Late tricuspid regurgitation and right ventricular remodeling after tricuspid annuloplasty.

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Abstract

Background. We sought to determine the relationship between tricuspid right ventricular (RV) and tricuspid valve (TV) remodeling and late failure of tricuspid annuloplasty. Methods. From May 2009 to December 2015, 423 patients undergoing tricuspid annuloplasty (TA) for functional TR at a single were analyzed. Residual TR was defined TR moderate-or-more at discharge. Recurrent TR was defined TR-moderate-or-more at follow up. RV remodeling was defined RV dysfunction and/or dilatation. Results. Residual TR after TA was recorded in 54. Five-year freedom from TR recurrence was 86.3±2.3% for patients without residual TR vs 57.6±7.6% for patients with residual TR, p<0.001. Evaluating late results of 369 patients without residual TR, following risk factors were identified: preoperative pulmonary pressure, pre RV remodeling, pre TR and TV remodeling, functional mitral regurgitation. Conclusions. Prophylactic tricuspid annuloplasty should be encouraged among surgeons. TA at the time of left-sided valve surgery should take into consideration not only annular size, but also tethering severity and RV remodeling.

INTRODUCTION

Functional tricuspid regurgitation (TR) can result from enlarged annular area and increased chordal tethering. Annular dilatation is a constant feature and is strongly related to right atrial or ventricle (RV) enlargement[1]. \soutTricuspid regurgitation (TR) was reported in 33% of men and in 37% of women, respectively[2]. \soutSevere TR was associated with a very poor prognosis, independently of age, RV dimensions, biventricular function and inferior vena cava size[3].

The observation that TR could progress after successful MV replacement or repair[2] leaded surgeons to correct even moderate-or-less TR with dilated annulus (>40 mm or >21 mm/m^2). The results of surgical TR correction are, however, still flawed, and prophylactic tricuspid annuloplasty remains underused[3], being performed in only 10% of patients with MV disease[4].

This retrospective study was aimed to evaluate the relationship between preoperative RV remodeling and both late TR recurrence and RV remodeling, so to identify subgroups of patients at higher risk of tricuspid annuloplasty (TA) failure, to adopt different surgical indications and treatment strategies.

MATERIAL AND METHODS

From May 2009 to December 2015, 688 patients undergoing TA for functional TR at Prince Sultan Cardiac Center, Riyadh, Saudi Arabia, were initially scheduled for this study according to the following criteria: (i) MV disease requiring surgical intervention; (ii) no pathologic changes in TV leaflets; (iii) no previous TV repair; (iv) not associated tricuspid valvuloplasty. Early results of this study have been already reported[6]. Twenty-six patients died in the early postoperative period, so they were excluded from the analysis. Moreover, 239 patients were lost at follow up because they came from very far cities or neighboring states of the Arabic peninsula.

Finally 423 patients, where transthoracic echocardiographic evaluation was performed preoperatively and at follow up, were included into the study. Retrospective analysis of our database was approved by the institutional review board, which waived patient consent. In 54 out of 423 (13%) a moderate-or-more TR was recorded at the discharge[5]. Hence, we analyzed the long-term results of two cohorts of patients: 54 with residual TR and 369 without residual TR, with particular attention to the latter one.

Preoperative characteristics of the study patients are summarized in Table 1.

Echocardiographic evaluation

In all patients, ejection fraction, left ventricular diameters were measured by echocardiography, according to the recommendations of the American Association of Echocardiography[6]. Tricuspid annulus, TV coaptation depth (CD) and tenting area were collected in apical 4-chamber view. TR severity was graded as mild, moderate, severe[6]. Recurrence of TR was defined as the presence of TR graded moderate-or-more. *TV remodeling* was defined according to at least one cutoff (CD[?]6.5 mm, tenting area [?]0.85 cm^2 and tricuspid annulus[?]35 mm)[5].*RV dilatation* was defined as a basal end-diastolic diameter >42 mm and/or mid-level diameter >35 mm[7,8]. *RV dysfunction* was defined as TAPSE <16 mm and/or TDI-S' velocity <10 cm/sec[7,8]. *Right ventricular remodeling* was defined as RV dilatation and/or dysfunction. A systolic pulmonary pressure (sPAP)>55mmHg was considered as severe pulmonary hypertension[7,8]. *Failure of MV surgery at follow-up* was defined MV area [?]1.5 cm2 and/or moderate-or-more regurgitation.

