Tricuspid valve regurgitation

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**TRICUSPID VALVE REGURGITATION:
ITS INTERPLAY WITH THE RIGHT VENTRICLE,
PROGNOSTIC ROLE, AND SURGICAL RESULTS
IN VARIOUS SETTINGS.**

Michele Di Mauro

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**TRICUSPID VALVE REGURGITATION:
ITS INTERPLAY WITH THE RIGHT VENTRICLE, PROGNOSTIC ROLE, AND SURGICAL RESULTS
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DISSERTATION

to obtain the degree of Doctor at the Maastricht University,
on the authority of the Rector Magnificus,
Prof. dr. Rianne M. Letschert
in accordance with the decision of the Board of Deans,
to be defended in public
on Thursday 11th November 2021 at 12:00 hours

by

Michele Di Mauro

From the theatrical comedy "Questi Fantasmi" (These Ghosts)

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Performed in 2007

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From the theatriacal tragedy "L'Uomo-Carbone" (The Coal-Man)

Authors: Michele Di Mauro e Federica Vicino

Performed from 2010 to 2016

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From the theatrical comedy "Azzardo" (Gambling)

Authors: Various

Performed from 2012 to 2013

1

GENERAL INTRODUCTION

Tricuspid regurgitation (TR) is one of the most common manifestations of valvular heart disease (VHD) and may affect even up to 65–85% of the population (1,2). The Framingham Heart Study, a large cardiovascular cohort study, showed that the presence of any severity of TR was 82% in men and 85.7% in women (1).

In a cohort of 5,507 consecutive patients undergoing echocardiography over a period of four years (2), 601 patients (11.5%) showed no TR, 3,805 (68.8%) mild TR, 620 (11.8%) moderate TR and 199 (3.8%) severe TR. Mortality increased with increasing severity of TR. The one-year survival was 91.7% with no TR, 90.3% with mild TR, 78.9% with moderate TR, and 63.9% with severe TR. Moderate or greater TR was associated with increased mortality regardless of PASP (hazard ratio [HR] 1.31, 95% confidence interval [CI] 1.16 to 1.49 for PASP >40 mm Hg; HR 1.32, 95% C 1.05 to 1.62 for PASP <40 mm Hg) and LVEF (HR 1.49, 95% CI 1.34 to 1.66 for EF <50%; HR 1.54, 95% CI 1.37 to 1.71 for EF >50%).

Primary or organic tricuspid regurgitation (TR) is relatively uncommon (10% of tricuspid regurgitation) and may be due to either acquired (rheumatic, degenerative, infectious, traumatic or iatrogenic) or congenital diseases. Conversely, secondary or functional TR, caused by dilatation and flattening of the tricuspid annulus along with increase of leaflet tethering due to the remodeling of the right ventricle (RV) has become in last decade an emerging entity (3-6).

The annulus is pear-shaped (7), whereas other studies have predominantly found the annulus to be more saddle-shaped (8,9). The non-planar configuration of the TV annulus plays a major role in the coaptation, mobility and the stress distribution in the TV leaflets and chordae tendineae (7-9). The fibrous annulus forms the antero-medial regions and continues with the connective tissues into the TV leaflets. Microscope-based study of the human TV annulus (10) indicated the presence of myofibers in the posterior and anterior annulus and collagen bundles in the septal annulus. Recent examination of the porcine valves leaflets demonstrated that the

TV leaflets are more translucent and thinner than their mitral valve (MV) counterparts as a result of fewer collagen proteins; indeed, histological analysis revealed the difference in the layered structure between the TV and MV leaflets (11). TV leaflet tissue layers are composed of extracellular matrix proteins—elastin, collagen, proteoglycans (PGs), and glycosaminoglycans (GAGs) populated with dynamic valvular interstitial cells (VICs). The connective tissue structure is organized into four morphologically and biomechanically distinct layers known as the *atrialis* (A), *spongiosa* (S), *fibrosa* (F), and *ventricularis* (V) (11).

The chordae tendineae are fibrous strings that originate from the ventricular papillary muscles or from the ventricle wall and transmit tensile force to the leaflets. The chordae split into three segments either soon after their origin or just before their attachment to the leaflets or the commissural region. Chordae tendineae are composed of elastin, GAGs, collagen fibers, and endothelial cells. The chordae tendineae are typically categorized as basal, marginal, strut, or commissural based on their leaflet attachment location. The marginal chordae that are connected to the free edges of the leaflets are stiffer than the basal chordae that are attached to the TV annulus (12).

The relationship between TR and the RV is complex and differs according to the mechanism of TR. Primary TR causes pure volume overload on initially normal right-sided cardiac chambers (13). Conversely, RV enlargement is the major cause of secondary TR, through tricuspid annular dilatation and valve tenting (14).

The severity of functional TR and RV dilatation is strongly correlated. Annular dilatation appears to be a secondary consequence of either atrial (i.e. permanent atrial fibrillation) or RV dilatation. RV enlargement is most often consequent to increased afterload due to pulmonary hypertension, mirroring increased left-side filling pressures (15-17).

In the study of Fukuda et al. (15), left ventricular (LV) ejection fraction, RV systolic area, RV spherical index and right atrial area were identified as independent factors

correlated with TV tethering height at stepwise multivariate regression analysis.

The RV has less muscle mass than the left ventricle, and RV systolic function is therefore more load sensitive. Thus, pulmonary hypertension results in an early fall in RV ejection fraction and associated RV enlargement (18).

RV enlargement is also responsible for complex interactions with the left ventricle, and left ventricular impairment may itself lead to reduced RV stroke volume (19).

The entity of tricuspid regurgitation can be assessed mainly and simply by 2-D echocardiography, using qualitative, semiquantitative or quantitative approaches; usually three grades are used, mild, moderate or severe. However, in the diagnosis for TR, an accurate evaluation of the complex tricuspid anatomy, as well as the remodeling of the right ventricle and pulmonary pressure, is pivotal (4)

In clinical practice, the simplest method used to evaluate the RV dimension and function is adjusting the echocardiographic apical 4-chamber view by rotation of the probe over the cardiac apex in order to measure basal, mid-cavity and longitudinal diameter. RV enlargement can be defined as basal diameter >42mm, mid-cavity diameter >33mm or apex-to-base length >86mm (21). Systolic function of the RV can be evaluated measuring the fractional area change (the percentage change in RV chamber area during the cardiac cycle that is normal if >35%), tricuspid annular plane systolic excursion (TAPSE) assesses the degree of tricuspid annular displacement towards the apex and accurately reflects RV longitudinal function (normal if >14mm) (22), tricuspid annular systolic velocity by Tissue Doppler (normal if <11 cm/s) (21)

However, these values may underestimate the extent of RV dysfunction in the presence of severe TR with volume overload and should be interpreted with caution. Therefore, when available, cardiac magnetic resonance has been performed.

Both ESC/EACTS (23) and AHA/ACC (24) guidelines recommend TV surgery in patients with severe TR undergoing left-sided valve surgery, irrespective of symptoms (Class I) and in asymptomatic with RV enlargement or RV function deterioration (Class IIa). TV repair is also recommended in patients with mild/moderate secondary TR and significant annular dilatation (≥ 40 mm or 21 mm/m^2) (Class IIa).

In two recent studies by our group (25,26), early and late failure of tricuspid annuloplasty (TAP) was investigated in a cohort of patients undergoing where TAP was associated to mitral valve surgery. Residual TR, defined as moderate or more TR at the time of discharge, was found in 85 (12.4%) patients out of 688 (25), and preoperative mild-moderate TR with TV apparatus and-or RV remodeling as well as patients with severe TR were resulted at significantly higher risk for early failure; TV apparatus remodeling was defined as TV coaptation depth ≥ 6.5 mm, tenting area $\geq 0.85 \text{ cm}^2$, and tricuspid annulus ≥ 35 mm. This finding supported a prophylactic TV annuloplasty in presence of less than severe TR, but with a tricuspid annulus larger than 35mm, even less than the cutoff proposed by the guidelines (23,24).

Both European and American (23,24) guidelines state that isolated TV surgery is indicated in symptomatic patients with severe primary TR (Class I) and should be considered in asymptomatic or mildly symptomatic patients with RV enlargement or deteriorating RV function (Class IIa). In fact, although such patients respond well to diuretic therapy, delayed surgery is likely to result in irreversible RV damage, organ failure and poor results of later surgical intervention.

TV repair shows lower perioperative mortality than valve replacement and is generally the preferred option.

In case of tricuspid annuloplasty, recurrent TR occurs in 3%–14% of patients in the early period, with the incidence steadily increasing over time and affecting up to 20% of

patients by 5 years (25-58). This risk appears to be lower in patients treated with a rigid annuloplasty band (59,60). Reoperation for recurrent TR is unusual, but is associated with up to 37% in-hospital mortality (27, 61). Risk factors for recurrence include baseline regurgitant severity, pulmonary, LV dysfunction, RV dilatation or dysfunction, device leads, leaflet tenting and degree of annular dilation (27, 26, 41, 62).

In our experience, in a cohort of 423 patients surviving surgery, undergoing late follow up, we also investigated the role of right ventricle remodeling to predict late failure (26). In 369 out of 423 no residual TR was recorded, with 53 (14%) patients showing recurrent TR, defined as moderate or more TR at follow up. At multivariable analysis some variables were found to be associated with higher risk to develop a further significant TR: Preoperative pulmonary pressure, preoperative RV remodeling (defined as enlargement and/or dysfunction), the presence of functional mitral regurgitation at the index surgery, preoperative TV apparatus remodeling and severity.

In patients with extreme annular dilation, previous failed TV repair or leaflet abnormalities, tricuspid valve replacement (TVR) may be required (63,63). Operative mortality in TVR is often reported to be higher than repair; however, this may be confounded by a greater number of comorbidities in this population.

In a propensity score-matched study of 68 pairs of patients (approximately half of whom underwent isolated surgery), no differences were observed in surgical mortality after matching (13% for TVR vs 18% for repair, $P=0.64$), suggesting when imbalances in comorbidities are adjusted for that operative mortality is similar (65). The choice of bioprosthetic versus mechanical valves has generated much debate. Bioprosthetic valves in the tricuspid position may be more durable than bioprosthetics in the mitral position, perhaps due to lower pressures and velocities (66). Advantages to bioprostheses include a lower risk of valve thrombosis and avoidance of anticoagulation; however, there is up to a 7% risk of

severe bioprosthetic degeneration at 7–8 years requiring stand-alone redo TVR (67,68).

Actually, there is no definite survival benefit of a mechanical versus a bioprosthetic valve, hence the final choice should be a shared decision between the patient and the physician. However, in older patients the lower rate of structural deterioration and possible future need for a pacemaker favor a bioprosthesis.

When surgery is the only definitive treatment for isolated TR, it is rarely performed. Of the 4000–8000 TV operations performed annually in the USA, roughly 80% are at the time of left valve surgery (69,70). Stand-alone surgery makes up only 20% of operations, and many surgeries are performed for indications such as endocarditis. The rarity of stand-alone surgery for isolated TR may result from concerns over in-hospital mortality (8%–10% in most series) and uncertainty surrounding long-term outcomes. Indeed, most studies are small sized and span multiple decades, so this result in widely variable estimations of in-hospital mortality with higher mortality associated with advanced heart failure and redo sternotomy (71).

Additionally, there is a lack of comparative outcomes for medically and surgically treated patients. To date, only a single study has compared long-term survival in patients with isolated TR treated with medical therapy versus surgery. In a series of 45 pairs of propensity score-matched patients (66% secondary TR, 33% primary TR) treated with stand-alone surgery, there was a non-significant trend towards improved survival in the surgical patients (HR 0.29, 95% CI 0.08 to 1.10, $P=0.07$) (72).

New transcatheter solutions for the treatment of TR are now emerging (73), most of which are still in development or in the initial phase of clinical application. Some devices mimic those already employed for the mitral valve, such as leaflet edge- to-edge repair (MitraClip, Abbott Vascular).

The FORMA repair system (Edwards Lifesciences) consists of a passively expanding,

foam-filled balloon that reduces the leaflet coaptation gap by occupying the regurgitant orifice area.

The PASCAL system (Edwards Lifesciences) combines design aspects from the MitraClip and FORMA devices that might overcome some technical limitations observed with these devices in the presence of large coaptation gaps.

Among the suture annuloplasty systems, the Trialign device (Trialign) reproduces the surgical Kay bicuspidization repair technique, the TriCinch Coil system (4Tech Cardio) consists of a corkscrew anchor implanted transfemorally in the anteroposterior commissure of the tricuspid annulus and connected to a self-expandable stent (implanted in the inferior vena cava) through a Dacron band; The Cardioband system (Edwards Lifesciences) is a transfemoral, surgical-like, incomplete, adjustable ring that is implanted directly on the atrial side of the tricuspid annulus and fastened by multiple repositionable anchors. The transatrial intrapericardial tricuspid annuloplasty (TRAIPTA) system is an indirect annuloplasty device, consisting of an adjustable nitinol loop inserted into the pericardial space through a right atrial appendage puncture, and applies indirect external compression to the tricuspid annulus along the atrioventricular groove.

Heterotopic CAVI aims to reduce systemic congestion by implanting balloon-expandable or self-expandable valves in the vena cava (inferior or in combination with the superior vena cava) with the purpose of abolishing systolic caval backflow associated with severe tricuspid regurgitation.

The first successful cases of orthotopic transcatheter tricuspid valve replacement with a dedicated bioprosthesis were reported in 2017 with the GATE tricuspid valved stent (NaviGate Cardiac Structures). Other dedicated transcatheter tricuspid valve platforms, including the Lux-Valve (Jenscare Biotechnology) and the Trisol valve (Mor Research Applications), are currently under preclinical evaluation (73).

Aim and outline of the thesis

The purpose of this thesis is to analyze the prognostic role of the tricuspid regurgitation and the results of the surgical treatment in various settings. Particularly, the interplay between tricuspid regurgitation and right ventricle.

This was achieved through original research, review and meta-analyses.

The prognostic role of tricuspid regurgitation was investigated in a cohort of patients undergoing mitral valve surgery. This is followed by a comprehensive review on functional tricuspid regurgitation, from the anatomy to surgical results.

The interplay between right ventricle, pulmonary hypertension and tricuspid regurgitation, in terms of prognosis, was evaluated in a cohort of patients undergoing tricuspid annuloplasty besides mitral valve surgery.

Then, the issue of isolated tricuspid regurgitation due to infective endocarditis was addressed, presenting a very long-term outcome of a cohort of patients from the INFECT-REGISTRY, the Italian Registry for Surgical Treatment of Valve and Prosthesis Infective Endocarditis.

A network meta-analysis was performed to compare four different approaches for secondary or functional tricuspid regurgitation: no treatment, suture annuloplasty, flexible ring and rigid ring annuloplasty, in order to establish the best treatment.

Finally, early and late outcomes of tricuspid valve repair compared to replacement, for treatment of isolated tricuspid regurgitation due to infective endocarditis, were analyzed.

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From the theatriacal commedy "Miles Gloriosus"
Author: Plauto
Performed from 2010 to 2012

2

MITRAL VALVE SURGERY FOR FUNCTIONAL MITRAL REGURGITATION. PROGNOSTIC ROLE OF TRICUSPID REGURGITATION.

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ABSTRACT

Background: The purpose of this study was to evaluate the impact of untreated moderate-or-more functional tricuspid regurgitation (FTR) on mid-term outcome of patients with functional mitral regurgitation (FMR) undergoing mitral valve surgery (MVS).

Methods: From January 1988 to April 2003, 165 patients having FMR underwent MVS with untreated FTR. Patients with organic mitral or tricuspid valve disease were excluded. The entire population was divided into two groups, group A: 102 patients (FTR 0/1+), group B: 63 patients (FTR 2+/ 3+). No statistical difference was found between two groups concerning preoperative and operative variables. MV was repaired in 137 and replaced in 28 cases; the impact of untreated moderate-or-more FTR was estimated by Cox analysis.

Results: Thirty-day mortality was 6.7 (5.9% group A vs 7.9% group B, $p = 0.607$). Five-year actuarial survival was 73.5% (66.6—80.4%); 88.2% (83.0—93.4%) group A versus 46.0% (33.7—58.3%) group B, $p < 0.001$; the possibility to be alive in NYHA class I—II was 65.8% (58.4—73.2%); 78.4% (72.3—84.5%) group A versus 41.2% (29.1—53.3%) group B, $p < 0.001$. Cox analysis confirmed the impact of untreated moderate-or-more FTR on 5-year survival (HR = 3.1, 95% CI = 1.8—5.1, $p < 0.001$) and possibility to be alive in NYHA class I—II (HR = 3.0, 95% CI = 1.8—4.9, $p < 0.001$). After a median interval time of 28 months (IQR = 11—60), TR grade was echocardiographically assessed in 122 (79.2%) of 154 patients surviving the first month. In group A (87 patients), TR grade decreased significantly from 0.7 ± 0.5 to 0.3 ± 0.5 ($p < 0.001$) in the early postoperative period. Then, it increased again to 0.6 ± 0.7 at follow-up ($p < 0.001$); no difference was found between preoperative and follow-up time ($p = \text{ns}$). In group B (35 cases), TR grade decreased significantly from 2.2 ± 0.4 to 1.3 ± 0.7 in the early postoperative period ($p < 0.001$), but then increased again to 2.2 ± 0.9 ($p < 0.001$ vs postoperative value; $p = 0.838$ vs preoperative value). Cox analysis confirmed that the progression of TR grade at follow-up is a risk factor for lower survival and possibility to be

alive in NYHA class I—II.

Conclusions: Patients with untreated moderate-or-more FTR had survival and survival in NYHA class I—II lower than patients with untreated less-than-moderate FTR at 5-year follow-up.

INTRODUCTION

Functional mitral regurgitation (FMR) affects the natural history of patients with ischemic MR or dilated cardiomyopathy [1—5]. Hence, mitral valve surgery (MVS) is considered the treatment of choice worldwide to improve the outcome of these patients.

However, even if the surgical procedures (mitral valve repair or replacement) are not particularly technical demanding, the results are not standardized; it can be due to different risk factors that can change early and late outcome, like preoperative heart failure, low left ventricular ejection fraction (LVEF), large LV dimensions, right ventricular dysfunction [6,7].

Functional tricuspid regurgitation (FTR) is a common finding in presence of mitral valve disease. However, for several years, FTR was not treated, as the common thinking was that it could be relieved simply by treating mitral valve disease [8,9].

So far, the prognostic role of untreated FTR has not yet been delineated. Therefore, the present retrospective study was aimed to evaluate the impact of untreated moderate-or- more FTR on 5-year outcome of patients undergoing mitral valve surgery for treatment of FMR.

MATERIAL AND METHODS

Population

From January 1988 to April 2003, 165 patients with FMR underwent MVS without treating FTR. Patients with organic mitral or tricuspid valve disease were excluded. The entire population was divided into two groups: group A, 102 patients, with FTR grade 1+ (grade 0 in 33 and grade 1+ in 69 cases) and group B, 63 patients, with FTR grade 2+ (grade 2+ in 53 and grade 3+ in 10 cases). Preoperative clinical, echocardiographic and surgical data are reported in the Table 1.

Use of our database was authorized by the institutional review board of the University of Chieti, on October 2004. The authorization waived patient consent

The end-points

The primary end-points were 5-year (mid-term) survival and survival in NYHA class I—II. Moreover, progression of FTR grade and its prognostic role over time have also been investigated.

Table 1
Preoperative data and surgical details.

	FTR □1+ n = 102	FTR 2:2+ n = 63	p value
Age (years)	65.7 ± 8.7	66.4 ± 9.5	0.678
Female gender	24 (23.5%)	18 (28.5%)	0.470
Mean NYHA class	3.0 ± 0.6	3.2 ± 0.7	0.110
Diabetes	27 (26.5%)	20 (31.7%)	0.466
Chronic AF	15 (14.7%)	8(12.7%)	0.713
MR	2.9 ± 0.8	3.1 ± 0.8	0.224
EF (%)	34.2 ± 12.4	32.3 ± 10.7	0.316
EDV (ml/m ²)	120.4 ± 40.4	124.2 ± 40.8	0.632
ESV (ml/m ²)	78.1 ± 31.8	77.0 ± 39.1	0.501
TAPSE (mm)	15.7 ± 3.4	15.2 ± 2.9	0.233
Reoperation	6 (5.9%)	9 (14.3%)	0.068
MV repair	89 (87.3%)	48 (76.2%)	0.066
MV replacement	13 (12.7%)	15 (23.8%)	0.066
CPB interval time (min)	101 (77,131)	106 (76,127)	0.824
XCLAo interval time (min)	81 (63,107)	81 (56,110)	0.796

NYHA: New York Heart Association, AF: atrial fibrillation, MR: mitral regurgitation, MV: mitral valve, EF: ejection fraction, EDV: end-diastolic volume, ESV: end-systolic volume, TAPSE: tricuspid annular plane systolic excursion, MV: mitral valve, CPB: cardiopulmonary bypass, XCLAo: aortic cross-clamping.

Echocardiography

A preoperative routine transthoracic echocardiogram (TTE) was performed by the same operator (SG). Methods used to assess mitral regurgitation, mitral valve apparatus changes, biventricular dimensions and function have been already reported [7]. The severity

of TR assessed by Doppler echocardiography was graded on a scale from 1 to 4 (1 mild, 2 moderate, moderate to severe, 4 severe) [10,11].

Surgery

Mitral valve surgical techniques have been already described [12]. The success of surgical correction in terms of reduction of MR was assessed by means of intra-operative transesophageal echocardiography (TEE). It was achieved in all investigated patients.

Postoperative course and follow-up

After surgery, all the patients were admitted in the intensive care unit (ICU) and from there moved to the surgery and later to the cardiology ward. Follow-up started on March 2007 and ended on June 2007 and it was 100% completed. All the patients were followed up in our outpatient clinic 3, 6 and 12 months after surgery and thereafter at yearly intervals. The more recent information was obtained by calling the patient or the referring cardiologists. Median follow-up time was 86 months (interquartile range, IQR = 66—104); 89 (65—102) in group A and 83 (72—112) in group B, $p = 0.937$.

Statistical methods

Results are expressed as mean value and standard deviation in case of normal distributed continue variables, as median and IQR in case of non-normal distributed continue variables. The Kolmogorov—Smirnov statistic with a Lilliefors significance level was used for testing normality.

In case of categorical variables, counts and percentages were reported. Statistical analysis comparing the two groups was performed with unpaired two-tailed t-test for continue normal distributed variables, with Mann—Whitney U-test for continue non-normal distributed variables and with Pearson's chi-square test (or exact Fisher's test) for categorical variables. Variation of TR grade across two periods (pre-, postoperative and follow-up) was evaluated

by means of Wilcoxon test. Nonparametric 5-year survival curves were obtained with the Kaplan—Meier method, the results were reported as percentage and 95% confidence interval (CI); significant difference between groups was evaluated with log-rank test. Time-to-event analysis was performed by a multivariable Cox proportional-hazard regression; the latter was adjusted for reoperation and mitral valve surgery. Candidates' variables (Appendix B), were tested by univariate approach. Variables with p value 0.2 were then entered in the Cox regression. Final models were validated in 500 bootstrap samples. Factors appearing in 50% or more of the analyses were considered reliably statistically significant. The results were reported as hazard ratio (HR), 95% CI and p value. For all tests, a p value <0.05 was considered significant. The SPSS software (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

Thirty-day mortality was 6.7% (11 patients), 5.9% in group A (6 patients) versus 7.9% group B (5 patients), $p = 0.607$; in all of them but 2, death was cardiac related. Forty-one of 154 survivors died (8/96, 8.3% in group A vs 33/58, 56.9% in group B); in 37 cases death was cardiac related (7/96, 7.3% in group A vs 30/58, 51.7% in group B). Among 113 survivors, functional status (NYHA class) improved from 3.1 $\pm$ 0.6 to 2.0 $\pm$ 0.6 ($p < 0.001$), an improvement of at least one NYHA class was recorded in 77 (68.1%) patients. Functional status was unchanged in 32 (28.3%) and impaired in 4 (4.5%) cases, without any significant difference between groups. Five-year actuarial survival was 73.5% (66.6—80.4%), 88.2% (83.0—93.4%) group A versus 46.0 (33.7—58.3%) group B, $p < 0.001$ (Fig. 1); possibility to be alive in NYHA class I—II was 65.8% (58.4—73.2%); 78.4% (72.3—84.5%) group A versus 41.2% (29.1—53.3%) group B, $p < 0.001$ (Fig. 2).

