

Long-term prognosis of mild functional tricuspid regurgitation after mitral valve replacement

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ABSTRACT

Objective: Functional tricuspid regurgitation (FTR) is the most common type of tricuspid insufficiency and occurs approximately in 30% of patients with mitral valve disease. The major etiologic factor in the triggering of right ventricular dilation and thus causing functional tricuspid regurgitation, is pulmonary artery hypertension secondary to mitral valve disease. We aimed to analyze long-term outcomes of patients with mild tricuspid regurgitation at the time of mitral valve replacement.

Methods: Sixty-six patients with mild tricuspid insufficiency who underwent mitral valve replacement were included in this observational retrospective study. Mean follow-up time was 8.3±0.7 years. Patients whose tricuspid regurgitation remained unchanged or decreased following operation were enrolled to group 1 (n=32), patients whose tricuspid regurgitation increased were included to group 2 (n=34) and data were compared statistically with t-test, Mann-Whitney U, Chi-square and Fisher Exact test. Multiple regression analysis was performed to determine independent risk factors for FTR progression.

Results: Preoperatively female gender (p=0.02), body surface area (p=0.04), left atrium diameter (p=0.01), functional capacity (p=0.03), right ventricle diameter (p=0.04), and left ventricle mass index (p=0.04) were found to be statistically significant between groups. In the follow-up; functional capacity, grade of tricuspid insufficiency, pulmonary artery pressure, vena contracta width (p<0.001), TAPSE (tricuspid annular plane systolic excursion index) (p=0.04), annulus diameter (p=0.02), right ventricle diameter (p=0.01), left ventricle mass index (p=0.05), and ejection fraction (p=0.02) were found to be statistically different between groups. In multiple logistic regression analysis; preoperative LA diameter (OR=5.05; 95% CI:1.49-17.12; p=0.009) and female gender (OR=10.93; 95% CI:1.77-67.31; p=0.01) were found as independent risk factors for FTR progression.

Conclusion: This study revealed that mild FTR might advance to moderate to severe grade in more than half of the patients in the follow-up. Thus, surgical approach to even mild FTR should be individualized based on patient's risk assessment. (*Anadolu Kardiyol Derg 2014; 14: 34-9*)

Key words: functional tricuspid regurgitation, mitral valve replacement, regression analysis, tricuspid annuloplasty

Introduction

Functional tricuspid regurgitation (FTR) is the most common type of tricuspid valve regurgitation and defines a valvular insufficiency without any structural disease of the tricuspid valve (1). Physiopathology of FTR is based on tricuspid annular dilatation, which is developed in response to pulmonary hypertension secondary to left ventricle disease or primary pulmonary arterial disorder. Mitral valve disease, dilated cardiomyopathy, aortic valve disease, chronic pulmonary disease, primary pulmonary hypertension, recurrent pulmonary embolism, congenital heart defects, Eisenmenger syndrome or myocardial infarction may also cause FTR.

FTR incidence was reported approximately in 30% of patients with both mitral stenosis and mitral regurgitation (2). Incidence

of moderate-severe post mitral valve replacement (MVR) FTR was reported to vary between 27-37% (2, 3). Similarly, FTR was reported to occur in 1 out of 3 patients with rheumatic mitral stenosis (MS), in 14% of patients with functional mitral regurgitation (MR), and in 15% of patients with mitral valve prolapsus (MVP) (4-6).

Surgical approach to FTR remained controversial until the last decade. So far the general belief was that 'spontaneous regression of FTR' following mitral valve surgery, but unfortunately long term follow-up studies showed that although some of the untreated FTR cases may regress or remain unchanged, most of them may eventually deteriorate, following mitral valve replacement (1, 7). Almost all of these studies investigated the faith of moderate to severe FTR following mitral valve replacement.

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Therefore, we aimed to analyze long-term outcomes of patients with mild tricuspid regurgitation at the time of mitral valve replacement.