Surgical indications and techniques

Moderate-or-severe TR was always corrected during MV surgery. Mild TR was treated if systolic dimension of the annulus was >24 mm[9]. All patients underwent surgery through a median sternotomy. TV repair was accomplished using De Vega annuloplasty, flexible bands (Sovering MiniBand, SMB50, Sorin, Saluggia, Italy; Cosgrove-Edwards, Edwards Lifesciences, Irvine, CA, USA; Duran, Medtronic, Inc, Minneapolis, MN, USA), or a rigid incomplete ring (MC3, Edwards Lifesciences, Irvine, CA, USA). Myocardial protection was achieved using intermittent warm antegrade and retrograde blood cardioplegia.

Follow-up

The most recent clinical information was obtained by calling the patient or the referring cardiologists. The median clinical follow-up was 41 (20-64) months. The average number of echocardiographic studies at follow up for patients was 1.5, but we reported the last one in all cases but when TR moderate-or-more was recorded. In those cases, the first echocardiogram reporting recurrence was collected. The median echocardiographic time was 35(18-58). Follow-up ended in December 2016.

Endpoints

The primary endpoint was *TR recurrence* . The secondary end-point was late RV remodeling later after surgery. Survival was also assessed.

Statistical analysis

Categorical variables are expressed as counts (percentages). Continuous variables are presented as mean+-SD if normally distributed, and as quartiles if non-normally distributed. Comparisons between groups were made using unpaired 2-tailed t -test or Mann-Whitney U test; Pearson's chi-square test for categorical variables.

Pre- and postoperative data of each group were compared by paired t -test or Wilcoxon-test. ROC curve analysis was used to determine different cut-offs. Cox proportional hazards regression models were used for either TR recurrence or late RV remodeling, and reported as the hazard ratio with 95% confidence intervals. In case of correlation between covariates, different models were built. For all tests, a p-value of <0.05 was considered statistically significant. The SPSS software (SPSS Inc., Chicago, IL, USA) and R Core Team (2013). (R: Vienna, Austria. URL*http://www.R-project.org/*) were used.

RESULTS

Preoperative and operative data are summarized in the table 1. At discharge, all patients received optimal medical treatment.

Sensitivity and specificity of TV cutoffs for TR recurrence were 66% and 88% for tricuspid annulus[?]35mm, 83% and 42% for CD[?]6.5mm, and 81% and 34% for tenting area[?]0.85cm^2)

Five-year freedom from TR recurrence was 74+-3%, significantly lower in patients with residual TR (41+-8% vs 81+-3%, p<0.001).

Patients with residual TR

Fifty-four patients showed residual TR. In 22 (41%) cases, the grade of TR at follow up was mild-or-less, conversely, in 32 (59%) cases, TR remained moderate-or-more. Five (9.3%) patients died after first month with a 8-year survival of 86+-6%.

Patients without residual tricuspid regurgitation

Recurrent TR after TA was recorded in 53 (14%) cases; 5-year adjusted freedom from TR recurrence was significantly lower in patients with preoperative RV remodeling (75+-4% vs 91+-3%, p<0.001; Figure 1).

In 114 (31%) patients RV was found remodeled at follow up; adjusted 5-year freedom from RV remodeling was 66+-3%, significantly lower in patients with preoperative RV remodeling (57+-4% vs 79+-5%, p<0.001, Figure 2).

At multivariable analysis, similar risk factors were identified for TR recurrence and RV remodeling: preoperative RV remodeling, preoperative mild-or-moderate TR with TV remodeling, severe TR, preoperative pulmonary pressure and functional MR (Tables 2-3).

Comparison between preoperative and follow up echocardiographic data are summarized in the table 4.

