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Original Article

Arterial Ischemic Stroke Secondary to Cardiac Disease in Neonates and Children

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ABSTRACT

Objective: We describe the risk factors for peri-procedural and spontaneous arterial ischemic stroke (AIS) in children with cardiac disease.
Methods: We identified children with cardiac causes of AIS enrolled in the International Pediatric Stroke Study registry from January 2003 to July 2014. Isolated patent foramen ovale was excluded. Peri-procedural AIS (those occurring during or within 72 hours of cardiac surgery, cardiac catheterization, or mechanical circulatory support) and spontaneous AIS that occurred outside of these time periods were compared.
Results: We identified 672 patients with congenital or acquired cardiac disease as the primary risk factor for AIS. Among these, 177 patients (26%) had peri-procedural AIS and 495 patients (74%) had spontaneous AIS. Among non-neonates, spontaneous AIS occurred at older ages (median 4.2 years, interquartile range 0.97 to 12.4) compared with peri-procedural AIS (median 2.4 years, interquartile range 0.35 to 6.1, $P < 0.001$). About a third of patients in both groups had a systemic illness at the time of AIS. Patients who had spontaneous AIS were more likely to have a preceding thrombotic event (16 % versus 9 %, $P = 0.02$) and to have a moderate or severe neurological deficit at discharge (67% versus 33%, $P = 0.01$) compared to those with peri-procedural AIS.

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Conclusions: Children with cardiac disease are at risk for AIS at the time of cardiac procedures but also outside of the immediate 72 hours after procedures. Many have acute systemic illness or thrombotic event preceding AIS, suggesting that inflammatory or prothrombotic conditions could act as a stroke trigger in this susceptible population.

Introduction

Neonates and children with cardiac disease comprise one of the highest risk populations for pediatric arterial ischemic stroke (AIS), with a reported annual incidence rate ranging from 132 of 100,000 children to one of 100 children[1,2] compared with two to eight of 100,000 in the general pediatric population.[3,4] This risk persists beyond childhood. The prevalence of ischemic or hemorrhagic stroke in adults with congenital heart disease is estimated to be 10 to 100 times higher than that expected in healthy adults of similar age.[5] The prevalence of cardiac disease among children with AIS did not change between 1978 and 2009 despite improvement in acute medical and surgical management and outcomes in children with cardiac disease during this time period.[1]

Underlying heart disease contributes to AIS risk through right to left shunting of blood, increased systemic venous pressure, depressed heart function with aberrant flow dynamics, arrhythmias, infective endocarditis, or thrombophilias.[6] In addition, life-saving interventions such as cardiac surgery, cardiac catheterization, and mechanical circulatory support come with the cost of AIS as a potential complication.[2,7-11] Infection and thrombosis are also complications of cardiac interventions and influence AIS risk.[12] Infection has been shown to play a major role in childhood AIS pathogeneses of all causes, including spontaneous cardioembolic stroke.[13] Both acute infection and prothrombotic conditions at the time of initial AIS presentation are predictive of AIS recurrence within a 10-year period in children with congenital heart disease.[14] At a 2014 symposium of Stroke in Children with Cardiac Disease, a collaborative group of pediatric cardiologists, hematologists, and neurologists prioritized further study of co-existing multiple risk factors as critical for the development of successful AIS prevention strategies.[15]

In a population-based study of children with ischemic or hemorrhagic stroke, the index stroke occurred more than five years after the last cardiac procedure in almost half of patients who had a congenital heart defect (CHD) as the primary stroke risk factor.[16] Stroke risk related to CHD continues to be elevated in adulthood, years after cardiac surgery.[5,17-19] Among 204 children with AIS and cardiac disease enrolled between 2003 and 2007 in the International Pediatric Stroke Study (IPSS), approximately one quarter had the index AIS with 72 hours of cardiac surgery or cardiac catheterization[7.]

Most children with AIS have multiple converging risk factors. Understanding the conditions that influence the risk of stroke in peri-operative and nonsurgical settings is a critical first step toward a more honed approach to stroke prevention. Since the first IPSS report on children with cardiac disorders, the registry has grown to include 4294 children with AIS or venous sinus thrombosis from 87 sites in 24 countries,[20] allowing a stratified examination of children with peri-procedural versus spontaneous cardioembolic AIS. The IPSS collects standardized data regarding acute systemic illness at stroke onset, prior thrombosis, hypercoagulable conditions, and family history of thrombosis. Using these data, we sought to compare the reported frequencies of these potential risk factors in two groups with pediatric AIS related to CHD: those with AIS occurring within 72 hours of a cardiac procedure versus those with spontaneous cardioembolic AIS. In both groups, we also described initial antithrombotic management and short-term outcomes.

