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Functional Status After Operation for Ebstein Anomaly

The Mayo Clinic Experience

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Objectives The objective of this study was to review the long-term functional outcome of patients with Ebstein anomaly who had cardiac operation at our institution.

Background Ebstein anomaly is a spectrum of tricuspid valvular and right ventricular dysplasia. Many patients will require operation in an attempt to improve quality of life.

Methods From April 1, 1972, to January 1, 2006, 539 patients with Ebstein anomaly underwent 604 cardiac operations at the Mayo Clinic in Rochester, Minnesota. Patient records were reviewed, and all patients known to still be alive were mailed a medical questionnaire or contacted by telephone.

Results At the initial operation at our institution, the mean age of the patients was 24 years (range 8 days to 79 years) and 53% were female patients. Survival at 5, 10, 15, and 20 years was 94%, 90%, 86%, and 76%, respectively. Survival free of late reoperation was 86%, 74%, 62%, and 46% at 5, 10, 15, and 20 years, respectively. Surveys were returned by 285 of 448 (64%) patients known to be alive at the time of this study. Two hundred thirty-seven (83%) patients were in New York Heart Association functional class I or II, and 34% were taking no cardiac medication. One hundred three patients (36%) reported an incident of atrial fibrillation or flutter, 5 patients (2%) reported having had endocarditis, and 1 patient (<1%) reported having a stroke. There were 275 pregnancies among 82 women. The recurrence of congenital heart disease was reported in 9 of 232 (3.9%) liveborn children.

Conclusions Patients have good long-term survival and functional outcomes after undergoing surgery for Ebstein anomaly. Atrial arrhythmias are common both before and after surgery. Many patients have had one or more successful pregnancies with a low-recurrence risk of congenital heart disease. (J Am Coll Cardiol 2008;52:460–6)

Ebstein anomaly is a spectrum of tricuspid valvular (TV) and right ventricular (RV) dysplasia (1). Morbidity and mortality are thought to be related to the degree of TV regurgitation, the size, thickness, and function of the RV, and the presence or absence of an atrial septal defect (ASD).

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Patients with mild forms of Ebstein anomaly may live normal life-spans, but many will require surgery. We have reported mortality and reoperation rates for 539 patients who underwent operation at the Mayo Clinic (2). However, because of the length and complexity of that paper, the functional status of these patients was not included in that report. Hence, the purpose of this report is to assess the long-term functional outcome and reproduction of patients with Ebstein anomaly who required operation.

Methods

Patients. From April 1, 1972, to January 1, 2006, 539 patients with Ebstein anomaly had an operation at the Mayo Clinic by 1 of 2 surgeons (G.K.D. and J.A.D.). Of the 448 patients not known to be deceased, we were able to obtain current information for 285 patients (64%). These patients form the basis of this report (Fig. 1). Excluded from this cohort were patients with pulmonary atresia with intact ventricular septum, complex conotruncal abnormalities, or atrioventricular discordance with ventriculoarterial discordance ("congenitally corrected transposition").

Indications for surgery. The indications for surgery included 1 or more of the following: symptoms of dyspnea or right heart failure (New York Heart Association [NYHA]

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functional class III or IV), progressive exercise intolerance, tachyarrhythmias not controllable by medication or amenable to catheter-based intervention, and significant associated lesions, including ASDs, ventricular septal defects, or pulmonary stenosis. In some patients, progressive cardiomegaly, a cardiothoracic ratio >0.65, severe cyanosis, and reduced left ventricular (LV) function were indications for surgery (2).

Data collection. Two of the investigators (M.L.B. and D.J.D.) collected all pertinent data from the medical record (2). These data included all follow-up information regarding reoperation and deaths that had been received from non-Mayo Clinic health care providers. Before mailing surveys, we determined the vital status of patients by using all medical records available and through Accurint (LexisNexus, Philadelphia, Pennsylvania), a commercial database.

