Development of Left Atrial Thrombus and Subsequent Cardioembolic Stroke in a 21-Year-Old Man With Ebstein Anomaly Who Previously Underwent Pulmonary Vein Isolation Ablation and Cox Maze III Procedure

Significance of Left Atrial Mechanical Function

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Foreword

Information about a real patient is presented in stages (boldface type) to an expert clinician (Dr Ammash), who responds to the information, sharing his reasoning with the reader (regular type). A discussion by the authors follows.

A 21-year-old man with a history of Ebstein anomaly and atrial fibrillation who had previously undergone tricuspid valve repair, pulmonary venous isolation, and the Cox maze III procedure was referred from an outside institution for the evaluation of an acute onset of left-sided upper- and lower-extremity weakness. The patient had initially presented 3 years earlier with abdominal pain and symptomatic palpitations. Physical examination at that time revealed a jugular venous pressure of 12 cm without a prominent V wave. Cardiac palpation noted a sternal heave. On auscultation, a grade II holosystolic murmur was appreciated at the left sternal border that increased with inspiration. Abdominal inspection noted an enlarged liver that was not pulsatile. A standard 12-lead ECG demonstrated sinus rhythm with right bundle-branch block, right atrial enlargement, or decreased amplitude of the R waves in V1 and V2. The presence of first-degree atrioventricular block, as noted in this case, is quite common and has been documented in up to 42% of patients with Ebstein anomaly. The apical displacement of the tricuspid valve compromises the continuity of the central fibrous body and septal atrioventricular ring, allowing for direct muscular connections between the atrium and ventricle and resulting in the subsequent development of accessory pathways.

The ECG is often abnormal in patients with Ebstein anomaly with typical findings including right bundle-branch block, right atrial enlargement, or decreased amplitude of the R waves in V1 and V2. The presence of first-degree atrioventricular block, as noted in this case, is quite common and has been documented in up to 42% of patients with Ebstein anomaly. The apical displacement of the tricuspid valve compromises the continuity of the central fibrous body and septal atrioventricular ring, allowing for direct muscular connections between the atrium and ventricle and resulting in the subsequent development of accessory pathways.

Given that ≤36% of patients with Ebstein anomaly develop accessory pathways, the clinician should carefully review the ECG for associated clues such as a short PR interval, slurred upstroke of the QRS complex, or a widened QRS.

The patient’s chest x-ray imaging indicates right atrial enlargement prompting the need for further structural evaluation of the heart. In Ebstein anomaly, the pulmonary vascularity may be decreased on chest x-ray imaging given the decreased forward flow from the right ventricle. Furthermore, marked cardiac enlargement, particularly a cardiothoracic ratio >0.65, in this patient population portends worse outcomes.
Echocardiographic evaluation is critical for delineating the underlying anatomy and diagnosis of Ebstein anomaly. Classic features of Ebstein anomaly depicted on echocardiography include failure of the tricuspid valve to delaminate as evident by adherence of the septal and posterior leaflets to the myocardium, dilatation of the tricuspid annulus, downward or apical displacement of the tricuspid valve of $\geq 8 \text{ mm/m}^2$, and marked enlargement of the right atrium with resultant atrialization of the right ventricle. In the current case, note the large sail-like anterior tricuspid valve leaflet in comparison with the smaller, truncated septal leaflet (Figure 3A). Furthermore, in relation to the mitral valve apparatus, the tricuspid valve leaflets are markedly displaced ($10 \text{ mm/m}^2$; Figure 3B). The resultant tricuspid annular dilatation results in tricuspid valve leaflet malcoaptation and severe tricuspid regurgitation as noted on the Doppler findings (Figure 3C).

Asymptomatic patients without evidence of an intracardiac shunt and mild cardiomegaly should be closely observed. However, if they develop symptoms of tachyarrhythmias, cyanosis, paradoxical emboli, or progressive cardiomegaly, then operative intervention by an experienced congenital heart surgeon should be strongly considered. Surgical repair of Ebstein anomaly, with either tricuspid valve repair or replacement, is associated with very good outcomes when performed before significant right and left ventricular dysfunction. However, similar to other congenital heart defects, the risk of recurrent atrial arrhythmias increases as the patient ages despite surgical repair. Therefore, lifelong follow-up by a congenital heart disease specialist is required even after surgical repair is performed.