Methods

The IPSS is a multinational registry of prospectively gathered data on neonates and children with AIS or venous sinus thrombosis enrolled between January 1, 2003, and July 31, 2014. Study approval was obtained from the Institutional Review Board at each study site, and informed consent (and if applicable, assent) was obtained from participating parents or guardian and patients.

Inclusion criteria are as follows: (1) neonates or children with AIS that occurred from birth to less than 19 years and (2) AIS identified by the site investigator to have cardiac disease as its primary etiology. Children with isolated patent foramen ovale (PFO) or presumed perinatal AIS were excluded (Fig 1).

Local site investigators collected data as previously described.[20] Presumptive risk factors for stroke are identified and recorded by site investigators onto standardized forms and include cardiac disease (categorized as congenital, acquired, or isolated PFO), prothrombotic states, acute systemic illnesses, and family history of coagulopathy among others. **Definitions**: *Cardiac disease* was defined as an acquired heart disease (AHD) such as myocarditis or cardiac mass, or CHD. *Peri-procedural AIS* was defined as arterial ischemic stroke that occurred during or within 72 hours of cardiac surgery or catheterization or, if noted, during mechanical circulatory support such as a ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO). *Spontaneous AIS* was defined as arterial ischemic stroke that occurred more than 72 hours after cardiac surgery, cardiac catheterization, decannulation from ECMO, VAD removal, or outside of interventional cardiac treatment. Patients with AIS occurring beyond 72 hours after cardiac procedure was performed were classified as "spontaneous" but noted to have a history of cardiac surgery or other cardiac procedure. *Acute systemic illnesses* at the time of the AIS was identified by site investigators; these included sepsis, viral gastroenteritis, fever lasting more than 48 hours, acidosis, shock, and anoxia or asphyxia. *Chronic medical disorder* included genetic syndromes, malignancies, or underlying medical conditions other than primary cardiac disease. *Prothrombotic states* included inherited or acquired prothrombotic conditions such as those identified on laboratory testing, reported use of oral contraceptives, and treatment with L-asparaginase. *Thrombotic events* were intracardiac, pulmonary or systemic venous or arterial clots, transient ischemic attacks, additional AIS, or cerebral sinovenous thrombosis. These were considered *preceding* thrombotic events if they were identified more than 24 hours preceding or concurrent if identified within 24 hours of the index AIS. *Short-term outcome* refers to *recurrent* thrombotic events (if they occurred 24 hours or more after the index AIS) and status at hospital discharge categorized by local investigators as normal; mild, moderate, or severe neurological deficit; or death. *Poor outcome at discharge* was considered moderate or severe neurological deficit at the time of discharge. *Neonatal* AIS occurred from birth to 28 days, and *childhood* AIS occurred from 29 days to 18 years.

Statistical analysis

Data analysis was performed using SAS 9.3 (SAS Institute, Cary, NC, USA) and GraphPad Prism (GraphPad Software, Inc, La Jolla, CA,

USA). We used summary statistics to examine demographics and prespecified variables including stroke presentation, CHD, AHD, family history, acute systemic illness, chronic conditions, prior cardiac surgery (as a marker for disease severity and completeness of treatment of cardiac disease), antithrombotic management, and outcomes in patients with peri-procedural or spontaneous AIS. We compared the two groups using Fisher's exact or chi-square tests for categorical variables and *t* test to compare continuous variables if normally distributed. Data were less than 5% missing except where indicated. Antithrombotic management and congenital versus AHD data were missing unequally in the spontaneous sand peri-procedural groups, so statistical comparisons for these variables were not presented.

Results

Overall study group

Among 3253 patients with AIS, 903 (28%) were identified as having cardiac disease as the primary etiology for AIS. After excluding 231 with isolated PFO, our study population included 672 patients (Fig 1). The majority (n = 495, 74%) had a spontaneous AIS. In the 177 patients with peri-procedural AIS, the index stroke occurred within 72 hours of cardiac surgery in 92, diagnostic cardiac catheterization in 33, interventional cardiac catheterization in 30, support with VAD or ECMO in 24. In two patients, the index stroke occurred within 72 hours of both a cardiac surgery and interventional cardiac catheterization. CHD was identified in 504, whereas 105 had AHD and four had both CHD and AHD (variable missing in n = 59). Demographics and characteristics of the study group are provided in Table and were similar to prior IPSS reports (20).