Fig. 1. Five-year survival stratified by groups: group A (solid line) and group B (dot line). 95% CI is reported.

Fig. 2. Five-year possibility to be alive in I–II NYHA class stratified by groups: group A (solid line) and group B (dot line). 95% CI is reported.

Proportional Cox analysis confirmed the impact of untreated moderate-or- more FTR on 5-year survival (HR = 3.1, 95% CI = 1.8–5.1, $p < 0.001$) and possibility to be alive in NYHA class I–II (HR = 3.0, 95% CI = 1.8–4.9, $p < 0.001$); other independent variables identified by Cox analysis were left ventricular ejection fraction and NYHA class (Table 2).

Table 2
Cox analysis.

Variables	5-Year mortality HR (95% CI); p value	5-Year mortality or NYHA class III–IV HR (95% CI); p value
Unadjusted models		
Moderate-or-more FTR	3.1 (1.8–5.1), <0.001	3.0 (1.8–4.9), <0.001
NYHA class	1.7 (1.1–3.0), 0.028	1.5 (1.1–2.3), 0.043
LVEF	0.96 (0.92–0.99), 0.020	0.97 (0.94–0.99), 0.045
Adjusted models		
Moderate-or-more FTR	3.3 (2.0–5.3), <0.001	3.4 (2.0–5.9), <0.001
NYHA class	1.7 (1.1–2.8), 0.032	1.5 (1.1–2.4), 0.046
LVEF	0.95 (0.91–0.99), 0.008	0.97 (0.94–0.99), 0.035

FTR: functional tricuspid regurgitation, NYHA: New York Heart Association, LVEF: left ventricular ejection fraction.

Progression of TR grade

After a median interval time of 28 months (IQR = 11–60), TR grade was assessed by TTE in 122 (79.2%) of 154 patients surviving the first month. In group A (87 patients), TR grade decreased significantly from 0.7 ± 0.5 to 0.3 ± 0.5 ($p < 0.001$) before hospital discharge. Then, it increased again to 0.6 ± 0.7 at follow-up ($p < 0.001$); no difference was found between preoperative and follow up time ($p = \text{ns}$).

In group B (35 cases), TR grade decreased significantly from 2.2 ± 0.4 to 1.3 ± 0.7 before hospital discharge ($p < 0.001$), but then increased again to 2.2 ± 0.9 ($p < 0.001$ vs postoperative value; $p = 0.838$ vs preoperative value). Mean TR grade was significantly higher ($p < 0.001$) in

Table 3
Residual tricuspid regurgitation.

TR grade	Group A			Group B		
	Pre 87	Post 87	Follow-up 87	Pre 35	Post 35	Follow-up 35
0	30 (34.5%)	57 (65.5%)	46 (52.9%)	0	4 (11.4%)	0
1+	57 (65.5%)	30 (34.5%)	36 (41.4%)	0	15 (42.9%)	8 (22.9%)
2+	0	0	3 (3.4%)	28 (80.0%)	16 (45.7%)	13 (37.1%)
3+	0	0	2 (2.3%)	7 (20.0%)	0	12 (34.3%)
4+	0	0	0	0	0	2 (5.7%)

TR: tricuspid regurgitation.

group B if compared to the corresponding ones in group A, at both postoperative and follow-up time. Sixteen (13.1%) patients showed a progression of TR grade to 3+ or 4+ (2, 2.3%, in group A vs 14, 40.0%, in group B, $p < 0.001$) (Table 3). Five-year survival was 94.3% (90.0—98.6%) in patients with TR degree 2 and 50.0% (25.0—75.0%) in those ones with TR 3 ($p < 0.001$). The same finding was found concerning the possibility to be alive and in III NYHA class, 83.0% (75.6—90.4%) versus 43.8% (19.0—68.6%), $p = 0.031$. Cox analysis confirmed that the progression of TR grade at follow-up was a risk factor for lower survival (HR = 11.2, $p < 0.001$) and possibility to be alive in NYHA Class I—II (HR = 4.4, $p < 0.001$).

In none of patients, the preoperative TR worsens more than two grade At multivariate analysis, predictors of TR grade 3+ at follow-up were preoperative moderate or more FTR grade (HR = 12.7, $p = 0.002$), presence of moderate or more residual FTR at discharge (HR = 2.6, $p = 0.048$) and left atrium diameter (HR = 2.7, $p = 0.002$). FTR progression was not related to FMR progression. Among 103 patients with MV repair who had an echocardiographic control at follow-up, progression to MR grade 3 or 4 [13] was found in 10 cases (9.7%), equally distributed among patients without (8/90, 8.9%) and with FTR progression (2/13, 15.4%), $p = 0.611$. All the 19 patients with MV replacement showed, at the echocardiographic control, a correct prosthetic function. Nevertheless, 3 of them had FTR progression.

DISCUSSION

Functional tricuspid regurgitation (FTR), defined as the incompetence of tricuspid valve (TV) in absence of any structural leaflet disease [14], is caused by TV annular dilatation. Functional tricuspid regurgitation is very often related to increased tethering of tricuspid leaflets due to RV enlargement and pulmonary hypertension [14–20]. A recent echocardiographic study [20] emphasized as moderate or greater TR can increase the mortality rate regardless of pulmonary hypertension or low ejection fraction (HR 1.31). In fact, Nath et al. [20] analyzed the prognostic impact of TR in a cohort of 5223 patients undergoing echocardiography at one of three Veterans Affairs Medical Center laboratories for any reason. At 4 years, more than 70% of patients with no or mild TR were still alive; on the other hand, patients with moderate-to-severe TR showed survival lower than 50%.

However, FTR has often been considered just the hemodynamic consequence of the mitral valve disease, being very commonly associated with this pathology [8,9]; the latter concept persuaded many surgeons to leave FTR untreated, thinking that it could be relieved simply treating mitral valve disease. Conversely, three recent retrospective analyses [21–23] have clearly demonstrated that leaving FTR untreated, at the time of mitral valve surgery, begets more TR at follow-up. Matsuyama et al. [21] evaluated the evolution of TR in a series of 174 patients having moderate or less TR undergoing MV surgery alone. At a mean follow-up of 8.2 years, 16% of cases showed a relevant progression of TR (3+ or 4+). Multivariate analysis identified uncorrected moderate TR (HR = 3.9) as predictor for TR worsening over time. In a very recent retrospective study by De Bonis et al. [22], the rate of moderately severe or severe FTR, at median follow-up of 1.8 years, was 10.2% (8/78 cases); when TR 3+ was combined with the worsening of at least two grades of preoperative value, the rate of FTR progression reached 17.9%. At multivariate analysis, the presence of RV dilatation (OR = 1.7), RV dysfunction

(OR = 13.7) and TR grade at discharge were predictors of TR 3+.

The evolution of untreated TR was even worse in a series of 163 patients undergoing isolated MV repair compared to 148 patients having both MV and TV repair [23]; in fact, TR increased by more than two grades in 48% of patients in MVR group and only in 2% of patients in MVR + TVR ($p < 0.001$). Nevertheless, none of these studies [21—23] demonstrated any impact of untreated moderate or more FTR on mid- or long-term clinical outcome. Although Dreyfus et al. [23] were able to find worse functional status (NYHA class) in case of untreated TR beside MV surgery, the authors failed to evidence any difference after 10 years in terms of survival (90.3% MV repair + TV repair vs 85.5% MV repair alone, $p = ns$) and of cardiac-related event free survival (92.8% MV repair + TV repair vs 90.5% MV repair alone, $p = ns$).

Conversely, in the present study, patients with moderate or more FTR undergoing MV surgery alone showed significant lower 5-year survival and possibility to be alive in NYHA class I—II than those ones with mild or less FTR. This result was also confirmed at multivariate analysis. The progression of FTR (grade 3+) was a strong predictor of worse 5-year outcome and, moreover, it was influenced, in turn, by moderate or greater FTR either in preoperative time or at discharge, as reported by others [21,22]. In our series, roughly half (45.7%) of patients with preoperative FTR 2+ showed the same FTR grade at hospital discharge; this situation begets FTR 3+ in 40% and FTR 2+ in even 77.1%, at follow-up time. It is possible to state that MV surgery alone is not able to relieve FTR either soon after surgery or afterward. In case of persistence of high-graded FTR at hospital discharge, worse evolution of FTR should be expected, independently from MR recurrence. It is reasonable to speculate that the progression of FTR can be due to further enlargement and dysfunction of right ventricle [22]; consequently TV annulus dilates over time, along with increase of papillary muscles displacement and tethering of TV leaflets. This vicious circle can explain the prognostic role of

untreated moderate or more FTR. In fact, the presence of RV dysfunction is a great determinant of worse outcome [7]; and, even in absence of a clear picture of right ventricular dysfunction, it is very likely that FTR might mask the decreased RV contractility as MR does for the LV.

Study limitations

Beside the retrospective nature of this study, there are some other limitations that should be addressed. No information about preoperative right atrial dimensions, tricuspid annular size, or degree of leaflets tethering are provided. Follow-up echocardiograms are lacking of consistent data on right ventricular dimension and function at support of conclusive speculations. Another important drawback is the relatively small sample of the size

Conclusions

Leaving untreated moderate-or-more FTR at the time of surgical treatment of functional mitral regurgitation could impair 5-year survival and survival in NYHA class I—II, given that FTR is likely to progress.

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Appendix B. Candidate variables entered in the univariate analysis

Age (years)

Gender

Etiology (ischemic or non-ischemic)

NYHA class

Heart failure

Chronic atrial fibrillation

Presence of diabetes

Preoperative creatinine value (mg/dl)

Left ventricular end-diastolic volume (ml/m²)

Left ventricular end-systolic volume (ml/m²)

Left ventricular end-diastolic diameter (mmm)

Left ventricular end-systolic diameter (mm)

Left ventricular ejection fraction (%)

Left ventricular end-diastolic sphericity index

Left atrium diameter (mm)

Mitral valve annulus (mm)

Mitral valve coaptation depth (mm)

Mitral regurgitation grade (from 1+ to 4+)

Tricuspid annular plane systolic excursion (mm)

Mitral valve repair/replacement

Coronary artery bypass grafting

Left ventricular reshaping

Reoperation

Cardiopulmonary bypass time (minute)

Cross-clamping time (minute)

Surgeon

From the theatricai tragedy “La Guerra dei Murales” (The Murales War)

Authors: Federica Vicino

Performed from 2013 to 2014

3

FUNCTIONAL TRICUSPID REGURGITATION: AN UNDERESTIMATED ISSUE.

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ABSTRACT

This review article focuses on functional tricuspid regurgitation (FTR) that has long been a neglected and underestimated entity. FTR is defined as leakage of the tricuspid valve during systole in the presence of structurally normal leaflets and chordae. FTR may be secondary to several heart diseases, more commonly mitral valve disease, pulmonary hypertension, atrial fibrillation, cardiomyopathies, right ventricular dysplasia, and idiopathic annular dilatation. The reported prevalence of moderate or greater FTR is roughly 16%, but it rises up to 89% when considering FTR of any grade. According to the recommendations of the European Association of Echocardiography, two-dimensional transthoracic echocardiography (TTE) is the first-line imaging modality for the assessment of valvular regurgitation, whereas three-dimensional TTE may provide additional information in patients with complex valve lesions. Transesophageal echocardiography may be used when TTE results are inconclusive. The natural history of FTR is unfavorable, even in less than severe tricuspid regurgitation. Data from the literature suggest that moderate or greater FTR is a risk factor for worse survival. In addition, FTR of any grade may worsen over time, which makes it reasonable to consider the correction of FTR at an early stage, preferably at the time of mitral valve surgery. Tricuspid valve annuloplasty is the gold standard surgical treatment for FTR and is associated with a recurrence rate, defined as postoperative moderate or severe FTR, ranging from 2.5 to 5.5% at 1-year follow-up.

INTRODUCTION

Functional tricuspid regurgitation (FTR) has long been a neglected and underestimated entity. As it usually occurs secondary to mitral valve (MV) disease, cardiologists and cardiac surgeons have long argued that if regurgitation was “functional”, then it should improve when the MV is treated. However, more recently, FTR has gained increasing recognition in both clinical and surgical settings. The purpose of this review was to discuss the insights of epidemiology, pathogenesis, natural history and surgery of FTR. A special focus was placed on the need for early identification and careful quantification of FTR in order to optimize surgical indications, because the clinical course of the disease may vary according to the several etiologies of FTR. The literature search was performed using primarily the Medline database, but other databases were also considered (CTSNet, CASPUR, Ovid, ScienceDirect).

DEFINITION

FTR is a complex valvular lesion in which the tricuspid valve (TV) leaks during systole in the presence of structurally normal leaflets and chordae. FTR is considered a “ventricular” disease.

ETIOLOGY AND EPIDEMIOLOGY

FTR can be secondary to several heart diseases, but it is usually associated with MV disease, pulmonary hypertension, atrial fibrillation, or cardiomyopathy [1].

Calafiore et al. [2] reported a prevalence of moderate to severe FTR of up to 63% of patients with mitral stenosis. The prevalence of moderate or severe FTR ranges largely

from 8% to 45% in patients undergoing MV surgery for mitral regurgitation (MR). Dreyfus et al. [3] found that 8% of patients had moderate to severe FTR at the time of surgery. Other studies reported a prevalence of moderate or severe FTR associated with MR of 14—37%

Fig. 1. Three-dimensional transthoracic echocardiography (A) and intraoperative echocardiographic view (B) of the tricuspid valve. SL = septal leaflet, AL = anterior leaflet, and PL = posterior leaflet.

[2,4—6] (14—27% for FTR + functional MR, 15% for FTR + MV prolapse [6], and 45% for FTR + primary MR [2]). FTR rate was 25—64% in patients with either ischemic or non-ischemic cardiomyopathy [7,8]. Finally, among 5223 consecutive patients undergoing echocardiography, moderate or severe FTR was observed in roughly 16% but in up to 84% of patients when considering FTR of any grade [9].

ANATOMICAL REMARKS

The TV apparatus is very complex.

The recent introduction of real-time three-dimensional echocardiography (RT3DE) has

allowed to obtain new important geometric insights into the pathophysiological mechanisms underlying FTR [10,11]. The TV consists of three leaf-lets and a non-planar, elliptical saddle-shaped annulus. The anterior leaflet is the largest, followed by the

posterior leaflet, which arises from the posterior margin of the annulus from the septum to the infero-lateral wall, whereas the septal leaflet is the smallest and arises directly from the tricuspid annulus above the interventricular septum (Fig. 1). The normal septal tricuspid leaflet inserts at a position that is slightly apical to the insertion of the anterior MV leaflet. The tricuspid annulus has a complex 3D structure, with the postero-septal portion being the lowest (towards the right ventricular [RV] apex) and the antero-septal portion the highest (towards the right atrium) (Fig. 2). The tricuspid annular area varies from 3.9 cm^2 to 5.6 cm^2 , with a percentage change of approximately 30% during the cardiac cycle [12].

The subvalvular apparatus of the TV consists of the chordae tendineae and two papillary muscles (anterior and posterior). A third papillary muscle is often present too. The anterior

Fig. 2. The tricuspid annulus has a complex three-dimensional asymmetric shape with the postero-septal portion being the lowest (towards the right ventricular apex), and the antero-septal portion the highest (towards the right atrium). With permission from [12].

papillary muscle provides chordae to the anterior and posterior leaflets, whereas the posterior papillary muscle provides chordae to the posterior and septal leaflets. Some chordae tendineae also arise directly from the septum.

PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING FUNCTIONAL TRICUSPID REGURGITATION

In FTR, the TV leaflets fail to coapt because of the geometrical distortion of the normal spatial relationships.

Dilatation of the tricuspid annulus occurs primarily in the anterior and posterior directions, as the small septal wall leaflet is fairly fixed (Fig. 3). The annulus becomes more circular with a decreased medial-lateral/antero-posterior ratio (1.11 ± 0.09 versus 1.32 ± 0.09 , $p < 0.001$) [13]. Both maximum (7.5 ± 2.1 versus $5.6 \pm 1.0 \text{ cm}^2/\text{m}^2$, $p < 0.003$) and minimum (5.7 ± 1.3 versus $3.9 \pm 0.8 \text{ cm}^2/\text{m}^2$, $p < 0.001$) tricuspid annular areas are significantly larger in patients with FTR [12]. Annular dilatation may become irreversible over time, as clearly demonstrated in patients with chronic thromboembolic pulmonary hypertension, in whom no significant changes in annular

dimensions were observed after successful pulmonary thromboendarterectomy [14]. This finding is in contrast with previous studies that considered annular dilatation as the main

determinant of FTR [15].

In addition, FTR results in loss of tricuspid annular contraction, especially in severe cases (from 29.6% to 14.6%). As determined by RT3DE studies, in healthy subjects the tricuspid annular area increases from mid-systole to early diastole, decreases during mid-diastole, and increases again in late diastole. Conversely, in patients with FTR, the early diastolic peak is less frequently observed [12]. Furthermore, annular flattening may also occur, by which the tricuspid annulus loses its bimodal shape [13] (Fig. 4).

Fig. 4. Antero-posterior view of the tricuspid valve annulus in a normal heart (A) and in functional tricuspid regurgitation (B, C). In the presence of functional tricuspid regurgitation, the annulus becomes flatter, with no distinct high point. Ant = anterior; Ao valve = aortic valve; Post = posterior; RV = right ventricle; and RA = right atrium. With permission from [13].

FTR may also be related to RV enlargement or dysfunction, which results in papillary muscle displacement and increased tethering forces with subsequent leaflet malcoaptation (Fig. 5). In the study of Fukuda et al. [16], left ventricular (LV) ejection fraction, RV systolic area, RV

Fig. 5. Two-dimensional transthoracic echocardiography: increased tethering forces upon the tricuspid valve leaflets with subsequent leaflet malcoaptation.

spherical index and right atrial area were identified as independent factors correlated with TV tethering height at stepwise multivariate regression analysis.

The more the right ventricle dilates, the more the RV diastolic pressure increases, with subsequent leftward septal displacement and LV compression. This leads to increased LV diastolic and pulmonary artery pressures that beget tricuspid regurgitation (TR). Kim et al. [17] identified several determinants of FTR severity; in particular, the RV end-systolic eccentricity index, TV tethering area and end-diastolic tricuspid annulus diameter showed an independent association with the regurgitant orifice area of FTR. Using RT3DE, some additional determinants of TR severity have been identified, namely tricuspid annular area, antero-posterior/high-low distance ratio (a measure of non-planarity), RV diastolic area, medial-lateral/antero-posterior distance ratio, antero-posterior diameter, and LV ejection fraction [13].

ECHOCARDIOGRAPHIC ASSESSMENT

According to the recommendations of the European Association of Echocardiography (EAE) [18], two-dimensional transthoracic echocardiography (2DTTE) is the first-line imaging modality for the assessment of valvular regurgitation. 3DTTE may provide additional information in patients with complex valve lesions and TEE may be used when TTE results are inconclusive

2DTTE imaging

Severity grading of tricuspid regurgitation

The assessment of the TV with 2DTTE is obtained from the apical four-chamber (AP-4CV), parasternal short- and long-axis (PT-SAX and PT-LAX) and subcostal views. Several methods can be used to quantify TR, which rely on qualitative, semiquantitative and quantitative measures of severity.

Qualitative echocardiographic parameters. The qualitative approach is based on the spatial distribution of the regurgitant jet with- in the right atrium on color Doppler flow mapping (Fig. 6): the

severity of TR is graded as mild if the jet area is $\leq 5 \text{ cm}^2$, moderate at $5-10 \text{ cm}^2$, and severe if $>10 \text{ cm}^2$; continuous wave Doppler of the TR jet. Similar to MR, the intensity and shape of continuous wave

Fig. 6. Two-dimensional transthoracic echocardiography: color flow mapping of the spatial distribution of the regurgitant jet.

Doppler signal are both affected by TR severity.

Semiquantitative echocardiographic parameters. Semiquantitative methods include the following:

- I. Measurement of the vena contracta width in AP-4CV. This requires optimization of color gain/scale and narrowing of the color sector size and imaging depth in order to maximize the frame rate and allow clear visualization of the three components of the regurgitant jet (vena contracta width, proximal isovelocity surface area [PISA], regurgitant jet into the right atrium). The smallest vena contracta is measured immediately distal to the regurgitant orifice, perpendicular to the direction of the jet at a Nyquist limit of 50–60 cm/s [18]. A vena contracta width $>7 \text{ mm}$ is consistent with severe TR with a sensitivity and specificity of 89% and 93%, respectively. However, in the presence of multiple jets this parameter has limited diagnostic value;
- II. The flow convergence method. According to the EAE recommendations, the PISA radius

in AP-4CV should be measured at mid-systole using the first aliasing and along the direction of the ultrasound beam. A TR PISA radius of > 9 mm at a Nyquist limit of 28 cm/s alerts to the presence of severe TR, whereas a TR PISA radius of ≤ 5 mm suggests mild TR;

III. Systolic flow reversal in the hepatic veins recorded from the subcostal view is highly specific for severe TR (80%);

IV. Anterograde velocity of tricuspid inflow. As for MR, in the absence of tricuspid stenosis, peak E-wave velocity is strongly correlated with TR severity. A peak E-wave velocity of ≥ 1 m/s suggests severe TR.

Quantitative echocardiographic parameters.

Quantitative methods include assessment of the effective regurgitant orifice area (EROA) and regurgitant volume (R Vol). Both approaches only allow to distinguish severe TR ($\text{EROA} \geq 40 \text{ mm}^2$; $\text{R Vol} \geq 45 \text{ mL}$) from non-severe TR.

Other echocardiographic parameters for tricuspid regurgitation quantification

In clinical practice, color Doppler flow mapping remains the most widely available and easy to use method. However, the color flow area of the regurgitant jet is not recommended to quantify TR because jet interrogation by continuous wave Doppler is insensitive to changes in TR severity [18]. Quantitative methods (EROA, PISA) should be applied whenever possible to quantify TR severity, except in case of mild or less TR. In addition, evaluation of TV morphology is mandatory, as the identification of large coaptation defects is suggestive of significant TR. It is also recommended to use a multiparametric approach that integrates indices of severity from 2D/3D imaging of TV morphology, right heart chambers, septal motion and inferior vena cava as well as Doppler measures of regurgitant severity [18].

Tricuspid annular diameter.

Assessment of the tricuspid annular diameter is obtained at end-systole and end-diastole in AP-4CV or PT-SAX, from the point of insertion of the septal tricuspid leaflet to the insertion of the anterior tricuspid leaflet. Contraction of the tricuspid annulus can also be calculated. Significant tricuspid annulus dilatation is defined by a diastolic diameter of 40 mm (21 mm/m²). However, 2DTTE does not allow complete visualization of the tricuspid annulus, resulting in an underestimation of annulus size between preoperative echocardiographic measures and intraoperative surgical view or of the actual annulus size by RT3DE. As a consequence, 65% of patients with normal tricuspid annulus diameter at 2D echocardiography show grade 1–2 TR compared with 30% of patients with normal tricuspid annulus size at RT3DE [10,19].

TV tethering.

