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VALVULAR HEART DISEASE (TL KIEFER, SECTION EDITOR)

Ebstein's Anomaly of the Tricuspid Valve: an Overview of Pathology and Management

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Abstract

Purpose of Review Ebstein's anomaly (EA) is a rare, but complex form of congenital heart disease consisting of a right ventricular myopathy and morphologic tricuspid valve disease leading to a high incidence of right ventricular dysfunction and arrhythmias. This review offers an updated overview of the current understanding and management of patients with EA with a focus on the adult population.

Recent Findings Increased understanding of anatomic accessory atrioventricular pathways in EA has resulted in an improvement in ablation techniques and long-term freedom of atrial arrhythmia recurrence.

Summary Despite an improvement in understanding and recognition of EA, significant disease heterogeneity and complex treatment options continue to challenge providers, with the best outcomes achieved at expert congenital heart disease centers.

Keywords Ebstein's anomaly · Congenital heart disease · ACHD · Tricuspid valve · Cone repair

Introduction

Ebstein's anomaly (EA) is a rare and complex congenital anomaly with a prevalence of between 0.39 and 0.72 cases per 10,000 births [1–3]. EA results from abnormal tricuspid valve development, which may lead to a cascade of associated structural abnormalities and is often associated with a right ventricular myopathy. Initially described in 1866, Wilhelm Ebstein characterized the abnormality from the autopsy of a 19-year-old patient who died of heart failure following long-standing cyanosis and a history of palpitations [4, 5], features we now regularly attributed to this pathology. Over the course of the past half century, there have been remarkable advances in our understanding and treatment of EA from transcatheter ablative techniques to complex tricuspid valve repairs. This review highlights several of the challenges in treating EA patients while offering insights into treatment advances.

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Anatomy

Ebstein's anomaly is a myopathy of the right ventricle characterized by failure of tricuspid valve tissue delamination from the ventricular myocardium during embryogenesis. The classical feature is the rotational displacement of the hinge points of the septal and posterior leaflets away from the atrioventricular junction towards the apex [6], while the hinge point of the anterosuperior leaflet retains its normal position. While the septal and posterior leaflets are typically small, dysplastic, and tethered, the anterosuperior leaflet becomes elongated. However, the function of the anterosuperior leaflet may also be impaired due to the presence of leaflet fenestrations and

chordal tethering [7]. The degree of rotational tricuspid valve displacement is widely variable resulting in a range of valve pathology from little to no regurgitation to severe regurgitation with significant leaflet malcoaptation. Additionally, displacement of the valve annulus results in a small functional right ventricle and an "atrialized" portion of the right ventricle which functions as part of the morphologic right atrium and is comprised of thin walled right ventricular myocardium.

In addition to tricuspid valve pathology, EA is often associated with other cardiac defects. An interatrial communication, either in the form of a patent foramen ovale (PFO) or an ostium secundum atrial septal defect (ASD), is present in a majority of patients [8]. Pulmonary valve stenosis or atresia is found in up to 30% of patients who present early in life [9]. Accessory conduction pathways leading to atrioventricular reentrant tachycardias are commonly associated with EA, found in up to 38% of patients [10, 11]. Furthermore, a significant minority of patients are found to have left ventricular abnormalities including left ventricular noncompaction (18%), mitral valve prolapse (15%), mitral valve dysplasia (4%), and bicuspid aortic valve (8%) [12, 13].

Clinical Presentation

Clinical presentation depends on the severity of EA and ranges from detection in utero with early manifestations of heart failure to incidental detection late in adulthood. Severe disease may present prenatally with hydrops, oligohydramnios, or tachyarrhythmias [14]. Neonates with severe displacement of the tricuspid valve and interatrial communication may present with heart failure and cyanosis with the need for early intervention [15].

Advances in fetal echocardiography and newborn pulse oximetry screening have increased the early diagnosis of EA; however, individuals with less severe phenotypes or those without access to routine healthcare may escape detection until adulthood. Often, EA is diagnosed in older patients due to progressive tricuspid regurgitation resulting in exertional decline and/or symptoms of right ventricular dysfunction. Initial presentation due to new onset arrhythmias is also common, given the high incidence of atrial tachyarrhythmias and prevalence of accessory pathways [16]. In those with interatrial communications, cyanosis may develop over time even in the absence of right ventricular outflow tract disease.