Peri-procedural versus spontaneous AIS

In the majority of patients (n = 495, 74%), AIS was spontaneous rather than peri-procedural. The proportion of neonates was similar in both groups (23% of spontaneous AIS and 19% of peri-procedural AIS, Table). Among those with childhood AIS, spontaneous AIS occurred in older children (median age 4.2 years, interquartile range 0.97 to 12.4) compared with the age of those with peri-procedural AIS (median age 2.4 years, interquartile range 0.35 to 6.1, $P < 0.001$). Acute systemic illness at the time of the AIS was common overall (documented in 37% of those with spontaneous AIS and 31% of those with peri-procedural AIS, $P = 0.17$) and was more frequent in patients with AHD compared with patients

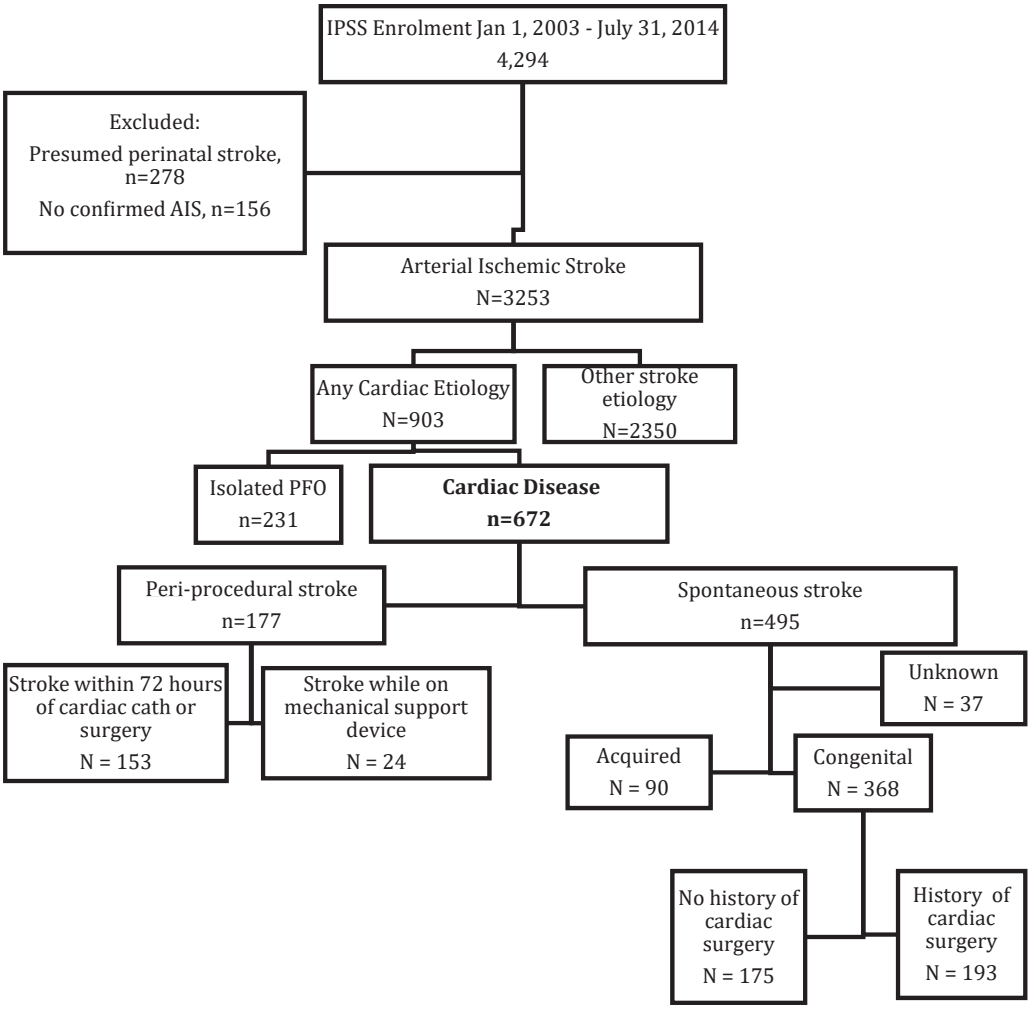

FIGURE 1. Among 672 neonates and children with cardiac disease in the International Pediatric Stroke Study, 26% had an arterial ischemic stroke within 72 hours of a cardiac procedure and 74% had a spontaneous cardioembolic arterial ischemic stroke.

with CHD (49% vs 34%, $P = 0.01$). A prothrombotic state was identified in 41 patients, including 34 of 495 (7%) patients with spontaneous AIS and 7 of 177 (4%) patients with peri-procedural AIS ($P = 0.7$). Preceding thrombotic events were more common among those with spontaneous AIS (16%) compared with those with peri-procedural AIS (9%, $P = 0.02$). Twenty-two patients (4%) with spontaneous AIS had preceding or concurrent intracardiac thrombi documented. A family history of thrombosis or hypercoaguability was reported in 11% of patients with spontaneous AIS and in 18% with a peri-procedural AIS ($P = 0.2$).

