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Original Article

Remodelling after surgical repair of atrial septal defects within the oval fossa

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Abstract In a retrospective study, we analysed the data from 101 adults with echocardiographic follow-up after surgical repair of defects within the oval fossa at a mean age of 35 ± 17 years; 56% of the cohort being above the age of 30 years. Mean age at follow-up was 44 ± 18 years, and length of follow-up was up to 40 years (11 ± 12 years). At follow-up, atrial fibrillation or flutter was present in one quarter. Dilation of the right atrium, found in 64%, of the left atrium, found in 44%, and of the right ventricle, found in 29%, were also frequent, as well as pulmonary arterial hypertension, which was found in 30%. Diminished right ventricular ejection fraction, in contrast, was very rare, found only in 1%, and abnormal left ventricular ejection fraction was not encountered. By multivariate analysis, predictors for right or left atrial, or right ventricular, dilation were age at follow-up, degree of tricuspid regurgitation, pulmonary hypertension, and/or atrial fibrillation. In a subset of 21 patients in sinus rhythm, we correlated prospectively the diastolic and systolic function of both ventricles with levels of brain natriuretic peptide, comparing values to those of 20 age-matched controls with a mean age of 46 ± 14 years. Levels of brain natriuretic peptide were significantly higher in patients than in controls ($p = 0.006$), and correlated significantly with diastolic dysfunction ($p = 0.007$) and left atrial size ($p < 0.0001$). In the long-term follow-up after surgical repair of defect within the oval fossa, therefore, complete normalization of heart size and function is rare. Despite preserved systolic function, persistent diastolic dysfunction is common and is associated with elevated levels of brain natriuretic peptide, which may explain the late occurrence of atrial arrhythmias.

Keywords: Atrial septal defect repair; diastolic dysfunction; remodelling; natriuretic peptides

ATRIAL SEPTAL DEFECTS WITHIN THE OVAL FOSSA account for 70% of all interatrial communications, these lesions themselves accounting for 7 to 10% of all congenital cardiac malformations. The defect of the atrial septum is the third most common congenital heart defect seen in adults after prolapse of the mitral valve and bicuspid aortic valve.[1,2] Since 1953, such defects have been successfully surgically corrected. The objectives of repair are reversal of the hemodynamic abnormalities, and prevention of late complications, including heart failure, arrhythmias, pulmonary vascular obstructive changes and paradoxical embolisation.

Right atrial and right ventricular dilation and dysfunction, pulmonary hypertension, mitral regurgitation and atrial fibrillation and flutter are well-known postoperative sequels after surgical repair.[1,3] Atrial arrhythmias occur in up to three-fifths of patients in the long-term follow-up, especially in those undergoing surgery after the age of 40 years.[1] The determinants of reversibility of right atrial and right ventricular dilation after repair have been poorly described. The relationship between function and size of both atriums and ventricles, and occurrence of arrhythmias, is largely unknown.

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Levels of atrial and brain natriuretic peptides are increased in patients with systolic and diastolic dysfunction.[4] Increased concentrations of the peptides in the plasma have been correlated with the presence of cardiac arrhythmias and the amount of hemodynamic compromise, and high concentrations are predictive of poor long-term survival.[5]

The purpose of our study, therefore, was to determine the frequency and etiology of right and left sided cardiac abnormalities in the long-term follow-up after surgical repair of defects within the oval fossa.

Material and methods

Population studied and design

The population studied consisted of all 101 adolescents, aged more than 16 years, and adults with prior surgical repair of a hemodynamically significant defect within the oval fossa who were referred for follow-up examination in our echocardiography laboratory between January 1990 and October 1999. In 11 of the 101 patients, concomitant commissurotomy for relief of pulmonary valvar stenosis had been performed at the time of repair of the septal defect. Otherwise, patients with associated complex congenital cardiac malformations were excluded. In 8 patients, 10 procedures had been performed on the mitral valve, 4 repairs and 6 replacements because of severe mitral regurgitation. All patients underwent complete cross-sectional and Doppler echocardiography. In the last phase of the study, involving 21 consecutive patients in sinus rhythm, we measured prospectively the levels of brain natriuretic peptide in the plasma, correlating the findings with a detailed echocardiographic examination and comparing them to 20 age- and gender-matched controls. Of these, half were men, with an age of 46 ± 14 years. The 21 patients did not have more severe mitral valvar disease ($p = 1.00$), pulmonary hypertension ($p = 0.80$), a history of arterial hypertension ($p = 0.65$) or residual atrial septal defects ($p = 0.49$) than did the patients in whom we did not measure levels of brain natriuretic peptide.