Twenty-six patients died after discharge, 18 from cardiac or unknown causes and 8 from non-cardiac causes. Eight-year survival was 88+-3%. Cox analysis with time-dependent variable confirmed TR recurrence and late RV remodeling as risk factors for lower survival (Table 5, Figures 3-4).

Surgery and late results

No protective effect of either flexible band/ring (HR 1.06, 0.28-3.97) or rigid ring (HR 1.99, 0.50-6.91) with respect to DeVega was found.

Similarly, late failure of MV surgery (HR 1.28, 0.78-3.78) did not influence the outcome of TR.

Etiology of MR

The cohort of 369 patients were finally divided according to MR disease, in functional MR (116 patients) and non-functional MR (253); the first group showed significantly worse left ventricle but similar RV than the second group (Table 6).

Discussion

This retrospective study confirms that TA besides left-sided valve surgery has still suboptimal results, with residual TR of 13%, within the range reported in the literature (9-39%)[10-14]. In our series, 20% of cases experienced TR recurrence at mid-term, lower than others (31-45%)[10,14,15]. However, the rate of late TA

failure increased significantly in patients discharged with residual TR. Kuwaki et al[11] reported an hazard ratio of even 15.1% TV reoperation in patients with residual TR.

In patients without residual TR at the discharge, preoperative severity of TR and TV remodeling, preoperative RV remodeling, functional MR and systolic pulmonary pressure were identified as risk factors for moderate-or-more late TR.

As expected[11,14-16], preoperative severe TR was found to be an important predictor for TR recurrence. Although TA can effectively reduce annular dimension, it further increases chordal tethering with aggravation of leaflet tenting as a consequence of increased interpapillary muscle distance and incomplete leaflet closure due to inward annulus displacement after TA, ultimately leading to TA failure.

Nowadays surgery is indicated in patients with severe TR and should be considered in patients with mild-or-moderate TR with a TA[?]40m[17]. However, besides TA dilatation, tethering severity plays a key-role for TA durability. Fukuda et al[15] proposed a tenting height of 5.1 mm and a tenting area>0.8 cm^2 as predictors for TV recurrence. In our study, a CD[?]6.5mm, tenting area[?]0.85cm^2 and a tricuspid annulus[?]35mm were predictive for recurrent TR even in presence of moderate-or-less TR. This result supports the rationale for performing prophylactic TA in low-graded TR with TV remodeling, since TA does not increase operative risk[18]. Shiran et al[19] suggested to perform TA for low-graded TR and tricuspid annulus[?]35mm. We believe that TA size alone cannot be used to identify patients who should receive prophylactic TA, but tethering severity should also be considered.

The purpose of surgery should be to interfere with the mechanisms leading to irreversible RV damage by correcting both left-sided lesions (to reduce pulmonary pressure) and TR (to eliminate volume overload)[20,21].

The main finding of this study is the strict correlation between the evolution of TA and RV remodeling. Risk factors impairing late result of TA are the same impairing late RV remodeling, demonstrating a synergistic relationship between these two entities. Failure of TA causes increased volume overload with possible RV dilatation and dysfunction, which in turn begets TR. The patients with preoperative severe-or-less TR with TA dilatation can show positive RV remodeling after TA[21]. However, in some cases, RV remodeling after TA[12] is not so positive as expected, likely due to irreversible maladaptive RV hypertrophy/enlargement with reduced RV contractility. RV enlargement can result in disproportionate dilatation along the free wall to the septum minor axis and a more spherical RV shape, which implies a greater displacement of the papillary muscles[22]. Yu and coworkers[22]demonstrated that patients undergoing TA who had a larger RV mid-cavity diameter along with larger TV tethering area, developed adverse events at 1-year follow up. So, TA may not be able to approximate displaced papillary muscle to achieve an effective TV closure.

Moreover, both late significant TR and RV remodeling were found to be risk factors for lower survival. In a recent echocardiographic analysis[23], 5-year survival was significantly worse in patients presenting RV dilatation or dysfunction than normal RV.