**Patient presentation (continued):** The patient subsequently underwent tricuspid valve repair with a 36-mm flexible annuloplasty ring and pericardial patch augmentation of the anterior tricuspid leaflet, right reduction atrioplasty, right atrial surgical ablation reproducing the Cox maze III lesion set with a radiofrequency probe, and bilateral surgical radiofrequency pulmonary vein isolation.

*Dr Ammash:* Initially described in 1995, the Cox maze III procedure entails pulmonary venous isolation coupled with the creation of small surgical incisions within the atria designed to impede the propagation of irregular electric wave fronts, thereby promoting sinus conduction. However, despite being considered the gold standard for the treatment of atrial fibrillation, the traditional cut-and-sew Cox maze III procedure is often not used to treat lone atrial fibrillation given its need for technical expertise, and concern for the development of accompanying complications, as well. Catheter-based ablation procedures that use radiofrequency ablation to electrically isolate the cardiac silhouette, particularly the right atrium (arrow).

![Figure 1. Resting 12-lead ECG demonstrating sinus rhythm with first-degree atrioventricular block and nonspecific T-wave abnormalities.](http://circ.ahajournals.org/)

![Figure 2. Patient chest x-ray demonstrated enlargement of the cardiac silhouette, particularly the right atrium (arrow).](http://circ.ahajournals.org/)
the pulmonary veins, and to target foci of electric irregularity, as well, that are identified during electroanatomic mapping have arisen as a minimally invasive alternative to the traditional surgical approach. Comparative effectiveness between these 2 treatment modalities has been studied recently at our institution. In this investigation, 97 patients who underwent a cut-and-sew Cox maze procedure were compared with 194 age, sex, and atrial fibrillation type–matched patients who received catheter-based ablation. Eighty-seven percent of patients receiving Cox maze treatment were free from recurrent atrial fibrillation at 5 years in comparison with 28% of patients in the catheter ablation group (P<0.001). The postoperative need for pacemaker implantation was similar between the Cox maze and the catheter ablation group (9.3% versus 7.3%, P=0.55). Ten percent of patients in the catheter ablation cohort experienced pulmonary vein stenosis of ≥50%. One cerebral vascular accident (0.01%) and 1 nonfatal myocardial infarction (0.01%) were reported in patients who underwent the Cox maze procedure, whereas no deaths occurred in either group.

Although patients with Ebstein anomaly may demonstrate decreased atrial arrhythmias following surgical repair of the tricuspid valve and right atrial reduction atroplasty, our practice is to perform a concomitant right-sided Cox maze procedure that further reduces the arrhythmogenic burden. A prior report at our institution by Porter et al reviewed 70 cases of patients with Ebstein anomaly and atrial fibrillation. Twenty-two of these patients were evaluated before the advent of either the Cox maze procedure or cryoablation and therefore did not have any operative intervention for treatment of atrial fibrillation. Fourteen of these patients had long-term follow-up with 6 (43%) of these experiencing recurrent atrial fibrillation. Of the 48 patients who underwent either the Cox maze procedure or cryoablation at the time of surgical repair, 25.6% had recurrent atrial fibrillation during long-term follow-up. There was no statistical difference between the 2 operative techniques in regard to the rate of atrial fibrillation recurrence. None of these patients underwent catheter-based ablation because it is not routinely implemented at our institution owing to its decreased efficacy in the Ebstein anomaly population.

**Patient presentation (continued):** Two years postoperatively, transthoracic echocardiography noted junctional rhythm with no evidence of left atrial mechanical function (LAMF), defined as the absence of both Doppler A wave on mitral inflow and tissue Doppler imaging A’ on medial mitral annular imaging, and the lack of left atrial ejection, as well (documented as the percent of reduction in the left atrial area during diastole). These echocardiogram findings from the patient are demonstrated in Figure 4. The absence of LAMF indicates an increased risk of developing a left atrial thrombus. Therefore, continued oral anticoagulation with warfarin was recommended.

