

Evolution of Tricuspid Regurgitation after Mitral Valve Surgery for Patients with Moderate-or-Less Functional Tricuspid Regurgitation

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ABSTRACT

Objectives: The purpose of this study was to evaluate the impact of moderate-or-less functional tricuspid regurgitation (TR) treatment on the clinical outcome of patients with mitral valve (MV) surgery.

Methods: From October 2001 to January 2005, 167 patients in our hospital with MV surgery and without organic tricuspid valve (TV) disease or pulmonary hypertension (PH) showed moderate-or-less functional TR preoperatively, and 41.9% of these patients were treated with TR (group T), compared with 58.1% untreated with TR (group no-T). According to tricuspid annulus dimension (TAD)/body surface area (BSA), these 167 patients were further divided into another 2 groups (A and B): group A (70 patients) represented TAD/BSA \leq 21 mm/m² with 32 patients from group T and 38 from group no-T, and group B (97 patients) represented TAD/BSA $>$ 21 mm/m² with 38 patients from group T and 59 patients from group no-T. There was no statistical difference in preoperative and operative variables between the 2 groups. Meanwhile, among the 167 patients with MV surgery, 157 patients were replaced with MV and 10 patients were repaired with MV, and De Vega technique was constantly used for TR treatment. All the results were estimated by multivariate analysis.

Results: The median follow-up time was 63 months (25th and 75th percentiles are 53 and 94 months, respectively); 30-day mortality was 3% (1.4% in group T versus 4.1% in group no-T; $P = .31$). Adjusted 5-year survival was 70.7% (66.6%-80.4%) with 85.3% (83.0%-93.4%) in group T and 64.7% (33.7%-58.3%) in group no-T, $P = .001$. Among the 70 patients with TAD/BSA \leq 21 mm/m², patients who received treatment of moderate-or-less TR and those who did not showed similar secondary TR grade at postoperative period (0.5 ± 0.6 in group T versus 0.9 ± 0.9 in group no-T;

$P = .02$) and follow-up (1.3 ± 1.1 in group T versus 1.8 ± 1.1 in group no-T; $P = .06$). In subgroup B (TAD/BSA $>$ 21 mm/m²), patients who received tricuspid valvoplasty manifested more significantly improved outcome than patients without functional TR at postoperative period (0.8 ± 0.8 in group T versus 1.6 ± 1.3 in group no-T; $P = .03$) and follow-up (2.0 ± 1.2 in group T versus 3.0 ± 1.1 in group no-T; $P = .005$). The multivariate analysis identified TAD/BSA $>$ 21 mm/m² and preoperative atrial fibrillation (AF) as the risk factors for lower survival at follow-up period.

Conclusions: Patients with MV surgery have better mid-term outcome when they receive either more aggressive and effective surgical treatment for functional TR or moderate-or-less TR preoperatively. Indexed TAD (TAD/BSA $>$ 21 mm/m²) is a more reliable surgical guideline for the treatment of TR. Preoperative tricuspid annulus dilation and AF might be predictors of late lower survival.

INTRODUCTION

It is well known that functional tricuspid regurgitation (FTR) can be defined as the incompetence of the tricuspid valve (TV) without any organic leaflet disease, usually associated with mitral valve (MV) disease [Fukuda 2006; Wang 2008; Shiran 2009]. For many years, it has been a challenging problem to determine whether functional TR accompanied by MV disease, especially moderate-or-less preoperative TR, needs surgical treatment. Usually, functional TR probably gradually disappears when patients receive MV treatment because MV treatment can decrease the right ventricular pressure and reduce volume overload [Guenther 2008]. However, a lot of patients with functional TR still face serious consequences after receiving MV treatment.

Recently, various research on the natural history of uncorrected TR has demonstrated that patients with FTR need surgical treatment [Matsuyama 2003; Matsunaga 2005], but a guide for this kind of surgical treatment is still unknown. Colombo et al reported that patients who received functional TR treatment could have better effective clinical outcome and late functional improvement when their indexed tricuspid annulus dimension (TAD) was greater than 21 mm/m² [Colombo 2001]. Nevertheless, some other studies determined, in spite of pulmonary hypertension (PH) or low

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ejection fraction, that patients with moderate-or-greater TR need the TV treatment [Koelling 2002; Nath 2004; de Bonis 2008].

