Master of Medicine

Comparison of outcomes between transcatheter versus surgical closure of atrial septal defect in patients with significant tricuspid regurgitation

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Comparison of outcomes between transcatheter versus surgical closure of atrial septal defect in patients with significant tricuspid regurgitation

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Comparison of outcomes between transcatheter versus surgical closure of atrial septal defect in patients with significant tricuspid regurgitation

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ABSTRACT

Background: The volume overload of right ventricle due to left to right shunt in atrial septal defect (ASD) patients causes functional tricuspid regurgitation (TR). Transcatheter ASD closure using device has been established as an effective treatment. However, clinical outcomes of patients with ASD and significant TR after this procedure has not been elucidated as compared with surgical treatment.

Methods: A total of 252 consecutive adult patients who showed a significant (moderate or more) TR before ASD closure were retrospectively enrolled. ASD device closure or surgical tricuspid annuloplasty (TAP) along with ASD closure were performed in 68 and 184 patients, respectively. The severity of TR and clinical events were followed up. The primary endpoint was a composite of any cause of death, stroke, and heart failure. The secondary endpoint was a remnant significant TR at 1 year after ASD closure.

Results: A significant TR remained in 81 (32%) out of 252 patients in immediately after ASD closure and in 52 (29%) out of 182 patients after 1 year. The severity of TR was significantly decreased after transcatheter ASD closure. In multivariable analysis, TAP and ASD diameter were independent predictors of the remnant significant TR immediately after treatment, while only TAP was the predictor after 1 year follow-up. After propensity score matching between two groups, there was no significant difference between the two groups in primary composite clinical outcomes during a median follow-up of 3.4 years.

Conclusions: TAP is effective for the treatment of significant TR, but transcatheter ASD closure also reduces TR. Transcatheter ASD closure showed comparable clinical outcomes to surgical closure and TAP in patients with moderate and severe TR, and therefore can be a reasonable treatment option.

Key words: Atrial septal defect, tricuspid regurgitation, device closure, tricuspid annuloplasty

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Introduction

Atrial septal defect (ASD) of secundum-type is a common congenital heart disease in adult.[1] Functional tricuspid regurgitation (TR) is frequently observed in ASD patients because of the volume overload of right ventricle (RV). Long standing left to right interatrial shunts in ASD patients causes RV dilatation and consequently results in dilatation of the tricuspid annulus, papillary muscle displacement and tethering of tricuspid leaflets, which are the main geometric mechanism of functional TR development.[2-4] Transcatheter ASD closure has become the first treatment choice for secundum ASD closure, when feasible.[5, 6] When comparing surgical and transcatheter closure in isolated ASD patients, most studies have shown no significant differences in clinical outcomes.[7-9] However, there is no evidence-based guidelines for the treatment of ASD patients who also show significant TR. AHA/ACC guidelines describe that tricuspid valve repair may improve RV remodeling, when there is moderate or greater TR in patients who undergo surgical ASD closure.[6] Some studies have suggested that transcatheter ASD closure can be valuable in patients with ASD complicated with TR, because the percutaneous procedure alone resulted in TR severity reduction in many patients.[10-14] On the other hand, 22% – 56% of patients reportedly showed remnant significant TR after this procedure. These results constitute clinical dilemma when treatment strategy is determined for patients with ASD and significant TR. However, there has been no study comparing transcatheter ASD closure alone and surgical treatment including ASD closure and TAP. Therefore, this study aimed to evaluate the changes in TR and clinical outcomes between patients with ASD and significant functional TR who have been treated with transcatheter ASD device closure or surgical ASD closure and TAP.

Methods

Patient population

A total of 252 consecutive adult secundum ASD patients more than 18 years old (mean age, 53.8 ± 13.8 years, 180 females) who showed a significant (moderate or more) secondary TR before ASD closure from June 2000 to January 2020 were retrospectively enrolled. Among a total of 252 patients, 68 patients underwent transcatheter ASD device closure (transcatheter closure group) and 184 patients underwent surgical ASD closure with TAP (surgical closure group), which constitute two groups of this study. The exclusion criteria for the study were as follows: (1) primary TR, (2) significant other valvular diseases, (3) absence of baseline echocardiographic images. The Institutional Review Board of our hospital approved this study protocol, and patients' informed consent was waived because of the retrospective nature of this study using general clinical practice. Our investigations were carried out in accordance with the Declaration of Helsinki.

Clinical and echocardiographic data

The baseline clinical and echocardiographic characteristics were reviewed from medical records. Baseline characteristics included age, gender, underlying comorbidities, heart rhythm, The New York Heart Association (NYHA) functional status and medication history.

All patients included in this study underwent 2-dimensional and Doppler transthoracic echocardiography (TTE) before and immediately after interventions. Immediate post-intervention echocardiography was performed on the average of 1 day after transcatheter ASD closure and 4 days after surgical ASD closure and TAP. Among a total of 252 patients, 182 patients underwent echocardiographic studies 1 year (range: 6 months - 2 years) after ASD closure.

ASD maximal diameter was measured using transesophageal echocardiography (TEE). The left ventricular (LV) volume and ejection fraction were determined using the modified Simpson's method from the apical views. Left atrial (LA) volume were measured using the same method at end-systole. RV systolic function was comprehensively assessed using fractional area change, tricuspid annular plane systolic excursion and tricuspid annular systolic motion velocity. The severity of TR was assessed comprehensively as recommended by ACC/AHA and ESC/EACTS guidelines and previous reports, and classified into mild, moderate, severe, massive, and torrential mainly by use of vena contract width (VCW).[15-18] A remnant TR after ASD closure was defined as moderate or more TR. Using the TR velocity determined by continuous wave Doppler echocardiography, the pulmonary artery systolic pressure was assessed using the modified Bernoulli equation by adding the right atrial pressure estimated from the size and respiratory collapse of the inferior vena cava.

Transcatheter and surgical ASD closure

Transcatheter ASD device closure was performed under general anesthesia and intra-procedure TEE for guidance. The occlusion devices used were Amplatzer (Abbott, USA) or Figulla Flex II (Occlutech, Switzerland) ASD occluders. The occluder size was selected according to the ASD diameters measured using 3-dimensional TEE.[19] When the device was implanted, its position and stability were assessed by fluoroscopy and TEE.

