Arterial ischemic stroke in children with cardiac disease

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ABSTRACT

Objective: To describe the spectrum of cardiac disorders, timing in relation to interventional procedures, and outcome in children with cardiac disease and arterial ischemic stroke (AIS).

Methods: Children younger than 18 years with cardiac disease and radiologically confirmed AIS admitted to the Royal Children's Hospital Melbourne between 1993 and 2010 were retrospectively identified using ICD-9 and ICD-10 searches.

Results: Seventy-six children with cardiac disease and radiologically confirmed AIS were identified with the median age at diagnosis of 5 months (interquartile range 0–58). Cardiac lesions included cyanotic congenital heart disease (CHD) in 42 (55%), acyanotic heart disease in 24 (29%), cardiomyopathies/myocarditis in 6 (8%), infective endocarditis in 3 (4%), and primary arrhythmias in 3 (4%). Stroke occurred following cardiac procedures in 52 patients (68%): 41 post cardiac surgery (4.6 strokes per 1,000 surgical procedures) and 11 post cardiac catheterization (1.7 strokes per 1,000 catheterizations). The median time from procedure to diagnosis of stroke was 3 days (interquartile range 2–7), with 68% (95% confidence interval 58%–79%) of strokes estimated to occur within the periprocedural period. Prevalence of periprocedural stroke varied by diagnostic category, but was most common in patients with cyanotic CHD undergoing palliative surgery (22/2,256, 1%) ($p < 0.005$). There were 3 AIS-related deaths, and 54 survivors (84%) had persisting neurologic deficits.

Conclusions: Infants with cyanotic CHD were most frequently affected by AIS during the periprocedural period. Prospective cohort studies are required to determine effective primary and secondary prevention strategies. *Neurology*® 2015;85:2053–2059

GLOSSARY

AIS = arterial ischemic stroke; **CHD** = congenital heart disease; **CI** = confidence interval; **ICD-9** = *International Classification of Diseases, Ninth Revision*; **ICD-10** = *International Classification of Diseases, Tenth Revision*; **IQR** = interquartile range; **MCA** = middle cerebral artery.

The incidence of arterial ischemic stroke (AIS) in children is estimated at 2 to 8 per 100,000 children per year. Although many cases of AIS have a multifactorial etiology, cardiac disorders are associated with 10% to 30% of strokes in children.^{1–3} In a large, prospective international cohort of 667 children, the International Pediatric Stroke Study identified cardiac disorders in 30% of children with AIS outside of the neonatal period, of which 25% had their stroke in the perioperative period.⁴ Cardiac disorders are one of the few potentially modifiable risk factors in the pediatric population and therefore are an obvious target for preventative strategies.

The aims of our study were to describe the spectrum of cardiac disorders associated with pediatric stroke, to describe their timing in relation to surgical or interventional procedures, and to describe the outcomes. We hypothesized that cardiac diagnosis is associated with increased risk of stroke.

Supplemental data
at Neurology.org

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METHODS All children younger than 18 years of age with cardiac disease and AIS treated at the Royal Children's Hospital Melbourne between July 1993 and February 2010 were retrospectively identified by performing an *ICD-9* and *ICD-10* search applied to discharge diagnosis of stroke, based on the standardized methodology recommended by the International Pediatric Stroke Study (table e-1 on the *Neurology*[®] Web site at Neurology.org). The study population, consisting of the subgroup of children with AIS and cardiac disease, were identified from the *ICD* search and then cross-referenced against the Department of Cardiology's electronic patient database, which commenced in 1993, to allow investigators to abstract data related to the child's specific cardiac diagnosis.