Methods

Study design

An observational retrospective study.

Study population

Following our institutional Ethics Committee approval, we investigated the progression of mild 'untouched' tricuspid regurgitation in 226 patients who underwent MVR in Istanbul University Institute of Cardiology, between 1995-2005. Inclusion criteria were; the presence of 1(+) tricuspid valve regurgitation at the time of isolated mitral valve replacement. Patients whose tricuspid regurgitation (TR) was higher than 1(+), who have any grade of aortic valve stenosis or insufficiency, who underwent concomitant interventions (coronary bypass surgery, aortic surgery, tricuspid valve annuloplasty) and patients with infective endocarditis were excluded. A hundred and ten patients with different grades of TR were found from our institutional database. Twelve of these patients, who had tricuspid annuloplasty and MVR simultaneously, 8 patients with 3(+) TR, and 16 patients with 2(+) TR were excluded. The remaining 74 patients were questioned by telephone and the information of 7 patients' death and 1 patient who underwent TVR late after MVR led us to exclude 8 more patients, finally yielding a study group of 66 patients with mild FTR at the time of their MVR operation (Fig. 1).

Data collection

All patients' preoperative demographic, echocardiographic as well as operative data were collected. Patients were composed of 40 females, 26 males and their mean age was 56.25 ± 9.19 years (24-76 years). Mean follow-up time was 8.30 ± 0.70 years (6-16 years).

Echocardiography

The tricuspid valve function was assessed according to jet flow, but actual parameters such as tricuspid annular plane systolic excursion (TAPSE), Tei indexes and vena contracta width values were not routine parameters used at the time when the patients were operated on. During the control examination, the same cardiologist re-examined all of the patients, and their functional capacity was assessed according to the New York Heart Association classification. The tricuspid valve function was evaluated by M-mode, Doppler and tissue Doppler transthoracic echocardiography with the same device (Vivid i GE Vingmed Ultrasound, Horten, Norway) at rest and in the left lateral decubitus position, according to the American Society of Echocardiography guideline (8). The left ventricular ejection fraction was calculated using modified Simpson formula (9). The pulmonary artery pressure was measured via tricuspid regurgitation. The left ventricle mass index was calculated using Devereux formula. Patients' body surface area was cal-

culated and reference effective orifice areas of prosthetic mitral valves were gained. The effective orifice area index was also calculated for each patient. Patients' demographic and preoperative-postoperative echocardiographic data were compared statistically.

Statistical analysis

Statistical analysis were performed with the statistical package for the social sciences (SPSS) computer program, version 16.0 (SPSS, Inc., Chicago, Ill, USA). Normality of distribution was evaluated with Kolmogorov-Smirnov test. Normally distributed data are expressed as mean \pm standard deviation. Data are expressed as median and Q1, Q3 if were not found normally distributed. Results were analyzed with the Student t-test for quantitative data normally distributed and Mann-Whitney U test for quantitative data, which were not found normally distributed. Categorical data were analyzed with the Chi-square or Fisher exact test (when Levene's test was significant). Logistic regression analysis was performed with enter logistic regression method. An independent variables (gender, preoperative left atrial diameter, preoperative right ventricle diameter, square root of left ventricle mass index, functional capacity, body surface area) which were found significantly different between groups were included to the multiple regression analysis. Presence of progression of FTR was dependent variable. A p value of less than 0.05 was considered statistically significant.

