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Prediction of early-onset atrial tachyarrhythmia after successful trans-catheter device closure of atrial septal defect

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Abstract

Atrial tachyarrhythmia is a well-known long-term complication of atrial septal defect (ASD) in adults, even after successful trans-catheter closure. However, the risk factors for early-onset atrial tachyarrhythmia after trans-catheter closure remain unclear. This retrospective study enrolled adults with secundum ASD undergoing trans-catheter closure from January 2000 to March 2014. We analyzed the clinical characteristics of patients and assessed risk factors for new-onset atrial tachyarrhythmia defined as a composite of atrial fibrillation or flutter (AF/AFL) after ASD closure. We enrolled a total of 427 patients; 123 were male (28.8%) and the median age was 37.0 (interquartile range [IQR]: 18.3–49.0). Nineteen (4.4%) patients had documented atrial tachyarrhythmia during the follow-up period (median: 11.4 months [IQR: 5.4–24]). Patients with transient AF/AFL during closure showed a greater incidence of new-onset atrial tachyarrhythmia during the follow-up period than patients with consistent sinus rhythm during closure (27.3% vs 3.8%; $P=0.01$). Most new-onset atrial tachyarrhythmias were documented within 6 months (median: 2.6 [IQR: 1.2–4.1] months) of closure. In the multivariate analysis, the risk for new-onset atrial tachyarrhythmia was significant in patients with AF/AFL during closure (hazard ratio [HR]: 9.90, 95% confidence interval [CI]: 2.86–34.20; $P<0.001$), deficient posteroinferior rim (HR: 5.48, 95% CI: 1.15–25.72; $P=0.04$), and age of closure over 48 years (HR: 3.30, 95% CI: 1.30–8.38; $P=0.01$). In conclusion, transient AF/AFL during trans-catheter closure of ASD as well as deficient posteroinferior rim and age of closure over 48 years may be useful for predicting early new-onset atrial tachyarrhythmia after device closure.

Abbreviations: AF/AFL = atrial fibrillation or flutter, ASD = atrial septal defect, AT = atrial tachycardia, CI = confidence interval, ECG = electrocardiogram, HR = hazard ratio, IQR = interquartile range, Qp/Qs = ratio of pulmonary perfusion to systemic perfusion, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography.

Keywords: atrial fibrillation, atrial septal defect, transcatheter closure

1. Introduction

Atrial septal defects (ASDs) are one of the most common congenital heart diseases in adulthood and are associated with atrial arrhythmias, right heart failure, stroke, and premature death.[1] Trans-catheter closure of ASDs has been shown to be safe and to improve long-term cardiac mortality and morbidity.[2–4] However, atrial arrhythmias remain an important determinant of late cardiac morbidity in this population. Although the signs of heart failure associated with large ASDs may present in childhood, a significant proportion of patients present with symptoms in the 3rd to 4th decade of life. Often asymptomatic until the onset of complications, the main cause of morbidity and mortality in ASD patients is attributed to the development of atrial tachyarrhythmia.[5] Recently, many studies have examined the impact of ASD closure on atrial tachyarrhythmia, suggesting that closure may initiate or discontinue the arrhythmia.[6] According to a previous study, trans-catheter closure of ASDs in patients under 40 years of age without a history of arrhythmias conferred the highest likelihood of a patient remaining arrhythmia-free during follow-up.[7] Van De Bruaene et al[8] also reported that mean pulmonary artery pressure ≥ 25 mm Hg is an independent predictor of late atrial arrhythmia. Although ASD results in chronic right volume overload with resultant right atrial stretch and right atrial remodeling, its effects on the left atrium (LA) remain unclear.[9–11] Atrial tachyarrhythmia, especially atrial fibrillation or flutter, increases thromboembolic risk after device closure, and this risk may be magnified by the thromboembolic risk of the device itself. It is important to predict arrhythmia and modify further thromboembolic events; however, a comprehensive

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analysis has not been performed to quantitatively review the available evidence. Therefore, we conducted this study to identify useful demographic, electrocardiographic, and hemodynamic parameters that may predict new-onset atrial tachyarrhythmia after trans-catheter closure of ASDs.

