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Cerebrovascular accidents in Ebstein's anomaly

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Abstract

Introduction: Mechanisms and risk factors for cerebrovascular accidents (CVAs) in Ebstein's anomaly (EA) are not well understood; hence, we aimed to clarify these in a large cohort of EA patients.

Methods: Patients with a confirmed diagnosis of EA were retrospectively reviewed. Baseline characteristics were compared between patients with and without a prior history of CVA using logistic regression modeling. Cox regression analysis was used to identify predictors of CVA following initial evaluation. CVA incidence from birth and following tricuspid valve surgery were estimated using the Kaplan-Meier method.

Results: Nine hundred sixty-eight patients (median age 21.1 years, 41.5% male) were included, in which, 87 patients (9.0%) had a history of CVA (54 strokes, 33 transient ischemic attacks; 5 associated with brain abscesses) prior to their initial evaluation. The odds of atrial septal defect/patent foramen ovale (odds ratio [OR] 4.91; 95% CI 2.60-21.22; p = .0002) and migraines/headaches (OR 2.38; 95% CI 1.40-4.04; p = .0013) but not atrial arrhythmias (OR 0.75; 95% CI 0.44-1.30; p = .31) were significantly higher among patients with prior CVA following multivariable adjustment. Seventeen patients experienced CVA following initial evaluation; no examined variables including atrial arrhythmias (HR 2.38; 0.91-6.19; p = .076) were predictive of CVA risk. The 10-year, 50-year, and 70-year incidences of CVA were 1.4%, 15.9%, and 23.5%, respectively, with paradoxical embolism heavily implicated.

Conclusion: Patients with EA are at substantive risk for CVA. Histories of migraines/headaches and interatrial shunts should prompt concern for paradoxical embolic CVAs. This has significant implications for all patients with atrial-level shunting.

KEYWORDS

cerebrovascular accident, Ebstein's anomaly, stroke

1 | INTRODUCTION

Ebstein's anomaly (EA) is predominantly a right-sided cardiomyopathy characterized by ventricular displacement of the tricuspid valve (TV) into the right ventricle (RV), a dilated TV annulus, enlarged and dysmorphic TV leaflets, as well as atrialization of the RV with right atrial (RA) enlargement.[1,2] Atrial septal defects (ASDs) and patent foramen ovales (PFOs) are frequently present in this complex malformation,[3-5] and atrial arrhythmias are often seen as well.[2,4-7] In patients with acquired heart disease, atrial arrhythmias are strongly associated

with cerebrovascular accidents (CVAs) or systemic thromboembolism.[6] While these events are relatively uncommon among young patients with structurally normal hearts and no other risk factors,[8-11] patients with congenital heart disease (CHD) are known to exhibit a 10-100-fold increased risk of CVA with associated morbidity and mortality.[12-14]

The incidence and risk factors for CVA in EA remain unclear, and given the profound clinical impact of such events, we therefore aimed to: (a) Describe the long-term incidence of CVA among a large cohort of patients with EA and (b) Identify clinical predictors associated with CVA in this CHD population.

2 | METHODS

2.1 | Patient population

All patients seen at Mayo Clinic Rochester with a confirmed diagnosis of EA between April 1972 and December 31, 2015 were retrospectively reviewed.[15] Inclusion criteria were EA with atrioventricular and ventriculo-arterial concordance and two ventricles. Exclusion criteria were: pulmonary atresia with intact ventricular septum; complex conotruncal abnormalities; and congenitally corrected transposition of the great arteries (ccTGA). Written informed consent was obtained for all participating patients. The study was in compliance with the principles outlined in the Declaration of Helsinki, and its ethical aspects were reviewed and approved by the Mayo Clinic Institutional Review Board.

2.2 | Data review

Paper and electronic medical records for included patients were reviewed. Demographics and pertinent clinical histories were recorded. In addition, baseline echocardiographic data, electrocardiography/electrophysiology studies, and cardiovascular surgical reports were reviewed. Perioperative (defined as period of hospitalization following surgery) conduction abnormalities or ventricular arrhythmias requiring permanent pacemaker (PPM) or internal cardioverter defibrillator (ICD) implantation were documented as well.

