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REVIEW

Secondary tricuspid regurgitation: Do we understand what we would like to treat?



Régurgitation tricuspide secondaire : comprenons-nous ce que nous voudrions traiter ?

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KEYWORDS

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Summary Tricuspid regurgitation has long been a neglected and underestimated entity; its prevalence is significant, and is increasing with the ageing population. Tricuspid regurgitation is often a consequence of chronic left cardiac pathologies or atrial fibrillation. Surgical treatment is recommended for patients with severe symptomatic tricuspid regurgitation or tricuspid annulus dilatation at the time of left heart valve surgery. Secondary tricuspid regurgitation is a complex disease; this review focuses on the need for better understanding of its mechanisms and quantification – mandatory with the advent of new percutaneous treatments.

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Abbreviations: 2D, two-dimensional; 3D, three-dimensional; EROA, effective regurgitant orifice area; PISA, proximal isovelocity surface area; RA, right atrium; RV, right ventricle/ventricular; STR, secondary tricuspid regurgitation; TA, tricuspid annulus; TR, tricuspid regurgitation; TV, tricuspid valve; VC, vena contracta.

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MOTS CLÉS

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Traitement

Résumé L'insuffisance tricuspide a été longtemps négligée. Sa prévalence est importante et augmente avec le vieillissement de la population. C'est souvent la conséquence d'une pathologie chronique du cœur gauche ou d'une fibrillation atriale. Le traitement chirurgical est recommandé pour les patients ayant une régurgitation sévère et symptomatique ou lorsque l'anneau tricuspide est dilaté au moment d'une chirurgie du cœur gauche. L'insuffisance tricuspide secondaire est une entité complexe. Cette revue est orientée sur les besoins d'une meilleure compréhension de ses mécanismes et de sa quantification avec l'avènement de nouveaux traitements percutanés.

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Background

Tricuspid regurgitation (TR) is one of the most frequent manifestations of valvular heart disease, and a common echocardiographic finding, the prevalence and severity of which increase with age [1]. It is estimated that moderate or severe TR may affect over 1 million patients in the USA, with higher prevalence in women [2]. The aetiology of TR is divided into two categories (Table 1). TR may be primary (or organic), defined by abnormalities of the tricuspid valve (TV) structure. There are many causes of primary TR, such as endocarditis, rheumatic heart disease, carcinoid syndrome, congenital heart disease (mainly Ebstein's anomaly), endomyocardial fibrosis, myxomatous disease, thoracic trauma or iatrogenic damage (including transvenous pacemaker or defibrillator leads, drug-induced valve disease and radiation) [3,4]. Most cases of TR, however, are

secondary (or functional), as a consequence of deformation of the TV complex with morphologically normal leaflets. Secondary TR (STR) is mainly related to right ventricular (RV) dilatation and/or dysfunction, annular dilatation and/or leaflet tethering, which are usually secondary to left-sided valvular heart disease (especially affecting the mitral valve), atrial fibrillation or pulmonary hypertension [5,6].

TR is an independent prognostic factor associated with significant excess mortality and morbidity that increase with TR grade in various clinical situations (Table 2). Surgery is mostly performed at the time of left-sided valve surgery for STR, whereas isolated TV surgery is rarely performed, but is recommended in patients with severe TR who are either symptomatic or are facing progressive RV dilation/dysfunction. However, the optimal timing for surgery is difficult to determine, as patients may be asymptomatic for a long period of time, symptoms are usually non-specific and RV size and function are difficult to assess in routine clinical practice.

The aim of this review is to look carefully at the determinants of TR.

Table 1 Aetiologies of tricuspid regurgitation.

Primary (organic) causes
Rheumatic heart disease
Congenital heart disease (mainly Ebstein's anomaly)
Endocarditis
Carcinoid syndrome
Endomyocardial fibrosis
Myxomatous disease
Thoracic trauma
Iatrogenic
Drug-induced
Radiation
Pacemaker or defibrillator leads
RV biopsy
Secondary (functional) causes
Left heart disease (valve disease or LV dysfunction)
Primary or secondary pulmonary hypertension from any cause
Atrial fibrillation
Chronic high stroke volume state
Any cause of RV dysfunction

LV: left ventricle; RV: right ventricle.

Anatomy of the TV complex (Fig. 1)

The TV has a more apical position than the mitral valve; it is a dynamic complex structure that separates the right atrium (RA) and the right ventricle (RV), and is generally associated with three leaflets of unequal size (anterior, posterior and septal – in decreasing order of size, and in a clockwise direction as seen by the surgeon) inserted in a fibrous annulus and connected by chordae tendineae to papillary muscles attached to the RV myocardium. TV function depends on the integrity and coordination of all these components.