2. Methods

2.1. Study population

All consecutive patients who underwent trans-catheter closure for secundum ASDs from January 2000 to March 2014 at Samsung Medical Center (SMC) were enrolled in the SMC-ASD registry. Among 623 patients in this registry, we excluded patients based on the following criteria: (1) a history of atrial fibrillation/atrial flutter (AF/AFL) or atrial tachycardia (AT), (2) a lack of Holter monitoring during the follow-up period, or (3) a greater than moderate degree of valvular heart disease. Patient selection was based on the evidence of right ventricular volume overload in transthoracic echocardiography (TTE). Baseline characteristics and procedural data were collected by research coordinators of the dedicated registry. This study complied with the Declaration of Helsinki, and the research protocol was approved and the informed consent was waived by the ethics committee of SMC.

2.2. Echocardiographic measurement

All patients underwent TTE and transesophageal echocardiography (TEE) before closure. Cardiac chamber size was measured by TTE according to the recommendations for chamber quantification.[12] Definitions of chamber enlargement/dilatation and pulmonary hypertension are as follows: LA enlargement was defined by the indexed LA volume $> 34\,mL/m^2$ from the apical 4-chamber and 2-chamber, using an area-length method; RA enlargement, RA diameter > 44 mm indicated at the end-diastole from the apical 4-chamber view; RV dilation, RV diameter >42 mm at the base and >35 mm at the mid-level estimated at the end-diastole from a right ventricle-focused apical 4-chamber view; pulmonary hypertension, a mean pulmonary artery pressure ≥ 25 mm Hg or right ventricular systolic pressure >40 mm Hg at rest on echocardiography. Based on recent guidelines, mitral and tricuspid valve functions were measured using TTE.[13] TEE was performed for precise measurement of the location, morphology, number and size of ASDs. The long and short diameters were measured at the end-systolic phase by reconstructed en-face images on 3-dimensional TEE from the right atrial side as previously described.[14] The surrounding rims of ASDs were also determined with multiplane measurement by TEE based on the previous literature.[15] Based on the previous definition, any rim length <5 mm was considered deficient.[16]

2.3. Cardiac catheterization and device implantation

All patients underwent right heart catheterization before closure with the standard protocol, and the ratio of pulmonary perfusion to systemic perfusion (Q_P/Q_S) was calculated.[17] Trans-catheter closure was performed by 2 pediatricians who specialized in interventional procedures. All procedures were performed with the Amplatzer Septal Occluder (ASO, AGA Medical, Golden Valley, MN). The balloon occlusive diameter was measured under intra-cardiac echocardiography guidance during catheterization.[18] Decisions regarding device size were based on balloon occlusive diameter; a device of the same size or a 1 to 2 mm larger device was initially chosen. A balloon-assisted technique was used as described previously to facilitate device closure of large ASDs, and the choice was made by the operator.[19] Electrocardiogram (ECG) monitoring was performed during closure. Arrhythmic events occurring during the procedure were recorded by a certified technician in electrophysiology and double checked by a pediatric cardiologist. All recorded arrhythmic events were reviewed by a cardiologist for this study. After device implantation, all patients were prescribed 100 mg per day of aspirin or 75 mg per day of clopidogrel for 6 months.

2.4. Electrocardiogram measurement and arrhythmia events

All patients underwent routine ECG when they visited the outpatient clinic 1 week, 3 months, 6 months, 1 year, and 2 years after closure. We investigated the duration and amplitude of the P wave in leads II and V_1, respectively. The presence or absence of biphasic P wave in V_1 and an RSR′ pattern in V_1 or V_2 were assessed. Follow-up Holter ECG monitoring was repeated every 3 to 6 months after ASD closure and again if palpitations recurred. All types of arrhythmias detected by standard 12-lead ECGs or 24-hour Holter ECG monitoring and each date of documentation were recorded. Atrial tachyarrhythmia was defined as a composite of AF and AFL. Considering procedural irritation, we regarded arrhythmia occurring >30 days after closure as new-onset atrial tachyarrhythmia.