The tenting area is measured from AP-4CV by tracing the area between the atrial surface of the leaflets and the tricuspid annular plane at the time of maximal systolic closure. TV coaptation depth is defined as the distance between the tricuspid annular plane and the leaflet coaptation point at mid-systole from the AP-4CV [15,20]. TR severity is related not only to tricuspid annulus dilatation, but also to leaflet tethering and RV dilatation, with subsequent displacement of papillary muscles. A thorough assessment of preoperative TV tethering is therefore essential to reduce the rate of TV repair failure and to establish surgical indication for patients with FTR [21]. A tenting area of > 1.63 cm² and a tethering distance of >0.76 cm are indicative of severe tethering and are good predictors of residual TR after TV surgery [15].

A comprehensive echocardiographic evaluation should always include the assessment of LV and RV dimensions and function as well as pulmonary artery pressure.

3D echocardiography

As reported above, 2D echocardiography suffers from some limitations in the assessment of TV anatomy (i.e., no simultaneous visualization of the three leaflets, incomplete visualization of the tricuspid annulus). RT3DE is now routinely used in clinical practice and, thanks to its unique capability of obtaining a short-axis plane of the TV, it allows users to visualize simultaneously the three moving leaflets during the cardiac cycle and their attachment to the tricuspid annulus [15]. This innovative echocardiographic technique contributed significantly to improve our understanding of the mechanisms underlying FTR, providing important information for planning surgery [10,11]. RT3DE allows a more objective and quantitative evaluation of TV anatomy and function by reducing subjectivity in image interpretation. RT3DE supplements 2DE with detailed images of TV morphology including leaflet size, annulus shape and dimensions, myocardial walls, and their anatomic relationships. Although there are no data supporting the use of RT3DE in selecting patients to be referred for surgical correction of FTR, a better understanding of leaflet morphology and the pathophysiological mechanisms underlying TR may help develop new and more effective techniques for TV repair. Min et al. [22] found that pre-TV annuloplasty tenting volume and antero-posterior annulus diameter measured using RT3DE are independent predictors of residual TR severity, and measurement of these parameters may help to identify patients at high risk for severe residual TR, assisting in the selection of the most appropriate surgical option [22]. Song et al. [23] evaluated the 3D features of vena contracta in FTR to determine the optimal cut-off values of vena contracta width obtained from different views at RT3DE. They found that the vena contracta cross-sectional shape in FTR is ellipsoid with a long antero-posterior dimension. This observation suggests that different width values should be used for quantifying TR severity (for severe FTR, the optimal cut-off values for septal-lateral

vena contracta width and antero-posterior vena contracta width were 0.84 cm and 1.26 cm, respectively) [23,24]. In addition, transesophageal RT3DE is an imaging modality with higher spatial resolution than TTE, though at the expense of lower temporal resolution. It has been validated against direct inspection made during cardiac surgery. Despite data supporting the use of RT3DE, at present there is no evidence that 3D assessment of TV anatomy and function may improve surgical results, and there is a lack of standardized measures and specific software. Notwithstanding this, assessment of TV anatomy and function with 3DE is feasible in ~ 90% of healthy subjects in whom good 2D echocardiographic images can be obtained.

CLINICAL PRESENTATION, NATURAL HISTORY AND SURGICAL INDICATIONS

FTR can arise from a variety of causes, including RV enlargement due to left-sided heart valve disease, LV or RV dysfunction, pulmonic stenosis or regurgitation, pulmonary hypertension, and dilated cardiomyopathy. Patients with FTR present with signs and symptoms of either right-sided heart failure or other underlying conditions. In TR, chronic RV volume overload results in right-sided congestive heart failure manifested by liver congestion, peripheral edema and ascites. In FTR secondary to LV dysfunction, patients may present with dyspnea on exertion, orthopnea and paroxysmal nocturnal dyspnea. Angina related to RV overload and strain is uncommon. Marked plasticity of the right-sided valvulo-ventricular complex leads to marked inspiratory TR accentuation. Such plasticity may explain the load sensitivity of FTR, which may rapidly regress with medical treatment. Although aggressive surgical TR management has been advocated, optimizing RV unloading before TR surgery may be desirable. The natural history of FTR is unfavorable, even in less than severe TR. Nath et al. [9] analyzed the prognostic significance of TR in a cohort of 5223 patients undergoing echocardiography. At 4-year follow-up, more than 70% of patients with mild or less TR were still alive, whereas the

survival rate for patients with moderate-to-severe TR was less than 50%. In addition, moderate or greater FTR was associated with increased mortality, even in the absence of pulmonary hypertension or LV dysfunction.

FUNCTIONAL TRICUSPID REGURGITATION IN DIFFERENT SETTINGS

Patients undergoing left-sided valve surgery

Recent retrospective surgical studies [3,5,25,26] have clearly demonstrated that leaving FTR untreated, at the time of MV surgery, gets more TR at follow-up. Matsuyama et al. [26] evaluated the evolution of TR in a series of 174 patients with moderate or less TR undergoing isolated MV surgery. At a mean follow-up of 8.2 years, progression of TR to moderate or severe degree was observed in 16% of patients. Multivariate analysis identified uncorrected moderate TR, atrial fibrillation and huge left atrium as statistically significant predictors of TR worsening after surgery. In the study of De Bonis et al. [5], at a mean follow-up of 1.8 years, the rate of moderate or severe FTR was 10.2% (8/78 cases) in patients undergoing isolated MV repair. When the presence of moderate or severe FTR at follow-up and worsening of at least two grades of untreated preoperative TR were considered together, the rate of FTR progression reached 18.6%. At multivariate analysis, preoperative RV dilatation or dysfunction and TR grade at discharge were independent predictors of significant TR at follow-up. In another study, TR increased by more than two grades in 48% of patients undergoing isolated MV repair and only in 2% of patients who were operated on both valves ($p < 0.001$) [3]. Dreyfus et al. [3] emphasized that even less than mild FTR can worsen of two grades at 5 years from surgery, if left untreated. In patients with moderate-or-more FTR undergoing isolated MV annuloplasty, Di Mauro et al. [25] observed a significant lower 5-year survival rate and possibility of being alive in NYHA classes I—II as compared to patients with mild or less FTR. Progression of FTR was a strong predictor of worse outcome at 5 years.

Roughly half (45.7%) of patients with preoperative moderate or severe FTR showed the same FTR grade at hospital discharge. This situation begets severe FTR in 40% of patients and moderate-or-more FTR in up to 77.1% of patients at follow-up.

All these observations suggest that FTR may not resolve after surgical relief of left-sided valve disease. In case of persistent high-grade FTR at hospital discharge, a worse evolution of FTR should be expected, regardless of the outcome of left-sided heart valve surgery. It is reasonable to speculate that FTR progression can be due to further RV enlargement and dysfunction [5], resulting in TV annulus dilatation over time, with increased papillary muscle displacement and leaflet tethering. This vicious cycle can explain the prognostic role of untreated moderate-or-more FTR. The reasons why moderate or more TR is correlated with higher mortality rates have not been clarified yet. However, it is likely that hemodynamically significant FTR is a marker of late-stage myocardial and valvular heart disease. More-over, FTR appears to be more frequent in patients with atrial fibrillation, LV or RV dysfunction, or pulmonary hypertension — all factors independently associated with a poor prognosis [27]. Even in the absence of a clear picture of RV dysfunction, it is very likely that FTR might mask the decreased RV contractility as MR does for the left ventricle. Additionally, elevated pulmonary artery pressures associated with persistent or worsening FTR might induce congestive hepatopathy with liver fibrosis, atrophy of hepatocytes, and even cirrhosis.

Isolated tricuspid regurgitation after mitral valve surgery

In patients with previous left heart valve surgery, indication for surgery is a challenging decision, as most of such patients are severely symptomatic. Recently, Kim et al. [28] found that preoperative RV end-systolic area $\geq 20 \text{ cm}^2$ was an independent

predictor of lower event-free survival. Operative mortality was 9.8% (6/61 patients), and most surviving patients showed clinical improvement after correction of TR.

Surgery should be considered in patients with significant isolated FTR after left-sided valve surgery, except for those with advanced RV dysfunction/dilatation or organ failure (mainly liver and kidneys). However, no specific recommendations are available because of the limited number of reported cases, and decisions should therefore be individualized.

Isolated tricuspid regurgitation in the absence of left-sided valve lesions

In patients with isolated significant TR, Lee et al. [29] found that older age, a large regurgitant jet area, high pulmonary artery systolic pressure (PAPs) and presence of RV dysfunction at initial presentation were independent predictors of all-cause mortality in medically treated patients. Surgical correction, performed in 57 out of 870 patients, was associated with higher 5-year survival rates.

Patients with left ventricular dysfunction

Preoperative LV dysfunction is a well established risk factor for early mortality in patients undergoing cardiac surgery. However, the presence of significant FTR was found to be associated with worse survival regardless of LV ejection fraction either in the general population [9] or in patients undergoing left heart valve surgery [8].

7.1.5 Patients with pulmonary hypertension

In a sample from the general population, Nath et al. [9] demonstrated that increasing FTR severity is associated with higher mortality regardless of the presence of pulmonary hypertension (PAPs $\geq$ 40 mmHg).

In patients undergoing MV surgery, Matsuyama et al. [26] reported that 17% of patients without preoperative pulmonary hypertension showed progressive TR, but only 13% of those with pulmonary hypertension developed TR during follow-up. In this study,

preoperative pulmonary hypertension failed to be a significant risk factor for late TR. Conversely, in the study of Lee et al. [29], pulmonary hypertension was found to be a risk factor for late mortality in patients with FTR.

According to the ACC/AHA guidelines [30], TV annuloplasty is indicated for patients with less than severe TR undergoing MV surgery who also have pulmonary hypertension or tricuspid annular dilatation. Although the presence of pulmonary hypertension is one

of the main

indications for

surgical intervention

[30], it is worth

noting that not every

patient with

pulmonary

hypertension will

develop significant TR

and vice versa. In a

recent

echocardiographic

Table 1
Risk factors in different patient subgroups.

	Worse late outcome	FTR worsening
<i>Patients undergoing left-sided valve surgery</i>		
Moderate or severe FTR	[25,33]	[5,25,26]
Older age		[32]
Atrial fibrillation		[26,32,33]
Huge left atrium		[25,26]
RV dilatation		[5]
RV dysfunction		[5]
LV dysfunction	[25,33]	
Preoperative NYHA class	[25]	
<i>Isolated FTR after MV surgery</i>		
Moderate or severe FTR	[28]	
RV dilatation	[28]	
RV dysfunction	[28]	
Anemia	[28]	
<i>Isolated FTR in the absence of left-sided valve lesions</i>		
Moderate or severe FTR	[29]	
Older age	[29]	
Pulmonary hypertension	[29]	
RV dysfunction	[29]	
<i>Patients with LV dysfunction</i>		
Moderate or severe FTR	[8,9,33]	
<i>Patients with pulmonary hypertension</i>		
Moderate or severe FTR	[9,29]	

FTR = functional tricuspid regurgitation; LV = left ventricle; MV = mitral valve; and RV = right ventricle.

study of 2139 patients with pulmonary hypertension, mild TR was observed in 65% of patients with PAPs 50–69 mmHg and in 46% of those with PAPs $\geq$ 70 mmHg [31]. Therefore, other factors (i.e., TV morphology and RV changes) seem to be more predictive of TR severity than pulmonary hypertension [13,31]. After successful pulmonary thromboendarterectomy, Sadeghi et al. [14] reported that 30% of patients exhibited persistent severe TR and had a less effective reduction in pulmonary artery pressure. Risk

factors for both poor late outcome and FTR progression are summarized in Table 1. Moderate-or-more FTR is a risk factor for worse outcome and FTR worsening either in the general population or in different patient subsets, regardless of the presence of LV dysfunction or pulmonary hypertension in most cases. These two variables, along with RV dysfunction and/or dilatation, atrial fibrillation and huge left atrium should be considered as additional risk factors that further exacerbate FTR and outcome. A more aggressive surgical approach is considered reasonable in these circumstances.

However, by definition, FTR severity may vary over time under different hemodynamic conditions. After successful left-sided valve surgery, Song et al. [32] observed that in patients with preoperative mild FTR, the overall incidence of late significant FTR was 7.7% at a mean follow-up of 101 ± 24 months. Patients who developed moderate-or-more FTR showed a lower 8-year event-free survival rate as compared to those without late significant FTR (76 ± 6 vs 91 ± 1 , $p < 0.001$). In the study of Kwak et al. [33], 26.9% of patients with preoperative mild FTR developed moderate-or-more FTR at a mean follow-up of 11.6 ± 2.1 years and showed a lower event-free survival rate than those who did not (62.0 ± 9.8 vs $85.9 \pm 2.6\%$ at 175 months, $p < 0.03$).

But, if FTR severity alone cannot be considered for surgical decision-making, what other parameters should be assessed to guide indications for surgery?

In several surgical reports, the decision to perform TV repair at the time of MV surgery was often left to the surgeon's discretion [8,34,35]. More recently, preoperative echocardiographic parameters as well as intraoperative findings have gained increasing importance for decision-making. Dreyfus et al. [3] performed TV annuloplasty only if the tricuspid annular diameter was greater than twice the normal size (≥ 70 mm) regardless of the grade of regurgitation. According to the ESC guidelines, TV annuloplasty should be considered in patients with moderate FTR with dilated annulus (≥ 40 mm from the AP-

4CV) undergoing left-sided valve surgery. This recommendation (class IIa) was made on the basis of a comparative study between normal subjects (31 ± 1 mm) and patients with idiopathic severe TR (41 ± 3 mm) [31].

However, annulus size is not the sole determinant of FTR. Chopra et al. [36] found that in patients with non-severe FTR (TR jet area/right atrial area ratio $\leq 34\%$, mean 27.5 ± 6.9) the maximal diastolic tricuspid annulus diameter was within the normal range (17.8 ± 2.5 mm/m²), suggesting that FTR may occur even in the absence of annular dilatation.

Calafiore et al. [2] based the decision to perform TV annuloplasty upon the preoperative echocardiographic systolic dimensions of the tricuspid annulus (sysTA), as FTR occurs during systole. Normal reference values (median sysTA 24 mm, maximum sysTA 28 mm) were established by evaluating 20 healthy volunteers. TV annuloplasty was performed in all patients with moderate or greater FTR and in those with mild FTR if sysTA was >24 mm. In patients with $\text{sysTA} \leq 24$ mm who underwent MV surgery without concomitant TV annuloplasty, no increase in FTR severity was observed, at least in the midterm. On the other hand, most untreated patients with $\text{sysTA} > 24$ mm who developed moderate or greater FTR during follow-up still had a sysTA within the normal range. Overall, 11% of untreated patients with preoperative mild FTR and $\text{sysTA} > 24$ mm showed TR worsening at follow-up.

In conclusion, patients undergoing valve surgery for FTR can be divided into two main groups. The first one includes patients undergoing prophylactic TV annuloplasty at the time of left-sided valve surgery (lesser degrees of preoperative FTR but dilated annulus). The second one includes patients for whom surgery can be considered essentially curative (significant FTR). Patients of the first group usually exhibit normal or slightly reduced RV function with no or mild RV dilatation, whereas patients of the second

group often show RV dysfunction with RV dilatation.

SURGICAL PROCEDURES AND RESULTS

Prophylactic surgical strategies for TV repair are directed mainly to the annulus. Reshaping of the tricuspid annulus can be obtained using suture annuloplasty or a support device that relieves stress on the native annulus, such as a pericardial strip, an incomplete ring (planar or shaped, rigid, or semi-rigid) (Fig. 7), or a flexible band [37,38].

In patients undergoing curative intent surgery, RV dilatation and severe tethering are frequently observed. In these circumstances, TV annuloplasty leads to increased tethering of the anterior and posterior leaflets, as the annulus is

Fig. 7. Tricuspid band annuloplasty.

displaced towards the septum. As a consequence, in the presence of RV dilatation, surgical tethering will result in postoperative FTR worsening rather than better leaflet coaptation.

Clinical and echocardiographic data from the literature are summarized in Table 2. Early mortality ranges from 0.6% to 8.9% [34,39], irrespective of the surgical technique used. Survival rates are available for different time intervals. Calafiore et al. [8] reported a 5-year survival rate of 75% in 51 patients undergoing FTR correction using the DeVega technique. Survival rates at 8 and 10 years largely vary from 50% [34] up to 96% [40] and from 44% [41] up to 78% [39], respectively. In general, survival curves according to surgical techniques did not differ significantly across the studies. However, Tang et al. [42] demonstrated that use of an annuloplasty ring is associated with improved 15-year

survival rates as compared to suture annuloplasty (49% vs 36%, $p = 0.007$).

Quite opposite results have been reported concerning postoperative moderate or severe TR, ranging from no residual TR [2,8,26,43] to rates of residual TR of 15—25% [35,40]. Navia et al. [41] documented a rate of moderate or severe FTR of 34% 3 months postoperatively and identified several risk factors for early recurrent TR, including use of flexible rings, DeVega annuloplasty, larger annuloplasty ring size, reduced LV ejection fraction, and history of heart failure. In a previous study of the same group, the severity of residual TR was also found to be associated with higher preoperative TR grade, RV and LV dysfunction, and tethering distance and area [37]. In particular, a tethering distance of >0.76 cm and a tethering area of >1.63 cm² were found to predict moderate to severe TR after surgery. More recently [22], a preoperative tenting volume of ≥ 1.68 mL and an anteroposterior annulus diameter of ≥ 36 mm were identified as the best cut-off values for predicting severe residual TR.

The recurrence rate of moderate or greater FTR ranges from 2.5% to 5.5% at 1-year follow up [2,8,44]. In some experiences, the midterm recurrence rate of FTR (3.3—5 years) remains very low (3.4—6%) [3,44]. At 5-year follow-up, Navia et al. [41] found that use of flexible bands or pericardial strips is associated with higher FTR recurrence rates. At 8 year-follow up, McCarthy et al. [34] reported a rate of repair failure of 17% with ring annuloplasty, 33% with the DeVega technique, and 37% with pericardial strip

annuloplasty. Use of a pericardial strip was also found to be a risk factor for recurrent FTR at multivariate analysis. In the study of Tang et al. [42] the DeVega procedure provided better results than ring annuloplasty at 15-year follow-up (34% vs 17%, $p = 0.01$). Finally, other authors have identified sysTA, increased tethering height or area, residual TR, preoperative TR grade, lower LV ejection fraction, female gender, permanent pacemaker, and presence of atrial fibrillation as additional risk factors for

recurrent TR [8,34,35,38].

Table 2
Results of tricuspid valve annuloplasty

	N pts	Technique	Early mortality	Survival	Residual TR*	Recurrent TR	Predictors of residual/recurrent TR
Isolated annuloplasty							
Calafiore [2]	167	142 DeVega 25 band	4.2%	87% at 2 years	None	5.5% at 1 year None to moderate or severe 8.4% at 5 years	Systolic TA dimension
Dreyfus [3]	148	Mostly DeVega	0.6%	90.3% at 8 years	N/A	N/A	
Calafiore [4]	51	All DeVega	2.0%	75% at 5 years	7%	3% at 1 year Rigid ring 17% at 8 years	Pericardial strip, LVF, Female gender
McCarthy [34]	790	139 rigid ring 289 flexible band 246 pericardial strip	6.0%	50% at 8 years	Rigid ring 15% Flexible band 15% Pericardial strip 10%	Flexible band 18% at 5 years Pericardial strip 37% at 8 years DeVega 33% at 8 years	
Fukuda [35]	39	6 rigid ring 12 flexible band 12 TD ring 4 suture annuloplasty	0	N/A	10% (considering only severe TR)	5.1% at >1 year (considering only severe TR)	Preoperative LVF, RV FAC, TV tethering area (>0.80 cm ²) TV tethering length (>4.51 cm) Postoperative LVF, RV pressure, TR severity
Genoa [18]	237	Resuspension 157 King band 80	6.0%	Resuspension 75% King band 61%	N/A	Resuspension 25% at 3 years King band 31% at 3 years	Preoperative TR Preoperative MR Postoperative PAFs
Kawahira [39]	260	Mostly DeVega	8.0%	78% at 10 years	25%	30% at 10 years	Residual TR
Chang [40]	334	DeVega/Kay 117 Pericardial strip 217	2.4%	DeVega/Kay 90% at 8 years Pericardial strip 92% at 8 years	DeVega/Kay 12% Pericardial strip 11% [†]	DeVega/Kay 28% at 8 years Pericardial strip 19% at 8 years	Preoperative TR Preoperative MR Suture annuloplasty
Navia [41]	2277	1052 flexible band 387 rigid ring 197 TD ring 185 pericardial strip 377 DeVega/Kay 79 edge-to-edge 493 DeVega 200 ring band	N/A	44% at 10 years	34% at 8 months	45% at 5 years	Flexible band Pericardial strip PFA/PAB
Tang [42]	782		N/A	DeVega 96% at 15 years Ring band 18% at 15 years $p = 0.003$	N/A	DeVega 17% at 15 years Ring 34% at 15 years $p = 0.01$	
Filice [43]	75	TD ring	5.3%	80% at 2 years	None	2.2% at 1.7 years	
Matsuyama [44]	45	28 DeVega 17 rigid ring	2.2%	100% at 6 years	None	DeVega 45% at 3.3 years Rigid ring 6% at 3.3 years $p = not\ sig$	
Fukuda [47]	136	TD ring	N/A	N/A	16%	14.0% at >1 year	Preoperative TR Tethering length (>1 cm)
Sarraf [48]	17	Adjustable segmental	0	94% at 3 years	8%	18% at 2.5 years	N/A
Annuloplasty + other technique							
Bushnell [31]	210	52 DeVega 53 rigid ring 53 DeVega + PFA 52 rigid ring + PFA	4.8%	N/A	DeVega 16% Rigid ring 8% DeVega + PFA 4% Rigid ring + PFA 23%	DeVega 28% at 1 year Rigid ring 1.4% at 1 year DeVega + PFA 10% at 1 year Rigid ring + PFA 8% at 1 year 0 at 0.5–1.7 years	N/A
Dreyfus [44]	15	Tricuspid leaflet augmentation + rigid ring	None	N/A	0	0 at 1.1 years	N/A
Delmonico [46]	14	Clover	7.1%	No late deaths	0	0 at 1.1 years	N/A

LVF = left ventricular ejection fraction; MR = mitral regurgitation; PAB = pacemaker; PAFs = pulmonary artery systolic pressure; PFA = pericardial patch augmentation; RV FAC = right ventricular fractional area change; TA = tricuspid annulus; TR = tricuspid regurgitation; and TV = tricuspid valve.
* Early after surgery (grade 1+ or 4+).

Calafiore et al. [2] used echocardiographic criteria to establish whether DeVega annuloplasty was the most appropriate procedure for correction of FTR. DeVega annuloplasty was reserved to patients with sysTA up to 28 mm, whereas band annuloplasty was used if sysTA was > 28 mm. In patients with mild FTR, the DeVega technique was adopted if sysTA ranged from 25 to 28 mm, whereas TV repair was performed using a band if sysTA was > 28 mm.

Fukuda et al. [35], in evaluating the tethering height (the distance between the tricuspid annular plane and the coaptation point of the septal and anterior leaflets), found that a preoperative cut-off value of 0.51 cm — lower than the 1 cm identified for the MV — was predictive of recurrent TR. Interestingly, early postoperative LV ejection fraction (63.6%) was associated with late failure of TV repair. This reinforces the concept that isolated annuloplasty cannot prevent TR recurrence, because the right ventricle fails in the setting of LV failure. The strict relationship observed in the left heart

system (MR recurrence due to LV remodeling) is mirrored in the right ventricle, even though multiple (either intrinsic or extrinsic) causes may contribute to RV remodeling.

Several alternative surgical strategies have been attempted to address severe tethering in FTR, including tricuspid leaflet augmentation [21,45] and the “clover” technique [46]. The latter consists in stitching together the middle point of the free edges of the tricuspid leaflets producing a valve with a characteristic “four leaflet clover” configuration. However, these surgical options need further investigation to determine the effectiveness of operations and are more technically demanding (Table 2) [21,45–48].