Surgical ASD closure was executed through a median sternotomy or minimally invasive incision under general anesthesia and cardiopulmonary bypass. Either direct closure or pericardial patch reconstruction of ASD was chosen by the anatomy as well as surgeon's preference. Among 184 patients who underwent surgical ASD closure, ring annuloplasty, De Vega method, and Kay method were used for TAP in 94 (51.1%), 81 (44.0%), and 9 (4.9%), respectively. Of the 94 patients who underwent ring annuloplasty, 4 patients received a Carpentier-Edwards ring (Edwards Lifesciences, Irvine, CA, USA), 69 patients received a

MC3 annuloplasty ring (Edwards Lifesciences), 19 patients received a Duran rings (Medtronic, Minneapolis, MN, USA) and 2 patients received a Tri-ad ring (Medtronic, Minneapolis, MN, USA). The surgical result was evaluated immediately by intraoperative TEE.

Outcomes

The primary outcome of the study was a composite of death from any cause, stroke, or re-hospitalization for heart failure. The secondary endpoint was a remnant significant TR at immediately after and 1 year after ASD closures. All stroke events were confirmed by trained neurologists or stroke specialists.

Statistical analysis

Continuous variables, which are presented as means with standard deviations, were compared using Student's t-test or Wilcoxon rank-sum test depending on their distribution. Categorical and ordinal variables, which are presented as frequencies and percentages, were compared using $\chi 2$ or Fisher's exact test, as appropriate.

To determine independent predictors for a significant remnant TR after procedures, univariate logistic regression analysis was performed. Subsequently, variables with p values <0.10 by univariate analyses were then included in a multivariate model.

The event-free survival rate was estimated by Kaplan-Meier analysis, and the difference was compared by the log-rank test. Multivariate Cox regression analysis using whole population was performed to identify the predictors for clinical events. To minimize the bias from the differences in baseline characteristics observed between the two groups, patients with moderate and severe TR in transcatheter and surgical ASD groups were matched by 1:2 ratio using the propensity score method. The covariates for calculating propensity score included age, sex, underlying comorbidities, such as atrial fibrillation, coronary artery disease,

hypertension, diabetes, pulmonary disease as well as echocardiographic finding including ASD diameter, TR grade and systolic pulmonary artery pressure.

All reported P values are two-sided, and a P value <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

Results

Baseline Patient Characteristics

Baseline patient characteristics are summarized in **Table 1**. There was no difference in gender, NYHA functional class, medication history between the two groups. Patients in transcathter group were older than those in surgical closure group. Regarding to the past comorbidities, transcatheter closure group showed higher prevalence of hypertension and previous cerebrovascular accident as compared with surgical closure group. When it comes to baselines echocardiographic characteristics, surgical closure group showed a larger ASD defect size, LA size, and a higher systolic pulmonary artery pressure and mitral E/e' ratio compared to transcatheter group. There were also significant differences in the TR VCW and TR grades, and the TR severity was higher in surgical closure group. A massive (14 patients) or torrential (1 patient) TR was presented only in surgical closure groups.

Tricuspid regurgitation before and after ASD closure

The severity of TR significantly decreased in immediate post-procedure echocardiography in patients of both groups (**Figure 1**). In immediate post-procedure echocardiography, the severity of TR decreased to mild in 10 patients (15%) while 58 patients (85%) showed a remnant significant TR after transcatheter closure. However, the proportion of severe TR was decreased from 40% to 19%. Of the 184 patients who underwent surgery, the grade of TR

reduced to mild in 161 (88%) patients in early postoperative echocardiography performed before discharge. Only 23 patients (13%) had persistent significant TR in this group.

When the change of TR after ASD closure was evaluated in 182 patients who underwent TTE examination around 1 year later the closure, the severity of TR decreased gradually and consistently until 1 year in transcatheter closure group, while TR was markedly decreased mainly immediately after surgery (**Figure 2**). A significant TR decreased from 100% to 65% in transcatheter closure group, while it decreased to 11% in surgical closure group after 1 year.

Predictors of significant remnant TR

Of 252 patients, 81 (32%) patients showed a significant remnant TR in early after ASD closure. Univariate analysis indicated that the early significant remnant TR was associated with patients' age, atrial fibrillation, RV diastolic dimension, mitral E/E', severe TR or more TR before closure, ASD maximal diameter, systolic pulmonary artery pressure before ASD closure, and TAP **(Table 2)**. In multivariate logistic analysis performed using these variables, TAP and ASD diameter were independent predictors.

In TTE examination performed around 1 year later ASD closure, 58 (31%) out of 182 patients showed a remnant significant TR. When the predictor of a remnant significant TR was evaluated using multivariable analysis, only TAP appeared to be independent predictor (**Table 3**).

Clinical outcomes in patients with moderate or severe TR

The predictors associated clinical events (death of any cause, stroke and re-hospitalization for heart failure) were evaluated in whole population. Multivariable cox regression analysis revealed that patients' age, initial NYHA functional class, cerebrovascular accident history, and baseline left ventricular ejection fraction were independently associated with clinical events, but TAP was not (**Table 4**).

There were significant differences in baseline characteristics between transcatheter and surgical ASD groups, especially in comorbidity and the severity of TR. The patients with massive or torrential TR underwent only surgery, while no such patients underwent transcatheter ASD closure. For appropriate adjustment of differences in baseline characteristics, only 237 patients with moderate and severe TR were included in propensity score matching **(Table 5)**. Among them, 68 patients underwent transcatheter closure while 169 patients underwent surgical closure. After propensity score matching by 1:2 ratio, 53 patients in transcatheter group and 84 patients in surgical closure group were included in propensity score-matched population. The median follow-up period was 3.4 years (interquartile range: 1.6-7.0 years). Event rates in both groups for up to 10 years are shown in the **Table 6**, and there were no differences between both groups. The Kaplan-Meier curves of primary composite outcomes in unmatched and propensity score-matched populations are presented in **Figure 3.** In unmatched population, there was no significant difference between the two groups in the freedom from death of any cause, stroke and re-hospitalization for heart failure (hazard ratio of surgical closure group compared to transcatheter group, 0.79 (95% confidence interval, 0.28, 2.18), p=0.643). In propensity score-matched population, there was no significant difference between the two groups in the freedom from death of any cause, stroke and re-hospitalization for heart failure (hazard ratio of surgical closure group compared to transcatheter group, 1.07 (95% confidence interval, 0.24, 4.75), p=0.932).