Now it is generally accepted that patients with severe TR and MV disease need surgical treatment for TR during the cardiac operation [Calafiore 2009], but surgical treatment for moderate-or-less preoperative FTR is still on debate. The present study was to evaluate the impact of treatment of moderate-or-less functional TR on clinical outcome of patients who underwent MV surgery.

MATERIALS AND METHODS

Population

From October 2001 to January 2005, 167 patients who underwent MV surgery in our hospital showed moderate-or-less functional TR, and they were divided into 2 groups according to odd or even numbers of their admission numbers (70 in TR treatment group named group T and 97 in group no-T). Meanwhile, moderate-or-less functional TR was defined by TR grade ≤ 2 and diagnosed by preoperative transthoracic echocardiography (TTE). So, patients with organic TV disease and preoperative pulmonary hypertension (PH) were excluded. PH was defined with a systolic pulmonary arterial pressure (PAP) more than 40 mmHg. Groups T and no-T were further divided into 2 subgroups: subgroup A with TAD/BSA ≤ 21 mm/m² contained 32 patients (45.7%) from group T and 38 patients (39.2%) from group no-T, and subgroup B with TAD/BSA > 21 mm/m² contained 38 patients (54.3%) from group T and 59 patients (60.8%) from group no-T. Differences between the 2 groups were displayed in Table 1.

Echocardiographic Measurements

Preoperative routine transthoracic echocardiography (TTE) was performed by the same operator. Methods used to estimate TR grade and left ventricular ejection fraction (LVEF) have been already reported. The severity of TR was graded as mild, 1+/4+ (jet area/right atrial area $< 10\%$); moderate, 2+/4+ (jet area/right atrial area $10\% - 20\%$); moderately severe, 3+/4+ (jet area/right atrial area $20\% - 33\%$); and severe, 4+/4+ (jet area/right atrial area $> 33\%$) [Zoghbi 2003; Ton-Nu 2006]. The tricuspid annulus diameter was measured in the apical 4-chamber view in late diastole at the time of maximal tricuspid opening. Functional TR was defined as the absence of significant tethering of tricuspid leaflets evaluated by TTE, which have been already reported. Pulmonary pressure was calculated from the TR velocity measured with Doppler echocardiography by the modified Bernoulli equation. PH was defined as a systolic PAP of more than 40 mmHg. Transesophageal echocardiography (TEE) was repeated in the operating room if MV repair was performed, and serial TTEs were then performed at hospital discharge and yearly intervals after surgery.

Surgery

All patients were operated on through median sternotomy with standard cardiopulmonary bypass on normothermia.

Table 1. Preoperative and Operative Patient Characteristics

Variable	Group T (n = 70)	Group no-T (n = 97)	P
Age, y	61.2 \pm 10.7	59.1 \pm 8.4	.425
Female sex	15 (21.4%)	30 (30.9%)	.172
Atrial fibrillation	27 (38.6%)	39 (40.2%)	.831
Tricuspid annulus dimension (TAD), mm	33.3 \pm 3.8	30.9 \pm 4.1	.329
Body surface area (BSA), m ²	1.55 \pm 0.16	1.57 \pm 0.12	.846
TAD/BSA ≤ 21 , mm/m ²	32 (45.7%)	38 (39.2%)	.398
TAD/BSA > 21 , mm/m ²	38 (54.3%)	59 (60.8%)	
New York Heart Association class	3.0 \pm 0.7	2.8 \pm 0.6	.412
Diabetes	8 (1.4%)	19 (19.6%)	.158
Left atrial dimension, mm	58.4 \pm 15.6	53.7 \pm 16.1	.345
Ejection fraction	42.4 \pm 1.1	40.5 \pm 13.9	.416
Tricuspid regurgitation grade			
None or 1+	58	83	.634
2+	12	14	
Mitral valve (MV) surgery			
Replacement	65	92	.593
Repair	5	5	
Pulmonary artery pressure, mmHg	39.6 \pm 7.6	38.9 \pm 6.9	.510
MV disease			
Stenosis	16	18	.768
Regurgitation	21	29	
Mixed	33	50	
Etiology of the MV disease			
Rheumatic	47	67	.263
Degenerative	18	28	
Congenital	5	2	

Myocardial protection was achieved with intermittent antegrade cold blood cardioplegia. In general, we tended to use MV replacement (157 patients; 94%) rather than MV repair (10 patients; 6%) in patients with MV lesions. The right atrium and atrial septum were routinely opened to explore the MV. The MV repair device included edge-to-edge technique (3 patients; 30%) and repair with an undersized annuloplasty ring (7 patients; 70%). The success of surgical correction in terms of MV repair was assessed by means of intraoperative TEE. TV repair was always performed by means of the classic De Vega technique. In our study, the tricuspid orifice was tightened until it could contain 3 fingers snugly.