Current surgical approaches to FTR mainly focus on annular size reduction, resulting in fluctuating results because the mechanisms underlying FTR are not always related to tricuspid annular dilatation. RV geometry seems to be a key determinant in the outcome of early and late TV repair. However, changes in RV geometry are often unpredictable, as positive remodeling depends on multiple factors, independent of the surgical technique used. At present, no surgical technique addresses RV geometry and, as a consequence, results of TV repair are not constant and are by far less predictable than those of MV repair.

If TV repair is considered at high risk of failure, the only option remains TV replacement, which consists in the insertion of a prosthetic valve with preservation of the entire valvular and subvalvular apparatus. Although long-term results of tissue or mechanical valves are similar, in the era of percutaneous valve replacement the use of a tissue valve is more attractive because it combines reduced thrombogenicity with the possibility of percutaneous insertion of a new prosthesis in case of valve dysfunction.

In conclusion, FTR is characterized by structurally normal leaflets and is due to the deformation of the valvulo-ventricular complex. This entity has often been neglected, but new insights suggest its impact on the prognosis and clinical course of the several

heart diseases to which FTR can be secondary. It is therefore mandatory to identify the mechanisms responsible for valvular dysfunction as well as the etiology and severity of valvular regurgitation to define criteria for clinical decision-making and improve appropriate patient selection for TV repair or replacement.

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From the theatriacal tragedy "Gente del Sud" (People of South)
Author: Federica Vicino
Performed in 2014

**ADDITIVE AND INDEPENDENT PROGNOSTIC ROLE OF
ABNORMAL RIGHT VENTRICLE AND PULMONARY
HYPERTENSION IN MITRAL-TRICUSPID SURGERY**

.

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ABSTRACT

Objective: To evaluate the additive and independent prognostic value of abnormal right ventricle (aRV) and pulmonary hypertension (PH) in patients undergoing mitral-tricuspid surgery.

Methods: From January 2009 to December 2012, 541 patients underwent mitro-tricuspid surgery. The entire cohort was divided into 6 subgroups: 63 cases had normal RV and no PH (Group A), 180 normal RV but moderate PH (Group B), 101 normal RV but severe PH (Group C), 15 abnormal RV and no-PH (Group D), 86 abnormal RV and moderate PH (Group E) and 96 abnormal RV and severe PH (Group F).

Results: Forty-two (7.8%) patients died in hospital due to any cause: 1.6% in group A, 3.9% in group B, 8.9% in group C, 13.3% in group D, 9.3% in group E, 15.6% in group F, $p = 0.005$. Among 78 patients with no-PH, mortality was significantly higher in patients with aRV (1.6% vs 13.3%, $p = 0.03$). Among 344 patients with normal RV, mortality was significantly higher in patients with severe PH (1.6% vs 3.9% vs 8.9%, $p = 0.03$). Comparing the presence of both abnormal RV and severe PH with the remaining patients, mortality was significantly higher in the first group (15.6% vs 6.1%, $p = 0.004$). Multivariable analysis confirmed either the independent or the additive role of RV and PH.

Conclusions: In patients undergoing mitral-tricuspid valve surgery, the presence of either RV dysfunction/dilatation or severe pulmonary hypertension, might play an independent prognostic role for mortality. The worst scenario is surely the contemporary presence of both conditions.

INTRODUCTION

The prognostic role of right ventricle has been clearly demonstrated in patients with myocardial infarction (MI) [1,2], heart failure (HF), either ischemic or not [3,4], or receiving cardiac resynchronization therapy [5]. This finding changed the insight of the cardiologists, resulting in a more careful evaluation of the right ventricle in order to assess the prognosis.

In cardiac surgery, although there are sufficient evidences [6–11] in favor of routine preoperative assessment of the right ventricle, the main surgical risk score systems [12,13] do not take into account neither dysfunction nor dilatation of the right ventricle.

On the contrary, pulmonary hypertension (PH) is considered a strong predictor for mortality after cardiac surgery; but, as already demonstrated in patients with HF, PH does not always mirror RV dysfunction, which has an independent and additive prognostic value [14]. In addition, RV dysfunction seems to be a better predictor of postoperative circulatory failure rather than pulmonary hypertension (PH), in patients undergoing mitral valve surgery (MVS) [8].

Hence, the purpose of this retrospective study is to evaluate the additive and independent prognostic value of abnormal right ventricle and pulmonary hypertension in a cohort of patients undergoing mitro- tricuspid surgery.

METHODS

Study population

From January 2009 to December 2012, 541 patients with mitral valvulopathy and secondary tricuspid regurgitation were consecutively operated on at Prince Sultan Cardiac Center in Riyadh. The study received the approval from local Institutional Review Board. The entire cohort was divided into 6 subgroups: group A (normal RV

and no-PH), group B (normal RV and moderate PH), group C (normal RV and severe PH), group D (abnormal RV and no-PH), group E (abnormal RV and moderate PH), group F (abnormal RV and severe PH). Table 1 summarizes difference among groups.

Echocardiography

All the patients underwent routine preoperative trans-thoracic echocardiography. Right ventricle (RV) dimension and function were assessed according to guidelines [15]. Briefly, right ventricular basal diameter (RVD) was assessed via 4 chamber view; RVD ≥ 42 mm was considered dilated. Tricuspid annular plane systolic excursion (TAPSE) was measured in M-mode, evaluating systo-diastolic excursion of lateral tricuspid annulus; Using the same view and tissue pulse Doppler, peak velocity of lateral tricuspid annulus (TDI S') was measured. Right ventricular dysfunction was defined as the presence of either TAPSE ≤ 16 mm or Pulsed Doppler peak velocity at TDI S' ≤ 10 cm/s. The presence of RV dilatation and/or dysfunction was labeled as "abnormal RV".

The systolic pulmonary artery pressure (sPAP) was estimated as the sum of the gradient across the tricuspid valve (calculated from the simplified Bernoulli equation) and the right atrial pressure. Right atrial pressure was estimated using the size and respiratory response of the inferior vena cava in the sub-costal view. Pulmonary hypertension was considered moderate with value of sPAP between 31 and 55 mm Hg and severe with sPAP ≥ 55 mm Hg according to their prognostic value in cardiac surgery [13]. Left ventricular ejection fraction was measured with modified Simpson biplane method [16]. Mitral and tricuspid valves were assessed according to the European recommendations [17].

Surgery

After a median sternotomy, the ascending aorta and both cavae were cannulated, the superior one directly. In all the cases, intermittent antegrade warm blood cardioplegia was used. The MV was approached transeptally via a right atriotomy. MA was always reshaped using the SMB40™ (Sorin, Saluggia, Italy). The band 40 mm long was inserted from A1 (that coincides with the left trigone) to A3 (the fibrous zone that represents the offshoots of the right trigone) with several interrupted sutures, leaving the only A2 insertion-free. In some cases, chordal replacement of chordal cutting was needed. Insertion of a prosthesis inside the mitral valve was performed sparing, where possible, the annular-subvalvular connection. Tricuspid repair was performed using a De Vega suture annuloplasty (38 cases), band annuloplasty with SMB50™ (Sorin Saluggia Italy) in 314 cases, with MC3™ (Edwards Lifescience, Irvin, CA, US) in 109 cases, Cosgrove band (Edwards Lifescience, Irvin, CA, US) in 10 cases and bicuspidalization in 4 cases. In 66 patients, tricuspid valve was replaced with mechanical prosthesis in 19 cases and with bioprosthesis in 47 cases. Average cardiopulmonary bypass and cross-clamping time were 135 ± 46 and 100 ± 34 min, respectively. Surgical details are reported in Table 1.

Table 1
Demographic, clinical and surgical and echocardiographic data.

Variables	Group A (63)	Group B (180)	Group C (101)	Group D (15)	Group E (86)	Group F (96)	p-Value
Age (years)	52 ± 17	55 ± 16	56 ± 15	52 ± 13	53 ± 13	53 ± 16	0.26
Gender M/F	26/37	70/110	51/50	8/7	32/54	51/45	0.16
Logistic ES II	3 (2-6)	4 (2-6)	6 (3-11)	5 (2-9)	6 (3-11)	7 (4-11)	0.00
LVEF (%)	49 ± 11	49 ± 11	47 ± 12	44 ± 14	47 ± 12	45 ± 14	0.12
LVEDD (mm)	54 ± 6	54 ± 8	56 ± 9	56 ± 7	53 ± 9	53 ± 12	0.11
LVESD (mm)	37 ± 8	38 ± 9	39 ± 9	42 ± 9	39 ± 10	39 ± 12	0.21
TAPSE (mm)	22 ± 4	21 ± 2	21 ± 3	14 ± 6	13 ± 3	12 ± 3	0.00
TDI S' (cm/s)	13 ± 2	12 ± 1	13 ± 1	8 ± 4	9 ± 2	8 ± 3	0.00
RVD (mm)	33 ± 5	36 ± 3	34 ± 4	41 ± 10	43 ± 4	43 ± 3	0.00
sPAP (mm Hg)	28 ± 2	47 ± 6	69 ± 10	28 ± 2	46 ± 2	73 ± 14	0.00
MR grade	3.0 ± 1.2	3.0 ± 1.2	3.2 ± 1.1	2.7 ± 1.5	2.8 ± 1.2	3.1 ± 1.1	0.12
TR grade	2.0 ± 0.9	2.4 ± 1.0	2.7 ± 1.0	3.0 ± 1.3	3.0 ± 1.1	3.3 ± 1.0	0.00
MV surgery							0.45
Repair	23 (36%)	63 (35%)	33 (33%)	5 (33%)	32 (32%)	34 (35%)	
Replacement	40 (64%)	117 (65%)	68 (67%)	10 (67%)	54 (68%)	62 (65%)	
TV surgery							0.00
Repair	62 (98%)	169 (94%)	92 (91%)	9 (60%)	63 (73%)	80 (83%)	
Replacement	1 (2%)	11 (6%)	9 (9%)	6 (40%)	23 (27%)	16 (17%)	

RV = right ventricle; pH = pulmonary hypertension; Group A (normal RV and no-PH); Group B (normal RV and moderate PH); Group C (normal RV and severe PH); Group D (abnormal RV and no-PH); Group E (abnormal RV and moderate PH); Group F (abnormal RV and severe PH); M/F = male/female; ES = Euroscore; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; TAPSE = tricuspid annular plane systolic excursion; TDI S' = tissue-Doppler imaging; RVD = right ventricular diameter; sPAP = systolic pulmonary artery pressure; MR = mitral regurgitation; TR = tricuspid regurgitation; MV = mitral valve; TV = tricuspid valve.

Endpoints

The primary end-point of this study is the additive and independent prognostic value of RV and PH on in-hospital mortality of patients undergoing mitral-tricuspid surgery.

Statistical analysis

Results are expressed as mean (±standard deviation). Categorical variables were re-ported as counts and percentages. Non-normally distributed variables were reported as median and 25th–75th percentiles. Comparison between groups was performed using chi-square test in case of categorical variables, with ANOVA test with post-hoc analysis in case of continuous variables; when continuous variables were non-normally distributed, Kruskal-Wallis. Finally, a multivariable analysis was used to verify the additive and independent prognostic value of RV and PH. ROC curve was used to assess the AUC of the final model (discrimination power) and the final model was validated in 1000 bootstrap samples, reporting distortion from AUC original AUC. Calibration was assessed by means of Hosmer-Lemeshow test. For all tests, a p-value ≤ 0.05 was significant. The SPSS software

(SPSS Inc., Chicago, IL, USA) was used.

RESULTS

Right ventricle

Among 541 enrolled patients, 344 (64%) had normal RV, 102 (18%) had either RV dilatation (72 cases) or dysfunction (30 cases) and 95 (18%) has contemporary RV dilatation and dysfunction. Hence, abnormal RV was recorded in 197 (36%) patients.

Pulmonary hypertension

Pulmonary hypertension was absent in 78 (14%) cases, moderate in 266 (49%) and severe in 197 (37%).

Stratification by RV and PH

Sixty-three cases (12%) had normal RV and no PH (Group A), 180 (33%) had normal RV but moderate PH (Group B), 101 (19%) had normal RV but severe PH (Group C), 15 (3%) had abnormal RV and no-PH (Group D), 86 (16%) had abnormal RV and moderate PH (Group E) and 96 (18%) had abnormal RV and severe PH (Group F).

Mortality

Forty-two (7.8%) patients died in hospital due to any cause, 27 (5%) within 30-day from surgery and 15 (2.8%) were never discharged from the hospital, dying after 30-day from surgery (median 3 months, 25th–75th percentiles 2–4 months).

In patients with normal RV was 4.9% (17), 9.7% (7) in patients with RV dilatation, 10% (3) in patients with RV dysfunction and 15.8% in patients with contemporary RV dilatation and dysfunction ($p = 0.005$).

In patients with normal sPAP, mortality was 3.8% (3), 5.6% (15) in patients with moderate PH and 12.2% (24) in patients with severe PH ($p = 0.01$) (Fig. 1).

If the entire cohort is divided according to both RV and PH, mortality was 1.6% (1) in

group A, 3.9% (7) in group B, 8.9% (9) in group C, 13.3% (2) in group D, 9.3% (8) in group E and 15.6% (15) in group F, $p = 0.005$ (Fig. 1).

Normal sPAP: the impact of RV

Among the 78 patients with no-PH, 63 showed also normal RV and 15 an abnormal RV. Mortality was significantly higher in patients with abnormal RV (1.6%vs 13.3%. $p = 0.03$). (Fig. 1).

Normal RV: the impact of PH

Among the 344 patients with normal RV, 63 showed normal sPAP, 180 moderate PH and 101 severe PH. Mortality was significantly higher in patients with severe PH (1.6%vs 3.9% vs 8.9%. $p = 0.03$) (Fig. 1); in particular, no difference was found between patients without PH and patients with moderate PH, but patients with severe PH had the worst outcome either versus no PH (0.01) or moderate PH ($p = 0.04$).

The additive prognostic role of severe PH and abnormal RV

Comparing the presence of both abnormal RV and severe PH (96 patients) with the remaining 445 patients, mortality was significantly higher in the first group (15.6% 6.1%, $p = 0.004$) (Fig. 2).

Fig. 2. Mortality rate: comparison between patients with both abnormal right ventricle and severe PH and the remaining group (blue blocks) (Panel D). nRV = normal right ventricle; aRV = abnormal right ventricle; pH = pulmonary hypertension. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Early results of surgery

Postoperative mitral regurgitation (MR) was absent in 488 patients (90%), graded as mild in 49 (9%), as moderate in 4 (1%). No difference among groups was found ($p = 0.55$). Postoperative tricuspid regurgitation (TR) was absent in 289 (53%) cases, graded as mild in 203 (38%), moderate in 45 (8%) and severe in 4 (1%). Neither postoperative MR nor TR impacted on mortality.

Multivariable analysis

Multivariable analysis confirmed either the independent or the additive role of RV

and PH (Table 2).

Table 2
Multivariable analysis for mortality.

	p-Value	OR	95% CI	
			Lower	Upper
Versus nRV-no-PH				
nRV-moderate PH	0.394	2.50	0.303	10.802
nRV-severe PH	0.041	6.06	1.78	9.08
aRV-no-PH	0.034	7.53	2.40	13.19
aRV-moderate PH	0.035	6.35	1.77	12.21
aRV-severe PH	0.020	11.48	3.47	18.28
EuroSCORE II	0.000	1.07	1.03	1.10
TV replacement	0.005	2.86	1.36	6.02

OR = odds ratio; nRV = normal right ventricle, no-PH = absence of pulmonary hypertension; aRV = abnormal right ventricle; TV = tricuspid valve. AUC = 0.80; Hosmer-Lemeshow chi-square 7.38 with $p = 0.5$.

Major complication

In-hospital major complications were: intra-aortic balloon pump (IABP) 22 (4%), ECMO 6 (1%), prolonged intubation 33 (6%), redo for bleeding 39 (7%), and acute kidney injury 81 (15%).

DISCUSSION

The importance of the right ventricle in cardiac surgery has been demonstrated in a variety of clinical settings such as high risk coronary or valvular heart disease, congenital heart disease, heart transplantation, in patients requiring mechanical assist devices and in the unstable postoperative patients [6–11]. Nevertheless, Euroscore II [13] reports only PH as risk factor, dividing patients in three categories: patients without PH, with moderate and with severe PH.

There are three main reasons: firstly, these studies focused on prognostic role of RV are retrospective with small sample size; the independent role of RV from PH has not

been well evidenced so far; and finally, difficult assessment of RV function with echocardiography discouraged cardiologists and surgeons to use routine RV assessment in risk stratification.

It is well known as correct that estimation of RV dimensions and function can be achieved with cardiac magnetic resonance [18] as well as pulmonary pressure should be evaluated with right catheterization, as stated by latest ESC guidelines [19], that gives to echocardiography just the chance to determine the probability to have pulmonary hypertension. Nevertheless, in cardiac surgery, preoperative routine evaluation cannot be included neither CMR nor right catheterization, especially in urgent patients. So, echocardiography plays a fundamental role for the estimation of both pulmonary pressure and right ventricular dimension and function, even using surrogate index as TAPSE or TDI S' [15], in patients undergoing cardiac surgery. It is crucial to understand how these two conditions have independent and additive effects on mortality.

We decided to use the end-point “in hospital mortality” instead of “thirty-day” mortality, as more commonly used, because 15 (2.8%) out of 42 cases died in ICU between 2 months (most of them) and 4 months after surgery due to complications after surgery. They were never discharged and so we believed it was more correct to include them into early mortality.

Hence, our mortality (7.8%) looks slightly higher, but almost the studies reported thirty-day mortality, which in our series is 5%, so perfectly within the range, considering also that 86% of patients had at least moderate PH with 34% with contemporary RV dilatation or dysfunction; 37% showed severe PH, with 18% having contemporary abnormal RV. Finally, most of the patients (65%) underwent mitral valve replacement necessarily, and 12% of cases had TV replacement, that have usually higher mortality.

In the study by Ghio et al. [14], patients with normal pulmonary pressure and low RVEF was 5.5%; in our series, the prevalence of patients with normal sPAP and abnormal RV is roughly 3%. Some patients show RV dysfunction despite normal pulmonary pressure, as in the presence of reduced RV function and low forward RV stroke volume due to tricuspid regurgitation [20].

Other possible explanations are RV volume overload due to tricuspid regurgitation, the primary involvement of RV by myocardial disease or an overtreatment with diuretic which can reduce pulmonary pressure, but not necessarily influence RV. Conversely, in our series, there are even 52% of patients with PH but normal RV. In fact, despite similar RV afterload not all the patients develop maladaptive RV hypertrophy, characterized by dilatation, ischemia, fibrosis and then RV failure [21].

Hence, considering pulmonary hypertension strictly linked to right ventricular dysfunction and dilatation and vice versa is not always true, and this is particularly important in the case of prognosis assessment.

In our series, in hospital mortality of patients without PH was significantly influenced by the presence of abnormal RV both at univariate analysis (1.6% vs 13.3%. $p = 0.03$) and at multivariate analysis, abnormal RV showed a 7.5-fold increase of risk for mortality. Moreover, considering only 197 patients with abnormal RV, PH loses its prognostic role, confirming as mortality, associated with PH, could depend more on RV adaptation to pulmonary vascular resistance than on the absolute presence of high pulmonary pressure [22–24].

Finally, among 344 patients with normal RV, only severe PH increased risk of in-hospital mortality by 6-fold.

Additive prognostic role of RV and PH

Beside their independent prognostic effect, the presence of both abnormal RV and severe pulmonary hypertension has to be considered the worst condition, increasing mortality by 11.5-fold. As already stated, in the presence of severe pulmonary hypertension, RV develops a maladaptive hypertrophy with ischemia, aerobic glycolysis and glutaminolysis, impairment of angiogenesis, manifestation of capillary rarefaction, and dysregulation of autonomic nervous system with reduced sensibility of alpha, beta and dopaminergic receptors in RV myocytes, and this process tend to involve left ventricle [25].

In such condition the patients undergoing cardiac surgery is more prone to develop intra- and postoperative complications. Myocardial dysfunction after cardiopulmonary bypass (CPB) is commonly mild without any consequence in terms of hemodynamics. However, both pulmonary pressure and ventricle can be impaired by the operation. Cardiopulmonary bypass may cause RV failure due to new onset of RV ischemia/infarction (bad myocardial protection, graft thrombosis; coronary air embolism); coronary air embolism; inadequate oxygenation or inflammation; loss of atrio-ventricular synchrony; and sepsis. So the presence of preoperative RV dysfunction or dilatation could be very likely the basis for a critical postoperative RV failure, making this condition irreversible. The presence of RV failure after CPB is associated with a mortality rate ranging from 44% to 86% [26].

Similarly, pulmonary hypertension can be exacerbated by lung atelectasis, systemic inflammatory response, blood transfusion, pulmonary vasoconstriction due to protamine, hypoxia, hypercarbia and pulmonary embolism [27].

Study limitations

There are some limitations to quote; firstly, this is a retrospective single center experience. Right ventricular dysfunction was assessed by TAPSE and TDI S' that, although

are well correlated with RVEF, ignores the outlet portion and the septal contribution to RV ejection, which may become important to maintain overall RV function. Moreover, neither 3D echocardiographic RV assessment nor novel echocardiographic indexes as speckle tracking were used.

CONCLUSIONS

In patients undergoing mitral-tricuspid valve surgery, the presence of either RV dysfunction/dilatation or severe pulmonary hypertension, might play an independent prognostic role for mortality, but the worst scenario is surely the contemporary presence of both conditions. Hence, the risk models should be updated including right ventricle evaluation.

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*From the theatriacal comedy "Ditegli Sempre di Sì" (Let's say always YES)
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Performed from 2016 to 2017*

SURGICAL TREATMENT OF ISOLATED TRICUSPID VALVE INFECTIVE ENDOCARDITIS: 25-YEAR RESULTS FROM A MULTICENTER REGISTRY

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ABSTRACT

Background: To assess early and late mortality in patients with isolated acute tricuspid valve infective endocarditis (TVIE) using data from a multicenter registry.

Methods: From 1983 to 2018, isolated acute TVIE was surgically treated in 157 (3.8%) patients [mean age 47 ± 16 years (range 15–86 years), 25% females]. Of these, 142 (90%) had native tricuspid regurgitation, 7 (5%) native tricuspid valve (TV) stenoregurgitation, and 8 (5%) prosthetic TVIE. Intravenous drug use (IVDU) was recorded in 38% of patients, infection involved cardiac implantable electronic device leads in 21%, and vascular catheters for dialysis in 1%; in the remaining cases, the cause was unknown. The primary endpoint was in-hospital outcome, long-term freedom from recurrence and overall survival.

Results: Overall, 77 (49%) patients underwent TV repair, 72 (46%) TV replacement, and 8 (5%) prosthetic TV replacement. Early mortality was 11% ($n = 17$). Expected early mortality according to EndoSCORE was 12%, with age (odds ratio 1.06) and redo (odds ratio 6.64) as risk factors. Late deaths occurred in 31 patients and TVIE recurrences in 4. Survival rates at 10, 20, and 25 years were 66%, 60%, and 44%, respectively. Risk factors were age [hazard ratio (HR) 1.06], mycotic TVIE (HR 4.2), IVDU (HR 4.90), infected prosthesis replacement (HR 4.4), and presence of cardiac implantable electronic device leads (HR 3.0). No significant difference was found in valve repair vs. replacement and in IVDUs vs. non-IVDUs.

Conclusions: Patients with isolated acute TVIE undergoing surgical treatment show acceptable early and late outcomes. TVIE recurrence was low, and repair of the affected valve does not seem to confer any advantage either at early or long term up to 25 years.

