EBSTEIN ANOMALY OF THE TRICUSPID VALVE IN AN ADULT COHORT

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Abstract

Objective: We examined the spectrum of adults with Ebstein anomaly of the tricuspid valve.

Methods: Clinical data, EKG, chest x-rays, echocardiograms and surgical details were reviewed in patients with Ebstein anomaly at the University of Toronto Congenital Cardiac Center for Adults.

Results: Seventy-four patients (27 M, 47 F) were seen at our clinic at a mean age of 33.2±13.6 years and were followed for a mean of 7.5 ± 5.8 years. Seven patients died. Thirty-eight patients (51%) presented with or developed sustained arrhythmia (atrial flutter/fibrillation n = 27, supraventricular tachycardia due to WPW n = 16); 7 of these patients with arrhythmia experienced transient ischemic attacks. Tricuspid valve surgery was undertaken in 24 patients; NYHA class improved in all 23 survivors. Of the 12 patients that experienced atrial flutter/fibrillation before surgery, arrhythmia persisted in 6. Only 2 of these 6 patients had intraoperative arrhythmia ablation. The other 6 patients undergoing ablative procedures converted to sinus rhythm. Right atrial size ($p<0.02$) and the presence of atrial septal defect ($p<0.02$) are independent predictors of atrial flutter/fibrillation (using Cox regression analysis), whereas cardiothoracic ratio ($p<0.03$) is predictive of death.

Conclusions: Atrial flutter/fibrillation is common in adults with Ebstein anomaly, and relates to RA size. Surgery for Ebstein anomaly results in symptomatic improvement. Atrial flutter/fibrillation may persist without concomitant intraoperative arrhythmia ablation.

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This thesis is dedicated to Dr. Gatzoulis who gave my academic career a clear direction.

This thesis is also dedicated to the undergraduate students who are unsure of how much more can be learned before entering medical school.

"I haven't failed, I've found 10,000 ways that don't work."

Sir Thomas Edison

"This is not the end. It is not even the beginning of the end. It is the end of the beginning."

Winston Churchill

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AF/Fib	Atrial flutter or fibrillation
ASD	Atrial septal defect
AV	Atria-ventricular
CHF	Congestive heart failure
CTR	Cardiothoracic ratio
CXR	Chest X Ray
EKG	Electrocardiogram
EPS	Electro-physiological study
LV	Left ventricle
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
PDA	Patent ductus arteriosis
PFO	Patent foramen ovale
RA	Right atrium
RV	Right ventricle
RVD	Right ventricular dysplasia
RVOT	Right ventricular outflow tract
RVOTO	Right ventricular outflow tract obstruction
SD	Standard deviation
SVT	Supraventricular tachycardia (due to WPW)
TCCCA	The Toronto Congenital Cardiac Center for Adults
TIA	Transient ischemic attack
TV	Tricuspid valve
VSD	Ventricular septal defect
WPW	Wolff-Parkinson-White syndrome

Chapter 1

Introduction:

Pathological Anatomy of Ebstein Anomaly

Introduction and Purpose of Study

Ebstein anomaly is a congenital cardiac anomaly that, although only contributing to <1% of congenital cardiac defects, accounts for 40% of anomalies associated with the tricuspid valve. [1]. The anomaly is one in which the tricuspid valve leaflets are apically displaced (into the ventricle) at their point of attachment to the myocardium. Usually it is the septal and/or posterior leaflets that are displaced. The degree of tricuspid valve incompetence varies, but the leaflets are often thickened and the anterior leaflet is commonly large and sail like [2]. The anterior leaflet, and less commonly, the posterior leaflet, may be tethered to the wall of the ventricle, promoting tricuspid incompetence and possible right ventricle outflow tract obstruction.

The displacement of the leaflet is caused by inability of the tricuspid leaflets to delaminate from the myocardial wall during embryogenesis [3]. The degree of delamination determines the displacement of the valve.

Tricuspid regurgitation in patients ranges from trivial to severe, but some degree of tricuspid regurgitation is common. Other anatomical abnormalities include abnormally numbered and placed chordal attachments, thin walled right ventricle with a small undilated cavity size (but, which may be dilated) and an "atrialized" portion of the ventricle (Figure 1). This "atrialized" ventricle is the region of the ventricle between the true tricuspid valve annulus and the displaced attachment of the valve leaflets, and is often thin walled and dilated. Conduction abnormalities are

also commonly associated with Ebstein anomaly, with WPW and other atrial arrhythmia being commonly present.

There is evidence for both genetic and environmental factors causing Ebstein anomaly [4]. Many cases of Ebstein anomaly have occurred within families, with a notable case of 6 reported cases of Ebstein anomaly in 2 generations [5]. Some studies have suggested that the intake of lithium by mothers may induce Ebstein anomaly in their children [6, 7]. Fetal parvovirus infection has also been implicated in causing Ebstein anomaly [8].

The natural history of Ebstein anomaly in an adult population is not known. Therefore, we hypothesized that the outcome for adults with Ebstein is relatively less favorable and their quality of life is compromised. We also hypothesized that surgical correction may have some positive impact in these patients. Accordingly, we studied 74 consecutive patients retrospectively to determine their outcome and factors accounting for favorable outcome.

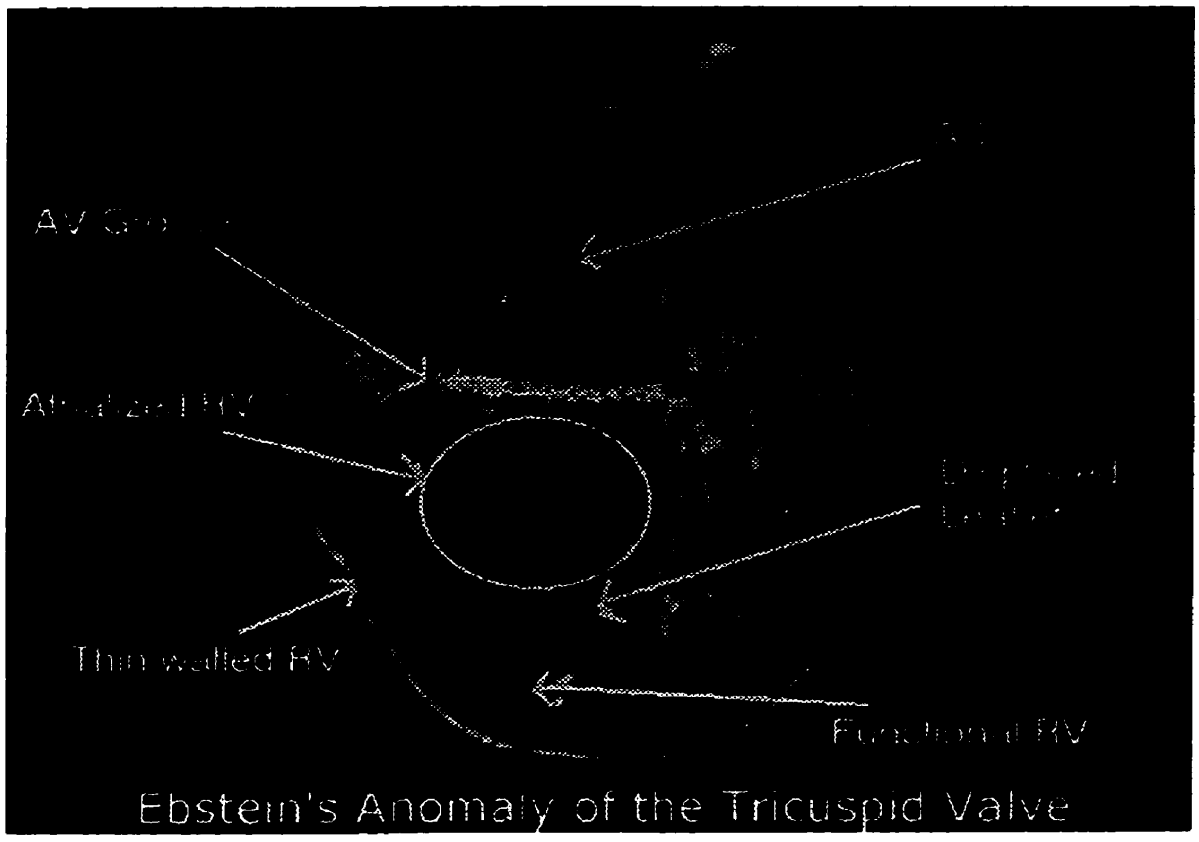


Figure 1. The features of Ebstein anomaly. The tricuspid leaflet is displaced into the ventricle, creating a large right atrium. Effectively, the right ventricle is small. Also, the right ventricle is thin walled. An ASD is often associated with Ebstein anomaly.

History

Ebstein anomaly was first described in Wilhelm Ebstein's 1886 publication [9]. Joseph Prescher was the first patient described to have this malformation, and was seen at the age of 19 years, in June 1864. This youth, who suffered from shortness of breath and palpitations, was seen by a colleague of Ebstein. Ebstein himself, evidently, did not see the patient alive, and described the patient's presentation from information gathered in his colleague's notes [2]. In the publication, Ebstein described, in detail, the anatomy of the heart, which he autopsied in July 1864 [9] (Figure 2).

The anomaly did not reach general recognition for some time after Ebstein's first description, with the next description of the disease appearing 20 years later [10]. It was in 1900 that Ebstein malformation was first described in English literature by W. MacCallum, where MacCallum described a museum specimen which he believed was identical to Ebstein's first description [10]. It was in 1927, 15 years after Ebstein's death that Alfred Arnstein, on publishing a case report of a patient with this anomaly, stated that the malformation with the displacement of the tricuspid valve should be termed "Ebsteinsche Krankheit" (Ebstein's disease). This was the 14th report of the anomaly [11].

In 1950, Enfle suggested that Ebstein anomaly could be diagnosed based on an associated clinical syndrome [12]. Such a diagnosis was made by Van Lingen [13] in 1951 using cardiac catheterization. The Glenn procedure (vena cava to pulmonary artery anastomosis) was first attempted, successfully, on a patient with Ebstein anomaly in 1959 [14], and prosthetic valve replacement of the

tricuspid valve was first documented in 1962 by Barnard and Schire [15]. The anatomy of Ebstein anomaly has been well studied and a clear anatomic description of the anomaly can be given.

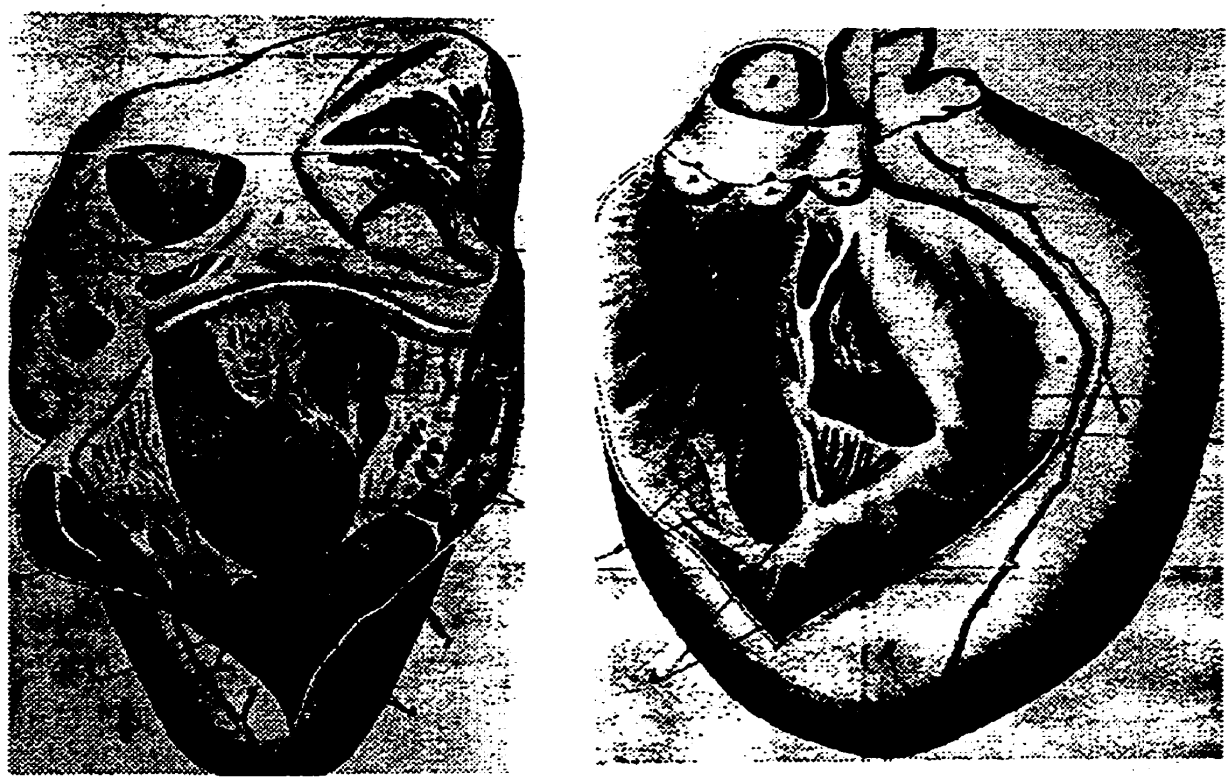


Figure 2. Ebstein's original drawings showing the details of Joseph Prescher's autopsied heart. The tricuspid valve is clearly seen to be displaced and malformed.

The Tricuspid Valve in Ebstein Anomaly

The defining feature of the anomaly is the apical displacement of the point of attachment of the tricuspid leaflets. Usually the posterior and/or septal leaflets are displaced, as opposed to the anterior leaflet that is rarely displaced [2]. The point of maximal displacement of the tricuspid valve is usually the point opposite the anterior leaflet, at the commissure between the posterior leaflet and the septal leaflet [16] (Figure 3). The posterior and septal leaflets are variable in size and may be small, in addition to being displaced, or even completely absent. The leaflets of the tricuspid valve are commonly thickened and dysplastic, with the septal leaflet most often exhibiting dysplasia. [16, 17].

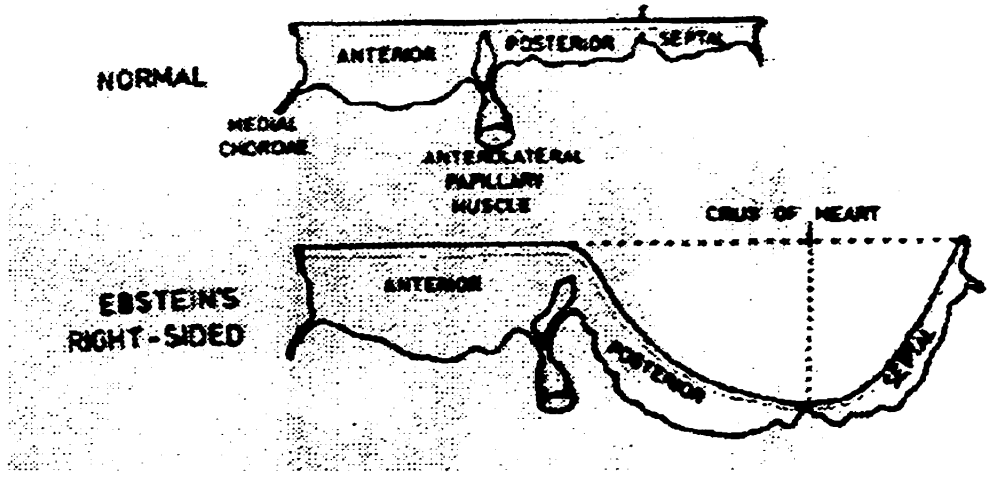


Figure 3. A diagrammatic representation of the tricuspid leaflets in Ebstein anomaly. The maximal point of displacement of the leaflets is at the commissure of the posterior and septal leaflets.

The leaflets may be partially adherent to the ventricular wall, as opposed to being displaced in their point of origin from the heart wall, or they may be "truly" displaced, with the point of origin of the leaflets being in the ventricle, with no identifiable leaflet tissue on the inlet septum. When the leaflets are adherent to the ventricular wall, it is the actual tethering of the leaflet that causes the anomalous origin of the leaflet from the body of the ventricle (Figure 4). In either case, the origin of the mobile valve is apically displaced. [16]. In addition, the chordal attachments of these valves are almost always abnormal [18].

The anterior leaflet is often enlarged and sail-like and this leaflet occasionally has an anomalous number and positioning of cordal attachments [18]. Very rarely is the anterior leaflet displaced in Ebstein anomaly. The lateral edge of the leaflet, instead of being completely free, as in the normal heart, is often attached to the ventricular wall [18]. The structure of the anterior leaflet is also anomalous, consisting of abnormal muscular strands running from the anterolateral papillary muscle to the origin of the leaflet in the heart wall [18].

