Factors predicting the progress of mitral valve disease in surgically treated adults with ostium primum atrial septal defects

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Objective: This study was undertaken to analyze the clinical profile, associated features, and surgical treatments of adults operated on for ostium primum atrial septal defects, particularly factors influencing progression of mitral valve disease.

Methods: We retrospectively studied all patients aged 18 years and older operated on at our institution with reference to patient clinical features, investigation findings, surgical records, and outpatient follow-up data.

Results: Fifty-one patients, 29 female and 22 male, underwent operation at a mean age of 27.3 years (SD 6.9). Of these, 80% were in New York Heart Association functional class I or II, with a most frequent presenting symptom of dyspnea. On echocardiography, 88% had cleft mitral valve, 35% had moderate mitral regurgitation, and 4% had severe mitral regurgitation. According to echocardiography and available cardiac catheterization data, 27% had moderate pulmonary arterial hypertension and 8% had severe. In-hospital mortality was 1.9%. At mean follow-up of 36 months, 94% of patients were in functional class I. Mitral regurgitation was moderate in 21% and severe in 8%, with 1 patient undergoing mitral valve replacement. Factors associated with increased risk of moderate or severe mitral regurgitation on follow-up were preoperative moderate or severe pulmonary arterial hypertension ($P = .008$) and female sex ($P = .009$).

Conclusion: Surgical correction of ostium primum atrial septal defects in adults can be undertaken successfully with low mortality and excellent symptomatic results. Regular follow-up is required to assess progression of mitral regurgitation, which is more likely in women and those with preoperative pulmonary arterial hypertension.

Most patients with ostium primum atrial septal defect (OPASD) are first seen in childhood, either with symptoms of a left-to-right shunt or with the finding of a murmur on routine examination. In developing countries, however, we still see patients in adulthood with recent onset of symptoms. Some are symptom free when they are seen for other, unrelated ailments and have OPASD diagnosed because of a murmur on examination. Also, many patients with symptoms may be seen late or defer surgical intervention for economic reasons.

Because there is only limited literature on this condition in adult patients, we aimed to assess the clinical presentation of this defect in adults as well as to examine surgical outcomes, in particular the fate of the left atrioventricular valve, which we can think of as the mitral valve.

MATERIALS AND METHODS

We retrospectively analyzed data from all patients 18 years old and older who underwent surgical correction. Clinical, electrocardiographic, radiologic, and echocardiographic details were gathered, along with cardiac catheterization data when available. The operative and postoperative notes

were analyzed, including echocardiography on discharge and at follow up. Other follow-up data, including New York Heart Association (NYHA) functional class and electrocardiographic findings, were assessed. Data for patients who did not undergo operation were not available to us. Echocardiographic grading of mitral regurgitation (MR) used in our study was based on jet area, with smaller than 4 cm² considered mild, 4 to 8 cm² considered moderate, and larger than 8 cm² considered severe. The study comprised patients through a number of years with a variety of cardiologists performing echocardiography in the early years, however, so the grading systems used may have differed in some cases.

Statistical Analysis

Analysis was performed with Microsoft Excel 2003 (Microsoft Corporation, Redmond, Wash) and SPSS 10.0 (SPSS Inc, Chicago, Ill). The χ^2 test was used to compare groups with discrete variables.

Study Group

The study group comprised 51 patients who underwent operation between June 1994 and June 2007 at our institution, all between the ages of 18 and 42 years, with a mean age of 27.3 years (SD 6.9 years). Twenty-nine were female and 22 were male. These patients were evaluated on the basis of clinical symptoms, physical examination, echocardiographic findings, and available cardiac catheterization data. The follow-up ranged from 3 months to 180 months, with a mean of 36 months.

Cardiac Catheterization

Cardiac catheterization was performed in 41 patients and not performed in 10 patients; the latter had all recently undergone operation and were considered to have adequate echocardiography. On the basis of cardiac catheterization or echocardiography, the patients were divided into those with normal pulmonary artery pressure, defined as right ventricular systolic pressure (RVSP) of less than 35 mm Hg, and those with pulmonary arterial hypertension (PAH), defined as RVSP of 35 mm Hg or more. PAH was categorized according to RVSP as mild (35–50 mm Hg), moderate (51–70 mm Hg), or severe (>70 mm Hg).