INTRODUCTION

Acute infective endocarditis (IE) is becoming increasingly prevalent among cardiovascular diseases [1,2]. In addition, patient profile and clinical presentation with related impact on outcome are rapidly changing, with more aggressive forms, higher rates of complex valvular involvement and complications, and more frequent need for surgical intervention [1,2]. Among IE, right-sided valvular infection represents a minority, accounting for 5—10% of all cases, but with a clear trend towards a higher incidence in recent years [1–4]. Tricuspid valve IE (TVIE) is therefore a rare entity, mainly observed in peculiar patient subgroups [3,4] and with a high success rate with conservative treatment [5]. Surgical treatment is usually required in $\geq 10\%$ of TVIE [3], but only a few reports have specifically addressed this issue, with only few reporting data on long-term outcome [3,4,6]. The National Registry for Surgical Treatment of Native or Prosthetic Valve Infective Endocarditis was created to collect and analyze data from IE patients with the participation of a multicenter working group, and focused on early and long-term patient outcome [7,8]. The aim of this study was to assess data from this registry and provide information about patients affected by isolated acute TVIE, particularly regarding early and late results of surgical treatment during a follow-up reaching 25 years.

MATERIALS AND METHODS

Study population

From February 1979 to January 2018, 4084 patients were included in the Italian Registry for Surgical Treatment of Native or Prosthetic Valve Infective Endocarditis, with the active participation of 21 Centers. From 1983 to 2018, isolated acute TVIE was surgically treated in 157 out of 4069 (3.8%) patients due to native tricuspid regurgitation (TR) in 142

(90%), tricuspid stenosis and regurgitation in 7 (5%), and prosthetic tri- cuspid valve (TV) endocarditis in 8 (5%).

Definition of terms and endpoints

All the variables collected in the dataset were defined according to EuroSCORE [8]. The primary endpoint was early mortality, defined as all-cause death within 30 days after surgery, and long-term survival free from TVIE recurrence. Secondary endpoints were long-term survival, 30-day mortality, and major complications [death, acute kidney injury, acute respiratory failure, multiorgan failure, sepsis, major bleeding, stroke, embolic events other than stroke, atrioventricular block requiring pacemaker (PMK) implantation, acute myocardial infarction, malignant ventricular arrhythmias, low output syndrome]. Moreover, the observed/expected mortality ratio was reported using the EndoSCORE [9].

Follow-up

All patients were followed up by phone interview or calling the patient referring physician or cardiologist. Follow-up ended on March 2018; median follow-up was 19.1 (14.3–23.8) years. Seven patients were lost to follow-up (11%).

Statistics

Normal distribution of continuous variables was assessed by Kolmogorov-Smirnov test. Normally distributed variables are reported as mean $\pm$ standard deviation, and non-normally distributed variables as median and interquartile range. Pairwise comparison was performed using *t*-test or Mann-Whitney *U* test for continuous variables and chi-square with Fisher exact test for categorical variables. Variables with a p-value of ≤ 0.2 at univariate analysis were entered into the multivariable model. A parsimonious logistic regression model was built to identify the best predictors for early outcome. Results are reported as odds ratio (OR), 95% confidence limits (95CLs) and p-value. The Kaplan- Meier

method was used to assess late survival and survival free from TVIE recurrence with log-rank test for univariate comparison. Cox regression was used to identify risk factors for late outcomes. Results are reported as hazard ratio (HR), 95CLs and p-value. SPSS software (version 23, IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. A p-value of <0.05 was considered as threshold for statistical significance.

RESULTS

Clinical profile and operative data

Overall, 157 (3.8%) patients [mean age 47 ± 16 (15–86) years, 25% female] underwent surgical treatment of isolated acute TVIE. *Staphylococcus aureus* was the most common causative agent (45%), followed by streptococci (22%), *Staphylococcus* other than *S. aureus* (9%), entero- cocci (3%), mycotic infection (2%), and other pathogens (6%). Blood cultures and specimens were both negative in 13% of patients, whereas data were missing in 8%. Intravenous drug use (IVDU) was recorded in 38% of patients, infection involved cardiac implantable electronic device leads in 21%, and vascular catheters for dialysis in 1%; in the remaining cases, the cause was unknown. TV repair and replacement was performed in 77 (49%) and 72 (46%) patients, respectively, whereas 8 (5%) patients underwent prosthetic TV replacement. Among the 77 patients who underwent TV repair, 22 had vegetectomy, 5 vegetectomy and reconstruction with patch, 34 vegetectomy and annuloplasty, 10 bicuspidalization, 6 unknown.

Differences between intravenous drug users (IVDUs) and non-IVDUs are reported in Table 1.

Early outcome

Early mortality was 11% ($n = 17$) (Table 2). Expected mortality according to EndoSCORE was 12% with an observed/expected ratio of 0.9. The 30-day major complication rate was 22% ($n = 35$). TV repair showed the lowest mortality and major complication rate (6% and 17%, respectively), followed by native TV replacement (11% and 25%, respectively), and prosthetic TV replacement (50% and 63%, respectively). However, no significant differences were found in TV repair vs. replacement. Regarding perioperative morbidity, one-fifth of the patients experienced major complications, but, interestingly, event rates related to active infection (sepsis), or to acute cardiac as well as renal failure, were low. No significant differences were recorded in mortality and morbidity between IVDUs and non-IVDUs. Multivariable analysis identified age and prosthetic TVIE as risk factors for both higher early mortality (age: OR 1.06, 95CLs 1.03–1.10, $p = 0.001$; TVIE: OR 6.64, 95CLs 1.52–18.25, $p = 0.014$) and major complications (age: OR 1.05, 95CLs 1.02–1.07, $p = 0.001$; prosthetic TVIE: OR 3.98, 95CLs 1.18–22.32, $p = 0.044$).

Late outcome

Late mortality was 19.8% ($n=31$), and survival rates were $66 \pm 5\%$, $60 \pm 6\%$, and $44 \pm 9\%$ at 10, 20, and 25 years, respectively. Patients still alive were 40, 15, and 7 at 10, 20, and 25 years, respectively. No significant differences were found in TV repair vs. replacement

Table 1
Preoperative and operative data.

	Overall (n = 157)	IVDUs (n = 60)	Non-IVDUs (n = 97)	p-Value
Age (years)	47 ± 16	36 ± 8	54 ± 17	<0.001
Sex (F/M)	39/118	43/17	75/22	0.426
TV disease				
TR	142 (90%)	57 (95%)	85 (88%)	0.427
TSR	7 (5%)	2 (3%)	5 (5%)	
TP	8 (5%)	1 (2%)	7 (7%)	
Source of infection				
IVDU	60 (33%)	60 (100%)	-	-
PMK/ICD leads	33 (21%)	0	33 (34%)	-
Vascular access for dialysis	2 (1%)	0	2 (2%)	-
Unknown	62 (39%)	0	62 (64%)	-
LVEF (%)	55 ± 9	57 ± 7	54 ± 10	0.086
SB hypertension	41 (26%)	3 (5%)	38 (39%)	<0.001
Diabetes	12 (8%)		12 (12%)	0.004
Obesity	10 (6%)	3 (5%)	7 (7%)	0.581
COPD	15 (10%)	4 (7%)	11 (11%)	0.333
Previous stroke	3 (2%)	1 (2%)	2 (2%)	0.687
Peripheral vasculopathy	4 (3%)	1 (2%)	3 (3%)	0.650
Heart failure	21 (13%)	8 (14%)	13 (13%)	0.847
Shock	10 (6%)	4 (7%)	6 (6%)	0.905
CRF	16 (10%)	2 (3%)	14 (14%)	0.030
Cirrhosis	6 (4%)	4 (7%)	2 (2%)	0.144
Abscess	9 (6%)	1 (2%)	8 (8%)	0.155
Vegetations	83 (53%)	36 (60%)	47 (49%)	0.159
Leaflet perforation	14 (9%)	5 (8%)	9 (9%)	0.840
Prosthesis dehiscence	4 (3%)	1 (2%)	3 (3%)	0.678
Blood/specimen germs (bacterial or fungal causative agents)				0.033
<i>Staphylococcus aureus</i>	75 (48%)	37 (62%)	38 (39%)	
Streptococci	22 (14%)	4 (7%)	18 (18%)	
<i>Staphylococcus</i> other than <i>S. aureus</i>	14 (9%)	1 (2%)	13 (13%)	
<i>Enterococcus</i>	4 (3%)	1 (2%)	3 (3%)	
Mycotic	3 (2%)	1 (2%)	2 (2%)	
<i>Pseudomonas</i>	1 (0.6%)	1 (2%)	0	
Other	5 (3%)	1 (2%)	4 (4%)	
Negative blood culture or specimen	21 (13%)	8 (13%)	13 (13%)	
Missing data	12 (8%)	6 (10%)	6 (6%)	
Surgery				0.055
TV repair	77 (49%)	25 (42%)	52 (54%)	
TV replacement	72 (46%)	34 (57%)	38 (39%)	
With bioprosthesis	46 (64%)	25 (74%)	21 (55%)	0.253
With mechanical prosthesis	13 (18%)	4 (12%)	9 (24%)	
Missing	13 (8%)	5 (15%)	9 (21%)	
Prosthesis replacement	8 (5%)	1 (2%)	7 (7%)	
With bioprosthesis	8 (100%)	1 (100%)	7 (100%)	1.000
CPB time (min)	72 (57-87)	72 (55-83)	72 (60-90)	0.113
Cross-clamping time (min)	46 (38-62)	50 (39-60)	45 (38-64)	0.890

Table 2
Early outcomes.

	Overall (n = 157)	IVDUs (n = 60)	Non-IVDUs (n = 97)	p-Value
Deaths	17 (11%)	4 (7%)	13 (13%)	0.187
Stroke	2 (1%)	0	2 (2%)	0.525
Embolic events other than stroke	4 (3%)	2 (3%)	2 (2%)	0.637
Ventricular arrhythmias	3 (2%)	1 (2%)	2 (2%)	1.000
Postoperative AV block requiring PMK	1 (0.5%)	0	1 (1%)	1.000
Low output syndrome	8 (5%)	0	8 (8%)	0.228
IABP	3 (2%)	0	3 (3%)	0.287
ECLS	2 (1%)	0	2 (2%)	0.263
Multi-organ failure	8 (5%)	2 (3%)	5 (5%)	0.734
Respiratory failure	4 (3%)	1 (2%)	3 (3%)	1.000
Acute kidney injury	4 (3%)	0	4 (4%)	0.299
Sepsis	9 (6%)	3 (5%)	6 (6%)	1.000
Major complications	35 (22%)	10 (17%)	25 (26%)	0.183

IVDU: intravenous drug user; AV: atrio-ventricular; PMK: pacemaker; IABP: intra-aortic balloon pump; ECLS: extracorporeal life support.

IVDU: intravenous drug user; TR: tricuspid regurgitation; TSR: tricuspid steno-regurgitation; TP: tricuspid prosthesis; PMK: pacemaker; ICD: implantable cardioverter-defibrillator; IE: infective endocarditis; LVEF: left ventricular ejection fraction; SB: systolic blood; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; TV: tricuspid valve; CPB: cardio-pulmonary bypass.

Five patients showed IE recurrence on the native or prosthetic TV, with 4 deaths. Survival free from TVIE recurrence was $65 \pm 5\%$, $59 \pm 6\%$, and $43 \pm 9\%$ at 10, 20 and 25 years, respectively (Fig. 1).

No significant differences were found in IVDUs vs. non-IVDUs ($48 \pm 12\%$ vs. $41 \pm 11\%$, $p = 0.234$). However, after adjustment for age, presence of *S. aureus*,

Fig. 1. Survival free from tricuspid valve infective endocarditis recurrence.

hypertension and chronic renal failure, IVDUs showed worse survival free from TVIE recurrence ($18 \pm 12\%$ vs. $58 \pm 10\%$, $p = 0.009$).

Among non-IVDUs, survival free from TVIE recurrence was 100% in patients on dialysis and $52 \pm 21\%$ in patients with unknown cause of TVIE. Patients with infected PMK/implantable cardioverter defibrillator (ICD) leads showed the worst survival free from TVIE recurrence ($20 \pm 12\%$; $p = 0.001$).

Among patients with isolated native TVIE, TV repair and replacement were associated with similar survival rates ($44 \pm 13\%$ and $44 \pm 13\%$, respectively). Patients undergoing surgery for prosthetic TVIE showed significantly lower survival free from TVIE recurrence ($25 \pm 20\%$, $p = 0.008$). Among patients with native TVIE undergoing TV

re- placement, those receiving a bioprosthesis showed a survival free from TVIE recurrence of $69 \pm 8\%$, whereas those receiving a mechanical prosthesis had a survival free from TVIE recurrence of $28 \pm 16\%$ ($p = 0.408$).

At multivariable analysis, age, prosthetic TV replacement, IVDU, and the presence of PMK/ICD leads were risk factors for both unfavorable late survival and lower survival free from TVIE recurrence (Table 3).

Among bacterial and fungal pathogens, mycotic TVIE was associated with worse late outcome, though without reaching statistical significance ($p = 0.052$) (Table 3).

Table 3
Multivariate analysis for late mortality and infective endocarditis recurrence.

Risk factor	HR	95% lower limit	95% upper limit	p-Value
Late death				
Age (years)	1.06	1.04	1.09	<0.001
Mycotic TVIE	2.50	0.98	10.2	0.056
IVDU	4.43	1.64	12.1	0.003
PMK/ICD lead	2.34	1.06	5.16	0.014
Prosthetic TVIE	3.65	1.29	10.2	0.014
Late death and IE recurrence				
Age (years)	1.06	1.03	1.09	<0.001
Mycotic TVIE	4.24	0.98	18.3	0.052
IVDU	4.89	1.74	13.7	0.002
PMK/ICD lead	3.02	1.32	6.89	0.008
Prosthetic TVIE	4.37	1.82	10.4	0.001

TVIE: tricuspid valve infective endocarditis; IVDU: intravenous drug use; PMK: pace-maker; ICD: implantable cardioverter-defibrillator; IE: infective endocarditis.

DISCUSSION

This retrospective multicenter study provides evidence that early and long-term outcomes of patients undergoing surgery for acute TVIE, despite the high-risk profile, are satisfactory. A younger patient age, valve repair rather than replacement, IVDU, and *S. aureus* as the most common pathogen, were the most relevant patient-related factors affecting outcomes. In-hospital mortality was ~10%, and a complicated perioperative course occurred in one-fifth of the patients. Post-discharge findings showed that IE

recurrence rates were low, with acceptable survival rates achieved up to 25 years. Predictors of unfavorable early outcome in terms of both perioperative complications and in-hospital mortality, were age and redo operation, whereas age, fungal TVIE, IVDU, redo operation, and presence of cardiac implantable electrical device leads, were negative determinants of late outcome.

The prevalence of TVIE is constantly increasing, though still representing a minority of cardiac valve-related endocarditis, accounting for 5% to 10% of all cases of valve IE [1–5]. Our findings are consistent with these figures, with TVIE accounting for nearly 4% of all IE recorded in the registry [7].

A substantial change in the “typical” patient profile in valve-related IE has been observed in recent years, shifting from IE affecting mainly rheumatic or congenital valves in the past, to IE affecting mostly patients with prosthetic valves, undergoing catheter-based treatments, on immunosuppression, or making use of intravenous drugs [1,2]. The patient profile of our study population was similar, showing a younger patient age on admission, with almost 40% of the cases diagnosed in IVDUs, and more than 20% of TVIE associated with cardiac electrical devices implanted. Notwithstanding this, native TVIE occurred in 90% of patients, but this finding accounts for the only few prosthetic valves in the TV position. The prevalence of TVIE due to IVDU in our series is in line with that reported by others (30—40%) [10]. Device- or lead- related infection is also a well-established risk factor for IE, with a ~100% increased incidence from mid-2000 s [11]. Cardiac implantable electrical device-related IE usually affects one-fifth of TVIE patients [12,13], and, in our population, it was found to be also a negative predictor of late survival.

Regarding the causative agent, our study confirmed the high prevalence of *S. aureus*-related infections, with a prevalence ranging between 40% and 90% in TVIE patients [3,5,12–14] and a substantial increase in methicillin resistance [1,5]. In

particular, the prevalence of *S. aureus* is significantly higher in IVDUs than in non-IVDUs.

As for the treatment strategy, a slight larger number of valve repair, as compared to valve replacement, was observed with no significant differences in outcome. Likewise, the application of reparative techniques in other experiences did not apparently confer any benefit or advantage over replacement, either at early or long term [15,16]. Other series have shown a protective role of reparative procedures in relation to 30-day mortality [14,17]. Also the type of prosthesis seemed not to provide any difference in outcome in TVIE [18,19]. Such controversial findings may suggest that, in right-sided IE, other factors than the surgical technique and the material or procedure used, play a crucial role in short- term morbidity and mortality. In our series, tricuspid valvectomy [20] found no application, indicating that such a technique is rarely considered by the vast majority of the surgical community, although it represented a surgical option in more than 7% of the TVIE operated in North America [15].

The improved diagnostic modalities, the use of multidisciplinary teams, and better therapeutic strategies, including a more aggressive and early surgical management during the last years, led to a significant reduction of early and mid-term mortality in right-sided IE [21,22]. Despite these undisputable advances, in-hospital mortality of acute TVIE remains significant, although lower than that observed for left-sided IE [1], with an in-hospital mortality, as in our series, ranging from 7% to 12.5% [4,13–15,23]. The lower in-hospital mortality observed in right-sided IE, particularly in TVIE, as compared to left-sided IE, may be related to the low invasiveness shown by this type of IE [24]. However, full understanding of the mechanisms and causes underlying these reduced adverse event rates is still lacking [25].

As opposed to medically managed cases, early outcome of patients undergoing surgery for TVIE did not change significantly over the last years [23]. Age and a complicated

postoperative course with the occurrence of major adverse events were stronger predictors of unfavorable early outcome. Interestingly, in this multicenter experience, the incidence of septic or low cardiac output events after surgical correction remained low, suggesting that severe infection and right ventricular dysfunction, well known factors associated with poor prognosis in TVIE, were most likely not prevented or adequately controlled by concurrent medical management. Immunosuppression status as well as renal and right ventricular failure have been shown to identify patients at high risk for in-hospital mortality in TVIE [26,27], and these factors should be closely considered in the decision making in order to guide surgical timing.

In our series, also long-term outcome was satisfactory, with 10, 20 and 25-year survival rates being consistent with previous data. Recurrence episodes were few, but with an extremely ominous prognosis, underlining the relevance and complexity of the disease in such circumstances. The type of surgical procedure did not seem to affect postoperative results in this setting [4,5,12–15,17,18], suggesting that patient condition and predisposing factors may play a major role. In our analysis, age, mycotic TVIE, IVDU, redo operation for an infected prosthetic valve, and the presence of PMK leads, were all predictors of unfavorable outcome. The presence of a prosthetic valve and the impact of mycotic infection in cardiac valve endocarditis in terms of IE recurrence and risk factors for outcome have been well underscored in recent guidelines as well as in other series [1,18,28]. The outcome related to IVDUs undergoing surgery as far as TVIE is concerned, remains a controversial issue. The high chance of early recurrent IE episodes after surgical treatment in active IVDUs has previously been reported [29]. Mid-term survival in this setting, however, does not appear prohibitive, and, therefore, the presence of active IVDU does not represent a contraindication for surgical treatment of TVIE, as repetitively reported [1–5,12–15], but it is definitely

associated with high chance of post- discharge IE recurrence, including reoperation.

Study limitations

Several limitations should be acknowledged. The retrospective nature of the study significantly impacts data interpretation. Furthermore, this is a 25-year follow-up study, with obvious influence on surgical and medical expertise and quality in patient care. Indications and patient clinical conditions varied greatly during the study period, including guidelines and recommendations for IE and, specifically, for TVIE. The clinical scenarios and management strategies showed remarkable variability. However, the National Registry for Surgical Treatment of Native and Prosthetic Valve Infective Endocarditis allowed early and long-term assessment of patients undergoing surgery for TVIE, with relevant information about actual results in this setting. Nonetheless, the obvious variability across centers in surgical indications, techniques, and perioperative management, and the impact of the different approaches used may have also influenced patient outcome.

In conclusion, although TVIE represents a well-known challenging setting, surgical treatment provides satisfactory results in terms of early and late outcomes. Preoperative patient profile and disease features may identify patients at higher risk for less favorable prognosis. Our overall results, however, suggest that surgically treated TVIE is associated with low recurrence rates and excellent survival, regardless of the surgical approach used

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From the theatriacal comedy "Il Cilindro" (The Top Hat)

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6

THE BEST APPROACH FOR FUNCTIONAL TRICUSPID REGURGITATION. A NETWORK META-ANALYSIS.

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ABSTRACT

OBJECTIVE. For many years, functional tricuspid regurgitation (FTR) was considered negligible after treatment of left-sided heart valve surgery. The aim of the present network meta-analysis is to summarize the results of four approaches in order to establish the possible gold standard.

METHODS A systematic search was performed to identify all publications reporting the outcomes of four approach for FTR, not tricuspid annuloplasty (no TA), suture annuloplasty (SA), flexible (FRA), rigid rings (RRA). All studies reporting at least one the four endpoints (early and late mortality, early and late moderate or more TFR) were included in a Bayesian network meta-analysis.

RESULTS There were 31 included studies with 9,663 patients. Aggregate early mortality was 5.3% no TA, 7.2% SA, 6.6% FRA and 6.4% RRA; Early TR moderate-or-more was 9.6%, 4.8%, 4.6% and 3.8%; Late mortality was 22.5%, 18.2%, 11.9% and 11.9%; Late TR moderate-or-more was 27.9%, 18.3%, 14.3% and 6.4%. Rigid or semirigid ring annuloplasty was the most effective approach for decreasing the risk of late moderate or more FTR (−85% vs. no TA; −64% vs. SA; −32% vs. FRA). Concerning late mortality, no significant differences were found among different surgical approaches, however, flexible or rigid rings reduced significantly the risk of late mortality (78% and 47%, respectively) compared with not performing TA mortality. No differences were found for early outcomes.

CONCLUSIONS. Ring annuloplasty seems to offer better late outcomes compare to either suture annuloplasty or not performing TA. In particular rigid or semirigid rings provides more stable FTR across time.

INTRODUCTION

Functional tricuspid regurgitation (FTR) is the most frequent picture among tricuspid valve (TV) disease; it is mainly due to TV annular dilatation alongside with leaflets tethering, and is commonly associated with left-sided heart valve disease [1,2].

For many years, FTR was considered negligible after treatment of left-sided heart valve surgery [3,4]. Since the mid of two-thousands, Dreyfus et al. [5] emphasized the need to treat FTR, even less than severe, otherwise it could worsen at 5 years. This concept has also been confirmed by some recent meta-analytic studies [6,7].

So, guidelines for the management of heart valve disease [8,9] as well as surgical consensus [10], updated the indications for treatment of FTR, suggesting to treat not only severe TR, but also FTR graded less than severe, in presence of tricuspid annular dilatation (TAD), right ventricular dysfunction or pulmonary hypertension (PHT).

On the other hand, the results of different surgical strategies, suture annuloplasty versus flexible rings or rigid rings are still controversial¹¹⁻¹⁶. Some meta-analyses report pairwise comparison¹⁴⁻¹⁶, however a global description of four most common approaches for functional tricuspid regurgitation (no tricuspid annuloplasty, suture annuloplasty, flexible and rigid ring annuloplasty) is still missing.

Hence, the aim of the present network meta-analysis is to summarize the results of these four approaches in order to establish the possible gold standard.

MATERIAL AND METHODS

Literature search strategy.

Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension for Network Meta-analysis¹⁷, electronic searches were performed by 3 authors (JMR, FR, GB). Details of the literature search strategy are provided in the Appendix.

Selection criteria.

Eligible studies for the present systematic review and network meta-analysis were those published in English that compared two or more strategies in case of non-isolated functional tricuspid regurgitation: no tricuspid annuloplasty (no TA), suture annuloplasty (SA), flexible annuloplasty (FRA) and semirigid/rigid ring (RRA). Studies that did not contain comparison were excluded. Detailed selection criteria are provided in the Appendix.

Data extraction and critical appraisal.

All data were extracted from article texts, tables and figures. Two investigators (MDM and FR) independently reviewed each included article. Details of study appraisal and quality scoring are provided in the Appendix. Discrepancies between the 2 investigators were resolved by discussion and consensus with the senior authors (AMC, RL, AP and UB).

