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CONSENSUS STATEMENT

Epidemiology, pathophysiology, diagnosis and management of chronic right-sided heart failure and tricuspid regurgitation. A clinical consensus statement of the Heart Failure Association (HFA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC

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Right-sided heart failure and tricuspid regurgitation are common and strongly associated with poor quality of life and an increased risk of heart failure hospitalizations and death. While medical therapy for right-sided heart failure is limited, treatment options for tricuspid regurgitation include surgery and, based on recent developments, several transcatheter interventions. However, the patients who might benefit from tricuspid valve interventions are yet unknown, as is the ideal time for these treatments given the paucity of clinical evidence. In this context, it is crucial to elucidate aetiology and pathophysiological mechanisms leading to right-sided heart failure and tricuspid regurgitation in order to recognize when tricuspid regurgitation is a mere bystander and when it can cause or contribute to heart failure progression. Notably, early identification of right heart failure and tricuspid regurgitation may be crucial and optimal management requires knowledge about the different mechanisms and causes, clinical course and presentation, as well as possible treatment options. The aim of this clinical consensus statement is to summarize current knowledge about epidemiology, pathophysiology and treatment of tricuspid regurgitation in right-sided heart failure providing practical suggestions for patient identification and management.

Keywords Right heart failure • Tricuspid regurgitation • Consensus statement

Preamble

Right-sided heart failure (RHF) and tricuspid regurgitation (TR) are common and strongly associated with poor quality of life and an increased risk of heart failure (HF) hospitalization and death.[1–7] There are multiple causes of TR and RHF, including left ventricular (LV) failure, irrespective of LV ejection fraction (LVEF), left-sided valvular heart disease (VHD), primary right ventricular dysfunction (RVD), pulmonary arterial hypertension and lung disorders.[5–8] Further, permanent atrial fibrillation (AF) and/or atrial disorders can cause secondary TR due to right atrial remodelling and tricuspid annulus dilatation. Lastly, right-sided leads (i.e. pacemaker, implantable cardiac defibrillator (ICD) or cardiac resynchronization therapy (CRT)) can cause or contribute to TR and RHF. Finally, primary TR, although rare in adult patients, can cause RHF.[6,9]

It is known that patients with severe TR often present at a late stage, when signs and symptoms of RHF are advanced and the treatment options for intervention are limited. Indeed, surgical treatment of isolated TR in patients with late indications is burdened by high intra-operative risk and medical therapies are often ineffective at these late stages.[10,11] Catheter-based interventions are emerging as possible treatment options in these patients. However, it is still unsettled how to identify the patients that can gain the greatest potential benefit from these procedures.[9] Therefore, proper management of RHF and TR and ideal timing of interventions remain a matter of debate.

The aim of this scientific statement is to provide a summary of current evidence about epidemiology, pathophysiology, diagnosis and treatment of RHF and TR and give practical suggestions on patient identification and management.

Definitions

Although often used interchangeably, RVD and RHF refer to two different conditions. RHF has been defined as 'a disturbance or dysfunction in any of the components that constitute the right heart circulatory system causing HF symptoms', that is, including everything from the systemic veins to the pulmonary circulation.[12] More clinically, RHF is defined as 'a clinical syndrome with signs and symptoms of HF resulting from RVD'.[13] Thus, similarly to what is generally stated for HF and LV dysfunction,[14] asymptomatic RVD may occur at an earlier stage than RHF and, on the other hand, RHF can develop in patients with significant TR in the absence of clinically relevant RVD.

Right-sided HF may be an acute or a chronic condition. Acute RHF as well as VHD in acute HF have been discussed in previous Heart Failure Association (HFA) position statements.[15,16] Thus, we will focus only on chronic HF and TR in the present article.

Epidemiology and prognosis

The prevalence of RHF is high, but varies widely among different aetiologies, populations and definitions. In the majority of previous studies, RHF is reported as RVD (online supplementary *Table S1*).[1,2,4] A meta-analysis including 11 studies of patients with HF with reduced ejection fraction (HFrEF) showed a wide range of prevalence of RVD, from 19% to 77%, because of a high heterogeneity in the definition of RVD.[2] Likewise, in a meta-analysis including 4835 patients with HF with preserved ejection fraction (HFpEF) the prevalence of RVD was 28% based on a tricuspid annular plane systolic excursion (TAPSE) <16 mm, 18% based on a right ventricular (RV) fractional area change (FAC) <35%, and 21% for RV S′ <9.5 cm/s.[1] Nevertheless, regardless of the definition and aetiology, RVD was found to be independently associated with an increased risk of both morbidity and mortality.[1,2] The impact of RHF on survival depends on the clinical presentation, with the most severe stage (i.e. combination of TAPSE <17 mm, New York Heart Association [NYHA] class IV, peripheral oedema and need for diuretic therapy) being associated with the lowest 5-year survival rate.[17]