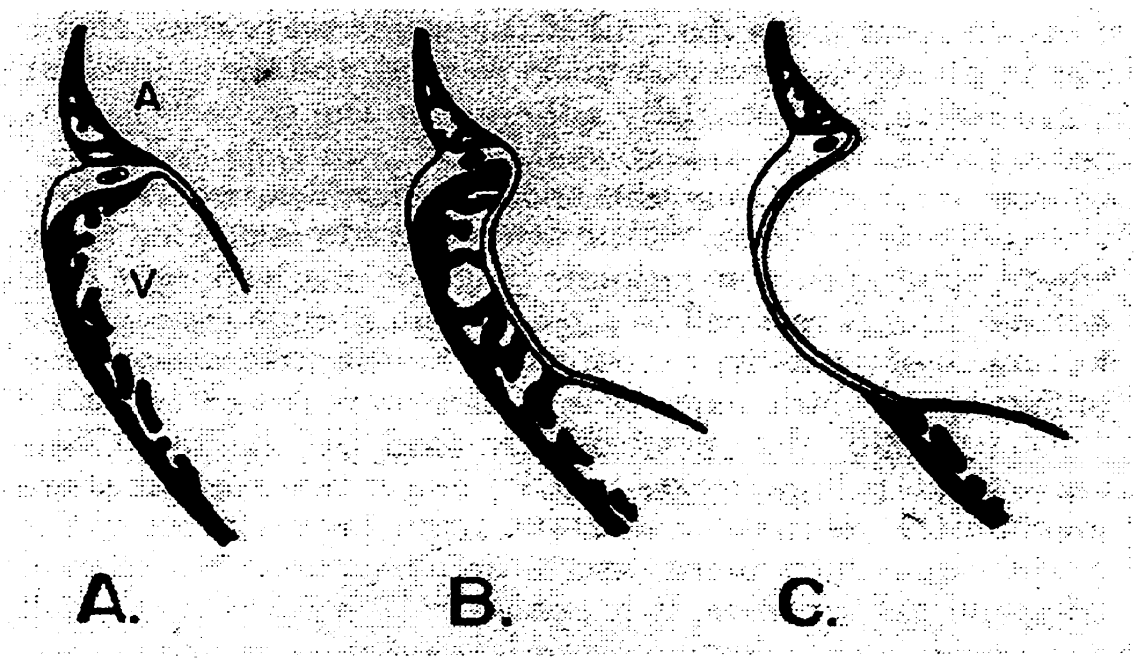


Figure 4. Tethering of the tricuspid valve leaflet to the right ventricular wall causes the origin of the leaflet to be in the ventricle. "B" shows such tethering, compared to a true displacement of the leaflet in "C". "A" represents a normal leaflet.

These anomalies often make the tricuspid valves incompetent, and almost always exhibit some degree of tricuspid regurgitation [19, 20]. Tricuspid valve stenosis is not common and is present in only a minority of patients [20].

The Right Ventricle

The displacement of the tricuspid valve causes the right ventricle to have a smaller volume, with part of the ventricle becoming "atrialized". Ebstein anomaly is also associated with an increased plasticity of the walls of the right ventricle [16]. Also, the thickness of the ventricular wall is seen to be thinner in patients with Ebstein anomaly, compared to normal hearts [16]. In addition, histologic studies of the right ventricle revealed that the walls to be not only thin walled, but also to contain a lower density and a less number of myocardial fibers [16]. In some cases, part of the right ventricular wall may consist solely of fibrous tissue and no muscle [18]. These factors make the ventricle hypoplastic.

The thin walled ventricle often becomes dilated due to the inability of the ventricular wall to resist a change in shape. Dilation of a right ventricle compensates for its small size and often makes the ventricle appear of normal size [18]. The dilatation involves both the body of the right ventricle and the right ventricular infundibulum [16].

The portion of the ventricle that becomes "atrialized", the section of the ventricle proximal to the tricuspid valve, is also thin walled [16]. This often promoted right atrial dilatation, a significant feature in patients with Ebstein anomaly.

The Right Atrium

The right atrium is often enlarged in patients with Ebstein anomaly for three reasons. Firstly, the cavity size is increased due to the downward displacement of the tricuspid valve. The right atrium, defined by the section of the right heart proximal to the tricuspid valve, includes the original right atrium, in addition to the right ventricle that is proximal to the tricuspid valves, or the "atrialized" portion of the right ventricle. This extension to the right atrial chamber accounts for an enlargement in the effective right atrial cavity size.

Secondly, the "atrialized" right ventricle is thin walled. This section of the atrium, like the right ventricle distal to the tricuspid valve, is made of a fewer number of myocardial fibers, and thus is hypoplastic. Thus, like the right ventricle, this section of the atrium becomes dilated. This dilatation also leads to inefficient emptying of the atrium into the right ventricle [21] (Chapter 2).

The third reason for the enlargement is regurgitation of the tricuspid valve. The malformed tricuspid valves are often incompetent and regurgitant. The regurgitation results in a large blood volume in the atrium during each contraction, increasing the load of each contraction. The right atrial volume overload causes the over development of the proximal right atrium. In addition, the proximal portion of the atrium has to compensate for the inefficient distal portion (derived from the thin walled ventricle), another cause of atrial hypertrophy. For these reasons, the atrium is often larger, and may be thick walled proximally [21].

Interatrial Communication in Association with Ebstein Anomaly

Atrial septal defects (ASD) or patent foraman ovale (PFO) are very commonly found in patients with Ebstein anomaly with prevalence ranging from 30%-90% in various studies [16, 20]. In a study of 505 patients, interatrial septum defects were present in 62% of operated patients and in 60% of patients undergoing necroscopy [22]. In early infancy, tricuspid incompetence, coupled with normally high right heart pressures, leads to higher right atrial pressures, resulting in right to left shunting through the PFO or ASD. Thus infants with Ebstein anomaly are often cyanotic. However, cyanosis diminishes as pulmonary resistance decreases during development, and right heart pressures drop. Right to left shunting also increases the chances of embolic events from a paradoxical embolus, and should be considered during treatment of Ebstein anomaly [23].
The presence of interatrial communication may be a result of the hemodynamic abnormalities caused by the incompetent tricuspid valve during development [22].

The Right Ventricular Outflow Tract and Pulmonary Artery

Pulmonary stenosis and pulmonary atresia are cardiac anomalies commonly present in patients with Ebstein anomaly [18, 22] and have been reported to be present in up to 30% of autopsied hearts [24]. Pulmonary stenosis has been reported to be present in 2% to 5% of patients with Ebstein anomaly [25, 26]. These associated defects, leading to right ventricular hypertension, affect the natural history of the disease [27]. Often the obstruction to the right ventricular outflow tract (RVOT) is caused by the abnormally large, sail like, anterior leaflet of the tricuspid valve overlapping at the level of the ostium infundibuli [28].

The Left Ventricle

Alterations in right heart morphology in patients with Ebstein anomaly have significant effects on left heart geometry [29, 30]. During diastole, the interventricular septum is seen to bow into the left ventricle, towards the left ventricular free wall. This, in turn, alters the left ventricular geometry and cavity size to an appreciable extent. Patients with Ebstein anomaly often show signs of left ventricular dysfunction as well as mitral valve prolapse [31, 32]. Fibrous thickening of the mitral leaflets has also been frequently reported [31]. These defects are usually not detected clinically, and become evident only after careful investigation by echocardiography and invasive angiocardiography [32]. Other mitral valve defects reported in patients include cleft mitral valve, valvular stenosis, parachute mitral valve, and supravalvular ring [29]. Mitral valve prolapse is also seen in patients with Ebstein anomaly (2%) [25, 31, 33] and the mitral valve may also be thickened or nodular [21].

Other Congenital Malformations

There are occasionally other congenital lesions associated with Ebstein anomaly. These lesions include congenitally corrected transposition, in which case the displaced tricuspid valve is actually a systemic valve (≈2%) [16], and tetrology of Fallot (≈2%) [34, 35]. Ventricular septal defects are also seen in Ebstein patients [36] well as transposition of the great arteries [35] and persistent ductus ateriosus (PDA) [22, 37]. Some of these lesions, when they occur, may mask the symptoms of Ebstein anomaly (such as in congenitally corrected transposition and tetrology of Fallot), while others may not be of clinical significance such as small VSDs.

These anatomic features of Ebstein anomaly lead to consequent physiological abnormalities in patients.

Chapter 2

Pathophysiology in Ebstein Anomaly

Tricuspid Valve with Regurgitation and Stenosis in Ebstein Anomaly

The tricuspid valve in patients with Ebstein anomaly is almost always incompetent and exhibits regurgitation [19, 20]. As a result of this regurgitation, blood refluxes into the right atrium during ventricular systole. The right atrium becomes volume overloaded and in turn leads to cardiomegaly [38, 39]. During fetal life, this may restrict the development of the lungs causing lung hypoplasia, leading to respiratory problems in the neonate [39].

Infants

Another consequence of tricuspid regurgitation is the ineffective pumping of blood through the right heart. With increased right atrial pressures resulting from regurgitation, patients with an ASD may exhibit right to left shunting [40]. For this reason, patients with Ebstein anomaly often present with cyanosis [22]. Cyanosis is more common in children, however, due to the normal higher pulmonary pressures, and more severe disease in this age group, that encourage right to left shunting [22].

Adults

In adults, tricuspid regurgitation and subsequent reduction in cardiac output does not manifest itself as cyanosis. Instead, adults usually present with arrhythmia and dyspnea, the former being more common [1, 25]. This is a consequence of right heart dilatation, which provides a substrate for right atrial arrhythmia development. SVT arrhythmias are also associated with WPW, which is commonly seen in patients with Ebstein anomaly.

Two additional features of the tricuspid valve are worth noting. Firstly, the annulus of the tricuspid valve is almost always enlarged [19]. This is due to the displaced valve forming an elongated annulus, which is invariably larger than an undisplaced annulus (Figure 5). Secondly, the displaced tricuspid valve never seems to originate from below the junction of the inlet and the trabecular zones of the right ventricle [16, 37]. There does not seem to be any explanation for this.

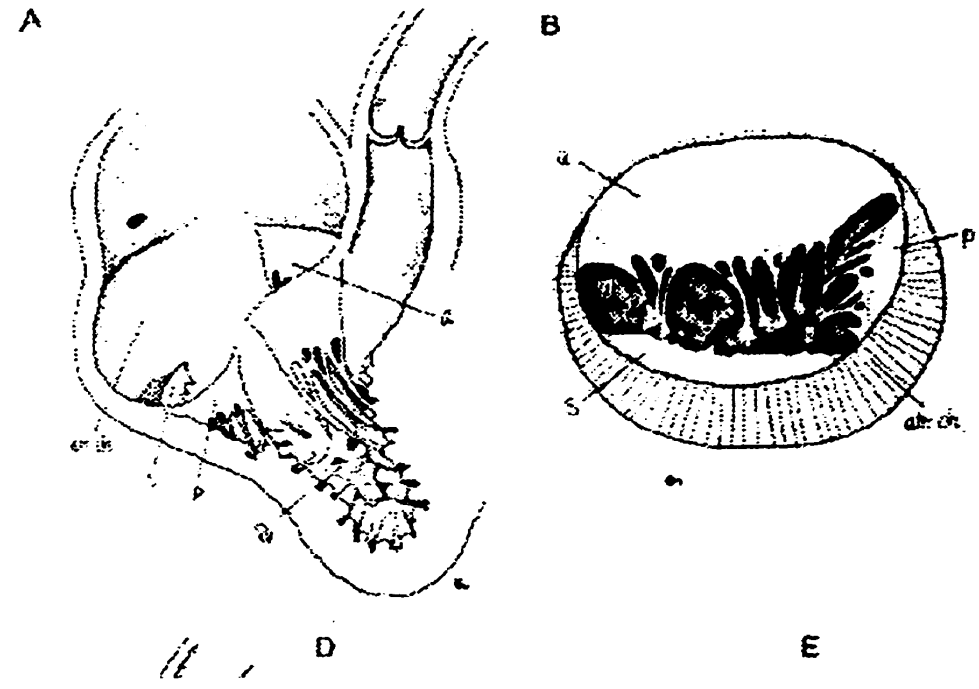


Figure 5. Enlarged annulus of tricuspid valve in Ebstein anomaly. The displacement of the valve increases the circumference of the valve, increasing the effective annulus.

Right Ventricular Dysfunction

Due to the thinning of the right ventricular wall with subsequent dilatation and the reduction of right ventricular unstretched cavity size, almost all cases of Ebstein anomaly exhibit right ventricular dysfunction. Right ventricular dilatation has been seen in about two-thirds of hearts with Ebstein anomaly, impeding blood flow through the right heart [16, 25] (Figure 6). Massive dilatation also negatively influences operative prognosis [16].

The right ventricle's ability to pump blood may be further compromised by right ventricular outflow tract obstruction (RVOTO) by the large anterior leaflet of the tricuspid [28]. Right ventricular outflow tract obstruction has also seen to be a significant predictor of death in patients with Ebstein anomaly [25]. A study of 220 patients with Ebstein anomaly by Celermajer et al [25] showed that RVOTO had an associated relative risk of 2.1 (confidence limits 1.1 to 4.4).

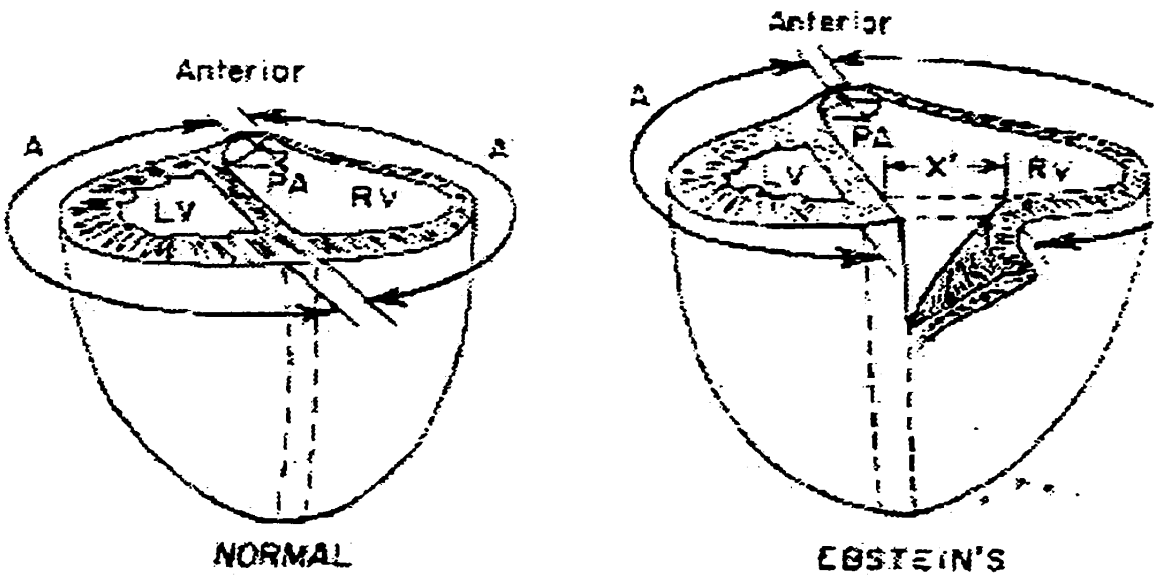


Figure 6. Enlargement of the right ventricle in Ebstein anomaly. The thin walled right ventricle does not resist a change in shape and dilates.

Right Atrium Dilatation

The right atrium in patients with Ebstein anomaly includes part of the atrialized right ventricle (a result of apical tricuspid valve displacement) which is often thin walled and hypoplastic and thus often dilated (Chapter 1). Tricuspid regurgitation and reduced ventricular size also promote retrograde motion of blood, from the ventricle back into the atrium. This causes right atrium overload, and as a chronic condition causes the proximal portion of the right atrium (the "true" atrium) to overdevelop [16, 41]. This enlargement and thickening right atrium increases the chances of atrial arrhythmia such as atrial fibrillation and atrial flutter (Chapter 3).

The proximally thick-walled and distally thin walled atrium often exhibits paradoxical motion during systole. When the atrium contracts, it is the proximal part of the atrium that exhibits most of the contraction, since the fibrous distal walls are deficient in muscle cells [16]. This increase in pressure during systole causes dilatation in the thin walled distal atrium, thus causing the motion to be paradoxical [41]. This malfunctioning section of the atrium, immediately proximal to the tricuspid valve, further impedes the efficient delivery of blood to the ventricle [42].

The atrialized portion of the ventricle is below the AV node, and is, therefore, electrically continuous with the functioning ventricle. This causes the atrialized ventricle to contract in synchrony with the right ventricle [41], further disrupting forward blood flow during true atrial systole.

Left Ventricular Dysfunction

Left ventricular abnormalities are more prevalent in adults than in children [21]. The left heart may exhibit a change in geometry due to the bulging of the interventricular septum into the left ventricle during systole [30] (Chapter 1) (Figure 7). This in turn results in a decrease in left ventricular cavity size, and a consequent reduction in LV diastolic volume and resting LV ejection fraction [30]. A study by Benson et al reported a LV ejection fraction of 45 ± 6%. During exercise, however, LV ejection fraction increases to normal as the heart compensates for low cardiac output. The normal free wall of the LV functionally counters the adverse effects of the abnormal septum [30].

Earlier studies by Monibi et al [32] showed signs of left ventricular dysfunction, but this is not evident clinically, and is documented only by cardiac catherization. LV ejection fraction has been shown to be closely related to prognosis in children [43] and a recent study by Luciano et al showed increased fibrosis in the LV parietal wall and ventricular septum [44]. Lee et al observed that, although the endocardial thickening develops in perinatal life, the interstitial fibrosis develops later in life, in patients with Ebstein anomaly [45].