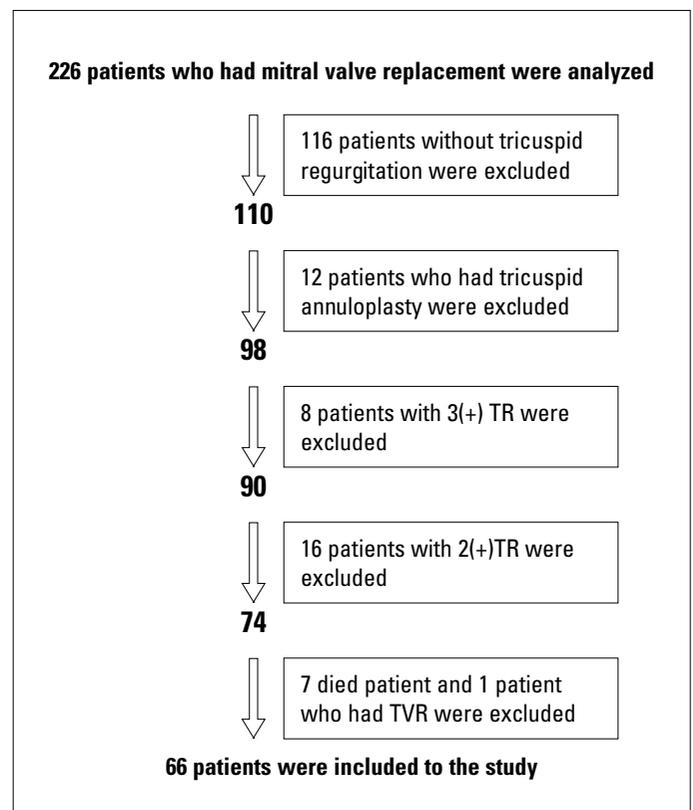


Figure 1. Flow diagram of the study

TR - tricuspid regurgitation; TVR - tricuspid valve replacement

Results

Sixty-six patients (40 female and 26 male) were investigated. The mean follow-up time was 8.30 ± 0.70 years (min:6-max: 16 years). The mean age was 56.25 ± 9.19 years (min:24-max:76 years). Following control data collection, patients were categorized based on their tricuspid valve function. Patients' FTR grades were compared with their preoperative values. Results showed that tricuspid regurgitation increased in 34 of 66 patients (Group 2) (51.5%) in the follow-up. FTR decreased or remained unchanged in the remaining 32 patients (Group 1) (48.5%) (Fig. 1). Preoperative demographic characteristics were compared and summarized at Table 1. Female gender ratio was significantly higher in group 2 ($p=0.02$). The body surface area was higher in group 1 ($p=0.04$). Functional capacity was lower in group 2 (1.56 ± 0.66 median:1.00, Q1:1, Q3:2 vs. 1.88 ± 0.59 median: 2.00, Q1:1.75, Q3:2; $p=0.03$). The follow-up time, age, atrial fibrillation rate, rheumatic disease rate, mitral stenosis and mitral regurgitation rates were similar between groups.

Comparison of patients' preoperative echocardiographic parameters showed that the left atrium ($p=0.01$) and right ventricle diameters ($p=0.04$) were significantly different between groups. The left ventricle mass index data was not in normal distribution, so we compared their square roots, and that difference was statistically significant between groups ($p=0.04$). Effective orifice area indexes, left ventricle end diastolic diameter, ejection fraction, mitral valve area, mean mitral gradient, pulmonary artery pressure values were similar (Table 2).

Postoperative data analysis showed that there were no FTR in only 9 of 66 patients (13.6%) while FTR remained unchanged in 23 (34.9%), 2(+) in 16 (24.2%), and 3(+) in 18 of the patients (27.3%) (Table 3). The mean TR grade was significant between groups ($p<0.001$), and functional capacity was lower in group 2 ($p<0.001$). Mean pulmonary artery pressure was 47.67 ± 10.2 mmHg in group 2 and 35.59 ± 9.6 mmHg in group 1 ($p<0.001$). Pulmonary artery pressure was decreased in group 1 (difference between postoperative and preoperative pulmonary artery pressure= 0.5 ± 11.87), but increased in group 2 (difference between postoperative and preoperative pulmonary artery pressure= 8.79 ± 17.63). Comparison of these differences was statistically significant ($p<0.001$). Ejection fraction was 55.21 ± 8.37 in group 1 (median:60, Q1:49.75, Q3:60) and 51.17 ± 8.49 in group 2 (median:50 Q1:45, Q3:60) ($p=0.02$). The right ventricle diameter was also significantly different ($p=0.01$). Comparison of tricuspid valve annulus, TAPSE, Tei indexes and vena contracta width values are summarized in Table 3.