Postoperative Course and Follow-Up

After surgery, all patients were admitted to the intensive care unit (ICU) and from there moved to cardiology wards. Follow-up started in March 2010 and ended in June 2010, and it was 100% completed. All patients were followed up

at 1, 3, and 6 months after surgery in our clinical visit, and thereafter all echocardiographic studies were carried out at yearly intervals by a skilled echocardiography technician. The more recent information was obtained by calling the patients or the referring cardiologists. Median follow-up time was 63 months (25th and 75th percentiles, 53 to 94 months); 79 months (25th and 75th percentiles, 68 to 111 months) in group T and 61 months (25th and 75th percentiles, 52 to 87 months) in group no-T ($P = .187$).

Statistical Analysis

Results are expressed as mean \pm SD or percentages in case of normally distributed continuous variables and as median and IQR in case of non-normally distributed continuous variables. Unpaired 2-tailed Student's *t* tests (for normally distributed continuous variables), Mann-Whitney U-test (for non-normally distributed continuous variables) and Pearson χ^2 test or Fisher's exact test (for categorical variables) were used to determine statistical significance. The log-rank test was used to evaluate differences between groups. Five-year survival curves were obtained with the Kaplan–Meier method, and the results were reported as percentage and 95% confidence interval (CI); variation of TR grade across 2 periods (preoperative, postoperative, and follow-up) was evaluated by means of Wilcoxon test. Cox analysis was undertaken to assess which clinical and echocardiographic parameters were independently associated with potential risk factors of 5-year survival, and the results were reported as hazard ratio (HR), 95% CI, and *P* value. All data were analyzed with SPSS 12.0 (SPSS Inc., Chicago, IL, USA). Results were considered significant if *P* values were less than .05.

The institutional ethics committee approved this study, and we had signed formal consent with each patient before the study.

RESULTS

General Features

There were no operative deaths. MV replacement was undergone in 157 patients (94%), the majority of whom used mechanical prostheses, especially bileaflet tilting discs (St. Jude bileaflet valve [St. Jude Medical, St. Paul, MN, USA] and Carbomedics valve [Carbomedics, Inc., Austin, TX, USA]). Thirty-day mortality was 3% (5 patients), 1.4% (1 patient) in group T versus 4.1% (4 patients; $P = .31$) in group no-T. Three patients died because of low output syndrome, and the other 2 patients died because of arrhythmia and multiorgan failure respectively. Sixty of the 162 survivors died (16 in group T versus 44 in group no-T) in follow-up period; 49 deaths were cardiac-related (12 in group T versus 37 in group no-T). Cardiac-related complications included heart failure in 27 death cases, cerebral hemorrhage or infarction in 13, sudden death in 5, endocarditis in 3, and myocardial infarction in 1. Non-cardiac-related deaths were caused by respiratory failure in 5 patients, multiorgan failure in 3 patients, hemolytic crisis in 2 patients, and sepsis in 1 patient. There were no patients requiring reoperation for significant TR during the follow-up period.

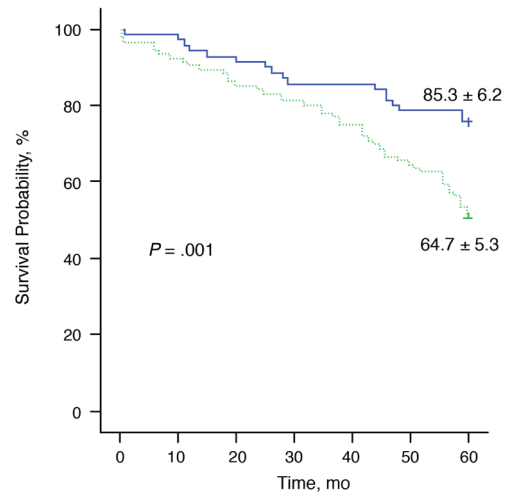


Figure 1. Five-year survival stratified by groups using the Kaplan–Meier method ($P = .001$): Group T (solid line) and Group no-T (dashed line).

