Review

Right ventricle assessment before tricuspid valve interventions

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Abstract: In new Guideline for the Management of Patients with Valvular Heart Disease for tricuspid regurgitation (TR) is focused the importance of measurement of right-sided diastolic pressures and right ventriculography, pulmonary artery pressures, and pulmonary vascular resistance. Assessment of right ventricular (RV) dimensions and function is pivotal to select patients with severe tricuspid regurgitation who may benefit from tricuspid valve intervention. However, with the exception of tricuspid valve annulus diameter, there is no other cut-off value that defines severe RV dysfunction or dilation for this specific group of patients. It's now that there is no other cut-off value that defines severe RV dysfunction or dilation for patients with severe TR with the exception of tricuspid valve annulus diameter.It may be difficult, if not impossible, to establish a cut-off value of RV dysfunction since the RV may be exposed to pressure and volume overload, myocardial ischemia, intrinsic myocardial disease or pericardial constraint. In this review we analyze the relationship between right ventricular (RV) and TR in term of outcomes and mortality predictor in patients undergoing percutaneous or invasive treatment for severe TR.

Keywords: right ventricular; tricuspid valve; tricuspid regurgitation; right ventricular remodeling

1. Introduction

In new Guideline for the Management of Patients with Valvular Heart Disease for tricuspid regurgitation (TR) (1) is focused the importance of measurement of right-sided diastolic pressures and right ventriculography, pulmonary artery pressures, and pulmonary vascular resistance. However, recent guidelines recommend medical therapy (only diuretics) for tricuspid regurgitation and treatment of underlying causes of secondary tricuspid regurgitation (class IIa recommendation). Therefore, the right heart failure (RHF) plays an important role in TR progression (2). It's now that there is no other cut-off value that defines severe RV dysfunction or dilation for patients with severe TR with the exception of tricuspid valve annulus diameter.It may be difficult, if not impossible, to establish a cut-off value of RV dysfunction since the RV may be exposed to pressure and volume overload, myocardial ischemia, intrinsic myocardial disease or pericardial constraint (3). Furthermore, the response of the RV to tricuspid valve intervention may vary according to each aetiology and the time course of the disease (acute or chronic). In this review we analyze the relationship between right ventricular (RV) and TR in term of outcomes and mortality predictor in patients undergoing percutaneous or invasive treatment for severe TR.

2. Right ventricle function in tricuspid regurgitation

At the beginning RV function was considered only a transferring chamber, in the last years it's know that RV response to disease can result first in volume overload and finally in pressure overload and myocardial disease. RV dimension is estimated at end-diastole from a right ventricle–focused

