Original Articles

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Progression of Tricuspid Regurgitation Early After Isolated Mitral Valve Repair

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Objective: Although some parameters have been defined for predicting late-onset tricuspid regurgitation (TR) after mitral valve (MV) repair, few studies have focused on the early TR progression. The aim of this study was to evaluate the changes in unrepaired TR early after isolated MV repair for degenerative MR, and investigate the predictors of TR progression.
Methods: We retrospectively identified 236 patients who underwent isolated MV repair in our institute between 2014 and 2019. Patients with severe preoperative TR, non-degenerative etiology, without echocardiography reports were excluded from the study. Early TR progression was defined as an increase in TR of at least one grade on pre-discharge echocardiography compared to preoperatively. Baseline characteristics were compared between patients with and without early TR progression.
Results: A total of 214 patients were analyzed. Mean age was 59 years and 32.7% were female. At baseline, 77.6% had no TR, 20.6% had mild TR, and 1.9% had moderate TR. At follow-up before discharge, 15.4% (n=33) had TR progression. The TR progression group was older and showed lower body mass index (BMI) than the no-TR progression group. Although not significant, renal function tended to be lower in the TR progression group than in the no-TR progression group. Multivariable analysis revealed higher age and lower BMI as independent predictors of TR progression early after MV repair.
Conclusions: Despite appropriate surgical correction of degenerative MR, progression of TR early after MV repair was observed in 15% of the patients. High age and low BMI were independently associated with TR progression early after MV repair. Further studies are necessary to examine the significance of early TR progression on long-term prognosis after MV repair.

Key words: tricuspid regurgitation (TR), mitral valve (MV) repair, degenerative mitral regurgitation

Introduction

Advanced mitral regurgitation (MR) is often associated with functional tricuspid regurgitation (TR). Historically, TR associated with MR has been managed conservatively, since the pathology was thought to improve after mitral valve (MV) surgery[1)] due to the reduction in right ventricular (RV) afterload. However, more recently, TR was revealed to show no improvement; rather, TR may progress after MV surgery in a substantial portion of patients[2) 3)]. Unoperated TR has been reported to adversely impact survival and functional outcomes in patients with MR who undergo MV surgery[4)]. Dreyfus *et al.* reported that concomitant tricuspid valve (TV) repair based on tricuspid annular size improves functional status irrespective of the grade of TR[5)]. TV surgery after previous MV surgery is associated with high in-hospital mortality[6)]; but concomitant TV surgery at the time of MV repair is reported as safe and effective[4) 5)]. Based on these findings, valvular heart disease guidelines currently recommend concomitant TV surgery not only for severe TR, but also for mild or moderate TR with

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tricuspid annular diameter (TAD) > 40 mm at the time of MV surgery[7) 8)]. Nevertheless, debate is ongoing about aggressive concomitant TV surgery for mild or moderate TR to prevent progression of TR[9) 10)]. Reflecting this controversy, the percentage of patients from high-volume centers undergoing concomitant tricuspid repair ranges from 7% to 65%[11)]. In clinical practice, we have observed some cases with progression of TR early after isolated MV repair who were deemed to be at low risk of TR progression at preoperative evaluation. Patients with TR progression early after MV repair may be at risk of reoperation or reduced QOL. Few studies have focused on the early progression of TR after MV repair. We therefore aimed to examine the changes in unrepaired TR early after isolated MV repair for degenerative MR, and investigate the predictors of TR progression.

Methods

1. Study population

This was a single-center, retrospective observational study. A total of 236 consecutive patients who underwent isolated MV repair for severe MR at the Juntendo University Hospital from January 2014 to October 2019 were identified from a cardiovascular surgery database. Isolated MV repair was defined as MV repair without concomitant aortic or tricuspid valve surgery, coronary artery bypass graft surgery, aorta graft replacement, or congenital defect closure. Patients for whom preoperative or in-hospital postoperative echocardiography reports were missing were excluded from the analysis. We also excluded patients with severe preoperative TR and non-degenerative MR. Finally, a total of 214 patients were analyzed (Figure-1).