**Dr Ammash:** Although surgical intervention for atrial arrhythmias, such as cryoablation or pulmonary venous isolation, is often successful in restoring sinus rhythm and is associated with greater freedom from recurrent atrial fibrillation, previous studies have suggested that surgical ablation may adversely affect LAMF. An investigation of 150 patients who underwent either radiofrequency or cryoablation maze procedures revealed that, at a mean follow-up of 24.5 months, 47 (31%) patients lacked LAMF. Moreover, lack of LAMF was associated with a 5-fold increase in the risk of stroke (P=0.02). The absence of LAMF after the Cox maze III procedure is as high as 39%; and has been demonstrated to persist up to 56 months. Moreover, the specific type of surgical intervention used may impact the degree of postoperative LAMF. For instance, a recent study of 126 patients with atrial fibrillation who underwent surgical intervention demonstrated that the cut-and-sew Cox maze III procedure and cryoablation lead to a greater decrease in postoperative LAMF than radiofrequency ablation. Therefore, given the high incidence of the absence of LAMF after the Cox maze procedure, and its associated risk of stroke, as well, the authors recommend investigation of LAMF after surgical intervention as part of the clinical decision-making process regarding thromboembolic prophylaxis administration.

Although physiological pacing (AAI or DDD pacing settings) has proven to reduce the development of atrial fibrillation, its effect on atrial mechanical function is less certain. Belham and colleagues demonstrated that, regardless of the location of pacing in the right atrium, pacing itself was detrimental to atrial electromechanical function in comparison with sinus rhythm. However, Quintana et al demonstrated that short-term atrial pacing improved LAMF. Whether this benefit persists after pacing or whether long-term pacing may have similar effects remains unknown.

![Figure 3. Transthoracic echocardiogram at the time of presentation demonstrating apical 4-chamber view depicting the right atrium (RA), right ventricle (RV), left atrium (LA), and left ventricle (LV).](image-url)
Before the initiation of anticoagulation for thromboembolic prophylaxis, the clinician must carefully consider the risk of stroke versus bleeding. Several clinical tools such as the CHADS2-VASc and HAS-BLED scores can be used to determine patient-specific risks in regard to stroke or bleeding outcomes. Current recommendations for the general population are to initiate antithrombotic prophylaxis in patients with a history of transient ischemic attack, stroke, or a CHADS2-VASc score of ≥2. However, it should be noted that the implementation of these scoring metrics has not been evaluated in the heterogeneous congenital heart disease population with some groups arguing for the initiation of anticoagulation in patients who have a CHADS2-VASc score of ≥1. Furthermore, debate persists regarding the risk of thrombotic formation in valve repair and how this may impact the decision to anticoagulate. The current patient’s CHADS2-VASc and HAS-BLED scores were both 0. However, given the 5-fold risk of stroke in patients lacking LAMF, thromboembolic prophylaxis was recommended.

Once the decision to initiate anticoagulation has been made, the clinician must then decide between warfarin therapy versus novel anticoagulants. Given that novel anticoagulants are only approved for nonvalvular atrial fibrillation, one must first determine whether or not the patient has valvular atrial fibrillation. The distinction between valvular and nonvalvular atrial fibrillation is not straightforward with a definition that has varied in both clinical trials, and in national guidelines, as well. Furthermore, prior recommendations focus on mitral valve disease with little to no mention of right-sided valvular heart disease. Last, there is some concern for the use of novel anticoagulants in patients with cyanotic congenital heart disease given altered hemostatic properties and a propensity toward bleeding.

Patient presentation (continued): Given the above-noted uncertainties with the use of novel anticoagulants in the congenital heart disease population and the likelihood that his significant structural heart disease is contributing to the patient’s underlying atrial fibrillation and thrombotic risks, it was decided to pursue warfarin anticoagulation in the current case.