2.5. Statistical analysis

We divided study patients according to the occurrence of early new-onset atrial tachyarrhythmia during the follow-up period. Continuous variables are presented as medians with interquartile ranges and categorical variables are described as number (n) and percentage (%). The Mann–Whitney U test was used to compare continuous variables and the chi-square test or Fisher's exact test was used to compare categorical variables between groups. Follow-up started on the date of closure and continued for 2 years after closure. During the follow-up period, all documented arrhythmic events were recorded. All baseline clinical, procedural, echocardiographic, electrocardiographic, and cardiac catheterization variables were analyzed by Cox proportional hazard regression to predict the risk for new-onset atrial tachyarrhythmia. The cut-off values of continuous variables were determined by receiver-operating characteristic analysis. Multivariate analysis was performed with a stepwise backward selection process to determine the risk of early onset atrial tachyarrhythmia after ASDs closure. The covariates used for multiple adjustment were age at closure and sex. The criteria for the entry and removal of variables on multivariate analysis were set at 0.05 and 0.10, respectively. All statistical analyses were conducted by means of 2-tailed tests using SPSS 18.0 software (SPSS Inc., Chicago, IL), and a P value of <0.05 was considered statistically significant.

3. Results

Among a total of 623 enrolled patients, 196 were excluded. One hundred and fifteen patients did not undergo regular Holter monitoring and 46 patients had a greater than moderate degree of tricuspid or mitral valve regurgitation. We also excluded patients with a history of AF/AFL (n = 19) or AT (n = 16). We thus enrolled a total of 427 patients; 123 were males (28.8%) and the median age was 37.0 (interquartile range [IQR]: 18.3–49.0)

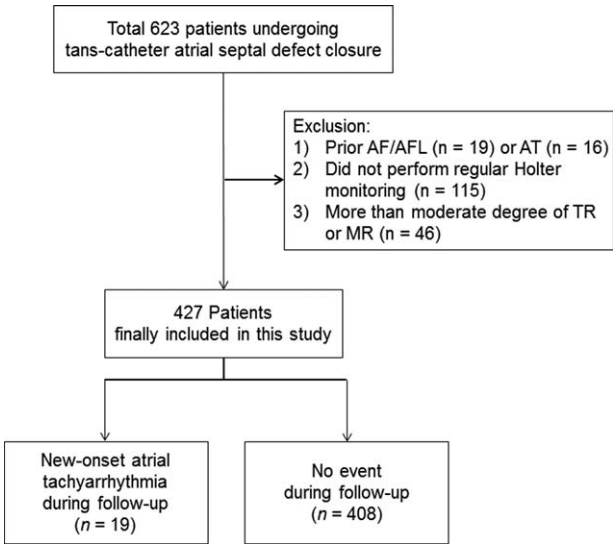

Figure 1. Study flow and occurrence of atrial arrhythmia after trans-catheter closure of atrial septal defect. AF/AFL = atrial fibrillation or atrial flutter, AT = atrial tachycardia, TR = tricuspid valve regurgitation, MR = mitral valve regurgitation.

(Fig. 1). The median follow-up duration was 11.4 (IQR: 5.4–24) months. All patients underwent ECG when they visited the outpatient clinic during the follow-up period. Events defined as new-onset atrial tachyarrhythmia were documented in 19 (4.4%) patients. Among the patients who did not have documented tachyarrhythmia events, 23 (5.6%) patients and 24 (5.9%) patients complained of palpitation and chest discomfort, respectively. They were evaluated with an additional 24 hours of Holter monitoring, but ultimately there was no definitive evidence of atrial tachyarrhythmia.

