FUNCTIONAL STATUS AND LEFT VENTRICULAR FUNCTION IN ADOLESCENTS AND ADULTS BEOFRE SURGICAL CLOSURE OF SECUNDUM ATRIAL SEPTAL DEFECTS : COMPARISON WITH PATIENTS BEFORE DEVICE CLOSURE

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Abstract

Aims : To analyze functional status and left ventricular (LV) function of adolescents and adults before surgical closure of secundum atrial septal defect (ASD) during the most recent years.

Methods and Results : We investigated 68 patients before surgical ASD closure (surgical group) and 95 patients before device ASD closure (device group). New York Heart Association (NYHA) class and echocardiographic variables including LV and right ventricular (RV) size, LV and RV contractility, LV and RV Tei indices, and severity of mitral (MR) and tricuspid regurgitation (TR) were determined. Compared to the device group, the surgical group had worse NYHA class and decreased LV and RV function : greater LV volume and RV area, decreased LV and RV contractility, and increased LV Tei index (all $p<0.05$). The surgical group also showed higher occurrence of paroxysmal atrial fibrillation and greater MR and TR than the device group (all $p<0.03$). In the surgical group, TR severity was associated with worse NYHA class, whereas age at the time of surgery and RV end-diastolic area were associated with increased LV Tei index (all $p<0.05$).

Conclusion : Adolescents and adults before surgical closure of secundum ASD showed worse functional status and decreased LV function than those before device closure. In these patients before surgical ASD closure, greater TR severity was associated with worse functional status, whereas advanced-age and dilated RV were associated with LV dysfunction.

Key words : atrial septal defects, left ventricle, functional status

Introduction

Atrial septal defect (ASD) is a congenital cardiac abnormality often encountered in adolescence and adult population, because many patients are free from overt symptoms for the first few decades[1)]. However, once exercise intolerance occurs, their functional status gradually worsens. Long-term volume overload to the right ventricle (RV) causes not only RV dysfunction but, to some extent, left ventricular (LV) dysfunction due to ventricular interdependence[2)]. Device closure is now offered as an acceptable alternative to surgery for selected patients with secundum ASD[3)]. Contraindications of this technique include large ASD diameter, inadequate rim to deploy the

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device, anomalous pulmonary venous connection, and substantial mitral regurgitation (MR). A previous study demonstrated that 75% of patients with secundum ASD were treated percutaneously in the last decade[4]. Consequently, characteristics of patients undergoing surgical closure of secundum ASD may have changed. However, little is known about functional status and ventricular performance in these patients.

The aim of this study was to compare functional status and LV function in adolescents and adults undergoing surgical closure of secundum ASD and those in patients undergoing device closure of secundum ASD. Furthermore, if worse functional status and LV dysfunction were shown in patients undergoing surgical closure of secundum ASD, we would seek factors associated with the impairment.

Methods

Patients

The records of 104 consecutive adolescents and adults who underwent surgical closure of secundum ASD at the age of older than 14 years and received echocardiographic examination at the Akita University Hospital between 2000 and 2017 were reviewed for this study. Exclusion criteria were patients with sinus venosus and coronary sinus ASD (n = 22), aortic valve disease (n = 4), coronary artery disease (n = 3), partial anomalous pulmonary venous connection (n = 3), organic mitral (MV) or tricuspid valve (TV) disease except MV prolapse (n = 2)[5], and inadequate echocardiographic images n = 2). The ultimate population of further study consisted of 68 patients (surgical group). In these patients, selection criteria for surgical closure were possibilities of corrective unavailability of the device (before 2006) in 25, inadequate rims to deploy the device in 22, large ASD diameters in 14, and multiple ASDs in 7. Surgical closure was performed at the Akita University Hospital in 36 and other hospitals in 32. The control group consisted of 95 adolescents and adults who underwent device closure of secundum ASD between 2006 and 2017 (device group). All the device closure was performed at other hospitals which were certified by the Board of Education in the Japanese Pediatric Interventional Cardiology Society and the Japanese Association of Cardiovascular Intervention and Therapeutics. The databases of surgery, interventional cardiology, and echocardiography utilized in this study were approved by the Institutional Review Board for clinical research.