How much preoperative pulmonary pressure can be improved by TA is still debated. Chickwe et al[24] analyzed results of 419 patients receiving TA along with MV repair, showing sPAP improved significantly at discharge and follow-up. Conversely, Chen et al[25] demonstrated that 43% of patients undergoing TA had residual PH; De Bonis et al[26] reported 26% of patients has still higher sPAP at follow up. In patients having MV surgery, residual PH is likely due to irreversible pulmonary vascular remodeling, and this barrage can produce both RV remodeling and TR recurrence over time[27].

In our experience, patients with FMR undergoing MV/ TV surgery showed more dilated and dysfunctioning LV than no-FMR, with higher sPAP. The underlying disease of FMR is both valvular and ventricular, so, despite surgical correction of MV, LV remodeling may not improve. Higher intraventricular end-diastolic pressure may persist after surgery, with consequent high post-capillary pulmonary pressure.[26]Moreover, most of the effects of LV contraction on the RV are mediated by the interventricular septum. In presence of cardiomyopathy, septal twisting is reduced due to septal damage, especially when pulmonary vascular resistances are increased.

The natural consequence is that RV remodeling may not improve, with increasing of tethering forces on TV leaflets and the inability to coapt despite TA.

Whether the surgical technique could influence TR recurrence remains debated[27-30] . In our experience, no difference was observed according to the surgical strategy.

Patients with severe TR and dilated RV represent a challenging subgroup where TA id not a reasonable treatment option. The clover technique[31] or anterior leaflet patch augmentation[32], may be valuable alternatives. We recently reported a strategy where the anterior and posterior leaflets are almost entirely detached (50% of the annulus) and a patch as large as the full tricuspid orifice is inserted without TA[33]. It is however evident that there is no definite solution yet to this problem, and perhaps it is time to think to a prospective randomized study to find the best treatment option.

Limitations of the study

Firstly, it is retrospective, then, TR grading could be exposed to operator's bias and was out of our control. Moreover, 3D echocardiography was not used in our study population.

Conclusions

Prophylactic tricuspid TA should be encouraged among surgeons even earlier than guidelines recommend, and decision-making for the treatment of low-graded TR at the time of left-sided valve surgery should consider not only annular size, but also tethering severity and RV remodeling. In these cases, the surgical approach should not be limited to TA, but surgeons should consider alternative techniques or prosthesis implantation.

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Figure legends

Figure 1. Adjusted freedom from tricuspid regurgitation (TR) recurrence according to the presence (yellow-line) or absence (blue-line) of preoperative right ventricular remodeling.

Figure 2. Adjusted freedom from late right ventricular (RV) remodeling according to the presence (yellow-line) or absence (blue-line) of preoperative right ventricular remodeling.

Figure 3. Adjusted survival according to the presence (yellow-line) or absence (blue-line) of TR recurrence.

Figure 4. Adjusted survival according to the presence (yellow-line) or absence (blue-line) of late RV remodeling.

Table 1. Preoperative and operative data according to residual or not tricuspid regurgitation.

	Overall N=423	Non-residual TR N=369	Residual TR N=54	p-value
Age (years)	52±16	52±15	52±17	0.887
BMI (Kg/m2)	28±6	28±6	28±7	0.513
Female gender	256(61%)	218(59%)	38(70%)	0.113
Creatinine (mmol/L)	69(55-85)	69(55-85)	68(59-84)	0.965
Diabetes	163(39%)	140(38%)	23(43%)	0.512
Rhythm status				0.107
Sinus rhythm	299(71%)	267(72%)	32(59%)	
Atrial fibrillation	122(28%)	100(27%)	22(41%)	
Pacemaker	2(1%)	2(1%)	0	
NYHA				0.311
I	18(4%)	17(5%)	1(2%)	
II	66(16%)	61(17%)	9(9%)	
III	274(65%)	237(64%)	37(69%)	
IV	65(15%)	54(15%)	11(20%)	
Status				0.773
Elective/Urgent	417(98%)	364(99%)	53(98%)	
Emergent	6(2%)	5(1%)	1(2%)	
MV disease				0.809
Functional MR	130(31%)	116(31%)	14(26%)	
Rheumatic	195(46%)	166(45%)	29(54%)	
Organic non rheumatic	64(15%)	57(15%)	7(13%)	
Myxomatous	20(5%)	18(5%)	2(4%)	
Prosthesis dehiscence	14(3%)	12(3%)	2(4%)	
LVEF (%)	48±12	48±12	48±12	0.810
LVEDD (mm)	54±9	54±9	52±8	0.049
LVESD (mm)	38±9	38±9	36±10	0.156
LVEDV (ml(m^2)	82±30	82±31	78±25	0.242
LVESV (ml(m^2)	41±24	41±25	37±23	0.336
TV annulus (mm)	35±4	35±4	38±3	<0.001