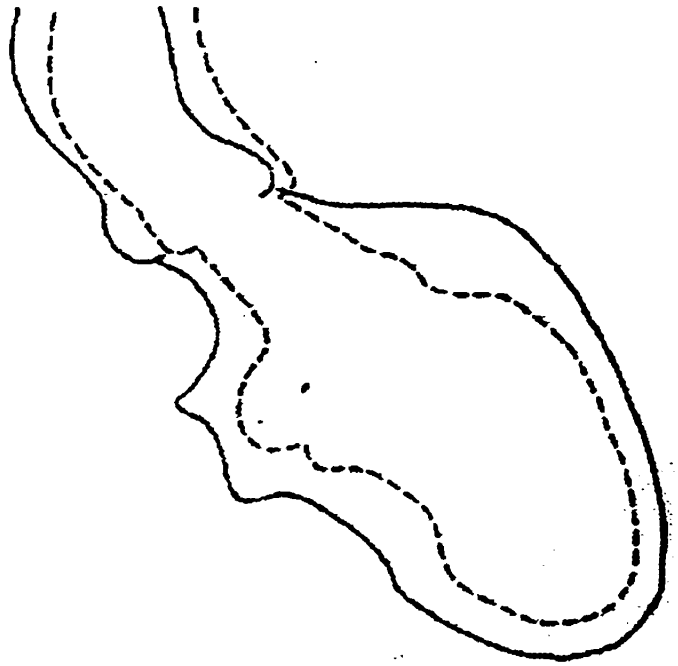


Figure 7. The deformed left ventricle. The left ventricle becomes banana-shaped when the interventricular septum bulges into the left ventricle.

Chapter 3

Clinical problems associated with Ebstein Anomaly

Clinical Findings in Ebstein Anomaly

Auscultation

Marked cardiomegaly often causes the left anterior chest to be prominent in patients with Ebstein anomaly. In addition, there may be a systolic thrill along the left sternal edge, originating from the tricuspid valve. There is a wide splitting of the first sound with accentuation of the delayed component caused by the closing of the large anterior leaflet. This leaflet also causes an opening snap in diastole, and in addition, there may be a 4th heart sound. A pansystolic murmur maximal at the lower left sternal edge is heard in about one third of patients an is due to tricuspid insufficiency [2].

Electrocardiogram in Ebstein Anomaly

The electrocardiogram in patients with Ebstein anomaly shows right bundle branch patterns, with a low amplitude R-wave. Inverted T-waves in leads V1 - V4 are fairly common. A delta wave is seen in patients with WPW and atrial flutter or fibrillation is common [2].

Chest X-ray

The chest x-ray in patients with Ebstein anomaly classically shows marked cardiomegaly, due to an enlargement of the right heart. The shape of the heart is often rounded or box-like beneath a narrow pedicle [2]. The posterior-anterior view shows a silhouette formed completely by the right atrium and the right ventricle, with a sharp edge.

Cyanosis

Most patients with Ebstein anomaly have interatrial communications (Chapter 1) [16, 32, 46]. During atrial systole, deoxygenated blood may escape through the interatrial septal defect to contaminate the systemic circulation. This contributes to cyanosis in patients with Ebstein anomaly. The degree of cyanosis can serve as an estimation of the degree of right to left shunting, and consequently the hemodynamic condition of the right heart [35].

Infants

Cyanosis is more common in younger patients than in adults, since the pulmonary resistance is higher, and subsequently the right heart pressures are also increased. This encourages a higher amount of right to left shunting [21, 35, 47]. The more severe disease spectra seen in children, with severe tricuspid regurgitation also accounts for the higher frequency of cyanosis in a pediatric cohort.

Adults

Adults, however, do not experience such a high degree of right to left shunting, since the pulmonary resistance, and consequently the right heart pressures, are relatively lower [21, 48]. Often, cyanosis is minimal or absent except during exercise, fatigue or cold weather [21]. In severe forms of Ebstein anomaly, however, cyanosis may be observed in an adult patient, since an increased right atrial pressure is caused by backward regurgitation of blood across the incompetent tricuspid valve.

Cyanosis in Ebstein anomaly causes various functional limitations. There is a strong correlation between exercise intolerance and rest oxygen saturation [20]. In neonates, cyanosis suggests a poor prognosis, with a mortality rate of 48% (at a median age of 2.5 years) in a series by Celermajer et al [34] and 70% (at a mean age of 1.2 years) by Yetman et al (versus 14% in neonates with Ebstein anomaly without cyanosis) [49]. Also, maternal cyanosis in Ebstein anomaly is associated with a significant decrease in birth weight of offspring [50] and increased risk of miscarriage or premature delivery.

Arrhythmia and Transient Ischemic Attacks

Wolff-Parkinson-White Syndrome (WPW)

Ebstein anomaly is the most common congenital malformation associated with WPW [51]: about 15% of patients with Ebstein anomaly experience SVT [52, 53]. It is the accessory pathways due to WPW that is the most common cause of SVT in patients [53]. Patients with WPW in the setting of Ebstein anomaly frequently have multiple accessory pathways, and these are almost always right sided [54]. The localization of these electrical pathways by catheter is often impeded by the multiplicity of these pathways, and by the presence of a large right atrium [54].

Atrial Fibrillation and Atrial Flutter

Tricuspid regurgitation in Ebstein anomaly leading to right atrial dilatation encourages atrial fibrillation of flutter [25]. Since this atrial enlargement develops over time, atrial fibrillation and atrial flutter are rare in a pediatric cohort, but more common in an adult cohort [51]. The enlargement of the right atrium increases the likelihood of reentry circuits in the right atrium, leading to atrial fibrillation or atrial flutter [21, 25]. Long-standing RA dilatation and stretch creates the substrate for sustained atrial flutter/fibrillation. Satoh et al recently showed prolonged and heterogeneous refractoriness resulting from atrial stretch in response to volume overload [55]. Similarly, Morillo et al showed a strong correlation between a 40% or greater increase in atrial area and inducibility of sustained atrial flutter/fibrillation [56]. These arrhythmias seem to be resistant to drug treatment and tend to be recurrent [25]. Patients with mild forms of Ebstein are also at a risk of developing arrhythmia due to the unpredictable deterioration in tricuspid valve function [57].

Transient Ischemic Attacks

Arrhythmias are associated with a higher risk of thrombus formation. As a consequence, incidence of TIA and strokes in patients with atrial arrhythmia is significantly increased, upto 5 fold [23, 58, 57]. The abnormal hemodynamics caused by atrial arrhythmia, such as areas of blood stasis, cause the blood to form emboli. These emboli, in the presence of an ASD or PFO, may cross the atrial septum and lodge in the systemic circulation, giving rise to paradoxical emboli [23, 51, 59, 60].

Arrhythmias also increase the risk of late sudden death in patients with Ebstein anomaly [25]

Exercise Capacity

Patients with Ebstein anomaly also exhibit limited exercise capacity [30]. During maximal exercise testing, these patients have significantly lower values of total achievable work, exercise time, maximum oxygen uptake, and oxygen saturation at rest and during exercise [61]. After surgery to correct the anomaly and any associated atrial defects, the patients may increase their exercise tolerance significantly [20, 62]. In a study by MacLellan et al, major predicators of increased exercise capacity included a young age, male gender and a low cardiothoracic ratio [20]. The study also showed that heart rate response is diminished in patients with Ebstein anomaly.

Another major predictor of exercise intolerance in MacLellan's study was hypoxia [20]. Limited exercise tolerance is seen in Ebstein patients with cyanosis at rest [63]. A study by Baber et al [61] also showed a positive correlation of hypoxemia and exercise tolerance in patients with interatrial communication, but not in patients with-out this communication.

Other factors influencing exercise capacity include the presence of significant tricuspid regurgitation, poor right ventricular function with decreased cardiac output, right to left shunting and cardiomegaly [20]. Also, paradoxical ventricular septal motion causes a decrease in left ventricular diastolic volume and resting ejection fraction [30]. This may contribute to a decreased exercise capacity.

Dyspnea and Easy Fatigability

Shortness of breath and fatigue with little exertion are the most common symptoms in patients with Ebstein anomaly, and often the only ones [20, 21, 35, 47]. Usually these symptoms have an early onset and gradually increase in severity. These symptoms are likely due to the lower cardiac output in Ebstein anomaly, which leads to a slower delivery of oxygenated blood to the systemic circulation [21]. Correction of the anomaly, for example by repairing the regurgitant tricuspid valve, can improve hemodynamics, and in turn decreases the symptoms of dyspnea [19].

Major Causes of Death

The greatest risk of death in patients with Ebstein anomaly is usually within the first year, with a 33% 1 year mortality [25]. In severe forms of Ebstein anomaly, death may occur in the fetal or neonatal stages [25]. However, there is currently no information on mortality in a purely adult cohort with Ebstein anomaly. Since patients with severe Ebstein have increased tricuspid regurgitation, these patients are likely to have congestive heart failure. Since few of these patients with severe Ebstein survive to adulthood, congestive heart failure is less common in adults. The long standing overload of the right atrium induces arrhythmia, and therefore, sudden death due to arrhythmia is more common in adults. We predict that arrhythmia will be the most common cause of death in our adult cohort of 74 patients.

Heart Failure

A study by Celermajer et al [25] showed 45% of deaths being due to congestive heart failure. In a study by Kumar et al [35], congestive heart failure was also the commonest form of death. Also, Genton and Blount showed a 33% heart failure death rate [21]. If heart failure is due to tricuspid regurgitation and right atrial enlargement, correction of the anatomy and restoration of hemodynamics should reduce mortality [25]. All of these studies, however, dealt with a primarily infant cohort.

There is a high risk of death due to congestive heart failure in the first few months of life [22]. Correction of Ebstein anomaly often corrects the hemodynamics consequently correcting the congestion [63]. Watson observed that in the age range of 1 to 25 years, half of the deaths were due

to congestive heart failure, and 20% were sudden, probably due to arrhythmia. In patients over the age of 25 years deaths that were sudden and due to heart failure seen to have equal frequency of occurrence [22].

Arrhythmia

Arrhythmia was noted to be the second most common cause of death. Celermajer reported an incidence of death (probably due to arrhythmia) of 14% and Genton and Blount observed 20% of deaths being sudden [25]. According to Gentles et al, arrhythmia contributes to a sudden increase in risk of death around the fifth decade of life and these arrhythmias are poorly tolerated due to diminished right ventricular function, tricuspid regurgitation and increase in atrial level shunting [64]. Bialostzky [63] also showed that arrhythmia was a significant cause of death. However, there is currently no study on a large adult cohort with Ebstein anomaly studying death as a risk factor, or the impact of current surgical treatment techniques on this endpoint.

Other significant predictors of death included presentation at a young age [35, 47] and a decreased oxygen saturation level [35, 47, 64]. Cardiomegaly was also associated with a poor prognosis [22, 35, 47, 64]. This is likely due to the impairment of hemodynamics, leading to heart failure and arrhythmia.

In a study by Genton and Blount [21], paradoxical emboli were a significant cause of death especially in older patients. Emboli accounted for 25% of the deaths in patients above the age of 50 years [21].

The clinical findings of Ebstein anomaly are clearly different in adults compared to children. There is a significant difference in the degree of cyanosis [21], arrhythmia [51], cause of death [21, 22, 64], and disease spectrum in adults compared to children. Thus an adult cohort should be studied as a separate population, which we hope to do in our study.

Chapter 4

Treatment of Ebstein Anomaly

Surgical Treatment of Ebstein Anomaly

Reconstruction and Replacement of the Tricuspid Valve

Basic repair of Ebstein anomaly involves the reconstruction of the tricuspid valve to relocate the origin of the leaflet to the atrioventricular annulus. If the valve can not be repaired, it is replaced with either a bioprosthetic valve or a mechanical valve. The atrialized right ventricle is also plicated, either transversely or longitudinally (see Table 1, pg. 43, for summary of techniques). Some operative techniques also include a bi-directional Glenn shunt, connecting the superior vena cava to the pulmonary artery, thus offloading the compromised right heart.

The first prosthetic valve replacement for patients with Ebstein anomaly was reported by Barnard et al [65] in 1963. Barnard et al reported 2 cases, the first of which was a 2 ½ year old boy with right sided heart failure and cyanosis. The corrective surgery involved the closure of the PFO and excision of the malformed valve (Figure 8). The prosthetic valve inserted was a low-flow University of Cape Town lenticular prothesis moulded in Ivalone. The second case involved a 25 year old man who suffered from refractory right sided heart failure and atrial dysrhythmia. The malfunctioning tricuspid valve was replaced with a similar prosthesis. To avoid damage to the conduction pathway, the valves were inserted above the coronary sinus. The resultant flow of blood from the coronary sinus directly into the ventricle did not seem to show any adverse effects. Consequently, the atrialized ventricle was continuous with the functional ventricle.

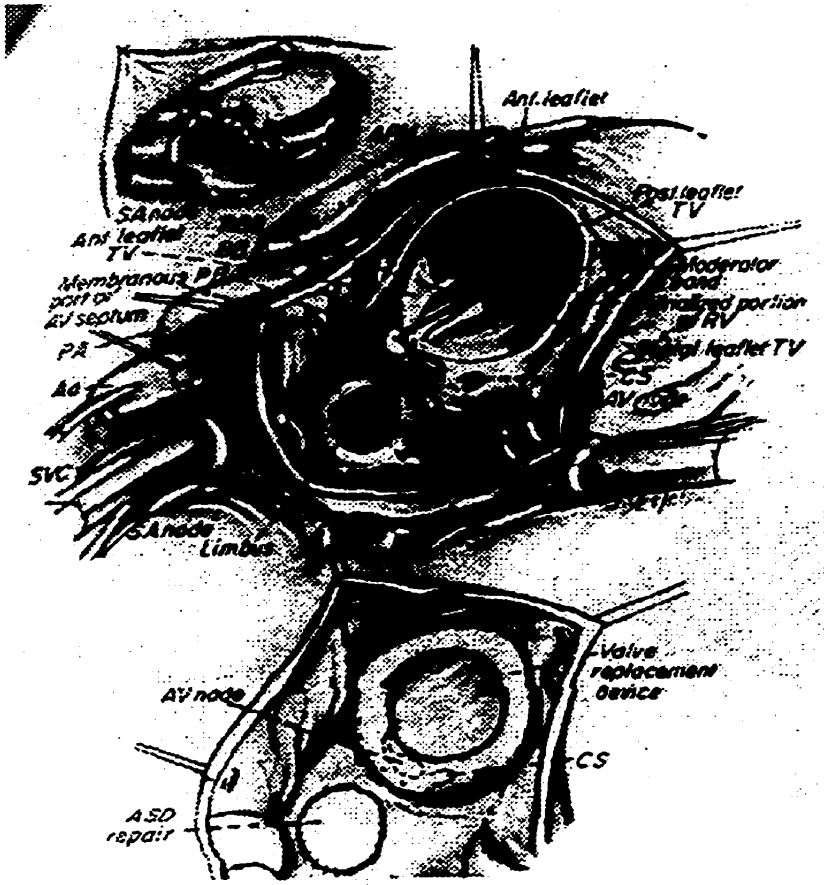


Fig 1. Replacement of the tricuspid valve and closure of the atrial septal defect in Ebstein's malformation, as originally described in Barnard and Schrire's historic article [1]. With exposure through an oblique right atriotomy, the downward displacement of the septal and posterior leaflets is illustrated, and the atrioventricular node is indicated adjacent to the commissure between the septal and anterior leaflets. The sutures for valve replacement are placed well posterior to the coronary sinus and membranous system. The remainder of the suture line then follows the actual tricuspid annulus. (Reproduced with permission from Bharati S, Lev M, Kirklin JW. Cardiac surgery and the conduction system. New York: Churchill Livingstone, 1983:3.46.)

Figure 8. Original repair by Bernard (1963). Repair involved closure of ASD and replacement of the tricuspid valve.

The next year, in 1964, Hardy et al [66] published a report of correction of Ebstein anomaly in a 42 year old lady, based on the principles put forward by Hunter and Lillehei [67]. This surgical correction involved the repair of the malformed valve as opposed to prosthetic replacement. Hardy's surgical procedure included a transverse plication of the atrialized right ventricle and formation of a competent valve using the anterior leaflet.

In 1979, Danielson et al [42] reported results of surgical correction of Ebstein anomaly involving the plication of free wall of the atrialized portion of the right ventricle, annuloplasty of the posterior leaflet of the tricuspid valve and right atrial reduction. The repair involved the formation of a monocuspid valve using the anterior leaflet, which is usually enlarged and sail like. This technique was later used in a study by Mair [68] (1985).

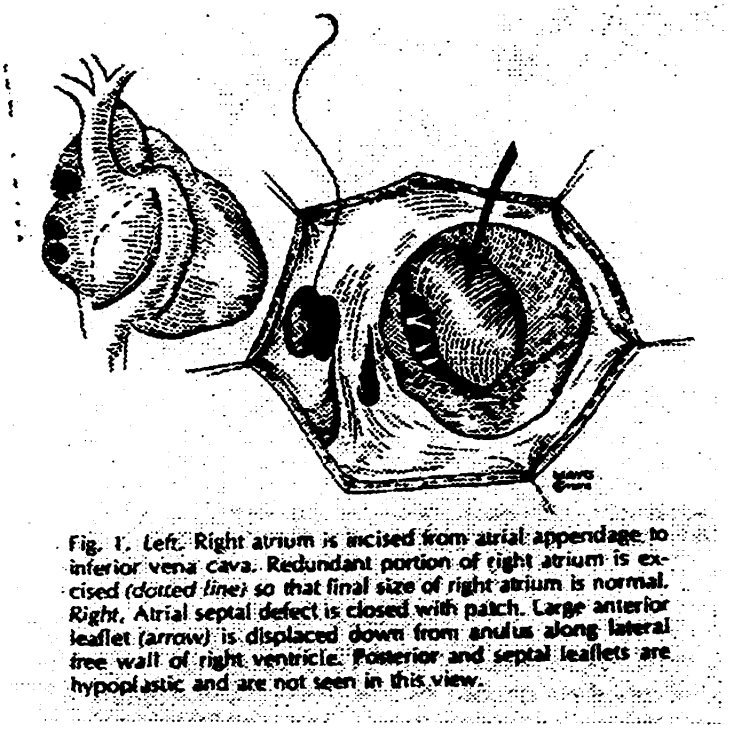


Fig. 1. *Left.* Right atrium is incised from atrial appendage to inferior vena cava. Redundant portion of right atrium is excised *(dotted line)* so that final size of right atrium is normal. *Right.* Atrial septal defect is closed with patch. Large anterior leaflet *(arrow)* is displaced down from anulus along lateral free wall of right ventricle. Posterior and septal leaflets are hypoplastic and are not seen in this view.