Statistics

In the present network meta-analysis, dichotomous outcome variables were compared with odds ratios (ORs) and 95% confidence intervals (CIs) for early (within postoperative 30 days) mortality and FTR moderate or more. For long-term outcomes with potentially different follow-up durations between groups, we derived the log incidence and corresponding standard error from numbers of reported events and accumulated person-years of follow-up. For each eligible study, if the associated information

was present merely in figures, Engauge Digitizer was used to collect data from the statistical graphs. Then log IRR and standard error were extracted using an excel calculator sheet based on previous reported literature¹⁸. Finally, IRR with 95% confidence interval (95%CI) were reported for late mortality or late TR moderate or more. Outcome variables were compared with incidence rate ratios (IRRs) and 95% confidence intervals (CIs).

Analyses were performed using Bayesian Markov chain Monte Carlo modeling¹⁹.

To provide a comparative hierarchy of procedural efficacy and safety, “Rankograms” with surface under the cumulative ranking curve (SUCRA) probabilities were reported. A SUCRA of 90% means that the treatment of interest achieves 90% of effectiveness or safety relative to other interventions. Thus, the larger the SUCRA value, the higher the rank of the treatment, indicating a safer or more effective treatment. The analyses were performed with NetMetaXL 1.6.1 (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada), R-studio version 1.1.463 (2009-2018) and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom).

Detailed statistical methods are provided in the Appendix.

RESULTS

Literature search.

A total of 7517 studies were initially identified (Figure 1 supplementary). After exclusion of duplicate or irrelevant references, 114 potentially relevant articles were retrieved. After application of the inclusion and exclusion criteria, 31 relevant articles were included in the study^{5,12,20-48}: randomized trials (n =3)^{23,41,44}, propensity score-adjusted (n=4)^{12,25,30,45} and observational non-adjusted (n=24)^{5,20-22,24,26-29,31-43,45-48}.

A total of 9663 patients were included for analysis, Among them 1371 did not receive concomitant TA (no TA), 1931 received suture annuloplasty, 3248 got a flexible and 3104 where a semirigid or rigid ring were used. Study characteristics are summarized in Table 1.

Study quality assessment is summarized in Table 1 supplementary. Inspection of the funnel plots did not show significant asymmetry to suggest publication bias with outcomes selected (Figure 2 supplementary).

TABLE 1 Study characteristics

Author	Year	Cohort size	Arms	Type of study	Age (year)	Female (%)	± Moderate TR (%)	Surgical indication: only severe	Surgical indication: also less than severe with TAD or RV dysfunction or PH [8-10]	Prophylactic TR	AF (%)	EF (%)	NYHA III-IV (%)	Follow up (year)
Roshanali ⁴⁵	2010	105	2	RCT	55	36%	100%	Yes	No	No		0.42		1
Benedetto ²⁴	2012	44	2		66	45%	25%	No	Yes	Yes	48%	0.53	70%	1
Pettinani ⁴²	2019	106	2		63	35%	N/A	No	Yes	Yes	20%	0.58		3.8
Calafiore ³⁸	2009	110	2	Propensity score	65	25%	100%	No	Yes	No	25%	0.3		5.6
Shim ¹¹	2016	296	2		71	43%	64%	No	Yes	No	59%	0.6	76%	7.4
Choi ²¹	2018	144	2		55	62%	0%	No	Yes	Yes	82%		41%	4.3
Sohn ⁴⁴	2019	218	2		60	67%	44%	No	Yes	No	83%	0.57	54%	6.5
Carrier ¹⁹	2004	463	3	Retrospective non-adjusted	60	79%	100%	Yes	No	No			88%	5
Dreyfus ⁵	2005	311	2		60	39%	8%	No	Yes	Yes	29%	0.6		4.8
Ghanta ³³	2007	237	3		67	53%	96%	No	Yes	No		0.48	53%	3
Izumi ³⁵	2010	117	2		72	39%	95%	No	Yes	No	76%	0.57		2
Nava ⁴¹	2010	2013	3		68	60%	96%	No	Yes	No	68%	0.47	49%	5
Calafiore ²⁷	2011	432	3		64	43%	41%	No	Yes	No	32%	0.47		1.8
Pfammüller ⁴³	2012	820	2		69	54%	83%	No	Yes	No	61%	0.57		1.75
Anyoshi ²³	2013	99	3		66	62%	100%	Yes	No	No			65%	4.6
Guenther ³⁴	2013	688	2		65	61%	99%	No	Yes	No	64%	0.55	60%	4.9
Koppers ¹⁸	2013	175	2		69	57%	100%	No	Yes	No		0.56		1
Bertrand ²⁵	2014	78	2		68	50%	17%	No	Yes	No		0.52		0.39
Lin ³⁹	2014	399	3		47	53%	98%	No	Yes	No	41%	0.54	64%	3.3
Murashit ³⁹	2014	162	2		63	48%	61%	No	Yes	No	64%	0.64	38%	5.3
Chikwe ⁴⁰	2015	645	2		59	37%	11%	No	Yes	No	19%	0.61		3.7
Ren ⁴⁴	2015	74	2		49	85%	70%	No	Yes	No		0.61	96%	2.8
Gatti ²²	2016	527	3		70	53%		No	Yes	No		0.55	64%	5.2
Jouan ³⁷	2016	201	2		60	45%	17%	No	Yes	No				3
Wang ⁴⁶	2016	106	2		57	54%	100%	No	Yes	No		0.51		2.9
Abdelgawad ²¹	2017	40	2		37	45%	100%	Yes	No	No	45%	0.53	80%	1
Ito ⁴³	2017	98	2		68	53%	42%	No	Yes	No	78%		43%	3.9
Verdonk ⁴⁷	2018	287	2		62	56%	34%	No	Yes	No	40%			0.08
Adas ²²	2019	200	3		34	59%	100%	No	Yes	No	48%			1.1
Calafiore ³⁸	2019	298	3		52	61%	83%	No	Yes	No	28%	0.48	80%	3
Zhong ⁴⁹	2019	170	3		53	77%	54%	No	Yes	No	67%	0.59	67%	1

Abbreviations: AF, atrial fibrillation; EF, ejection fraction; NYHA, New York Heart Association; PH, pulmonary hypertension; RV, right ventricular; TAD, tricuspid annular dilatation; TR, tricuspid regurgitation.

Network diagrams were reported in the figure 1. Network characteristics are summarized in the table 2 supplementary.

Figure 1. Network diagram for early mortality (yellow), early moderate or more FTR (dark blue), late mortality (green) and late moderate or more FTR (light blue). No TA = not tricuspid annuloplasty; SA = suture annuloplasty; FRA = flexible ring annuloplasty; RRA = rigid or semirigid ring annuloplasty.

Early mortality.

Estimates of early mortality were extracted from 25 studies (7383) with 469 events (Table 2 supplementary). In the network meta-analysis, no TA showed aggregate early mortality of 5.3% (0.9-13.1), 7.2% (1.4-20.6) for SA, 6.6% (0.8-14.2) for FRA and 6.4% (0.7-13.5) for RRA (Table 2). No significant differences were found among the 4 different approaches (Figure 2A). Inconsistency was low (Figure 3A suppl.). Heterogeneity was very low ($I^2=0\%$).

No TA			
0.95 (0.54-1.53)	SA		
1.06 (0.62-1.64)	1.12 (0.81-1.59)	FRA	
1.12 (0.62-1.78)	1.18 (0.85-1.65)	1.06 (0.71-1.62)	RRA

Figure 2A. League tables for early mortality; No TA = not tricuspid annuloplasty; SA = suture annuloplasty; FRA = flexible ring annuloplasty; RRA = rigid or semirigid ring annuloplasty; Red boxes = not statistically significant; White boxes = statistically significant.

Table 2. Intervention characteristics

Treatment	Studies	Events	Patients	Aggregate rate	Min. rate	Max. rate
Early mortality						
No TA	10	45	850	5.3	0.9	13.1
SA	12	113	1580	7.2	1.4	20.6
FRA	13	154	2340	6.6	0.8	14.2
RRA	17	167	2613	6.4	0.7	13.5
Early TR $\geq 2+$						
No TA	6	33	344	9.6	5.6	45.7
SA	9	32	668	4.8	1.4	15.4
FRA	10	68	1488	4.6	1.7	13.6
RRA	10	40	1043	3.8	2.8	9.2
Late mortality						
No TA	8	73	654	22.5	5.3	55.6
SA	10	197	874	18.2	4.1	32.0
FRA	12	168	1414	11.9	2.6	23.0
RRA	13	198	1658	11.9	1.2	22.6
Late TR $\geq 2+$						
No TA	10	229	819	27.9	3.1	77.1
SA	17	323	1762	18.3	4.1	45.2
FRA	16	353	2464	14.3	13.3	55.6
RRA	18	149	2328	6.4	0.25	37.3

Abbreviations: FRA, flexible ring annuloplasty; RRA, rigid ring annuloplasty; SA, suture annuloplasty; TA, tricuspid annuloplasty; TR, tricuspid regurgitation.

Early TR moderate or more.

Estimates of FTR moderate or more were extracted from 16 studies (3543) with 173 events (Table 2 supplementary). In the network meta-analysis, no TA showed aggregate early rate of FTR moderate or more of 9.6% (5.6-45.7), 4.8% (1.4-15.4) for SA, 4.6% (1.7-13.6) for FRA and 3.8% (2.8-9.2) for RRA (Table 2). No significant differences were found among the 4 different approaches (Figure 2B). Inconsistency was low (Figure 3B suppl.). Heterogeneity was very low ($I^2=0\%$)

No TA			
1.35 (0.72-2.41)	SA		
1.45 (0.68-2.85)	1.07 (0.58-1.84)	FRA	
1.56 (0.55-3.32)	1.16 (0.56-2.64)	1.08 (0.54-2.15)	RRA

Figure 2B. League tables for early moderate or more FTR; No TA = not tricuspid annuloplasty; SA = suture annuloplasty; FRA = flexible ring annuloplasty; RRA = rigid or semirigid ring annuloplasty; Red boxes = not statistically significant; White boxes = statistically significant.

Late mortality

Estimates of late mortality were extracted from 21 studies (4600) with 636 events (Table 2 supplementary). In the network meta-analysis, no TA showed aggregate late mortality of 22.5% (5.3-55.6), 18.2% (4.1-32.0), for SA, 11.9% (2.6-

13.6) for FRA and 11.9% (1.2-22.6) for RRA (Table 2). No significant differences were found among different surgical approaches FRA vs SA (IRR 1.52, 0.99-2.34), RRA vs SA (IRR 1.10, 0.68-1.77), and RRA vs FRA (IRR 0.72, 0.45-1.15) (Figure 2C). Conversely, prosthesis TA, either with flexible rings or rigid rings reduced significantly the risk of late mortality (78% and 47%, respectively) compared with not performing TA. Bayesian Markov chain Monte Carlo modeling demonstrated that FRA had the highest probability of having the lowest rate of late mortality (SUCRA 90%), followed by RRA (70%), SA (20%), and no TA (19%) (Figure 3A). Inconsistency was low (Figure 3C suppl.). Heterogeneity was moderate (I²=40%)

Figure 2C. League tables for late mortality; No TA = not tricuspid annuloplasty; SA = suture annuloplasty; FRA = flexible ring annuloplasty; RRA = rigid or semirigid ring annuloplasty; Red boxes = not statistically significant; White boxes = statistically significant.

Late TR moderate or more

Estimates of late FTR moderate or more were extracted from 26 studies (7373) with 636 events (Table 2 supplementary). In the network meta-analysis, no TA

showed aggregate late rate of FTR moderate or more of 27.9% (3.1-77.1), 18.3% (4.1-45.2) for SA, 14.3% (13.3-55.6) for FRA and 6.4% (0.25-37.3) for RRA (Table 2). Different risks among the 4 approaches are summarized in the league table (Figure 2D).

No TA			
2.44 (1.65-3.61)	SA		
4.58 (3.05-6.88)	1.87 (1.47-2.39)	FRA	
6.69 (4.41-10.15)	2.74 (2.04-3.68)	1.46 (1.11-1.91)	RRA

Figure 2D. League tables for late moderate or more FTR; No TA = not tricuspid annuloplasty; SA = suture annuloplasty; FRA = flexible ring annuloplasty; RRA = rigid or semirigid ring annuloplasty; Red boxes = not statistically significant; White boxes = statistically significant.

Bayesian Markov chain Monte Carlo modeling demonstrated that RRA had the highest probability of having the lowest rate of late FTR moderate or more (SUCRA 99%), followed by FRA (67%), SA (34%), and no TA (0%) (Figure 3B).

Figure 3. Rankogram with area under curve for late mortality (A) and late moderate or more FTR (B). Not tricuspid annuloplasty (black line); suture annuloplasty (red line); flexible ring annuloplasty (green line); rigid or semirigid ring annuloplasty (dark blue line).

Hence, RRA provides a significant risk reduction of 85%, 64%, 32% with respect to no TA, SA and FRA, respectively (Figure 4).

FIGURE 4 Risk reduction late moderate or more. TV, tricuspid valve

FRA provides a risk reduction of 78% and 47% with respect to no TA and SA, respectively. Even SA is able to provide a risk reduction of 59% with respect to no TA. Inconsistency was low (Figure 3D suppl.). Heterogeneity was mild ($I^2=18\%$).

Prophylactic TA

Among the 31 selected studies, 4^{5,23,30,41} evaluated the effect of prophylactic TA in 295 patients, implanting rings (flexible 22, semirigid/rigid 273), compared with 310 patients who did not receive TA at the time of left-sided surgery. No differences were found between the two groups concerning early mortality (OR TA vs no TA = 0.65, 0.21-2.01), TR moderate or more (OR = 0.13, 0.01-1.12), late mortality (IRR = 0.59, 0.20-1.71). Conversely, prophylactic TA with rings provided significant risk reduction of FTR moderate or more at follow-up (IRR 0.09, 0.04-0.24) (Figure 5).

FIGURE 5 Subgroup analysis for prophylactic tricuspid annuloplasty: Forest plot of pairwise comparison between not tricuspid annuloplasty and ring annuloplasty.

Figure 5. Subgroup analysis for prophylactic tricuspid annuloplasty: forest plot of pairwise comparison between not tricuspid annuloplasty and ring annuloplasty.

DISCUSSION

The present network meta-analysis confirms that treating FTR at the time of left-sided heart valve surgery is absolutely crucial to achieve both lower mortality and tricuspid regurgitation at follow up. In almost all the studies, TA was performed according to Guidelines⁸⁻¹⁰, even in presence of moderate or mild FTR with tricuspid annulus dilatation or right ventricular dysfunction or PHT.

In contrast with the study by David et al.³, FTR recurrence is not so uncommon, accounting for 27.9% (3.1-77.1%) without any TA. The rate decreased to 18.3% with suture annuloplasty, to 14.3 with flexible rings and even to 6.4% with rigid ring implant (Table 2).

The role of TA for FTR is summarized in recent meta-analyses^{6,7}. Tam et al⁶ reported the results of 56,027 patients where tricuspid valve was repaired at time of left-sided heart valve surgery compared with 11,787 patients where an observational approach was adopted, leaving untreated FTR. The pooled effect evidenced a significant protective effect of TV repair (IRR 0.28, 0.17-0.47) with respect to late FTR. Paganesi⁷ analyzed the pooled effect of 15 studies, confirming that surgery for FTR at the time of the left-sided heart valve surgery provides a significant risk reduction (-81%) rather than observational approach.

In those studies^{5,23,30,41} where TA was performed prophylactically, the rate of late FTR moderate or more was very low (2.8%) when compared to the rate collected in patients without TA (48.7%).

However, the main finding of the present network meta-analysis is the significant risk reduction for late FTR, implanting rigid rather than flexible rings (-49%), or performing suture annuloplasty, mainly DeVega, but also Kay or bicuspidalization, (-64%) and mostly with respect to leaving untreated FTR when performing left-sided heart valve surgery (-84%). Electing this procedure could be the best approach for the stabilization of FTR over time. Veen

KM et al¹⁴ pooled the results of 14 studies comparing suture vs ring annuloplasty, even if only 4 studies reported data for a pairwise comparison between suture and ring annuloplasty, failing to found out any significant differences between these two procedures in terms of late moderate or more TR (RR 0.98, 0.72-1.32). Contrariwise, Parolari et al¹⁵, in a meta-analysis of 9 studies, reported a significant reduction of risk for TA failure performing ring rather than suture annuloplasty (RR=0.76, 0.60-0.95).

The introduction of the flexible rings was driven by some features such as the advantage for annular contraction during cardiac cycle due to their flexibility, the simple design and implantation procedure. Moreover, right coronary occlusion or damage due to flexible ring were anecdotal⁴⁹⁻⁵¹. Less device dehiscence rate may be another possible benefit of flexible with respect to rigid rings⁴².

Nevertheless, the stability of tricuspid annulus offered by rigid ring seems to be greater than the one by flexible rings. In fact, if results of comparison between suture and ring annuloplasty are still controversial, the literature seems to be more concordant to recognize the superiority of rigid over flexible ring^{14,16}. In fact, both meta-analyses by Veen¹⁴ (RR flexible versus rigid: 1.84, 1.24-2.74) and by Wang¹⁶ (RR rigid versus flexible: 0.44, 0.20-0.99) confirm a more stable FTR over time after rigid versus flexible ring TA. The former pairwise comparison was performed with data from 4 studies, but rigid ring was demonstrated to be more effective than flexible rings (RR 1.84, 1.24-2.74).

The main argument invoked by the detractors of TA at the time of left-sided heart valve surgery has been for years the possible increase in the risk of postoperative mortality. This fear has been disproved by many studies⁵² that have clearly reported similar mortality rate either with or without TA. In the present network meta-analysis, no differences were found among the four different approaches.

No differences were found even in terms of FTR at discharge, inducing us to some speculations. It is very likely that in the short-term, performing only left-sided heart valve surgery can lead to a temporary reduction in pulmonary pressure and right ventricular overload, which can be an apparently satisfying result. Actually, this finding can be the result of high dosages of diuretics in postoperative stay and so be independent from TA or no TA.

Although any surgical treatment showed more stable FTR over time than leaving untreated FTR, only ring implant guarantees lower risk of death at follow-up. In particular, risk reduction was higher in case of flexible rings than rigid rings, even if not statically significant. This is very likely to be explained considering that late mortality is not only driven by late FTR, but also by possible right ventricular positive remodeling which can happen regardless the type of surgery²⁵.

Study Limitations

Among the enrolled studies, there are only three randomized trials with small sample size. Unadjusted summary estimates were used for meta-analysis and confounders could not be ruled out. However, the network meta-analysis offers greater power and precision for rare events while controlling for publication bias and small-study effects.

The network model was tested for consistency and heterogeneity. There was a moderate amount of heterogeneity for late mortality, so these results should be interpreted with caution.

We had no chance to test whether type of left-side surgery influenced the results or not. All the included studies had a follow up less than five year. Many of the studies have not defined the extent of suture annuloplasty De Vega vs Kay or bicuspidization.

CONCLUSIONS

To our knowledge, this is the first network meta-analysis comparing early and late outcomes following four different approaches in case of FTR. The results suggest that more stable FTR over time can be achieved only with ring TA, and in particular with rigid ring implant. Performing or not TA at the time of left-sided heart valve surgery does not add any early risk, but can provide better long-term survival.

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SUPPLEMENTARY MATHATERIALS

APPENDIX

Supplemental Methods

Literature Search Strategy

Electronic searches were performed using Ovid Medline, Pubmed, EMBASE, from 2004 to April 2020. To achieve maximum sensitivity of the search strategy, we combined the terms “tricuspid regurgitation”, “tricuspid valve”, “tricuspid annuloplasty”, “tricuspid valve repair”, “tricuspid valve plasty”, “tricuspid recurrence”, “recurrent tricuspid regurgitation”, “residual tricuspid regurgitation”, “mortality”, “failure” as both text keywords and exploded MeSH headings where possible. For an additional review of randomized and non-randomized studies comparing the use of single versus double aortic clamp in on-pump CABG, the terms “single”, “double”, “multiple”, “partial-occluding”, “clamp”, “cross-clamp”, “clamping”, “on-pump”, “coronary artery bypass grafting”, “stroke”, “neurological complications”, “cerebral ischemia”, and “cerebrovascular accident” were combined as both text keywords and exploded MeSH headings where possible.

Selection Criteria

Studies specifying comparison among different (two or more) of the following approaches for secondary tricuspid regurgitation were included in the network and pairwise meta-analyses: no treatment at the time of other cardiac surgery, suture annuloplasty, use of flexible ring or band, use of semirigid or rigid ring. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included. All publications were limited to those involving human subjects. Abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded. Language was English. Exclusion criteria were: no comparative study (n=30). Undistinguishable strategies for tricuspid annuloplasty (n = 27), reporting only echocardiographic data without specifying residual or recurrent TR (n = 5), pediatric cohorts (n = 4), redo cohorts (n = 4), not available full-texts (n = 3), , not only secondary tricuspid regurgitation (n = 3), not conventional tricuspid valve repair (n = 2), comparison between tricuspid replacement and tricuspid annuloplasty (n = 2), comparison between suture annuloplasty and pericardial strip (n = 1), reporting late tricuspid regurgitation as mean and standard deviation (n=1).

Data Extraction and Critical Appraisal

Because quality scoring is controversial in meta-analyses of observational studies, two reviewers (MDM and AP) independently appraised each article included in our analysis according to a critical review checklist of the Dutch Cochrane Centre proposed by MOOSE [1]. The key points of this checklist include: (I) clear definition of study population; (II) clear definition of outcomes and outcome assessment; (III) independent assessment of outcome parameters; (IV) sufficient duration of follow-up; (V) no selective loss during follow-up; and (VI) important confounders and prognostic factors identified.

End-points

The primary end-point was late tricuspid regurgitation, defined as the presence of moderate or more TR at follow up. The secondary end-points were early mortality and early TR moderate or more. Early was defined as within 30 postoperative days; late mortality, defined as all-cause death at follow-up.

Statistical Analysis

Both random and fixed effects analyses were conducted for the Bayesian Markov chain Monte-Carlo model. Predictive distributions (informative priors) for between-study heterogeneity were applied to random effects analyses [2]. The random effects model was adopted for final interpretation of results for its more conservative estimates. Convergence was achieved at 20,000 iterations for all outcomes and lack of autocorrelation was checked and confirmed. A further 30,000 iterations were taken after discarding the burn-in simulation. The variability of results across studies over and above chance (heterogeneity [I^2]) was evaluated, with $I^2 \leq 25\%$ suggesting more homogeneity, $25\% < I^2 \leq 75\%$ suggesting moderate heterogeneity, and $I^2 > 75\%$ suggesting high heterogeneity [3,4]. Along with the between-studies heterogeneity, NM shows an additional source of variability that is called “inconsistency”. Inconsistency is the uncertainty due to discrepancies between direct and indirect inference on the pairwise comparisons [5]. Method by Lu & Ades [6,7] for evaluating inconsistency of NM was used. For testing asymmetry and publication bias, two testes were used [8,9], the one based on a weighted linear regression of the treatment effect on its standard error using the method of moments estimator for the additive between-study variance component [8]. The test statistic follows at distribution with number of studies - 2 degrees of freedom; the second test was based on the rank correlation between standardized treatment estimates and

variance estimates of estimated treatment effects; Kendall's tau is used as correlation measure [9].

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Supplementary Table 1. MOOSE quality assessment for included studies in network meta-analysis.