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apical 4-chamber view. A Diameter > 42 mm indicates RV dilatation (4). Through trans thoracic echocardiography (TTE) we evaluate two-dimensional measure as tricuspid annular systolic plane excursion (TAPSE) and tissue Doppler imaging of the tricuspid annulus (S' TDI) that represent RV long axis function and peak systolic motion (a longitudinal myocardial fibre shortening) (6). RV disfunction is considered for a TAPSE < 16 mm and a S'TDI < 10 msec (5).
Furthermore Pulmonary arterial systolic pressure (PASP) and its ratio with TAPSE (TAPSE/PASP) have been described as an index of in vivo RV shortening in the longitudinal axis versus developed force and represents the RV afterload. TAPSE/PASP has been validated as an independent and strong predictor of RHF and left ventricular heart failure (7-9), and a most important marker of severe TR (10). Moreover, a dilated right ventricle and right atrium suggest a chronic state of right ventricular dysfunction (11). Short axis function is represented by Fractional area change (FAC). It is obtained from the apical four-chamber view, and is calculated as the difference in end-diastolic area and end-systolic area divided by the end-diastolic area (6). RV systolic dysfunction is considered for a FAC < 35% (5). RV global longitudinal strain (GLS) is defined as the degree of myocardial deformation compared with its original length, expressed in percentage. GLS has emerged as a technique to evaluate myocardial contractility (4, 10, 12).Therefore, three-dimensional echocardiography may calculate right ventricular volumes and represents an alternative to cardiac magnetic resonance (CMR) imaging that remains the gold standard for calculating RV volumes and RV ejection fraction (RVEF) (13) Infact, right ventricular ejection fraction, stroke volume index, and right ventricular end- systolic volume index are informative measures for prognosis and risk stratification (14). Strain imaging (2-dimensional speckle tracking echocardiography or feature tracking CMR) has been shown more sensitive than TAPSE or S' to detect RV early dysfunction (13-18).Right ventricular free-wall longitudinal strain has emerged as a sensitive measure of right ventricular dysfunction, which is prognostic across a wide spectrum of cardiovascular diseases (18).For TR regurgitation, determining the optimal time for the correction of valvulopathy remains a difficult clinical problem. RV functional assessment is the key on top of other parameters (quantitative proximal isovelocity surface area (PISA), effective regurgitant orifice area (EROA > 40 mm2), regurgitation volume (RGV > 45 ml) and the vena contracta (VC > 7 mm) to determine severe TR reparation outcomes and its evaluation before and after severe TR reparation must be necessary (19). According to recent guidelines (1), treatment of severe TR is subject to its etiology. Primary tricuspid regurgitation derives from congenital anomalies, infective endocarditis, rheumatic disease, carcinoid tumor, toxic effects or myxomatous degeneration. As opposite, alterations of the right atrium, tricuspid annulus or right ventricle that result in leaflet malcoaptation (20). Usually, primary TR is responsible by RV volume overload, right atrial (RA) dilatation and consequently RV disfunction. The mechanism of primary severe TR is an annular enlargement due to degenerative alteration of fibrous structure (21). Treatment of severe primary TR is indicated if it is symptomatic and repair surgery is preferred to percutaneous repair (1,20). Instead, severe secondary TR repair surgery is indicated if left ventricular is compromised and RV also begins to be dysfunctional (1,2,20).
Therefore it's imperative to diagnose and treat severe TR early to avoid RHF (22,23,25,26).
Ingrham et al (25) demonstrated patients with larger EROA, better RV function and more severe symptoms were receive TR intervention, despite those with severe TR and advanced comorbidities, such as severe pulmonary hypertension or end-stage renal disease.

3. Right ventricle function in patients surgically treated for Tricuspid regurgitation

In severe TR, surgical correction is preferred to medical and percutaneous treatment (1,2). For severe primary TR a tricuspid valve replacement is preferred despite valve surgery that is indicated when is concomitant with another cardiac surgical procedure (1,2,28).cAbove all, tricuspid annuloplasty is the preferred technique given its superior long-term outcomes (8). The TRILUMINATE Pivotal Trial (29), highlight the incidence of death or tricuspid-valve surgery and hospitalization for heart failure is similar in the tricuspid valve surgery and medical therapy groups after 1 year of follow-up. Chikwe et al (30) reported a better right ventricular remodeling in patients who undergo tricuspid valve repair. As opposite, Calafiore et al (27) demonstrated TR annuloplasty it is associated

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with worsening surgical and survival outcomes if it is associated with the presence of RV remodeling. Therefore, optimizing right ventricular function may allow patients with prohibitive RV dysfunction into better surgical candidates with improvement of outcomes (24,26,31). In fact, Dreyfus J et al (32) demonstrated concomitant RV disfunction increased in-hospital mortality during and after TR surgical treatment.It'is important, also, underline that not all echocardiographic parameters of RV are collected before TR surgery and that often, an evaluation of this parameters after TR surgery are absent (29-33).

RV dysfunction is an indicator of irreversible myocardial dysfunction. Patients with reduced right ventricular function were in poorer clinical condition and had worse NYHA functional class before surgery. In these patients postoperative mortality increased, despite tricuspid valve surgery improved RV dimension and function, so TR reparation should be considered in this patients (34- 38). Calafiore AM et al (27) highlighted patients with severe TR and RV dilation represent a challenging subgroup where TA is not a reasonable treatment option because the presence of RV remodeling (evaluated through TAPSE, PASP, S'TDI, RVBD (right ventricular basal diameter); RVMD,(right ventricular mid-cavity diameter)), before TR annuloplasty worsens surgical and survival outcomes. Furthermore TV repair (annular dilatation, TR 2þ, increased sPAP) should not only be seen as a combination but evaluated separately in patients with poor RV function (39). In the Prihadi EA et al's Kaplan-Meier survival curve (28) demonstrated worse survival in patients with reduction of RV GLS compared with those with preserved RV GLS, in contrast to decreased RV FAC (hazard ratio, 0.997; 95% CI, 0.977–1.117; P=0.115), or reduced TAPSE (hazard ratio, 0.988; 95% CI, 0.953–1.016; P=0.396). TAPSE was significantly lower after surgery, RVFAC did not change postoperatively. This finding suggests TAPSE is not a suitable method to assess RV function after tricuspid annuloplasty. Consequently, RVFAC, should be used to assess RV systolic function after tricuspid annuloplasty instead of TAPSE (10,13,40). In fact, patients with reduced RV function and concomitant severe TR were in poorer clinical condition and had worse NYHA functional class before surgery, this contributes to the operative mortality (34) (Table 1).