Within the group of 146 neonates, there was no difference between the peri-procedural and spontaneous AIS groups with regard to preceding thrombotic events, acute systemic illness, location of the infarct, and number of infarcts (single or multiple).

Anti-thrombotic management after AIS

Data were available regarding antithrombotic management in 643 patients. Providers initiated antithrombotic treatment after AIS in 460 of 643 patients. Of these patients, 236 (51%) initially received anticoagulation alone (low-molecular-weight heparin, coumadin, or unfractionated heparin). Another 164 patients (36%) received antiplatelet agents (aspirin or clopidogrel) alone, and 36 patients (8%) received combined antiplatelet agents and anticoagulation (6%). No other types of anticoagulation or antiplatelet agents were utilized. The initial antithrombotic treatment was not available for 24 (5%) patients. At discharge, over half of patients (58%) remained on an antithrombotic medication, with aspirin being the most common choice followed by low-molecular-weight heparin (Fig 2). Patients with CHD were more likely to be discharged home on an antithrombotic therapy (84.3% of patients with CHD) than patients with AHD (15.7%), $P = 0.02$.

Short-term outcomes after AIS

Stroke recurrence was reported after peri-procedural AIS (n = 7, 4%) and spontaneous AIS (n = 36, 7%). There were no differences between the groups in the frequency of recurrent AIS, recurrent thrombotic events, or outcome at the time of discharge (Table). Nine neonates (8%) with spontaneous AIS had recurrent thrombotic events, and eight of these were recurrent AIS or transient ischemic attack. Two neonates (6%) in the peri-procedural group had a recurrent thrombotic event, neither of which were AIS. There were 47 in-hospital deaths (7%). Of the patients who survived to hospital discharge, 392 (58%) had a moderate or severe neurological deficit.

Discussion

In this large, international registry of children with AIS, nearly one-third of the patients had cardiac disease as the primary underlying etiology. Children with cardiac disease are at known risk for AIS following cardiac procedures, especially children with cyanotic CHD.[8,21] Spontaneous AIS was reported three times more frequently than peri-procedural AIS. However, our study was not designed to directly compare peri-procedural versus spontaneous stroke risk; thus this finding should not be used to de-emphasize the risk of cardiac procedures. The short time at-risk for peri-procedural stroke represents only a small percentage of a child's lifetime, yet 26% of the strokes in this study occurred during this period. Our data show that both peri-procedural and spontaneous AIS are important morbidities of pediatric heart disease. Stroke mechanisms are often multifactorial in children with cardiac disease, related to co-morbid polycythemia, chronic hypoxia, embolic or thrombotic disease, and abnormal flow and foreign devices or materials. Identifying and addressing risk factors for AIS that are not directly procedure related and those that increase stroke risk at the time of a cardiac procedure are the first steps toward improving stroke prevention in these children.

Children with peri-procedural AIS tended to be younger (median age 2.4 years) than those with spontaneous strokes (4.2 years). Although a number of factors may contribute to this age discrepancy, we speculate that this is primarily driven by the typical timing of invasive cardiac procedures and complicated cardiac surgeries during the first few years of life in children with single ventricle physiology and more severe forms of congenital heart disease. Although stroke risk is not homogeneous across all cardiac procedures, we had limited details to differentiate between the procedures in the registry. For example, ECMO was included as a

TABLE
Demographics, Characteristics, and Secondary Stroke Prevention in 672 Neonates and Children With Stroke due to Complex Cardiac Disease

Variable	Total, N = 672*	Spontaneous, n = 495	Peri-procedural, n = 177	*P* Value
	n (%)	n (%)	n (%)	
Neonatal	146 (22)	112 (23)	34 (19)	0.34
Male sex	387 (58)	298 (60)	91 (51)	0.04
Congenital heart disease (of N = 619)	508 (75)	368 (79)	140 (93)	
Preceding events				
Preceding thrombotic event	97 (14)	81 (16)	16 (9)	0.02
Chronic disorder	217 (32)	176 (36)	41 (23)	0.002
Prior cardiac surgery	252 (36)	241 (49)	11 (6)	<0.001
Presentation				
Hemiparesis (of n = 641)	391 (63)	291/456 (64)	100/162 (62)	0.64
Seizures	267 (40)	179 (36)	88 (50)	0.001
Acute systemic illness at time of stroke	237 (35)	182 (37)	55 (31)	0.17
Stroke location and type				
Anterior circulation only	429 (64)	322 (65)	107 (60)	0.46
Large-vessel stroke	289 (43)	211 (43)	78 (44)	0.22
Bilateral	182 (27)	120 (24)	62 (35)	0.006
Multiple strokes (of n = 551)	262 (48)	186/403 (46)	76/148 (51)	0.33
Outcome				
Died before discharge	47 (7)	37 (7)	10 (6)	0.4
Poor outcome at discharge (of N = 625 survivors)	392 (58)	333 (67)	59 (33)	<0.001
Recurrent thrombotic events	52 (8)	42 (8)	10 (6)	0.22
Recurrent stroke or TIA	43 (6)	36 (7)	7 (4)	0.12