2.3 | Assessment of clinical outcome

CVA was defined as: (a) Acute onset neurovascular event with brain imaging abnormalities congruent with the clinical presentation (stroke) or (b) Acute onset neurologic dysfunction due to focal ischemia without evidence of infarction (transient ischemic attack [TIA]).[16,17] History of stroke or TIA was identified for verification on chart review—an event was recorded if the clinical scenario and available imaging were consistent with the diagnosis. All neurologic symptoms that were identified at our institution were evaluated clinically and with imaging. The mechanism of CVA was ascertained via chart review of the clinician(s) who evaluated the patient. Paradoxical embolism was assumed to be the cause if an interatrial shunt was present and there was no other evidence of other etiologies such as atrial arrhythmias. Perioperative CVAs occurred intraoperatively or within the hospitalization for surgery.

2.4 | Statistical analysis

Univariable associations with history of CVA were tested using logistic regression. Statistically and clinically significant associations were further examined with multivariable logistic regression; variables selected for the model included hypertension, diabetes, gender, ASD/PFO, migraine/headache, coronary artery disease (CAD), atrial arrhythmias, and prior PPM/ICD. Univariable logistic regression analysis was also used in the subset of patients with atrial arrhythmias to determine associations between prior CVA and components of the CHA_2DS_2VASC score.

Overall CVA rates occurring after initial evaluation were estimated with the Kaplan-Meier method. Associations were tested using univariable Cox proportional hazards modeling for clinical/demographic parameters.

For patients who underwent TV surgery at our institution, Kaplan-Meier analysis of the postoperative incidence of CVA was performed. Additionally, Cox proportional hazards modeling was used to identify potential associations between surgical procedures performed and CVA after surgery.

3 | RESULTS

3.1 | Baseline characteristics

Nine hundred sixty-eight patients (median age 21.1 years [range 0-82 years], 41.5% male) were included (Table 1). Ninety CVAs occurring prior to evaluation and 22 CVAs occurring postevaluation at our institution were identified (Figure 1). Forty-four CVAs did not have imaging available for review, primarily because these predated the routine use of cross-sectional head imaging (before 1980). Eight hundred eight patients underwent TV surgery at our institution following initial evaluation. Eighty-seven patients (9.0%) had a prior history of nonperioperative CVA (54 strokes, 33 TIAs), of whom 5 developed brain abscesses. All strokes identified were ischemic in nature. Patients with positive CVA histories were older at the time of evaluation (median age 38.0 years vs 18.8 years); in addition, they had higher proportions of migraines/headaches, ASD/PFO, CAD, and hypertension. With multivariable logistic regression, the odds of ASD/PFO (OR 7.43; 95% CI 2.60-21.22; $p = .0002$) and migraine/headache (OR 2.38; 95% CI 1.40-4.04; $p = .0013$) were significantly higher among patients with prior CVA (Table 2). In contrast, prior PPM/ICD (OR 0.65; 95% CI 0.13-3.31; $p = .61$) and atrial arrhythmias (OR 0.75; 95% CI 0.44-1.30; $p = .31$) were not associated with a history of CVA.

For the subset of patients with atrial arrhythmias (total $n = 285$), median CHA_2DS_2VASC scores among patients with and without prior CVA were 2 and 0, respectively (Table 3). Of all the components comprising the CHA_2DS_2VASC score, only age was significantly associated with prior CVA (OR 1.03; 95% CI 1.00-1.05; $p = .008$).

3.2 | Incidence of cerebrovascular accidents throughout life

The 10-year, 50-year, and 70-year incidences of CVA were 1.4%, 15.9%, and 23.5%, respectively (Figure 2). The median age at first CVA was 28.3 years.

TABLE 1 Comparison of study cohort clinical and echocardiographic characteristics among patients with and without a prior history of CVA (*N* = 968)