Demographic data, clinical data, and surgical information were collected from institutional medical records. Clinical data included cardiovascular risk factors, prevalence of paroxysmal or persistent atrial fibrillation (AF), hemoglobin levels, estimated glomerular filtration rate (eGFR), and brain natriuretic peptide (BNP) levels. Body mass index (BMI) was calculated as follows: BMI = weight (kg)/height $(m)^2$. European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was used to estimate the risk of surgical mortality[12)].

2. Echocardiographic data

Pre- and postoperative transthoracic echocardiography (TTE) measurements were collected from the Juntendo University echocardiography database. All standard examinations, including Doppler color flow measurements, were made according to the current guidelines[13)] using commercially available ultrasound systems by several

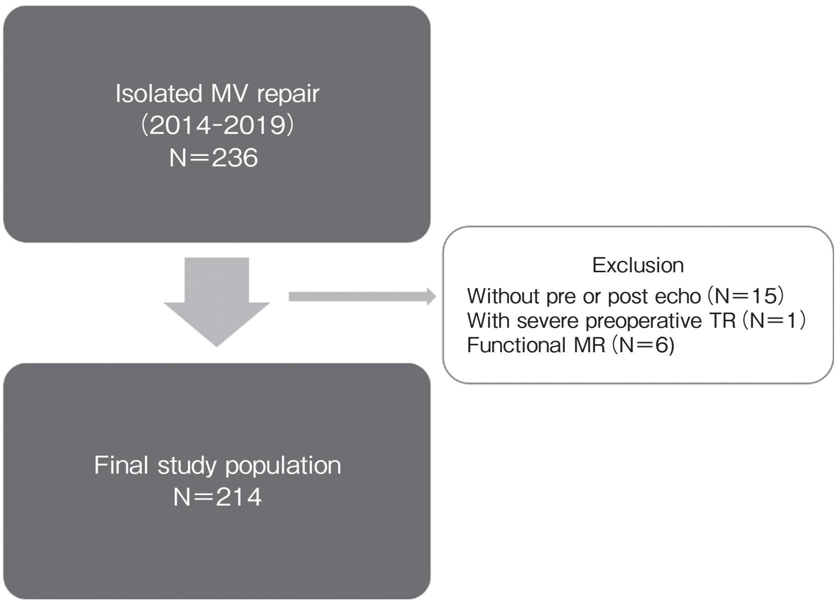

Figure-1 Flow chart of patient selection in this study
Isolated MV repair was defined as repair without concomitant aortic or tricuspid valve surgery, coronary artery bypass graft surgery, aorta graft replacement, or congenital defect closure.

certified sonographers. From the apical two- and four-chamber views, left ventricular ejection fraction (LVEF) was quantified using the Simpson's biplane method. Valvular regurgitation severity was graded as none, mild, moderate, or severe, according to standard quantitative and semi-quantitative methods recommended by guidelines[14]. Integrative assessment of TR severity was performed using a multiparametric approach (including jet size, jet eccentricity, and vena contracta width). Trivial TR was considered as no TR in this study. RV systolic function was evaluated using tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular peak systolic velocity (TVs'). Since the dimension of the tricuspid annulus (TAD) was not recorded in some cases, TAD was measured from an apical four-chamber view, in late diastole when the tricuspid valve was maximally opened, as recommended by Foale *et al.*[15], by reviewing stored digital images. Early TR progression was defined as an increase in TR of at least one grade on pre-discharge echocardiography compared to preoperative echocardiography. Patients were divided into two groups: a TR progression group; and a no-TR progression group.

3. Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD). Categorical variables are expressed as numbers and percentages. Differences between groups were compared using Student's t-test and the chi-square or Fisher's exact test, respectively, for continuous and categorical variables. To normalize the skewed distribution, log-transformed BNP level was used as a continuous variable.