First Author (Year)	Clear definition of study population	Clear definition of outcomes and outcome assessment	Sufficient duration of follow-up	Sufficient sample size	No selective loss during follow-up ^d	Important confounders and prognostic factors identified
Abdelgawad (2017)	YES	YES	YES	NO	YES	NO
Adas (2019)	YES	YES	YES	NO	YES	NO
Ariyoshi (2013)	YES	YES	YES	NO	YES	YES
Benedetto (2012)	YES	YES	YES	NO	YES	YES
Bertrand (2014)	YES	YES	YES	NO	YES	YES
Calafiore (2009)	YES	YES	YES	YES	YES	YES
Calafiore (2011)	YES	YES	YES	YES	YES	YES
Calafiore (2019)	YES	YES	YES	YES	YES	YES
Carrier (2004)	YES	YES	YES	YES	YES	YES
Chikwe (2015)	YES	YES	YES	YES	YES	YES
Choi (2018)	YES	YES	YES	YES	YES	YES
Dreyfus (2005)	YES	YES	YES	YES	YES	YES
Gatti (2016)	YES	YES	YES	YES	YES	YES
Ghanta (2007)	YES	YES	YES	YES	YES	YES
Guenther (2013)	YES	YES	YES	YES	YES	YES
Ito (2017)	YES	YES	YES	NO	YES	YES
Izutani (2010)	YES	YES	YES	YES	YES	YES
Jouan (2016)	YES	YES	YES	YES	YES	YES
Koppers (2013)	YES	YES	YES	YES	YES	YES
Lin (2014)	YES	YES	YES	YES	YES	YES
Murashita (2014)	YES	YES	YES	YES	YES	YES
Navia 2010	YES	YES	YES	YES	YES	YES
Pettinari (2019)	YES	YES	YES	YES	YES	YES
Pfannmüller (2012)	YES	YES	YES	YES	YES	YES
Ren (2015)	YES	YES	YES	NO	YES	YES

Roshanali (2010)	YES	YES	YES	YES	YES	YES
Shinn (2016)	YES	YES	YES	YES	YES	YES
Sohon (2019)	YES	YES	YES	YES	YES	YES
Verdonk (2018)	YES	YES	NO	YES	YES	YES
Wang (2016)	YES	YES	YES	YES	YES	YES
Zhong (2019)	YES	YES	YES	YES	YES	YES

Supplementary Table 2. Network characteristics.

Characteristic	Early Mortality	Early TR $\geq$ 2+	Late Mortality	Late TR $\geq$ 2+
Number of Interventions	4			
Number of Studies	25	16	21	26
Total Number of Patients in Network	7383	3543	4600	7373
Total Number of Events in Network	479	173	636	1054
Total Possible Pairwise Comparisons	6	6	6	6
Total Number Pairwise Comparisons With Direct Data	6	6	6	6
Number of Two-arm Studies	20	20	20	20
Number of Multi-Arms Studies	4	4	4	4
Number of Studies With No Zero Events	22	8	19	21
Number of Studies With At Least One Zero Event	3	8	2	5
Number of Studies with All Zero Events	3	4	3	0

Legend. TR = tricuspid regurgitation.

Supplementary Figure

Figure 1 supplementary. PRISMA flowchart

Figure 2 supplementary. Funnel plots for early mortality (A), early moderate or more FTR (B), late mortality (C) and late moderate or more FTR (D). No TA = not tricuspid annuloplasty; SA = suture annuloplasty; FRA = flexible ring annuloplasty; RRA = rigid or semirigid ring annuloplasty

Figure 3 supplementary. Inconsistency distribution diagrams for early mortality (A), early moderate or more FTR (B), late mortality (C) and late moderate or more FTR (D).

"L'Uomo-Carbone" (The Coal Man), a novel, 2013

SIMILAR OUTCOME OF TRICUSPID VALVE REPAIR AND REPLACEMENT FOR ISOLATED TRICUSPID INFECTIVE ENDOCARDITIS. RESULTS FROM INFECT REGISTRY

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On behalf of The Italian Group of Research for Outcome in Cardiac Surgery (GIROC)

Submitted for publication

ABSTRACT

Background. To compare early and late mortality of acute isolated tricuspid valve infective endocarditis (TVIE) treated with valve repair or replacement.

Methods. Patients who were surgically treated for TVIE from 1983 to 2018 were retrieved from the Italian Registry for Surgical Treatment of Valve and Prosthesis Infective Endocarditis. All the patients were followed up by means of phone interview or calling patient referral physician or cardiologist. Kaplan-Meier Method was used to assess late survival and survival free from TVIE recurrence with log-rank test for univariate comparison. The primary end-points was early mortality (30 days after surgery) and long-term survival free from TVIE recurrence.

Results. A total of 4084 patients were included in the registry. Among them, 149 patients were included in the study. Overall, 77 (51.68%) underwent TV repair and 72 (48.32%) TV replacement. Early mortality was 9% (13 patients). Expected early mortality according to EndoSCORE was 12%). Tricuspid valve repair showed lower mortality and major complication rate (7% and 16%), compared to tricuspid valve replacement (11% and 25%), but statistical significance was not reached. median follow up was 19.1 years months (14.3-23.8). Late deaths were 30 and IE recurrences were 5. No difference in cardiac survival free from IE was found between the two groups after 20 years ($80\pm6\%$ Repair Group vs $59\pm13\%$ Replacement Group, $p = 0.3$)

Conclusions. Overall results indicate that once surgically addressed, TVIE has a low recurrence rate and excellent survival, regardless the type of surgery used to treat it.

INTRODUCTION

Acute infective endocarditis (IE) is becoming a more common entity that cardiac surgeons have to face[1–3]. Besides left-sided valvular infections, also right-sided valvular infections are increasing in prevalence (up to 12%)[4,5], probably due to an augmented numbers of cardiac implantable devices and of adults treated for congenital conditions [3,6], moreover an increase in injectable-vein drug use (IVDU) has been documented[7]. Despite a different medical presentation of the two conditions, the mortality is similar[8].

Among right-sided valvular infections, tricuspid valve is involved in 90% of cases[9]. Nevertheless, medical treatment of tricuspid valve infective endocarditis (TVIE) has a high rate of success, and surgery is indicated in 10-20% of patients[10]. Surgical treatment of TVIE includes valvectomy (which is performed less and less commonly[11] and associated with an increased mortality)[12], replacement and repair. Given the rarity of the procedure, few reports addressed optimal surgical treatment of TVIE, and most of them have short- to medium- term follow up[10,12] or come from previous era[13]. The aim of this study is to retrieve information from the National Registry for Surgical Treatment of Valve and Prosthesis Infective Endocarditis[11] to compare early and very long term results of patients undergoing either repair or replacement of tricuspid valve in a setting of TVIE.

METHODS

Study population

The ItaliaN registry For surgical trEatment of valve and prosthesis infeCtive endocardiTis (INFECT-REGISTRY): includes 4084 patients from February 1979 to January 2018, with 21 Centers actively participating. The Registry is endorsed by the Italian Society for

Cardiac Surgery (SICCH) with the Italian Group of Research for Outcome in Cardiac Surgery (GIROC).

From 1983 to 2018, isolated acute tricuspid valve IE (TVIE) was surgically treated in 157 out of 4069 (3.8%) patients, with 142 (90%) cases for native tricuspid regurgitation (TR), 7 (5%) for stenosis and regurgitation (TSR), and 8 (5%) for tricuspid prosthesis endocarditis^[11]. Excluding the latter group, 149 patients with native TVIE were included, 77 had valve repair (Repair Group) and 72 replacement (Replacement Group).

Definition of terms and end-points

All the variables collected in the dataset were defined according to Euroscore⁹. The primary end-points was early mortality, defined as death by 30 days after surgery due to any cause, and long-term survival free from TVIE recurrence.

The secondary end-points were long-term survival, 30-day mortality, and major complications (death, acute kidney injury, acute respiratory failure, multiorgan failure, sepsis, major bleeding, stroke, embolisms other than stroke, atrioventricular block needing PMK, acute myocardial infarction, malignant ventricular arrhythmias, low output syndrome). Moreover, observed/expected mortality ratio was reported using the Endoscore^[14]

Follow up

All the patients were followed up by means of phone interview or calling patient referral physician or cardiologist. Follow up ended on March 2018; median follow up was 19.1 years months (14.3-23.8). Seven patients were lost at follow up (11%).

Statistics

Normal distribution of continuous variables was assessed by Kolmogorov-Smirnov test. Normally distributed variables are reported as mean and standard deviation; conversely

non-normally distributed variables are reported as median and quartiles. Pairwise comparison was performed with T-test or Mann-Whitney U-test in case of continuous variables and chi-square with Fisher exact test in case of categorical variables. Kaplan-Meier Method was used to assess late survival and survival free from TVIE recurrence with log-rank test for univariate comparison. SPSS software (vers. 24, IBM corporation, US) and R-studio version 1.1.463 (2009-2018) were used to perform statistical analyses. $P < 0.05$ was considered as threshold for statistical significance.

RESULTS

Clinical profile and operative data

Mean age was 47 ± 17 and 24% were females. Staphylococcus aureus was the most common germ (50%), followed by Streptococci (14%), Staphylococcus other than aureus (9%), Enterococcus (1%), Mycotic (1%), and others pathogens (3%). In 13% of the subjects, either blood cultures or specimen were negative, and in 8% of the patients the datum was missing. Regarding patient profile, 37% of the population was IDUs, 22% had to PMK/ICD leads, 1% had vascular access for dialysis, and in the remaining cases the cause was unknown

Among 77 patients undergoing TV repair, 22 had vegetectomy, 5 vegetectomy and reconstruction with patch, 34 vegetectomy and annuloplasty, 10 bicuspidalization, 6 unknown.

Among 72 patients undergoing TV replacement, 46 had a bioprosthesis, 13 a mechanical prosthesis and in 13 data are missing.

The table 1 summarized differences between the two groups.

Table 1	Overall N = 149	Repair Group N = 77	Replacement Group N = 72	p-value
Age (years)	47±17	49±17	44±15	0.089
Female /Male	36/113	62/15	51/21	0.185
TV disease				
TR	142 (90%)	73 (95%)	69 (96%)	0.368
TSR	7 (5%)	4 (5%)	3 (4%)	
Source of infection				0.123
IVDU	59 (37%)	25 (33%)	34 (47%)	
PMK/ICD leads	32 (22%)	21 (27%)	15 (11%)	
Vascular access for dialysis	2 (1%)	2 (3%)	0	
Unknown	56 (37%)	29 (38%)	27 (38%)	
LVEF (%)	54±9	54±10	55±8	0.295
SB Hypertension	39 (26%)	24 (31%)	15 (21%)	0.152
Diabetes	11 (7%)	9 (12%)	2 (3%)	0.079
Obesity	10 (7%)	5 (7%)	5 (7%)	1.000
COPD	14 (9%)	7 (9%)	7 (10%)	1.000
Previous stroke	3 (2%)	0 (2%)	3 (4%)	0.110
Peripheral vasculopathy	4 (3%)	4 (5%)	0	0.121
Heart failure	18 (12%)	9 (12%)	9 (13%)	1.000
Shock	7 (5%)	3 (4%)	4 (6%)	0.712
CRF	15 (10%)	10 (13%)	5 (7%)	0.221
Cirrhosis	6 (4%)	2 (3%)	4 (6%)	0.430
Abscess	7 (5%)	2 (3%)	5 (7%)	0.264
Vegetations	81 (54%)	37 (48%)	44 (61%)	0.110
Leaflet perforation	12 (8%)	6 (8%)	6 (8%)	1.000
Blood/Specimen bacteria or fungal				0.115
Staphylococcus aureus	74 (50%)	36 (47%)	38 (53%)	
Streptococci	21 (14%)	9 (12%)	12 (17%)	
Sthaphylococcus other than aureus	13 (9%)	10 (13%)	3 (4%)	
Enterococcus	2 (1%)	1 (1%)	1 (1%)	
Mycotic	2 (1%)	2 (3%)	0	
Pseudomonas	1 (0.6%)	0	1 (1%)	
Others	4 (3%)	3 (4%)	1 (1%)	
Negative blood culture or specimen	20 (13%)	7 (9%)	13 (18%)	
Missing data	12 (8%)	9 (12%)	3 (4%)	
Surgery				N/E
TV replacement	--	--		
with bioprosthesis	--	--	46 (64%)	

with mechanical prosthesis	--	--	13 (18%)	
missing	--	--	13 (8%)	
TV repair				N/E
Vegetectomy	22 (29%)	--	--	
Vegetectomy + TA	34 (44%)	--	--	
Vegetectomy + Patch	5 (6%)	--	--	
Bicuspidalization	10 (13%)	--	--	
Unknown	6 (5)	--	--	
CPB time (minutes)	72 (57-85)	71 (52-83)	74 (62-87)	0.145
Cross-clamping time (minutes)	45 (38-62)	44 (30-56)	48 (41-67)	0.091
EndoSCORE[14] %	12 (7-16)	10 (6-17)	12 (7-16)	0.818

Legend. TR: tricuspid regurgitation; TSR: tricuspid steno-regurgitation; IVDU: intra-venous drug use PMK/ICD: pacemaker/implantable cardioverter defibrillator; IE: infective endocarditis; LVEF: left ventricular ejection fraction; SB: systolic blood; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; TV: tricuspid valve; TA = tricuspid annuloplasty; CPB: cardio-pulmonary;

Early outcome

Early mortality was 9% (13 patients). Expected mortality according to EndoSCORE[14] was 12% with O/E ratio 0.75. The 30-day major complications rate was 20% (30 patients). Tricuspid valve repair showed lower mortality and major complication rate (7% and 16%), compared to tricuspid valve replacement (11% and 25%), but statistical significance was not reached. Regarding perioperative morbidity, one fourth of the patients experienced major complications, but, interestingly, event rates related to active infection (sepsis), or to acute cardiac as well as renal failure, were low (Table 2).

Table 2. Early outcomes

	Overall N = 149	Repair Group N = 77	Replacement Group N = 72	p-value
Deaths	13 (9%)	5 (7%)	8 (11%)	0.318
Stroke	1 (1%)	1 (1%)	0	1.000
Embolisms other than stroke	3 (3%)	1 (1%)	3 (4%)	0.354
Ventricular arrhythmias	1 (1%)	1 (1%)	1 (1%)	1.000
Postoperative AV block needing PMK	1 (0.7%)	0	1 (1%)	0.483
Low output syndrome	7 (5%)	2 (3%)	5 (7%)	0.264
IABP	3 (2%)	2 (3%)	1 (1%)	0.600
ECLS	2 (1%)	1 (1%)	1 (1%)	1.000
Multi-organ failure	7 (5%)	3 (4%)	4 (6%)	0.712
Respiratory failure	4 (3%)	1 (1%)	3 (4%)	0.354
Acute kidney injury	4 (3%)	3 (4%)	1 (1%)	0.621
Sepsis	8 (5%)	2 (3%)	6 (8%)	0.156
Major complications	30 (20%)	12 (16%)	18 (25%)	0.152

Legend. AV: atrio-ventricular; IABP: intra-aortic balloon pump; ECLS: extracorporeal life support

Late outcome

Survival at 5, 10, and 20-year was $74\% \pm 4$, $69\% \pm 5$ and $48\% \pm 9$, respectively (Figure 1).

No difference was found between repair and replacement after 20 years ($47\% \pm 13\%$ Repair Group vs $51\% \pm 12\%$ Replacement Group, $p = 0.78$; Figure 2)

Figure 1. Twenty-year survival of overall cohort; 95% confidence limits were reported.

Figure 2. Twenty-year survival stratified by tricuspid valve (TV) repair (blue line) and replacement (red line); 95% confidence limits were reported.

At follow up deaths cardiac-related were 13, infective endocarditis relapse on tricuspid valve were 5, with 4 deaths. Cardiac survival-free from IE relapse at 5, 10 and 20-year was 86 ± 3 , $81\pm4\%$ and $69\pm8\%$, respectively (Figure 3). No difference was found between the two groups after 20 years ($80\pm6\%$ Repair Group vs $59\pm13\%$ Replacement Group, $p = 0.35$; Figure 4).

Figure 3. Twenty-year cardiac survival-free from infective endocarditis relapse of overall cohort; 95% confidence limits were reported.

Figure 4. Twenty-year cardiac survival-free from infective endocarditis relapse stratified by tricuspid valve (TV) repair (blue line) and replacement (red line); 95% confidence limits were reported.

COMMENT

Infective endocarditis is a very dangerous and potentially deadly infection of cardiac valve[15]. Involvement of the right side is usually connected with intravenous drug use[12], intracardiac device and their manipulation. Right IE represent approximately 5% -10% of all IE cases[16] and its incidence has been increasing in the last years[4]. Moreover, the virulence of IE is increasing, probably due the etiological agent (*S. Aureus* is the causative agent in 60-90% of cases) and the fast spreading antibiotic resistance[17]. Generally predictors of poor outcome in IE are related to patient characteristic (older age; prosthetic valve; diabetes mellitus and comorbidity), clinical complications (heart and kidney failure, brain hemorrhage,

ischemic stroke and septic shock), infective agent and finally echocardiogram findings (periannular complications, pulmonary hypertension, large vegetation, severe prosthetic valve dysfunction, signs of elevated diastolic pressure, etc). Fever, multiple septic pulmonary emboli and bacteremia, associated to chest pain and caught or hemoptysis, are characteristic signs of right side IE. Also we can find paradoxical embolism when left side IE is associated. Anyway, given the high response to medical therapy, according with 2020 ACC/AHA Guidelines[1] surgery is limited to few symptomatic cases. Conversely in TVIE surgery is considered (Class IIa, Level C) in persistent valve vegetation >20mm after recurrent pulmonary emboli (with or without concomitant right heart failure), right Heart failure (secondary to severe tricuspid regurgitation) and/or persistent infective status or bacteremia >7 days despite adequate antimicrobial therapy[15].

Our study is a retrospective multicenter study, result of Italian experience on isolated TVIE surgically treated. The data were extrapolated from the Italian Registry for Surgical Treatment of Valve and Prosthesis Infective Endocarditis[11]. TVIE represent around 4%[2,15,18,19] of the total IE of the Registry cases[20]. According to Endoscore[14], early mortality was 9%. Early outcome of tricuspid valve repair shows lower mortality and major complication rate compared to tricuspid valve replacement, also sepsis or acute cardiac as well as renal failure, were low.

In our series *S. Aureus* was the most common germ, followed by Streptococci, Staphylococcus other than aureus, Enterococcus, Mycotic, and others pathogens. Specifically, the prevalence of *S. Aureus* is significantly higher in IVDUs than non-IVDUs. Regarding patient profile, according to previous series published, the majority of the population was IDUs, following by intracardiac leads, and vascular access for dialysis, the cause was unknown in the remaining cases.

Removal of infected tissue (vegetation, perforated leaflet and abscesses) is the first goal of surgical treatment. Therefore, it could be sometimes necessary the removal of all leaflets or a part of them and then proceed to valve reconstruction[21] (autologous pericardium, neochordae or bicuspidalization techniques). In our series, valve repair and valve replacement were considered. Cardiopulmonary bypass was used in all patients, with the maximum time of 60 minutes of aortic-cross clamping time, just in case of complex reconstruction. We did not considered valvectomy, even if it is performed in more than 7% of surgical TVIE in North America[22].

Indeed, Slaughter et al.[12] show that in IDU-associated TVIE, valvectomy is an independent predictor of operative mortality, and valve repair should be the preferred management for tricuspid valve endocarditis degeneration whenever possible. The 51.68% of our patients underwent TV repair and 48.32% TV replacement, without difference in operative mortality between biological and mechanical prosthesis, as other authors reported[23–25]. However, in accordance with others[13], we did not find a significant statistical difference between TV repair and TV replacement. Despite a very long follow-up (up to 20 years), no difference in cardiac survival-free from IE relapse was found between Repair Group vs Replacement Group. This is very likely due to the choice of the rightest surgical approach for each TVIE condition. In half of cases, the presence of a highly destroyed valve forced surgeons to implant a prosthesis rather than try a complex valve reconstruction.

Interestingly, new devices have been proposed to treat TVIE with good results[16]. Therefore, As Veve MP. Et al.[26] suggested, percutaneous mechanical aspiration of TV vegetation could be considered in young IVDU patients as bridge to surgery during addiction rehabilitation.

Another important risk factor in right IE, after IVDU, is implantable electronic device[27]. It is a severe event associated with high mortality[28]. It is often caused by insertion site infection of hardware, but it is a distinct separate disease, according to Guidelines[1]. Local device infection is limited to the pocket of generator device, it manifests with local edema, wound dehiscence and purulent drainage. Cardiac device related IE is defined as “an infection extending to the electrode leads, cardiac valve leaflets or endocardial surface”[15]. In our series, such condition represented the second cause of right IE and it was found to be a negative predictor for late survival.

In the last years, the idea of IE evolved from a single specialist pathology to a disease needing a multidisciplinary approach. The real severity of disease derived from number and gravity of organ involved, the microorganism and the presence of complications. The final diagnosis and the following strategy, either surgical or conservative, should be performed by an Endocarditis Team[29,30] involving different specialists.

A more aggressive and an early surgical approach has been proved to have better outcomes, with a significant reduction of early mortality. As aforementioned, long-term outcomes in our series showed good results in accordance to published data. Recurrences of IE were few, but with an extremely poor prognosis.

According to guidelines, and other series[1,31] our analysis showed that age, mycotic TVIE, IVDU, reoperation for an infected prosthetic valve, and presence of right device, as the presence of prosthetic valve and of mycotic infection are negative predictors of unfavorable outcome.

Study Limitations

Study limitations are connected with patient population and the retrospective nature of the data analysis. This is a 20-year study evaluation, in this long period the surgical and

medical expertise and quality in patient care have increased. Likewise, guidelines have changed for valvular disease management, being the most common published on 2020. Clinical scenarios and type of surgical and medical approaches showed remarkable variability also for new technologies introduction, like percutaneous aspiration system, antibiotic therapy in order to antimicrobial resistance and most diffuses culture of endocarditis team approach.

CONCLUSIONS

In conclusion, TVIE represents at today a well-known and challenging pathology. Preoperative patient profile and disease features may indicate patients at higher risk. Overall results indicate that once surgically addressed, TVIE has a low recurrence rate and excellent survival, regardless the type of surgery used to treat it. Surgical strategy should be tailored on valve condition.

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*"Kaleido, il circo delle donne" (Kaleido, the women's circus),
a novel, 2015*

8

GENERAL DISCUSSION

Tricuspid regurgitation has been a neglected issue for several years, even affecting 65-80% of the population, worldwide (1). However, in last two decades, the interest for this valve disease has been growing, both from a cardiological and surgical point of view (2).

Since Nath (3), in 2004, highlighted the prognostic influence of any grade of tricuspid regurgitation in a population undergoing echocardiography for any reason, also the community of cardiac surgeons began to evaluate the impact of functional tricuspid regurgitation at the time of left-sided heart valve surgery (4,5). In that scenario, we reviewed our experience where tricuspid regurgitation, secondary to functional mitral regurgitation and dilated cardiomyopathy, was treated or not according to surgeons' personal choice. Although the retrospective nature of the study, the results confirmed that "treating mitral disease means treating secondary tricuspid regurgitation" was a misleading concept, lasted too long among cardiac surgeons. Indeed, when even moderate grade of secondary tricuspid regurgitation was leaved untreated at the time of left-sided heart valve surgery, at two years it progresses to severe in 40% of cases, while it remained still moderate in 37%. In this sense, Dreyfus et al (4) introduced the proposal to treat prophylactically secondary tricuspid regurgitation when tricuspid annulus was dilated.

Prophylactic tricuspid annuloplasty in patients with dilated annulus >40 mm was demonstrated to be associated with a reduced rate of tricuspid regurgitation progression, improved right, in a randomized trial (6); this finding was confirmed by in other small trial (7), by two meta-analyses (8,9) and some propensity matched studies (10,11)

Nowadays, both European and American guidelines (12,13), in fact, suggest to handle secondary tricuspid regurgitation even less than severe in presence of pulmonary hypertension, right ventricular dilatation or dysfunction and dilated tricuspid annulus, testifying the change of attitude of cardiac surgeon regarding this entity.