Table 1 Patient demographics and cardiac diagnoses

	Total (n = 76)	Periprocedural (n = 52)	Nonperiprocedural (n = 24)
Sex, M/F	50/26	36/16	14/10
Age, mo	5 (0–58)	3 (1–36)	33 (0–101)
Neonates (<1 mo of age), n (%)	18 (24)	13 (25)	5 (20)
Cardiac diagnosis, n (%)			
Cyanotic heart disease	42 (55)	33 (63)	9 (38)
TOF, PA/VSD, DORV	10 (13)	8 (13)	2 (8)
TA	1 (1)	1 (2)	0 (0)
PA/IVS, critical PS	3 (4)	2 (4)	1 (4)
TGA	4 (5)	3 (6)	1 (4)
ccTGA	3 (4)	2 (4)	1 (4)
SV	22 (29)	18 (35)	4 (17)
Acyanotic heart disease	22 (29)	17 (33)	5 (21)
PFO/ASD	1 (0)	0 (0)	1 (4)
VSD	2 (3)	2 (4)	0 (0)
CoA	4 (5)	4 (8)	0 (0)
AS, SAS	5 (7)	5 (10)	0 (0)
AVSD	1 (1)	1 (2)	0 (0)
ALCAPA	1 (1)	1 (2)	0 (0)
PA sling	1 (1)	1 (2)	0 (0)
Repaired CHD	6 (8)	3 (6)	3 (13)
Post OHT	1 (1)	0 (0)	1 (4)
Cardiomyopathy/myocarditis	6 (8)	2 (4)	4 (17)
Infective endocarditis	3 (4)	0 (0)	3 (13)
Primary arrhythmia	3 (4)	0 (0)	3 (13)
VF arrest	2 (3)	0 (0)	2 (8)
CCHB	1 (1)	0 (0)	1 (4)

Abbreviations: ALCAPA = anomalous origin of the left coronary artery from the pulmonary artery; AS = aortic stenosis; ASD = atrial septal defect; AVSD = atrioventricular septal defect; CCHB = congenital complete heart block; ccTGA = congenitally corrected transposition of the great arteries; CHD = congenital heart disease; CoA = coarctation of the aorta; DORV = double outlet right ventricle; IVS = intact ventricular septum; OHT = orthotopic heart transplant; PA = pulmonary atresia; PA sling = pulmonary artery sling; PFO = patent foramen ovale; PS = pulmonary stenosis; SAS = supraaortic stenosis; SV = single ventricle; TA = tricuspid atresia; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VF = ventricular fibrillation; VSD = ventricular septal defect. Numbers are expressed as median (interquartile age) and number of patients (percentage) as appropriate.

The identified patients were also cross-referenced with our institutional stroke registry (which commenced in 2003) to minimize patients being missed inadvertently. AIS was diagnosed with radiographic imaging (MRI or CT) showing parenchymal infarction in an arterial territory or external border zone region. A tissue-based definition was used because of difficulty in identifying acute neurologic events in children who were ventilated or sedated at the time of diagnosis. AIS that occurred within 1 month of procedure or during the same hospital stay was defined as periprocedural AIS, and all others were defined as nonperiprocedural AIS.^{5,6} Cardiac disease included both congenital heart disease (CHD) and acquired heart disease. Patient demographic, procedural and postprocedural data, radiologic findings, anticoagulation treatment, and outcome were reviewed from the medical records and departmental databases. Neuroimaging findings were classified based on neuroradiology reports and summarized in terms of vascular territory or external border zone “watershed” infarction and presence of hemorrhage. Neurologic deficits were defined as documented motor, speech, visual, or sensory deficits, and epilepsy was defined as 2 or more remote seizures.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Royal Children's Hospital Human Research Ethics Committee, and the procedures followed were in accordance with institutional guidelines for retrospective record review and protection of patient confidentiality.

