrit level at 24% to 27%. Flow was maintained at 150 mL · kg⁻¹ · min⁻¹ except in patients requiring aortic arch reconstruction. For regional cerebral perfusion, the aortic cannula was removed and the innominate artery cannulated with a 2-mm olive-tipped arteriotomy cannula through an incision in the aorta. Flows of 30 to

50 mL · kg⁻¹ · min⁻¹ were titrated to maintain prebypass regional cerebral saturations measured by near-infrared spectroscopy (INVOS 5100A; Somatest, Troy, Mich) and to keep pressure in the arterial line below 300 mm Hg. After the repair and separation from CPB, all patients underwent modified ultrafiltration to remove the crystalloid priming volume. Aprotinin was used until 2007 (first 82 cases).

At UBC, anesthesia was induced with fentanyl and rocuronium and maintained with fentanyl (30–100 µg/kg total dose for the operation) and isoflurane (0.2%–1.4% with titration to an appropriate blood pressure and level of sedation). The CPB prime included Plasma-Lyte A electrolyte solution, albumin, sodium bicarbonate, and magnesium, and patients also received methylprednisolone and cefazolin intravenously before the initiation of bypass. Packed red blood cells and fresh frozen plasma were added to the prime to maintain a hematocrit level between 24% and 28%. Neonates in this cohort did not receive aprotinin. CPB was established with aortic and bicaval cannulation, and patients were cooled with a pH-stat management strategy to 32°C for full-flow bypass or to 18°C for circulatory arrest or low-flow regional perfusion. Flow was established at 135 to 150 mL · kg⁻¹ · min⁻¹ for full bypass with arterial line pressures being maintained below 250 mm Hg. For low-flow bypass, a rate of 30 to 50 mL · kg⁻¹ · min⁻¹ was accepted with arterial line pressures being maintained below 50 mm Hg. In this cohort, regional cerebral perfusion was not used as a predominant bypass strategy; in 1 of 2 patients with deep hypothermic circulatory arrest, antegrade cerebral perfusion was provided at a rate of 50 mg/kg intermittently for a total of 9 minutes. All patients were monitored with near-infrared spectroscopy, and any significant change from prebypass levels led to a re-examination of the bypass strategy or an increase in flow rate or hematocrit value. After separation from bypass, all patients underwent a 10-minute period of modified ultrafiltration.

Data Analysis

Data were analyzed with the Stata/SE 9.2 package (Stata Corporation, College Station, Tex). Clinical variables were compared in neonates with and without preoperative brain injury with the Mann–Whitney *U* test for continuous or ordinal variables and Fisher's exact test for categorical variables. Relative risks (RR) with 95% confidence intervals (CI) were calculated to describe the univariable association between preoperative injury and dichotomous clinical variables. Logistic regression was used to describe the univariable association between preoperative injury and continuous clinical variables. Clinical variables that were significantly associated with the risk of preoperative brain injury on univariable analysis were included in a multivariable logistic regression model.

RESULTS

Study Subjects

Ninety-two neonates were enrolled (Table 1): 69 at UCSF and 23 at UBC. Of these, 62 (67%) had TGA and 30 (33%) had single ventricle physiology. Cardiac operations performed were arterial switch in 59 neonates, Norwood procedure in 27, Blalock–Taussig shunt in 4, and ductal stent with bilateral pulmonary artery banding in 1. Three neonates required 2 operations before their second MRI: 2 needed coarctation repair before the arterial switch, and 1 required re-exploration for bleeding. The neonates had a preoperative MRI at a median age of 5 days after birth (interquartile range [IQR], 3–7). Seventy-eight neonates had a postoperative MRI at a median age of 21 days (IQR, 16–27). Fourteen neonates were not scanned postoperatively: 9 died, 4 needed permanent pacemaker, and 1 family withdrew from the study after a Blalock–Taussig shunt.

TABLE 1. Clinical description of the cohort by study center: University of British Columbia (UBC) and University of California San Francisco (UCSF)