Detailed health status questionnaires were mailed to all participants who were thought to be alive. Patients who did not return or complete the questionnaire were sent a second questionnaire. If the second questionnaire was not returned or completed, attempts were made to contact the patient by telephone. Questionnaires were sent to 468 patients, and 20 of these patients were found to be deceased. Of the 448 patients not known to be deceased, questionnaires were returned and Health Insurance Portability and Accountability Act (i.e., HIPAA) forms completed by 285 (64%) patients (Table 1).

Statistical analysis. Patients were placed into 1 of 3 groups based on their late functional outcome: excellent, good, and poor. Patients who were determined to have an excellent outcome were required to fulfill all of the following at late follow-up: described their health as excellent or good, reported no current cardiac symptoms, described no hospitalizations for heart or heart-related problems, rated their ability to exercise relative to other people the same age as the same or greater, and were employed despite their heart condition. Patients were classified as a poor outcome if they reported any one of the following: unable to walk up one flight of stairs without resting, were unemployed or only employed part time because of their heart condition, or underwent reoperation. The remaining patients were placed in a good outcome group.

Abbreviations and Acronyms

ASD = atrial septal defect
LV = left ventricle/ventricular
NYHA = New York Heart Association
RV = right ventricle/ventricular
TV = tricuspid valve

When comparing patient characteristics between patients who responded to the survey and those who did not, the Fisher exact test or chi-square test was used to compare categorical variables whereas the 2-sample *t* test or Wilcoxon rank sum test was used to compare continuous variables where appropriate. Univariate and multivariate logistic models with the use of SAS version 9.1 (SAS Institute, Cary, North Carolina) were created to identify predictors of functional outcome. Patients were grouped into 2 categories for these models: excellent/good and poor outcome. Univariate and multivariate predictors of reoperation and rehospitalization were determined with log-rank tests and Cox proportional hazard models. Multivariate Cox regression models were built based on univariately significant variables ($p \leq 0.05$) with a stepwise selection method. This method constructs a model by evaluating all factors and selecting the most significant factor. That factor is entered, and all other factors are evaluated, adjusting for the entered variable. This process continues until no other factors are significant after adjusting for the variables in the model. Kaplan-Meier curves were drawn for any reoperation, reoperation on TV, and rehospitalization. Only 2-tailed probability values were reported; $p \leq 0.05$ was considered significant.

We assessed variables including, among others, patient age at operation, year of operation, surgeon, patient gender, patient age at diagnosis, cardiothoracic ratio on chest x-ray, presence and type of preoperative arrhythmia, rhythm on electrocardiogram, blood oxygen saturation (oximetry), hemoglobin, hematocrit, and previous cardiac procedures (for a complete list and definitions, see the Online Appendix). Associated cardiac defects and type of operation (including TV repair, TV replacement, and miscellaneous concomitant procedures) were also included.

Echocardiographic variables included pre-operative and post-operative RV size and function, degree of TV stenosis and or regurgitation, degree of pulmonary valve stenosis or

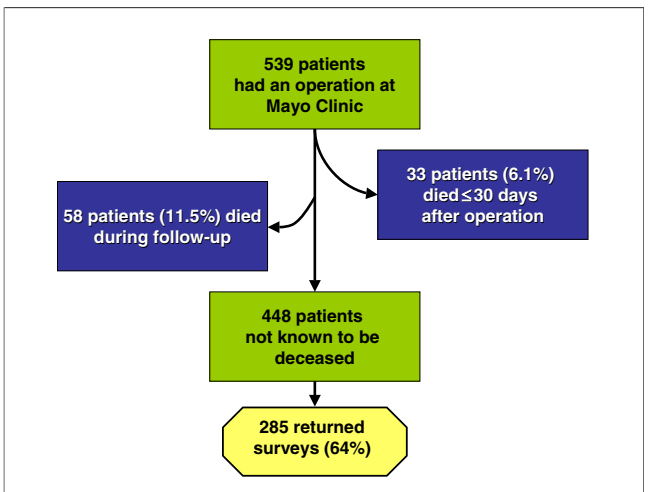

Figure 1 Patient Cohort Studied

Table 1 Questionnaires

Questionnaires	n = 468
Responded	285
Unable to contact: foreign, unlisted, physical or mental barrier	49
Nonresponse	43
Questionnaire completed but no HIPAA form completed	43
Refusal	28
Found to be deceased	20