Multivariate analysis using logistic regression modeling was applied to determine risk factors for early TR progression. Results are presented as odds ratios with 95% confidence intervals (CI). All tests were two-tailed, and values of $p < 0.05$ were considered to indicate statistical significance. All statistical analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics are shown in Table-1. Preoperative echocardiographic measurements are shown in Table-2. Of the total 214 study patients, 70 patients (32.7%) were female, and mean age was 59.0 ± 13.4 years. Mean time until pre-discharge echocardiography was 6.4 ± 1.8 days after surgery. At baseline, 166 patients (77.6%) had either no TR or trivial TR, 44 patients (20.6%) had mild TR, and 4 patients (1.9%) had moderate TR. At follow-up echocardiography before discharge, 33 patients (15.4%) showed an increase in TR severity of at least one grade (TR progression group). Twenty-two patients (10.3%) showed an improvement and 159 patients (74.3%) showed no change in TR severity. That is, 181 patients (84.6%) had no TR progression (no-TR progression group).

Prevalence of moderate TR at discharge was only 1.9% (n = 4). All patients with moderate TR at discharge showed no or only mild TR preoperatively (Figure-2). Patients in the TR progression group were significantly older and displayed a smaller BMI than those in the no-TR progression group (65.3 ± 11.2 years vs. 57.9 ± 13.5 years, p = 0.003 and 21.3 kg/m^2 ± 2.3 vs. 22.9 ± 3.6 kg/m^2, p = 0.017, respectively). Although not significant, eGFR was lower in the TR progression group (69.2 ± 17.3 vs. 76.9 ± 22.2, p = 0.06). The prevalence of AF did not differ significantly between the TR progression and no-TR progression groups (12.1% vs. 14.4%, p = 1.00). Left ventricular diastolic dimension (LVDd) tended to be smaller in the TR progression group than in the no-TR progression group, but this difference was not significant (52.1 ± 5.8 vs. 54.5 ± 6.8, p = 0.057). LVEF did not differ significantly between groups (68.7 ± 8.0 % vs. 68.1 ± 7.5 %, p = 0.69). Tricuspid annular plane systolic excursion (TAPSE), tricuspid annular velocity, and TAD did not differ significantly between groups. Only five patients (2.7%) showed TAD ≥40 mm.

Table-3 summarizes the surgical data. All patients were repaired with flexible or semi-rigid annular rings. Ring size and percentage of concomitant Maze procedures did not differ significantly between groups. Only two patients (0.9%) had early recurrence of more than moderate MR after MV repair. Patients underwent MV repair with complete (n = 174) or partial median sternotomy (n = 28) or mini-thoracotomy (n = 12). At the time of post-operative echocardiography, AF was observed in 6.1% of TR progression group and 3.3% of no-TR progression group (p = 0.36).

Table-1 Baseline patient characteristics

	All (N=214)	TR progression (n=33)	No TR progression (n=181)	p-value
Age	59.0 ± 13.4	65.3 ± 11.2	57.9 ± 13.5	0.003
Female sex	70 (32.7%)	12 (36.4%)	58 (32%)	0.63
BMI	22.6 ± 3.5	21.3 ± 2.8	22.9 ± 3.6	0.017
NYHA class ≥ 2	123 (57.5%)	18 (54.5%)	105 (58.0%)	0.71
Medical history				
Hypertension	91 (42.5%)	17 (51.5%)	74 (40.9%)	0.26
Diabetes	11 (5.1%)	1 (3%)	10 (5.5%)	1.00
Dyslipidemia	67 (31.3%)	7 (21.2%)	60 (33.1%)	0.17
CAD	8 (3.7%)	2 (6.1%)	6 (3.3%)	0.36
Atrial Fibrillation	30 (14.0%)	4 (12.1%)	26 (14.4%)	1.00
COPD	7 (3.3%)	1 (3.0%)	6 (3.3%)	1.00
Laboratory data				
Log BNP	1.7 ± 0.5	1.6 ± 0.4	1.7 ± 0.5	0.74
Hb [g/d*l*]	13.4 ± 1.5	13 ± 1.4	13.4 ± 1.6	0.092
eGFR [m*l*/min/m^2]	75.7 ± 21.6	69.2 ± 17.3	76.9 ± 22.2	0.060
Hemodialysis	3 (1.4%)	0 (0%)	3 (1.7%)	1.00
Medications				
Beta blockers	57 (26.6%)	9 (27.3%)	48 (26.5%)	0.93
ACEI/ARB	69 (32.2%)	14 (42.4%)	55 (30.4%)	0.17
Diuretic	68 (31.9%)	11 (34.4%)	57 (31.5%)	0.83