Figure 9. The Danielson technique described in 1979. The technique involves transverse plication of the atrium, right atrial reduction and a formation of a monocuspid valve using the anterior leaflet.

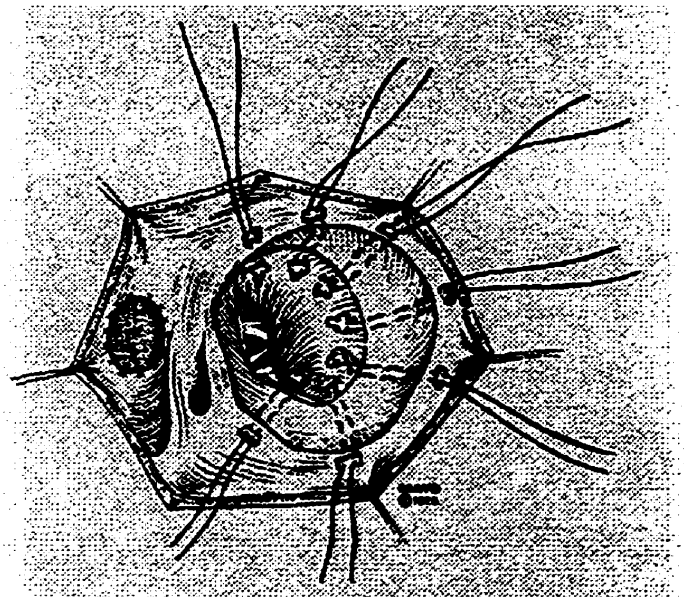


Fig. 2. Mattress sutures passed through pledgets of Teflon felt are used to pull tricuspid anulus down to insertion of tricuspid valve in wall of right ventricle. Sutures are placed in atrialized portion of right ventricle as shown so that when they are subsequently tied, atrialized ventricle is plicated and aneurysmal cavity is obliterated.

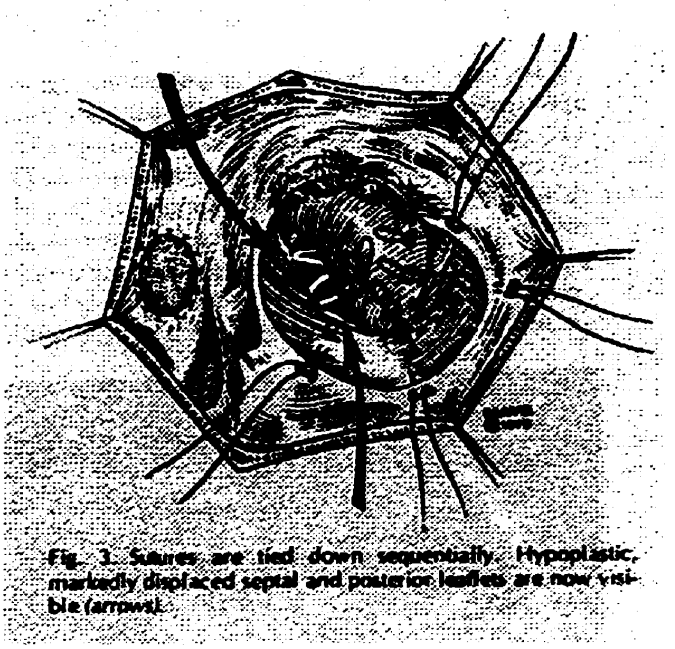


Fig. 3. Sutures are tied down sequentially. Hypoplastic, markedly displaced septal and posterior leaflets are now visible (arrows).

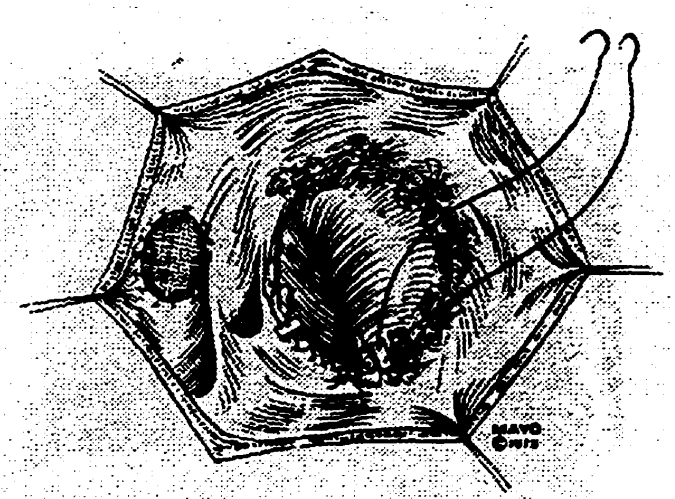


Fig. 4. Posterior annuloplasty is performed to narrow diameter of tricuspid anulus. Coronary sinus marks posterolateral extent of annuloplasty, which is terminated there to avoid injury to conduction bundle. Occasionally, one or two additional mattress sutures are required to obliterate posterior aspect of annuloplasty repair in order to render valve totally competent. Tricuspid anulus at this time will generally admit two fingers.

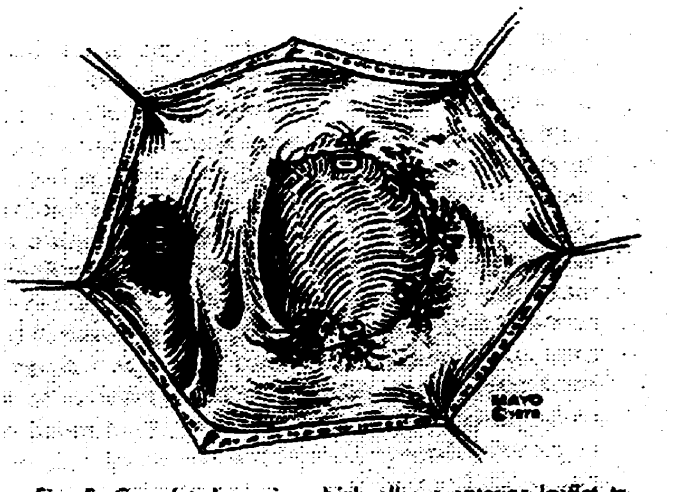


Fig. 5. Completed repair, which allows anterior leaflet to function as a monocusp valve.

Figure 9. (Continued)

Carpentier et al [69], in 1988, offered a new approach, which was an improvement on both the Hardy and the Danielson original techniques. Previous methods of surgical correction either applied to too narrow a group of patients or neglected to repair the morphology of the right ventricle. In Hardy's technique of transverse plication of the right ventricle, the right ventricle ended up being distorted in its shape.

In Carpentier's technique, the anterior leaflet and the adjacent portion of the posterior leaflets are partially detached from the ventricular wall. The atrialized right ventricle is then longitudinally plicated, thus reconstructing and reducing the size of the right atrium. The anterior and posterior leaflets are then repositioned at the normal atrioventricular annulus. The annulus is then remodeled and reinforced with a prosthetic ring. This repair technique, however does mildly increase the risk of damaging the conduction systems. This was apparent when 2 out of the 14 patients undergoing this repair developed first degree heart block and one patient developed complete heart block, requiring the insertion of a permanent pacemaker.

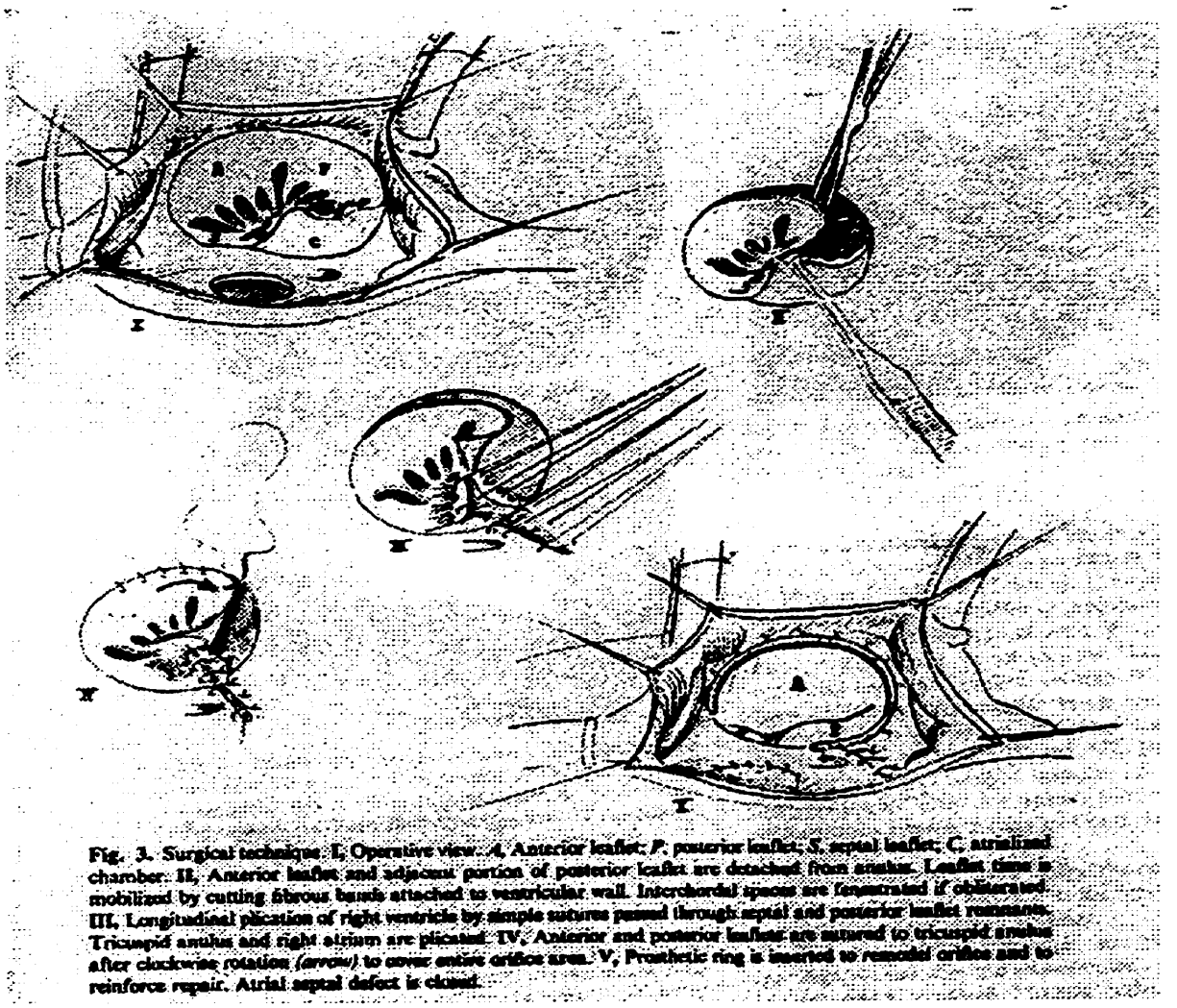


Fig. 3. Surgical technique. I, Operative view. A, Anterior leaflet; P, posterior leaflet; S, septal leaflet; C, atrialized chamber. II, Anterior leaflet and adjacent portion of posterior leaflet are detached from annulus. Leaflet tissue is mobilized by cutting fibrous bands attached to ventricular wall. Interchordal spaces are fenestrated if obliterated. III, Longitudinal plication of right ventricle by simple sutures passed through septal and posterior leaflet remnants. Tricuspid annulus and right atrium are plicated. IV, Anterior and posterior leaflets are sutured to tricuspid annulus after clockwise rotation *(arrow)* to cover entire orifice area. V, Prosthetic ring is inserted to remodel orifice and to reinforce repair. Atrial septal defect is closed.

Figure 10. Carpentier repair of Ebstein anomaly. The ventricle is plicated longitudinally and the anterior leaflet is detached and repositioned to form a monocuspid valve.

Carpentier divided Ebstein anomaly into 4 classes, A to D. "A" consisted of a condition where the anterior leaflet was mobile and not tethered to the ventricular wall and the atrialized right ventricle was small and contractile. "B" included a mobile anterior leaflet, but the atrialized chamber was large and non contractile. Type "C" included patients which had a non mobile anterior leaflet teathered to the ventricular wall in addition to a large, non-contractile, atrialized chamber. "D" consisted of an adherent sac formed by the leaflets making a continuous sac (Figure 11). This classification of Ebstein anomaly was subsequently also used by other investigators to categorize the lesions [70].

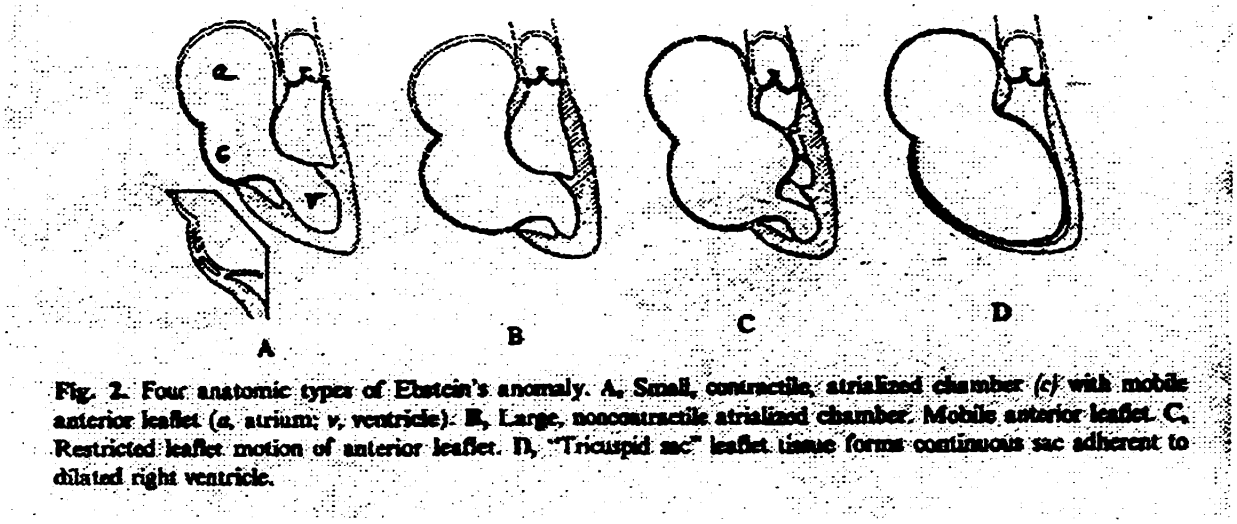


Fig. 2. Four anatomic types of Ebstein's anomaly. A, Small, contractile, atrialized chamber (*c*) with mobile anterior leaflet (*a*, atrium; *v*, ventricle). B, Large, noncontractile atrialized chamber. Mobile anterior leaflet. C, Restricted leaflet motion of anterior leaflet. D, "Tricuspid sac" leaflet tissue forms continuous sac adherent to dilated right ventricle.

Figure 11. Carpentier's classification of Ebstein anomaly. The 4 types are described in the diagram.

A more recent study by Fiane et al [71] in 1996 showed that, although valve replacement in children is common, somatic growth leading to valve patient mismatch is a problem that arises. Fiane further noted in his study that although there was an 83% survival rate after 10 years, half of the 6 patients thrombosed their valves (mostly CarboMedics prosthetic valves and one Bjork Shiley prosthetic valve). Even valve repair often leads to reoperation in children, thus suggesting a high morbidity and mortality in children with sever forms of Ebstein anomaly. Valve replacement, is thus avoided when valve repair is feasible.

In 1992, Danielson [72] published another report on experience with 189 patients. Danielson had defined his basic procedure for repair: 1) electrophysiological mapping, localizing accessory pathways, 2) Patch closure of any existing ASD or PFO, 3) Transverse plication of the atrialized right ventricle, 4) reconstruction of the tricuspid valve, if possible, else tricuspid valve replacement, 5) correction of any associated anomalies, such as pulmonary stenosis, or cryoablation of accessory pathways, and 6) excision of the redundant right atrial wall. The repair of the valve followed his 1979 technique [42] of formation of a monocuspid valve using the anterior leaflet that is usually large and the least malformed of the tricuspid valve leaflets.

If the anterior leaflet is fenestrated or perforate, it can be repaired with fine running sutures. In the case of smaller anterior leaflets, a monocuspid leaflet can still be made with a small but acceptable amount of tricuspid stenosis. If replacement was necessary, then the new valve should be inserted above the atriventricular node and the coronary sinus so as to decrease the risk of electrical pathway damage.

In this study by Danielson, 58% of patients underwent tricuspid repair whereas 37% required tricuspid valve replacement (2 out of 7 patients had mechanical valve insertion, while the remaining 5 had a bioprosthetic valve). The majority of the patients were in NYHA I or II one year post-operatively. There were, however, 12 hospital deaths and 10 late deaths (7 cardiac of which 4 were sudden). There was a significant increase in maximum oxygen uptake in patients, from 47% of predicted maximum pre op to 72% post op. Arrhythmias in these patients were reduced but not eliminated after surgery. Of the 110 patients that underwent valve repair, 4 needed reoperation 1.4 to 14.1 years later.

Danielson theorized that the plication of the atrialized right ventricle not only corrected the hemodynamic complications associated with it, but also decreased the bulging of the ventricular septum into the left ventricle and, therefore, was beneficial hemodynamically. If valve replacement was undertaken, both mechanical and bioprosthetic valves functioned better in patients with Ebstein anomaly that those without surgery. Danielson thought this might be due to the larger right ventricle, which decreased the chances of fibrous tissue in-growth.