	Overall N=423	Non-residual TR N=369	Residual TR N=54	p-value
[?]35mm	232(55%)	186(50%)	46(85%)	<0.001
CD (mm)	5.2±1.4	5.1±1.4	6.1±1.6	<0.001
[?]6.5mm	81(19%)	56(12%)	25(46%)	<0.001
TV tenting area	1.06±0.56	1.01±0.53	1.31±0.65	0.027
[?]0.85cm^2	109(26%)	82(22%)	27(50%)	<0.001
sPAP (mmHg)	53±18	52±18	55±18	0.383
TAPSE (mm)	18±6	18±6	16±5	0.009
TDI S' (cm/s)	13±4	13±4	12±4	0.227
RVBD (mm)	42±5	42±5	45±5	<0.001
RVMD (mm)	37±5	37±5	40±5	<0.001
RV remodeling	258(61%)	250(56%)	50(93%)	<0.001
TR grade				<0.001
Mild	70(17%)	69(19%)	1(2%)	
Moderate	232(55%)	212(57%)	20(37%)	
Severe	121(28%)	88(24%)	33(61%)	
TV surgery				0.424
DeVega	24(6%)	21(6%)	3(6%)	
Rigid Ring	76(18%)	69(19%)	7(13%)	
Flexible ring/band	323(76%)	279(75%)	44(81%)	
CABG	129(31%)	114(31%)	15(28%)	0.642
MV surgery				0.011
MV repair	160(38%)	148(40%)	15(22%)	
MV replacement	263(62%)	221(60%)	42(78%)	
AVR	89(21%)	82(22%)	7(13%)	0.117
SVR	38(9%)	35(10%)	3(6%)	0.346

Legend. BMI = body mass index, NYHA = New York Heart Association, MV = mitral valve, MR = mitral regurgitation, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, TV = tricuspid valve, CD = coaptation depth, sPAP = systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, TDI = tissue Doppler imaging, RVBD = right ventricular basal diameter, RVMD = right ventricular mid-cavity diameter, TR = tricuspid regurgitation, CABG = coronary artery bypass grafting, AVR = aortic valve replacement, SVR = surgical ventricular reconstruction.

Table 2. Risk factors for recurrent tricuspid regurgitation.

Model 1	**HR**	**95% CI**	**p**
Pre sPAP (mmHg)	1.013	1.008–1.027	0.042
Pre RV remodeling*	**2.316**	**1.172–4.574**	**0.015**
Functional MR	1.880	1.046–3.376	0.034
Model 2	**HR**	**95% CI**	**p**
Pre sPAP (mmHg)	1.013	1.009–1.029	0.041

Model 1	HR	95% CI	p
Pre mild or moderate TR (reference) without TV apparatus remodeling			
Pre mild or moderate TR with TV apparatus remodeling	**8.545**	**2.562–28.495**	**<0.001**
Pre severe TR	**14.591**	**4.356–48.864**	**<0.001**
Functional MR	2.206	1.209–4.024	0.009

HR, hazard ratio; CI, confidence interval; Pre, preoperative; sPAP, systolic pulmonary artery pressure; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve; MR, mitral regurgitation.

C-statistic 0.75 (model 1); C-statistic 0.78 (model 2)

**RV remodeling and TV remodeling are correlated*

Table 3. Risk factors for late right ventricular remodeling.