We addressed this theme in a network meta-analysis where leaving untreated functional tricuspid regurgitation was compared to three different surgical procedure, suture annuloplasty, flexible ring and rigid or semirigid ring implantation. The pooled analysis decreed tricuspid annuloplasty with rigid or semirigid ring as the best option both in terms of late survival and durability of the annuloplasty. In 2010, Navia et al (5) reported the experience of the Cleveland Clinic comprising different techniques in a cohort of 2277 patients. At 5 years, only 22% had no tricuspid regurgitation and 33% had mild TR, meaning that roughly half of patients undergoing tricuspid annuloplasty with any technique had late TR recurrence. In particular, the authors confirmed that the best treatment was rigid ring annuloplasty (14% by 5 years) compared to 16% for those receiving flexible rings and 24% for those with DeVega annuloplasty. This item was subject of some meta-analysis (14-16). Veen et al (14) reported the pooled results of 14 and 6 articles comparing suture versus ring and flexible versus rigid ring, respectively. The authors failed to evidence any difference between 586 patients undergoing suture annuloplasty and 1425 ring annuloplasty in terms of late survival (Rate ratio 0.67, $p=0.264$) and of late recurrence ($RR = 0.98$, $p = 0.604$). In 6 studies focused on flexible vs. ring repair encompassing 749 (flexible) and 745 (rigid) patients, the authors found that TR recurrence was significantly higher in the flexible group (7.5%/year) vs. the rigid group (3.9%/year, $P=0.002$) with a RR equal to 1.84 ($p=0.002$).

Conversely, Parolari et al (15) were able to find difference in terms of durability of tricuspid annuloplasty between ring and suture annuloplasty. The meta-analysis pooled the results of 9 studies, encompassing for 3262 patients having ring annuloplasty and 1534 having suture annuloplasty. The comparison showed as ring annuloplasty was associated with 24% risk reduction of late TR recurrence.

Some conditions, such as right ventricular changes and pulmonary hypertension, have been introduced as determinants to intervene on less than severe TR, because they are associated with both pathophysiological features at the basis of tricuspid regurgitation progression over time, and to the prognosis (17-20).

In mitral-tricuspid valve disease, pulmonary hypertension has been deemed a prognostic determinant of bad outcome for years. Actually, right ventricle was considered only a part of the issue labeled “pulmonary hypertension”, while there are some evidences (20), even in fields other than cardiac surgery, such as for heart failure, that right ventricular remodeling, defined as dilatation and/or dysfunction, plays a role per se, so the prognosis in mitral-tricuspid surgery may be affected either independently or summarily by these two pathological conditions, since we can have some patients showing pulmonary hypertension without any right ventricular remodeling, likewise some others may have normal pulmonary pressure with right ventricular remodeling.

Whilst functional tricuspid regurgitation has been gaining more visibility in last decades, surgical treatment of primary tricuspid regurgitation, especially as isolated feature, is still controversial, even if the prevalence of this entity appears to be rising due to the growing incidence of both permanent atrial fibrillation (which cause annular dilatation) and of endocarditis due mainly to intravenous drug user and intracardiac devices. (21-23)

In the field of tricuspid valve endocarditis, there are few reports on short and mid-term results of tricuspid valve surgery, given the rarity of the procedure (up to 10-20% of patients with TV endocarditis) (24,25)

The Italian Registry For surgical treatment of valve and prosthesis infective endocarditis (INFECT-REGISTRY) was created in 2015 to aggregate data from more than

twenty Italian Cardiac Surgery centers. From our experience, we were able to reported very-long-term results of patients with isolated tricuspid annuloplasty for the treatment of infective endocarditis, showing as intravenous drug abuse and device leads predisposed to lower survival free from relapse and that tricuspid valve repair and replacement showed similar results.

The issue of treating intravenous drug abuser developing endocarditis is still debated in many Countries. Pfannmueller et al (26) reported a prevalence of 20% of IDVU in a small cohort of 56 patients with isolated tricuspid endocarditis undergoing surgery. At Cleveland Clinic, among 536 patients with infective endocarditis, isolated TR undergoing surgery was recored only in 30 patients, 12 out of them were IDVUs. The authors demonstrated that after 180 days, survival curve free from recurrence of patients with IDVU started to deverge from the others. Similarly we showed IDVUs was a risk factor for survival free from relapse and this might be due to the reluctancy of these patient to give up their unhealthy habits (27)

Similarly the presence of device leads, such as PM leads, is not only involved in the developing of isolated primary regurgitation due to leaflet lesions but also is a predisposing factor for infective endocarditis and it is associated with lower survival and higher rate of recurrence (23,28)

Finally, an hamletic doubt rises in this field, to repair or to replace the vale?.

In a meta-analysis (25) of 12 unmatched retrospective studies, 90 patients undergoing tricuspid valve repair were compare to 54 patient undergoing replacement. There was no difference in perioperative mortality and long-term all-cause mortality between tricuspid valve repair versus replacement (RR 0.62, $p = 0.3$ and RR 0.61, $p = 0.4$, repsectively). However valve repair was associated with lower recurrent IE (RR 0.17, $p = 0.004$) and need for

reoperation (RR 0.26, $p = 0.04$) but a trend toward greater risk of moderate to severe tricuspid regurgitation (RR 4.14, $p = 0.09$).

In some large experiences (29), valves are more commonly replaced rather than reconstructed due to the extensive valve destruction requiring very likely complex repairing. However, the ratio of repair to replacement can vary widely among the studies (1:6 to 6:1), as reported by Yaganawa et al (25). In our experience, the prevalence of repair and replace are quite similar.

A very recent study from Taiwan (30), 333 patients with isolated tricuspid IE underwent either repair (196) or replacement (137). The authors were able to find only a trend toward a lower all-cause mortality rate in the repair group (35.7% versus 48.3%; hazard ratio [HR], 0.66; 95% CI, 0.42–1.04). However the repair group had lower incidences of composite outcome (redo surgery, heart failure, pacemaker, and major bleeding) and hospital readmission (57.7% versus 70.1%; SHR, 0.64; 95% CI, 0.46–0.91) compared with the replacement group.

Once the decision to replace has been made, bioprosthetic valves were used more commonly than mechanical valves. That is not surprising given that several surgeons used biologic prostheses exclusively in the intravenous drug use population despite the reduced durability citing the lower likelihood to adhere to anticoagulation regimens (Yaganawa). Bioprosthetic valves have shown good long-term freedom from structural valve deterioration and need for reoperation given the low transvalvular gradients in the tricuspid position (31)

CONCLUSIONS

Our data show that the functional tricuspid regurgitation deserves to be treated either when it is secondary to left-sided heart valve surgery or when it is isolated, due to infective endocarditis. In the first case, there are many evidences that even less than severe TR has to

be treated, especially in presence of tricuspid annulus, right ventricular and pulmonary circulation modifications. The results of surgery appear to be more durable when a rigid or semirigid ring is implanted. In the second case, very long-term results seem to endorse a surgical approach, regardless the type of surgery performed, but taking into account some subset of patients particularly at risk for worse outcome. In both cases, larger cohort studies and trials are required to better clarify all the questions.

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Lesina, my birthplace

IMPACT

Tricuspid regurgitation (TR) is a frequent condition that has been overlooked compared to left-sided valve diseases. Epidemiological studies suggest that moderate or severe TR affects over 1.6 million individuals in the USA.(1,2). Multiple studies, in various settings such as heart failure (HF) with reduced left ventricular ejection fraction (LVEF), tricuspid flail, or isolated functional TR, have shown that the presence and severity of TR are associated with an increased risk of mortality and of cardiovascular (CV) events (3-8).

Although total numbers had increased over time, TV surgery remained seldom performed, and mainly concomitant with another surgical procedure and rarely isolated. TR is often left untreated. Intervention (surgery or transcatheter) is the only curative treatment for severe TR and medical therapy should be considered as only palliative.

The main objectives of this thesis were: to analyze the prognostic role of the tricuspid regurgitation, to evaluate the results of the surgical treatment in various setting; to assess the interplay between tricuspid regurgitation and right ventricle. In this chapter clinical and surgical impact of the thesis is reported.

Clinical Impact

The first part of this thesis (Chapter2) describes the prognostic role of untreated functional tricuspid regurgitation (TR), graded moderate or severe, at the time of mitral valve surgery. Particularly, the study confirmed that leaving untreated functional tricuspid regurgitation, it may worsen over time. The study was performed in period when most of surgeons still embraced the concept that treating mitral valve disease could solve also secondary tricuspid regurgitation. This retrospective study endorsed the incoming thought that a more aggressive and prophylactic approach had to be taken in order to stabilize also function tricuspid regurgitation.

This is followed by a comprehensive dissertation on functional tricuspid regurgitation (Chapter 3), starting from anatomy to pathophysiological mechanisms, from clinical

presentation to imaging, from prognostic role and surgical indication to surgical outcome, summarizing factors that can impact on worsening of tricuspid regurgitation whenever surgeon decides to leave it untreated, or on durability of tricuspid valve repair.

in Chapter 4, the additive and independent prognostic role of right ventricle and pulmonary pressure in mitral-tricuspid surgery has been investigated. The interplay between these two variables and function tricuspid regurgitation is nowadays well recognized, so that even less than severe tricuspid regurgitation are recommended to be operated on in presence of abnormal right ventricular size and function as well as in case of pulmonary hypertension. In this retrospective study, the prognostic role of either right ventricular size/function or pulmonary hypertension has been confirmed at multivariable analysis, supporting the thesis that, in mitral-tricuspid surgery, pulmonary hypertension per se cannot mirror necessarily a right ventricular remodeling and vice versa, so both variables should be included in the risk models, either independently or as adding risk features.

Surgical impact

In Chapter 5, another interesting issue was addressed, the very long-term outcome of patients with isolated tricuspid regurgitation due to infective endocarditis. In the literature, small sized experiences are reported, so this retrospective study, extrapolated from INFECT-REGISTRY, the The Italian registry For surgical treatment of valve and prosthesis infective endocarditis, reported one of the largest series ever reported. The reported results were satisfactory either in terms of early and late outcomes. Preoperative patient profile and disease features may identify patients at higher risk for less favorable prognosis, such as elderly, redo and intravenous drug user. This issue was then argued also in the chapter 7, where we compared two surgical approaches, repair or replacement, showing no difference in terms of both early and late outcome.

In the chapter 6, a network meta-analysis of 31 studies was performed to compared four different approaches to functional tricuspid regurgitation, leaving untreated compared to suture annuloplasty, flexible ring or rigid ring implant. We provided so a summarizing picture of the main studies, randomized, propensity matched or unmatched on this issue, so to find the best approach. Our results confirmed the need to treat even less than severe functional TR as well as the need to use a prosthetic ring rather than suture annuloplasty. Moreover, in case of ring implant, a semirigid or rigid one should be preferable to achieve a longer stability of the repair

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*From the theatriacal comedy "Kaleido, il circo delle donne" (Kaleido, the women's circus),
Authors: Michele Di Mauro
Performed from 2013 to 2018*

SUMMARY

Chapter 2. In this study, prognostic role of moderate or greater functional tricuspid regurgitation (FTR) at the time of mitral valve surgery was investigated. Both 5-year survival (88.2% vs 46, $p < 0.001$) and possibility to be alive and in NYHA class I-II (78.4% vs 41.2%, $p < 0.001$) were significantly higher in patients with lower graded FTR (no-or-mild vs. moderate-or-greater). Multivariable analysis confirmed that patients with moderate or greater FTR has three-fold higher risk to died or to have heart failure. Moreover, FTR worsen over time in only 5.7% of patients having preoperative no-or- mild FTR compared to 77.1% of the remaining patients.

Chapter 3. We reviewed the literature on functional tricuspid regurgitation in to summarize all the aspects of functional tricuspid regurgitation, since it has been a neglected and underestimated entity for years. Functional tricuspid regurgitation may be secondary to several heart diseases, more commonly mitral valve disease, pulmonary hypertension, atrial fibrillation, cardiomyopathies, right ventricular dysplasia, and idiopathic annular dilatation. It is characterized, from a pathophysiological point of view, by annular dilatation along with increased tricuspid leaflet tethering, associated with both increased right ventricular pre-load or after-load. Echocardiography is the main diagnostic tool to assess both TR gravity and morpho-functional changes accompanied by right ventricular changes. Moderate or greater FTR is a risk factor for worse survival and it can worsen over time. This makes it reasonable to treat FTR at an early stage, preferably at the time of left-sided valve surgery. Tricuspid valve annuloplasty is the gold standard surgical treatment for FTR but is still associated with a high recurrence rate (from 17% to 33% at 5 year-follow up).

Chapter 4 In mitral-tricuspid surgery, where FTR is treated, either right ventricle (RV) and pulmonary circulation might play an prognostic role for early outcome. However, most of risk score models include only pulmonary hypertension (PH) as independent

variable of risk. Conversely, there are many evidences that the two entities can have independent, but also additive, prognostic impact. In this retrospective study, we investigated this hypothesis. We divided the entire cohort in 6 different subsets, according to the presence or not of RV abnormality (for size and/or function), and no, moderate or severe PH. We concluded that in patients undergoing mitral-tricuspid valve surgery, the presence of either RV dysfunction/dilatation or severe pulmonary hypertension, might play an independent prognostic role for mortality. The worst scenario is surely the contemporary presence of both conditions.

Chapter 5. From 4084 patient of the INFECT-REGISTRY (the Italian Registry for Surgical Treatment of Native or Prosthetic Valve Infective Endocarditis), we extrapolated a cohort of 157 (3.8%) patients undergoing isolated tricuspid valve surgery to treat tricuspid regurgitation due to infective endocarditis. Most of patients were intravenous drug use (38% IVDU), in 21% infection was due cardiac implantable electronic device leads. Early mortality was 11% with age and redo as risk factors. Late survival at 25 years was 44%, negatively influenced by age, mycotic infection, IVDU, infected prosthesis replacement and presence of cardiac implantable electronic device leads.

Chapter 6. We performed a network meta-analysis with the aim to specifically investigate the differences in late recurrence of TR (primary outcome) and in early and late survival as well as early TR recurrence (secondary outcomes) according to the type of approaches, no tricuspid annuloplasty compared to different surgical procedures (suture vs flexible ring vs rigid ring annuloplasty). The use of the rings was associated with better late survival compared to leaving untreated TR, while the best procedure for the durability of TV annuloplasty was the implant of rigid ring.

Chapter 7. From 4084 patient of the INFECT-REGISTRY (the Italian Registry for Surgical Treatment of Native or Prosthetic Valve Infective Endocarditis), we extrapolated a cohort

of 149 (3.6%) patients with native TR due endocarditis undergoing isolated tricuspid valve surgery in order to evaluated differences in terms of early and late outcome according to type of surgery. Hence 77 undergoing TV repair were compared with 72 undergoing TV replacement Early mortality was 9% (13 patients). Tricuspid valve repair showed lower mortality and major complication rate (7% and 16%), compared to tricuspid valve replacement (11% and 25%), but statistical significance was not reached. median follow up was 19.1 years months (14.3-23.8). No difference in cardiac survival free from IE was found between the two groups after 20 years ($80\pm 6\%$ Repair Group vs $59\pm 13\%$ Replacement Group, $p = 0.3$)

Makalle, Ethiopia, 2012

SAMENVATTING

Hoofdstuk 2. In deze studie werd de prognostische rol van matige of grotere functionele tricuspidalisregurgitatie (FTR) tijdens mitralisklepooperaties onderzocht. Zowel de 5-jaarsoverleving (88,2% vs 46, p <0,001) als de mogelijkheid om te leven en in NYHA klasse I-II (78,4% vs 41,2%, p <0,001) waren significant hoger bij patiënten met een lager gegradeerde FTR (geen- of mild vs. matig-of-hoger). Multivariabele analyse bevestigde dat patiënten met matige of hogere FTR een drievoudig hoger risico hebben om te overlijden of hartfalen te krijgen. Bovendien verslechtert FTR in de loop van de tijd bij slechts 5,7% van de patiënten met preoperatieve geen of milde FTR vergeleken met 77,1% van de overige patiënten. Hoofdstuk 3. We hebben de literatuur over functionele tricuspidalisregurgitatie gerecenseerd om alle aspecten van functionele tricuspidalisregurgitatie samen te vatten, aangezien het jarenlang een verwaarloosde en onderschatte entiteit is geweest. Functionele tricuspidalisregurgitatie kan secundair zijn aan verschillende hartaandoeningen, vaker mitralisklepaandoening, pulmonale hypertensie, atriale fibrillatie, cardiomyopathiën, rechterventrikeldysplasie en idiopathische ringvormige dilatatie. Het wordt, vanuit pathofysiologisch oogpunt, gekenmerkt door ringvormige dilatatie samen met verhoogde tricuspidalisklepafsluiting, geassocieerd met zowel verhoogde rechterventrikelvoorbelaasting als nabelasting. Echocardiografie is het belangrijkste diagnostische hulpmiddel om zowel TR-zwaartekracht als morfofunctionele veranderingen te beoordelen, vergezeld van veranderingen in het rechterventrikel. Matige of hogere FTR is een risicofactor voor slechtere overleving en kan na verloop van tijd verslechteren. Dit maakt het redelijk FTR in een vroeg stadium te behandelen, bij voorkeur tijdens een linkerzijdige klepooperatie. Annuloplastiek van de tricuspidalisklep is de gouden standaard chirurgische behandeling voor FTR, maar wordt nog steeds geassocieerd met een hoog recidiepercentage (van 17% tot 33% na 5 jaar follow-up). Hoofdstuk 4 Bij mitralis-tricuspidalis chirurgie, waarbij FTR wordt behandeld, kunnen de rechter ventrikel (RV) en de pulmonale circulatie een prognostische rol spelen voor een vroege uitkomst. De meeste risicoscore-modellen bevatten echter alleen pulmonale hypertensie (PH) als onafhankelijke risicovariabele. Omgekeerd zijn er veel bewijzen dat de twee entiteiten een onafhankelijke, maar ook additieve, prognostische impact kunnen hebben. In deze retrospectieve studie hebben we deze hypothese onderzocht. We verdeelden het hele cohort in 6 verschillende subsets, op basis van de aanwezigheid of niet van RV-afwijking (voor grootte en / of functie), en geen, matige of ernstige PH. We concludeerden dat bij patiënten die een mitralis-tricuspidalisklepooperatie ondergaan, de aanwezigheid van RV disfunctie / dilatatie of ernstige pulmonale hypertensie een onafhankelijke prognostische rol zou kunnen spelen voor mortaliteit. Het ergste scenario is

ongetwijfeld de huidige aanwezigheid van beide voorwaarden. Hoofdstuk 5. Van 4084 patiënten van de INFECT-REGISTRY (het Italiaanse register voor chirurgische behandeling van inheemse of prothetische klepinfectieve endocarditis), hebben we een cohort van 157 (3,8%) patiënten geëxtrapoleerd die een geïsoleerde tricuspidalisklepchirurgie ondergingen om tricuspidalisregurgitatie als gevolg van infectieuze endocarditis. De meeste patiënten waren intraveneus drugsgebruik (38% IVDU), bij 21% was de infectie te wijten aan cardiale implanteerbare elektronische apparaatdraden. De vroege mortaliteit was 11% met leeftijd en overdoen als risicofactoren. De late overleving na 25 jaar was 44%, negatief beïnvloed door leeftijd, mycotische infectie, IVDU, geïnfecteerde prothesevervanging en aanwezigheid van implanteerbare elektronicakabels voor het hart. Hoofdstuk 6. We hebben een netwerk meta-analyse uitgevoerd met als doel om specifiek de verschillen te onderzoeken in laat recidief van TR (primaire uitkomst) en in vroege en late overleving, alsook in vroege TR recidief (secundaire uitkomsten) volgens het type benaderingen, geen tricuspidalis annuloplastie in vergelijking met verschillende chirurgische procedures (hechting versus flexibele ring versus stijve ring annuloplastie). Het gebruik van de ringen werd geassocieerd met een betere late overleving vergeleken met het onbehandeld laten van TR, terwijl de beste procedure voor de duurzaamheid van TV-annuloplastiek het implanteren van een stijve ring was. Hoofdstuk 7. Van 4084 patiënten van de INFECT-REGISTRY (de Italiaanse registratie voor chirurgische behandeling van inheemse of prothetische klepinfectieve endocarditis), hebben we een cohort van 149 (3,6%) patiënten met inheemse TR als gevolg van endocarditis geëxtrapoleerd om een geïsoleerde tricuspidalisklepoperatie te ondergaan. om verschillen in termen van vroege en late uitkomst te evalueren volgens het type operatie. Derhalve werden 77 die een tv-reparatie ondergingen, vergeleken met 72 die een tv-vervanging ondergingen. De vroege mortaliteit was 9% (13 patiënten). Tricuspidalisklepherstel vertoonde een lagere mortaliteit en ernstige complicaties (7% en 16%), vergeleken met tricuspidalisklepvervanging (11% en 25%), maar statistische significantie werd niet bereikt. mediane follow-up was 19,1 jaar maanden (14,3-23,8). Er werd geen verschil in cardiale overleving zonder IE gevonden tussen de twee groepen na 20 jaar ($80 \pm 6\%$ reparatiegroep versus $59 \pm 13\%$ vervangingsgroep, $p = 0,3$)

My lovely wife Mariapina

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My family, Me, my wife, my daughter Giulia, my son Vincenzo and my dog Miele

ABOUT THE AUTHOR

Dr. Michele Di Mauro is Research Fellow in the Department of Cardiothoracic Surgery, in the Heart and Vascular Centre, Maastricht University Medical Centre (MUMC) and Cardiovascular Research Institute Maastricht (CARIM).

Dr. Di Mauro earned his medical degree at the University “G. D’Annunzio” of Chieti and Pescara, Italy, Faculty of Medicine and Surgery in 1999. He subsequently completed his residency in Cardiac Surgery under the supervision of Prof. Antonio M Calafiore in 2004 at the same University. During his residency he attempted the Bristol Heart Institute of Bristol, UK, under the supervision of Prof Gianni D Angelini (2003-2004).

After his residency, he was staff surgeon at University Hospital of Chieti, Catania and Messina, Italy, and at Private “CBH” Hospital in Bari, Italy, till 2010 when he started the second residency in Cardiology at the University of L’Aquila, Italy, till 2015.

After that, he was staff surgeon at University Hospital in Chieti till January 2020 and interventional cardiologist from June 2020 up to now.

From 2004, he was also contract lecturer at the University “G. D’Annunzio” of Chieti-Pescara and University of L’Aquila.

In 2017 he earned a post-doctoral degree in Cardiovascular Science at the University of L’Aquila and in 2019 he has got a II level Master in Advanced Biostatistics in Clinical Research at the University of Padua, Italy.

In addition to his clinical expertise, Dr. Gaudino is currently the Director of the GIROC (The Italian Group for Research for Outcome in Cardiac Surgery) part of SICCH (the Italian Society for Cardiac Surgery). Moreover, he is the Chairman of INFECT-REGISTRY (The Italian registry For surgical treatment of valve and prosthesis infective endocarditis).

Throughout his career, Dr. Di Mauro has authored roughly than 200 peer-reviewed

journal articles along with numerous book chapters. He is the Associate Editor for Cardiac Surgery of the Italian Journal of Cardiology and serves on the editorial boards of the Journal of Thoracic and Cardiovascular Surgery, Journal of Cardiac Surgery, Journal of Cardiovascular Medicine, Journal of Thoracic Disease.

Dr. Di Mauro's interests include all aspects of adult cardiac surgery and cardiology, particularly, mitral and tricuspid valve disease along with diagnosis and management of heart failure.

He was missionary cardiologist at Makalle Hospital with "Save a life4life Onlus", Ethiopia (2011 and 2012) to screen patients with either rheumatic heart valve disease or congenital heart defect to submit to operation in Sudan at Emergency Salam Centre.

Michele is also a theatre actor, director and script-writer, and narrative novelist. He published two novels and many short tales. Now he is going to publish the third novel (a noir set in a cardiac surgery department). He likes music and books. He adores his family and his dog Miele.

My sweet dog Miele

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