Table 1. Differences in baseline characteristics between patients underwent transcatheter ASD closure and surgical ASD closure with TAP

Characteristics	Overall (N = 252)	Treatment option		p-value[1]
		Transcatheter closure (N=68)	Surgical closure (N=184)	
Age	53.8 ± 13.8	58.7 ± 14.6	51.9 ± 13.1	0.001
Gender, n (%)				1.000
female	180 (71%)	49 (72%)	131 (71%)	
male	72 (29%)	19 (28%)	53 (29%)	
NYHA, n (%)				0.169
1	99 (39%)	34 (50%)	65 (35%)	
2	104 (41%)	25 (37%)	79 (43%)	
3	39 (15%)	7 (10%)	32 (17%)	
4	10 (4.0%)	2 (2.9%)	8 (4.3%)	
Medical history				
Atrial fibrillation, n (%)	84 (33%)	18 (26%)	66 (36%)	0.210
Hypertension, n (%)	58 (23%)	26 (38%)	32 (17%)	<0.001
DM, n (%)	20 (7.9%)	8 (12%)	12 (6.5%)	0.269
Coronary artery disease, n (%)	13 (5.2%)	3 (4.4%)	10 (5.4%)	>0.9
Pulmonary disease, n (%)	12 (4.8%)	4 (5.9%)	8 (4.3%)	0.861
Cerebrovascular accident, n (%)	9 (3.6%)	7 (10%)	2 (1.1%)	0.002
Medication history				
Diuretics use, n (%)	76 (30%)	17 (25%)	59 (32%)	0.352
Antiplatelet drug use, n (%)	53 (21%)	19 (28%)	34 (18%)	0.144
Anticoagulation use, n (%)	40 (16%)	11 (16%)	29 (16%)	1.000

Echocardiography finding				
ASD maximal diameter (mm)	27.1 ± 10.5	20.2 ± 5.7	29.6 ± 10.8	<0.001
LA_size(mm)	43.6 ± 8.1	40.5 ± 6.9	44.7 ± 8.3	<0.001
LV EF	61.4 ± 7.3	60.6 ± 7.3	61.7 ± 7.	0.303
RV dysfunction, n (%)	55 (22%)	10 (15%)	45 (25%)	0.131
TR_vena contracta width (mm)	7.8 ± 3.1	6.7 ± 1.6	8.2 ± 3.4	<0.001
TR_grade, n (%)				0.053
moderate	127 (50%)	41 (60%)	86 (47%)	
severe	110 (44%)	27 (40%)	83 (45%)	
massive	14 (5.6%)	0 (0%)	14 (7.6%)	
torrential	1 (0.4%)	0 (0%)	1 (0.5%)	
Systolic PAP (mmHg)	49.0 ± 17.9	42.5 ± 12.4	51.5 ± 19.0	<0.001
Mitral E/E’	10.6 ± 6.4	9.3 ± 3.4	11.2 ± 7.4	0.01

[1] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

ASD, atrial septal defect; DM, diabetic mellitus; EF, ejection fraction; LA, left atrium; LV, left ventricular; NYHA, New York Heart Association; PAP, pulmonary artery pressure; RV, right ventricle; TR, tricuspid regurgitation.

Table 2. Predictors of significant remnant TR in echocardiography immediately after ASD closure

Variables	Univariate analysis		Multivariate analysis	
	OR	**p value**	**OR (95% CI)**	**p value**
Age	**1.08**	**<0.001**	1.03 (0.98-1.09)	0.3
Gender - Male	1.65	0.18		
Atrial fibrillation	**3.17**	**0.002**	2.22 (0.55-9.61)	0.3
LA diameter, mm	1.00	0.983		
RV diastolic dimension, mm	**0.94**	**0.044**	1.02(0.91-1.14)	0.6
RV systolic dimension, mm	0.85	0.143		
RV dysfunction	0.98	0.963		
Mitral E/E'	**0.89**	**0.064**	0.95 (0.77-1.05)	0.6
Baseline TR ≥ Severe	**2.08**	**0.048**	2.05 (0.62-6.92)	0.2
Systolic PAP, mmHg	**0.97**	**0.043**	0.98 (0.93-1.03)	0.5
ASD maximal diameter, mm	**0.92**	**<0.001**	**0.90 (0.82-0.99)**	**0.040**
TAP	**0.09**	**< 0.001**	**0.07 (0.77-1.05)**	**<0.001**
Maze procedure	0.76	0.531		

Variables with p values <0.1 were then inserted in a multivariate model.

ASD, atrial septal defect; CI, confidence interval; LA, left atrial; OR, odds ratio; PAP, pulmonary artery pressure; RV, right ventricular; TAP, tricuspid annuloplasty; TR, tricuspid regurgitation.

Table 3. Predictors of significant remnant TR one year after ASD closure

Variables	Univariate analysis		Multivariate analysis	
	OR	**p value**	**OR (95% CI)**	**p value**
Age	1.02	0.120		
Gender - Male	0.89	0.763		
Atrial fibrillation	1.39	0.364		
LA diameter, mm	0.98	0.376		
RV diastolic dimension, mm	**0.94**	**0.056**	1.08 (0.97-1.22)	0.2
RV systolic dimension, mm	0.92	0.240		
RV dysfunction	0.84	0.667		
Mitral E/E'	0.96	0.321		
Baseline TR ≥ Severe TR	0.78	0.482		
Systolic PAP, mmHg	0.99	0.284		
ASD maximal diameter, mm	**0.96**	**0.016**	0.94 (0.86-1.01)	0.10
TAP	**0.06**	**< 0.001**	**0.08 (0.02-0.24)**	**<0.001**
Maze procedure	0.51	0.124		

Variables with p values <0.1 were then inserted in a multivariate model.

ASD, atrial septal defect; CI, confidence interval; LA, left atrial; OR, odds ratio; PAP, pulmonary artery pressure; RV, right ventricular; TAP, tricuspid annuloplasty; TR, tricuspid regurgitation.