Echocardiography

Patients underwent transthoracic echocardiography in the left supine position with commercially available Hewlett-Packard Sonos 1000, 2500, 5500, GE Vingmed System Five and Accuson Sequoia 256 ultrasound systems. A complete cross-sectional and Doppler-echocardiographic examination, including M-mode measurements, was performed in every patient according to the guidelines of the American Society of Echocardiography. In addition, right atrial end-systolic and right ventricular end-diastolic sizes were measured from the apical 4-chamber view as previously described.[6,7] We had previously determined normal values of right atrial width (<4.1 cm) and length (<5.1 cm), as well as right ventricular width (<4.1 cm), in a normal control population of 20 adults.[6]

Systolic pulmonary arterial pressure was estimated by using the velocity of the tricuspid regurgitant jet, which was obtainable in 69 patients, and the Bernoulli equation. In the absence of obstruction within the right ventricular outflow tract, known pulmonary hypertension (as shown by an increased pulmonary arterial systolic pressure) was defined as a peak tricuspid regurgitation velocity in excess of 30 mmHg.[8]

In a subset of 21 patients in sinus rhythm, and in 20 control patients, complete echocardiographic assessment of annular motion of the annuluses of the tricuspid and mitral valves[9] was obtained, with diastolic function being assessed by Doppler echocardiography.[10] Fractional change was calculated in the area of the right ventricle. The right ventricular endocardium was traced at enddiastole and endsystole in the apical 4-chamber view. Fractional change in area was defined as the area at enddiastole minus the area at endsystole divided by the area at enddiastole. The normal value was greater than 25% in a control population of 20 adults.

Brain natiuretic peptide

For determination of brain natriuretic peptide, blood samples were taken 15 minutes after reaching a steady state in the supine position. Venous blood was taken into chilled tubes containing EDTA and aprotinin at a final concentration of 500 kU/ml blood. Plasma was separated immediately by centrifugation at +4°C. Aliquots were snap-frozen in liquid nitrogen and stored at −80°C until the assay was done. Concentrations of the peptide in the plasma were determined in duplicate without prior extraction by commercial radioimmunoassays employing 125I as a tracer (Shionogi Pharmaceutical Company, Osaka, Japan, solid-phase immunometric assay) strictly according to the instructions of the manufacturer. Normal values for brain natriuretic peptide are less than 10 ng/l in our laboratory.

Statistical analysis

Continuous and ordinal data are presented as means ± 1 standard deviation. Patients with and without dilation of the right atrium, left atrium and right ventricle, as well as atrial fibrillation/flutter at follow-up, were compared using the Mann-Whitney test for continuous and ordinal data and Fisher's exact test for nominal data. Independent risk factors

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for types of right atrial, left atrial and right ventricular dilation, as well as atrial fibrillation/flutter, were analyzed using stepwise (forward Wald) logistic regression. Dependencies between levels of brain natriuretic peptide and continuous variables were analyzed using Spearman rank correlations. Dependencies between nominal variables and levels of brain natriuretic peptide were analyzed using the Mann-Whitney test.

Results

Patients

Clinical characteristics are shown in Table 1. Age at repair was between 2 and 71 years. Repair at age younger than 16 years was rare, occurring in only 14%. Length of follow up ranged from less than one month up to 40 years. In 69% of patients, follow-up was for more than 1 year, with a mean of 16 ± 11 years. Chronic atrial fibrillation was found in 19%, and paroxysmal atrial fibrillation or flutter in 6% at follow-up.

Table 1. Characteristics of 101 adults after repair of defects within the oval fossa.