Values are mean ± standard deviation or number (%)
BMI = body mass index, NYHA = New York Heart Association, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, Log BNP = Brain natriuretic peptide (log-transformed), Hb = hemoglobin levels, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker

Table-2 Baseline echocardiographic parameters

	All (N=214)	TR progression (n=33)	No TR progression (n=181)	p-value
LVDd [mm]	54.1 ± 6.7	52.1 ± 5.8	54.5 ± 6.8	0.057
LVDs [mm]	33.1 ± 5.9	31.6 ± 5.2	33.4 ± 6.0	0.10
IVS [mm]	9.5 ± 1.4	9.3 ± 1.2	9.6 ± 1.4	0.32
PW [mm]	9.6 ± 1.3	9.5 ± 1.1	9.6 ± 1.4	0.87
LVEF [%]	65.5 ± 7.3	68.7 ± 8	68.1 ± 7.5	0.69
LAVI [m*l*/m^2]	55.6 ± 20.4	52.5 ± 17.7	56.1 ± 20.8	0.36
PASP [mmHg]	29.9 ± 9.9	28.7 ± 6.3	30.1 ± 10.4	0.46
TAPSE [cm]	23.5 ± 4.5	24.1 ± 4.7	23.4 ± 4.5	0.44
TVs' [cm/s]	12.8 ± 2.8	12.9 ± 3.3	12.8 ± 2.7	0.87
TAD [cm]	3.0 ± 0.5	3.1 ± 0.5	3.0 ± 0.5	0.49
Preoperative TR				0.049
none	166 (77.6%)	31 (93.9%)	135 (74.6%)	
mild	44 (20.6%)	2 (6.1%)	42 (23.2%)	
moderate	4 (1.9%)	0 (0%)	4 (2.2%)	

Values are mean ± standard deviation or number (%)
LVDd = left ventricular diastolic dimension, LVDs = left ventricular systolic dimension, IVS = interventricular septum, PW = posterior wall, LVEF = left ventricular ejection fraction, LAVI = left atrial volume index, PASP = pulmonary artery systolic pressure, TAPSE = tricuspid annular plane systolic excursion, TVs' = tricuspid annular velocity, TAD = tricuspid annular diameter