Abbreviation:
TIA = Transient ischemic attack
* Values do not always add up to 672 total as data were missing for some patients.

cardiac procedure, but is associated with uniquely high stroke risk.[22] In some cases, more than one procedure (for example, ECMO and a catheterization or surgery) may have occurred in the preceding 72 hours that were not captured separately.

Acute systemic illness was frequently reported in both groups of patients. Mackay et al. found that postprocedural infection increases the odds of stroke fivefold in children with CHD after a cardiac procedure.[8] Acute infection at the time of sentinel stroke also has been reported to increase the risk of recurrent stroke in neonates and children with CHD.[14] Acute illness may further exacerbate the risk of thrombosis in children with cardiac disease by worsening acidosis (and potentially cardiac function) or decreasing oxygenation (e.g., those with pulmonary hypertension). In the Vascular effects of Infection in Pediatric Stroke study, infection within the week before stroke increased the risk of AIS by 6.3-fold, and was reported in 22% of the children with spontaneous cardioembolic AIS.[13] We cannot draw a causal relationship between acute systemic illness and AIS from our data, but further investigation into the role of acute systemic illness in AIS in children with cardiac disease is warranted. Elucidation of the mechanisms whereby infection might lead to AIS, including endocarditis or acquired prothrombotic states may improve early identification of cardiac patients who are at high risk for AIS.

Among the children with spontaneous AIS, we found that preceding or concurrent thrombotic events were common. However, the group with spontaneous AIS was older with more time at risk