Female (%)	59
Age at repair (years)	35 ± 17
Age at repair ⩾30 years (%)	56
Age at follow-up (years)	44 ± 18
Length of follow-up (years)	11 ± 12
Follow-up >1 year (%)	69
Prior commissurotomy pulmonary valve (%)	11
Prior anomalous pulmonary venous drainage (%)	7
Atrial fibrillation/flutter at follow-up (%)	25
Mitral valve surgery (replacement or repair) (%)	8
Pacemaker implantation (%)	3

Echocardiographic findings

The echocardiographic findings are summarized in Table 2. Mean left atrial size was 4.2 ± 0.9 cm. Left atrial dilation greater than 4.0 cm was observed in 44%, albeit that only 16 of these 45 patients had atrial fibrillation. Mean left ventricular end-diastolic diameter was 4.7 ± 0.7 cm, our normal value being less than 6 cm. Left ventricular dilation was found in only 4%, and no patient had reduced left ventricular ejection fraction. Mean right atrial length was 5.1 ± 1.0 cm and mean right atrial width 4.4 ± 0.9 cm. Right atrial dilation was the most frequent echocardiographic finding, occurring in 64% of all patients. Right ventricular dilation was seen in 29%. Even in the 14 patients of our group who were repaired at an age below 16 years, persisting dilation of the right atrium was found in 36%, and of the right ventricle in 21%. Residual interatrial shunting was present in 13%, being trivial in 11 patients and moderate, with a jet width of 4 to 7 mm, in 2 patients. Of the patients, 83% had no or trivial mitral regurgitation at follow-up. Moderate or severe mitral regurgitation was found in only 2%, comprising one patient with moderate mitral valve prolapse and one patient with severe mitral regurgitation due to cordal rupture. Among the 8 patients with prior mitral valvar surgery,

Table 2. Summary of echocardiographic findings at long-term follow-up.

		Follow-up		
	All (101 patients)	<1 year (31 patients)	>1 year (70 patients)	p value
Left atrial dilatation (%)	44	48	49	0.39
Left ventricular dilatation (%)	4	6	3	0.59
Shortening fraction (%)	38 ± 8	37 ± 8	41 ± 8	0.06
Reduced left ventricular EF (%)	0	0	0	1.00
Reduced right ventricular function	1	0	1	1.00
Right atrial dilatation (%)	64	68	63	0.66
Right ventricular dilatation (%)	29	34	27	0.64
Residual interatrial shunting (%)	13	10	14	0.23
Mitral valve prolapse (%)	22	26	20	0.77
Mitral regurgitation,				0.46
None/trivial (%)	83	94	78	
Mild (%)	15	6	19	
Moderate/severe (%)	2	0	3	
Tricuspid regurgitation				0.55
Moderate/severe (%)	3	0	4	
Pulmonary regurgitation				1.00
Moderate/severe (%)	6	7	6	
Pulmonary hypertension (%)	30	23	33	0.79

Abbreviation: EF: ejection fraction

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no patient had more than trivial regurgitation. Thus, overall 10% had significant mitral valvar disease defined as moderate or more mitral regurgitation or prior mitral valvar replacement. Moderate or severe tricuspid regurgitation was rare. In patients with prior commissurotomy, the mean instantaneous systolic gradient across the pulmonary valve ranged from 0 to 17 mmHg.

In 70 patients having a follow-up greater than 1 year, there was no significant difference in echocardiographic findings compared to patients with a follow-up of less than 1 year apart from a further improvement in left ventricular shortening fraction which tended to be significant ($p = 0.06$).

Both preoperative and postoperative echocardiography had been undertaken in 39 patients at our hospital. A postoperative decrease in right atrial size was found in 33 of these patients, and a decrease in right ventricular size in 34.

Predictors of right atrial, right ventricular and left atrial dilation as well as atrial fibrillation at follow-up

Univariate predictors of persistent dilation of the atriums or the right ventricle are shown in Table 3. The most significant correlators for persisting right atrial dilation were age at follow-up and at surgical repair, atrial fibrillation/flutter, severity of tricuspid and mitral regurgitation, and dilation of the left atrium or right ventricle. Left atrial dilation showed a highly significant correlation with age at repair, older age at repair, age at follow-up, atrial fibrillation/flutter, mitral valvar disease, as well as both right atrial and right ventricular dilation. Right ventricular dilation correlated significantly with pulmonary hypertension, severity of tricuspid or mitral regurgitation, residual interatrial shunting, and with dilation of both atriums.