Table 4. Predictors of clinical events in patients with moderate and severe TR

Risk factors	Univariate analysis		Multivariate analysis	
	HR	p value	HR (95% CI)	p value
Age	**1.07**	**<0.001**	**1.05 (1.01-1.10)**	**0.009**
Gender, male	1.16	0.716		
NYHA functional class	**2.09**	**<0.001**	**1.84 (1.19-2.83)**	**0.006**
Medical history				
Atrial fibrillation	**3.33**	**0.001**	0.86 (0.30-2.50)	0.8
Hypertension	1.82	0.134		
DM	**5.59**	**<0.001**	2.67 (0.95-7.49)	0.062
Coronary artery disease	1.18	0.818		
Pulmonary disease	**5.81**	**<0.001**	1.69 (0.54-5.34)	0.4
Cerebrovascular accident history	**5.43**	**0.007**	**9.22 (2.34-36.4)**	**0.002**
Procedure				
TAP	0.79	0.645		
Maze procedure	**2.50**	**0.009**	1.12 (0.39-3.23)	0.8
Echocardiography finding				
ASD maximal diameter (mm)	1.01	0.448		
LA size(mm)	1.08	**0.002**	1.00 (0.94-1.07)	>0.9
LV EF	0.96	**0.095**	**0.95 (0.91-1.00)**	**0.036**
RV dysfunction	1.07	0.867		
Baseline Severe TR	0.94	0.842		

Systolic PAP (mmHg)	1.00	0.913
E/E’	1.01	0.742

Median follow-up duration: 3.4 years (IQR, 1.6-7.0)

ASD, atrial septal defect; CI, confidence interval; DM, diabetic mellitus; EF, ejection fraction; ; HR, hazard ratio; LA, left atrium; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricle; PAP, pulmonary artery pressure; TAP, tricuspid annuloplasty; TR, tricuspid regurgitation.

Table 5. Balance assessment between the unmatched and matched samples.

Variables	level	Unmatched sample				PS-matched sample		
		Transcatheter closure (N=68)	**Surgical closure (N=169)**	SMD	P	**Transcatheter closure (N=53)**	**Surgical closure (N=84)**	SMD
Age (mean (SD))		58.71 (14.55)	51.24 (13.08)	0.539	<0.001	56.23 (14.02)	54.82 (12.02)	0.108
Sex (%)	female	49 (72.1)	122 (72.2)	0.003	0.984	40 (75.5)	63 (75.0)	0.011
	male	19 (27.9)	47 (27.8)			13 (24.5)	21 (25.0)	
Atrial fibrillation (%)	0	50 (73.5)	113 (66.9)	0.146	0.317	41 (77.4)	62 (73.8)	0.083
	1	18 (26.5)	56 (33.1)			12 (22.6)	22 (26.2)	
Hypertension (%)	0	42 (61.8)	142 (84.0)	0.517	<0.001	40 (75.5)	66 (78.6)	0.074
	1	26 (38.2)	27 (16.0)			13 (24.5)	18 (21.4)	
DM (%)	0	60 (88.2)	158 (93.5)	0.183	0.178	48 (90.6)	78 (92.9)	0.083
	1	8 (11.8)	11 (6.5)			5 (9.4)	6 (7.1)	
Coronary artery disease (%)	0	65 (95.6)	160 (94.7)	0.042	1	50 (94.3)	79 (94.0)	0.012
	1	3 (4.4)	9 (5.3)			3 (5.7)	5 (6.0)	
Pulmonary disease (%)	0	64 (94.1)	161 (95.3)	0.051	0.747	51 (96.2)	80 (95.2)	0.049
	1	4 (5.9)	8 (4.7)			2 (3.8)	4 (4.8)	
RV dysfunction (%)	0	58 (85.3)	128 (75.7)	0.243	0.105	46 (86.8)	72 (85.7)	0.031
	1	10 (14.7)	41 (24.3)			7 (13.2)	12 (14.3)	
ASD diameter (mean (SD))		20.25 (5.72)	29.42 (10.81)	1.06	<0.001	21.64 (5.42)	22.29 (6.24)	0.11
TR_jet_area (mean (SD))		11.69 (3.96)	13.24 (5.38)	0.328	0.049	11.85 (4.26)	12.25 (4.64)	0.09
TR grade (%) [1]	moderate	41 (60.3)	86 (50.9)	0.19	0.189	31 (58.5)	49 (58.3)	0.003

	severe	27 (39.7)	83 (49.1)			22 (41.5)	35 (41.7)	
Systolic PAP (mean (SD))		42.55 (12.40)	51.30 (19.11)	0.543	0.001	43.72 (12.42)	43.98 (14.17)	0.019

*For continuous variables, t-test or Wilcoxon-rank sum test was used, and mean (SD) was reported.

*For categorical variables, Chi-squre test or Fisher's exact test was used, and n (%) was reported.

1:2 Greedy nearest neighbor matching without replacement within specified caliper widths.

[1] The grade of TR on the basis of the tricuspid regurgitation vena contracta width.

ASD, atrial septal defect; DM, diabetic mellitus; EF, ejection fraction; HR, hazard ratio; LA, left atrium; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricle; PAP, pulmonary artery pressure; PS, propensity score; SD, standard deviation; SMD, standardized difference; TAP, tricuspid annuloplasty; TR, tricuspid regurgitation.

Table 6. Event frequencies and Kaplan-Meier estimates of clinical outcomes

Events	Follow-up period	Unmatched sample				PS-matched sample			
		Overall (n=237)	**Transcatheter closure (n=68)**	**Surgical closure (n=169)**	**P***	**Overall (n=137)**	**Transcatheter closure (n=53)**	**Surgical closure (n=84)**	**P****
Composite outcomes	5-year	18 (10.9%)	5 (13.6%)	13 (10.2%)	0.540	6 (6.5%)	2 (10.3%)	4 (5.5%)	0.963
	10-year	30 (30.6%)	5 (13.6%)	25 (30.3%)	0.643	11 (31.1%)	2 (10.3%)	9 (30.8%)	0.932
Admission for HF	5-year	19 (10.0%)	4 (7.6%)	15 (10.6%)	0.647	5 (4.7%)	2 (4.1%)	3 (4.7%)	0.744
	10-year	21 (13.5%)	4 (7.6%)	17 (14.3%)	0.623	6 (8.1%)	2 (4.1%)	4 (8.4%)	0.813
Stroke	5-year	4 (1.9%)	1 (1.5%)	3 (2.0%)	0.933	2 (1.9%)	0 (0.0%)	2 (2.9%)	NA
	10-year	4 (1.9%)	1 (1.5%)	3 (2.0%)	0.933	2 (1.9%)	0 (0.0%)	2 (2.9%)	NA
Death	5-year	8 (4.4%)	2 (3.1%)	6 (4.5%)	0.958	3 (2.5%)	0 (0.0%)	3 (4.0%)	NA
	10-year	14 (16.1%)	2 (3.1%)	12 (16.3%)	0.994	5 (15.6%)	0 (0.0%)	5 (16.9%)	NA

*Log-rank test was used. **Wald-test with robust variance estimation was used. HF, heart failure; PS, propensity score.