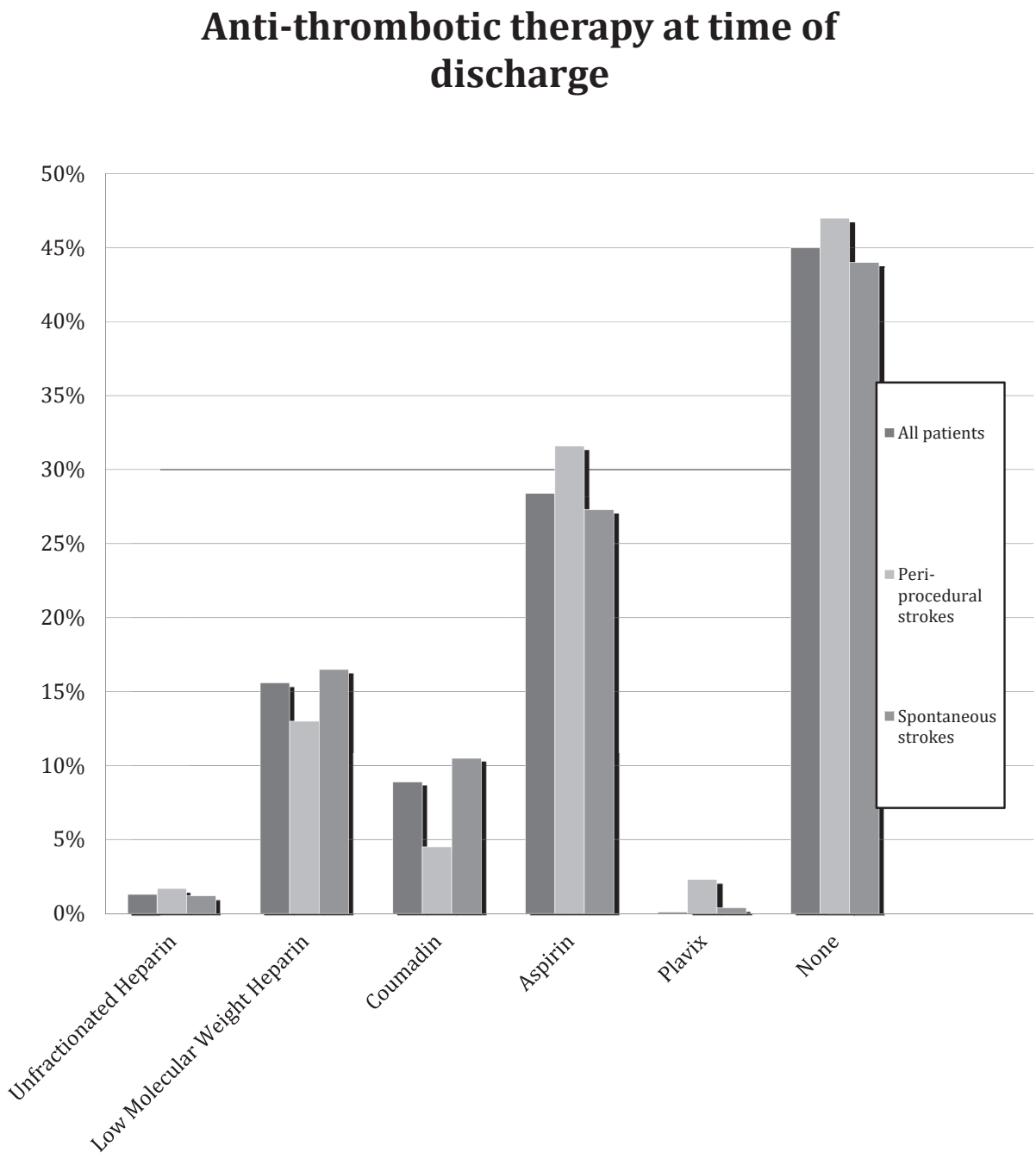

FIGURE 2. Among 672 neonates and children with arterial ischemic stroke related to cardiac disease, antithrombotic therapy data was available for 643 patients; 57% (n = 371) were discharged from the hospital with an antithrombotic medication. Antithrombotic management did not vary whether the stroke was peri-procedural or a spontaneous cardioembolic stroke.

for a preceding thrombotic event. Approximately half of the children with spontaneous AIS had a remote history of cardiac surgery. Although some surgical interventions such as Fontan surgery are associated with increased risk of thromboembolic events,[23] we did not have the specific surgeries performed in all the patients and are unable to compare spontaneous AIS risk for particular subtypes of surgical procedures. Stroke risk after palliative cardiac surgery may differ from stroke risk after completed surgical repair (8). We were unable to precisely determine how many had an acquired or congenital underlying thrombophilic condition due to incomplete testing, but some studies suggest these are[24] common in neonates and children with complex cardiac defects.[25-28] Neonates and children with cardiac disease and stroke were more likely to have an elevated lipoprotein a, protein C deficiency, or positive anticardiolipin antibodies than age-matched controls.[28] D-dimer level, a functional measurement of coagulation activation, is acutely elevated in children with cardioembolic AIS compared with other types of AIS and remains persistently elevated over months.[12] Markers of active thrombosis were transiently elevated in 18 of 18 children after cardiac surgery.[27] Cardiac surgery itself may induce an imbalance between pro- and antithrombotic states in the coagulation cascade, especially in single-ventricle patients who are considered to be at higher risk for thrombosis than patients with other CHDs.[24,25]

A thromboembolic recurrence was only reported in a small number of patients. Generally, recurrent stroke after neonatal AIS overall is uncommon, but we found that 8% of neonates with CHD had a recurrent AIS. Because the length of follow-up after hospitalization varied, this proportion should be considered a minimum proportion. Prothrombotic states predict stroke recurrence in children with CHD,[14] yet investigators reported thrombophilia testing in only a small percentage of patients with cardiac disease in the IPSS (12.4%). Thrombophilia testing may have been underreported; these studies are often completed in a delayed fashion and may have been captured later. The American Heart Association (AHA) Guidelines on Management of Stroke in Infants and Children suggests reasonable evaluation for the more common prothrombotic states even when another stroke risk factor has been identified (Class IIa, Level of Evidence C).[29] The updated 2019 AHA guidelines for Management of Stroke in Neonates and Children[30] and the AHA Guidelines on Prevention and Treatment of Thrombosis in Pediatric and Congenital Heart Disease concur with these recommendations and suggest considering evaluation for inherited or acquired prothrombotic risk factors in children with heart disease who have a stroke (Class IIa, Level of Evidence B).[6] Although routine testing for hypercoaguability after neonatal stroke may not be indicated in the absence of cardiac disease,[31] in neonates and children with CHD, a thrombophilia evaluation may be appropriate. Consistent thrombophilia testing in children with cardiac disease may help identify children with additional risk factors for AIS who accordingly, should be considered for more intensive or longer-term antithrombotic treatment for primary or secondary AIS prevention.