The number of leaflets can be restricted to only two or extended to four or five. The septal leaflet is located medially, at the level of the septum. The posterior leaflet frequently comprises multiple scallops. Indeed, tricuspid anatomy differs greatly from one patient to another. Papillary muscle anatomy is highly variable: there are generally two or three, but there can be up to nine. The anterior papillary muscle is the most prominent, and arises from the moderator band or from the adjacent myocardial wall. The

Table 2 Prognostic value of secondary tricuspid regurgitation according to clinical situation.

Clinical situation	Prognostic value	References
General population	Increased mortality	Nath et al., 2004 [45]
Heart failure with preserved ejection fraction	Prognostic marker	Mascherbauer et al., 2017 [46]
LV systolic dysfunction	Severe TR: +55% mortality	Koelling et al., 2002 [47]
Patients referred for heart transplantation	Severe TR: +50% cardiovascular events	Neuhold et al., 2013 [48]
Significant isolated TR	Increased mortality	Hung et al., 1998 [49]
Severe aortic regurgitation	TR $\geq 2/4$; mortality relative risk 1.47	Lee et al., 2010 [50]
Mitral valve disease	Worse survival; increased heart failure; reduced functional capacity	Topitsky et al., 2019 [2]
Aortic valve surgery for aortic stenosis	Worse postoperative survival	Varadarajan et al., 2012 [51]
		Shiran et al., 2009 [52]
		Sagie et al., 1997 [53]
		Mascherbauer et al., 2015 [54]

LV: left ventricle; TR: tricuspid regurgitation.

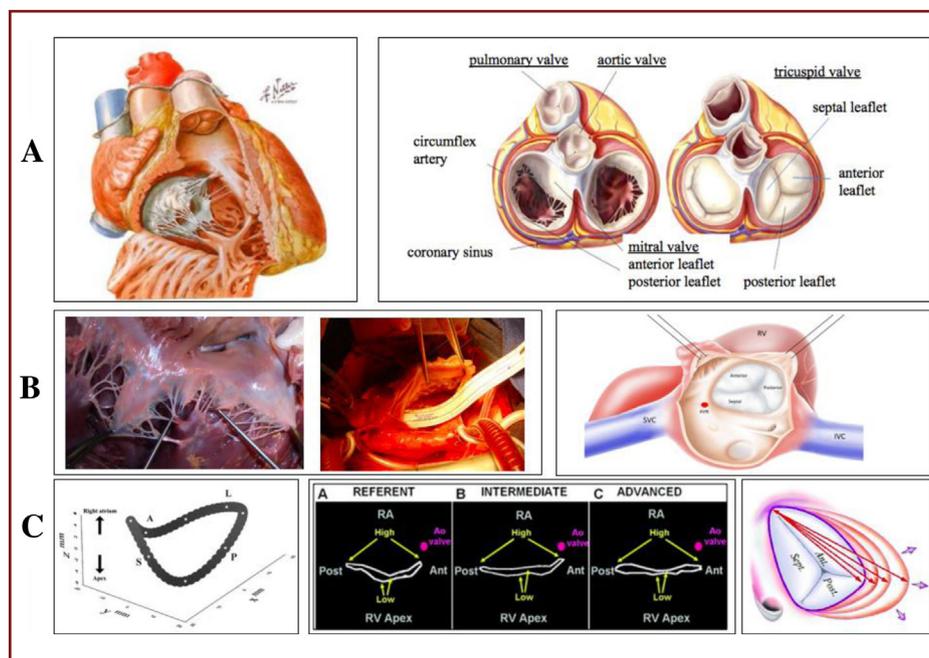


Figure 1. Anatomy of the tricuspid valve complex [12,35,36]. A. Drawings illustrating the anatomy of the tricuspid valve and its relationships with the mitral valve, aortic valve, coronary arteries and veins, displaying the chordae tendineae and papillary muscles. B. Pictures (and drawing illustrating the surgical view) of the complexity of the chordae tendineae, and of measurement of the mitral annular diameter during a surgical intervention. C. Saddle shape of the mitral annulus; the saddle shape is lost when the atrium is enlarged and the tricuspid annulus is enlarged; the enlargement of the tricuspid annulus is mainly in the lateral direction. A, Ant: anterior; Ao: aortic; AVN: atrioventricular node; IVC: inferior vena cava; L: lateral; P, Post: posterior; RA: right atrium; RV: right ventricle; S, Sept: septal; SVC: superior vena cava.

posterior papillary muscle is often bifid or trifid, and arises from the inferior wall. Finally, the septal papillary muscle is the least prominent, and can be absent in 20% of cases. Three types of chordae tendineae can be distinguished: the primary or marginal, attached to the free leaflet margin; the secondary or intermediary, attached to the body of leaflets; and the tertiary or basal. Some chordae tendineae arise directly from the myocardial wall.