Statistical analysis. Analysis of periprocedural stroke events was performed by determining the total number of surgical procedures performed during the study period and subgrouping patients by broad clinical groups based on cardiac diagnosis and associated surgical management into (1) cyanotic CHD post palliative surgery (residual right to left shunting), (2) cyanotic CHD post definitive surgery (no residual right to left shunting), and (3) acyanotic CHD postsurgery. The χ^2 and Fisher exact tests were used to compare the prevalence of periprocedural stroke across the 3 diagnostic categories, and between pairs of categories. All patients admitted at our institution during the study period who underwent these procedures were used as reference groups. Odds ratios and corresponding 95% confidence intervals (CIs) were estimated. Continuous variables were summarized as median with interquartile range (IQR) and categorical variables were summarized as number of cases and percentage with 95% CIs. All statistical analyses were performed using Stata Statistical Software, release 11 (StataCorp LP, College Station, TX).

RESULTS Patient characteristics. There were 156 children identified by the *ICD* search, but the following patient groups were excluded: primary hemorrhagic stroke (36), hypoxic ischemic encephalopathy (20), cerebral venous sinus thrombosis (4), and imaging studies unavailable (18). Another 2 children were excluded because of unavailability of medical records. A total of 76 patients were included in the study (figure e-1). The median age was 5 months (IQR 0–58 months) with 18 of 76 (24%) younger than 1 month. The demographic data and cardiac diagnosis are listed in table 1. Children with cyanotic heart disease accounted for more than half of the cases of radiologically confirmed stroke. We estimated that 68% (95% CI 58%–79%) of strokes occur within the periprocedural period.

Prothrombotic testing was performed in 21 of 76 patients (28%), and congenital prothrombotic tendencies were identified in 7 of 21 (33%); antithrombin deficiency was the most common abnormality. Multiple abnormalities were identified in 2 children.

Interventional procedures. Fifty-two of the patients who experienced AIS (66%) had strokes following cardiac procedures (periprocedural AIS): 41 were post cardiac surgery and 11 were post cardiac catheterization. The details of the procedures are shown in table 2. During the study period, there were a total of

8,891 cardiac surgical procedures at our center giving a prevalence of 4.6 periprocedural AIS cases per 1,000 procedures (95% CI 3.4–6.2). Likewise, the total number of cardiac catheter procedures performed was 6,478, giving a prevalence of 1.7 periprocedural AIS cases per 1,000 catheterizations (95% CI 0.9–3.1). The risk of stroke was highest in the patients in the cyanotic CHD group who underwent palliative cardiac surgery leaving a right to left shunting post-operatively, being triple the risk of periprocedural AIS among patients with acyanotic CHD and 4 times the risk in patients with cyanotic CHD undergoing biventricular repair (table 3).

Clinical and radiologic features. The presenting clinical symptoms and radiologic features are shown in table 4. Seizures were the most common presenting symptom. In the periprocedural AIS group, the median time from procedure to onset of clinical symptoms was 3 days (IQR 2–6 days), of which 42 patients had stroke within 2 weeks of procedure. Of the 11 patients who were asymptomatic, 5 patients had neuroimaging following an episode of cardiac arrest (3 in the periprocedural AIS group and 2 in the nonperiprocedural AIS group), 4 patients had routine preoperative imaging (2 in the periprocedural AIS group who had a previous atrial septostomy and 2 in the nonperiprocedural AIS group), and 2 patients underwent imaging as part of screening for septic embolization following the diagnosis of infective endocarditis (both in the nonperiprocedural AIS group). The most common single territory affected was the middle cerebral artery (MCA) territory in 42% of children. Thirteen patients (17%) had evidence of secondary hemorrhagic conversion.

Anticoagulation therapy. The details of antithrombotic regimen were available in 75 patients (table 5). A total of 35 patients (45%) were receiving antithrombotic treatment before the stroke event; 30 of 51 (59%) and 5 of 24 (21%) were in the periprocedural AIS group and nonperiprocedural AIS group, respectively. Of the 19 patients receiving unfractionated heparin before stroke in the periprocedural AIS group, 16 patients were on a low dose (10 U/kg/h) as part of routine prophylaxis for central venous access. These patients did not have routine measurement of their activated partial thromboplastin time. One patient was on low-molecular-weight heparin because of a known central venous thrombus. Forty-four patients (58%) commenced treatment or their antithrombotic regimen was escalated. There was no change in anticoagulant treatment in 31 of 75 patients (42%); 12 of 75 (16%) remained on no treatment following the stroke event. Of the 22 patients who did not have a watershed lesion in the nonperiprocedural group, 15 of 22 patients (68%)