We noted substantial variation in antithrombotic treatment, finding that only 60% of patients were discharged home on an antithrombotic medication. Among patients who received antithrombotic treatment, the majority initially received anticoagulation rather than antiplatelet agents. In contrast, the majority of patients were discharged with an antiplatelet agent (usually aspirin) rather than anticoagulation. Some of the patients in the IPSS may have had prior indications for aspirin related to stents or their cardiac disease, or may have had a contraindication to anticoagulation. However, small studies suggest aspirin may not be an adequate agent for AIS prevention in these children. In a series of 20 children with single-ventricle palliative shunt surgery who were monitored with thromboelastography to measure platelet function, 80% were aspirin resistant in the postoperative period.[32] Aspirin resistance is associated with increased risk of thrombosis in pediatric patients undergoing cardiac surgery.[26] AHA guidelines suggest that low-molecular-weight heparin or warfarin treatment for at least one year (or until the lesion responsible for the risk has been corrected) is reasonable in children with a risk of cardiac embolism,[29] but in practice it appears that a limited proportion of patients with cardiac disease and AIS are managed in this way.

Among neonates and children with AIS in the IPSS registry, congenital heart disease is associated with a higher rate of in-hospital mortality than other stroke etiologies.[20] We found that 58% of survivors of cardiac-related stroke had a poor outcome at the time of discharge. We only reported short-term outcomes (at hospital discharge) because longer follow-up was not included in the initial IPSS data collection. This finding should be interpreted cautiously. Stroke outcome at hospital discharge may not be representative of the ultimate degree of neurological recovery, particularly in children who may also be recovering from a cardiac surgery. Conversely, language or motor deficits may become more prominent over time in infants or young children with a stroke.

There are several limitations in the use of the IPSS database. The definition we used for peri-procedural AIS (one that occurs within 72 hours of a cardiac procedure) is narrow, and the proportion of patients with peri-procedural AIS may have been higher if a longer interval had been allowed. Estimating the time that AIS occurred can be difficult and imprecise because sedation limits the discovery of clinical symptoms and imaging is often delayed in post-surgical or critically ill patients. The database only includes patients captured by the site investigators and does not represent all pediatric patients with AIS secondary to cardiac disease during this time period; thus the prevalence of variables analyzed may have been over- or under-represented in the IPSS database. Differentiation of cyanotic versus non-cyanotic heart disease and single-ventricle status were not available. Follow-up after hospital discharge varied, and the prevalence of recurrent thrombotic events in our study is likely underestimated.

Summary

Many cardiac-related pediatric AIS occur outside the immediate peri-procedural window. A high proportion of the patients in our study appeared to have an acute systemic illness as an additional trigger for the AIS or a prior thrombotic event. Choice and duration of treatment with antithrombotic therapy was inconsistent. These findings reflect uncertainties in optimal clinical care for a complicated and heterogeneous group; additional data are required to guide evidence-based management. Further multicenter prospective studies are needed to determine best the practices for secondary stroke prevention in this vulnerable population.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2019.06.008.