HIPAA = Health Insurance Portability and Accountability Act.

regurgitation, degree of mitral valve stenosis or regurgitation, and LV ejection fraction. The degree of TV regurgitation, RV or LV dysfunction, and RV or LV enlargement were graded as none, mild, moderate, moderate-to-severe, and severe by the use of transthoracic echocardiography. If a variable was present in fewer than 5 patients, it was not considered in the analysis.

In the entire cohort (n = 539), the initial operation at Mayo Clinic was TV repair for 182 patients, TV replacement for 337 patients, and a variety of nonvalve operations for 20 patients. Survival and reoperation have previously been reported (2). We included in the rubric of "functional outcome": the need for reoperation, the presence of cardiac symptoms, NYHA functional classification, cardiac-related hospitalizations, perceived exercise limitation, ongoing need for cardiac medication, the presence of arrhythmia, and reproductive ability.

Results

Patient characteristics. Patients who responded to the survey (n = 285) were compared with patients who did not return the survey but who were known to be alive (n = 185). Patients who did not return the survey were more likely to have moderate-to-severe to severe reduced pre-operative RV function (p = 0.002, chi-square test). Responders were more likely to have had their first operation at Mayo Clinic at a later date (mean year 1994 vs. 1993, p = 0.017). Except for these factors, the groups were similar.

Survival free of reoperation. For the 285 long-term survivors who completed the Health Status Questionnaire the 1-, 5-, 10-, 15-, and 20-year survival and freedom from any reoperation (on the TV or other cardiac operation) were 97%, 91%, 82%, 72%, and 56%, respectively. In a multivariate model, age ≥12 years at operation was associated with greater freedom from reoperation. Hypoplastic or stenotic pulmonary arteries or need for intraaortic balloon pump post-operatively was associated with increased risk for reoperation (Fig. 2, Table 2).

Table 2 Univariate and Multivariate Predictors of Any Reoperation

	Hazard Ratio	p Value
Univariate predictors		
Younger age at first operation at Mayo (<12 yrs)	3.56	<0.001
Younger age at diagnosis (<4 yrs)	2.56	<0.001
Later date of operation (per 10 yrs)	1.62	0.030
Pulmonary valve stenosis greater than mild	3.66	0.021
Abnormal pulmonary artery architecture	6.58	<0.001
Any previous cardiac procedure	2.10	0.007
Previous systemic-pulmonary artery shunt	3.86	<0.001
Previous cavopulmonary shunt	7.13	<0.001
Closure of shunt	3.07	0.003
Low cardiac output state post-operatively	3.32	0.008
Intraaortic balloon pump post-operatively	5.94	0.006
Respiratory insufficiency post-operatively	4.60	<0.001
Renal insufficiency post-operatively	6.32	<0.004
Multivariate predictors		
Younger age at first operation at Mayo (<12 yrs)	3.23	<0.001
Abnormal pulmonary artery architecture	3.50	0.004
Intraaortic balloon pump post-operatively	12.27	0.001

Prediction of functional status. On the basis of the 285 patients who completed and returned the Health Status Questionnaires, 43% of the patients were in NYHA functional class I, 40% in class II, 12% in class III, and 4% were in class IV. One percent did not respond to the questions regarding functional status. One-half of the subjects reported that their exercise tolerance was equal to or greater than their peers (Fig. 3, Table 3).