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Abbreviations and Acronyms

MR	= mitral regurgitation
NYHA	= New York Heart Association
OPASD	= ostium primum atrial septal defect
PAH	= pulmonary arterial hypertension
RVSP	= right ventricular systolic pressure
TR	= tricuspid regurgitation

Surgery

All surgical approaches were through a median sternotomy. Cardiopulmonary bypass was established with aortobicaval cannulation, cardiac arrest was achieved with antegrade cold blood cardioplegia, and core temperature was cooled to 28°C. Autologous pericardium was used to close the defect in 46 patients, a Dacron polyester fabric patch was used in 4 patients, and bovine pericardium was used in 1 patient. All patients underwent cleft closure by alignment of the lead edges and approximation of the fibrotic edges of the cleft with interrupted sutures. In addition to the cleft closure, mitral commissuroplasty was done in 2 patients and tricuspid valve repair was performed in 1 patient with severe tricuspid regurgitation (TR). In another 3 patients with severe TR repair was not performed on the basis of the water test done on the beating heart and also the lack of obvious annular dilatation at surgery. The lack of moderate or severe TR in these patients on follow-up appears to justify this approach. None of the patients required mitral valve replacement as the primary operation. In 18 patients, the coronary sinus was committed to the right atrium, and in 32 patients it was committed to the left atrium. One patient did not have any coronary sinus and had multiple Thebesian veins. In 2 cases an unroofed coronary sinus was encountered; two patches were used, and the coronary sinus was committed to the right atrium. One patient had a left superior vena cava draining to the left atrium; this was ligated at the base of the left atrial appendage and reattached to the left pulmonary artery. In 1 patient a small inlet ventricular septal defect was encountered and closed directly with pledgeted sutures.

RESULTS

The main patient characteristics are given in Table 1. Among the important associated features were common atrium in 10 patients (20%) and Ellis-van Creveld syndrome in 3 (6%). Cleft in the mitral valve was found on echocardiography in 45 patients (88%). Preoperative echocardiography also showed 31 patients (61%) to have mild MR, 18 (35%) to have moderate MR, and 2 (4%) to have severe MR. Eighteen patients (35%) had moderate TR, 4 patients (8%) had severe TR, and the remainder had mild or no TR.

The mean systolic pulmonary arterial pressure was 46 mm Hg (range 20–88 mm Hg). Fifteen patients (29%) had RVSP between 35 and 50 mm Hg (mild PAH), 14 (27%) had RVSP between 51 and 70 mm Hg (moderate PAH), and 4 (8%) had RVSP more than 70 mm Hg (severe PAH). The mean basal shunt was 3.4 (range 1.1–7.8) and the median pulmonary vascular resistance index was 2.4 woods units m² (range 0.7–19.4) in patients who underwent cardiac catheterization.

The median stay in the intensive care unit was 2 days (range 1–13 days), and the median total postoperative stay was 6 days (range 3–27 days). There were no operative

TABLE 1. Preoperative characteristics of the 51 patients

Age (y)	
Mean	27.3
Range	18–42
Sex (No.)	
Male	22 (43%)
Female	29 (57%)
New York Heart Association functional class	
I	11
II	30
III	10
Common symptoms (No.)	
Dyspnea on exertion	44 (86%)
Palpitations	21 (41%)
Rhythm (No.)	
Sinus	49
Atrial fibrillation	1
Junctional rhythm	1

deaths and only 1 in-hospital death. The female patient who died had mild MR on postoperative echocardiography but died of severe lower respiratory tract infection 13 days after the operation.

Complications

All complications are listed in Table 2. The patient who had postoperative development of complete heart block needed temporary pacing and recovered normal sinus rhythm. One patient had second-degree heart block but recovered to normal sinus rhythm within 3 days.

Follow-up

Of 50 surviving patients, 2 were unavailable for follow-up. They both had mild MR at discharge.

The follow-up involved assessment of the NYHA class, clinical examination, and echocardiography. Follow-up ranged from 3 months to 180 months, with a mean of 36 months and a median of 23 months. Forty-five patients (94%) were in NYHA functional class I, and 3 patients (6%) were in NYHA functional class II. None of the patients were in NYHA functional class III or IV. On last follow-up echocardiography, 34 patients (71%) had trivial or mild MR, 10 (21%) patients had moderate MR, and 4 (8%) patients had severe MR. Immediate postoperative TR was mild or less in 46 patients and moderate or severe in 2 patients (neither of whom had either severe TR or PAH before the operation). The echocardiographically estimated pulmonary arterial pressures (by RVSP) were normal in 46 patients, moderate in 1 patient, and severe in 1 patient. This last patient had a preoperatively RVSP of 74 mm Hg and borderline pulmonary vascular resistance index for operation (19.6 before oxygen and 4.3 after oxygen). Although the immediate postoperative RVSP was 96 mm Hg, the last follow-up RVSP was 55 mm Hg, and the patient's preoperative symptoms had resolved.