Figure 1. The changes of tricuspid regurgitation severity immediate after closure in the patients who underwent transcatheter ASD closure using device and the patients who underwent surgical ASD closure and TAP.

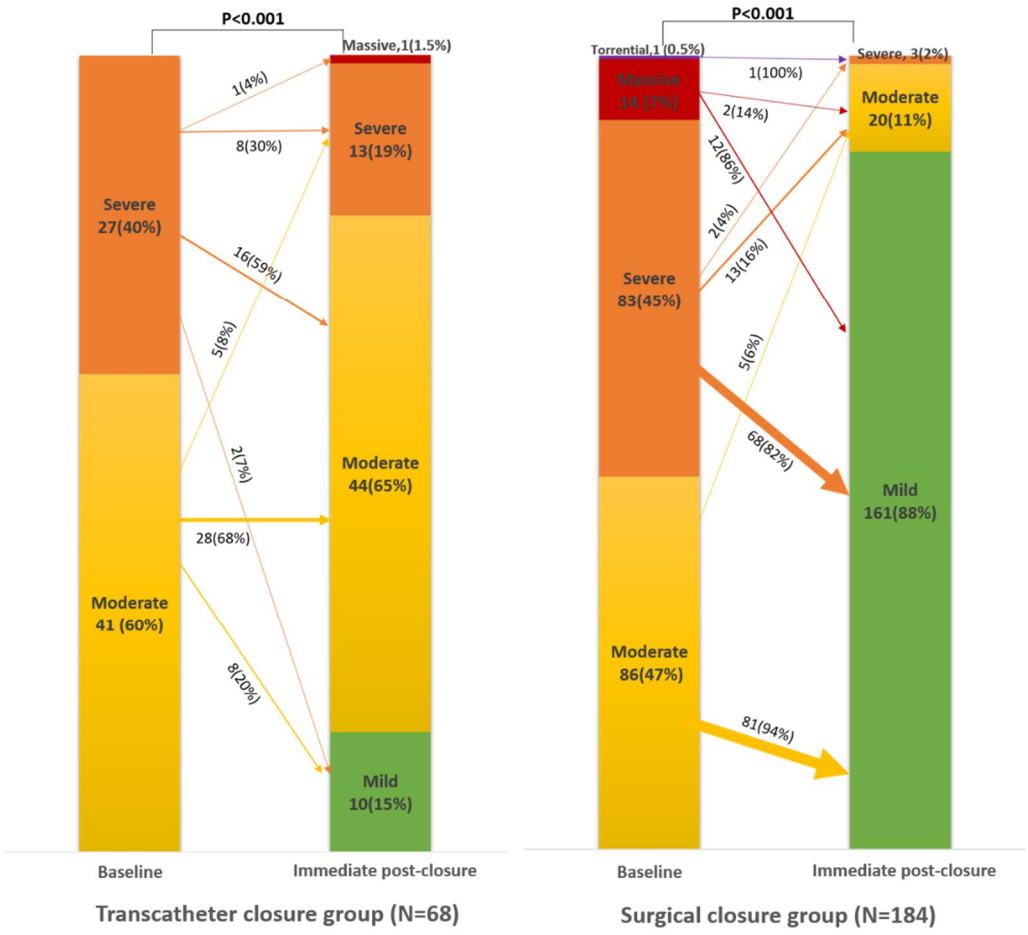


Figure 2. The changes of tricuspid regurgitation severity during 1 year after ASD closure in the patients who underwent transcatheter ASD closure using device and the patients who underwent surgical ASD closure and TAP.