Atrial fibrillation/flutter correlated with age at repair, age at follow-up, length of follow-up, enlargement of both atriums, and severity of both mitral and tricuspid regurgitation (Table 3).

By multivariate analysis, right atrial dilation was independently associated with age at follow-up ($p = 0.0003$; OR 1.06) and severity of tricuspid regurgitation ($p = 0.004$; OR 3.4). Left atrial dilation correlated with age at follow-up ($p = 0.007$, OR 1.08), pulmonary hypertension ($p = 0.005$, OR 6.2) and atrial fibrillation/flutter ($p = 0.02$, OR 6.4). Right ventricular dilation was independently associated with pulmonary hypertension ($p = 0.0004$, OR 6.1). Atrial fibrillation independently correlated with age at repair ($p = 0.006$, OR 0.93), and age at follow-up ($p < 0.0001$, OR 1.16).

Detailed analysis of right and left ventricular systolic and diastolic function and correlation with levels of brain natriuretic peptide

These data are summarized in Table 4. Right and left atrial sizes, as well as right ventricular width, are larger in patients after repair than in controls. Tricuspid annular motion tended to be more diminished than mitral motion in those undergoing repair, which was only slightly diminished compared to controls. Diastolic dysfunction was present in half those undergoing surgical repair.

Table 3. Univariate predictors of postoperative persistent dilation of right and left atriums and right ventricle as well as atrial fibrillation/flutter.

	Right atrial dilatation	Left atrial dilatation	RV-dilatation	Atrial fibrillation
Age at atrial septal defect repair	0.002	<0.0001	0.48	0.04
Age at repair ⩾30 years	0.02	<0.0001	0.26	0.01
Age at follow-up	<0.0001	<0.0001	0.19	<0.0001
Length of follow-up	0.38	0.03	0.58	<0.0001
Pulmonary hypertension	0.04	0.001	0.0007	0.46
Prior pulmonary valve commissurotomy	0.99	0.74	0.71	0.45
Residual interatrial shunting	0.77	0.38	0.047	1.0
Prior anomalous pulmonary veins	0.42	0.99	0.41	0.68
Atrial fibrillation/flutter at follow-up	0.006	0.0003	0.07	–
Severity of tricuspid regurgitation*	0.002	0.002	0.001	0.0003
Severity of pulmonary regurgitation*	0.09	0.12	0.10	0.99
Severity of mitral regurgitation*	0.004	0.0002	0.04	0.01
Significant mitral valve disease#	0.09	0.0001	0.15	0.26
Right atrial dilatation	–	<0.0001	0.0006	0.0006
Left atrial dilatation	<0.0001	–	0.0003	0.0003
Right ventricular dilatation	0.0006	0.0003	–	0.07

p values are shown. RV indicates right ventricle; *analyzed as ordinal variable; #indicates operated or moderate or more mitral valve disease

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Table 4. Detailed analysis of right and left ventricular systolic and diastolic function in 21 patients in sinus rhythm compared to 20 controls.

	Patients	Controls	p value
Right ventricle			
End-diastolic area (cm^2)	19 ± 4	17 ± 4	0.12
Fractional area change (cm^2)	46 ± 9	52 ± 7	0.03
Width	3.6 ± 0.6	2.9 ± 0.6	0.0008
Lateral tricuspid annulus motion (mm)	15 ± 2	23 ± 4	<0.0001
Right atrium			
Length	4.8 ± 0.8	4.5 ± 0.4	0.20
Width	4.2 ± 0.5	3.6 ± 0.5	0.002
Diastolic function left ventricle			0.01
Normal (%)	50	85	
Relaxation abnormality (%)	33	15	
Pseudonormalization (%)	11	0	
Restrictive filling pattern (%)	6	0	
Lateral mitral annulus motion (mm)	15 ± 3	17 ± 4	0.02
Left atrium (cm)	3.9 ± 0.5	3.4 ± 0.6	<0.005

Levels of brain natriuretic peptide were significantly higher in those undergoing surgical repair (42 ± 46 ng/l) than in controls (12 ± 8 ng/l; $p = 0.01$), and correlated significantly with age at follow-up ($p = 0.004$), age at repair ($p = 0.007$), the presence of diastolic dysfunction ($p = 0.007$), and left atrial size ($r = 0.59$, $p < 0.0001$), but only slightly with right atrial dilation ($p = 0.02$). There was no correlation with right ventricular dilation ($p = 0.97$).