After classifying patients as outlined in the Methods section, 21 (7.4%) patients had an excellent outcome, 206 (72.3%) had a good outcome, and 58 had a poor outcome (20.4%). In a multivariate model, later year of operation and

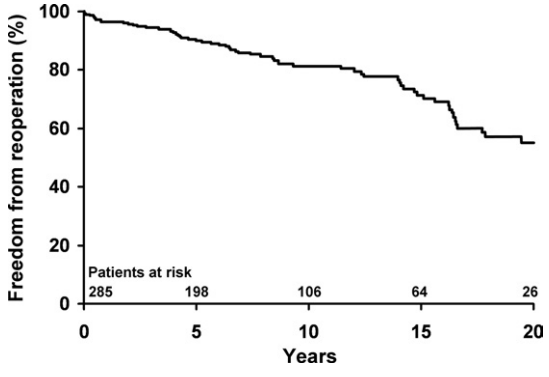

Figure 2 Freedom From Any Reoperation in Patients Who Responded to Survey Questionnaires

Time zero is the first operation at Mayo Clinic. The number of patients was 285.

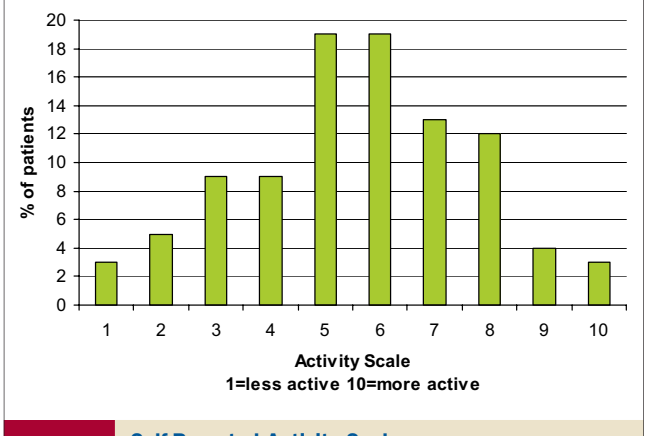

Figure 3 Self-Reported Activity Scale After Operation for Ebstein Anomaly

Shown are the percentage of survey responders who rated their exercise tolerance related to other people their own age on a scale of 1 to 10.

Table 3 Self-Reported Exercise Tolerance

My Ability of Exercise Relative to Peers Is	n = 285	%
Much greater	7	2.5
Slightly greater	29	10.2
About the same	105	36.8
Slightly less	89	31.2
Much less	43	15.1
I am unable to exercise	5	1.8
Unknown	7	2.5

right reduction atrioplasty were associated with excellent or good functional outcomes, and previous cardiac operation and pre-operative history of arrhythmia were associated with a poor outcome (Table 4). Whether the tricuspid valve was repaired or replaced at the first operation at Mayo Clinic had no effect on the patients' functional classification ($p = 0.30$).

Self-reported symptoms. Early fatigue and shortness of breath were reported by slightly more than one-third of the responders. Close to 40% of patients reported a history of tachyarrhythmias (Table 5).

Cardiac medications. Eighty-four of 251 patients (34%) were taking no cardiac medications. Digoxin was the most common cardiac medication (taken by 22% of patients) followed by warfarin (taken by 20% of patients) and furosemide (taken by 16% of patients) (Table 6).

Subsequent hospitalizations. The reasons for all hospitalizations at any hospital subsequent to operation at the Mayo Clinic are recorded in Table 7 for the 285 respondents to the medical status questionnaire. Freedom from rehospitalization for cardiac causes, including reoperation of any type, was 91%, 79%, 68%, 53%, and 35% at 1, 5, 10, 15, and 20 years, respectively. Multivariate analysis demonstrated that age <12 years at time of operation, later date of operation, previous cavopulmonary shunt insertion, need for postoperative intraaortic balloon pump, pre-dismissal thrombus in the right atrium or on the TV, the need for a permanent pacemaker, and a more than moderate enlargement of the RV on pre-dismissal echocardiography were predictive of

Table 4 Univariate and Multivariate Predictors or Excellent/Indeterminate or Poor Outcomes