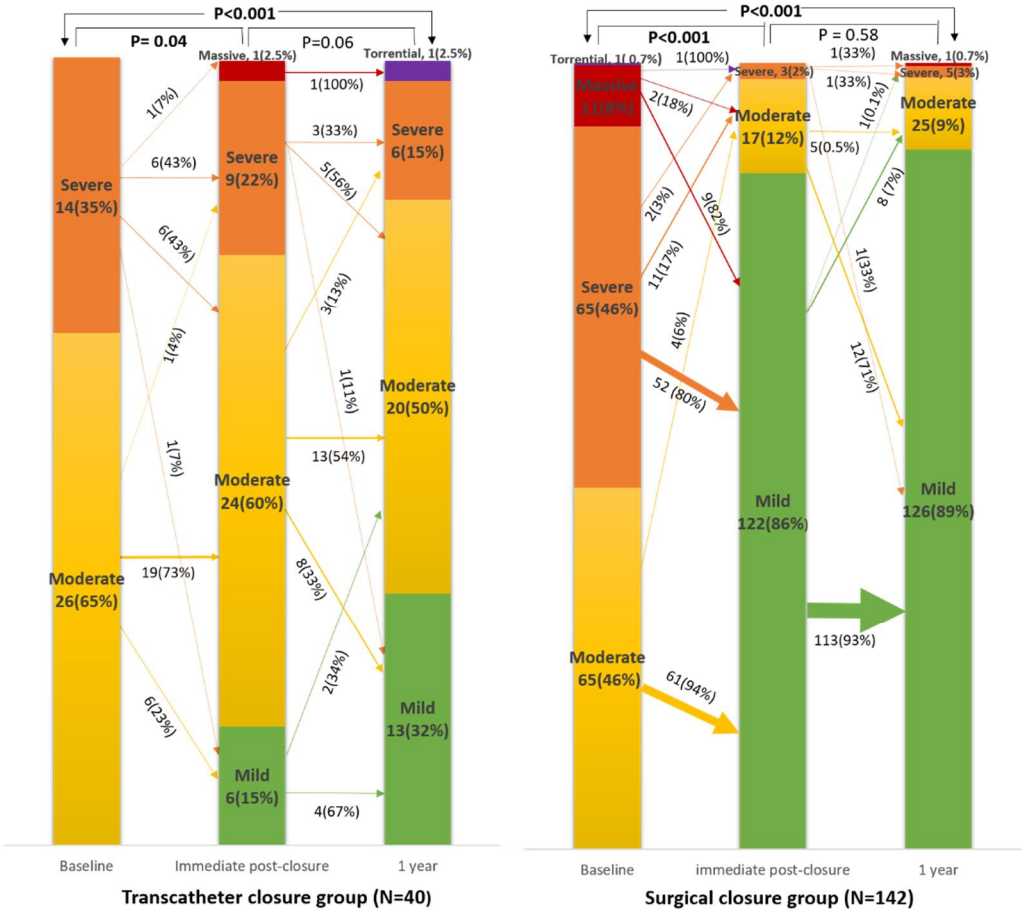
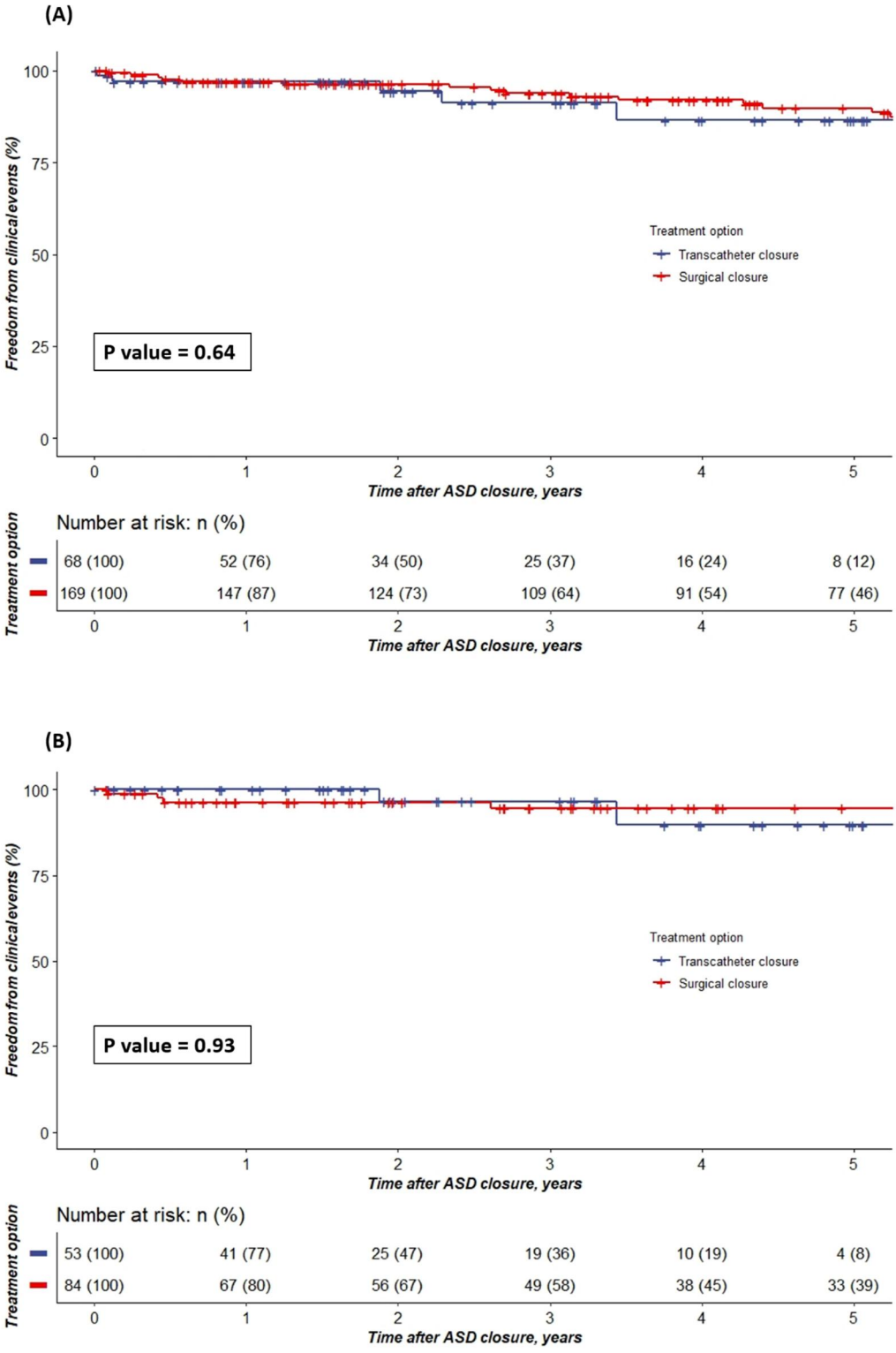


Figure 3. Kaplan-Meier curves for composite clinical events in patients with moderate and severe TR. (A) unmatched population, (B) propensity score-matched population.



Discussion

In this study, we evaluate the changes in TR and clinical outcomes between patients with ASD and significant functional TR who have been treated with transcatheter ASD device closure or surgical ASD closure and TAP. The main findings of our study can be summarized as follows. First, the severities of TR decreased significantly compared to those before ASD closure in both transcatheter and surgical closure groups. Second, TAP was the main independent factor associated with eliminating significant TR. Third, there was no significant difference in clinical events between the two groups composed of moderate and severe TR before ASD closure.

Long standing left to right interatrial shunts in adult patients with ASD can cause RV dilatation, resulting in functional TR. Functional TR independently predicts cardiovascular morbidity and mortality, especially if it is moderate and severe.[20-22] Therefore, it is important to decide whether corrective TAP should be performed in the treatment of ASD patient with significant TR. It was reported that significant TR can be reduced after transcatheter ASD closure or surgical closure without TAP.[10-14] However, it should be also noted that 22% – 56% of patients showed remnant significant TR after ASD closure alone. TAP is indicated and can be performed when the ASD patients with significant TR undergo surgery. Transcatheter ASD closure, which can also reduce TR, has become the first treatment choice for secundum ASD closure, when feasible.[5, 6] Therefore, it is remained as a clinical dilemma to choose treatment strategy for such patients, but to our knowledge, there has been no report comparing clinical and echocardiographic outcomes between those two treatment options.