References

1. Hoffman JL, Mack GK, Minich LL, et al. Failure to impact prevalence of arterial ischemic stroke in pediatric cardiac patients over three decades. Congenit Heart Dis. 2011;6:211–218.
2. Cheng HH, Rajagopal S, McDavitt E, et al. Stroke in acquired and congenital heart disease patients and its relationship to hospital mortality and lasting neurologic deficits. Pediatr Crit Care Med. 2016;17:976–983.
3. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. Neurology. 2003;61:189–194.
4. Giroud M, Lemesle M, Gouyon JB, Nivelon JL, Milan C, Dumas R. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993. J Clin Epidemiol. 1995;48:1343–1348.
5. Hoffmann A, Chockalingam P, Balint OH, et al. Cerebrovascular accidents in adult patients with congenital heart disease. Heart. 2010;96:1223–1226.
6. Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2013;128:2622–2703.
7. Dowling MM, Hynan LS, Lo W, et al, International Paediatric Stroke Study Group. International Paediatric stroke study: stroke associated with cardiac disorders. Int J Stroke. 2013;8(Suppl A100):39–44.
8. Asakai H, Cardamone M, Hutchinson D, et al. Arterial ischemic stroke in children with cardiac disease. Neurology. 2015;85:2053–2059.
9. Chen J, Zimmerman RA, Jarvik GP, et al. Perioperative stroke in infants undergoing open heart operations for congenital heart disease. Ann Thorac Surg. 2009;88:823–829.
10. Trittenwein G, Nardi A, Pansi H, et al, Verein zur Durchfuhrung wissenschaftlichter Forschung auf dem Gebeit der Neonatologie und Padiatrischen I. Early postoperative prediction of cerebral damage after pediatric cardiac surgery. Ann Thorac Surg. 2003;76:576–580.
11. McQuillen PS, Barkovich AJ, Hamrick SE, et al. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. Stroke. 2007;38(Suppl 2):736–741.
12. Bernard TJ, Fenton LZ, Apkon SD, et al. Biomarkers of hypercoagulability and inflammation in childhood-onset arterial ischemic stroke. J Pediatr. 2010;156:651–656.
13. Fullerton HJ, Hills NK, Elkind MS, et al. Infection, vaccination, and childhood arterial ischemic stroke: results of the VIPS study. Neurology. 2015;85:1459–1466.
14. Rodan L, McCrindle BW, Manlhiot C, et al. Stroke recurrence in children with congenital heart disease. Ann Neurol. 2012;72:103–111.
15. Sinclair AJ, Fox CK, Ichord RN, et al. Stroke in children with cardiac disease: report from the International Pediatric Stroke Study Group Symposium. Pediatr Neurol. 2015;52:5–15.
16. Fox CK, Sidney S, Fullerton HJ. Community-based case-control study of childhood stroke risk associated with congenital heart disease. Stroke. 2015;46:336–340.
17. Lin YS, Liu PH, Wu LS, Chen YM, Chang CJ, Chu PH. Major adverse cardiovascular events in adult congenital heart disease: a population-based follow-up study from Taiwan. BMC Cardiovasc Disord. 2014;14:38.
18. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Hansson PO, Dellborg M. Ischemic stroke in children and young adults with congenital heart disease. J Am Heart Assoc. 2016;5.
19. Jensen AS, Idorn L, Thomsen C, et al. Prevalence of cerebral and pulmonary thrombosis in patients with cyanotic congenital heart disease. Heart. 2015;101:1540–1546.
20. Beslow LA, Dowling MM, Hassanein SMA, et al, International Pediatric Stroke Study I. Mortality after pediatric arterial ischemic stroke. Pediatrics. 2018;141(5).
21. Ziesmann MT, Nash M, Booth FA, Rafay MF. Cardioembolic stroke in children: a clinical presentation and outcome study. Pediatr Neurol. 2014;51:494–502.
22. Werho DK, Pasquali SK, Yu S, et al. Epidemiology of stroke in pediatric cardiac surgical patients supported with extracorporeal membrane oxygenation. Ann Thorac Surg. 2015;100:1751–1757.
23. Alsaied T, Alsidawi S, Allen CC, Faircloth J, Palumbo JS, Veldtman GR. Strategies for thromboprophylaxis in Fontan circulation: a meta-analysis. Heart. 2015;101:1731–1737.
24. Odegard KC, Zurakowski D, DiNardo JA, et al. Prospective longitudinal study of coagulation profiles in children with hypoplastic left heart syndrome from stage I through Fontan completion. J Thorac Cardiovasc Surg. 2009;137:934–941.
25. Emani S, Zurakowski D, Baird CW, Pigula FA, Trenor 3rd C, Emani SM. Hypercoagulability markers predict thrombosis in single ventricle neonates undergoing cardiac surgery. Ann Thorac Surg. 2013;96:651–656.
26. Emani S, Zurakowski D, Baird CW, Pigula FA, Trenor 3rd C, Emani SM. Hypercoagulability panel testing predicts thrombosis in neonates undergoing cardiac surgery. Am J Hematol. 2014;89:151–155.
27. Heying R, van Oeveren W, Wilhelm S, et al. Children undergoing cardiac surgery for complex cardiac defects show imbalance between pro- and antithrombotic activity. Crit Care. 2006;10:R165.
28. Strater R, Vielhaber H, Kassenbohmer R, von Kries R, Gobel U, Nowak-Gottl U. Genetic risk factors of thrombophilia in ischaemic childhood stroke of cardiac origin. A prospective ESPED survey. Eur J Pediatr. 1999;158(Suppl 3):S122–S125.
29. Roach ES, Golomb MR, Adams R, et al, American Heart Association Stroke C, Council on Cardiovascular Disease in the Y. Management of stroke in infants and children: a scientific statement from a special Writing group of the American Heart Association Stroke Council and the Council on cardiovascular disease in the young. Stroke. 2008;39:2644–2691.
30. Ferriero DM, Fullerton HJ, Bernard TJ, et al, American Heart Association Stroke C, Council on C, Stroke N. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. Stroke. 2019;50:e51–e96.
31. Curtis C, Mineyko A, Massicotte P, et al. Thrombophilia risk is not increased in children after perinatal stroke. Blood. 2017;129:2793–2800.
32. Mir A, Frank S, Journeycake J, et al. Aspirin resistance in single-ventricle physiology: aspirin prophylaxis is not adequate to inhibit platelets in the immediate postoperative period. Ann Thorac Surg. 2015;99:2158–2164.