No. (%), and median (25th–75th percentile)	UBC (n = 23)	UCSF (n = 69)
<i>Preoperative factors</i>		
Gestational age at birth (wk)	39 (38–40)	39 (38–40)
Birth weight (g)	3250 (2955–4015)	3364 (3000–3609)
Male	13 (57%)	46 (67%)
Apgar score at 5 min	8 (7–9)	8 (8–9)
Cesarean delivery	5 (22%)	19 (28%)
Heart lesion		
TGA	21 (91%)	41 (59%)
SVP	2 (9%)	28 (41%)
Days mechanically ventilated	5 (3–7)	6 (4–9)
<i>Intraoperative factors</i>		
Operation type		
Arterial switch	19 (83%)	40 (58%)
Norwood	2 (9%)	25 (36%)
Other	2 (9%)	4 (6%)
Bypass type		
None	2 (9%)	3 (4%)
Low flow	1 (4%)	5 (7%)
Full flow	18 (78%)	44 (64%)
RCP	—	12 (17%)
DHCA	2 (9%)	2 (3%)
Other	—	3 (4%)
<i>Postoperative factors</i>		
ECLS	4 (17%)	7 (11%)
<i>MRI 1</i>		
MRI day (at days after birth)	5 (4–12)	5 (3–6)
Acquired injury	12 (52%)	28 (41%)
WMI	7 (30%)	14 (20%)
IVH	3 (13%)	4 (6%)
Stroke	8 (35%)	15 (22%)
<i>MRI 2</i>		
MRI day (at days after birth)	21 (17–29)	20 (16–25)
Acquired injury	8 (47%)	24 (40%)
New WMI	5 (29%)	19 (32%)
New IVH	—	1 (2%)
New stroke	3 (18%)	5 (8%)

TGA, Transposition of the great arteries; SVP, single ventricle physiology; RCP, regional cerebral perfusion; DHCA, deep hypothermic cardiac arrest; ECLS, extracorporeal life support; MRI, magnetic resonance imaging; WMI, white matter injury; IVH, intraventricular hemorrhage

Preoperative Brain Injury

Brain injury was identified in 40 (43%) neonates on preoperative MRI (Table 2, part A): stroke in 23 (Figure 1), WMI in 21 (Figure 1), and IVH in 7. The incidence of preoperative brain injury did not differ significantly by center (*P* = .3, Table 1). Eleven neonates had multiple lesions: 6 with stroke and WMI, 3 with stroke and IVH, and 2 with WMI and IVH. Strokes were solitary (23/23) and small (22/23), with most involving the middle cerebral artery territory (19/23) and a minority in the posterior cerebral artery territory (4/23). Strokes were clinically silent in all neonates.

TABLE 2. Patterns of brain injury

A. Preoperative brain injury								
Preoperative injury		Stroke		WMI			IVH	
		<1/3	1/3–2/3	Mild	Moderate	Severe	Grade 1	Grade 2
TGA (62)	28 (45%)	17 (27%)	1 (2%)	9 (15%)	3 (5%)	1 (2%)	2 (3%)	2 (2%)
SVP (30)	12 (40%)	5 (17%)	—	3 (10%)	4 (13%)	1 (3%)	—	3 (10%)
Total (92)	40 (43%)*	23 (25%)		21 (23%)			7 (8%)	

B. New postoperative brain injury							
Postoperative injury		Stroke		WMI			IVH
		<1/3	1/3–2/3	Mild	Moderate	Severe	Grade 3
TGA (56)	20 (36%)	3 (5%)	—	12 (21%)	3 (5%)	2 (4%)	—
SVP (22)	12 (54%)	4 (18%)	1 (5%)	1 (4%)	6 (27%)	—	1 (4%)
Total (78)	32 (41%)	8 (10%)		24 (31%)			1 (1%)

WMI, White matter injury; IVH, intraventricular hemorrhage; TGA, transposition of the great arteries; SVP, single ventricle physiology. *The incidence of preoperative brain injury is not significantly different by heart lesion ($P = .7$)

Ten neonates had solitary white matter lesions (Figure 2): 5 classified as strokes (>3 mm) and 5 as WMIs (≤ 3 mm). One neonate had evidence of watershed injury after perinatal depression (delivered “flat” after shoulder dystocia, Apgar of 5 at 5 minutes, cord pH = 7.02); no other neonate had a pattern of injury typical of global hypoxia–ischemia in the term neonate.¹³ Small subdural hemorrhages without mass effect were seen in 13 neonates.

Risk Factors for Preoperative Brain Injury

Higher preoperative SaO_2 was protective for preoperative brain injury (odds ratio [OR] = 0.96; 95% CI, 0.94–0.99; $P = .007$). Balloon atrial septostomy (BAS) doubled the risk for preoperative brain injury (RR = 2; 95% CI, 1.29–3.65; $P = .003$) (Table 3). The risk of preoperative brain injury was not associated with the center ($P = .3$), the location (catheterization laboratory vs bedside; $P = .2$), or the route of BAS (femoral vs umbilical vein) ($P = .9$). When BAS and preoperative SaO_2 were included in a multivariable model, BAS remained a significant risk factor for acquired brain injury (OR = 3.6; 95% CI, 1.2–10.7; $P = .02$) whereas SaO_2 did not (OR = 0.98; 95% CI, 0.95–1; $P = .3$).