Discussion

We have demonstrated that, despite frequent immediate postoperative reduction in the size of the right-sided cavities, persisting dilation of both atriums and the right ventricle is commonly seen in the long-term follow-up after surgical repair of defects in the oval fossa. On long-term follow-up, systolic function of both ventricles is preserved, but diastolic dysfunction, and increased levels of brain natriuretic peptide, are common.

When repair is performed electively while patients are young, right ventricular hypertrophy and dilation may often resolve within six months to one year after operation.[11,12] It has been suggested that the decrease in right ventricular size correlates with the length of follow-up.[13] Our data show that almost always there is a postoperative regression of cavity size. Still, persisting dilation is common in the long-term follow-up, even in those patients repaired below the age of 16 years. Significant regression after the first year of follow-up was not seen, and the size of both atriums and ventricles were no different in patients seen less or more than 1 year postoperatively. This confirms other studies.[3,12] In 25 children undergoing repair at a median age of 6.8 years, a significant immediate postoperative decrease was noted in the size of the right atrium and right ventricle, with the greatest decrease occurring in the first postoperative year, and no significant change being found in the later follow-up.[12] Incomplete remodelling of the right ventricle, therefore, is common after repair, and difficult to prevent. One other study has suggested that the upper age limit may be as low as 3 years, with only surgical correction within the first three years of life leading to rapid and complete normalization of right ventricular size.[14] Thus, the upper age limit for surgical repair of defects within the oval fossa to prevent any postoperative sequels seems to be very low.

We observed significant mitral valvar disease, with moderate or severe regurgitation found in one-tenth of our patients, necessitating surgical treatment in 8%. The association between defects within the oval fossa and mitral valvar disease has long been recognized. It is especially due to an increased incidence of mitral valvar prolapse, found in from one to three quarters of patients.[2,15,16] The occurrence of significant mitral regurgitation, nonetheless, is rare. It was found in 4% in one study,[16] similar to our observations. Histologically, the mitral valves in patients with atrial septal defect do not commonly show the classical findings of myxoid degeneration, but instead occasionally show fibrosis of the leaflets with short, fibrotic tendinous cords.[16] Additionally, the postoperative frequency of mitral valvar prolapse has been described to diminish due to decrease in volume overload of the right side normalizing left ventricular geometry.[16] This might be the explanation that the frequency of prolapse in our patients after repair of the atrial defect was only 22%. It has also been suggested that the incidence of significant mitral regurgitation may increase in patients with advancing age. Still, hemodynamically significant mitral regurgitation does not seem to be a major problem in the long-term follow-up after surgical repair of defects within the oval fossa.

Hemodynamically relevant tricuspid or pulmonary regurgitation were rare in our patients, and not an important cause of persisting abnormalities of heart size and function. Surprisingly, prior pulmonary valvar commissurotomy and repair of anomalous pulmonary veins had no significant impact on occurrence of dilation of the right cavities, arrhythmias, or high levels of brain natriuretic peptide.

In our patients, systolic function of both ventricles was commonly preserved. Systolic function of the right ventricle was assessed in our study by fractional change in area, and was abnormal in only 1 of 21 patients in

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whom it was measured. In a previous study by Liberthson and colleagues,[17] 20 adults had a radionuclide scan before and more than 6 months after repair to assess right ventricular function. In elderly patients, with a mean age of 52 years, and with preoperatively decreased right ventricular function, in only 1 of these 11 patients was there normalization of postoperative function, despite an improvement in cavity size. Contrarily, in patients having repair at a mean age of 25 years, despite a comparable preoperative ratio of pulmonary to systemic flow, between 2 : 1 to 5 : 1, as in the previously mentioned elderly patients, right ventricular wall motion was normal pre- and postoperatively. Right ventricular end-diastolic pressure in the older patients was from 4 to 16 mmHg, and in the younger patients was from zero to 8 mmHg, possibly reflecting underlying diastolic dysfunction in elderly patients. This also underlines the importance of early repair.