The tricuspid annulus (TA) has a non-planar three-dimensional (3D) elliptical “saddle shape” in healthy

individuals. The “lowest point” from the RA (towards the RV apex) is the posteroseptal segment where the coronary sinus ends, whereas the anteroseptal and posterolateral segments are closer to the RA; the “highest point” of the TA is located at the anteroseptal segment, close to the RV outflow tract and aortic valve. The shape and size of the annulus change during the cardiac cycle and breathing. The TA size decreases by up to 25% during systole in healthy individuals. The TA becomes more planar and more circular when it dilates. Dilatation of the TA occurs mainly in the direction of

its free wall, meaning at the level of the anterior and posterior leaflets, but not the septal leaflet, because the septal annulus is part of the cardiac fibrous skeleton.

The TV is closely related to two important structures that can be injured at the time of intervention. First, the bundle of His crosses the septal segment of the TA approximately 5 mm from the anteroseptal commissure. Secondly, the right coronary artery runs in the right atrioventricular groove, a few millimetres from the anteroposterior segment of the TA.

The challenging anatomy, the importance of the interactions between each of the components (septum, RV, RA, pericardium, etc.), and variations in the cardiac cycle and breathing make assessment of the mechanisms and severity of STR difficult [7].

Do we understand the mechanisms of STR?

The TV is the largest orifice among the four cardiac valves. STR is not a disease of the leaflets, but the consequence of loading conditions and right chamber remodelling [8]. Two main processes seem to lead to STR. The first mechanism relies on valvular leaflet tethering and restricted motion induced by RV dilatation (most often as a consequence of increased afterload caused by pulmonary hypertension), leading to papillary muscle displacement and then chordal traction. The second mechanism relies on TA dilatation as a result of the enlargement of the RA extending to the RV, which may result in loss of coaptation or malalignment of the leaflets [6]. Atrial fibrillation is known to enlarge the RA, as patients with STR and atrial fibrillation have a larger TA diameter and a smaller tethering angle compared with patients with STR in sinus rhythm [9]. Thus, annular dilatation is a fundamental condition for STR onset [10] (Fig. 2). It has been shown that STR cannot develop when the TA diameter is < 33 mm [11]. However these two mechanisms, annular dilatation and leaflet tethering, can be associated [12]. Indeed, ventricular volume overload occurring in patients with TR may lead to progression of myocardial dysfunction and right chamber enlargement. This process of RV remodelling affects the structure and function of the tricuspid apparatus, and further increases the magnitude of STR through a vicious cycle.

It is mandatory to assess the characteristics of right chamber remodelling and the two types of STR mechanisms for a better understanding of the pathological process leading to STR and, further, for individualizing therapeutic management. As data on these two mechanisms were scarce, we initiated a French registry (TRAP) looking at the mechanisms of STR and their consequences for prognosis.

How to assess STR?

Clinical evaluation

Patients with STR remain asymptomatic for a long period of time; then, they develop non-specific symptoms, such as asthenia, or symptoms that reflect low cardiac output, dyspnoea as a consequence of elevated pulmonary or LV filling pressures and, finally, signs of right heart failure (peripheral lower limb oedema, ascites, etc.). Murmur

(soft pansystolic murmur at the lower sternal border that increases in intensity during inspiration) is also not easily audible. Unfortunately, STR is mostly diagnosed very late in the course of the disease, when there is end-stage organ damage with RV dysfunction and renal and liver failure.

Echocardiography

Two-dimensional (2D) transthoracic echocardiography is the cornerstone for assessing TV morphology, TA dilatation and/or leaflet tethering and the grade of TR in routine practice. However, only two leaflets can be seen simultaneously using 2D echocardiography, and the use of 3D echocardiography (either transthoracic or transoesophageal) is mandatory to see the entire TA with all leaflets at the same time. Thus, assessment of the TA diameter using 2D transthoracic echocardiography is difficult, especially as it has a non-circular, non-planar shape. It is recommended to measure the TA diameter in the apical four-chamber view (septal-lateral) at the time of maximum TV diastolic opening between the two hinge points at the junction between the valvular leaflets and the TA, but we should keep in mind that this measurement systematically underestimates the long axis of the TA compared with 3D echocardiography [13] and cardiac magnetic resonance imaging (Fig. 3). The normal TA diameter is 28 ± 5 mm in the apical four-chamber view in diastole in healthy adults. Current guidelines from the European Society of Cardiology/European Association for Cardio-Thoracic Surgery and the American College of Cardiology/American Heart Association suggest a threshold diameter of > 40 mm or 21 mm^2 to recommend combined TV annuloplasty at the time of left-sided valve surgery.