Table 1. Evaluation of RV function as a predictor of mortality in preoperative and postoperative in severe TR surgical treatment.

Study	Patients involved	TR repair or replacement	Parameters of RV function	HR for mortality in patient with RV disfunction	Outcomes
Ingraham BS et al 22	9	Both	TAPSE, PASP	No	Better RV function despite symptoms and EROA is the most important parameter for TR surgical treatment and survival **(p 0.320)**
Calafiore AM et al 24	688	Repair	TAPSE, S'TDI, RVBD RVMD, PASP	2.316 (CI 95% 1.172-4.574) p 0.015	Parameters considered for RV remodelling shown RV remodeling before TR annuloplasty worsen surgical and survival outcomes
Prihadi EA et al 25	1292	Both	TAPSE, S'TDI, RVBD RVMD,	1.029; 95% CI, 1.010–1.049; P=0.003	The presence of RV systolic dysfuction before severe TR

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			PASP, FAC, GLS		treatment is responsible by worse clinical outcomes despite RV dilatation
Dreyfus J et al 28	466	Both	TAPSE, S'TDI, RVBD, PASP	OR = 2.6 (1.2–5.8), P = 0.02	Concomitant RV disfunction increased mortality during and after TR surgical treatment.
Dreyfus GD et al 29	148	Repair	Absent	Absent	Absence of evaluation
Fukunaga et al 30	14	Both	Absent	Absent	Absence of evaluation
Subbotina et al 31	191	Reparation	TAPSE	TAPSE: OR 0.859 (CI 95% 0.75–0.98) p 0.026	RV reduced is a parameter of perioperative mortality

3. Right ventricle function in patients transcatheter treated for Tricuspid regurgitation

Percutaneous repair of severe TR regurgitation is indicated in patients with prohibitive surgical risk or when biventricular function is seriously compromised (1,2,20).

Few data exist in patients with RV dysfunction undergoing transcatheter severe TR treatment.

The multinational TriValve Registry (41) demonstrated transcatheter tricuspid-valve intervention was associated with a lower incidence of the composite end point of death and rehospitalization and of the individual outcomes.

Ingrham et al (25) demonstrated TAPSE was greater in the intervention group compared with the medically managed group (0.11±0.04 m/s vs 0.09±0.03 m/s, p=0.013) but does not have a clear position on the prendiction and outcomes of RV in the percutaneous treatment of TR. While Karam N et al (42) proved TAPSE, RV FAC, and sPAP did not influence the rate of procedural success and there was no difference in the combined endpoint of survival free from hospital admission for HF at 1 year according to baseline TAPSE. Instead, in the study of Muntané-Carol G et al (26) TAPSE and PASP (parameters measured to evaluate the RV function) don't have significant changes before and after TR treatment (TAPSE HR 0.98 (CI 95% 0.91-1.06) p 0.677, PASP HR 0.99 (CI 95% 0.97-1.005) p 0.193.

It's demonstrated that percutaneous tricuspid valve intervention reduces mortality but there is not a common definition of right ventricular dysfunction (evaluated as TAPSE and PASP improvements) as a predictor of mortality before and after severe TR treatment (26,42-47).

Only Schlotter F et al (44) demonstrated an improved survival in patients undergoing percutaneous repair, with mid-range RV function (evaluated with TAPSE, range 13-17 mm) (Table 2).

Table 2. RV function in preoperative and postoperative in severe TR percutaneous treatment.