TABLE 2. Postoperative complications

Complication	No.	Resolution
Postoperative lower respiratory tract infection	6	5 recovered, 1 died after 13 d in intensive care
Pericardial effusion	3	2 needed pericardiocentesis, 1 resolved spontaneously
Complete heart block	1	Needed temporary pacing, recovered within 3 d
Second-degree heart block	1	Managed conservatively, resolved
Junctional rhythm	2	Managed conservatively (1 had same finding on preoperative Holter report)
Atrial fibrillation	4	Rate-controlling drugs and oral anticoagulation
Obstructive uropathy from small ureteric stone	1	Managed conservatively, stone passed spontaneously

Patients With Moderate or Severe MR on Follow-up

We specifically looked at patients who showed development of significant MR on follow-up. We sought preoperative and intraoperative factors that could predict the development of moderate or severe MR. We also charted the actuarial freedom from moderate or severe MR (Figure 1).

Of 10 patients who had moderate MR at last follow-up, 2 were male and 8 were female. Of these, before the operation only 5 had mild MR, 4 had moderate MR, and 1 had severe MR. Two patients had severe PAH and 5 had moderate PAH; all had moderate MR after the operation. MR at discharge had little bearing on late development of moderate MR.

Of the patients who had severe MR at last follow-up, 1 had increasing left ventricular dimensions and dyspnea on exertion and required mitral valve replacement 5 years after the initial surgical repair. One patient was pregnant at last follow-up and was advised to undergo valve replacement after delivery. Two patients with severe MR were symptom free without increasing left ventricular dimensions and are under close follow-up. Four patients were in atrial fibrillation. There were no late deaths. Table 3 shows characteristics of the patients with severe MR. All were female, and 2 had moderate PAH before the operation. In 1 patient the MR jet was from the cleft site as a result of inadequate repair, which was apparent on immediate postoperative echocardiography. In all other cases, the MR developed centrally. Moderate or severe MR developed during follow-up signif-

FIGURE 1. Kaplan–Meier plot of freedom from moderate or severe mitral regurgitation (MR) with time.

icantly more commonly in female patients ($P = .009$) and in those with preoperative moderate or severe PAH ($P = .008$). In female patients, development of moderate or severe MR was independent of age, preoperative MR, and preoperative PAH ($P > .05$ for each variable). Those with moderate or severe preoperative MR did not have a tendency toward development of moderate or severe MR on follow-up ($P = .45$; Table 4).

DISCUSSION

OPASD, or partial atrioventricular canal defect, arises as a result of deficient formation of embryonic atrioventricular canal by the endocardial cushions. The hallmark of the OPASD is the presence of an atrial septal defect low in the atrial septum along with a single atrioventricular junction but two separate atrioventricular orifices, with the left ventricular outflow tract displaced anteriorly.¹ The left atrioventricular valve is actually a trileaflet structure, which does not resemble a normal mitral valve but is often regarded as a mitral valve with an anterior leaflet cleft. The right atrioventricular valve is more like the normal tricuspid valve in that it has three leaflets, although again there are morphologic differences. OPASDs thus usually include a cleft anterior mitral leaflet, which is often associated with some degree of MR. There may or may not be an associated small inlet ventricular septal defect. In some cases, the atrial septal defect is so large that a common atrium results. The coronary sinus may be unroofed and thus connect to the left atrium in some cases.

To our knowledge, this report represents the largest series of patients who underwent operation for OPASD in

TABLE 3. Patient characteristics of severe mitral regurgitation in follow-up

Case	Age (y)	Preop PAH	Preop MR	Immediate postop MR	MR at last follow-up	Other characteristics	Current status
1	34	Mild	Moderate	Mild	Severe	AF	MVR after 5 y
2	22	Moderate	Mild	Mild	Severe	Pregnant	Awaiting MVR
3	35	Mild	Mild	Mild	Severe	None	Close follow-up
4	22	Moderate	Moderate	Moderate	Severe (from cleft site)	None	Close follow-up

All patients were female. *Preop*, Preoperative; *PAH*, pulmonary arterial hypertension; *MR*, mitral regurgitation; *postop*, postoperative; *AF*, atrial fibrillation; *MVR*, mitral valve replacement.