At the last follow-up, the mean New York Heart Association (NYHA) class was 1.3 ± 0.4 in group T and 1.8 ± 0.7 in group no-T ($P < .001$) among 102 survivors, with significant difference between the 2 groups. Five-year actuarial survival was 70.7% (66.6%–80.4%): 85.3% (83.0%–93.4%) in group T versus 64.7% (33.7%–58.3%) in group no-T, $P = .001$ (Figure 1). The independent variables as the risk factors for lower survival identified by Cox analysis were TAD/BSA > 21 mm/m² (HR, 1.56; 95% CI, 1.14 to 2.15; $P = .006$) and preoperative AF (HR, 1.41; 95% CI, 1.02 to 1.95; $P = .035$) (Table 2).

Table 2. Risk Factors for 5-Year Survival by Cox Analysis

Variables	Hazard Ratio	95% Confidence Interval	<i>P</i>
Preoperative atrial fibrillation	1.41	1.02 – 1.95	.035
Tricuspid annulus dimension/body surface area > 21 mm/m ²	1.57	1.14 – 2.15	.006

Progression of TR Grade

After a median interval time of 63 months (25th and 75th percentiles, 53 to 94 months), TR grade was assessed by TTE in 102 (63.0%) of 162 patients surviving the first month. In group T (53 patients), TR grade decreased significantly from 0.9 ± 0.6 to 0.6 ± 0.7 ($P = .01$) in the postoperative period, but then increased to 1.6 ± 1.2 at follow-up ($P = .001$); significant differences were found between postoperative and follow-up times ($P < .001$).

In group no-T (49 cases), TR grade increased from 0.8 ± 0.6 to 1.2 ± 1.1 in the early postoperative period ($P = .22$), and increased significantly to 2.3 ± 1.2 ($P < .001$ versus postoperative value; $P < .001$ versus preoperative value). No significant differences were found between pre- and postoperative times.

Table 3. Tricuspid Regurgitation Grade Measured by Transthoracic Echocardiography

TR Grade	Before Surgery		After Surgery		Follow-Up	
	T	no-T	T	no-T	T	no-T
0	1	15	25	17	9	5
1+	35	28	23	15	19	10
2+	7	6	4	1	13	10
3+	0	0	1	4	8	15
4+	0	0	0	2	4	9
Mean tricuspid regurgitation grade	0.9 ± 0.6	0.8 ± 0.6	0.6 ± 0.7	1.2 ± 1.1	1.6 ± 1.2	2.3 ± 1.2
P	.35		.02		.004	

Mean TR grade was significantly higher in group no-T if compared with the corresponding values in group T at both postoperative ($P = .02$) and follow-up ($P = .004$). At follow-up time, 36 (35.3%) patients of 102 patients showed a progression of TR grade to 3 or 4 (22.6%, in group T versus 49.0%, in group no-T; $P = .005$) (Table 3).

Subgroup Analysis According to TAD/BSA

In subgroup A with preoperative TAD/BSA ≤ 21 mm/m², TR grade decreased from 0.8 ± 0.6 to 0.5 ± 0.6 in group T ($P = .08$) and increased from 0.7 ± 0.6 to 0.9 ± 0.9 in group no-T ($P = .67$) at postoperative period, then increased respectively to 1.3 ± 1.0 in group T ($P = .10$) and to 1.8 ± 1.1 in group no-T ($P < .001$) at follow-up; no differences were found with the corresponding mean TR grade values between groups T and no-T at postoperative ($P = .2$) and follow-up times ($P = .06$) (Figure 2).

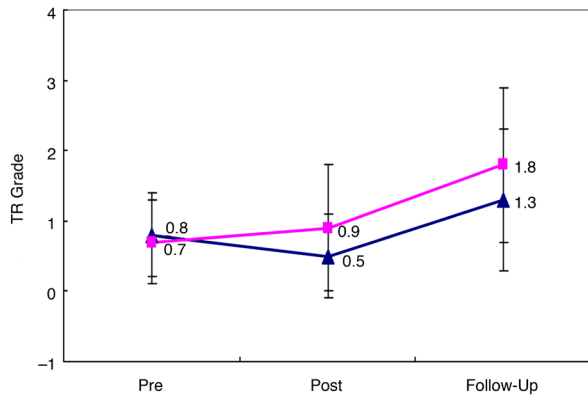


Figure 2. Variation of average tricuspid regurgitation (TR) grade from preoperative to postoperative and follow-up period on patients with tricuspid annulus dimension/body surface area (TAD/BSA) ≤ 21 mm/m²: Group T (triangle) and Group no-T (square). Results are expressed as mean ± standard deviation.