	Odds Ratio	p Value
Univariate predictors		
Earlier year of operation (↓ 10 yrs)	1.50	0.041
Any previous cardiac procedure	2.11	0.016
Right reduction atrioplasty	0.50	0.037
Previous history of a specific arrhythmia	2.24	0.009
Multivariate predictors (all risk factors)		
Right reduction atrioplasty	0.51	0.045
Previous history of a specific arrhythmia	2.23	0.11
Multivariate predictors (only pre-operative risk factors)		
Earlier year of operation (↓ 10 yrs)	1.72	0.004
Any previous cardiac procedure	2.68	0.003

Table 5 Symptoms Reported by 285 Survey Responders

Symptom	Total (n = 285)	%
Early fatigue	120	42.1
Palpitations	111	38.9
Your doctor told you that you had tachycardias	106	37.2
Your doctor told you that you had atrial flutter/fibrillation	103	36.1
Shortness of breath	87	30.5
Abnormally rapid heart rate	74	26.0
Ankle or leg swelling	41	14.4
Your doctor told you that you had bradycardia	35	12.3
Chest pain	30	10.5
Your doctor told you that you had ventricular tachycardia	26	9.1
Your doctor told you that you had premature ventricular contractions	27	9.5
Abdominal fluid retention	23	8.1
Abnormally slow heart rate	20	7.0
Fainting	7	2.5

rehospitalization. The most common cause for readmission to hospital was an arrhythmia. Five patients reported hospitalization for infectious endocarditis; 3 patients had previous TV replacement (2 bioprosthetic, 1 mechanical) and 2 had previous TV repair. We were unable to determine whether all cases had positive blood cultures.

Reproduction and inheritance. A total of 82 of the 109 female respondents reported at least 1 pregnancy (Table 8). Before undergoing surgery, 59 women had a total of 140 pregnancies and, after surgery, 27 women had 62 pregnancies. The miscarriage rate before surgery was 19% and after surgery was 33%. There were 232 liveborn children: 88 to fathers and 144 to mothers with Ebstein anomaly. Nine of the liveborn children were reported to have a heart defect; 6 were born to mothers and 3 were born to fathers with Ebstein anomaly. The cardiac abnormalities in the children were tricuspid atresia, atrial fibrillation, patent ductus arteriosus, "hole in heart" (that was surgically closed), Down syndrome with complete atrioventricular septal defect, an

Table 6 Medications Indicated by Survey Responders

Cardiac Medications	Total (n = 285)	%
None	97	34.0
Digoxin	62	21.8
Warfarin	56	19.6
Furosemide	45	15.8
Angiotensin-converting enzyme inhibitor	25	8.8
Spironolactone	16	5.6
Beta-blocker	16	5.6
Amiodarone	16	5.6
Unspecified diuretic	9	3.2
Verapamil	8	2.8
Thiazide diuretic	7	2.5
Quinidine	3	1.1
Procainamide	1	0.4
Norpace	2	0.7
Other cardiac medication	121	42.5

Table 7 Reasons for Subsequent Hospitalization After First Operation at Mayo Clinic as Reported by Survey Responders

Reason for Hospitalization	No. of Hospitalizations, n (%)							
	Admission #1	Admission #2	Admission #3	Admission #4	Admission #5	Admission #6	Admission #7	Admission #8
Arrhythmia	59 (21)	22 (11)	13 (5)	9 (3)	6 (2)	2 (1)	1 (<1)	1 (<0)
Heart failure	9 (3)	3 (1)	4 (1)	3 (1)	1 (<1)	0	0	0
Endocarditis	5 (2)	0	0	0	0	0	0	1 (<1)
Stroke	1 (<1)	0	0	0	0	0	0	0
Cardiac transplantation	1 (<1)	0	0	1 (<1)	2 (1)	0	0	0
Pacemaker or implantable cardiac-defibrillator	14 (5)	11 (4)	12 (4)	3 (1)	3 (1)	2 (1)	2 (1)	0
Abdominal swelling	4 (1)	2 (1)	1 (<1)	1 (<1)	1 (<1)	0	0	0
Leg swelling	9 (3)	3 (1)	0	0	0	0	0	0
Valve repair/replacement	21 (7)	11 (4)	5 (2)	2 (1)	0	0	0	0
Other heart surgery	11 (4)	11 (4)	6 (2)	5 (2)	3 (1)	2 (1)	1 (<1)	2 (1)

unspecified "valve problem," mitral valve prolapse, Ebstein anomaly, and ASD.