TABLE 4. Characteristics of patients with mild versus moderate or severe mitral regurgitation on follow-up

	Mild	Moderate or severe
Sex (No.)		
Male	19	2
Female	15	12
Mean age at operation (y)	26.7	28.9
Preoperative mitral regurgitation		
None	12	0
Mild	14	7
Moderate	6	6
Severe	2	1
Preoperative pulmonary arterial hypertension		
None or mild	21	5
Moderate	12	7
Severe	1	2

adulthood. It has been previously documented that OPASD detected at any age is an indication for surgery,² because these patients have symptoms develop with increasing frequency and also have increased MR without surgical correction.³ In addition, long-term survival after repair in this set of patients is good,^{3,4} as is also evident from our series with an in-hospital mortality of 1.9%. Forty-five patients were in NYHA functional class I, and 3 patients were in NYHA functional class 2 at last follow-up. The long-term results of mitral valve repair were also good, and only 1 patient has undergone reoperation to date, with another awaiting surgery. This is a lower frequency of reintervention than in most adult series.^{3,5} There was no subaortic stenosis found after repair, and 42 of the 48 patients followed up were in sinus rhythm. Unlike in other series, we also did not see any higher incidence of heart block in our follow-up.⁴

Correlation of PAH, Sex, and Mitral Valve Disease

We analyzed and compared the data of those with trivial or mild MR and those with moderate or severe MR on long-term follow-up with respect to mean age, sex, NYHA functional class, cardiothoracic ratio on x-ray, preoperative MR, and PAH. The only statistically significant differences were with respect to female sex and preoperative PAH. Patients with trivial or mild MR on follow-up were 41% female, whereas the moderate or severe MR group was 86% female. The trivial or mild group had 24% with preoperative moderate or severe PAH, whereas the moderate or severe group had 64% with preoperative moderate or severe PAH. It is obvious that satisfactory technical repair is reflected as good outcome on immediate postoperative echocardiography; however, good outcome on immediate postoperative echocardiography alone did not seem to influence the long-term outcome of the mitral valve disease in most of these patients. To summarize the group of patients who had moderate or severe MR at follow-up, 12 were

female and 2 were male. Of these 14 patients, at the time of discharge 3 had moderate MR and 11 had mild MR. In 1 case the moderate MR was the result of a technical failure to close the cleft, as mentioned previously.

Presence of PAH and female sex were found to have a significant influence on patient outcomes during follow-up. Patients with moderate or severe PAH had worse symptoms at follow-up, as suggested in previous studies.^{3,6} Many of those patients with moderate or severe MR on follow-up had significant preoperative PAH. We also found that the severe MR seen at follow-up had no correlation with the MR found at discharge with most having mild or no MR at discharge. A significant and previously unreported finding is that female patients had a higher propensity toward development of moderate or severe MR in our series. We did not find that preoperative MR had a significant bearing on MR on follow-up, as has been reported in the pediatric population.^{7,8}

We had repaired the cleft in all the patients, and commissuroplasty to improve valve competence was required in only 2 cases. The improved results in our series relative to other series of partial atrioventricular canal defects in adults may be due to several factors, such as the younger mean age of the patients, which makes the valve apparatus more amenable to repair, and routine closure of the cleft. Also, fewer of our patients were in atrial fibrillation than in other adult series.^{5,9} Longer follow-up, however, may show a greater progression of MR.¹⁰ It appears from our studies and from others that the fate of the mitral valve is not dependent on the technique alone. Patient symptoms and to some extent MR on follow-up appear to be influenced by preoperative PAH, with female patients also having more frequent deterioration of the mitral valve with time. Clearly, significant PAH is a prognostic factor for a tendency toward worse symptomatic class on long-term follow-up. It is also clear that PAH and female sex are important prognostic indicators for increased risk of development of moderate or severe MR at late follow-up. Associated defects, such as Ellis-van Creveld syndrome (a rare genetic disorder characterized by chondral and ectodermal dysplasia and associated with cardiac manifestations in 60% of cases)¹¹ and common atrium, were actually seen in patients with mild or no MR at follow-up. Clearly, such defects were not influencing the progression of mitral valve disease.

Study Limitations

The main limitation of our study was its retrospective nature. Despite this, we were able to shed some light on factors that influence outcomes in this subset of patients. Longer follow-up is required to confirm our findings, and we continue to analyze data from these patients in the realization that data on adult OPASD are difficult to collect in Western countries because of earlier diagnosis and younger age at operation.

CONCLUSIONS

In conclusion, low operative risk and good long-term results support the policy of early elective repair of OPASD in adults. There is a propensity toward increasing MR, however, particularly in female patients and those with significant preoperative PAH. Close follow-up is recommended.

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