Nonpharmacological options for thromboembolic prophylaxis in the atrial fibrillation population include surgical amputation, ligation of the left atrial appendage (LAA), or percutaneous closure of the LAA. The efficacy of surgical ligation to prevent thromboembolism has previously been studied in 208 patients undergoing mitral valve surgery, 58 of whom underwent LAA ligation. Multivariate analysis revealed that, in those patients with incomplete or no LAA ligation, the odds of developing thromboembolism was 11.9 times higher than in those patients who had confirmed LAA ligation (95% confidence interval, 1.5–93.6; P=0.02). Indeed, for LAA ligation or amputation to be effective, complete isolation of the LAA must be achieved. Unfortunately, incomplete LAA isolation is common with ≤36% of patients demonstrating communication between the left atrial body and the LAA by Doppler echocardiography after surgical intervention. Nevertheless, current national guidelines recommend LAA amputation concomitantly with mitral valve surgery. In the current case presentation, the patient only underwent tricuspid valve intervention and a right-sided Cox maze procedure without surgical entry into the left atrium, thereby precluding LAA ligation or amputation. Minimally invasive isolation of the left atrial appendage achieved via catheter-based procedures is a subject of active investigation. The Watchman (Boston Scientific) device uses...
a nitinol cage coated with polyethylene terephthalate that expands once deployed in the LAA. In the Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) noninferiority study, the efficacy of the Watchman device to prevent thromboembolic events was compared with traditional warfarin therapy in patients with nonvalvular atrial fibrillation. Noninferiority was proven during this trial, but several complications with Watchman implantation were also noted, including pericardial effusions requiring pericardiocentesis. Other percutaneous LAA closure or isolation devices currently under investigation include the Amplatzer Cardiac plug (St. Jude Medical) and the LARIAT system (SentreHeart, Inc). Until further trials are performed, the use of these devices is currently relegated to those patients with an elevated thromboembolic risk and contraindications to traditional oral anticoagulation therapy.

The patient in the current case presentation had no apparent contraindications to warfarin therapy, and, therefore, this option was chosen for thromboembolic prophylaxis.

Patient presentation (continued): Six months after his last follow-up the patient presented to an outside institution with acute onset of left-sided upper- and lower-extremity weakness and recurrent falls toward his left side. He indicated that a week before his presentation, he had been noncompliant with his warfarin therapy and had a documented subtherapeutic international normalized ratio of 1.09.

An emergent head MRI demonstrated an acute ischemic stroke in the right middle cerebral artery (Figure 5). Thrombolysis was administered, but repeat cerebral angiogram demonstrated persistent occlusion of the right middle cerebral artery. Consequently, a mechanical thrombectomy was successfully performed. Follow-up imaging noted a residual stroke in the deep right middle cerebral artery territory.

![Figure 5. Diffusion head MRI demonstrating acute ischemic stroke in the territory of the right middle cerebral artery (arrow).](image-url)

Dr Ammash: A pooled meta-analysis has demonstrated a marked improvement in morbidity with early administration of alteplase defined as within 4.5 hours from the onset of stroke symptoms. Indeed, the beneficial effect of thrombolytics correlates with the promptness of administration with a 2.55 reduction in morbidity if given within the first 90 minutes of presentation and falling to a 1.22 decline in morbidity if used after 4 hours. Before the administration of thrombolytic therapy, the clinician must ensure that there are no absolute contraindications to its use including intracranial neoplasm, prior hemorrhagic stroke, or prior ischemic stroke within the past 3 months. Recanalization of the occluded artery occurs spontaneously in 24% of cases. However, intra-arterial thrombolysis can raise the rate of recanalization to 64% with an associated improvement of morbidity and mortality. Clot size, and age and composition, as well, are associated with the rates of recanalization. Thrombolysis accompanied by mechanical thrombectomy has demonstrated equipoise ion comparison with thrombolysis alone with a trend toward improved outcomes.

Patient presentation (continued): The patient was transferred to our institution the following day for further management. Vital signs at the time of admission noted bradycardia at 41 bpm, blood pressure of 124/75 mmHg, oxygen saturations of 95% on room air, and a temperature of 37.1°C. Physical examination revealed a regular bradycardia, with auscultation of the first heart sound and physiological splitting of the second heart sound with no appreciable murmurs, gallops, or rubs. The point of maximal impulse was palpated and was neither accentuated nor displaced, and a sternal heave was no longer appreciated. The neurological examination noted mild decreased dexterity in the left hand without appreciable weakness or sensory deficit. The abdomen was soft and nontender with mild hepatomegaly, and the lungs were clear to auscultation bilaterally.