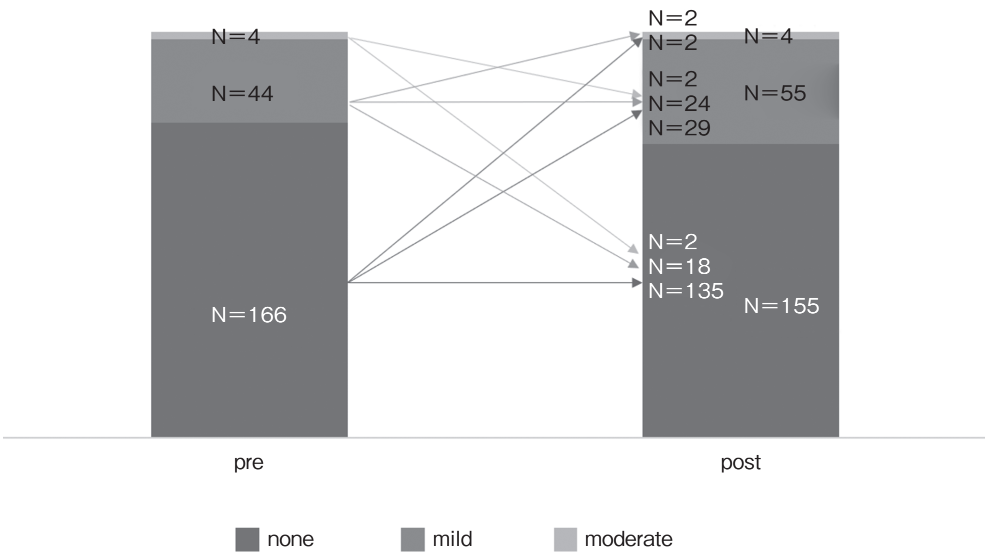

Figure-2 Changes in severity of tricuspid regurgitation pre- and post-MV repair
Thirty-three patients (15.4%) had TR progression, 22 patients (10.3%) had TR improvement, and 159 patients (74.3%) had unchanged TR severity at pre-discharge echocardiography.

Table-3 Surgical data

	All (n=214)	TR progression (n=33)	No TR progression (n=181)	p-value
Ring type				0.10
Physio	102 (47.7%)	17 (51.5%)	85 (47%)	
Duran	91 (42.5%)	10 (30.3%)	81 (44.8%)	
Memo 3D	14 (6.5%)	5 (15.2%)	9 (5%)	
CG Future	7 (3.3%)	1 (3.0%)	6 (3.3%)	
Ring size [mm]	29.1 ± 1.9	29.0 ± 1.6	29.1 ± 2.0	0.90
Maze procedure	24 (11.2%)	2 (6.1%)	22 (12.2%)	0.55
MR after repair (≥moderate)	2 (0.9%)	0 (0%)	2 (1.1%)	1.00
LVEF after repair	61.5 ± 8.5	61.8 ± 8.3	61.4 ± 8.5	0.85
AF after repair	8 (3.7%)	2 (6.1%)	6 (3.3%)	0.36

Values are mean ± standard deviation or number (%)
Physio: Phisyo I or II ring (Edwards Lifesciences Inc. Irvine, CA), Duran: Duran flexible ring (Medtronic Inc, Minneapolis, MN), MEMO 3D: MEMO 3D RECHORD ring (Sorin group Italia S.r.l), CG Future: CG Future annuloplasty band (Medtronic Inc, Minneapolis, MN), MR = mitral regurgitation, LVEF = left ventricular ejection fraction

Univariate analysis showed that age and BMI were significantly associated with TR progression. When age, BMI, hemoglobin level, and LVDd were included as covariates in the multivariate analysis, age and BMI were independent predictors of TR progression (Table-4).

Discussion

This study investigated the prevalence and factors associated with TR progression early after isolated MV repair for degenerative MR. We found that 15% of our study population showed TR progression of at least one grade after MV repair. In the multivariate analysis, age and BMI were independent factors associated with early TR progression.

There are few papers that describe changes in the severity of TR in the early stage after MV repair. Murashita *et al.*[16] reported that the mean TR grade at discharge was significantly reduced (0.7 ± 0.5) compared to preoperative (0.9 ± 0.5) in the patients who underwent MV repair without

Table-4 Predictors of early postoperative TR after isolated MV repair

	Univariate			Multivariate		
	OR	95%CI	p-value	OR	95%CI	p-value
Age	1.05	1.01-1.09	0.004	1.04	1.01-1.08	0.010
BMI	0.87	0.77-0.98	0.019	0.88	0.78-0.99	0.043
eGFR	0.98	0.97-1.00	0.98			
Hb	0.81	0.64-1.04	0.093			
LVDd	0.94	0.89-1.00	0.059			
LVEF	0.68	0.96-1.06	0.68			