Table 2 Details of cardiac procedures performed in periprocedural AIS

	Total (n = 52)	Cyanotic heart disease (n = 33)	Acyanotic heart disease (n = 19)
Time from procedure to stroke, d	3 (2–7) ^a		
Procedure preceding stroke, n (%)			
Cardiac surgery	41/52 (79)	26/33 (79)	15/19 (79)
With CPB	33 (80)	21 (81)	12 (80)
Without CPB	8 (20)	5 (19)	3 (20)
Palliative surgery	22/41 (54)	22/26 (85)	0/15 (0)
Shunt	8 (20)	8 (31)	0 (0)
BCPC	3 (7)	3 (12)	0 (0)
Fontan	5 (12)	5 (19)	0 (0)
Norwood	4 (10)	4 (15)	0 (0)
Others	2 (5)	2 (8)	0 (0)
Complete repair	19/41 (46)	4/26 (15)	15/15 (100)
PA/VSD, MAPCA repair	1 (2)	1 (4)	0 (0)
Truncus repair	1 (2)	1 (4)	0 (0)
ASO	2 (5)	2 (8)	0 (0)
VSD closure	2 (5)	0 (0)	2 (13)
AVSD repair	1 (2)	0 (0)	1 (7)
Aortic valve/aortic arch repair	6 (15)	0 (0)	6 (40)
OHT	1 (2)	0 (0)	1 (7)
VAD implantation	1 (2)	0 (0)	1 (7)
RVOTR	2 (5)	0 (0)	2 (13)
ALCAPA	1 (2)	0 (0)	1 (7)
PA sling repair	1 (2)	0 (0)	1 (7)
Cardiac catheterization	11/52 (21)	7/33 (21)	4/19 (21)
Diagnostic procedure	3 (27)	3 (43)	0 (0)
Interventional procedure	8 (73)	4 (57)	4 (100)
Postprocedural complications, n (%)			
Cardiac arrest	7/52 (13)	7/33 (21)	0/19 (0)
Mechanical circulatory support	9/52 (17)	4/33 (12)	5/19 (26)

Abbreviations: AIS = arterial ischemic stroke; ALCAPA = anomalous origin of the left coronary artery from the pulmonary artery; ASO = arterial switch operation; AVSD = atrioventricular septal defect; BCPC = bidirectional cavopulmonary shunt; CPB = cardiopulmonary bypass; MAPCA = main aortopulmonary collateral arteries; OHT = orthotopic heart transplant; PA = pulmonary artery; RVOTR = right ventricular outflow tract reconstruction; VAD = ventricular assist device; VSD = ventricular septal defect.

^aNo. = 47; 5 patients were asymptomatic and the onset of stroke is unclear.

Table 3 Odds risk of periprocedural AIS for acyanotic vs cyanotic cardiac disease

Type of surgery ^a	Total (n = 8,891)	AIS (n = 41)	Prevalence, % (95% CI)	OR (95% CI) ^b	p Value
Acyanotic	4,965	15	0.3 (0.15–0.45)	1	
Cyanotic palliative ^c	2,256	22	1 (0.57–1.38)	3.2 (1.7–6.3)	0.00022
Cyanotic biventricular repair	1,670	4	0.2 (0.01–0.47)	0.8 (0.3–2.4)	0.68

Abbreviations: AIS = arterial ischemic stroke; CI = confidence interval; OR = odds ratio.

^ap = 0.0002 for comparing all 3 types of surgical groups.

^bOR and 95% CI compared with acyanotic group.