3.1. Baseline clinical characteristics and procedural findings

Baseline clinical characteristics and procedural findings of study patients are shown in Tables 1 and 2, respectively. There were 283 (66.3%) patients with right atrial enlargement and 421 (98.6%) patients with right ventricular dilatation. Left atrial enlargement was documented in 107 (25.1%) patients. The median ASD size measured by balloon occlusive diameter was 20.0 mm (IQR: 17.0–24.0), and the median device size was 22.0 (IQR: 17.3–26.0) mm. The median size discrepancy between ASD and device was 1.0 (IQR: 0.3–2.5) mm. Deficient anterior rim and posterior rim were reported in 365 (85.5%) and 39 (9.1%) patients, respectively. Based on cardiac catheterization, Qp/Qs >2.0 was reported in 300 (70.3%) patients and pulmonary hypertension was documented in 28 (6.6%) patients. A total of 11 (2.6%) patients experienced atrial tachyarrhythmia (either atrial fibrillation or atrial flutter) during closure. The median procedure time was 47 minutes (IQR: 35.0–71.5). A total of 377 (88.3%) patients underwent follow-up echocardiography after closure. Twelve (3.2%) patients were reported to have residual shunt, but the amount was minimal in all cases. Two patients experienced immediate cardiac tamponade after the procedure that resolved after pericardiocentesis, and 1 patient had device migration found during the 3rd month follow-up. None of the patients who reported postprocedural complications

Table 1

Baseline clinical characteristics.

	Total (n = 427)
Male	123 (28.8)
Age at closure, y	37.0 (18.3–49.0)
Height, cm	160.2 (156.0–167.0)
Weight, kg	58.4 (52.0–67.4)
BMI, kg/m^2	22.7 (20.8–25.0)
Hypertension	49 (11.5)
Diabetes mellitus	17 (4.0)
Dyslipidemia	45 (10.5)
Cerebrovascular accident	26 (6.1)
Dyspnea	55 (12.9)
Palpitations	69 (16.2)
Chest discomfort	79 (18.5)
NT-proBNP, pg/mL	59.1 (33.5–106.4)

Values are presented as median (interquartile range) or n (%).
BMI = body mass index, NT-proBNP = N-terminal pro-brain type natriuretic peptide.

Table 2

Baseline echocardiographic, electrocardiographic, cardiac catheterization data and findings during atrial septal defect closure.

	Total (n = 427)
Echocardiographic date	
Size of RV, mm*	45.0 (42.0–50.0)
Size of RA, mm*	46.0 (43.0–48.3)
Volume of LA, mL/m^2†	35.3 (32.1–39.0)
Size of defect, TEE, mm	18.0 (14.0–21.0)
Anterosuperior rim, mm	4.0 (2.5–6.6)
Anteroinferior rim, mm	11.3 (5.3–15.0)
Posterosuperior rim, mm	12.0 (9.0–15.1)
Posteroinferior rim, mm	13.0 (10.0–16.9)
Deficient anterosuperior rim	268 (62.8)
Deficient anteroinferior rim	97 (22.7)
Deficient posterosuperior rim	20 (4.7)
Deficient posteroinferior rim	19 (4.4)
Multiple ASD	19 (4.4)
Electrocardiographic date	
P wave duration in lead II, ms	100 (80–100)
P wave amplitude in lead II, mV	0.12 (0.10–0.18)
P wave duration in V_1, ms	60 (40–80)
P wave amplitude in V_1, mV	0.10 (0.06–0.10)
Biphasic P wave in V_1	365 (85.5)
RSR′ pattern in V_1 or V_2	126 (29.5)
RBBB	32 (7.5)
Cardiac catheterization	
Qp/Qs	2.4 (2.0–3.1)
Mean RAP, mm Hg	5.0 (3.0–6.0)
Mean PAP, mm Hg	17.0 (15.0–20.0)
Procedure time, min	47.0 (35.0–71.5)
Findings during ASD closure	
Size of defect, BOD, mm	20.0 (17.0–24.0)
Size of device, mm	22.0 (17.3–26.0)
Balloon-assisted technique	40 (9.4)
Atrial fibrillation/flutter	11 (2.6)
Residual shunt‡	12 (3.2)

Values are presented as median (interquartile range) or n (%).
ASD = indicates atrial septal defect, BOD = balloon occlusive diameter, LA = left atrium, PAP = pulmonary artery pressure, *Qp/Qs* = pulmonary-systemic flow ratio, RA = right atrium, RAP = right atrial pressure, RBBB = right bundle branch block, RV = right ventricle, TEE = trans-esophageal echocardiography.
* Size was measured in the apical 4-chamber view.
† Volume was measured from the apical 4-chamber and 2-chamber, using an area-length method.
‡ Measured by transthoracic echocardiography after closure in 377 patients.