Clinical Data

Information on cardiovascular symptoms was obtained for the patients at the time of echocardiographic examination. Functional status was assessed by New York Heart Association (NYHA) classification. All standard 12-lead electrocardiograms were reviewed to examine history of atrial fibrillation.

Echocardiography

All the patients received echocardiographic examination before surgical (median, 5 days ; range, 1 to 98 days) and device closure (median, 20 days ; range, 10 to 90 days). Of the surgical group, 25 patients received follow-up echocardiographic examination later than 6 months after ASD closure. Among them, 10 patients who underwent simultaneous MV and/or TV surgery at the time of ASD closure were excluded from follow-up evaluation. The population of postoperative study ultimately consisted of 15 patients (median, 21 months ; range, 6 to 38 months). Of the device group, 58 patients received follow-up echocardiographic examination later than 6 months after ASD closure (median, 7 months ; range, 6 to 41 months).

Two-dimensional and Doppler transthoracic echocardiography was performed in a standard manner with 2 commercially available echocardiographic systems : ProSound Alfa 7 and F37 (Hitachi Ltd, Tokyo, Japan). Data analyses were performed on an on-line measurement system. Chamber area quantification was performed according to the guidelines from the American Society of Echocardiography[6]. LV volume and ejection fraction were determined using the modified Simpson algorithm[7]. Minimal MV and TV annulus diameters were measured during mid-systole in the apical 4-chamber view using frame-by-frame technique. Diameters of secundum ASD were measured in the subcostal short- and apical 4-chamer views, and the largest diameter was used. To avoid the risk of overestimating ASD diameters in color

Doppler images, only measurements from 2-dimesnional echocardiography were used. To evaluate LV diastolic function, peak early (E) and late diastolic transmitral flow velocities (A), A-wave duration (Adur), and duration of pulmonary venous atrial reversal flow velocity (ARdur) were measured[8]. Then, the ratio of E to A (E/A) and the difference between Adur and ARdur (Adur-ARdur) were computed[8,9]. Severity of MR and tricuspid regurgitation (TR) were assessed by color Doppler flow mapping of the regurgitant jets within respective atria. On color Doppler flow mapping, MR jet area and the left atrium as well as TR jet area and the right atrium in the same frame were measured by planimetry. Then, the ratio of maximal MR jet area to left atrial area (%MR) and the ratio of maximal TR jet area to right atrial area (%TR) were obtained[10,11]. Measurement of LV and RV Tei indices, combined systolic and diastolic Doppler parameters, was performed according to the established techniques[2,12]. After recording of transtricuspid flow velocity with continuous-wave Doppler echocardiography, RV systolic pressure was calculated with the simplified Bernoulli equation[13]. An average of 3 or more determinations of each variable was analyzed. In postoperative study, the absence of residual shunts was judged by combination of color Doppler flow mapping with Valsalva maneuver. Although patients with history of paroxysmal atrial fibrillation were included in this study, all the echocardiographic parameters were measured at the time of sinus rhythm.

Statistical Analysis

Quantitative data are presented as mean±standard deviation. Categorical data were presented as percentages. Comparisons between the 2 groups were performed by the Student paired or unpaired *t*-test for quantitative data and by the Mann-Whitney U test for categorical data. To assess factors associated with worse NYHA class and increased LV Tei index in the surgical group, correlations with measured variables were determined by the Pearson correlation coefficient for quantitative data and by the Spearmann rank correlation for categorical data. Analyzed variables were age at the time of surgery, male gender, NYHA class, atrial fibrillation, LV end-diastolic volume, LV ejection fraction, RV end-diastolic area, RV fractional area change, left and right atrial areas, MV and TV annulus diameters, ASD diameter, the E/A ratio, Adur-ARdur, LV and RV Tei indices, %MR, %TR, and RV systolic pressure. Significant data for univariate analyses were entered into multivariate stepwise linear regression analysis. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using commercially available software (IBM SPSS Statistics 24 for Windows, IM Corporation, Armonk, New York, United States).

Inter- and intraobserver variabilities for LV and RV Tei indices were obtained from analyzing 10 random images by 2 independent observers and by the same observer at different time points, respectively. Analysis of differences in the measurements was performed by the Pearson correlation coefficient and the Bland-Altman technique[14].