^cOR = 4.1 (95% CI 1.4–12, p = 0.005) in cyanotic palliative vs cyanotic biventricular repair.

commenced treatment or their antithrombotic regimen was escalated. One patient was treated conservatively because of concerns about malignant transformation of a cerebellar infarct.

Outcome of AIS. Three patients died immediately after stroke, all of whom had secondary hemorrhagic conversion of their infarcts. One patient presented with collapse at home and was subsequently diagnosed with a large left MCA infarct with mass effect. The patient was on therapeutic warfarin for severe ventricular dysfunction, and this was changed to therapeutic unfractionated heparin and aspirin. Two patients had periprocedural strokes. One patient had large bilateral

MCA infarcts and the other had multifocal anterior and posterior infarcts. They were both on low-dose unfractionated heparin before stroke and one patient received aspirin following the diagnosis of stroke. There were 10 additional deaths during long-term follow-up, but these were all due to cardiac causes. Of the 65 survivors, 54 (83%) had persistent neurologic deficits and 13 (20%) had symptomatic epilepsy. Eleven patients (17%) had recurrent stroke at a median time of 21 days (IQR 10.5–141 days) following the index event. Two patients had periprocedural strokes 3 and 10 years after the initial event.

DISCUSSION The key findings of this study are that stroke occurs in 1 in 217 cardiac surgical procedures and 1 in 588 cardiac catheterizations. Stroke is more likely to occur in the periprocedural period and is 3 to 4 times more likely in children undergoing palliative procedures for cyanotic heart disease compared with children who have acyanotic heart disease or cyanotic heart disease undergoing biventricular repair.

We estimated that the prevalence of AIS in our center is 4.6 strokes per 1,000 pediatric cardiac surgical procedures. The prevalence of stroke with cardiac surgery in the adult population is estimated to be 2% to 6%.^{7,8} There are limited data on the prevalence of periprocedural stroke associated with cardiac surgery in children, and on the incidence of stroke overall in this patient group. A prospective study of 122 infants younger than 6 months undergoing cardiac surgery with cardiopulmonary bypass reported a prevalence of stroke of 10%, half of which occurred preoperatively.⁹ A small case-control study of 30 children who had stroke after cardiac surgery reported the prevalence of vasoocclusive stroke in children with CHD undergoing cardiac surgery to be 5.4 cases per 1,000 children (1 in 185 children).¹⁰ This is slightly higher than the fraction observed in our study, but both may be an underestimate because many events are clinically unrecognized, particularly in young infants undergoing surgery for complex cyanotic heart disease.^{11,12}

Stroke was more common in children with cyanotic CHD and right to left shunting than in those with acquired heart disease. More than two-thirds

Table 4 Clinical and radiologic features of AIS

	Total (n = 76)	Postprocedural (n = 52)	Nonprocedural (n = 24)
Symptom			
Asymptomatic	11 (14)	5 (10)	6 (25)
Seizures	31 (41)	26 (50)	5 (21)
Facial/limb weakness	27 (36)	19 (37)	8 (33)
Syncope	7 (9)	2 (3)	5 (21)
Visual disturbance	1 (1)	0 (0)	1 (4)
Apnea	2 (2)	1 (4)	1 (4)
Irritability	1 (1)	0 (0)	1 (4)
Altered conscious state	1 (1)	1 (4)	0 (0)
Headaches	1 (1)	1 (4)	0 (0)
Hypothermia	1 (1)	1 (4)	0 (0)
Location of lesion			
Multiple territories	22 (29)	16 (31)	6 (25)
Watershed	7 (9)	5 (9)	2 (8)
Single territory	47 (62)	31 (60)	16 (67)
MCA	32 (42)	18 (35)	14 (58)
ACA	7 (9)	6 (12)	1 (4)
Subcortical	7 (9)	7 (13)	0 (0)
Cerebellar	1 (1)	0 (0)	1 (4)

Abbreviations: ACA = anterior cerebral artery; AIS = arterial ischemic stroke; MCA = middle cerebral artery.