Table 3

Risk assessment for new-onset atrial tachyarrhythmia after trans-catheter atrial septal defect closure.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Male	2.26	0.92–5.55	0.08	–	–	–
Age ≥48 years at closure	3.30	1.30–8.38	0.01	3.30*	1.30–8.38	0.01
Hypertension	2.83	1.02–7.87	0.048	–	–	–
RV dilatation	3.00	0.42–21.09	0.28	3.00†	0.42–21.09	0.28
RA enlargement	38.26	0.02–NA	0.48	–	–	–
LA enlargement	2.18	0.59–8.06	0.24	2.18†	0.59–8.06	0.24
Mean PAP >25 mm Hg	2.46	0.56–10.76	0.23	2.51†	0.56–11.35	0.23
Deficient anterosuperior rim	4.32	0.53–35.12	0.17	4.97†	0.61–40.52	0.14
Deficient anteroinferior rim	2.94	0.89–9.64	0.08	–	–	–
Deficient posterosuperior rim	0.05	0.00–NA	0.66	–	–	–
Deficient posteroinferior rim	5.35	1.16–24.79	0.03	5.48†	1.15–25.72	0.04
AF/AFL during closure	8.67	2.52–29.78	<0.001	9.90†	2.86–34.20	<0.001
Procedure time ≥75 min	1.95	0.72–5.30	0.19	2.73†	0.95–7.88	0.06

Values are presented as n (%). Multivariate analysis was performed with a stepwise backward selection process.

AF/AFL = indicates atrial fibrillation or atrial flutter, CI = confidence interval, HR = hazard ratio, LA = left atrium, NA = not applicable, PAP = pulmonary artery pressure, RA = right atrium, RV = right ventricle.

* Hazard ratio adjusted for sex.

† Hazard ratio adjusted for sex and age at closure.

had new-onset atrial tachyarrhythmia during the follow-up period.

3.2. Atrial tachyarrhythmia after closure during the follow-up period

A total of 19 patients experienced new-onset atrial tachyarrhythmia after closure and most events were initially documented within 6 months. Among them, 7 (36.8%) patients had persistent atrial tachyarrhythmia and 12 (61.2%) patients had paroxysmal atrial tachyarrhythmia. Among the 11 patients who experienced AF/AFL during the procedure, 3 (27.3%) patients experienced new-onset atrial tachyarrhythmia after closure. Among the other 416 patients who maintained sinus rhythm during the procedure, atrial tachyarrhythmia after closure developed in 16 (3.8%) patients. Compared with patients with consistent sinus rhythm during closure, atrial tachyarrhythmia was reported more frequently in patients with transient AF/AFL during closure ($P < 0.001$).

3.3. Risk prediction for early-onset atrial tachyarrhythmia after closure

All measured variables were included in risk prediction models for the occurrence of atrial tachyarrhythmia after ASD closure. In univariate analysis, age over 48 years at closure (area under the curve: 0.64, sensitivity: 63.2%, specificity 67.4%, $P = 0.04$), hypertension, deficient posteroinferior rim, and AF/AFL during closure were significantly associated with an increased risk of atrial tachyarrhythmia (Table 3). After multiple adjustments for sex and age, the risk for atrial tachyarrhythmia was consistently significant in patients with AF/AFL during closure (hazard ratio [HR]: 9.90, 95% confidence interval [CI]: 2.86–34.20; $P < 0.001$) and deficient posteroinferior rim (HR: 5.48, 95% CI: 1.15–25.72; $P = 0.04$). The procedure time was not associated with atrial tachyarrhythmia occurrence after ASD closure in this analysis. Kaplan–Meier curves for new-onset atrial tachyarrhythmia after ASD closure according to each risk are shown in Fig. 2. Event-free survival was significantly lower in patients with AF/AFL during closure ($P < 0.001$), age <48 years ($P = 0.01$), and those without deficient posteroinferior rim ($P = 0.02$).