When specific brain injuries were being examined, the risk of stroke was even more strongly related to BAS (RR = 4; 95% CI, 1.5–9.3; $P = .0015$) and lower SaO_2 (OR = 0.95; 95% CI, 0.92–0.98; $P = .002$). Neither the center ($P = .3$), the location of the BAS procedure ($P = .3$), nor the route ($P = .9$) of BAS significantly affected this risk. All 18 neonates with TGA and stroke required a BAS. Neonates with WMI were more likely to have cesarean section delivery (31% vs 10%; $P = .05$) and preoperative cardiac arrest (10% vs 0%; $P = .05$).

Given the difficulty coding a solitary white matter lesion as WMI or stroke, we repeated our main analyses recoding all solitary white matter lesions as strokes and again considering them all as WMI. The relationship of BAS and SaO_2 with

stroke remained significant even if all the solitary white matter lesions were classified as strokes (BAS: $P = .002$; SaO_2 : $P = .002$) or WMIs (BAS: $P = .015$; SaO_2 : $P = .005$).

Progression of Brain Injury

Preoperatively identified brain injury did not progress or extend from the preoperative to postoperative MRIs (0/40 [95% CI, 0%–7%]).¹⁴ Progression of injury was not observed in the 2 neonates with preoperative injury who did not require CPB for surgery. The median time interval between the preoperative MRI scan and cardiac operation was 2 days (IQR, 1–5), whereas the interval between BAS and the cardiac operation was 7 days (IQR, 5–12) and that between the preoperative and postoperative MRI scans was 14 days (IQR, 9–20). The age at operation did not significantly differ in neonates with and without preoperative brain injury (Table 3). A number of the preoperative lesions became smaller and more difficult to detect on the postoperative MRI (3/23 strokes, 3/21 WMIs, and 2/7 IVHs).

New Postoperative Brain Injury

New postoperative brain injury was seen in 32 (40%) neonates (Table 2, part B): stroke in 8, WMI in 24, and IVH in 1. Strokes were solitary (8/8) and small (7/8), with 7 in the middle cerebral artery territory (7/8) and 1 in the posterior cerebral artery territory. Strokes were clinically silent in all neonates. WMI was mild in 13 neonates, moderate in 9, and severe in 2. Patterns of injury suggestive of global hypoxia–ischemia were not seen. New subdural hemorrhage was seen in 12 neonates, but none showed mass effect. The incidence of new postoperative brain injury did not differ significantly by center ($P = .8$; Table 1). Of the 5 neonates requiring extracorporeal life support and surviving to the second MRI scan, new postoperative brain injury was seen in 2 (40%); new postoperative brain injury was seen in 29 of 68 neonates not requiring extracorporeal life support

FIGURE 1. Patterns of brain injury: stroke and white matter injury (WMI). The abnormal hypersignal (*black arrow*) in the left basal ganglia is an example of a small preoperative stroke in a term neonate with TGA. It is localized in the middle cerebral territory and appears as a hyperintensity on the (A) T1-weighted image and an area of restricted diffusion on the (B) ADC map. The images on the *right* are an example of preoperative WMI in a term neonate with TGA and show a small focus (*white arrow*) of hyperintensity in the right parietal lobe on (C) the axial T1-weighted imaging. There is no corresponding area of restricted diffusion on (D) the ADC map. TGA, Transposition of the great arteries.

($P > .9$). Among the 3 neonates not requiring CPB who underwent a second MRI scan, new postoperative brain injury was seen in 1 (33%; $P > .9$ relative to the remainder of the cohort). New postoperative brain injury was seen in 13 (39%) of 33 neonates with preoperative brain injury and in 29 of 44 with normal preoperative scans. Thus, the presence of preoperative brain injury was not a significant risk factor for acquiring new injury on postoperative MRI studies (RR = .9; 95% CI, 0.53–1.56; $P = .8$).

DISCUSSION

In this dual-center prospective cohort study, preoperative brain injuries were commonly identified in neonates with

CHD before heart surgery and were predominantly clinically silent, small focal lesions: stroke, WMI, and IVH. The rate of these clinically silent injuries is substantially higher than that found in normative populations.¹⁵ These lesions did not show signs of progression or extension on a repeat MRI scan after cardiac surgery with CPB. Furthermore, preoperative brain injuries were not a significant risk factor for acquiring new postoperative lesions.