The etiology of left ventricular failure in the long-term follow-up after repair has been debated in the past. Left ventricular systolic function usually normalizes, with normalization of the response of the left ventricular ejection fraction to exercise.[18] None of our patients had diminished left ventricular ejection fraction. Other postulated causes have included an underutilized, hypoplastic left ventricle, encroachment on left ventricular filling by an hypertrophic ventricular septum, and an intrinsic left ventricular abnormality.[18,19] None of these was present in our patients. The only possible explanation for signs of left heart failure was the frequent finding of diastolic dysfunction. Diastolic dysfunction in our patients was reflected by decreased motion of the annuluses of the tricuspid and mitral valves, and an abnormal Doppler filling pattern of left ventricular inflow and pulmonary veins. This contrasts to a study where ventricular diastolic function was completely normal in patients operated during childhood.[12] These authors have found no mechanical sequels of right ventricular volume overload in the follow-up after repair. The data in our patients differ considerably, with diastolic dysfunction of the left ventricle occurring in half of our patients. Earlier operation may protect against postoperative left ventricular diastolic dysfunction. With our study, we could not determine the exact cause of left ventricular diastolic dysfunction. Possible explanations include preoperative underutilization of the left ventricle, postoperative changes with abnormal septal motion and interventricular mechanical interaction, or an intrinsic abnormality of the left ventricle.

Atrial fibrillation is found at late follow-up in up to three-fifths of all adults who had closure of an atrial septal defect at an age greater than 41 years, and in up to two-fifths with closure between 25 and 41 years.[1,20] Recently it was shown in a large group of 213 adults undergoing surgery at ages between 16 and 80 years that the risk of atrial fibrillation or flutter after repair is related to the age at the time of repair and preoperative pulmonary arterial pressure.[21] In our patients, with one-sixth of the patients being less than 16 years old at the time of surgery, the occurrence of atrial fibrillation/flutter correlated negatively with age at repair but positively with age at follow-up. This might reflect the fact that patients operated at a very young age were more symptomatic due to a larger defect.

Natriuretic peptides are increased in systolic and diastolic heart failure and correlate with development of cardiac arrhythmias and the degree of hemodynamic compromise. High concentrations, especially of brain natriuretic peptide, predict poor long-term survival.[4,22,23] In a previous study, it was shown that natriuretic peptides are elevated in patients with an atrial septal defect both pre- and postoperatively.[24,25] In patients with pressure overload of the right ventricle, only brain natriuretic peptide correlates positively with mean pulmonary arterial pressure, total pulmonary resistance, mean right atrial pressure, right ventricular end-diastolic pressure and right ventricular mass. Brain natriuretic peptide seems to be more sensitive and specific than the atrial peptide as an indicator of ventricular disorders.[26] In our patients, levels of brain natriuretic peptide were elevated in three-quarters, and correlated with the presence of diastolic dysfunction and left atrial dilation. The elevated levels in our patients might reflect persistent or increasing stiffness of both ventricles in patients after surgical repair, or be a reflection of persistent right ventricular stretch. It has recently been shown that levels of brain natriuretic peptide may correlate better in patients with atrial dilation than levels of the atrial peptide, and perhaps better reflect diastolic dysfunction.[27]

A limitation of our study is that, in 84% of our patients, repair was performed at an age greater than 16 years, and 56% were repaired at an age greater than 30 years. We are not able, therefore, to define a cut-off concerning the age at which surgical repair should be performed to prevent significant irreversible changes of cardiac size and function. Also, we could not determine the impact of surgical repair on parameters of systolic and diastolic function. This would have been of great importance in these days of device closure.

We conclude that, in the long-term follow-up after surgical repair of defects within the oval fossa, postoperative reduction in right ventricular size is common. Persisting dilation of the right-sided cavities and left atrium is also frequent, continuing during long-term follow-up. Size and systolic function of both

ventricles are usually normal. Diastolic dysfunction reflected by dilated atriums, and high levels of brain natriuretic peptide are common. Postoperative diastolic dysfunction may be the main cause of atrial arrhythmias in the postoperative follow-up. The question remains as to whether early closure may reduce the incidence of diastolic dysfunction and atrial arrhythmias.

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