4. Discussion

We investigated the risk factors for new-onset atrial tachyarrhythmia after trans-catheter ASD closure. In this study, 19 (4.4%) patients developed new atrial tachyarrhythmia during the follow-up period. The incidence of new-onset atrial tachyar-

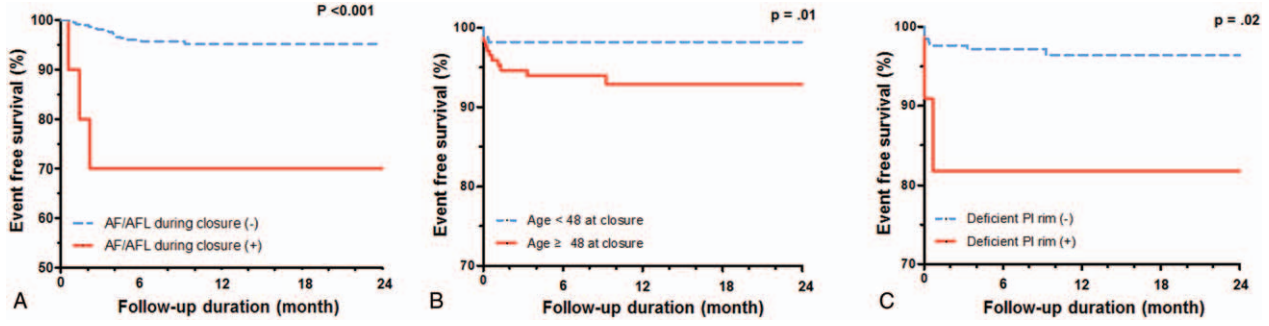

Figure 2. Event-free survival curves for new-onset atrial arrhythmia after trans-catheter closure of atrial septal defect during the follow-up period. Comparison of survival curves between (A) patients with AF/AFL during closure and those without AF/AFL during closure, (B) patient age <48 years at closure and ≥48 years at closure, (C) patients with and without deficient PI rim. AF/AFL = atrial fibrillation or atrial flutter, PI = posteroinferior.

rhythmia was significantly higher in patients with AF/AFL than in those without AF/AFL during closure. In addition to age over 48 years, a deficient posteroinferior rim was also significantly associated with new-onset atrial tachyarrhythmia in the early postprocedure period.

AF is commonly encountered in clinical practice, and it is generally accepted that most causes of AF are attributed to LA condition.[20–22] The occurrence of AF in patients with uncorrected ASD is estimated to be 20%, and the prevalence of atrial arrhythmia increases with age and mean pulmonary arterial pressure.[7,17,20,21] Long-standing volume overload due to left-to-right shunts causes enlargement of the right atrium. Even many years after correction, this may result in conduction disturbances in the atrial myocardium.[22–26] According to Morton et al[27], chronic right atrial stretch causes electrical remodeling with modest increases in the right atrial effective refractory period, and the right atrial remodeling persists after ASD closure and contributes to long-term atrial arrhythmia. Roberts-Thomson et al[28] also reported that ASDs are associated with chronic left atrial stretch, resulting in remodeling characterized by LA enlargement, loss of myocardium, and electrical scarring, which produce widespread conduction abnormalities, but do not lead to changes or increases in the effective refractory period. These abnormalities were associated with a greater propensity for sustained AF. However, an early ASD closure might lead to atrial reverse remodeling and the prevention of new-onset atrial fibrillation, much like positive cardiac resynchronization therapy response has a favorable role in the prevention of atrial fibrillation.[25,26] Atrial tachyarrhythmia, especially AF or AFL, is an independent predictor for recurrent ischemic neurologic events after ASD device closure.[29] Therefore, predictors of the development of atrial tachyarrhythmia after successful ASD closure would be very useful. In this study, the incidence of new-onset atrial tachyarrhythmia was significantly higher in patients with AF/AFL than in those without AF/AFL during closure. Although the exact mechanism of early postoperative atrial tachyarrhythmia in patients undergoing ASD closure with an occlusion device remains unclear, mechanical irritation by the device can account for the development of some arrhythmias.[30,31] Residual shunt and postintervention inflammation may also contribute to new-onset atrial tachyarrhythmia.[32] However, there is a paucity of information on the transient development of arrhythmias during ASD device closure, as well as on their associated role in new-onset atrial tachyarrhythmia after closure.