Results

Clinical Data (Table 1)

There were no significant differences in age, gender distribution, and body size between the surgical and the device groups. The surgical group showed significantly increased heart rate and significantly decreased systolic blood pressure as compared with the device group. In the surgical group, NYHA class was significantly worse as compared with the device group. Recorded symptoms and history in the surgical group were exertional dyspnea in 41 (60%), palpitations in 21 (31%), fatigue in 16 (24%), and chest pain in 10 (15%). History of paroxysmal atrial fibrillation was significantly higher in the surgical group than in the device group. Persistent atrial fibrillation did not occur in the both groups.

Echocardiographic Data (Table 2)

The surgical group had significantly greater LV end-diastolic volume, RV end-diastolic area, left atrial area, and MV annulus diameter than the device group. In the surgical group, LV end-diastolic volume was significantly correlated with %MR ($r = 0.33$, $p = 0.007$). Right atrial area, TV annulus diameter, and ASD diameter did not significantly differ between the 2 groups. The surgical group showed significantly lower LV ejection fraction and

Table 1. Clinical data in ASD patients before surgical and device closure

	Surgery (n = 68)	Device (n = 95)	p value
Age (years)	37±16	40±16	0.3
Gender, male	34%	34%	0.9
Body height (cm)	159±8	158±11	0.5
Body weight (kg)	49±17	45±19	0.2
Heart rate (beats/min)	76±14	69±10	<0.001
Systolic blood pressure (mmHg)	112±15	119±21	0.01
Diastolic blood pressure (mmHg)	64±10	66±10	0.2
NYHA class I / II / III	28% / 65% / 7%	49% / 48% / 3%	0.009
Paroxysmal atrial fibrillation	24%	9%	0.02

ASD, atrial septal defect ; NYHA, New York Heart Association

Table 2. Echocardiographic data in ASD patients before surgical and device closure

	Surgery (n = 68)	Device (n = 95)	p value
LV end-diastolic volume (ml)	94±38	76±26	0.002
LV ejection fraction (%)	54±8	58±4	<0.001
RV end-diastolic area (cm^2)	33±11	26±6	0.002
RV fractional area change (%)	36±14	44±11	0.008
Left atrial area (cm^2)	24±13	20±6	0.04
Right atrial area (cm^2)	25±11	22±7	0.07
MV annulus diameter (cm)	2.9±0.6	2.3±0.4	<0.001
TV annulus diameter (cm)	3.3±0.8	3.2±0.7	0.7
ASD diameter (cm)	2.3±1.1	2±0.6	0.07
E/A	1.4±0.7	1.5±0.8	0.7
Adur-ARdur (ms)	62±45	65±42	0.3
LV Tei index	0.46±0.26	0.35±0.23	0.04
RV Tei index	0.46±0.27	0.36±0.17	0.08
%MR	13±23	2±5	<0.001
%TR	17±22	9±17	0.03
RV systolic pressure (mmHg)	40±14	37±15	0.4

Adur-ARdur, time difference between duration of late diastolic transmitral flow velocity and duration of pulmonary venous atrial reversal flow velocity ; ASD, atrial septal defect ; E/A, ratio of peak early-to-late diastolic transmitral flow velocities ; LV, left ventricle ; MV, mitral valve ; %MR, ratio of maximal mitral regurgitation jet area to left atrial area ; %TR, ratio of maximal tricuspid regurgitation jet area to right atrial area ; RV, right ventricle ; TV, tricuspid valve

RV fractional area change than the device group. No parameters were significantly correlated with LV ejection fraction in the surgical group. Sixteen patients (24%) in the surgical group had LV ejection fraction <50%, whereas only 2 patients (2%) in the device group showed LV ejection fraction <50% (p <0.001). In contrast, neither the E/A ratio nor Adur-ARdur showed significant differences between the 2 groups. LV Tei index were significantly increased in the surgical group as compared with the device group. RV Tei index were increased in the surgical group as compared with the device group, although it did not reach statistical significance. The sur-