Data represent n (%). Overlapping symptoms occurred in several patients. Postprocedural group: 1 seizure + hemiparesis, 1 syncope + hemiparesis, 1 seizure + syncope + hemiparesis. Nonperiprocedural group: 2 syncope + hemiparesis, 2 seizure + hemiparesis.

Table 5 Details of anticoagulation treatment

	Postprocedural (n = 51) ^a		Nonperiprocedural (n = 24)	
	Pre	Post	Pre	Post
No treatment	21 (41)	3 (6)	19 (79)	9 (38)
Treatment	30 (59)	48 (94)	5 (21)	15 (62)
Single agent				
Aspirin	7 (14)	7 (14)	4 (17)	3 (13)
Low-dose UFH	16 (31)	14 (27)	0 (0)	3 (13)
Therapeutic UFH	3 (6)	6 (12)	0 (0)	4 (17)
LMWH	1 (2)	1 (2)	0 (0)	0 (0)
Warfarin	1 (2)	1 (2)	1 (4)	1 (4)
Low dose UFH + aspirin	1 (2)	6 (12)	0 (0)	0 (0)
Combination therapy				
Therapeutic UFH + aspirin	0 (0)	7 (14)	0 (0)	0 (0)
Therapeutic UFH + warfarin	0 (0)	3 (6)	0 (0)	3 (13)
Therapeutic UFH + LMWH	0 (0)	0 (0)	0 (0)	1 (4)
Therapeutic UFH + aspirin + warfarin	0 (0)	3 (6)	0 (0)	0 (0)
Aspirin + warfarin	1 (2)	0 (0)	0 (0)	0 (0)

Abbreviations: LMWH = low-molecular-weight heparin; UFH = unfractionated heparin. Data represent n (%).

^aThe details of anticoagulation therapy in one patient were not available.

of AIS occurred in association with surgical procedures or catheterization. Various risk factors associated with periprocedural stroke in children with CHD have been reported. A small case series focusing on strokes associated with cardiac surgery in children identified older age at the time of the procedure, longer duration of cardiopulmonary bypass, number of days in the hospital postoperatively, and reoperation to be associated with stroke.¹⁰ In a cohort of infants aged 6 months or younger, risk factors identified included low birth weight, preoperative intubation, low intraoperative hematocrit, and high blood pressure upon cardiac intensive care unit admission.⁹ In another study of 62 neonates with CHD requiring neonatal surgery, brain injury was observed in 56%. Stroke was the most common form of preoperative brain injury, seen in 39%, and was associated with balloon atrial septostomy. Postoperative brain injury was most commonly white matter injury and was particularly common in neonates with single ventricle physiology and aortic arch obstruction.¹³ Recently, the Hearts and Minds Study has reported white matter injury to be the most common type of brain injury following surgery for CHD in early infancy, with the prevalence increasing from 20% presurgery to 44% postsurgery. The new onset of white matter injury was associated with the duration of cardiopulmonary bypass, postoperative lactate level, brain maturity, and white matter injury before surgery.¹⁴

Our study also demonstrates that higher risk occurs in younger patients because half of the patients were younger than 1 year of age. This relationship with age found in our study and others is necessarily dependent on the timing of intervention. The majority of children (>2/3) at our institution undergo cardiac surgery in infancy.

The most frequent location of AIS was the anterior circulation. A stroke registry in the adult population¹⁵ has demonstrated that most procedural infarcts occur in the anterior circulation. The International Pediatric Stroke Registry has also shown that infarcts in children with cardiac disease are frequently in the anterior circulation.^{2,4} More than 30% had AIS in multiple territories, which supports the notion that there may be an underlying cardioembolic mechanism. Children with cardiac stroke have a higher prevalence of bilateral strokes in both anterior and posterior circulation, frequently with a hemorrhagic component.⁴ This suggests that anticoagulation in such a setting needs to be administered cautiously with a low threshold for repeat scanning in the event of clinical deterioration.