In this study, age over 48 years was an important risk factor for the development of atrial tachyarrhythmia. Furthermore, a deficient posteroinferior rim before ASD closure was also associated with the occurrence of atrial tachyarrhythmia after closure. There have been reports that a deficient anterior rim is associated with atrial tachyarrhythmia after device closure in patients with ≥25-mm ASD.[33] However, in this study, posteroinferior rim deficiency was a predictor for the development of atrial tachyarrhythmia in patients with a median 20-mm ASD. We could not explain exactly why this rim deficiency caused the development of new-onset atrial tachyarrhythmia. It might be related to the difficulty of implanting an ASD device of this type because it requires more manipulation and causes irritation of the atrium. However, the comparison of procedural time between groups did not support this hypothesis. The induction of atrial arrhythmia after mechanical irritation during the procedure may be related to changes in the myocardium due to long-standing volume overload. Also, implanted devices in ASD with rim deficiency start to have direct contact with the atrial wall at the area of rim deficiency and get even more deep contact along with reverse remodeling of both atrium. The above changes may be related to early-onset atrial arrhythmia. Although we did not measure RA volume, the progression of RA remodeling might affect the development of atrial tachyarrhythmia. We should not ignore the incidental development of AF/AFL during the ASD closure procedure, an important risk factor for new-onset atrial tachyarrhythmia, which may lead to cerebrovascular events. In patients with AF/AFL during ASD closure, we suggest that the clinician consider more intensive monitoring such as regular Holter and ECG monitoring to detect occurrence of atrial tachyarrhythmias and prevent further cerebrovascular events, especially during the first 6 months after closure. Furthermore, more active antithrombotic therapy should be considered in these patients with high thromboembolic risk. Although the incidence of atrial tachyarrhythmia in this study was lower than that of other studies, the findings in this study may support the implementation of management plans for patients with atrial tachyarrhythmia during ASD closure that will prevent further adverse clinical outcomes. The physiologic and pathologic basis for the noted differences associated with the occurrence of atrial AF/AFL during device closure warrant further prospective study.

4.1. Limitations

First, as a retrospective study, there may have been a selection bias in study enrollment. Second, the incidence of atrial tachyarrhythmia in this study was lower than that observed in previous studies. It is possible to underestimate the occurrence of atrial tachyarrhythmia in patients who are symptomatic, but who have normal ECG and Holter monitoring. Furthermore, even frequent Holter ECG monitoring cannot detect substantial percentages of paroxysmal AF/AFL, especially in asymptomatic patients. We also suggest that the younger age of the patients enrolled in this study may be a factor influencing the incidence of atrial arrhythmias. Third, echocardiographic changes such as atrial remodeling and reverse remodeling after ASD closure may be predictors of late arrhythmic events. However, because not all patients undergo echocardiographic follow-up at our center, serial echocardiographic changes could not be examined.

5. Conclusions

Transient AF/AFL during trans-catheter ASD device closure, age over 48 years, and a deficient posteroinferior rim were associated with an increased risk of atrial tachyarrhythmia after closure. These results suggest that, in patients who develop arrhythmias during ASD device closure, close follow-up is required for early detection of atrial tachyarrhythmia. Furthermore, clinicians should consider management that will address stroke prevention in these patients.

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