Leaflet tethering is the consequence of the displacement of the papillary muscles with RV dilatation, and can be assessed by measuring the coaptation height (the distance between the annulus plane and the point of coaptation) and the tenting area (the area between the atrial surface of the leaflets and the annulus plane) in the apical four-chamber view at maximal systolic closure. 3D echocardiography allows measurement of tenting volume. A coaptation height > 10 mm, a tenting area > 16 mm^2 and a tenting volume > 2.3 mL are associated with severe TR and TV repair failure immediately after surgery [14], consequently favouring TV replacement.

The grade of TR can change according to the cardiac cycle, notably during respiration. Indeed, inspiration is associated with an increase in right cardiac chamber volumes and TA size that can worsen TR. A decreased peak of TR velocity during inspiration of > 0.6 m/s compared with expiration is associated with severe TR (sensitivity of 66% and specificity of 94%) [15].

TR grade can be assessed by qualitative, semiquantitative and quantitative variables (Fig. 4). Visual evaluation using colour flow Doppler is a good qualitative approach for moderate-to-severe TR, but is insufficient to accurately quantify the leak [16]. To assess TR, guidelines [17,18] recommend 2D and colour Doppler echocardiography in all standard views (parasternal tricuspid inflow view and short-axis view at the level of the aortic valve, apical view and subcostal view). Several variables have been proposed, and should be used in a multivariable approach to assess TR, because no single variable is ideal for STR quantification.

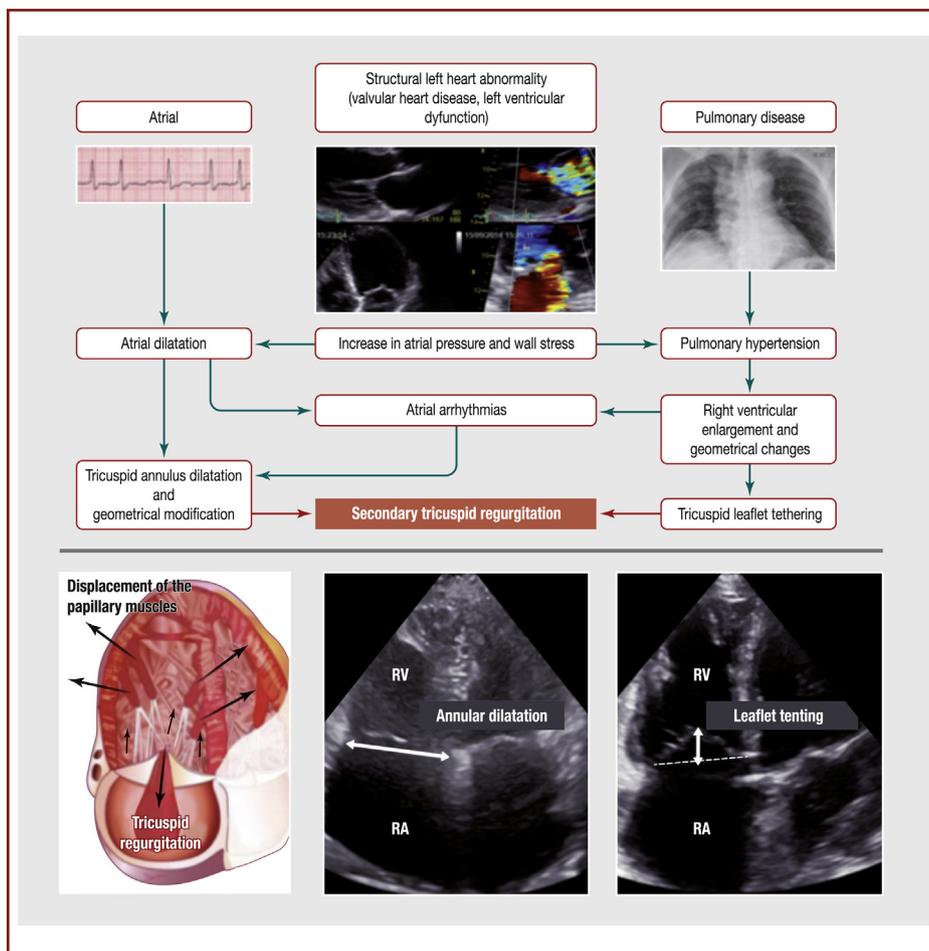


Figure 2. Mechanisms of secondary tricuspid regurgitation [37].