Serum studies noted a normocytic anemia of 11.7 g/dL (mean corpuscular value, 77.6 fl), leukocytosis of 11.9×10^9 cells/L with a neutrophilia of 9.21×10^9 cells/L. Creatine (0.9 g/dL), sodium (137 mmol/L), and potassium (4.0 mmol/L) were within normal limits. The international normalized ratio was therapeutic at 2.3.

ECG revealed a junctional bradycardia without electric evidence of atrial function (absence of P waves) as shown in Figure 6.

A transesophageal echocardiogram revealed a laminated left atrial appendage thrombus and severe left atrial enlargement (Figure 7).

Dr Ammash: Transesophageal echocardiogram is indicated to look for the source of embolism especially in patients with structural heart disease and prior history of atrial arrhythmias. The most common source of embolism noted on echocardiography in an undifferentiated patient following an ischemic neurological event include left atrial thrombi or spontaneous echo contrast, left ventricular thrombi, infective or thrombotic vegetations, intracardiac tumors such as myxoma, fibroelastomas, atrial shunt such as atrial septal defect or patent foramen ovale, and atherosclerotic plaques of the aorta, not in any particular order.
There are several unique characteristics in the congenital heart disease population that should be considered when evaluating for the etiology of either a stroke or transient ischemic event. First, as previously alluded to, atrial arrhythmias are common in the patient with Ebstein anomaly, and, therefore, the patient should be evaluated initially with a standard 12-lead ECG followed by a 24-hour Holter monitor, and ultimately a cardiac event monitor if no underlying rhythm abnormality is initially detected. Second, Ebstein anomaly is associated with the presence of intracardiac shunts resulting in paradoxical emboli. Therefore, careful anatomic evaluation of the heart via echocardiography must be performed to evaluate for this possibility. In the current case, underlying atrial fibrillation with subsequent development of a left atrial appendage thrombus was the likely source for the patient’s ischemic stroke.

However, in other adult congenital heart disease populations, specifically cyanotic heart disease, secondary erythrocytosis may lead to increased blood viscosity and ultimately impede cerebral blood flow. An evaluation of 162 patients with cyanotic congenital heart disease at our institution noted that the incidence of cerebral vascular events was 16.6%. Furthermore, this study was the first to report an association between iron-deficiency anemia and resultant microcytosis and the risk for stroke (P<0.01). It is postulated that microcytic, iron-deficient blood cells are less deformable than their normal iron-replete counterparts, thereby inhibiting the ease with which they pass through the microvasculature. This finding has significant therapeutic implications, in particular, with regard to iron repletion and phlebotomy. First, iron deficiency anemia should be avoided with iron supplementation initiated when the mean corpuscular volume falls below 82 fL. Second, therapeutic phlebotomy should be used judiciously typically when the hemoglobin is >20 g/dL or the hematocrit rises above 65%.

**Discussion**

This is a unique case that illustrates the complex cardiovascular issues that arise when caring for the patient with congenital heart disease. It provides critical teaching points with regard to the diagnosis and management of patients with Ebstein anomaly, the approach to anticoagulation in the atrial fibrillation population, and the management of an acute cerebrovascular event. Finally, it introduces the concept of LAMF and how it may impact decision making in regard to the management of patients with atrial fibrillation.

First, as highlighted by the case presentation, Ebstein anomaly is characterized by the failure of the tricuspid valve to delaminate and by apical displacement of the tricuspid valve toward the apex. The degree of displacement can be quantified by calculating the displacement index. This is achieved by measuring the distance in millimeters from the mitral valve to the tricuspid valve and then dividing that distance by the patient’s body surface area. In the patient without congenital heart disease the tricuspid valve will be slightly...
more displaced toward the apex than the mitral valve, but the overall displacement index should be <8 mm/m². If >8 mm/m², Ebstein anomaly should be suspected.5,8 As noted in Figure 3A through 3C, the underlying structural abnormalities of the tricuspid valve coupled with its unusual anatomic positioning lead to the development of severe tricuspid regurgitation and marked right atrial enlargement. This patient population is predisposed to several cardiac sequelae, including arrhythmias2 and heart failure,3 and therefore should be followed closely by a congenital heart disease specialist who can help determine when and if surgical intervention is indicated.