After these 3 major techniques (Hardy, Danielson and Carpentier) for the repair of Ebstein anomaly had been established, there were no drastic changes in the methods of Ebstein repair over a relatively long period of time.

In 1991, Quaegebeur [70] published results of a study with ten patients that had undergone tricuspid valve repair using the Carpentier method. This was the largest study using this technique at the time. As in the Carpentier repair, the anterior and posterior leaflets were dissected from the heart

wall, but not completely detached. The abnormal attachments were cut and the papillary muscle attachments were disected from the ventricular wall. The atrialized right ventricle was plicated with continuous 5-0 Prolene.

The redundant right atrial wall was not excised as the atrialized right ventricle was already plicated to reduce cavity size. All ten patients showed a decrease in tricuspid regurgitation after surgical correction as well as an improvement in NYHA functional class. Cardiothoracic ratio was also seen to decrease (Figure 12).

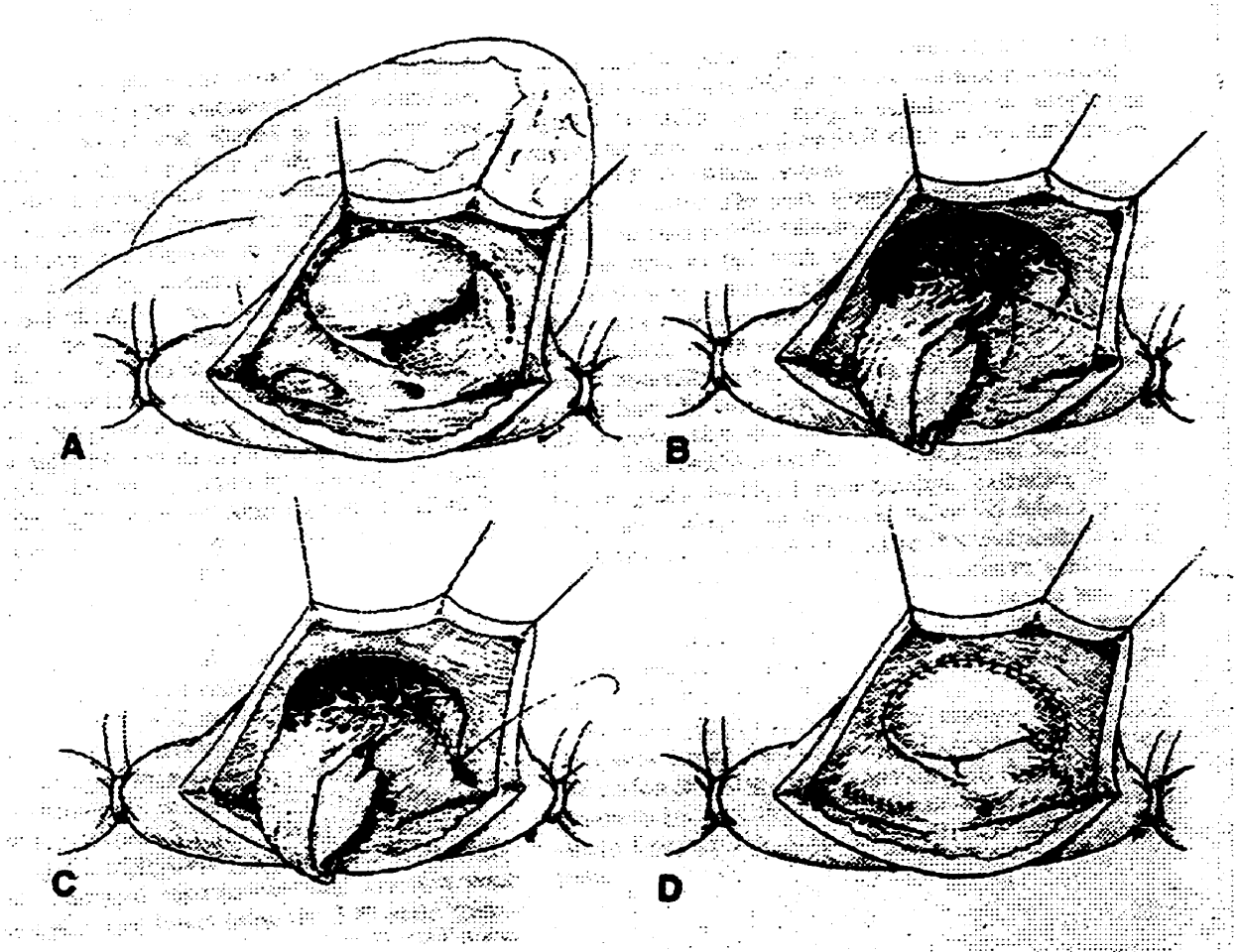


Figure 1. The operative technique, modelled after Carpentier et al. A. Surgeon's view after opening the right atrium. a = anterior leaflet of the tricuspid valve; ac = atrialized ventricular chamber; p = posterior leaflet. B. Detachment of the anterior and posterior tricuspid valve leaflets and their chordal attachments to the ventricular wall. The dashed lines denote the suture insertion points. C. Longitudinal plication of the atrialized portion of the right ventricle. D. Clockwise spreadout of the anterior and posterior leaflets on the newly created tricuspid valve anulus, and direct closure of the atrial septal defects without right atrial reduction.

Figure 12. Quaegebeur repair, a modification of the Carpentier repair.

In 1997, Augustin et al published a large study on surgical treatment of Ebstein anomaly with 60 patients [73]. The type of repair used in this study was pioneered by Fritz Sebening and involved the formation of a monocuspid valve, similar to the Danielson procedure. Of the 60 patients, 93% had appropriate valves to fashion a monocuspid valve intraoperatively. The other 7% of patients underwent bioprosthetic valve replacement. Plication of the atrialized ventricle was not thought to be necessary since there is no real evidence of this benefit, especially in the long term [73]. The results showed a substantial improvement in NYHA functional class (with 94% of the patients in NYHA functional class I or II postoperatively). There was also a slight/moderate decrease in heart size and well as an improved function of the right ventricle. Two patients formed complete heart block requiring pacemaker insertion. Despite the tricuspid valve treatment, 8 patients developed atrial fibrillation.

Another study by Hetzer et al [19] of 19 patients in 1998 used the technique of reconstructing the tricuspid valve utilizing the most mobile leaflet without plication of the atrilized right ventricle. This technique, unlike any of the previous studies, did not depend on the existence of a large anterior leaflet since only the posterior part of the anterior leaflet was used. There was a reduction in the tricuspid orifice, but this did not produce significant stenosis. There were no perioperative deaths. No late functional deterioration was observed and NYHA functional class improved from 2.8 to 1.9 (all patients showed an improvement in NYHA functional class except for 2 patients that remained in NYHA class II). Of the 18 patients showing cyanosis at rest or at exercise, no patients showed recurrent cyanosis.

Table 1. Summary of various classic techniques used to repair Ebstein anomaly.

Technique	*Plication of ventricle*	*Details*
Bernard, 1963	No	First valve replacement and ASD closed
Hardy, 1964	Transverse	Monocuspid valve using anterior leaflet
Danielson, 1979	Transverse	Monocuspid valve using anterior leaflet, RA reduced
Carpentier, 1988	Longitudinal	Anterior leaflet detached and repositioned to form valve
Augustin, 1997	No	Monocuspid valve using anterior leaflet
Hetzer, 1998	No	Monocuspid valve using anterior or posterior leaflet

Other surgical procedures

New techniques of repair evolved when unusual cases of Ebstein were presented. Such was the case in 1992 when Leung et al [74] reported using a modified Fontan procedure in a severe case of Ebstein anomaly with tricuspid stenosis. Two children exhibited severe Ebstein with cyanosis. The tricuspid valve was stenosed to a point of leaving very little atrioventricular communication in the right heart. The dysplastic leaflets were excised and an additional atriopulmonary connection was made. The modified Fontan procedure improved the post op NYHA functional class in both patients and increased atrial saturations from 70% pre op to 95% post op. This paper exemplified how the wide spectrum of Ebstein anomaly requires an individualized approach to treatment.

The Glenn Shunt and the Bi-directional Cavo-pulmonary Shunt

Another type of shunt, the Glenn shunt, also became more commonly used in the surgical correction of Ebstein anomaly. This was first reported in a patient with stenotic Ebstein anomaly by Mercelletti [75] in 1980. In the Glenn procedure [76], the superior vena cava is connected to the pulmonary. This offloads the compromised right ventricle. In the classic Glenn, the right pulmonary artery is detached and connected to the superior vena cava, so that the superior vena cava solely supplies the right lung. The left lung continues to be supplied by blood from the right heart. In the bi-directional cavo-pulmonary the SVC is connected to the pulmonary artery, without detachment of the right pulmonary artery. A 1996 study by Van Arsdell et at [76] reported that bi-directional cavo-pulmonary shunt decreases blood flow to the right ventricle which often exhibits a decrease in contractility in patients with Ebstein anomaly. However, there may be circular flow with blood flowing through the SVC, to the right heart, up the pulmonary artery but shunting back into the SVC. Although the clinical indications of the bi-directional cavo-pulmonary shunt have been positive [76], further study on the effects of potential circular blood flow has yet to be undertaken.

A recent study by Chauvand et al [77] supported the positive clinical outcomes of patients with a bi-directional cavo-pulmonary shunts. Since the right ventricular function, subsequent to repair, determines patient's prognosis, maintaining good right ventricular function greatly benefits patients. For this reason, a bi-directional cavo-pulmonary shunt procedure was added to tricuspid valve repair in their center to decrease preload in the compromised right ventricle. These shunting procedures, when compared to earlier procedure that dealt only with cardiac procedures, showed a significant decrease in operative mortality (from 24% to 0%) as well as a decrease in

reoperations. This may be due to the advance in surgical techniques, but Chauvand also suggested that the energy saving effect on the right ventricle during systole may cause the improvement.

Surgical treatment of arrhythmia

Since WPW is commonly associated with Ebstein anomaly, patients often have accessory pathways associated with the lesion [51]. The increase in right atrial size may lead to the development of other pathways causing atrial fibrillation and atrial flutter, causing potential mortality or morbidity [38]. These often develop despite tricuspid valve repair or replacement of the tricuspid valve [38, 73] (Chapter 3).

Cryoablation

In the case of WPW with Ebstein anomaly, the accessory pathways are almost always right-sided [51, 54] (unlike patients without Ebstein anomaly who usually have left sided accessory pathways associated with WPW)[57]. A study by Misaki et al in 1995 described the surgical treatment of WPW by dividing the accessory pathways associated with the lesion in 42 patients. The pathways were located using epicardial mapping. Division of pathways was achieved by cryocoagulation with scalpel dissection of the atrioventricular groove. Misaki reported a significant decrease in atrial fibrillation after the procedure, dropping from 55% preoperatively to 5.1% postoperatively. It should be noted that patients with mild Ebstein anomaly were seen to be at risk of the same severe arrhythmogenic events as patients with more severe forms of the disease, suggesting that WPW, unlike atrial flutter/fibrillation, does not become more prevalent with age. Two patients that needed reoperation due to tachycardia had residual second accessory pathways in a different position from the first [57].

Surgical repair for atrial fibrillation associated with Ebstein anomaly was described by Lin et al in 1996 [23]. This study describes a right atrial division procedure in which the atrium was divided into several smaller compartments with a U-shaped incision (Figure 13). An incision was made 1cm lateral and parallel to the sulcus terminalis and curved along the upper and lower borders of the atrial septum. Cryolesions were created at –60°C for 180 seconds. Although there were only 3 patients in this study (only one with Ebstein anomaly), all patients reverted to sinus rhythm post operatively. There were a few postoperative instances of arrhythmia that were effectively treated with medication. The compartmentalization procedure provided a simple surgical procedure for treating atrial arrhythmia [23].

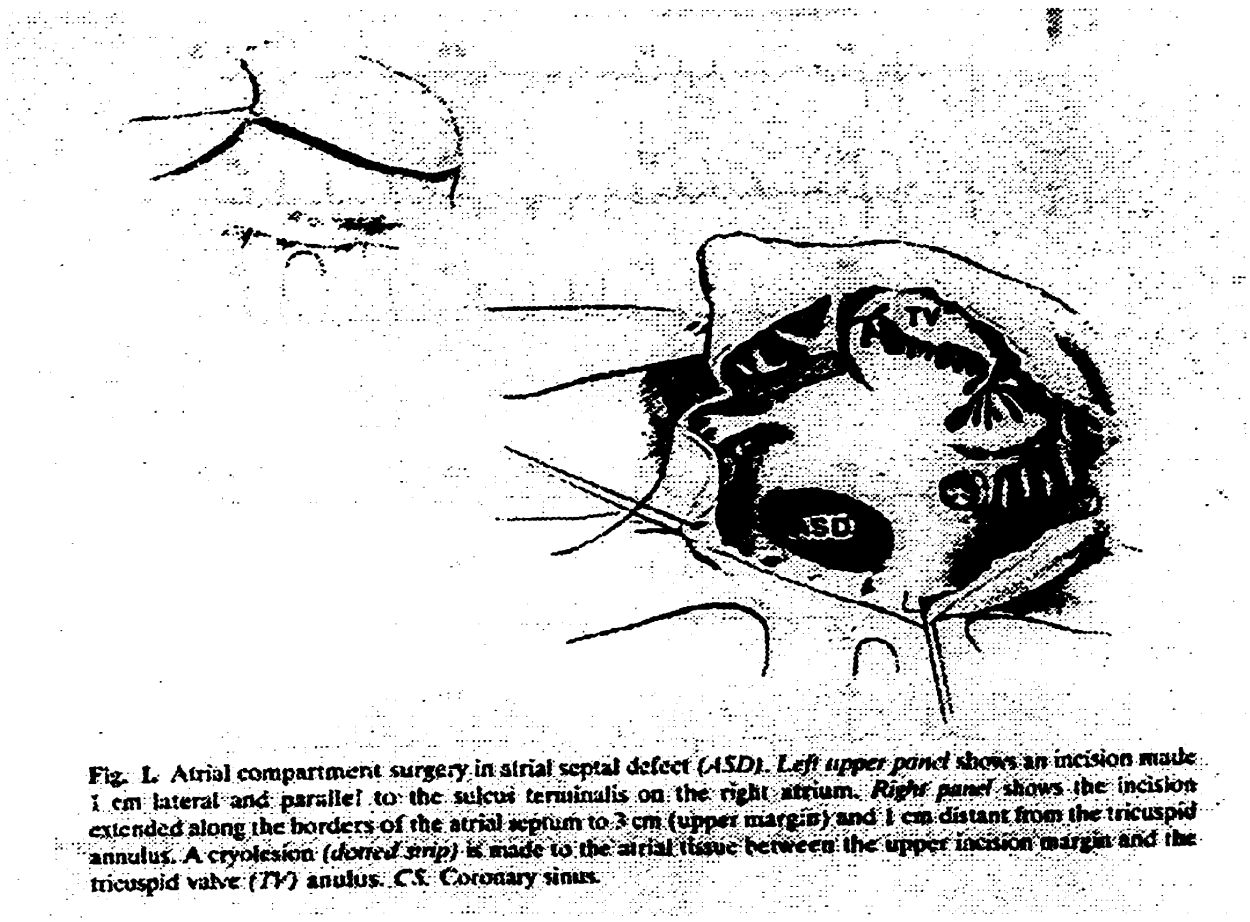


Fig. 1. Atrial compartment surgery in atrial septal defect (*ASD*). *Left upper panel* shows an incision made 1 cm lateral and parallel to the sulcus terminalis on the right atrium. *Right panel* shows the incision extended along the borders of the atrial septum to 3 cm (upper margin) and 1 cm distant from the tricuspid annulus. A cryolesion (*dotted strip*) is made to the atrial tissue between the upper incision margin and the tricuspid valve (*TV*) anulus. *CS*, Coronary sinus.

Figure 13. Compartmentalization of the right atrium as described by Lin et al. Surgically dividing the right atrium reduces the incedience of arrhythmia.

Right Atrial Maze Procedure

Another procedure, the right atrial maze procedure, used a similar technique of compartmentalization. This Maze procedure, however is more meticulous, forming more compartments than the Lin technique [23] but at the same time more time consuming [23]. The right

atrial Maze was used by Theodore et al [38] on 15 patients with Ebstein anomaly. The procedure was a modification of the Cox III operation [78, 79]. In this study, all the patients exhibited large right atria. Danielson method of tricuspid valve repair was undertaken, if possible, else the valve was replaced. The Danielson protocol was followed (Chapter 4, Surgery)[72] of localization of accessory pathways by electrophysiological mapping first, patch closure of ASD or PFO, selective plication of the atrialized right ventricle, reconstruction/repair of valve, followed by repair of any associated anomnalies and right atrial wall reduction if necessary. In addition to this protocol, the right atrial Maze procedure was performed.

There were no early deaths, complete heart blocks, reoperations or significant reoccurrence of arrhythmia. In contrast, patients that did not undergo the right atrial Maze procedure showed no significant decrease in arrhythmia postoperatively [38].

Non surgical treatment of arrhythmia

The development of SVT immediately postoperatively is very poorly tolerated [51]. For this reason, Van Hare et al [51] advised that SVT be treated prior to cardiac surgery. Also, the results of surgery were much better if a full mapping procedure were done preoperatively. If the heart is being mapped by catheterization, it is advisable that the accessory pathways also be ablated at the same time [51].