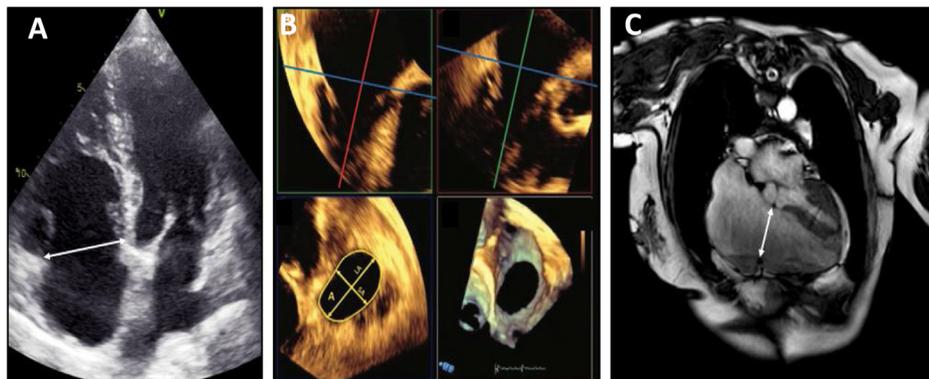


Figure 3. Measurement of the tricuspid annulus diameter. A. Using two-dimensional transthoracic echocardiography. B. Using three-dimensional transoesophageal echocardiography. C. Using cardiac magnetic resonance imaging [13].

In addition, TR grade is influenced by loading conditions that vary from time to time (for instance, a change in the patient's position or diuretic treatment), RV compliance and respiratory cycle.

The TR jet area in the RA does not correlate well with TR severity, unlike vena contracta (VC) width and proximal isovelocity surface area (PISA) measurements. A VC width ≥ 6.5 mm is correlated with severe TR [19]; this variable is relatively unaffected by loading conditions, but

one limitation is its reliance on the complex regurgitant orifice geometry, which is not necessarily circular. A TR PISA radius > 9 mm at a Nyquist limit of 28 cm/s has been associated with severe TR (corresponding to an effective regurgitant orifice area [EROA] ≥ 40 mm² and a regurgitant volume ≥ 45 mL). The PISA method has several specific limitations. First, alignment with the beam of ultrasound may be difficult for eccentric jets. Second, leaflets are tenting, and the outer angle formed by leaflets should be accounted for

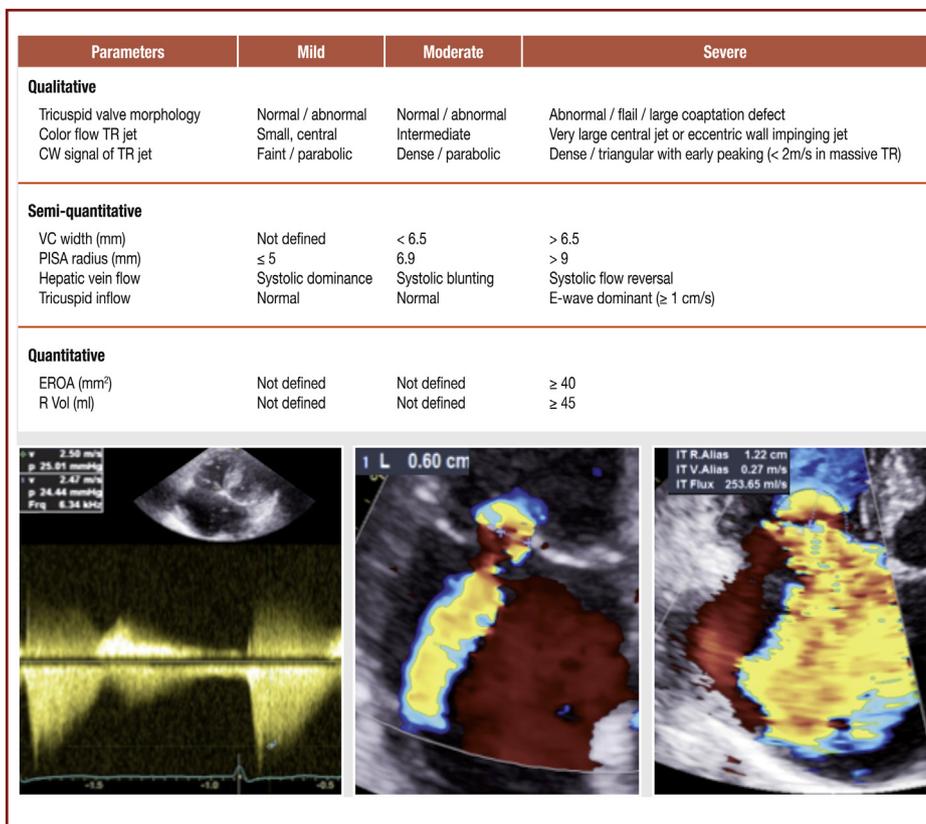


Figure 4. Echocardiographic assessment of tricuspid regurgitation (TR) severity [17]. CW: continuous wave; EROA: effective regurgitant orifice area; PISA: proximal isovelocity surface area; R Vol: regurgitant volume; VC: vena contracta.