Table 3. Relationships between NYHA class and clinical and echocardiographic data in ASD patients before surgical closure

	r	Univariate p value	Multivariate p value
Age		0.4	
Gender, male		0.6	
Paroxysmal atrial fibrillation	0.34	0.004	0.08
LV end-diastolic volume	0.27	0.03	0.09
LV ejection fraction		0.4	
RV end-diastolic area		0.5	
RV fractional area change	−0.3	0.02	0.1
Left atrial area	0.28	0.03	0.2
Right atrial area		0.1	
MV annulus diameter		0.3	
TV annulus diameter		0.4	
ASD diameter		0.4	
E/A		0.2	
Adur-ARdur		0.1	
LV Tei index		0.2	
RV Tei index		0.4	
%MR		0.2	
%TR	0.33	0.02	0.04
RV systolic pressure		0.2	

Adur-ARdur, time difference between duration of late diastolic transmitral flow velocity and duration of pulmonary venous atrial reversal flow velocity ; ASD, atrial septal defect ; E/A, ratio of peak early-to-late diastolic transmitral flow velocities ; LV, left ventricle ; MV, mitral valve ; NYHA, New York Heart Association ; %MR, ratio of maximal mitral regurgitation jet area to left atrial area ; %TR, ratio of maximal tricuspid regurgitation jet area to right atrial area ; RV, right ventricle ; TV, tricuspid valve

gical group showed significantly greater %MR and %TR than the device group. In the surgical group, %MR >20 (greater than mild MR)[15] and %TR >20 (greater than mild TR)[16] were observed in 13 (19%) and 17 patients (25%), respectively.

Among the surgical group, 28 patients (41%) had history of atrial fibrillation and/or greater than mild MR and/or TR. When these patients were categorized as a discrete group, they had significantly worse NYHA class (I / II / III, 18% / 64% / 18% vs. 35% / 65% / 0%), significantly greater LV end-diastolic volume (107±42 ml vs. 85±32 ml), left atrial area (31±17 cm^2 vs. 19±5 cm^2), right atrial area (29±14 cm^2 vs. 22±7 cm^2), and MV annulus diameter (3.1±0.8 cm vs. 2.8±0.4 cm), and significantly increased LV Tei index (0.54±0.31 vs. 0.4±0.2) as compared with those without atrial fibrillation and/or greater than mild MR and/or TR (all p <0.05).

Associated Factors of Worse NYHA Class (Table 3)

In the surgical group, atrial fibrillation, LV end-diastolic volume, RV fractional area change, left atrial area, and %TR showed significant correlations with NYHA class by univariate analysis. When these significant variables were entered into multivariate analysis, only %TR emerged as a factor associated with worse NYHA class.

Associated Factors of Increased LV Tei Index (Table 4)

In the surgical group, age at the time of surgery, atrial fibrillation, RV end-diastolic area, left and right atrial areas, TV annulus diameter, ASD diameter, and RV Tei index showed significant correlations with LV Tei index by

Table 4. Relationships between LV Tei index and clinical and echocardiographic data in ASD patients before surgical closure

	r	Univariate p value	Multivariate p value
Age	0.41	0.006	0.01
Gender, male		0.2	
Paroxysmal atrial fibrillation	0.44	0.001	0.06
LV end-diastolic volume		0.1	
LV ejection fraction		0.8	
RV end-diastolic area	0.43	0.005	0.004
RV fractional area change		0.2	
Left atrial area	0.33	0.009	0.09
Right atrial area	0.39	0.002	0.2
MV annulus diameter		0.5	
TV annulus diameter	0.34	0.009	0.8
ASD diameter	0.27	0.04	0.2
E/A		0.3	
Adur-ARdur		0.2	
RV Tei index	0.26	0.04	0.6
%MR		0.5	
%TR		0.3	
RV systolic pressure		0.6	

Adur-ARdur, time difference between duration of late diastolic transmitral flow velocity and duration of pulmonary venous atrial reversal flow velocity ; ASD, atrial septal defect ; E/A, ratio of peak early-to-late diastolic transmitral flow velocities ; LV, left ventricle ; MV, mitral valve ; %MR, ratio of maximal mitral regurgitation jet area to left atrial area ; %TR, ratio of maximal tricuspid regurgitation jet area to right atrial area ; RV, right ventricle ; TV, tricuspid valve

univariate analysis. When these significant variables were entered into multivariate analysis, age at the time of surgery and RV end-diastolic area emerged as factors associated with increased LV Tei index. The risk of LV dysfunction, which was defined as LV Tei index of >0.45[2,12], increased steeply with advanced-age at the time of surgery ; 42% at age of 40 years, 61% at age of 50 years, and 88% at age of 60 years.