In subgroup B with TAD/BSA > 21 mm/m², TR grade decreased from 1.0 ± 0.5 to 0.8 ± 0.8 in group T ($P = .08$) and increased from 1.0 ± 0.7 to 1.6 ± 1.3 in group no-T ($P = .14$) at postoperative period, then increased significantly to 2.0 ± 1.2 in group T ($P = .002$) and to 3.0 ± 1.1 in group no-T ($P < .001$) at follow-up. Mean TR grade was significantly higher

in group no-T if compared with the corresponding values in group T at both postoperative ($P = .03$) and follow-up periods ($P = .005$) (Figure 3).

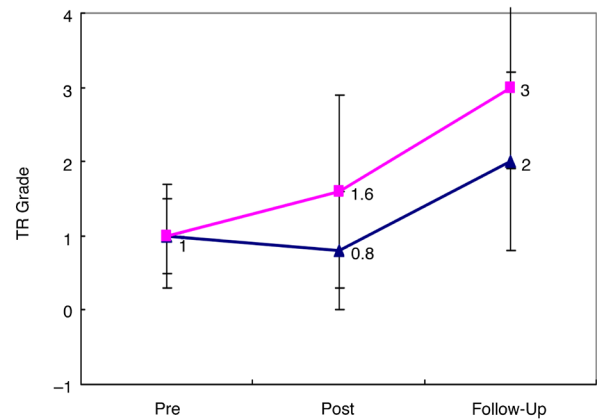


Figure 3. Variation of average tricuspid regurgitation (TR) grade from preoperative to postoperative and follow-up period on patients with tricuspid annulus dimension/body surface area (TAD/BSA) ≤ 21 mm/m²: Group T (triangle) and Group no-T (square). Results are expressed as mean ± standard deviation.

DISCUSSION

Functional TR, incompetence of TV without any structural leaflets, is often correlated with left-side valve diseases such as mitral stenosis and MR [Wang 2008; Shiran 2009]. Surgical treatment for secondary TR caused by left-side heart valve lesions is still under debate. Recently, more and more studies have demonstrated that moderate-or-more TR is clearly associated with both the lower mid- and long-term survival rate and the possibility to be alive in NYHA class I-II. By using echocardiography, Nath et al analyzed the prognostic effect of TR in 5223 patients during the 4 follow-up years [Nath 2004]. Four years later, he found that the survival rate of patients with mild-or-less TR was more than 70%, whereas that of patients with moderate-or-more TR was below 50%. Recently, Calafiore et al reported that after patients with moderate-or-more functional TR underwent MV surgery and TV repair, the rate of patients with follow-up significant functional TR (≥3+) was only 5%, while that of patients without TR treatment was 40% ($P < .001$) [Calafiore 2004]. Therefore, we conclude here that

patients with significant TR (3+ to 4+) should be treated when they received surgical correction of left-sided valve disease [Calafiore 2009; Mauro 2009].

However, moderate-or-less preoperative functional TR is always ignored by doctors because they believe that TR usually regresses consequently after MV surgery. Meanwhile, we cannot assess the severity of TR precisely because there are lots of influential factors including preload, afterload, and right ventricular function, all of which are probably responsible for the results of TR function. Even patients without any TR diseases or with moderate-or-less TR diseases probably have anatomic abnormality for tricuspid orifice, such as TA dilatation, and TA dilatation usually does not lead to significant TR in a relatively short time [Kim 2006]. Matsuyama et al reported that tricuspid dilatation can be objectively measured and is considered as an important indication for surgical treatment of TR [Matsuyama 2003]. Dreyfus et al reported the criterion that tricuspid annular diameter is ≥ 70 mm regardless of the grade of tricuspid regurgitation [Dreyfus 2005]. Although there were no significant differences with hospital mortality and actuarial survival rate between the patients with and without concomitant TV repair, a significant improvement TR grading and NYHA functional class were discovered at postoperative period when TR was treated. These results implied that TV annuloplasty is a safe and effective procedure to avoid functional TR progression. However, the threshold size for tricuspid annuloplasty may seem very conservative, and a further study was required to re-establish a more reasonable threshold size for TV repair to expect better clinical outcome.