Variable	No history of CVA (*N* = 881)	History of CVA (*N* = 87)
Clinical characteristics		
Age at evaluation, years	18.8 (8.4, 36.4)	38.0 (26.3, 49.6)
Age of CVA, years	N/A	28.5 (18.2, 43.6)
Female gender	514 (58.3%)	52 (59.8%)
Age at surgery, years (*N* = 808)	20.7 (10.9, 38.1)	40.7 (26.8, 50.7)
Hypertension	67 (7.6%)	13 (14.9%)
Diabetes	18 (2.0%)	2 (2.3%)
Heart failure	197 (22.7%)	23 (26.4%)
CAD	46 (5.4%)	10 (12.0%)
Smoking	87 (9.9%)	11 (12.6%)
Hyperlipidemia	71 (8.1%)	12 (13.8%)
Paradoxical myocardial infarction	3 (0.3%)	1 (1.1%)
Migraine/headache	160 (18.2%)	29 (34.1%)
Atrial arrhythmias	256 (29.5%)	29 (34.1%)
Prior cardiovascular surgery	245 (27.8%)	20 (23.0%)
Number of cardiovascular surgeries	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Prior TV surgery	146 (59.6%)	7 (35.0%)
Number of TV surgeries	1 (0.0, 1.0)	0 (0.0, 1.0)
Prior Glenn shunt	24 (2.7%)	4 (4.6%)
Prior ASD/PFO closure	145 (59.2%)	12 (60.0%)
Prior transcatheter ASD/PFO closure	8 (0.9%)	2 (2.3%)
Prior PPM/ICD	20 (2.3%)	2 (2.3%)
Echocardiographic parameters		
LVEF	60 (55.0, 63.0)	60 (55.0, 63.0)
LV noncompaction	26 (3.0%)	3 (3.4%)
LA enlargement	124 (16.6%)	15 (19.0%)
Degree TR		
None/trivial	11 (1.2%)	0 (0.0%)
Mild	38 (4.3%)	4 (4.6%)
Moderate	114 (12.9%)	11 (12.6%)
Severe	718 (81.5%)	72 (82.8%)
Severity EA		
Mild	60 (6.9%)	5 (5.7%)
Moderate	122 (14.1%)	5 (5.7%)
Severe	684 (79.0%)	77 (88.5%)
RV enlargement	832 (97.9%)	85 (100.0%)
RV function		
Normal	99 (12.5%)	6 (8.0%)
Mild	178 (22.4%)	12 (16.0%)
Moderate	326 (41.0%)	40 (53.3%)
Severe	192 (24.2%)	17 (22.7%)
Interatrial shunting (ASD or PFO)	678 (77.0%)	82 (94.3%)
ASD	508 (57.7%)	73 (83.9%)
PFO	170 (19.3%)	9 (10.3%)

(Continues)

TABLE 1 (Continued)

Variable	No history of CVA (*N* = 881)	History of CVA (*N* = 87)
VSD	55 (6.2%)	3 (3.4%)
CVA type		
TIA	N/A	33 (37.9%)
Stroke	N/A	54 (62.1%)

Notes: Median and IQR are presented for continuous variables, and frequency and percent are presented for categorical variables. Information was unavailable regarding hypertension (*n* = 1), heart failure (*n* = 12), CAD (*n* = 29), family history of CHD (*n* = 36), migraines/headaches (*n* = 4), accessory pathway (*n* = 12), atrial arrhythmias (*n* = 16), prior transcatheter ASD/PFO closure (*n* = 3), LA enlargement (*n* = 144), EA severity (*n* = 15), RV enlargement (*n* = 33), RV function (*n* = 98), and MVP (*n* = 1).

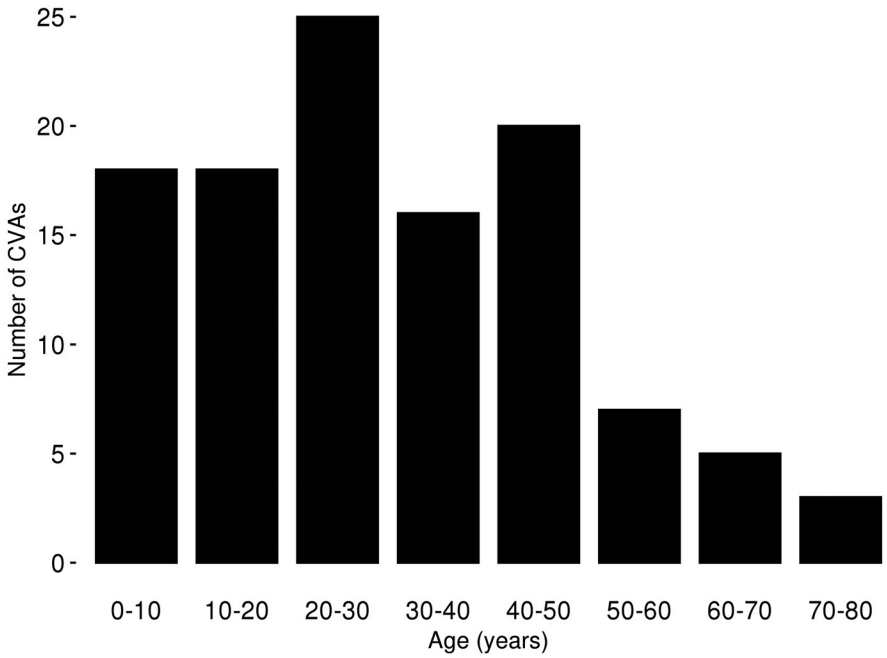


FIGURE 1 Breakdown of CVA events by age in decades (patient *N* = 968)