Discussion

Reoperation. Ebstein anomaly is a complex congenital abnormality involving both the TV and RV and may require further hospitalization or reoperation after the original operative repair. Symptomatic arrhythmias continue to be a problem in a significant number of patients. However, patients' perception of their exercise capability is similar to their peers.

Reoperation for patients with Ebstein anomaly and significant TV dysfunction remains a long-term issue for patients after TV repair or replacement. For the entire cohort of 539 patients, the 10- and 20-year survival free from any reoperation was 74% and 46% (2), and for the 285 questionnaire respondents in this study, it was 82% and 56%. For the 285 questionnaire respondents, the 10-, 15-, and 20-year freedom from reoperation on the TV was 92%, 84%, and 68%, respectively, for patients who had TV repair at their initial surgery and 82%, 70%, and 56%, respectively, for patients who had TV replacement at their initial surgery at Mayo Clinic. The rates of reoperation for patients who had a TV repair or replacement were not statistically different among questionnaire respondents. Innovations in valve repair techniques should be continued to develop more durable results. For valves that cannot be repaired, more durable biological valves and less thrombotic mechanical valves must be sought.

Hospitalizations. Hospitalizations are common even after operation. Reoperation for TV dysfunction is a reality after either TV repair or replacement for many patients. However, arrhythmias were the most common reason for hospitalization (~39%), underscoring their importance in these patients. Efforts to reduce the frequency of post-operative tachyarrhythmias require further investigation and may include: 1) earlier operation to prevent excessive enlargement of the right heart chambers; 2) routine addition of the maze procedure; and 3) manipulation of atrial incisions to reduce the likelihood of re-entrant rhythms. Interestingly, we found that a later date of operation was associated with rehospitalization, which may be related to referral bias, recall bias, or changes in medical practice.

Symptoms and functional status. In the current study, more that one-third of patients continued to have subjective fatigue and shortness of breath. This finding is not surprising because patients with Ebstein anomaly have a myopathic RV (3). These patients often continue to have some elements of RV enlargement and dysfunction. Also, many of these patients have had significant cardiomegaly, which can have detrimental effects on lung growth and pulmonary function. Right ventricular dilation may displace the interventricular septum and compress the LV, thus impairing LV function.

Atrial tachyarrhythmias are a common ongoing problem for patients with Ebstein anomaly, even after operation. In the current study, approximately one-third of patients reported palpitations and showed evidence of supraventricular tachycardia after operation. Previously, we reported (4) that the incidence of supraventricular tachycardia was significantly lower early after operation for Ebstein anomaly, but with longer follow-up, the number of patients experiencing

Table 8 Pregnancies Reported by 82 of 285 Respondents

Time of Pregnancy	Women, n	Pregnancies, n	Miscarriages, n (%)	Therapeutic Abortions, n	Liveborn Children, n*	
					Affected Father	Affected Mother
Before operation	59	140	27 (19)	22	57	101
After operation	27	62	21 (33)	3	31	43
Total	86	202	48	25	88	144

*Children of affected men and women.

supraventricular tachyarrhythmias increases. This finding is not unexpected, because the vast majority of these patients had chronically distended right atria and, after operation, had surgical scars on the right atrium. Thus, control of supraventricular tachyarrhythmias remains a challenge in these patients.