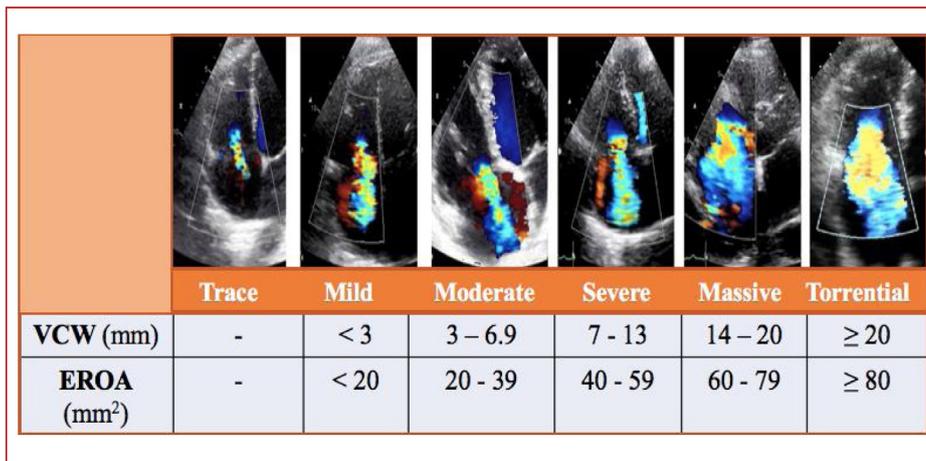


Figure 5. New classification of tricuspid regurgitation grades, proposed by Hahn and Zamorano [22]. EROA: effective regurgitant orifice area; VCW: vena contracta width.

in the calculation of the regurgitant volume. Peak E velocity > 1 m/s on anterograde tricuspid flow (in the absence of TV stenosis) and systolic flow reversal in the hepatic vein are also markers of severe TR. Assessment of pulmonary pressure level (with maximal velocity of TR) as well as right chamber volumes and RV function (with tricuspid annular plane systolic excursion [TAPSE], tricuspid annular systolic velocity, fractional area change, etc.) are mandatory.

Other imaging methods

Cardiac magnetic resonance imaging is considered as the gold standard technique for evaluating the size (volumes) of the right chambers and RV function. Cine cardiac magnetic resonance sequences and 3D reconstructions can be useful for assessing TV morphology and TA motion. Regurgitant tricuspid volume can also be quantified [20].