There are, however, various technical considerations to be taken into account when catheter ablation of accessory pathways in the heart is undertaken:

Vascular Access: Access to the right heart is usually through the femoral vein into the right atrium [53]. Often, patients who have had multiple prior procedures or indwelling lines have limited access due to iliofemoral thrombosis. This can prevent a normal approach to the right atrium. Also, patients that have undergone bidirectional Glenn shunts have no direct access to the right atrium from the superior vena cava, due to the direct connection of the superior vena cava to the pulmonary artery. In both cases, the right atrium can be reached via the other vena cava (i.e., the superior vena cava is used in patients with iliofemoral thrombosis and the inferior vena cava for patients with a Glenn shunt). The left side of the heart is reached by the retrograde approach through the femoral artery [51].

Ablation of Accessory Pathways: Ablation of septal accessory pathways offers the risk of complete atriaventricular (AV) block. This, however, can be avoided by a detailed knowledge of

the position of the AV node and the bundle of His, relative to other anatomical structures. Patients with primum atrial septal defects, however, have the AV conduction tissue displaced posteriorly, towards the conorary sinus. Therefore, ablation of the posteroseptal accessory pathways would carry a high risk of complete AV block [51].

Catheter ablation of accessory pathways in patients with Ebstein anomaly can be additionally challenging. Significant tricuspid regurgitation can makes stabilization of the catheter difficult. Also, the displacement of the leaflets makes keeping the catheter steady at the AV groove challenging. This dysplastic tricuspid annulus is a region where abnormal endocardiac electrocardiograms have been observed [54]. In addition, the large right atrium makes achieving an adequate catheter tip temperature very difficult. Patients with Ebstein anomaly also often have additional accessory pathways [51, 54] and atrial fibrillation [51], further impeding the localization of the accessory pathways [51].

For this reason, certain precautions are suggested for catheter ablation for patients with Ebstein anomaly [51]: Various catheter approached may be required. The use of long venous sheaths that allow for better catheter stability may be considered. The use of temperature monitoring is also important to distinguish between failure to ablate the pathways due to incorrect positioning and failure due to inadequate catheter temperature

A study by Cappato et al [54] examined 21 patients with accessory pathways with associated symptomatic tachycardias. Radiofrequency energy was used to interrupt accessory atrioventricular connections.

The criteria for determining the region to be ablated were as follows:

1. For manifest accessory pathways: the site of earliest ventricular activation relative to the onset of the delta wave.
2. For both manifest and concealed pathways: the site of earliest retrograde activation.

This procedure showed a 76% success rate. There was, however, a 25% recurrence in patients with Ebstein anomaly. This is most likely due to the presence of other accessory pathways since 52% had multiple accessory pathways [54].

All the mentioned studies either deal with a cohort of both adult and pediatric patients, or have a small number of patients. The adult spectrum is Ebstein anomaly is different from that seen in children. Adult patients have different presentations and outcomes that warrants study. To this end, we conducted a study of 74 adult patients with Ebstein anomaly.

Chapter 5

Methods

There are numerous reports on the natural and operated history of patients with Ebstein anomaly [2, 25, 47, 48, 63, 64, 80]. None of them, however, deal with a purely adult cohort. The aim of our retrospective study was to address the specific issues relating to Ebstein anomaly in the adult, with a particular focus on clinical arrhythmia and its potential interplay with surgery for this condition.

Hypotheses:

- The anatomic variables, such as right heart abnormalities, have an adverse impact on outcome in adults with Ebstein anomaly.

- Procedures targeting arrhythmia that are undertaken concomitant with surgery will significantly decrease the frequency of developing arrhythmia.

Patients and Methods

The database of The University of Toronto Congenital Cardiac Center for Adults (TCCCA) was examined to identify all adult patients (i.e. age ≥ 17 years) who were first seen at the adult clinic for assessment and treatment of Ebstein anomaly of the tricuspid valve. Patients with congenitally corrected transposition of the great arteries and so called "Ebsteinoid" anomalies of the left AV valve are not included.

The clinical records, EKG, Holter monitor, chest x-rays, echocardiograms, resting oxygen saturation and surgical details of all identified patients were examined. Available autopsy reports were also reviewed. Current status of patients, including New York Heart Association (NYHA) functional status, was assessed between January and July 1998 at clinic reviews and by patient contact.

Arrhythmia

Particular emphasis was paid to patients who presented or developed clinical arrhythmia during follow up. EKGs as well as electrophysiology study reports were used to observe presence of WPW and associated SVT. EKG and EPS were also used to determine the presence of other atrial arrhythmia such as sustained atrial flutter or atrial fibrillation. In patients who underwent cardiac catherterization, it was also observed whether or not any accessory pathways had been ablated. Patients were classified as having sustained atrial flutter/fibrillation (AF/Fib), sustained supraventricular tachycardia due to WPW (SVT) or patients free of sustained arrhythmias. Sustained was defined as arrhythmia lasting > 30 second. Patients with non-sustained episodes of asymptomatic arrhythmia on Holter monitor were included in the third group. We did not differentiate between chronic and paroxysmal atrial flutter/fibrillation.

Echocardiograms

The most recent echocardiogram was reviewed to record the presence of atrial septal defect (ASD), degree of tricuspid valve displacement (displacement of septal leaflet from the

atrioventricular junction), severity of tricuspid regurgitation (assessed by color Doppler), right atrial size, right ventricular systolic pressure (as assessed from tricuspid regurgitation assuming an estimated right atrial pressure of 10mmHg) and presence of right ventricular outflow tract obstruction (Doppler pressure gradient >20mmHg). The RA size was graded on the basis of the maximal end diastolic RA diameter from 4 chamber apical echocardiographic views into 4 grades: 1) being normal [<40mm]; 2) mild enlargement [40-50mm]; 3) moderate enlargement [50-60mm]; and 4) severe enlargement [>60mm].

Left-sided echocardiogram measurements included LV function (grade 1 = normal, 2 = mild dysfunction, 3 = moderate dysfunction, 4 = severe dysfunction) and the degree of mitral regurgitation (grade 1 = none/trivial, 2 = mild, 3 = moderate, 4 = severe). The presence of any left ventricular outflow tract obstruction was also noted.

For patients who underwent surgery, the last echocardiographic study, prior to surgery was used for the analysis.

Cardiac Surgery

Details from cardiac surgery reports were obtained and we determined whether patients underwent tricuspid valve surgery, or if the surgery dealt only with an associated ASD. Indications for surgery were categorized as being exercise intolerance, fatigue, dyspnea, cyanosis,

previous occurrence of TIA, severe tricuspid regurgitation, history of arrhythmia or other indications. This was based on clinical notes as well as operative reports.

Details of surgery were recorded, including whether patients had their valve repaired or replaced, underwent ASD closure, Glenn shunt, fenestration procedures, right atrial reduction, ablation procedures or right atrial maze procedures.

Other Measurements

Present or absence of ASD was determined from available echocardiographic or catherterization data. Oxygen saturation of patients was measured using a portable oximeter and readings were made in room air. The cardiothoracic ratio of the patient was measured from chest X rays by comparing the maximum horizontal width of the heart relative to the maximum width of the chest (Figure 14).

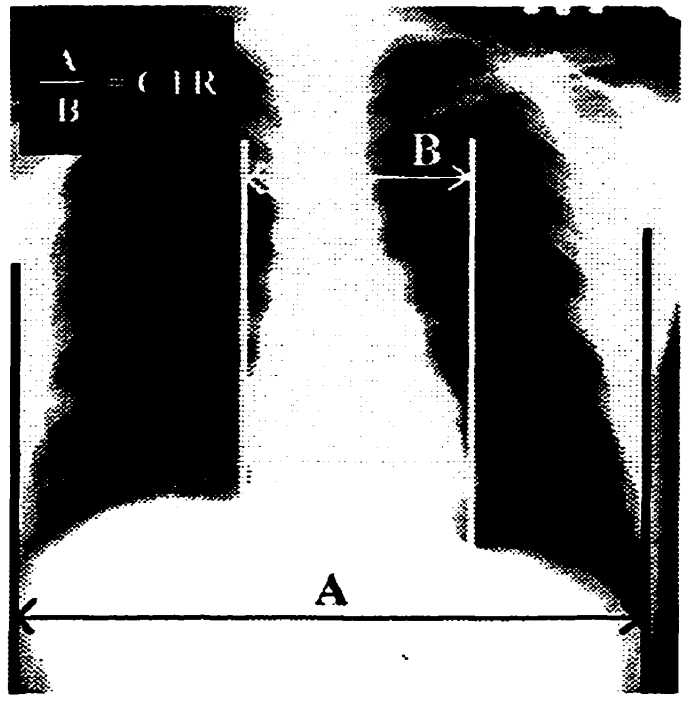


Figure 14. Measurement of Cardiothoracic Ratio (CTR). Maximum horizontal width of the chest is divided by the maximum horizontal width of the heart to obtain CTR.

Clinical notes were also used to determine any occurrence of transient ischemic attacks (TIA) in patients.

In patients who died, the cause of death was determined from clinical letters or autopsy reports when available. Time of death after surgery was also determined in patients that had undergone surgery.

All surviving patients were recently contacted by telephone, and questioned about their current health, from which present NYHA functional class was determined as well as current

medications, and any other symptoms including palpitations, syncope, angina or exertional dyspnea.

Statistical Analysis

We analyzed the data using SPSS for Windows (version 7.0, SPSS Inc., Chicago). Descriptive data for continuous variables are presented as frequency, means ± SD or medians with ranges as appropriate. Separate analyses were performed for the endpoints of death and atrial flutter / fibrillation. Univariate analysis was performed with Cox proportional-hazards model. The predictive role of the following variables were analyzed: gender, NYHA at first visit, Wolff-Parkinson-White syndrome, presence of an atrial septal defect, transient ischemic attacks, TV displacement, tricuspid regurgitation, RV outflow tract obstruction, mitral regurgitation, Glenn anastomosis, cardiothoracic ratio and age at presentation. Collinearity between variables was examined and highly correlated variables (correlation coefficient > 0.70) were combined into a composite variable. Variables with a significance level < 0.2 on univariate analysis were entered into the multivariate analysis using a stepwise forward selection algorithm. The level of significant for the multivariate analysis was set at 0.05.

Chapter 6

Results

Results

Patient characteristics at presentation:

Seventy-four adult patients with a diagnosis of Ebstein anomaly were identified. Of the 74 patients, there were 27 males and 47 females. Mean age at presentation is 33.2 ± 13.6 years (range 17 to 72 years, median: 29.5 years). Most of the patients were in good functional status at initial evaluation, as depicted in Figure 15.

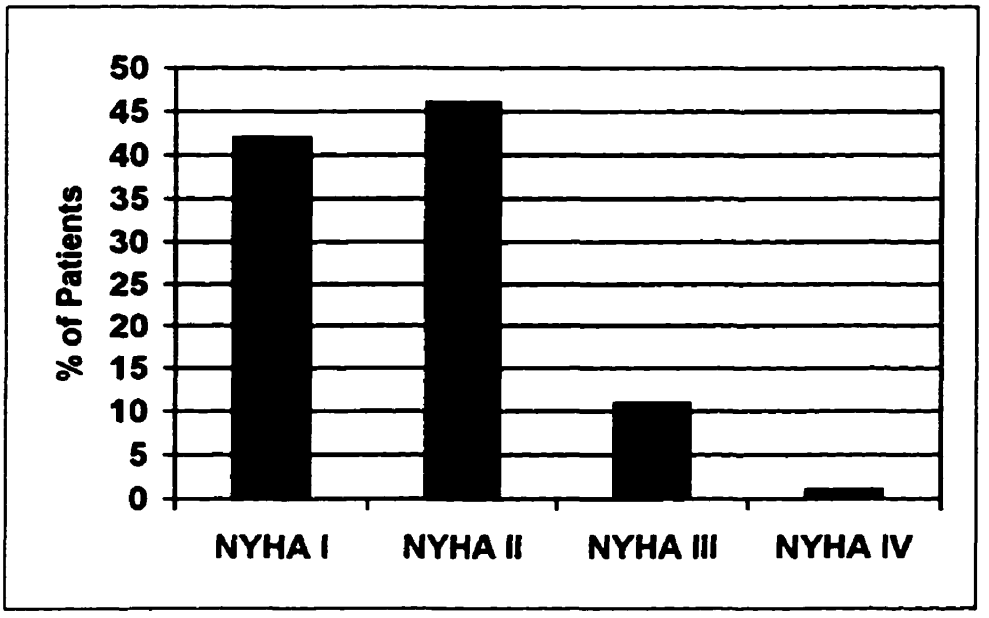


Figure 15. New York Heart Association (NYHA) functional class at presentation of patients with Ebstein anomaly. Most of the patients presented in functional class I or II.

The mean rest oxygen saturation at presentation was 94.4 ± 6.2 % (median 96%) with only 5 patients (6.8%) having recorded oxygen saturation below 90%.

Cardiothoracic ratios ranged from 0.40 to 0.77 (mean: 0.58 ± 0.1, median: 0.58).

Follow up of the 74 patients is complete. The mean follow-up time from the first visit to December 1998 is 7.5±5.8 years. During the follow up period, 7 patients died (Figure 16). Thirty-eight patients (51.4%) presented with or developed clinical arrhythmia; atrial flutter or fibrillation in 27 and supraventricular tachycardia (due to accessory pathways) in 16 patients. Thirty-six patients remained arrhythmia free by the study end.

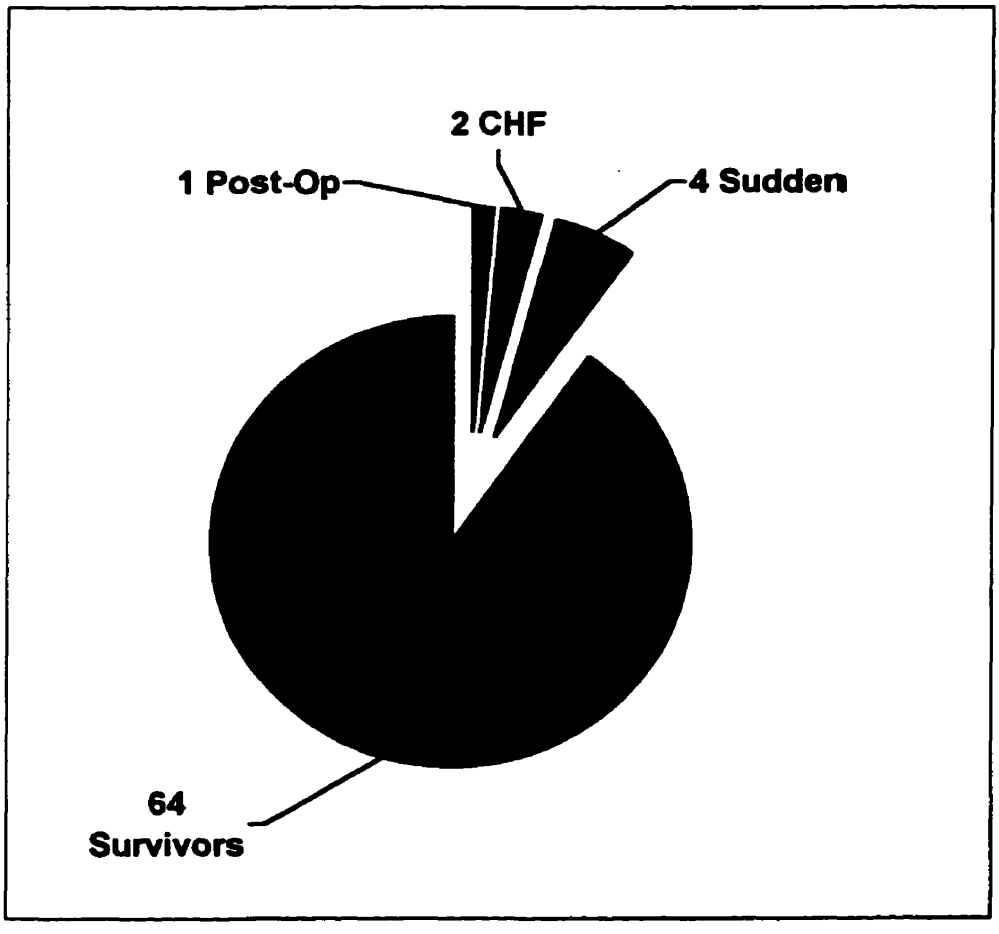


Figure 16. Modes of death of patients with Ebstein anomaly *(n = 74)*. Most patients died suddenly, presumable due to arrhythmia.
CHF, congestive heart failure

Echocardiography:

Echocardiographic data revealed a mean displacement of the tricuspid valve by 29.3 ± 13.3 mm (range: 10 to 63 mm, maximum displacement of septal leaflet from the AV junction) and a mean estimated RV systolic pressure of 33 ± 7.4 mm Hg . Forty-four patients had ASDs and 2 patients exhibited RV outflow tract obstruction. Tricuspid regurgitation ranged from trivial to severe, with most of the patients (78.7%) having moderate or severe regurgitation. Moderate to severe RA dilatation was seen in 39 patients (52.7%) while 21 patients showed moderate or severe RV dilatation and small RV sizes were observed in 17 patients. Seven patients had mild LV dysfunction while the remaining patients had normal LV function. No patient had LV outflow tract obstruction, except one patient who had mild systolic turbulence due to the bulging of the septum into the LV.