Previously, we reported the results of formal exercise testing for a very small subset of our patients (5,6). In those studies, there was a significant improvement in exercise tolerance in patients after they underwent surgery for Ebstein anomaly; this improvement resulted mainly from elimination of the right-to-left shunt at the atrial level. In the current study, exercise tolerance was assessed with the medical status questionnaire. It is apparent from Figure 2 that the patients' perceived exercise ability was distributed in a Gaussian fashion around the mean. There are limitations to this type of survey, most importantly the lack of a control group and incomplete ascertainment of information.

Medications. Only 34% of patients were taking no cardiac medications after operation. Although one might suggest that the need for continued use of medication may indicate a less-than-optimal result of operation, it must be remembered that operation does not cure the cardiomyopathy component of Ebstein anomaly. The ongoing use of medication is appropriate for patients with abnormal ventricular function and with post-operative arrhythmia; it also is appropriate for the prevention of thromboembolic events. We recommend systemic anticoagulation for the few patients who had insertion of a mechanical valve and for patients with persistent atrial fibrillation. We use systemic anticoagulation for 3 months post-operatively after insertion of a bioprosthesis in the tricuspid position.

Reproduction and inheritance. The miscarriage rate for our patients was 19% before operation and 33% after operation, which is comparable to the miscarriage rate in the general population of 13.7% to 26.1% (7,8). In the second Natural History Study of Congenital Heart Defects (9), the miscarriage rate for women with aortic stenosis, pulmonary stenosis, or ventricular septal defect was 12.8%, 13.7%, and 21.1%, respectively. Recently, Drenthen et al. (10) reported a miscarriage rate for women with Ebstein anomaly of 18% and that 3.9% of 127 pregnancies were complicated by arrhythmias and 3.1% by heart failure.

We recorded a total of 275 pregnancies among 82 women (Table 8). The incidence of congenital heart disease in children of a parent with Ebstein anomaly was 3.9%, which is significantly greater than the expected incidence of 0.75% in the general population. However, it is nearly identical to the incidence in Ebstein anomaly reported by Drenthen et al. (10) of 4% and previous reports from our institution (11). In addition, it is consistent with the incidence in children born to a parent with aortic stenosis, pulmonary stenosis, or ventricular septal defect (1.2% to 3.9%, 95% confidence interval: 0.01% to 7.5%) (10).

Study limitations. In this study, we hoped to identify the determinants of poor outcome and the determinants of good outcome. Intuitively, and based upon previous small studies, one might suggest that RV size and function as well as LV function and other measures of severity of TV dysplasia would correlate with outcome. Because our study is retrospective, we had to use echocardiographic data obtained during a 33-year period. These data were not collected in a uniform fashion. Measurement of RV size and function remains difficult with the use of echocardiography. Also, because of leftward displacement of the ventricular septum, which often is associated with paradoxical septal motion, it is difficult to know the implications of estimated LV ejection fraction. Despite these caveats, RV size and both RV and LV function are important determinants of outcome. Improved measurements of ventricular size and function, such as could be obtained with magnetic resonance imaging, may increase the usefulness of ventricular size and function in predicting outcome.

Survivors who did not return a health questionnaire had a statistically significant greater likelihood of greater than moderate RV dysfunction post-operatively ($p = 0.002$). This finding may have skewed the functional outcomes findings toward more positive results. Finally, despite the availability of classifications of anatomic subtypes of Ebstein anomaly (12), we were unable to retrospectively classify most patients. We did include echocardiographic measurements of severity and reparability. These measurements were not statistically significant predictors in any of our analyses.

Conclusions

The functional outcome after operation for Ebstein anomaly is good, and reported exercise tolerance is comparable with patients' peers. Reoperation, rehospitalization, and atrial tachyarrhythmias continue to be problematic. Assessment of the late results of novel methods to repair the TV is required. A more durable biological prosthesis is needed for patients whose valves are irreparable. Continued efforts to reduce the occurrence of atrial arrhythmias in patients with Ebstein anomaly are critical.

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Key Words: valves ■ surgery ■ heart defects congenital ■ Ebstein anomaly.

APPENDIX

For a list of the primers used for PCR and sequencing of αE-catenin, please see the online version of this article.