Physical Findings

Physical exam findings are highly dependent on underlying pathology. In patients with significant right-to-left shunting, cyanosis may be present. In those with severe apical displacement of the tricuspid valve, the first and second heart sounds are often widely split and an early systolic click, or "sail sound," may be heard [17]. A systolic murmur along the left or right sternal border may be present in the setting of significant tricuspid regurgitation; however, large coaptation defects within the tricuspid valve leaflets may result in more laminar regurgitant flow and early pressure equalization between the right ventricle and atrium. Thus, a systolic murmur may be absent despite the presence of severe tricuspid regurgitation. The presence of a mid-diastolic murmur has been described in cases of severe tricuspid regurgitation as a result of a substantial pressure gradient between the volume loaded right atrium and the right ventricle. Jugular venous distension is often absent, even in the presence of significant tricuspid regurgitation, due the enlarged and compliant right atrium.

Electrocardiogram

Patients with EA often have an abnormal baseline electrocardiogram. Prominent P waves result from right atrial dilation. Those with significant right ventricular atrialization may exhibit very high P wave amplitudes, sometimes referred to as "Himalayan" P waves. PR interval prolongation may be observed. In others, PR shortening exists as a result of preexcitation in the presence of one or more accessory pathways. Atypical right bundle branch block morphology is also frequently found.

Imaging

Chest radiograph may show a globular cardiac silhouette due to severe right atrial dilation. Transthoracic echocardiography is the primary imaging modality used to diagnose EA. The defining echocardiographic criterion of EA is apical displacement of the hinge point of the septal or posterior leaflets of $\geq$ 8 mm/m^2 body surface area measured on an apical four chamber view (Fig. 1) [18]. Color and spectral Doppler are used to assess tricuspid valve regurgitation. Right atrial size, displacement of the functional tricuspid annulus, size and function of the right and left ventricle, right ventricular outflow tract anatomy, and atrial septal anatomy are important features of a comprehensive echocardiographic evaluation. Agitated saline injection demonstrates interatrial shunt.

Cardiac magnetic resonance imaging (MRI) complements echocardiographic assessment contributing to the overall understanding of intracardiac anatomy. MRI is particularly helpful in quantifying tricuspid regurgitation, right ventricular size, right ventricular function, and shunting. Both the functional and anatomic right ventricle can be measured and the volume of the atrialized right ventricle can be quantified [19].