Cardiac Surgery

Twenty-seven patients underwent surgery at a mean age 34.0 ± 14.7 years. Indications for surgery included one or more of the following: progressive exercise intolerance/dyspnea (12), sustained arrhythmia (12), fatigue (9), right ventricular dysfunction (5), severe tricuspid regurgitation (5) and occurrence of TIA (3). Surgery on the tricuspid valve was performed in 24 of the 27 patients. The remaining 3 patients had ASD closure only. In 6 (25%) of the 24 patients who underwent tricuspid valve surgery, the valve was repaired, whereas in 18 (75%) the valve was replaced. Nine (38%) of the 24 patients undergoing valvar surgery underwent a concomitant Glenn procedure. In addition, 8 patients (33%) underwent concomitant intraoperative procedures targeting the arrhythmia (4 cryoablation, 2 right atrial maze, 2 surgical division of accessory pathways (for

WPW)). Death occurred post-operatively in 1 patient (4.2%) with advanced disease, marked cardiomegaly and oxygen saturation of 67%, secondary to poor cardiac output and overt heart failure occurring both before and following tricuspid valve repair. (Table 2).

Table 2. Characteristics and outcome of Ebstein patients with or without surgery. *(1965 to 1998; n = 74)*

	Surgery		No Surgery	
Total	27		47	
Gender	F=16 M=11		F=31 M=16	
Deaths	3 (11%) (1 peri-operative)		4 (9%)	
NYHA	Pre-Op	Most Recent (Dec 98)	Initial	Most recent (Dec 98)
I	0.0%	24.0%	55.3%	33.3%
II	12.5%	52.0%	42.6%	50.0%
III	79.2%	24.0%	2.1%	16.7%
IV	8.3%	0%	0%	0%
Mean resting saturation	92.6 ± 8.9%		95.4 ± 3.7%	
Clinical Arrhythmia	18 (67%)		20 (43%)	
Supraventricular tachycardia	5 (19%)		11 (23%)	
Atrial flutter / fibrillation	15 (56%)		12 (26%)	
Transient ischemic attacks	6 (22%)		1 (2%)	
Atrial septal defects	21 (78%)		23 (49%)	
Wolff-Parkinson-White syndrome	5 (19%)		13 (28%)	
Cardio-thoracic ratio (mean)	0.62 ± 0.07		0.55 ± 0.09	
Tricuspid Regurgitation				
≥ moderate	87.6%		75.5%	
Mean TV septal leaflet displacement	35.3 ± 12.6 mm		27.2 ± 13.1 mm	
Right atrium size (% of measured)				
≥ moderate (≥50 mm)	87.6%		62.5%	
Surgery	27 (3 only ASD closure)			
TV repaired	6			
TV replaced	18			
ASD Closure	18			
Glenn procedure	9		NA	
Fenestration	2			
RA reduction	4			
Arrhythmia procedure	8			
Age at Surgery	34.0 ± 14.7 years		NA	

Late Follow-up

At the time of follow-up, 7 patients experienced transient ischemic attacks (TIAs). Five patients were known to have had atrial arrhythmia, the sixth known to have palpitations and in the seventh patient, atrial arrhythmia was not documented until 5 years after the episode of TIA. At the time of TIA, the medications taken by the patients included ASA (2), anti-arrhythmic medication (2) and Digoxin (2). No patients were taking Coumadin prior to the TIA.

During the study period, 7 patients required pacemaker insertion for symptoms of presyncope (4 for sinus node dysfunction and 3 for atrioventricular block).

Surgical Patients

Patients undergoing surgery were followed for a mean of 9.6 ± 9.0 years. During follow-up of 26 operative survivors, 2 deaths occurred, 1 a sudden cardiac death 2 years after valve replacement and 1 from congestive heart failure 8 years after valve repair. Functional class of the surgical group was significantly improved after surgery, compared to preoperative NYHA class (Figure 17).

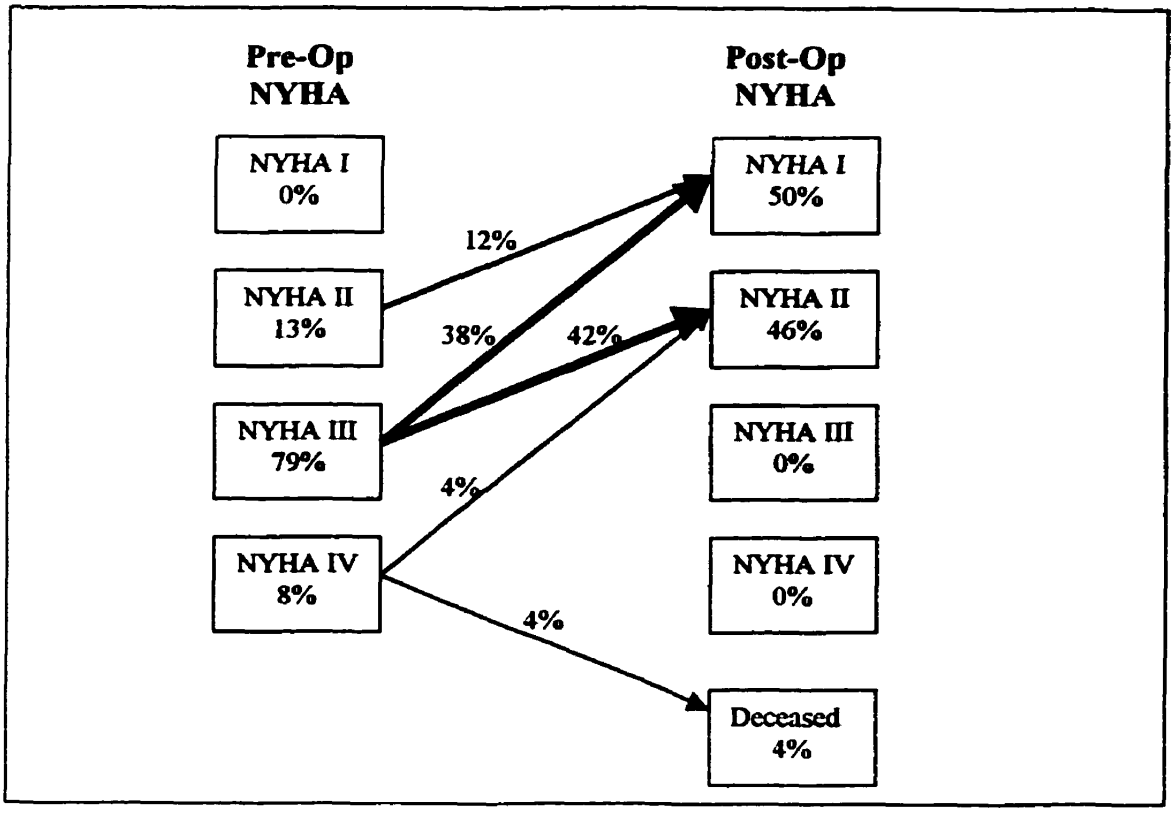


Figure 17. New York Heart Association (NYHA) functional status before and after surgery. All surviving patients reported an improvement in functional status from tricuspid valve surgery.

Non-surgical Patients

The mean follow-up time of the 47 patients that did not undergo surgery was 6.9±4.3 years. During this time 4 patients died (3-sudden, including 1 patient awaiting transplant and 1 with congestive heart failure). Functional class improved in from class II to class I in 2 patients (4%), remained the same in 23 patients (49%) and deteriorated in 22 patients (47%).

Arrhythmia

Thirty-eight patients experienced sustained arrhythmia. Sixteen of them had SVT associated with WPW, 22 had sustained atrial flutter/fibrillation, whereas 5 had both and were included as patients with primarily atrial flutter/fibrillation. Additionally, 2 patients had WPW but no history of symptomatic SVT.

SVT

Three of the 16 patients with SVT underwent valve surgery. In one of these patients, SVT persisted after surgery, no arrhythmia procedure having been undertaken at the time of surgery. In contrast, SVT did not recur postoperatively in 2 patients, who underwent surgical division or ablation of the accessory pathway(s), at the time of surgery. Twelve of the non-surgical patients experienced SVT.

Atrial Flutter/Fibrillation

Of the 12 patients who experienced AF/Fib prior to valve surgery, AF/Fib persisted in 6 postoperatively. Only 2 of these patients had undergone a procedure targeting their arrhythmia concomitant with surgery (1-surgical division, 1-ablation). In contrast, of the 6 patients in which AF/Fib did not persist after surgery, 4 patients underwent arrhythmia-targeting procedures at the time of surgery (2-RA Maze, 2-ablation). (Table 3).

Table 3. Characteristics and outcome of Ebstein patients with or without atrial flutter/ fibrillation. *(1965 to 1998; n = 74)*

	Sustained Afib/Aflutter		No Afib/Aflutter	
Total	27		47	
Gender	F=18 M=9		F=29 M=18	
Deaths	2 (7%)		5 (11%)	
NYHA when first seen	Initial	Most Recent (Dec 98)	Initial	Most Recent (Dec 98)
I	23.1%	12.0%	52.2%	40.5%
II	65.4%	56.0%	34.8%	47.6%
III	11.5%	32.0%	10.9%	11.9%
IV	0%	0%	2.2%	0%
Mean resting saturation	94.8 ± 4.8%		94.0 ± 7.1%	
Supraventricular tachycardia	5 (19%)		11 (23%)	
Transient ischemic attacks	4 (15%) (All had AF/Fib)		3 (6%) (2 SVT, 1 "palpitation")	
Atrial septal defects	21 (78%)		23 (49%) *	
Wolff-Parkinson-White syndrome	5 (19%)		13 (28%)	
Cardio-thoracic ratio (mean)	0.61 ± 0.08		0.56 ± 0.09	
Tricuspid Regurgitation				
≥ moderate	66.6%		63.8%	
Mean TV septal leaflet displacement	30.8 ± 14.3 mm		28.5 ± 12.8 mm	
Right atrium size				
≥ moderate (≥50mm)	90.5%		57.1% *	
Surgery	15 (56%)		12 (26%) (3-only ASD closed)	
TV repaired	4		2	
TV replaced	11 (1 mechanical)		7	
ASD Closure	9		9	
Glenn procedure	4		5	
Fenestration	2		0	
RA reduction	3		1	
Arrhythmia procedure	7		1 (for WPW)	
Age at Surgery	34.6 ± 13.3 years		33.3 ± 16.8 years	

• *see Table 4 for significance*

There were three patients in whom AF/Fib developed after valve surgery at a mean time of 7.6 ± 5.9 years (range 10 months to 11 years).

Twelve of the 47 patients treated medically experienced sustained AF/Fib during the study. Only 2 of these 12 patients currently free of arrhythmias. One of these 2 patients underwent catheter cryoablation of their arrhythmia.

Thus arrhythmia persisted in 83% of non-surgical patients with AF/Fib, compared to 50% of patients post-operatively in patients undergoing surgery. Of the patients undergoing surgery, AF/Fib persisted in 25% of those undergoing interoperative ablative procedures. Of the surgical patients with pre-operative AF/Fib who did not undergo interoperative ablation, these arrhythmias persisted in 67% of patients (Figure 18).

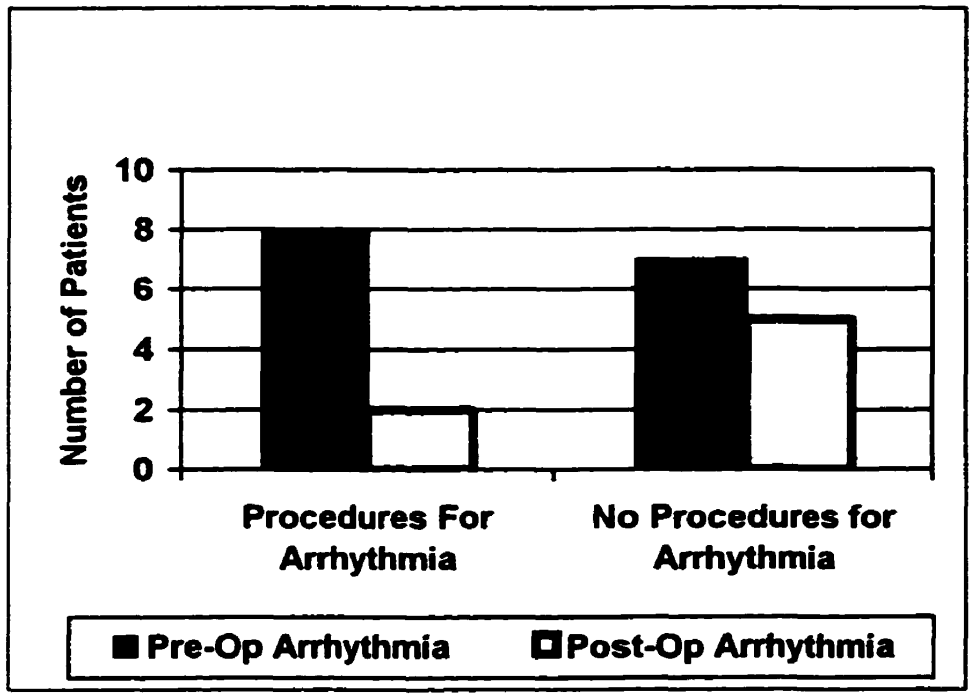


Figure 18. Arrhythmia in patients with Ebstein anomaly before and after surgery, based on ablative procedures undertaken at the time of surgery. Arrhythmia tended to persist in patients who did not undergo any arrhythmia ablative procedures. Although the difference is not significant statistically, due to the small numbers, a trend is evident.

Predictors

Right atrial size, the presence of atrial septal defects, cardiothoracic ratio and age at presentation were entered into the multivariate analysis for predicting atrial flutter or fibrillation. Cardiothoracic ratio, gender, presence of atrial septal defects, degree of tricuspid regurgitation, age at presentation and functional status were used for multivariate analysis for predicting death.

Multivariate analysis showed moderate-to-severe enlargement of the right atrium ($p<0.05$) and the presence of an atrial septal defect ($p<0.03$) to be independent predictors of atrial flutter or

fibrillation (Table 4), whereas cardiothoracic ratio ($p<0.04$) was the only predictor of death (Table 5).

Table 4. Univariate and multivariate analysis using Cox regression analysis with atrial flutter or fibrillation as the end-point.

Univariate analysis for atrial flutter or fibrillation

Variable	Risk Ratio	Confidence Interval	P value
Gender	0.97	0.43-2.17	0.93
NYHA ≥ 3 at first visit	0.56	0.17-1.91	0.36
Wolff-Parkinson-White	0.99	0.37-2.63	0.98
Right atrial size ≥3	12.81	1.67-98.0	**0.014**
Atrial septal defect	2.95	1.19-7.33	**0.020**
Transient ischemic attack	1.57	0.53-4.63	0.42
TV displacement	1.01	0.72-1.43	0.43
Tricuspid regurgitation ≥ 3	2.23	0.51-9.64	0.29
RV outflow tract obstruction	0.03	4.53×10^{-5}-20.66	0.29
Mitral regurgitation ≥ 3	0.05	1.81×10^{-11}-1.28×10^{8}	0.78
Glenn anastomosis	0.50	0.16-1.57	0.23
Cardiothoracic ratio	31.86	0.25-4.05×10^{3}	0.16
Age at presentation ≥ 30 years	0.42	0.18-0.98	**0.046**

Multivariate analysis for atrial flutter or fibrillation

Variable	Risk Ratio	Confidence Interval	P value
Right atrial size ≥ 3	3.16	1.05-9.58	**0.041**
Atrial septal defect	9.80	1.29-74.7	**0.028**

Table 5. Univariate and multivariate analysis using Cox regression analysis with death as the end-point.

Univariate analysis for death

Variable	Risk Ratio	Confidence intervals	P value
Gender (male)	8.12	0.95-69.6	0.056
NYHA ≥ 3 at first visit	4.12	0.92-18.5	0.065
Wolff-Parkinson-White	0.03	2.45×10^{-5}-33.6	0.33
Atrial septal defect	4.23	0.51-35.3	0.18
Transient ischemic attack	0.91	0.10-7.94	0.93
TV displacement	0.77	0.54-1.11	0.16
Tricuspid regurgitation ≥ 3	0.15	0.03-0.84	0.031
RV outflow tract obstruction	0.04	2.67×10^{-9}-7.46×10^{5}	0.71
Mitral regurgitation ≥ 3	0.05	3.01×10^{-31}-7.80×10^{27}	0.93
Glenn anastomosis	114.61	7.37×10^{-4}-1.78×10^{7}	0.44
Cardiothoracic ratio	6.59×10^{13}	47.6-9.11×10^{25}	0.026
Age at presentation ≥ 30 years	0.22	0.043-1.17	0.077

Multivariate analysis for death

Variable	Risk Ratio	Confidence Interval	P value
Cardiothoracic ratio	4.45×10^{11}	7.43-2.66×10^{22}	0.034

Chapter 7

Discussion

Discussion

The adult patient with Ebstein presents with arrhythmia and exertional dyspnea, which differs from the common presentation patterns in pediatric patients [2, 25].

In one of the largest studies by Celermajer et al [25] of 220 patients with Ebstein, 74% of neonates and 47% of patients under the age of 18 presented with cyanosis. In our adult cohort cyanosis was not a common presenting feature; only 5 patients (6.8%) in our series had oxygen saturation < 90%. A decrease in pulmonary artery pressure occurring during the 1st month of life enhances forward pulmonary artery flow and decreases the right to left shunting through the ASD, hence contributes to improved oxygen saturation beyond the neonatal period in these patients [25, 47]. A different spectrum of disease at different ages is the likely explanation for cyanosis being the presenting feature during infancy and not adulthood. Infants presenting with profound cyanosis often represent the extreme degree of morphological anomalies.