No Progression of Brain Injury on MRI

The lack of progression of preoperative brain lesions with cardiac surgery and CPB is somewhat surprising. We anticipated that term neonates with CHD would be at high risk

FIGURE 2. Solitary white matter lesions. The coronal T1-weighted imaging (A) and axial ADC map (B) show a small preoperative white matter (WM) stroke (black arrow) in a term newborn with TGA. The lesion is localized in the left middle cerebral artery territory and characterized by an abnormal T1 hyperintensity (A) and an area of restricted diffusion (B) in left parietal lobe. The images on the right are an example of white matter injury (WMI) in another term newborn with TGA (same patient as in Figure 1) and show a small focus (white arrow) of hyperintensity in the right parietal lobe on (C) the coronal T1-weighted imaging. There is no corresponding area of restricted diffusion on (D) the ADC map. TGA, Transposition of the great arteries.

for injury progression owing to the unavoidable exposure to some degree of ischemia with surgery and CPB. Previous studies have linked postoperative factors, such as hypotension, to the risk of WMI on postoperative MRI.^{3,16} These postoperative factors might lead to progression of existing brain injury. We also expected that anticoagulation would carry a risk for hemorrhage into existing strokes.

The small size of the preoperative lesions in this cohort might have attenuated the risk of hemorrhagic transformation with anticoagulation required for CPB. It is also possible that current surgical and bypass techniques, including the avoidance of prolonged deep hypothermic cardiac arrest, helped to prevent a degree of ischemia sufficient to worsen preoper-

ative brain lesions.¹⁷⁻²¹ Despite these improvements in CPB, critically ill neonates, including those with CHD, are at risk of impaired cerebrovascular autoregulation,²² making any exposure to ischemia more likely to be poorly tolerated. In fact, none of the preoperative brain injuries progressed from the preoperative to the postoperative scans. The lack of progression at 2 centers with different bypass management strategies suggests a generalizability of our findings to other centers.

These present results cannot exclude the possibility that preoperative brain injuries worsen in a manner not detectable even by the optimized high-resolution MRI techniques used in this study. Further evidence in support of this contention will require analysis of the relative associations of

TABLE 3. Clinical description of newborns with preoperative brain injury relative to those without preoperative brain injury

No. (%), and median (25th–75th percentile)	Preoperative brain injury (n = 40)	No preoperative brain injury (n = 52)	P value
Gestational age at birth (wk)	39 (38–40)	39 (38–40)	.7
Birth weight (g)	3300 (2880–3670)	3418 (3000–3675)	.9
Male	26 (65%)	33 (63%)	1.0
Apgar score at 5 minutes	8 (8–9)	8 (8–9)	.6
SNAP-PE	15 (11–24)	14 (10–19)	.1
Neonatal resuscitation score	2 (1–4)	2 (1–2)	.2
Cesarean delivery	8 (20%)	16 (31%)	.3
Hear lesion			
TGA	28 (70%)	34 (65%)	.7
SVP	12 (30%)	18 (35%)	
Mechanical ventilation (d)	6 (4–9)	6 (4–8)	.9
Umbilical artery catheter	26 (67%)	32 (64%)	.8
Umbilical venous catheter	25 (64%)	26 (51%)	.3
BAS	27 (68%)	18 (35%)	.003
Lowest Sao ₂	55 (45–70)	70 (60–80)	.007
Preoperative arrest	2 (5%)	—	.2
MRI day after birth	5 (4–6)	5 (3–7)	.9
Surgery day after birth	9 (7–11)	7 (5–11)	.1
Range	2–30	2–38	

SNAP-PE, Score for Neonatal Acute Physiology–Perinatal Extension; TGA, transposition of the great arteries; SVP, single ventricle physiology; BAS, balloon atrial septostomy; Sao₂, arterial oxygen saturation; MRI, magnetic resonance imaging.

preoperative and postoperative brain injuries with subsequent late neurodevelopmental outcomes.

Absence of Hemorrhagic Transformation With CPB After Preoperative Stroke

Hemorrhagic transformation is one of the most feared complications of ischemic stroke *in adults*. In addition to treatment with recombinant tissue plasminogen activator, risk factors for hemorrhagic transformation include the size of the lesion, mechanism of the stroke (cardioembolic vs atherothrombotic),²³ age, anticoagulation, and systolic blood pressure. Molecular and cellular mechanisms thought to be important for hemorrhagic transformation include ischemia–reperfusion with resulting oxidant injury to vascular endothelium. Although hemorrhagic strokes account for half of all strokes in children,²⁴ risk factors for hemorrhagic transformation of pediatric stroke are less widely described.²⁵ Although strokes are now commonly associated with CPB in both infants and adults,²⁶ these strokes are most commonly embolic and rarely hemorrhagic. Despite the potential for increased exposure with CPB to shared pathogenic mechanisms including ischemia–reperfusion, oxidative stress, and inflammation, the present data suggest that the risk of hemorrhagic transformation of small focal preoperative strokes is low.