Model 1	HR	95% CI	p
Pre sPAP (mmHg)	1.009	1.005–1.018	0.048
Pre RV remodeling*	**2.551**	**1.616–4.024**	**<0.001**
Functional MR	1.504	1.016–2.226	0.041
Model 2	**HR**	**95% CI**	**p**
Pre sPAP (mmHg)	1.010	1.002–1.019	0.045
Pre mild or moderate TR (reference) without TV apparatus remodeling			
Pre mild or moderate TR with TV apparatus remodeling	**1.203**	**1.008–1.938**	**0.046**
Pre severe TR	**2.478**	**1.560–3.937**	**<0.001**
Functional MR	1.603	1.081–2.380	0.019

HR, hazard ratio; CI, confidence interval; Pre, preoperative; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve;

MR, mitral regurgitation. *C-statistic 0.75 (model 1); C-statistic 0.75 (model 2)*

**RV remodeling and TV remodeling are correlated*

Table 4. Comparison of echocardiographic data between preoperative and follow up.

	Preop 369	Follow up 369	p-value
LVEF (%)	48±12	47±12	0.321
LVEDD (mm)	54±8	50±8	<0.001
LVESD (mm)	38±9	37±10	<0.001

	Preop 369	Follow up 369	p-value
sPAP (mmHg)	54±18	43±14	<0.001
TAPSE (mm)	18±6	20±6	<0.001
TDI S' (cm/s)	13±4	14±4	<0.001
RVBD (mm)	42±5	39±5	<0.001
RVMD (mm)	37±5	34±5	<0.001
RV remodeling	208(56%)	114(31%)	<0.001
TR grade			<0.001
No TR	0	128(35%)	
Mild	69(19%)	188(51%)	
Moderate	212(56%)	41(11%)	
Severe	88(24%)	12(3%)	

Legend. LVEF=left ventricular ejection fraction, LVEDD=left ventricular end-diastolic diameter, LVESD=left ventricular end-systolic diameter, sPAP=systolic pulmonary artery pressure, TAPSE=tricuspid annular plane systolic excursion, TDI=tissue Doppler imaging, RVBD=right ventricular basal diameter, RVMD=right ventricular mid-cavity diameter, TR=tricuspid regurgitation.

Table 5. Cox with time-dependent variable: Risk factors for late mortality.

Model 1	**HR**	**95% CI**	**p**
Pre creatinine (mmol/l)	1.002	1.001-1.005	0.024
Late TR[?]2+	**3.106**	**1.519-6.349**	**0.002**
Functional MR	4.497	2.101-9.625	<0.001
LVEF (%)	0.9718	0.938-0.992	0.044
Model 2	**HR**	**95% CI**	**p**
Pre creatinine (mmol/l)	1.002	1.001-1.004	0.006
Late RV remodeling	**6.468**	**3.884-10.773**	**0.001**
Functional MR	1.819	1.134-2.918	0.013
Diabetes	1.808	1.131-2.890	0.013

HR, hazard ratio; CI, confidence interval; Pre, preoperative; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve;

MR, mitral regurgitation. *C-statistic 0.84 (model 1); C-statistic 0.80 (model 2)*

Table 6. Comparison of preoperative echocardiographic data between functional and non-functional mitral regurgitation.

	FMR n = 116	No-FMR n =253	p-value
LVEF (%)	35±12	53±8	<0.001
LVEDD (mm)	58±9	53±8	<0.001
LVESD (mm)	44±9	36±8	<0.001
sPAP (mmHg)	57±16	52±19	0.035
TAPSE (mm)	18±6	18±6	0.257
TDI S' (cm/s)	13±4	13±4	0.328
RVBD (mm)	42±5	42±5	0.716
RVMD (mm)	37±5	37±6	0.956
RV remodeling	67 (58%)	141 (56%)	0.715

	FMR n = 116	No-FMR n =253	p-value
TV remodeling	61 (53%)	148 (59%)	0.287
TR grade			0.011
Mild	28 (24%)	41 (16%)	
Moderate	71 (61%)	141 (56%)	
Severe	17 (15%)	71 (28%)	

Legend. LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, sPAP = systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, TDI = tissue Doppler imaging, RVBD = right ventricular basal diameter, RVMD = right ventricular mid-cavity diameter, TR = tricuspid regurgitation.