Postoperative Data

Of 15 patients who received postoperative study, improvement in NYHA class by I grade was shown in 11 (73%). Before surgical ASD closure, 10 and 5 patients were in NYHA class II and III, respectively. However, these patients showed significant improvement in functional status after surgery ; NYHA class I in 6 and II in 9 ($p = 0.04$). No patients who received postoperative study had atrial fibrillation before and after ASD closure. After surgical ASD closure, TV annulus diameter was significantly decreased (3.8±0.4 cm vs. 3.4±0.6 cm, $P = 0.03$), although changes in LV end-diastolic volume (85±10 ml vs. 90±28 ml), LV ejection fraction (56±11% vs. 60±6%), RV end-diastolic area (33±12 cm^2 vs. 28±6 cm^2), RV fractional area change (39±13% vs. 37±6%), right atrial area (21±7 cm^2 vs. 18±8 cm^2), LV Tei index (0.45±0.11 vs. 0.45±0.07), RV Tei index (0.5±0.22 vs. 0.48±0.24), %MR (10±10 vs. 14±10), %TR (13±9 vs. 16±9), and RV systolic pressure (43±21 mm Hg vs. 39±16 mm Hg) were not statistically significant.

Of 58 patients who underwent echocardiographic study mid-term after device ASD closure, NYHA class, occurrence of atrial fibrillation (14% vs. 6%), LV end-diastolic volume (76±25 ml vs. 97±28 ml), RV end-diastolic area (29±8 cm^2 vs. 24±9 cm^2), right atrial area (24±6 cm^2 vs.

22±8 cm^2), and TV annulus diameter (3.2±0.6 cm vs. 2.7±0.6 cm) were significantly decreased (all p <0.04).

Reproducibility

There was good agreement in LV and RV Tei indices between 2 independent observers (r = 0.96 and 0.92, respectively, both p = 0.001). Mean differences in LV and RV Tei indices were 0.02±0.02 and 0.03±0.02, respectively. Excellent correlations were also observed in intraobserver measurements of LV and RV Tei indices (r = 0.97 and 0.96, respectively, both p = 0.001). Mean differences in LV and RV Tei indices were 0.01±0.01 and 0.02±0.01, respectively.

Discussion

This is a detailed clinical and echocardiographic study investigating functional status and LV function of adolescents and adults before surgical closure of secundum ASD in the device closure era. Patients before surgical ASD closure showed worse functional status and impaired LV function than those before device ASD closure. These results could be affected by procedure selection bias : more hemodynamically compromised patients were selected for surgery. In patients before surgical ASD closure, worse functional status was associated with severity of TR, whereas LV dysfunction, judged by increased LV Tei index, was associated with advanced-age and dilated RV end-diastolic area.

Functional Status

Common initial symptoms in ASD patients are exertional dyspnea and subsequently, fatigue or palpitations may occur at older than 40 years of age[17]. On account of the slowly progressive nature of the disease, most ASD patients are shown to be in NYHA class I or II[18]. Attie *et al.*[19] reported that only 6% of patients in NYHA class I or II at the mean age of 52 years deteriorated to class III over mean follow-up of 6 years. Similarly, this study showed that 93% of patients before surgical ASD closure and 97% patients before device ASD closure were in NYHA class I or II. In agreement with previous studies[20], this study demonstrated that cardiovascular symptoms worsened in the unrepaired ASD patients, as TR developed. This finding is also similar to a large population study[21] demonstrating the significant associations between worse functional status and substantial TR in other cardiac diseases.