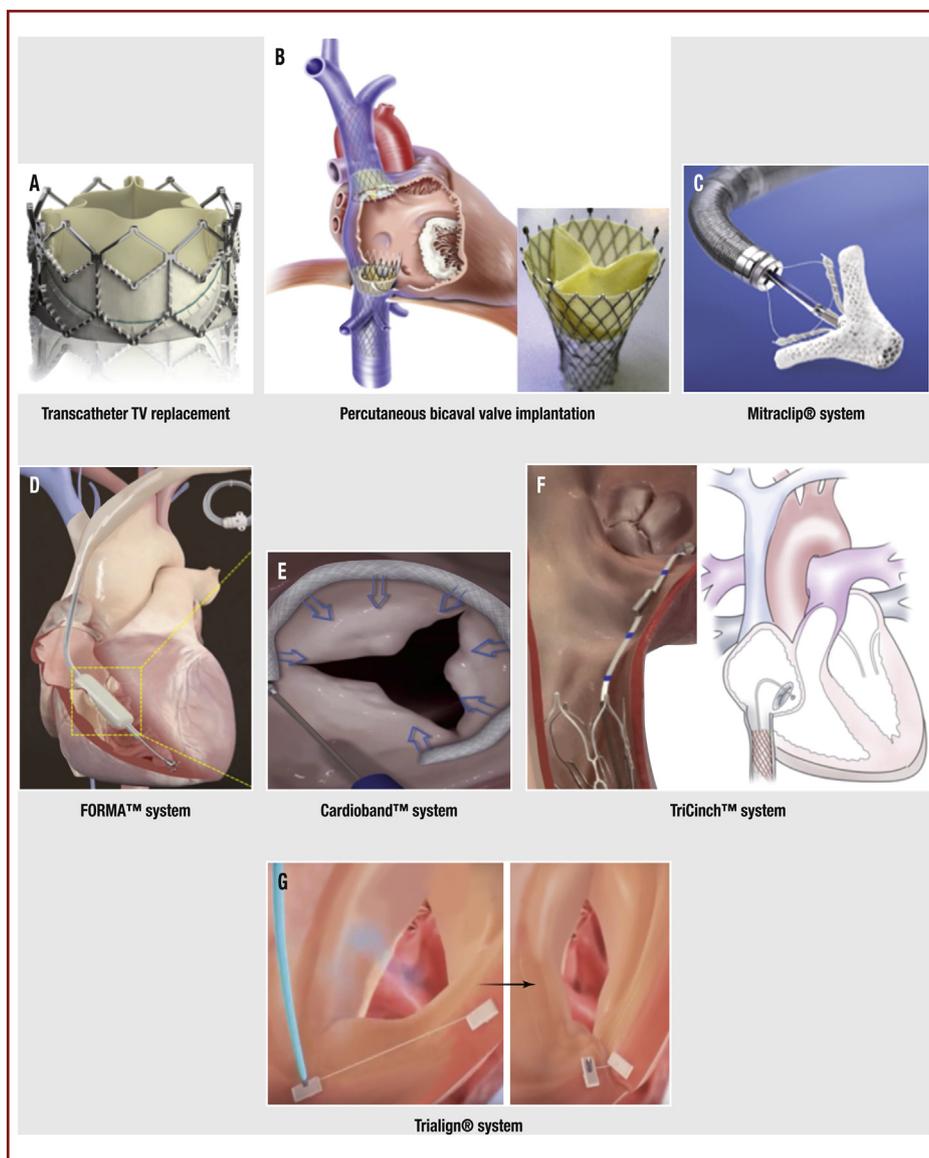


Figure 6. Percutaneous treatment of tricuspid valve (TV) regurgitation [38–44]. A. Prosthetic approach on the TV. B. Prosthetic approach in the vena cava. C. Mitraclip® system (Abbott, Abbott Park, IL, USA): the clip can be used as for the mitral valve, trying to grasp the anterior and septal leaflets. D. The FORMA™ system (Edwards Lifesciences, Irvine, CA, USA): a balloon is positioned in the middle of the regurgitant TV to decrease the defect between leaflets. E. The Cardioband™ system (Edwards Lifesciences, Irvine, CA, USA): the percutaneous annulus placed on the tricuspid annulus is trying to mimic surgical tricuspid annuloplasty, which is the current gold standard technique for treating tricuspid regurgitation. G. The Trialign™ system (Mitralign, Inc., Tewksbury, MA, USA) is a technique for achieving bicuspidization of the TV, and trying to decrease and change the geometry of the tricuspid annulus. F. The TriCinch™ system (4Tech Cardio Ltd., Galway, Ireland) acts on the tricuspid annulus shape and size (F). None of these techniques has been validated as yet, but some are under investigation.

Multislice computed tomography only informs about static anatomy, but can be relevant for measuring tethering height, tethering angle, annular diameter and the distance between each commissure before tricuspid annuloplasty [21]. This technique also reveals the right coronary artery anatomy, providing a landmark before a percutaneous intervention.

Right heart catheterization is essential in the clinical work-up of TR, not for TR quantification, but rather for measuring pulmonary artery pressures, especially when laminar TR precludes reliable assessment, as severe pulmonary

hypertension can be a contraindication for surgical intervention.

Evolution of TR gradation

The development of percutaneous or transcatheter solutions to treating severe TR highlighted the limited value of guidelines for assessing TR grade. Not only were mild and moderate TR not defined clearly on a quantitative basis, but the need to define very severe (massive) or worse than massive (torrential) grades has emerged, in order to

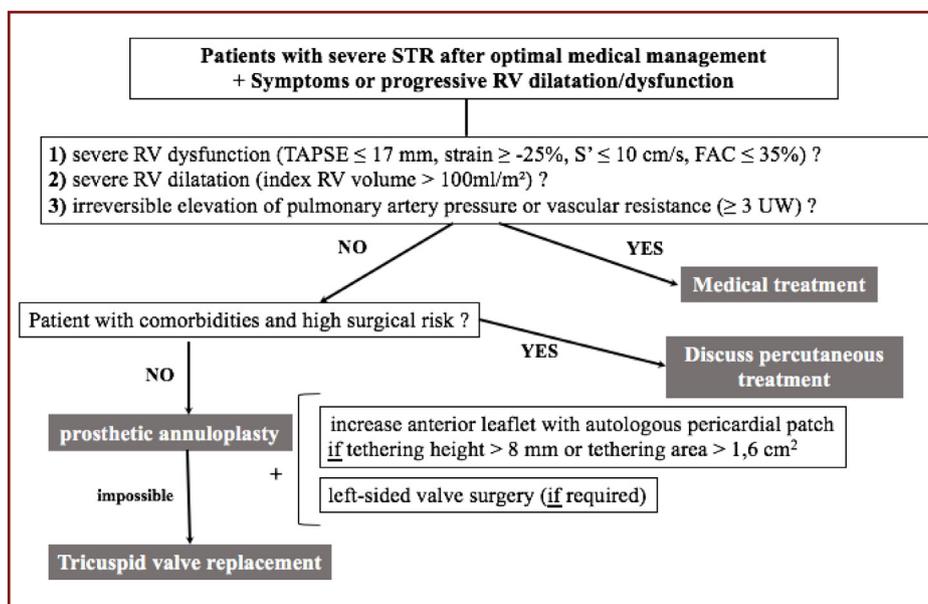


Figure 7. Proposal for management of severe secondary tricuspid regurgitation (STR). FAC: fractional area change; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; UW: Wood units.