Multiple logistic regression analysis of statistically significant factors influencing FTR progression such as; gender, preoperative left atrial diameter, preoperative right ventricle diameter, square root of left ventricle mass index, functional capacity, body surface area were performed and preoperative left atrial diameter (OR=5.05; 95% CI:1.49-17.12; $p=0.009$) and female gender (OR=10.93; 95% CI:1.77-67.31; $p=0.01$) were found as independent risk factors for FTR progression (Table 4).

Discussion

In this study, we aimed to investigate prognosis of mild functional tricuspid regurgitation following mitral valve replacement. Patients with mild FTR in the operation time, were reevaluated and results were compared statistically. This study revealed that mild FTR may advance to moderate to severe grade in more than half of the patients in the follow-up and female gender and preoperative left atrial diameters are independent predictors for progression of FTR.

The first experience on the prognosis of FTR was reported by Braunwald in 1967. Braunwald claimed that untreated FTR improves naturally following treatment of mitral valve disease (10). Subsequently, Carpentier advised surgical intervention to FTR in patients with mitral valve disease (11). Braunwald's report on this controversial issue remained as a hinge point until the last two decades, but after then long-term follow-up studies revealed that untreated FTR might be progressive (1-3, 7). The results of these studies changed surgeons' approach to FTR. Based on the STS database, the percentage of simultaneous intervention to moderate-severe FTR during mitral valve surgery has increased from 36.8% to 61.6% between 2000 and 2009 (12).

Following mitral valve surgery, pulmonary hypertension, which triggers FTR does not regress in all patients. Morphologic changes of pulmonary arterioles may be irreversible and this phenomenon causes persistence of pulmonary hypertension, which is one of the major risk factors for FTR progression (13-15). Incidence of persistent pulmonary hypertension was reported to occur between 46 to 64% following mitral valve surgery (16, 17). In our study, pulmonary artery pressure persisted or even increased in group 2. We believe that this increase is the major determinant of FTR progression variation between the study groups. Patient prosthesis mismatch (PPM) is one of the most important risk factors for persistent pulmonary hypertension seen following mitral valve replacement (18-20). Jamieson et al. (19) found a strong correlation between PPM and moderate-severe persistent pulmonary

Table 1. Preoperative characteristics of patients

Variables	Group 1	Group 2	*P
n	32	34	0.947
Age, years	55.97 ± 10.01	56.86 ± 9.77	0.818
Female gender, %	46.90	74.30	0.021
BSA, m ²	1.74 ± 0.18	1.62 ± 0.14	0.048
Follow up, years	$8.13 \pm 3, 05$	8.60 ± 2.63	0.619
FC (NYHA)	1.56 ± 0.66	1.88 ± 0.59	0.032
AF, %	41.90	62.50	0.083
RHD, %	18.80	34.30	0.123
MS, n (%)	21 (65.6)	24 (70.5)	0.515
MR, n (%)	14 (43.7)	18 (52.9)	0.442

Data are presented as mean \pm SD and number (percentage)

*t-test for independent samples and Chi-square test

AF - atrial fibrillation; BSA - body surface area; FC - functional capacity, MR - mitral regurgitation; MS - mitral stenosis; RHD - rheumatic heart disease