LV Volume and Ejection Fraction

In this study, LV end-diastolic volume in the surgical group was significantly greater than that in the device group. Attie *et al.*[19] have found that most ASD patients with significant shunts had decreased LV volume. However, these studies were different from this study in that they recruited younger and less symptomatic patients as compared with those in this study. In addition, they had a bias excluding patients with substantial MR from the study. We showed that increase in LV end-diastolic volume was associated with severity of MR in the surgical group.

LV ejection fraction has been known to be normal in adult patients with ASD. Attie *et al.*[19] have demonstrated that average LV ejection fraction was 66±11% in 241 unrepaired ASD patients who were older than 40 years. Giardini *et al.*[18] have shown that average LV ejection fraction was 74±7% in 32 ASD patients before device closure at the age of 43±17 years. However, they have excluded patients with substantial MR and TR as well as LV dysfunction from the studies. Therefore, characteristics of patients might be different from those of patients in this study. A study by Bonow *et al.*[22], in which no patients were excluded, have shown that average LV ejection fraction was 57% in unrepaired ASD patients at the mean age of 36 years. LV ejection fraction in this study is agreement with that of Bonow et al., although their study consisted of a small number of patients.

LV Tei Index

Tei index is a simple and quantitative measurement of ventricular function that is applicable regardless of distorted ventricular morphologies presented in congenital heart disease and is relatively independent of loading conditions on the ventricles[12,23]. This index comprises systolic and diastolic time intervals ; therefore, it can estimate global cardiac function. This index has also been shown to correlate well with invasive hemodynamic vari-

ables of LV function[12]. Furthermore, LV Tei index has been demonstrated to predict the prognosis of patients with congestive heart failure[24].

However, only limited information is known about LV Tei index in adult patients with ASD. Kim *et al.*[25] have reported that unrepaired ASD patients (age, 39±11 years) with normal LV ejection fraction showed equivalent LV Tei index (0.36±0.03) with healthy controls. In contrast, LV Tei index of the surgical group in this study was evidently higher than those of the previous study. In the study by Kim *et al.*, patients recruited had relatively younger than those in this study and no information on RV size was available. This study demonstrated that advanced-age and dilated RV end-diastolic area were the independent factors associated with increased LV Tei index in the surgical group. Early intervention is recommended for adolescents and adults with secundum ASD.

Izumi et al.[26] have demonstrated that RV Tei index showed a good correlation with pulmonary capillary wedge pressure in patients LV systolic dysfunction. In addition, patients who improved in functional class after treatment showed decrease in RV Tei index. In contrast, this study showed that preoperative LV Tei index was useful for assessment the severity of RV dilation in patients with significant secundum ASD. However, LV Tei index did not decrease after successful surgical closure by echocardiographic examination of a part of patients. Advanced age and long-standing RV dilation has been reported as important factors associated with LV stiffening in ASD[27]. Key parameters of ventricular dysfunction should take the structural abnormality in consideration.

In this study, paroxysmal atrial fibrillation tended to correlate with increase in LV Tei index in the surgical group before ASD closure although it did not show statistical significance. A previous study[28] has demonstrated that the presence of atrial fibrillation is related to left atrial enlargement and grade of MR severity in ASD adults. Our study showed that left atrial area also has a tendency of predictor of increase in LV Tei index. Further investigations may render the effect of paroxysmal atrial fibrillation accompanied with left atrial enlargement and MR on LV Tei index.

Limitations

In this study, there are a few limitations. First, because this is a retrospective study, only routine echocardiographic evaluation was performed. New modalities, such as real-time 3-dimensional echocardiography or deformation imaging, may have the potential to provide more accurate information on LV and RV remodeling.[29,30] Second, this study could not provide data on the prognosis, thus clinical significance of LV dysfunction in the ASD patients was unclear. Further research is necessary to clarify the meaning of LV dysfunction resulting from the ASD. Lastly, the number of patients with long-term follow-up after ASD closure was small. Further follow-up study should be accomplished with larger samples.

Conclusions

Adolescents and adults before surgical closure of secundum ASD showed worse functional status and impaired LV function than those before device closure. In ASD patients before surgical closure, severity of TR was associated with worse functional status, whereas advanced-age and dilated RV end-diastolic area were associated with LV dysfunction. Early intervention is recommended for adolescents and adults with secundum ASD.

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