We found that TAP can dramatically eliminate a significant TR immediately after surgery, while transcatheter ASD closure was found to reduce TR gradually until 1 year after ASD closure. In our population, the patients with massive and torrential TR underwent only surgical

treatment, and this must be attributed to attending physicians' discretion that those TRs could not be reduce to less than moderate degree after ASD closure alone.

Some previous studies reported that predictors of the remnant significant TR after ASD closure alone in patients with moderate and severe TR were pulmonary artery systolic pressure or persistent atrial fibrillation.[10, 11, 13, 14] In our current study, those variables appeared to be associated with the remnant significant TR in univariate analyses, but only TAP and ASD maximal diameter were found to be independent predictors after multivariate analysis. This differences must be ascribed to the difference of study population. We included all patients who underwent transcatheter closure and surgical closure along with TAP, while previous report only included the patients who underwent ASD closure alone. Therefore, TAP is certainly a powerful tool for reduction of significant TR, compared to pulmonary hypertension or atrial fibrillation. Interestingly, we found that ASD maximal diameter was negatively associated with remnant significant TR. We cannot explain this result clearly with our data, but it might be conceivable that RV volume overload is larger in patients with larger ASD and it can be more substantially reduced after ASD closure resulting in a greater reduction of TR.

Despite a definite effect of TAP in reducing TR, we could not find a significant difference in clinical outcome between the two groups among the patients with moderate and severe TR during the median follow-up of 3.4 years. No difference was found even after propensity score matching between the two groups. For this analysis, we did not include the patients with massive or torrential TR who were only found in surgical closure group. It might be reasonable to think that lack of difference in clinical outcomes is at least in part attributed to the long-term spontaneous reduction of TR after ASD closure alone, resulted from RV reverse remodeling. Therefore, our data suggest that transcatheter ASD closure alone can be a reasonable treatment option for patients with moderate and severe TR.

Our study has several limitations. First, this is a retrospective single-center cohort study with inherent limitations. Baseline characteristics of the two groups were different in many

variables, a complete adjustment of them might not be possible, although we performed propensity score matching. Due to a relatively small patient number, we could not completely exclude the possibility that clinical outcomes might be different between the two groups if more patients were included. However, no difference between the two groups in clinical outcomes were corroborated by our multivariate analysis including whole population and showing that TAP was not independent predictor of clinical events. After all, this study may represent an important step forward to a prospective study involving larger population. Second, the patients with massive or torrential TR underwent only surgical ASD closure and TAP, then as a consequence our data could not compare clinical outcomes of these patients of the two groups. We only noticed that physicians recommend surgery for those patients in real world practice.

Conclusion

TAP is effective for the treatment of significant TR, but transcatheter ASD closure also reduces TR. Transcatheter ASD closure showed comparable clinical outcomes to surgical closure and TAP in patients with moderate and severe TR, and therefore can be a reasonable treatment option.

References

1. Hoffman JI, Kaplan S and Liberthson RR. Prevalence of congenital heart disease. *Am Heart J*. 2004;147:425-39.

2. Pascotto M, Caso P, Santoro G, Caso I, Cerrato F, Pisacane C, D'Andrea A, Severino S, Russo MG and Calabrò R. Analysis of right ventricular Doppler tissue imaging and load dependence in patients undergoing percutaneous closure of atrial septal defect. *Am J Cardiol*. 2004;94:1202-5.

3. Fukuda S, Gillinov AM, Song JM, Daimon M, Kongsaerepong V, Thomas JD and Shiota T. Echocardiographic insights into atrial and ventricular mechanisms of functional tricuspid regurgitation. *Am Heart J*. 2006;152:1208-14.

4. Spinner EM, Shannon P, Buice D, Jimenez JH, Veledar E, Del Nido PJ, Adams DH and Yoganathan AP. In vitro characterization of the mechanisms responsible for functional tricuspid regurgitation. *Circulation*. 2011;124:920-9.

5. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, Lung B, Kluin J, Lang IM, Meijboom F, Moons P, Mulder BJM, Oechslin E, Roos-Hesselink JW, Schwerzmann M, Sondergaard L and Zeppenfeld K. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;42:563-645.

6. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, Crumb SR, Dearani JA, Fuller S, Gurvitz M, Khairy P, Landzberg MJ, Saidi A, Valente AM and Van Hare GF. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:e81-e192.

7. Butera G, Carminati M, Chessa M, Youssef R, Drago M, Giamberti A, Pomè G, Bossone E and Frigiola A. Percutaneous versus surgical closure of secundum atrial septal defect: comparison of early results and complications. *Am Heart J*. 2006;151:228-34.

8. Kutty S, Hazeem AA, Brown K, Danford CJ, Worley SE, Delaney JW, Danford DA and Latson LA. Long-term (5- to 20-year) outcomes after transcatheter or surgical treatment of hemodynamically significant isolated secundum atrial septal defect. *Am J Cardiol*. 2012;109:1348-52.

9. Kotowycz MA, Therrien J, Ionescu-Ittu R, Owens CG, Pilote L, Martucci G, Tchervenkov C and Marelli AJ. Long-term outcomes after surgical versus transcatheter closure of atrial septal defects in adults. *JACC Cardiovasc Interv*. 2013;6:497-503.

10. Takaya Y, Akagi T, Kijima Y, Nakagawa K and Ito H. Functional Tricuspid Regurgitation After Transcatheter Closure of Atrial Septal Defect in Adult Patients: Long-Term Follow-Up. *JACC Cardiovasc Interv*. 2017;10:2211-2218.

11. Toyono M, Krasuski RA, Pettersson GB, Matsumura Y, Yamano T and Shiota T. Persistent tricuspid regurgitation and its predictor in adults after percutaneous and isolated surgical closure of secundum atrial septal defect. *Am J Cardiol*. 2009;104:856-61.