Table 2. Preoperative echocardiographic parameters of patients

Variables	Group 1	Group 2	*P
EOAI, cm ² /m ²	1.1±0.12	1.11±0.15	0.77
LVMlpre, g/m ²	100.30±15.62	129.44±44	0.06
√LVMl	9.98±0.78	11.26±1.67	0.04
LADpre, cm	4.65±0.68	5.22±0.70	0.01
LVEDD, cm	5.16±0.73	5.23±0.95	0.79
RVD, cm	2.41±0.31	2.59±0.24	0.04
EF, %	57.14±5.60	56.80±5.59	0.55
MVA, cm ²	1.32±0.48	1.36±0.41	0.78
MMG, mm Hg	10.07 ±3.66	11.53±4.73	0.36
PAP pre, mm Hg	34.09±9.47	37.11±11.93	0.20

Data are presented as mean±SD
*t-test for independent samples
EF - ejection fraction; EOAI - effective orifice area index; LADpre - left atrium diameter preoperative; LVEDD - left ventricle end diastolic diameter; LVMl pre-preoperative left ventricle mass index; √LVMl-square root of left ventricle mass index; MVA - mitral valve area; MMG - mitral mean gradient; PAPpre - preoperative pulmonary artery pressure, right ventricular diameter

Table 3. A comparison of postoperative clinic and echocardiographic data

Variables	Group 1	Group 2	*P
TRpost	0.71±0.45	2.52±0.50	<0.001
FCpost	1.37±0.60	2.67±0.68	<0.001
PAPpost, mm Hg	35.59±9.60	47.67±10.20	<0.001
LADpost, cm	143.62±103.14	160.47±78.03	0.08
LVMlpost, gr/m ²	94±9.56	114±26.06	0.05
EFpost, %	55.21±8.37	51.17±8.49	0.02
LVEDDpost, cm	5.07±0.60	5.03±1.0	0.84
RVDpost, cm	2.61±0.34	2.84±0.4	0.01
Annulus, cm	3.55±0.58	3.86±0.41	0.02
TAPSE	1.97±0.25	1.83±0.28	0.04
Tei index	0.51±0.13	0.53±0.13	0.52
VC, cm	0.38±0.1	0.79±0.45	<0.001
MMG, mm Hg	4.93±1.95	4.72±1.58	0.61

Data are presented as mean±SD
*t-test for independent samples
EFpost - postoperative ejection fraction; FCpost - postoperative functional capacity; LADpost - postoperative left atrium diameter; LVEDDpost - postoperative left ventricle end-diastolic diameter; LVMlpost - postoperative left ventricle mass index; PAPpost - postoperative pulmonary artery pressure; RVDpost - postoperative right ventricle diameter; TAPSE - tricuspid annular plane systolic excursion; TRpost - postoperative tricuspid regurgitation; VC - vena contracta

hypertension in the follow-up of 2440 patients, 15 years after mitral valve replacement. In our study, only two of 66 patients' EOAI were lower than 0.9 cm²/m², which is defined as the cut-off value for severe PPM for mitral valve thus our patient population was not suitable to evaluate the association between PPM and persistent pulmonary hypertension.

FTR influences functional capacity and life quality (21, 22). In our study, we found strong difference between functional

Table 4. Multiple logistic regression analysis of risk factors for FTR

Risk factor	P	Odds ratio	Confidence Interval
FC preoperative	0.73	1.27	0.31-5.08
√LVMl	0.11	13.47	0.53-342.60
BSA, m ²	0.35	0.008	0-223.09
RVD preoperative, cm	0.55	3.198	0.07-144.27
Female gender	0.01	10.93	1.77-67.31
LAD preoperative, cm	0.009	5.05	1.49-17.12

BSA - body surface area; FC-functional capacity; FTR - functional tricuspid regurgitation; LADpre - left atrial diameter preoperative; √LVMl - square root of left ventricular mass index; RVD - right ventricular diameter

capacities of the groups. Mean functional capacity was significantly lower in group 2 (1.37±0.60 median 1.00, Q1:1.00 Q3:2.00 vs 2.67±0.68 median 3.00, Q1:2.00, Q3:3.00) and was found to be decreased when compared to preoperative values.