3.3 | Univariable Cox proportional hazards modeling of predictors associated with cerebrovascular accidents

Twenty-two patients experienced CVA events (16 strokes, 6 TIAs) following initial evaluation at our institution (Table 4); all strokes were ischemic in nature. Five were perioperative CVAs and were excluded from the analysis. Prior transcatheter ASD/PFO closure was significantly associated with CVA, with a hazard ratio (HR) of 21.43 (95% CI 2.62-175.10; p = .004). There was no increased CVA risk with migraine/headache (HR 1.29; 95% CI 0.42-3.98; p = .65), ASD/PFO (HR 1.96; 95% CI 0.45-8.57; p = .78), hypertension (HR 0.88; 95% CI 0.12-6.68; p = .90), or CAD (HR 1.13; 95% CI 0.15-8.55; p = .91). Additionally, no significant associations between CVA and atrial arrhythmia history (HR 2.38; 95% CI 0.91-6.19; p = .076) were observed.

3.4 | Incidence of cerebrovascular accidents posttricuspid valve surgery

Ten patients had CVA events between their initial evaluation and surgical procedure. Five patients also suffered intraoperative CVAs. Hence, excluding these events, there was a total of four CVAs that occurred post-TV surgery among 803 patients. The 5-year, 10-year, and 20-year incidences of CVA following TV surgery were 0.4%, 0.6%, and 1.3%, respectively (Figure 3).

3.5 | Investigation of associations between cerebrovascular accidents and surgical procedures performed

Table 5 shows the HRs for the procedures performed in association with CVA among patients who underwent TV surgery at our institution. There was no evidence of associations between CVA risk and any of the procedures performed.

3.6 | Mechanisms of cerebrovascular accidents

Paradoxical embolism was the most common mechanism of CVA implicated (Table 6). Eight patients also experienced CVAs in the perioperative setting. Ten patients had multiple risk factors for CVA, with the combination of interatrial shunting and atrial arrhythmias being the most common.

TABLE 2 Multivariable logistic regression analysis of clinical variables associated with a history of CVA (*N* = 968)

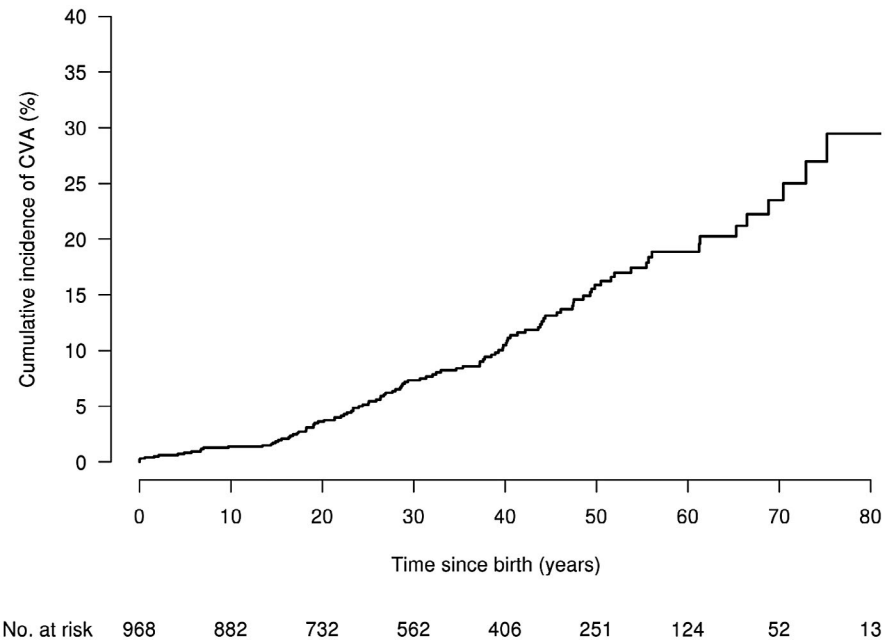
Variable	Unadjusted odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Age at evaluation	1.04 (1.03, 1.05)	<.0001	1.05 (1.03, 1.07)	<.0001
Male gender	0.94 (0.60, 1.48)	.80	1.28 (0.77, 2.13)	.35
Hypertension	2.13 (1.12, 4.04)	.020	0.97 (0.45, 2.09)	.93
Diabetes	1.13 (0.26, 4.95)	.87	0.69 (0.14, 3.38)	.65
CAD	2.41 (1.17, 4.98)	.017	1.10 (0.47, 2.59)	.83
Atrial arrhythmias	1.24 (0.77, 1.98)	.38	0.75 (0.44, 1.30)	.31
ASD/PFO	4.91 (1.96, 12.27)	.0007	7.43 (2.60, 21.22)	.0002
Migraine/headache	2.33 (1.44, 3.76)	.0006	2.38 (1.40, 4.04)	.0013
Prior PPM/ICD	1.01 (0.23, 4.41)	.99	0.65 (0.13, 3.31)	.61