Seizures were the most common presenting symptom, observed in more than one-third of the cases and more often than focal signs. These findings suggest that cardiac stroke has different presenting features than other etiologic groups such as cerebral arteriopathies where focal signs are very common.² However, these differences may be a reflection of age because seizures are the most common presenting problem in neonatal stroke.¹⁶ Seizures in the pediatric cardiac unit should therefore alert the clinician to the possibility of cerebral injury and prompt brain imaging.

Prothrombotic studies were infrequently performed in our study population, but one-third of the patients tested had congenital prothrombotic tendencies. Previous research has highlighted the importance of prothrombotic disorders as risk factors for stroke in children with cardiac disease, and suggests that prothrombotic testing should be routinely performed in this patient group.¹⁷

A large number of AIS in cardiac patients were treated conservatively with 16% receiving no anticoagulation and 42% having no change in antithrombotic treatment despite recommendations in clinical practice guidelines.¹⁸ Furthermore, one-third of nonperiprocedural cases had no escalation of treatment following stroke diagnosis. This is concerning because American Heart Association guidelines recommend unfractionated heparin or low-molecular-weight heparin while warfarin therapy is initiated in children with cardiac embolism, based on Class IIa, level B evidence.¹ It was not possible to determine factors influencing clinicians' treatment decisions but these findings suggest the need for better dialog among

pediatric cardiologists, hematologists, and neurologists to optimize care of this high-risk population.

Stroke is among the foremost causes of morbidity and mortality in both adults and children.^{1,19} Associated long-term neurologic impairments include cerebral palsy, cognitive deficits, visual disturbances, and epilepsy.²⁰ In our study, more than 80% of survivors with cardiac disease and AIS had poor neurologic outcomes. This is in the higher end of the reported rate for the overall pediatric AIS population (30%–80%).^{21–24} Poor outcome may be explained by bilateral strokes, which were found in close to one-third of our patients, compared with <15% in other reports.² Seventeen percent of the survivors had recurrent stroke at a median time of 21 days from the index event, a finding that is consistent with previous reports that risk of recurrent stroke decreases over time.²⁵

There are also concerns regarding data regarding preexisting deficits in cerebral development in children with CHD. MRI of the fetal brain has demonstrated lower brain volume, more immature structure, and altered cerebral metabolism.²⁶ Similarly, preoperative MRI scans have demonstrated a high incidence of white matter changes in children with heart disease.¹¹ Adverse neurologic outcomes may in part be attributable to these changes and possibly further exacerbated by subsequent AIS.

Our study is limited to a single-center, retrospective study. It is likely that children with stroke were missed because cases were ascertained by ICD coding and we only captured data on children who were symptomatic or who underwent brain imaging for other reasons. Neuroimaging was classified based on the neuroradiology reports. We did not perform a detailed review of neuroimaging findings because MRI was not performed in all cases. The relatively poor sensitivity of CT to detect subtle areas of ischemia or punctate hemorrhage limited our ability to analyze the infarct characteristics across the study population. Changes in surgical practice over the 17-year period of the study may have influenced interpretation of findings regarding risk of periprocedural stroke. Furthermore, the study was conducted in a tertiary center and therefore the findings may not be generalizable to the broader pediatric cardiac population.

There is a high prevalence of AIS in children with cardiac disease. With advances in surgical and catheter procedures and novel anticoagulation agents, systematic research protocols are important to identify targets for stroke prevention. Multicenter studies are required to improve outcomes in this complex patient population.

AUTHOR CONTRIBUTIONS

Hiroko Asakai: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final

approval, acquisition of data. Michael Cardamone: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, wrote the first draft and collected the initial data. Darren Hutchinson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Belinda Stojanovski: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. John C. Galati: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Michael M.H. Cheung: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding. Mark T. Mackay: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding.

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DISCLOSURE

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