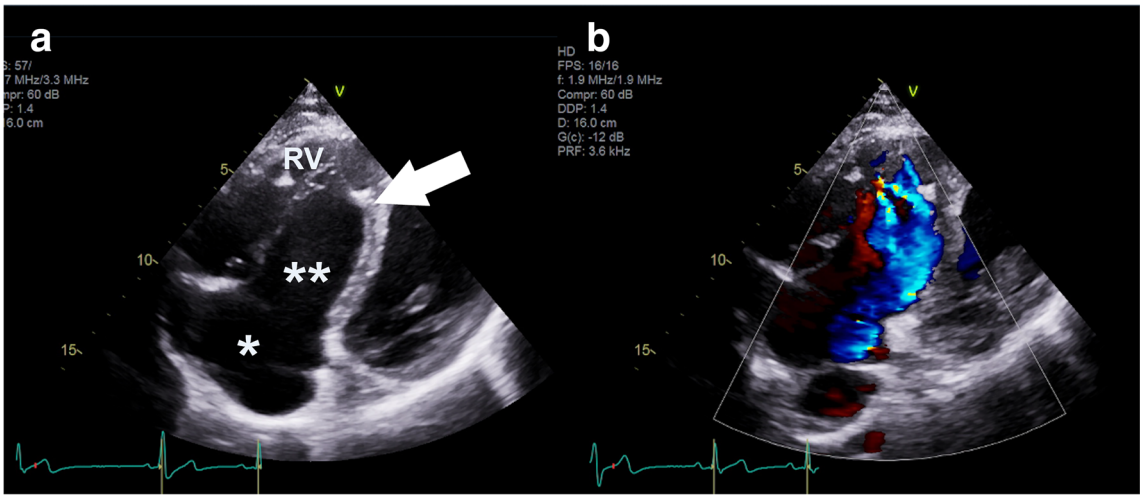

Fig. 1 Transthoracic images of a patient with a severe form of Ebstein's anomaly with severe apical displacement of the hinge point of the septal leaflet (*arrow*), elongated and a sail-like anterosuperior leaflet, a small functional right ventricle (RV) and a large right atrium including the morphologic right atrium (*) and the atrialized portion of the thin walled right ventricular myocardium (**) (**a**). There is significant tricuspid regurgitation with an eccentric jet directed to the septal portion of the functional right atrium (**b**)

Arrhythmias

Progressive right atrial dilation and postoperative surgical substrates put patients with EA at high risk for atrial tachyarrhythmias. The most frequently encountered atrial arrhythmia is macro-re-entrant atrial tachycardia, seen in up to 60% of patients. This may occur as either isthmus-dependent flutter or reentry circuit around scar tissue or a surgical patch [16, 20, 21]. Focal atrial tachycardias occur in up to 20% [21]. Atrial fibrillation is less common but may develop in the setting of left atrial dilation due to right-to-left shunting across an ASD.

The strong association of EA and accessory pathways has long been recognized with an estimated prevalence of up to 38% [11, 16]. Accessory pathways are predominantly right-sided and located along the septal and posterior borders of the tricuspid valve [16]. The presence of multiple accessory pathways is associated with an increased risk for sudden cardiac death [22] with the potential for atrial arrhythmias to lead to rapid antegrade conduction through an accessory pathway resulting in hemodynamic deterioration [23]. More recently, histologic specimens have confirmed the presence of nodoventricular, nodofascicular, and fasciculo-ventricular pathways; however, their role as arrhythmogenic substrates remains unclear at this time [24].

Patients with EA are at increased risk for ventricular arrhythmias and sudden cardiac death with an arrhythmia prevalence of 6% and a 70-year risk of sudden cardiac death of 15% [25]. Rare cases of intrinsic monomorphic ventricular tachycardia arising from atrialized right ventricular myocardium have been described [16, 20, 26]. Polymorphic ventricular tachycardia and ventricular fibrillation, in the setting of advanced myocardial disease, are of additional concern.

Management

Due to the substantial phenotypic heterogeneity of EA, management varies widely from patient to patient. Individuals presenting in infancy with cyanosis and right ventricular outflow tract obstruction may require early surgical intervention with either right-atrial reduction arterioplasty, tricuspid valve repair, and right ventricular outflow tract reconstruction or single ventricle palliation [27–29], whereas asymptomatic patients with less severe disease variants may require only observation.

The criteria for surgical intervention in EA are controversial. In those with significant tricuspid regurgitation, surgical intervention is appropriate for those with symptoms or congestive heart failure. Asymptomatic patients pose a greater challenge. Surgical referral is appropriate for patients with progressive right ventricular dysfunction and likely in patients who demonstrate declining performance on exercise testing. In one large, single center review of 122 operative tricuspid valve interventions on patients with EA, New York Heart Association functional class greater than II and right ventricular enlargement were independent predictors of long-term postoperative mortality [30]. Thus, routine clinical and echocardiographic assessment should occur on a 1–2-year basis in asymptomatic patients with mild to moderate tricuspid regurgitation and preserved right ventricular function, or as often as every 6–12 months for patients with severe tricuspid regurgitation who do not yet meet criteria for surgical intervention [31••]. Once surgical indications are met, early intervention regardless of surgical strategy should be pursued to avoid rising morbidity and mortality observed in patients with EA with delayed intervention [32].

Valve repair at experienced centers may offer the best option for eligible patients given the improved long-term mortality of tricuspid valve repair over replacement [33, 34]. In patients with severe right ventricular systolic dysfunction or restriction, atrial septal fenestration or bidirectional superior cavopulmonary anastomosis may be necessary adjuncts to valve intervention, ensuring adequate post-operative cardiac output and right ventricular unloading [35].