In the present study, we analyzed the midterm outcome of tricuspid annuloplasty in patients according to indexed TA dimension, which was advocated by Colombo and his coworkers [Colombo 2001]. They considered that indexed TA dimension ($TAD/BSA > 21$ mm/m²) was a good surgical indication to TV repair. Among 70 patients with $TAD/BSA \leq 21$ mm/m² in our study, 32 patients underwent MV surgery alone and 38 patients underwent MV surgery plus TV annuloplasty. We did not find significant difference with the mean TR grade between the 2 groups at postoperative and follow-up times. But among the other 97 patients with $TAD/BSA > 21$ mm/m², of whom 38 underwent MV surgery alone and 59 underwent MV surgery plus TV annuloplasty, TR grade was significantly higher in patients who underwent MV surgery alone than those who received MV surgery plus TV annuloplasty at both postoperative and follow-up periods. The Cox analysis identified $TAD/BSA > 21$ mm/m² (HR, 1.56; $P = .006$) as the independent predictors of TR progression later after MV surgery. TA dilatation is closely correlated with dilatation of the right ventricle, which is a mark of right ventricular dysfunction. A possible mechanism of late TR includes the increase in postoperative cardiac output, which may increase right ventricular load and prevent the recovery of tricuspid annular dilatation. To our disappointment, 12 patients (4/28 [14.3%] in group T versus 8/25 [32%] in group no-T) showed the progression of TR grade to 3 or 4 at follow-up time despite the fact that tricuspid annuloplasty was performed. In this study, MV replacement

was performed in almost all patients (157/167, 94%) and MV repair was used in the remaining (10/167, 6%). The procedure of MV replacement can reduce the incidence of residual MR effectively and minimize the impact to TR of operative factors. The later negative results of TV repair may be associated with the surgical technique we used. Because of all subjects with moderate-or-less TR only, De Vega technique was always adopted to treat insufficient TV, which may lead to content results recently. Nevertheless the midterm follow-up outcome remains very disappointing. It is very likely that deformation and crimple of tricuspid valve leaflets, induced by De Vega technique, may cause the right ventricle overloading further and result in more TR. Ring implantation as a better choice might be paid more attention to [McCarthy 2004; Tang 2006; Ghanta 2007].

Another independent risk factor for secondary significant TR was preoperative AF confirmed by the Cox analysis in this study (HR, 1.41; $P = .035$). It was well known that chronic AF can induce mechanical remodeling of left atria and enlarge left atrium. Persistent pressure or volume overload of the left ventricle, closely associated with AF, may be transmitted backward passively and lead to increase in right ventricular afterload [Vaturi 2001; Ngaage 2007]. Eventually, right-sided chamber enlarged gradually can contribute to the progression of late TR. In addition, AF has been reported to be associated with right atrial size and directly result in further right atrium dilatation [Alexiou 2007]. Kim et al clearly demonstrated that AF is the only independent factor for late significant TR [Kim 2005]. The MAZE procedure is an ideal surgical method of effectively controlling AF in combination with surgical management of mitral valve disease. The benefit of elimination of AF by MAZE is not only to prevent subsequent complications related to AF, such as heart failure and thromboembolism [Louagie 2009], but also to effectively prevent the development of TR after MV surgery. Despite such advantages, only 2 patients with $TAD/BSA > 21$ mm/m² received MV replacement plus TV annuloplasty and radiofrequency modified MAZE in the present study, and both obtained good clinical outcome and no significant postoperative TR occurred. The reason for so few patients receiving radiofrequency-modified MAZE in our country, where effective health insurance coverage is not accessible to most patients, is that operations are too expensive and most patients, particularly those who undergo MV replacement, cannot afford them. More subjects who underwent MAZE are required to confirm the impact of MAZE procedure on progression of TR late after surgery.

Study Limitations

Although this study is randomized and controlled, there are several limitations that need to be acknowledged. First, the dimension and function of the right ventricle are not provided in this study. Similarly, the relationship between the occurrence of late TR and right ventricular dysfunction are not mentioned here. Second, the measurement used to quantify TR has drawbacks due to the influence of cardiac function and irregular jets on the assessment of TR jet size at the given time. And the third shortcoming is the relatively small sample size in present study.

CONCLUSIONS

The results of this study demonstrate that a more aggressive attitude to deal with accompanying moderate-or-less TR should be accepted at the time of initial MV surgery, especially in patients with TA dilation and preoperative AF. Indexed TAD (TAD/BSA > 21 mm/m²) can be considered as a more reliable surgical guideline than TR grade when functional TR is treated.

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