BMI = body mass index, LVDd = left ventricular diastolic dimension, LVEF = left ventricular ejection fraction, Hb = hemoglobin levels, eGFR = estimated glomerular filtration rate, OR = odds ratio, CI = confidence of interval

concomitant TV repair ($p<0.001$). Yilmaz *et al.* reported that there was no significant difference in mean TR grade between preoperative and at discharge in patients with isolated MV repair. However, in patients with at least moderate preoperative TR, the TR grade decreased at discharge and until the third year ($p<0.001$)[17]. Similar to this result, all patients with moderate preoperative TR had decreased TR levels early after MV repair in our study (Figure-2). David *et al.* showed that early postoperative TR (< 1 month) offered an independent predictor of mortality in multivariate analysis[10]. About 15% of the patients in our study experienced early TR progression after MV repair. Early postoperative TR, as well as late progression TR, may play important roles after MV repair. Further studies are necessary to examine this hypothesis.

In 2005, Dreyfus *et al.* showed that TV annuloplasty on tricuspid dilatation (> 70 mm with direct intraoperative measurement), irrespective of the grade of preoperative TR, improved functional status after MV repair[5]. Several studies have shown that TAD > 40 mm with preoperative transesophageal echocardiography (TEE) represents a reasonable threshold for the indication of concomitant TV repair[9) 18) 19]. Conversely, Sordelli *et al.* reported that neither 2D-TTE nor 3D-TEE analysis of TV predicted TR progression after MV repair for degenerative MR[20]. In our study population, TAD measurements did not differ between the TR progression and no-TR progression groups. In addition, only five patients (2.7%) displayed TAD ≥40 mm. This is because most MR patients with dilated TA underwent concomitant TV repair by our surgeons, in accordance with the current guidelines, and were not included in this analysis.

In multivariate analysis, age and BMI were independent predictors for early TR progression in our study. Many studies have shown preoperative AF as an independent predictor of TR progression late after MV surgery[2) 10) 17]. Patients with advanced AF may show no improvement in RV size or function, even after a reduction in RV afterload by MV repair. In our study population, the majority of AF patients underwent concomitant Maze procedure. This may have led to our result differing from those of previous reports. Although not statistically significant, postoperative AF was observed more frequently in the TR progression group than in the no-TR progression group. Aggressive rhythm control may suppress TR progression in MR patients with AF.

In our study, patients in the TR progression group showed lower BMI than those in the no-TR progression group. Why lower BMI is associated with TR progression remains unclear. BMI is not only an indicator of obesity, but is also affected by cardiac cachexia or fluid retention, so further studies are necessary in this regard.

This study has several limitations. First, this was a single-center, retrospective study with a relatively small cohort. Second, selection bias may have occurred because we excluded patients without echocardiographic data. Third, although multivariate analysis was used, we could not account for other potential confounders. Fourth, the body fluid volume at the time of echocardiography may affect the severity of TR, but details of body weight changes and doses of diuretics have not been obtained. Finally, we did not evaluate the impact of early postoperative TR on long-term survival and functional outcomes. Further studies are required to examine this issue.

Conclusion

Despite appropriate surgical correction of degenerative MR, progression of TR early after MV repair was observed in 15% of the patients. High age and low BMI were independently associated with TR progression early after MV repair. Larger prospective studies are necessary to evaluate the impact of early TR progression on long-term prognosis after MV repair.

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Disclosures

The authors declare that there are no conflicts of interest.

Contributions

EK did the data acquisition, data analysis and wrote the manuscript. SM designed the work and interpreted the analyzed data. TY prepared surgical information and gave advice on surgical findings. AA revised the manuscript critically for important content. HD revised the manuscript critically for important content.

TM made final approval of the version to be published.

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