objectively evidence the severity of TR and the decrease in severity after percutaneous interventions [22]. Hence, Hahn and Zomorano proposed a new classification for severe-to-torrential TR. Severe TR was defined as a VC diameter of 7–13 mm or an EROA of 40–59 mm², massive TR was defined as a VC diameter of 14–20 mm or an EROA of 60–79 mm², and torrential TR was defined as a VC diameter ≥ 21 mm or an EROA ≥ 80 mm². Although this classification adds new information about TR magnitude, and will help clinicians to explain to their patients that percutaneous interventions are actually effective in reducing TR (e.g. torrential or massive to severe, rather than severe to severe), the most important aspect is the absolute need for a quantitative approach to TR rather than the qualitative approach used by most clinicians (Fig. 5).

Therapeutic management

Intervention is the only curative treatment for severe TR, as medical therapy – mainly with diuretics – has only a palliative effect, by decreasing volume overload. Although significant TR with progressive RV dilatation and dysfunction may remain clinically silent for a prolonged period, it compromises individual patient outcome. In addition, the timing of surgical intervention for TR remains controversial, and surgery is commonly undertaken at a late stage.

Recent international guidelines on valvular heart disease contain sparse recommendations regarding the management of STR. The guidelines from both Europe [23] and the USA [24] state that isolated TV surgery should be considered after previous left-sided valve surgery in patients with severe STR who are symptomatic or have progressive RV dilatation/dysfunction in the absence of severe RV or LV dysfunction and severe pulmonary hypertension (Class IIaC in the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines and class IIbC in the

American College of Cardiology/American Heart Association guidelines). Isolated TV surgery may also be considered for those patients, even if there was no previous left-sided valve surgery [25].

The mortality rate for isolated TV surgery is still high (between 8% and 10% in the most recent studies) because patients are referred to the surgeon too late after congestive heart failure, RV dysfunction, liver disease and/or renal failure onset [26,27]; surgery should be performed earlier in the course of the disease, before irreversible RV dysfunction.

TV surgery for STR should be a repair whenever possible. TV replacement (almost exclusively a biological prosthesis) will be performed only when the TV leaflets are significantly tethered and the annulus is severely dilated, because it is associated with poorer perioperative and long-term outcome than TV repair [28]. TV surgery is mostly performed via median sternotomy under cardioplegia, although beating-heart surgery may prevent atrioventricular block and reduce ischaemic time. High mortality (around 10% at 1 year), and high rates of permanent pacemaker implantation remain a matter of concern [29,30]. Several surgical techniques have been proposed for TV repair, with either plication suture of the annulus (De Vega's annuloplasty), suture bicuspidization (Kay's annuloplasty), suture of the leaflets ("clover") or a ring around the annulus (flexible or rigid). The aim of these techniques is to narrow the valve orifice to achieve leaflet coaptation. The best option is still a matter of debate, but annuloplasty with an open prosthetic oval-shaped ring (to avoid injury to the bundle of His) is usually associated with the best early and long-term results [31]. To take into account both tethering leaflet and annular dilatation, Dreyfus et al. suggested a technique for treating severe STR, increasing anterior leaflet size with an autologous pericardial patch and annuloplasty [32].

New transcatheter solutions are now emerging for high-risk patients with severe STR; they are still in development or in the initial phase of clinical application to demonstrate

their safety and efficacy, but seem really promising (Fig. 6) [33,34].

STR remains poorly understood, and we have to separate isolated STR and STR associated with left-valve disease to reflect upon it. The identification of prognostic factors and characterization of the population seems essential for clinical decision making, including the possibility of correcting STR surgically or percutaneously. The optimal therapeutic strategy is still to be defined, although many technical advances are already showing promise (Fig. 7).

Conclusions

STR is frequent, significantly influences outcome and needs specific management, but is often diagnosed late in the course of the disease and poorly quantified. The TV is no more the forgotten valve, but identification of the mechanisms and accurate grading of STR are still challenging. As a consequence, we need to improve understanding of this disease through dedicated studies, such as the TRAP registry, with the ultimate goal of offering the most appropriate treatment to patients.

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Disclosure of interest

The authors declare that they have no competing interest.

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