Study	Patients involved	Parameters of RV function	HR for mortality in patient with RV disfunction	Significant changes of TAPSE before and after TR treatment	RV disfunction as predictor of mortality
Ingraham BS et al 22	13	TAPSE, PASP	No	Yes , TAPSE 0.11±0.04	No

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Muntané-Carol G et al 23	300	TAPSE, S'TDI, PASP	No	No, HR 0.98 (CI 95% 0.91-1.06) p 0.677	No
Schlotter F et al 38	684	TAPSE, PASP	0.22 (CI 95% 0.09, 0.57).	Only for TAPSE 13-17	Only for a subcategory
Karam N et al 39	249	TAPSE, PASP, FAC	No	No, p 0.041	No
Hahn RT et al 40	15	TAPSE, S'TDI, FAC , PASP	No	No, p 0.31	No
Nickenig G 41	85	TAPSE, S'TDI, RVBD RVMD, PASP, GLS	No	Yes, p 0.015	Yes
Perlman et al 42	18	TAPSE, S'TDI, RVBD RVMD, PASP	No	No, p 0.12	Yes

4. Discussion

RV dysfunction is an important predictor of survival and exercise capacity (48-51). Studies demonstrated severe RV dysfunction is related to poor prognosis (4-23). Despite it is considered "indisputable" there is no a parameter considered the "gold standard" that to better define when RV could be defined as dysfunctional. In most of the studies analyzed above, the most used parameter for the evaluation of RV dysfunction and concomitant severe TR is TAPSE. However, it has some limitations: it cannot be evaluated after pericardiotomy, so the RV outcomes such as mortality and improvement cannot be considered. Above all TAPSE is a parameter that does not represent the entire RV function and that can be subject to over or underestimated through 2D dimension (TTE) (4,10,12).

Larger EROA, better RV function and functional impairment were more common in patients receiving TR intervention (23-27).

Still, the treatment of TR is considered subordinate to LV dysfunction and to concomitant mitral regurgitation MR. Data suggests Mitral valve repair is most important that that severe TR repair. Infact TR repair is considered if there is concomitant Mitral dysfunction and not if RV dysfunction is associated or not (1). Infact, Dreyfus GD et al (32) and Fukunaga et al (34) pay special attention to LV disfunction before and after cardiac surgery but they do not evaluate the RV echocardiographic parameters.

RV systolic function deteriorated postoperatively, but there was a tendency to improve at the follow-up period regardless of tricuspid annuloplasty, whereas diastolic function worsened in patients with tricuspid annuloplasty. RV diastolic function may potentially be impaired when TR was regulated by tricuspid annuloplasty at the time of left-sided valve surgery (1,2, 15,27, 33-38).

For new transcatheter device therapies Perlman et al (47) highlited that after 1 year of implantation of the FORMA transcatheter tricuspid spacer device, there was a significant improvement of RV function after 1 year of device placement (evaluated through TAPSE, S'TDI, RVBD RVMD, PASP, p 0.02). Furthermore, Weckbach LT et al (52) evidenced right ventricular reverse remodeling (RVRR) throughout a significant reduction of right ventricular end-diastolic volume (RV-EDV, $p < 0.0001$) and right ventricular end-systolic volume (RV-ESV, p 0.049) measured by computed tomography (CT) in patients with severe tricuspid regurgitation undergoing transcatheter tricuspid valve replacement (TTVR) with the EVOQUE system (Edwards Lifesciences). It would be optimal to early investigate the dysfunction of the RV with other parameters (GLS, FAC, EFRV) that better represents RV global function instead of mere TAPSE. Echocardiography plays an important role in the successful pre-procedural, intraprocedural, and post-procedural analysis of tricuspid valve morphology and RV function both in surgical and percutaneous treatment.

More studies are needed that evaluate the relationship between RV disfunction and severe TR in term

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of improvement of RV parameters after severe TR correction, evaluated by new techniques such as CMR, 3D Echography and spackle tracking.

5. Conclusions

RV function in patients with TR is challenge to be assessed; this is mainly due to the fact that, RV function per se requires multiparametric approach, the cutoff values of normality are coming from studies including patients without severe TR, severe TR allows to the RV a "unloading" that can underestimate the RV function. Therefore RV function in patients undergoing surgery for TR has been related to prognosis of patients operated for TR; TAPSE less than 17 mm has been related to increased risk of hospitalization, relapse severe TR. No studies assessed the role of strain and 3d assessment in patient undergoing surgery for TR.

In patients treated transcatheter RV function assessment allows a prognostic stratification but some evidence are still discordant. Anyway severe RV dysfunction is related to poor prognosis. New imaging techniques will open the field to new risk stratification-models; these include: GLS, EFRV, use of CMR for study of myocardial fibrosis.

Assessment of right ventricular function remains challenging and imperfect in the management of tricuspid disease. The right ventricle should be considered in clinical trial designs as part of the inclusion criteria therapeutic response stratification.

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