In contrast, patients with Ebstein presenting in adulthood generally have milder forms of the disease. Symptoms in these adult patients seem to be the result of long-standing, progressive hemodynamic abnormalities on the basis of a partially atrialized and dysfunctioning right ventricle. Tricuspid regurgitation, the result of tricuspid valve dysplasia is clearly the predominant hemodynamic lesion, leading to further right atrial enlargement. The frequent co-existence of an ASD, with the potential for left-to-right atrial shunting early in the disease process, may also contribute to further right atrial enlargement [19, 20, 38, 39]. Long-standing RA dilatation and stretch in turn, creates the substrate for sustained atrial flutter/fibrillation. Satoh et al recently showed

prolonged and heterogeneous refractoriness resulting from atrial stretch in response to volume overload [55]. Similarly, Morillo et al showed a strong correlation between a 40% or greater increase in atrial area and inducibility of sustained atrial flutter/fibrillation [56]. Indeed, moderate to severe right atrial dilatation and the presence of an ASD were independent predictors of atrial flutter/fibrillation in our study. It should not be forgotten that adult patients with Ebstein anomaly are also at risk of paradoxical embolism. Seven of our patients had TIA, all but one were known to have clinical arrhythmia. Five of them underwent subsequent surgery, whereas 2 were started on anticoagulation with no further TIA recurrence by the study end.

Fifty-one percent of our patients from this series presented or developed sustained arrhythmia during the study. Celermajer et al in his report showed arrhythmia to be the presenting feature of Ebstein anomaly in only 10% of patients under the age of 18 years, increased to 43% when presentation occurred in adulthood. [25]. Van Hare in his recent review pointed out that atrial fibrillation is rare in the pediatric population [51]. Atrial flutter/fibrillation (27 patients, 36%), and not supraventricular tachycardia due to WPW syndrome (11 patients, 15%), was the most common arrhythmia in our purely adult cohort. It is well known that accessory pathways can be part of Ebstein anomaly and give rise to early or late re-entrant supraventricular tachycardia. Our data indicates that in the adult with Ebstein anomaly and moderate to severe right atrial dilatation, atrial flutter/fibrillation is more prevalent than supraventricular tachycardia due to an accessory pathway. This should be taken into account when medical and surgical management options are considered.

Twenty-seven of our patients underwent surgery, primarily for exertional dyspnea and/or arrhythmia. There was one peri-operative deathdue right heart failure, marked cardiomegaly and profound cyanosis. MacLellan-Tobert et al reported improved exercise tolerance in adults with Ebstein anomaly following tricuspid valve surgery [20]. Although serial cardiopulmonary exercise data from our patients are incomplete, it is clear that the surgical subgroup manifested significant and sustained improvement in NYHA class compared to pre-operative status. The majority of our patients underwent valve replacement with a porcine bioprosthesis. Other groups have reported excellent results with valve repair [69, 81], indicating that despite different surgical preferences and variable anatomic substrates, tricuspid valve surgery can be very effective in relieving symptoms in adults with Ebstein anomaly.

Nine of our patients underwent a concomitant bi-directional cavo-pulmonary procedure, with a view to offloading the intrinsically abnormal right ventricle. This is an appealing strategy shown by Chauvaud and colleagues [77] to reduce operative mortality and residual tricuspid regurgitation in high-risk patients with Ebstein anomaly. It may be that, with this latest surgical modification, patients should be considered for surgery at an earlier stage. The number of patients who underwent a cavo-pulmonary shunt from our series is small and does not allow for direct comparisons, however. Larger and longer-term follow-up data will be required before definitive conclusions can be drawn.

Of the 6 late deaths, 4 were sudden cardiac death, presumably arrhythmic. Patients who died had a large heart from the chest radiograph, underscoring the common relationship between impaired

hemodynamics and clinical arrhythmia/sudden death in congenital heart disease. CTR was the only predictor of death from this series.

It is of concern that while the hemodynamic abnormalities resulting from Ebstein anomaly can be improved by repairing or replacing the malfunctioning tricuspid valve (with or without right heart offloading with a bi-directional cavo-pulmonary shunt), arrhythmia seems to persist. Cordes et al [82] showed persistence of late postoperative arrhythmia in 49% of patients with preexisting SVT and atrial flutter/fibrillation who underwent surgical correction for Ebstein anomaly. Pressley et al [83] showed that atrial fibrillation persisted in patients with moderate to severe Ebstein anomaly who underwent combined tricuspid valve and accessory pathway ablative surgery. Similarly, in our series atrial flutter/fibrillation was more likely to persist at late follow-up in patients who underwent tricuspid valve surgery alone, compared to those who had a concomitant ablative procedure at the time of surgery. Arrhythmia persisted in 83% of patients who did not have RA reduction or other concomitant anti-arrhythmia procedures during surgery. Most patients (75%) that had an ablative or maze procedure, however, converted and remained in sinus rhythm (Figure 18). There is mounting evidence to suggest that older patients with long-standing right atrial dilatation and established arrhythmia are at risk of late post-operative arrhythmia [84]. Such patients may well benefit from an elective RA maze procedure at the time of surgery, as demonstrated by Theodoro et al[38].

Our study has shown that adult patients with Ebstein anomaly, moderate to severe right atrial dilatation and an ASD are at risk of developing sustained atrial arrhythmia even after surgical restoration of hemodynamics. Although prospective larger scale studies are required, our data

suggest that electrophysiological studies and operative treatment for atrial flutter or fibrillation [38, 51, 78, 79, 85, 86] in patients with Ebstein anomaly referred for surgery should be considered.

Conclusion

Atrial flutter or fibrillation is common in adults with Ebstein anomaly. It relates to RA size and can cause important pre- and post-operative morbidity. Surgery for Ebstein anomaly is safe and results in symptomatic improvement. For patients with moderate to severe right atrial dilatation and an ASD, additional procedures targeting atrial flutter/fibrillation may be required at the time of tricuspid valve surgery.

Although the retrospective study provided valuable information on the presentation and outcome of Ebstein anomaly, little is known of the relationship between morphology and functional ability of patients with Ebstein anomaly. MRI is considered the gold standard for right heart imaging, and only 2 studies can be found looking at Ebstein using MRI [87, 88]. These studies contained only 2 or 3 patients, and did not deal with exercise tolerance in these patients. This indicates a strong need for further study looking at MRI imaging of hearts with Ebstein anomaly and exercise capacity in these patients.

Chapter 8

Further Research

Prospective Pilot Study on Ebstein Anomaly of the Tricuspid Valve

Background

Patients with Ebstein anomaly almost universally have tricuspid valve incompetence. This contributes further to dilatation of the RA. Atrial arrhythmias are often associated with this state. Patients with Ebstein anomaly have a wide spectrum of symptoms, ranging from asymptomatic to NYHA class IV. It is likely that the severity of symptoms may be associated with some morphological abnormality.

In this study, we prospectively examine the status of adult patients followed up at the Toronto Congenital Cardiac Center for Adults (TCCCA), at rest as well as on exertion, and seek correlation with the morphological and functional features of their heart using MRI images. We hope to find a correlation between the symptoms and the morphology of the heart. In addition, we are looking at patients that have undergone surgery and examine relative changes based on different surgical approaches.

Hypotheses

1. There is a correlation between clinical symptoms (including clinical arrhythmia and exertional dyspnea) and the morphology of the heart of patients with Ebstein anomaly.

2. Surgery for Ebstein anomaly with concomitant procedures targeting arrhythmia impact on survival, clinical status and prevalence of arrhythmia.

Study Design

Clinical data, EKG, CXR, echo and surgical details of all patients are reviewed and patients are invited to participate in a Stage 1 exercise test and an MRI.

Stage 1 Exercise Test protocol:

Patients are exercised on a bicycle to maximum exertion, using a modified Bruce protocol. Workload is increases by 20 Watts every 2 mins. Blood pressure is taken before exercise and immediately after exercise. Patients are asked for the main reason they stopped.

The following are examined from the exercise data:

- Total Lung Capacity, TLC (L)
- Forced Residual Capacity, FRC (L)
- Vital Capacity, VC (L)
- Residual Volume, RV (L)
- Forced Vital Capacity, FVC (L)
- Forced Expiatory Volume , FEV (L)
- Max. Voluntary Ventilation, MVV (L/min) (To test muscle strength)
- Lung Diffusing Capacity, LDC (mL/min/mmHg) (using CO diffusion)
- Max. Inspiratory Pressure, MIP (cmH2O)
- Max. Expiatory Pressure, MEP (cm H2O)
- Max. O2 Uptake, VO2 (L/min)

- Max. O2 Uptake, VO2 (L/Kg)
- Ventilation, V (L)
- Max. Heart Rate
- Max. Work, (Watts)
- Anaerobic Threshold
- Max. Pulse O2 (ml/b)
- Max. Respiratory Rate (b/min)
- O2 Saturation at Rest (%)
- O2 Saturation at Peak Exercise (%)

MRI Protocol

Right ventricular dysplasia (RVD) protocol

- Axial T1 weighted images.
- 5mm slices, interleaved with 5mm slices, effectively contiguous 10 mm thick slices.
- Matrix 256 x 192 pixels
- 2 NEX (number of excitations)
- Superior/inferior saturation pulses (to decrease slow flow signal)
- Min TR, TE=20 msec

- Multiple axial segmented K space
- cine gradient-echo images
- FMP6R (fast multiplanar gradient echo)
- 10mm contiguous slices
- 256 x 128 pixels
- 6 NEX
- >12 phases/cardiac cycle
- TR 10-12 msec, TE 2-4 msec

The images are viewed slice by slice. Images at end systole and end diastole are chosen for measurements of the right atrium, right ventricle and the left ventricle. Due to the high quality images obtainable from MRI, the chambers are clearly defined, and thus measurements are highly reproducible.

Measurements on MRI for Patients with Ebstein's Anomaly (13/3/99)

Right Atrium

RA Volume (End Diastolic):

ASD (Y/N):

Right Ventricle

RV Volume (End Diastolic): (End Systolic):

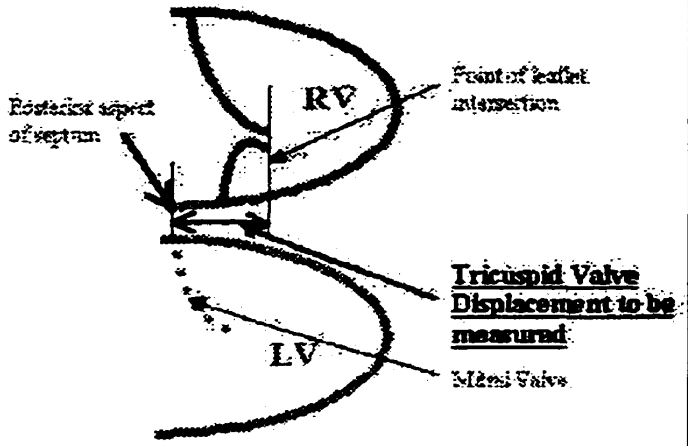
RV Function (Normal/Abnormal): Ejection Fraction:

Paradoxical septal motion:

Tricuspid Valve

Maximum leaflet displacement (maximum distance of leaflet intersection, see diagram): (Measurement taken where whole septum visible/Mid systole)

Displacement:



Left Side

LV Volume:

LV Function:

LV Ejection Fraction:

LV Posterior Wall Thickness (Max) (End-diastolic):

Septum

Interventricular Septal Thickness (Max) (End-diastolic):

RV/LV portion:

Atrialized RV Portion:

Figure 19. MRI information sheet. All variables on this sheet were recorded from MRI films

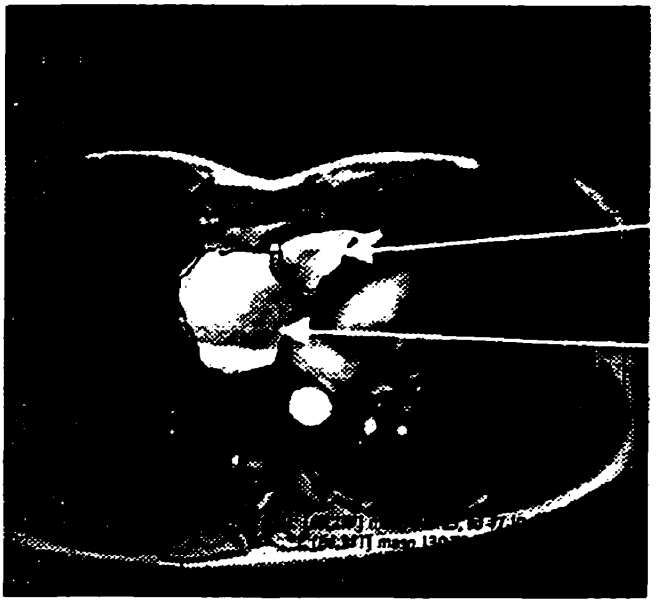


Figure 20. MRI image of one slice at end ventricular systole. The volume areas are traced by hand and the software calculates the enclosed area.

Primary endpoints

- Data collected Post-op (at least 2 months) for patients undergoing surgery
- Data collected now for other patients

Patient Selection

All patients were identified from the TCCCA database as having Ebstein anomaly except those with other, more significant, cardiac diseases that may obscure the symptoms of Ebstein anomaly, like congenitally corrected transposition or teratology of Fallot.

Demographics, Tests Data and Surgical History

LName	Last Name
Fname	First Name
TTH	Hospital Number (MRN)
DOB	Date of Birth
Male	Gender 0=female 1=male
ASD	Presence of ASD 0=no 1=yes
WPW	Presence of WPW 0=no 1=yes
Detail	Details of WPW (eg ablated? etc)
PaceMake	Presence of pacemaker? 0=no 1=yes
Reason	Reason for pacemaker
Other	Other diagnosis
TTHVisit	First time seen at TTH
Age	Age when first seen at TTH
NYHA	NYHA when first seen at TTH
Sats	Most recent resting O2 sats
CTR	Cardio-thoracic ratio, as per chest most recent xray
EKG	Copy of EKG? 0=no 1=yes
Holter	Results of Holter monitor? 0=no 1=yes
Arythm	Patient experienced clinical arrhythmia 0=no 1=yes
SVT	Patient had **Supraventricular Tachicardia** 0=no 1=yes
AFAFIB	Patient had **Atrial Flutter** or **Atrial Fib** 0=no 1=yes

AF	Patient had **Atrial Flutter** 0=no 1=yes
Afib	Patient had **Atrial Fibrillation** 0=no 1=yes
Med	Patient is taking cardiac medications? 0=no 1=yes
Echo	Patient had an echo 0=no 1=yes
EchoDate	Date on which patient had an echo
Shunt	Shunt seen at atrial level 0=no, 1=yes, 2=left to right, 3=right to left 4= bidirectrional
Regurg	TV regurgitation as per echocardiogram 0=no, 1=trivial, 2=mild, 3=moderate, 4=severe
Displcmt	Max displacement of TV leaflets for AV junction (mm) (Lateral View)
ASDSize	Size of ASD (mm)
Rasize	Dimensions of RA (4 Chamber Apical View)
RAGrade	RA enlargement 1=normal (<40mm*), 2=mild (40-50mm*), 3=moderate (50-60mm*), 4=severe (>60mm*) (*Maximum dimension in 4 chamber apical view of echo)
RVSP	RVSP in mmHg
RVOTO	Evidence of RVOTO 0=no 1=yes
Lvfunc	LV function 1=normal, 2=mild, 3=moderate, 4=severe
CP	Had Stage 1? 0=no 1=yes
MRI	Had MRI? 0=no 1=yes
CATH	Had Cath? 0=no 1=yes
CathDate	Date of Cath
PrOpCTR	Pre op Cardiothoracic ratio

PrOpNYHA	Pre op NYHA functional class
PrOpArth	Pre op arrhythmia
PrOpSats	Pre op O2 Sats
Oper	Had surgery? 0=no 1=yes
OpDate	Date of surgery?
TVRepair	Was TV repaired? 0=no 1=yes
TVReplac	Was TV replaced? 0=no 1=yes
ASDclos	Was ASD closed? 0=no 1=yes
Glenn	Did pt have a Glenn Shunt? 0=no 1=yes
Fenestra	Was fenestration done? 0=no 1=yes
RAReduc	Was RA reduced? 0=no 1=yes
Ablation	Was ablation done? 0=no 1=yes
PoOpStay	Length of post op stay in days
ReOp	Was pt reoperated on?
ReOpDate	When was the reoperation?
PoOpCTR	Post op Cardiothoracic ratio
PoOpNYHA	Post op NYHA functional class
PoOpArth	Post op arrhythmia
PoOpSats	Post op O2 Sats
Preg	Has the patients been pregnant? 0=no 1=yes
NumPreg	Number of pregnancies
NumBirth	Number of births
LastFU	Date last time seen at TTH

TimeFrst	How long after the first visit was the last visit?
NYHALast	Last reported NYHA?
NYHAnow	NYHA now as per questionnaire
AgeNow	Present age of pt.

Progress and Initial Results

Right heart volumes have been measured in 19 control patients, and 22 Ebstein patients have had their MRIs and measurements are pending. The average right atrial sided volumes are as follows:

RA, end diastolic volume: 85.1 ml

RV, end systolic volume: 40.1 ml

RA, end diastolic volume: 87.9 ml

Twenty-five patients have undergone exercise testing, of which data has been compiled for 21 patients. The initial measurements are as follows:

VO2/Kg: 19.6 ± 7.2 ml/min/kg (average 58% of predicted)

Time of exercise: 12.4 ± 4.3 mins

Maximum work: 105 ± 40 Watts

Anaerobic threshold: 953 ± 336 ml/min

These preliminary results suggest that patients with Ebstein anomaly are limit in respect to their exercise tolerence.

This study can be completed as a large study with more patients. The goal of such a study would be to recruit 30 to 50 patients, providing a sample size that is less vulnerable to outlyers. This

should provide information about the morphology and exercise tolerance in Ebstein anomaly, as well as, invaluable reference data for right-sided volumes obtained by MRI.

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