TABLE 3 Univariable logistic regression analysis of clinical variables associated with CVA in the subset of patients with atrial arrhythmias (total *N* = 285)

Variable	No history of CVA (*N* = 256)	History of CVA (*N* = 29)	OR (95% CI)	*p* value
Heart Failure	77 (30.3%)	7 (24.1%)	0.73 (0.30, 1.78)	.49
Hypertension	29 (11.3%)	4 (13.8%)	1.25 (0.41, 3.85)	.69
Age	31.3 (15.6, 47.5)	40 (32.8, 56.2)	1.03 (1.00, 1.05)	.008
Diabetes	7 (2.7%)	0 (0.0%)	N/A	N/A
CAD	14 (5.6%)	2 (7.4%)	1.34 (0.29, 6.23)	.71
CHA_2DS_2VASC score	0 (0, 1)	2 (2, 3)	6.38 (3.58, 11.38)	<.001

Notes: Median and IQR are presented for continuous variables, and frequency and percent are presented for categorical variables. Information was unavailable regarding heart failure (*n* = 2), CAD (*n* = 10), and CHA_2DS_2VASC score (*n* = 12).

FIGURE 2 Kaplan-Meier curve of CVA rates in study population from time of birth



4 | DISCUSSION

In our study, CVA is a major clinical issue among EA patients, with recognition at a relatively young age (median 28.3 years), and almost a quarter afflicted over a 70-year period. Paradoxical embolism appears to be the predominant etiology, given the strong links to pre-existing ASD/PFO and migraine/headache.

The incidence and risk factors of CVA specific to adult CHD have recently been alluded to in large registries across North America.[12,18] For example, the cumulative risk of ischemic stroke in a cohort of 29 638 adult CHD patients from Quebec was 6.1% in women and 7.7% in men, respectively.[18] Our data confirm that there is a high CVA burden specifically among EA patients. Interatrial shunting, present in the majority of EA patients (~80% in our study),[3,4] may lead to CVA

TABLE 4 Associations of CVA after initial evaluation with clinical variables in overall cohort, adjusted for TV surgery (*N* = 968)

Variable	Hazard ratio (95% CI)	*p* value
Clinical characteristics		
Age at evaluation, years	1.01 (0.98, 1.04)	.44
Female gender	0.93 (0.35, 2.44)	.88
Age at surgery, years (*N* = 803)	1.02 (0.99, 1.05)	.14
Hypertension	0.88 (0.12, 6.68)	.90
Diabetes	4.02 (0.53, 30.50)	.18
Heart failure	0.97 (0.32, 2.99)	.96
CAD	1.13 (0.15, 8.55)	.91
Smoking	N/A	N/A
Hyperlipidemia	0.87 (0.12, 6.61)	.89
Migraine/headache	1.29 (0.42, 3.98)	.65
Atrial arrhythmias	2.38 (0.91, 6.19)	.076
Prior cardiovascular surgery	1.22 (0.45, 3.31)	.70
Number of cardiovascular surgeries	0.89 (0.12, 6.39)	.90
Prior TV surgery	1.32 (0.24, 7.27)	.75
Number of TV surgeries	1.00 (0.26, 3.84)	1.00
Prior surgical ASD/PFO closure	1.02 (0.19, 5.63)	.98
Prior transcatheter ASD/PFO closure	21.43 (2.62, 175.10)	.004
Prior PPM/ICD	N/A	N/A
Echocardiographic parameters		
LVEF	0.96 (0.92, 1.01)	.087
LV noncompaction	2.37 (0.31, 17.98)	.40
LA enlargement	0.92 (0.21, 4.05)	.92
Degree TR		
None/trivial	REF	REF
Mild	N/A	N/A
Moderate	N/A	N/A
Severe	N/A	N/A
Severity EA		
Mild	REF	REF
Moderate	2.30 (0.24, 22.32)	.47
Severe	1.46 (0.19, 11.20)	.71
RV enlargement	N/A	N/A
RV function		
Normal	REF	REF
Mild	1.29 (0.12, 14.24)	.84
Moderate	2.02 (0.25, 16.47)	.51
Severe	3.11 (0.37, 26.01)	.29
Interatrial shunting (ASD or PFO)	1.96 (0.45, 8.57)	.37
ASD	1.16 (0.41, 3.34)	.78
PFO	1.61 (0.45, 5.73)	.46
VSD	2.22 (0.51, 9.74)	.29
MVP	2.19 (0.29, 16.65)	.45
Prior CVA	N/A	N/A