12. Fang F, Wang J, Yip GW and Lam YY. Predictors of mid-term functional tricuspid regurgitation after device closure of atrial septal defect in adults: Impact of pre-operative tricuspid valve remodeling. *Int J Cardiol*. 2015;187:447-52.

13. Chen L, Shen J, Shan X, Wang F, Kan T, Tang X, Zhao X and Qin Y. Improvement of tricuspid regurgitation after transcatheter ASD closure in older patients. *Herz*. 2018;43:529-534.

14. Nassif M, van der Kley F, Abdelghani M, Kalkman DN, de Bruin-Bon R, Bouma BJ, Schalij MJ, Koolbergen DR, Tijssen JGP, Mulder BJM and de Winter RJ. Predictors of residual tricuspid regurgitation after percutaneous closure of atrial septal defect. *Eur Heart J Cardiovasc Imaging*. 2019;20:225-232.

15. Writing Committee M, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM, 3rd, Thompson A, Toly C, Members AAJC, O'Gara PT, Beckman JA, Levine GN, Al-

Khatib SM, Armbruster A, Birtcher KK, Ciggaroa J, Deswal A, Dixon DL, Fleisher LA, de Las Fuentes L, Gentile F, Goldberger ZD, Gorenek B, Haynes N, Hernandez AF, Hlatky MA, Joglar JA, Jones WS, Marine JE, Mark D, Palaniappan L, Piano MR, Spatz ES, Tamis-Holland J, Wijeysundera DN and Woo YJ. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Thorac Cardiovasc Surg*. 2021;162:e183-e353.

16. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Juni P, Pierard L, Prendergast BD, Sadaba JR, Tribouilloy C, Wojakowski W, Group EESD and Group ESCSD. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2021.

17. Hahn RT and Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging*. 2017;18:1342-1343.

18. Miura M, Alessandrini H, Alkhodair A, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter J, Himbert D, Ho E, Juliard JM, Kaple R, Besler C, Kodali S, Kreidel F, Kuck KH, Latib A, Lauten A, Monivas V, Mehr M, Muntane-Carol G, Nazif T, Nickenig G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodes-Cabau J, Schafer U, Schofer J, Sievert H, Tang GHL, Thiele H, Rommel KP, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Maisano F, Hahn RT, Taramasso M and TriValve I. Impact of Massive or Torrential Tricuspid Regurgitation in Patients Undergoing Transcatheter Tricuspid Valve Intervention. *JACC Cardiovasc Interv*. 2020;13:1999-2009.

19. Jang JY, Heo R, Cho MS, Bae J, Hong JA, Lee S, Ahn JM, Park DW, Kim DH, Kang DH, Song JK and Song JM. Efficacy of 3D transoesophageal echocardiography for

transcatheter device closure of atrial septal defect without balloon sizing. *Eur Heart J Cardiovasc Imaging*. 2018;19:684-689.

20. Nath J, Foster E and Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol*. 2004;43:405-9.

21. Bartko PE, Arfsten H, Frey MK, Heitzinger G, Pavo N, Cho A, Neuhold S, Tan TC, Strunk G, Hengstenberg C, Hülsmann M and Goliasch G. Natural History of Functional Tricuspid Regurgitation: Implications of Quantitative Doppler Assessment. *JACC Cardiovasc Imaging*. 2019;12:389-397.

22. Benfari G, Antoine C, Miller WL, Thapa P, Topilsky Y, Rossi A, Michelena HI, Pislaru S and Enriquez-Sarano M. Excess Mortality Associated With Functional Tricuspid Regurgitation Complicating Heart Failure With Reduced Ejection Fraction. *Circulation*. 2019;140:196-206.

국문요약

연구 배경: 심방중격결손 환자에게서 좌우단락으로 인한 우심실의 용적과부하는 기능적 삼첨판 역류를 유발한다. 심방중격결손 환자에서 기구를 이용한 경피적 심방중격폐쇄술은 효과적인 치료법으로 확립되었지만 유의한 삼첨판 역류가 동반된 심방중격결손 환자의 이 시술 후 임상 결과는 수술적 치료와 비교하여 명확하게 밝혀지지 않았다.

방법: 심방중격결손 폐쇄 전 중등도 이상의 유의한 삼첨판 역류를 동반한 252 명의 성인 환자가 후향적으로 등록 되었다. 경피적 심방중격결손 폐쇄술을 받은 환자가 68 명이었고 수술적 심방중격결손 폐쇄와 삼첨판륜 성형술을 함께 받은 환자가 184 명이었다. 삼첨판 역류의 중증도와 임상적 사건 발생을 추적하였다. 일차적 종말점은 모든 원인에 의한 사망, 뇌졸중의 발생 그리고 심부전이었으며 이차적 종말점은 심방중격결손 폐쇄 후 1 년 뒤 중등도 이상의 유의한 잔여 삼첨판 역류였다.

결과: 유의한 삼첨판 역류는 심방중격결손 폐쇄 직후에 252 명의 환자 중 81 명(32%) 에서, 1 년 추적 검사에서 182 명 환자 중 52 명(29%) 에서 남아 있었다. 삼첨판 역류의 중증도는 경피적 심방중격결손 폐쇄술 후에도 유의하게 감소하였다. 다변량 분석에서 심방중격결손 크기와 삼첨판륜 성형술이 치료 직후 유의한 잔여 삼첨판 역류의 독립적인 예측 변수였으나, 삼첨판륜 성형술만이 1 년 추적 심초음파에서에서 유의한 잔여 삼첨판 역류의 예측 변수였다. 두 그룹 간의 성향 점수 매칭 후 3.4 년의 중간 추적 기간 동안, 두 그룹 사이에 일차적 종말점에서는 유의미한 차이가 없었다.

결론: 삼첨판륜 성형술은 삼첨판 역류의 치료에 효과적이지만, 경피적 심방중격결손 폐쇄도 삼첨판 역류를 감소 시킨다. 중등도, 중증의 삼첨판 역류를 가진 환자에게서 경피적 심방중격결손 폐쇄는 삼첨판륜 성형술을 동반한 수술적 폐쇄와 유사한 임상 결과를 보여, 합리적인 치료 옵션으로 생각된다.

줌심 단어: 심방중격결손, 삼첨판 역류, 경피적 폐쇄술. 삼첨판륜 성형술