A second key discussion point prompted by the current case is how to approach thromboembolic prophylaxis in the atrial fibrillation population. Use of validated risk stratification tools such as the CHA₂DS₂-VASc or HAS-BLED scores provides an initial starting point for determining if anticoagulation should be initiated.24 However, as will be elaborated on further in the discussion, other factors including the presence or absence of LAMF should impact decision making regarding thromboembolic prophylaxis. Once it has been decided to pursue anticoagulation, the clinician must determine whether or not their patient is a candidate for novel anticoagulant therapies in lieu of the traditional warfarin protocol. Before considering the use of novel anticoagulants, one must consider the patient’s age and renal function, and note the limited reversibility of these agents., as well Furthermore, the clinician must determine whether or not their patient is classified as having valvular or nonvalvular atrial fibrillation, because the role of LAMF in clot formation and how this may impact the patient's age and renal function, and note the limited reversibility of these agents. Additionally, the clinician must also consider the patient’s age and renal function, and note the limited reversibility of these agents. As noted in Figure 2, the severity of tricuspid regurgitation coupled with surgical valve repair compelled us to choose warfarin therapy.

A third critical issue proposed by the present case discussion is the management of cerebral vascular events in patients with congenital heart disease. This patient population is prone to atrial arrhythmias, particularly atrial fibrillation, and therefore is inclined to the development of atrial clots (Figure 7). However, the clinician must also entertain several other etiologies for stroke or transient ischemic events unique to the congenital heart disease population such as paradoxical emboli from atrial or ventricular shunts or sludging of poorly deformable microcytic red blood cells in the cerebral vasculature.40

A particularly unique component to this case presentation is the role of LAMF in clot formation and how this may impact follow-up and clinical decision making. Left atrial function as defined by pressure-volume relationship analysis consists of 3 phases.43 First, pulmonary venous blood flow enters the left atrium during systole. Second, in early diastole, the left atrium serves as a conduit to allow passive blood flow into the left ventricle from the pulmonary veins. The third component is defined by left atrial contraction that contributes a further 20% to left ventricular stroke volume.44 Several methods have been used to define left atrial mechanical function, including left atrial appendage emptying velocity, left atrial spontaneous echocardiographic contrast, and pulmonary vein blood flow velocity.45 Left atrial mechanical function was determined in the current case by examining Doppler A wave on mitral inflow, tissue Doppler imaging A’ on medial mitral annular imaging, and left atrial ejection fraction, which have been defined and implemented in prior reports.46-48

The role of LAMF and the risk of developing an initial or recurrent arrhythmia following cardiac interventions has become a topic of several investigations. For instance, American College of Cardiology/American Heart Association/European Society of Cardiology standard-of-care guidelines recommend 4 weeks of anticoagulation following cardioversion in patients who present >48 hours after the onset of atrial arrhythmia to prevent thromboembolism.49 Grimm and colleagues45 have demonstrated decreased LAMF following cardioversion and have postulated that the lack of atrial mechanical function may be the underlying mechanism of atrial clot formation and subsequent thromboembolism. Thomas et al40 demonstrated that LAMF is compromised to a further extent in patients after they undergo linear radiofrequency ablation than patients who had undergone cardioversion only and markedly less than a control population.

Surgical interventions to address atrial fibrillation also appear to affect LAMF. Buber and colleagues conducted a prospective study of 150 patients who underwent radiofrequency and cryoablation maze (without atrial incisions) and noted that up to 31% of patients had no evidence of LAMF postoperatively. Multivariate analysis demonstrated that the lack of LAMF was associated with a 5-fold increase in the risk for stroke (P=0.02).46 The current case study involves a patient whom underwent pulmonary vein isolation, and the Cox maze III procedure, as well, and had a marked absence of LAMF postoperatively. This case illustrates the importance of evaluating LAMF after the Cox maze procedure or pulmonary vein isolation to determine the length of anticoagulation needed to prevent thromboembolic sequelae. Further investigation is needed to determine the prevalence, duration, and clinical importance of impaired atrial mechanical function in the postsurgical atrial fibrillation patient population.

Disclosures

None.

References

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Keywords: atrial fibrillation, atrial function, left, cerebral infarction, heart defects, congenital
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