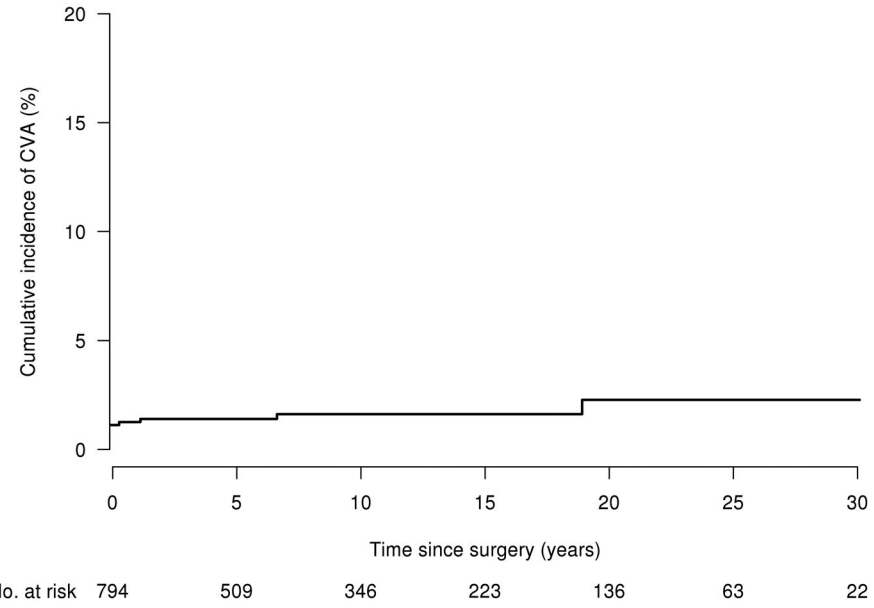


FIGURE 3 Kaplan-Meier curve of CVA rates following TV surgery at our institution

TABLE 5 Associations of CVA following TV surgery at institution (*N* = 803)

Procedure	Hazard ratio (95% CI)	*p* value
Tricuspid valve surgery		
Repair	REF	REF
Replacement	1.86 (0.19, 18.16)	0.60
Atrialized right ventricle plication	0.53 (0.05, 5.18)	0.58
Right reduction atrioplasty	0.45 (0.06, 3.17)	0.42
ASD/PFO closure	N/A	N/A
Cavotricuspid isthmus ablation	N/A	N/A
Intraoperative Maze	N/A	N/A

via paradoxical embolism when combined with RV dysfunction and positive right-to-left atrial pressure gradient.[19] The above-mentioned mechanisms, observed in varying degrees within our cohort, underscore the basis for the substantive lifetime risk of CVA recorded in the present study.