Rheumatic disease may affect the tricuspid valve primarily or may cause FTR secondary to rheumatic mitral valve disease. Tricuspid valve disease had been reported in 1 of 3 patients with rheumatic mitral valve disease simultaneously (4). Song et al. (13) noted that rheumatic disease increases the risk of FTR progression following mitral valve repair. In their study, rheumatic disease percentage was 74% in the FTR group, but 42% in 'no FTR group' and proportion of the groups was 56.7%. In our study, rheumatic disease ratio was 18.8% in group 1 and 34.3% in group 2 and proportion of the groups was 54.8%. Although our results were similar with Song et al. (13) we are unable to find statistically significant results due to our small sample size.

Atrial fibrillation and FTR relationship is well established following mitral valve replacement (1, 13, 23). Atrial fibrillation increases the left atrium pressure, which triggers FTR pathogenesis (24-26). Rhythm restoration with MVR simultaneously prevents FTR progression (27). In our study, no patient received concomitant ablation therapy, and preoperative atrial fibrillation rate was higher in group 2 similarly to previous studies, but the difference was not statistically significant due to our sample size (13/32 (40.6%) vs 21/34 (61.7%); p=0.083).

The predictive role of left atrium size in FTR progression following MVR was well described by previous retrospective studies (13, 28, 29). In our study, the left atrium diameter was found to be significantly different both preoperative and postoperatively between groups. Right ventricle and tricuspid annulus sizes were also different, as predicted. Preoperative left atrium size is one of two independent risk factors in the result of logistic regression analysis.

In our study 61.2% of patients were female. It is well known that the female gender is predisposed to valvular heart disease (1, 13, 30). Our results showed that the female gender is an independent risk factor for FTR progression following MVR, similarly to Song's and to Varadarajan's series (13, 30). On the other hand, the body surface area was significantly different between the

groups, but we think that it is due to the higher female patient content of group 2. Age does not appear to influence FTR progression, based on our results.

Preoperative ejection fraction was not shown as a risk factor for FTR but almost all studies as well as ours also investigated patients with normal or mildly decreased ejection fraction (1, 13, 28, 29). Therefore, we believe that more studies are required to evaluate patients with moderate or severe left ventricular dysfunction.

TAPSE and Tei indexes are actual echocardiographic right ventricular function parameters. TAPSE reflects the right ventricle systolic function, whereas Tei shows both systolic and diastolic functions (31, 32). In our study, TAPSE was found significantly different between groups, but the difference of Tei index was not significant.

Mild FTR is a generally neglected lesion. In the literature there are few studies investigating mild FTR. Smid et al. (33) evaluated mild-moderate FTR patients with and without ring annuloplasty. They declared that FTR grade increased at least by 1 grade in 32% of patients without annuloplasty. In this study Smid et al. (33) emphasized that ring annuloplasty should be performed if tricuspid annulus is greater than 40 mm, regardless of the TR grade knowing that FTR and tricuspid annular dilatation may progress and cause right ventricle dysfunction in almost half of the patients.

Briefly, our study showed that female gender, low preoperative functional capacity, low body surface area, enlarged left atrium size, enlarged right ventricle size, and increased square root of left ventricle mass index values effect FTR progression. These parameters were included in multivariate logistic regression analysis and only 'female gender' and 'left atrial size' were found as independent risk factors.

Study limitations

In this study we analyzed relatively small sample size to evaluate all factors influencing progression of tricuspid regurgitation. In preoperative echocardiographic examination, TAPSE, Tei indexes, vena contracta width, and right ventricle annulus diameter were not routine echocardiographic measurements so unfortunately, we could not have a chance to compare these parameters.

Conclusion

As we observed progression in more than half of our patients with mild FTR following MVR, we can conclude that; the decision of surgical intervention to the FTR should be individualized following a thorough evaluation of the case, especially in high risk patients and indications for more aggressive interventions to the mild FTR during MVR should be considered in or may be even reserved to 'female patients' and to 'cases with left atrial enlargement'.

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