Atrial arrhythmias are a source of significant morbidity in patients with EA and development of any new rhythm abnormality should prompt a comprehensive assessment of structural function and an electrophysiologic evaluation. Patients with atrial arrhythmias, accessory pathways, or rapidly conducting antidromic pathways should be referred for catheter ablation by a congenital electrophysiologist [21, 36]. Even in the absence clinical arrhythmia, electrophysiologic study should be considered prior to surgery as ablation may be difficult or impossible post-operatively if an accessory pathway is anatomically isolated within a plication or shielded by a prosthetic valve.

Atrial septal defects can lead to resting or exertional hypoxemia due to right to left shunting as tricuspid regurgitation may be directed across an ASD or PFO. This can occur even in patients without pulmonary hypertension or right ventricular failure. ASD closure can relieve cyanosis and improve symptoms either when performed as an isolated transcatheter procedure or when combined with surgical tricuspid valve intervention. However, ASD closure should be approached with caution in patients with right-to-left shunting. Those with significant restriction to right ventricular filling due to severe apical tricuspid valve displacement may rely on a right-to-left atrial level shunt to offload an undersized right ventricle and maintain adequate cardiac output.

Surgical Considerations

When technically feasible, repair of the tricuspid valve is usually preferable to replacement. In addition to tricuspid valve repair, surgical management of EA also should include plication of the atrialized right ventricle, right atrial reduction, and either complete or subtotal closure of the atrial septal defect. When there is a history of paroxysmal atrial fibrillation or atrial flutter, a right sided maze or cavotricuspid isthmus ablation should be performed.

Strategies for repair of the tricuspid valve have evolved over the last several decades. Initial techniques focused on creating a monocusp valve out of the anterior leaflet tissue. Danielson et al. [37] described a technique that focused on repositioning the anterior leaflet to the true tricuspid annulus with plication stitches through the atrialized portion of the right ventricle. This left a monocusp valve completely formed by the anterior leaflet. Carpentier and Chauvaud et al. [38] developed a technique that involved anterior leaflet mobilization and reattachment to the annulus, also leaving a monocusp valve. The tricuspid annulus was further stabilized with an annuloplasty ring.

The cone procedure is an option at certain centers with extensive experience in Ebstein surgery. In this operation, the surgeon uses the large anterior leaflet as well as the diminutive posterior and septal leaflets to reconstruct a functional tricuspid valve [39]. The leaflets are mobilized and rotated before being attached to the true tricuspid annulus. The anterior edge of the septal leaflet is attached to the septal edge of the anterior leaflet. This leaves the patient with near-normal tricuspid valve anatomy and function that is not achievable with the previously described techniques. Modifications of the original cone reconstruction include the addition of annular stabilization with a flexible annuloplasty ring and leaflet augmentation to improve coaptation when native tissue is inadequate.

Relative contra-indications to the cone procedure include older age (> 60 years), left ventricular dysfunction (ejection fraction < 30%), lack of septal leaflet tissue, minimal delamination of the anterior leaflet (< 50%), and severe dilation of the right ventricle and/or atrioventricular junction (true tricuspid annulus) [40]. When valve repair is not feasible, valve replacement with a bioprosthetic valve is performed. Mechanical prostheses are rarely used because of the risk of thrombosis. While early degeneration of bioprosthetic valves in the tricuspid position remain a source of morbidity, transcatheter valve-in-valve replacement can extend the life of failing bioprostheses. If the space between the coronary sinus and atrioventricular node is insufficient to accommodate valve implantation, seating the prosthesis within the right atrium, allowing the coronary sinus to drain directly into the right ventricle, may avoid heart block.

Some patients with a small functional right ventricle or significant right ventricular systolic dysfunction may not tolerate tricuspid valve repair or replacement. In these patients, a bidirectional cavopulmonary shunt (BCPS, or Glenn) can be performed to offload the right ventricle. Pre-operative characteristics that should prompt consideration of a BCPS include a right ventricular end diastolic volume > 250 mL/m^2 and a right ventricular ejection fraction of < 25%.