Given that paradoxical embolism appears to be a major concern for EA patients, it stands to reason that interatrial shunt closure (particularly before age 30) may be helpful in mitigating this risk. However, the role of closure even in isolated ASD has not been without controversy. A recent Danish registry study showed that there was an increased risk of first-time atrial fibrillation following ASD closure,[20] which can in turn promote CVA via left-sided cardiac emboli. Patients who underwent surgical closure at older ages also had higher incidences of stroke and heart failure versus age- and gender-matched counterparts.[21] Whether these observations can be extrapolated to EA patients is unclear, given the obvious clinical/demographic differences. Furthermore, an important clinical consideration is that isolated ASD/PFO closure without addressing the TV can lead to worsening right heart failure.[22] There is some evidence that percutaneous ASD closure can be performed safely in selected EA patients[23-25]; however, more extensive studies will be needed to further clarify whether isolated ASD/PFO closure should be considered in the selected patient with minimal TV disease and whether this modifies the risk of CVA, especially given the noted association between CVA and prior transcatheter ASD/PFO closure in the current study.

The correlation between migraines and right-to-left cardiac shunts has been attributed to several postulated mechanisms, including the transmission of small thrombi or biogenic amines triggering migraines.[26,27] Larger ASD/PFO studies will be needed to clarify whether a positive migraine/headache history contributes to higher CVA risk or if it is simply a marker of right-to-left shunting.

The $CHADS_2$ and CHA_2DS_2VASC scores have been validated as useful CVA risk prediction models for individuals with AF.[28,29] However, no such tools exist for adults with CHD.[30,31] Among EA patients with atrial arrhythmias, CHA_2DS_2VASC scores for patients with and without CVA histories were similar (after subtracting points for prior CVA). There was also no significant association between CHA_2DS_2VASC score and CVA following initial evaluation. This suggests that conventional risk prediction tools may be of limited utility in EA, likely due to the multiple other pathways beyond left-sided cardiac emboli that cause CVA in these patients. Furthermore, right-sided atrial flutter occurs more commonly in EA patients,[32] and the relationship between such right-sided arrhythmias and CVA is less clear compared to that of atrial fibrillation. Hence, this may explain why atrial arrhythmias and the CHA_2DS_2VASC score did not exhibit predictive utility in our patient population.

4.1 | Limitations

This was a single quaternary referral center experience where patients were presented with more complex disease or in need of surgical repair; hence, these findings may not be generalizable to a wider spectrum of EA patients. Related to the referral nature of our institution, a

TABLE 6 Suspected mechanisms of CVA in study cohort (total CVA *N* = 112)

Mechanism	Total CVA events (*N* = 112)	Historical CVA (*N* = 90)	CVA occurring after initial evaluation (*N* = 22)
Paradoxical embolism	86	78	8
Left-sided thromboembolism secondary to atrial arrhythmias	0	0	0
Perioperative	8	3	5
Polycythemia	1	1	0
Carotid occlusion	2	0	2
Multifactorial	10	5	5
ASD/PFO and atrial arrhythmia	6	2	4
ASD/PFO and valvular mass	2	2	0
ASD/PFO and oral contraceptive	1	1	0
Atrial arrhythmia vs periprocedural	1	0	1
Cryptogenic or unknown	5	3	2

significant number of patients were lost to follow-up after undergoing treatment or surgery. A large proportion of CVA events occurred prior to arrival at our institution, thereby limiting our ability to accurately draw conclusions with incomplete clinical data. Furthermore, a sizeable fraction of patients did not have imaging, largely because clinical events predated the advent of cross-sectional imaging. Many CVAs identified in the study were TIAs, which are arguably less severe compared to strokes. Finally, we cannot exclude the possibility that patients with CVA were seen and tested more intensively compared to patients without CVA, which in turn may lead to selection and recall biases (eg, more imaging studies, recollection of neurologic symptoms such as headaches or visual auras) when ascertaining predictors of CVA.

5 | CONCLUSION

Patients with EA are at substantial risk for CVA throughout their lifetime, with paradoxical embolism being the most likely mechanism behind these events. Histories of migraines/headaches or interatrial shunting but not atrial arrhythmias may be helpful predictors for CVA events and should be actively sought.

CONFLICT OF INTEREST

The authors have no conflicts of interest or financial disclosures to report.

AUTHOR CONTRIBUTIONS

As joint first authors, Nicholas Tan and Christine Attenhofer Jost were responsible for study design, data collection, and manuscript preparation. Murray Polkinghorne was involved in the study design, data collection, and manuscript editing. Emily Vargas and David Hodge provided substantial input into the study design, statistical analysis, and manuscript editing. Joseph Dearani, Heidi Connolly, and Samuel Asirvatham gave expert input into the concept/rationale of the study and provided critical revisions for the final manuscript. Christopher McLeod was the primary investigator and supervised the study design and execution. All authors reviewed and approved the final version of the manuscript.

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