This study addresses a clinically relevant question posed in previous studies: when should neonates with CHD and preoperative brain injury undergo cardiac surgery so that the risk of

preoperative brain injuries to progress is minimized?^{4,27,28} Possible advantages of deferring surgery after identifying preoperative brain injury include the potential for recovery of autoregulation and lower risk of hemorrhagic transformation. Potential advantage of proceeding with surgery without delay is the observation that the risk of WMI increases with a longer interval from birth to surgery.⁶ In the present study, neonates underwent surgery with a median of 2 days between the preoperative MRI scan and surgery, and we did not observe injury progression. Our data suggest that it is not necessary to postpone clinically indicated cardiac surgery in neonates with these clinically silent focal brain injuries.

Risk Factors for Preoperative Brain Injury

In 4 previous reports, very few risk factors for preoperative brain injury have been identified to date: low Sao₂, brain immaturity, and BAS.^{3,4,6,29,30} McQuillen and associates³ originally reported a link between BAS and preoperative stroke in a prospective cohort of neonates with TGA, an observation confirmed in a larger cohort with many types of CHD. Subsequently, 2 reports have failed to confirm this association. Petit and colleagues⁶ reported on 26 neonates with TGA, of whom 14 received BAS. In this study, stroke was not observed, yet WMI was detected in 10 and IVH in 6; only the time to surgery and low Sao₂ were significant risk factors for preoperative brain injury.⁶ Beca and coworkers²⁹ reported preoperative MRI findings in 44 neonates with TGA (33 had BAS), 13 with hypoplastic left heart syndrome and 7 with pulmonary atresia. Brain injury occurred in 19 (30%) infants: WMI in 17 and stroke in 3; clinical risk factors for preoperative brain injury were not detected. Despite differences in risk factors identified and variability in the patterns of brain injury across these cohorts, the rate of preoperative brain injury remains unacceptably high (≥30%).

In the present study, the rates of preoperative injury, including stroke, were similar at both centers. Consistent with earlier reports, all neonates with TGA who had acquired a stroke had received BAS.^{3,4} In addition to practice variability across neonatal cardiac centers, differences in stroke incidence and identified risk factors may also relate to patient-specific factors such as illness severity. Regardless the etiology, preoperatively identified brain injury has a low risk of progression. Another plausible reason for the difference in rates of stroke and WMI across cohorts is variability in the classification of solitary white matter lesions as either stroke or WMI.^{3,6,28} In our study, we prospectively classified small punctuate white matter lesions as WMI and larger solitary lesions as stroke. Inasmuch as there is no objective imaging measure to distinguish these patterns of injury, we performed a sensitivity analysis by recoding the 10 solitary white matter lesions in this cohort uniformly as either stroke or WMI, and the main associations persisted. The clear benefits of BAS must be weighed against the risk of stroke and the procedure reserved for those neonates with

significant hypoxemia, a consideration made even more difficult by the lack of information on the impact of small strokes for subsequent neurodevelopmental outcome.

Limitations

Despite being the largest reported group of neonates with CHD scanned with MRI preoperatively and postoperatively, given our sample size (0/40 injuries), we cannot completely exclude a low risk of progression of preoperative focal brain lesions with surgery of up to 7%.¹⁴ Unlike some previous studies in which neonates were scanned on the date of surgery, we were not able to assign a specific time frame from preoperative MRI to surgery, nor the time from surgery to postoperative MRI. Given this, very small increases in lesion size may have been missed by the time of the postoperative MRI; we would not expect these changes to be clinically relevant. This study also highlights the need for uniformity of both image acquisition and nomenclature describing and quantifying injuries for comparison across centers. Inasmuch as physiologic data from intensive care monitoring, such as Sao_2 values, were collected from review of the nursing record and not stored electronically, more sophisticated analyses such as the effect of a specific duration of a value below a lower limit on the risk of brain injury could not be assessed. We also note that these data apply only to term neonates with CHD. Importantly, the association of both preoperative and postoperative brain injuries with school-age neurodevelopmental outcomes will be addressed as this cohort develops through childhood.

CONCLUSION

In this study, clinically silent preoperative brain injuries in neonates with CHD, including stroke, have a very low risk of progression on imaging after cardiac surgery and CPB. Given this, the identification of similar lesions should not delay clinically indicated surgery.

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