In patients who do not tolerate weaning from cardiopulmonary bypass following valve repair or replacement, “bail-out” BCPS can be performed during the initial hospitalization. BCPS can also be appropriate if there are prohibitively high diastolic gradients through the tricuspid valve following weaning of bypass. If a patient develops a low-cardiac output state post-operatively despite appropriate post-operative resuscitative efforts, return to the operating for BCPS should be considered. BCPS should not be performed in the setting of significantly elevated pulmonary vascular resistance or significant left ventricular dysfunction. An alternative to BCPS is atrial fenestration or partial ASD closure.

Early mortality in a modern series of surgical repair of EA is < 5%. Early post-operative care strategies focus on minimization of right ventricular dilation and prevention of arrhythmias. The right ventricle is supported with infusions of epinephrine and milrinone as well as inhaled nitric oxide when necessary. Temporary atrial pacing at a rate of 100 to 120 beats per minute can also help minimize right ventricular dilation. Patients who require nitric oxide due to right ventricular failure can be transitioned to an oral pulmonary vasodilator for 1–2 months. Amiodarone can be considered prophylactically for the first 3 months after surgery because of the propensity for atrial arrhythmias.

Follow-up and Outcome

Routine follow-up with an adult congenital cardiologist is recommended for all patients with EA regardless of disease severity. Frequency of follow-up depends on the patient specific anatomic, physiologic, and clinic characteristics, and ranges from every 1–2 years to every 6 months [31••]. Post-operative patients require similar longitudinal follow-up with routine assessment of valvular function, ventricular function, and presence of new or worsening arrhythmias.

Overall survival has improved dramatically over the past several decades for patients with EA; however, all-cause mortality of both pre- and post-surgical patients remain high at up to 20 times that of the general population [41•]. Ten-year survival rates in post-surgical patients are estimated at 90% [42, 43], with frequent reoperation of the order of 18% and 44% at 10 and 20 years, respectively [42].

Exercise and Pregnancy Recommendations

Exercise Asymptomatic patients with near normal right ventricular function and mild to moderate tricuspid valve dysfunction require no exercise restrictions. Patients with more severe forms of EA resulting in right ventricular dysfunction, severe tricuspid valve dysfunction, or recurrent arrhythmias should avoid competitive exercise and require individualized counseling for further risk stratification.

Pregnancy All female patients with EA are encouraged to undergo pre-pregnancy counseling with a congenital cardiologist in collaboration with maternal fetal medicine trained obstetricians. Pregnancy risk and specific recommendations depend on the severity of underlying pathology, although, in the absence of severe right ventricular or valvular dysfunction, patients often tolerate pregnancy well. The presence of an atrial level communication may result in paradoxical embolism or worsening cyanosis in the peripartum period and should prompt consideration of anticoagulation throughout pregnancy and cesarean section in the setting of significant hypoxia [44]. A high degree of suspicion should be maintained throughout pregnancy for the development of new or worsening arrhythmias with consideration of suppressive therapy and anticoagulation. Fetal echocardiography during the 19th–22nd week of gestation is recommended to evaluate for fetal congenital heart disease, helping to inform post-natal care requirements.

Conclusion

Ebstein's anomaly remains one of the most morphologically variable forms of congenital heart disease resulting in a wide range of severity. Most patients with EA will experience some degree of tricuspid valve dysfunction over the course of their lifetime, many requiring surgical intervention. Associated cardiac defects are common and include atrial septal communications, right ventricular outflow tract obstruction, and a small functional right ventricle. Arrhythmias are a common source of morbidity and mortality with a high incidence of multiple accessory pathways.

Since its initial description more than 150 years ago, our understanding and management of EA have markedly improved patient outcomes. Early surgical intervention, evolving tricuspid valve reparative techniques, and advances in catheter- and surgical-based ablation have all contributed to improved morbidity and mortality. However, the lifetime expectancy of patients with EA remains markedly lower than that of the general population and, despite early and aggressive disease management, late complications remain high. Patients with EA should receive lifetime cardiovascular care from adult congenital cardiology providers to ensure optimal outcomes.

Compliance with Ethical Standards

Conflict of Interest Zachary L. Steinberg reports he is a consultant for Medtronic, but this work has no relationship to the submitted manuscript.

The other authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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