Table 1 Causes of right-sided heart failure

Right atrial remodelling	Primary RV dysfunction	Secondary RV dysfunction	
	Primary decrease in RV function (contractility or lusitropy)	RV pressure overload	RV volume overload
Atrial fibrillation	Amyloidosis	Congenital heart disease	Extracardiac arteriovenous shunt
Atrial myopathy (i.e. associated with HFpEF)	Cardiotoxicity	Pre-capillary or post-capillary pulmonary hypertension[a]	High-output states, including concomitant LV volume overload
Tricuspid regurgitation	Constrictive pericarditis	Pulmonary artery stenosis	Intracardiac left-to-right shunt
	Myocarditis	Pulmonary valve stenosis	Post-LVAD
	Post-cardiac surgery or post-LVAD		Pulmonary regurgitation
	RV cardiomyopathy		Tricuspid regurgitation
	RV myocardial infarction		
	Sarcoidosis		
	Systemic sclerosis		

HFmrEF, heart failure with midly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVAD, left ventricular assist device; RHF, right heart failure; RV, right ventricular.
[a]Pulmonary arterial hypertension, left-sided heart disease (including left-sided valvular heart disease, HFrEF, HFmrEF and HFpEF), lung disease and/or hypoxia, chronic thromboembolic pulmonary hypertension, or other mechanisms.

Moderate or severe TR has a prevalence of about 3–6% in the general population,[18,19] but is much higher in patients with left-sided valve disease, and especially with HF (both HFrEF and HFpEF), ranging between 10% and 23%.[3,8,20–22] In patients with HF, TR is associated with increased mortality and HF hospitalization.[23–25] This prognostic impact increases with increasing TR severity[3,20,26,27] and is independent of RVD, pulmonary hypertension, concomitant mitral regurgitation, LV dysfunction, and AF.[28]

Pathophysiology and classifications

In patients with chronic RHF, we can distinguish two conditions: RVD, classified in primary RVD, due to a primary decrease in RV function (contractility and/or lusitropy), and secondary RVD, due to RV pressure and/or volume overload[7] and right atrial remodelling (*Table 1* and *Figure 1*). From an aetiological perspective, different conditions may lead to pulmonary hypertension and, in turn, RV pressure overload, including pulmonary vascular disorders (pre-capillary pulmonary hypertension) or left heart disease (post-capillary pulmonary hypertension) (*Figure 1*).[29,30] Excessive RV afterload causes RV adaptations ('coupling') to maintain adequate flow, but may lead to RV dilatation, RVD and worsening TR, thus directly contributing to the progression of RHF.[7,31] Notably, increases in RV filling pressures can be transmitted to the interventricular septum altering LV geometry and resulting in a reduced cardiac output as well as LV backward failure; a phenomenon called ventricular interdependence.[13] Reduced RV inotropy and/or lusitropy may be caused by myocardial infarction, myocarditis, cardiomyopathies with RV involvement, cardiotoxicity, post-surgery or post-LV assist device. RHF may be a direct consequence of primary RVD in all the conditions mentioned above.[7,29] Of note, TR is frequently observed as a consequence of RV dilatation and dysfunction, but it also leads to RV volume overload, thus contributing to a vicious cycle leading to further RV impairment and RHF progression.[32] Indeed, TR represents the most frequent cause of RV volume overload.[29] Involvement of the right atrium is also common as a consequence of or as a contributor to RHF. In patients with long-standing AF or HFpEF, right atrial remodelling, often associated with atrial functional TR and mild or even absent RVD, can be observed and contribute to RHF progression.[33,34]

Tricuspid regurgitation can be a consequence and/or a possible cause of RVD. It is classified in primary-, cardiac implantable electronic device (CIED)-related-, and secondary TR (*Figure 1*), the latter including atrial TR and ventricular TR.[9,28,33,35] Details regarding specific causes, mechanisms and echocardiographic findings of the different types of TR are reported in *Table 2*. Primary TR accounts for 5–10% of cases and is caused by structural abnormality of the tricuspid valve (TV) apparatus that can be either acquired or congenital. CIED-related TR has been identified as a separate entity because of its peculiar characteristics. It has a growing prevalence, because of the diffusion of devices with right-sided leads, and requires specific interdisciplinary management including electrophysiologists with expertise in device therapy and transvenous electrode extraction. It can be due to mechanical interference of the lead with the TV apparatus, or pacing-induced RVD. Secondary TR (about 85% of all TR) is the most common phenotype observed in adult patients with RHF, with post-capillary pulmonary hypertension due to left-sided diseases and AF being the most common causes. Ventricular TR develops in the presence of RV dilatation, remodelling and dysfunction, whereas atrial secondary TR develops in the presence of predominant right atrial remodelling, usually (but not exclusively) associated with high burden AF. Different definitions of atrial TR have been proposed, mostly as a 'rule-out' diagnosis based on the exclusion of RV involvement

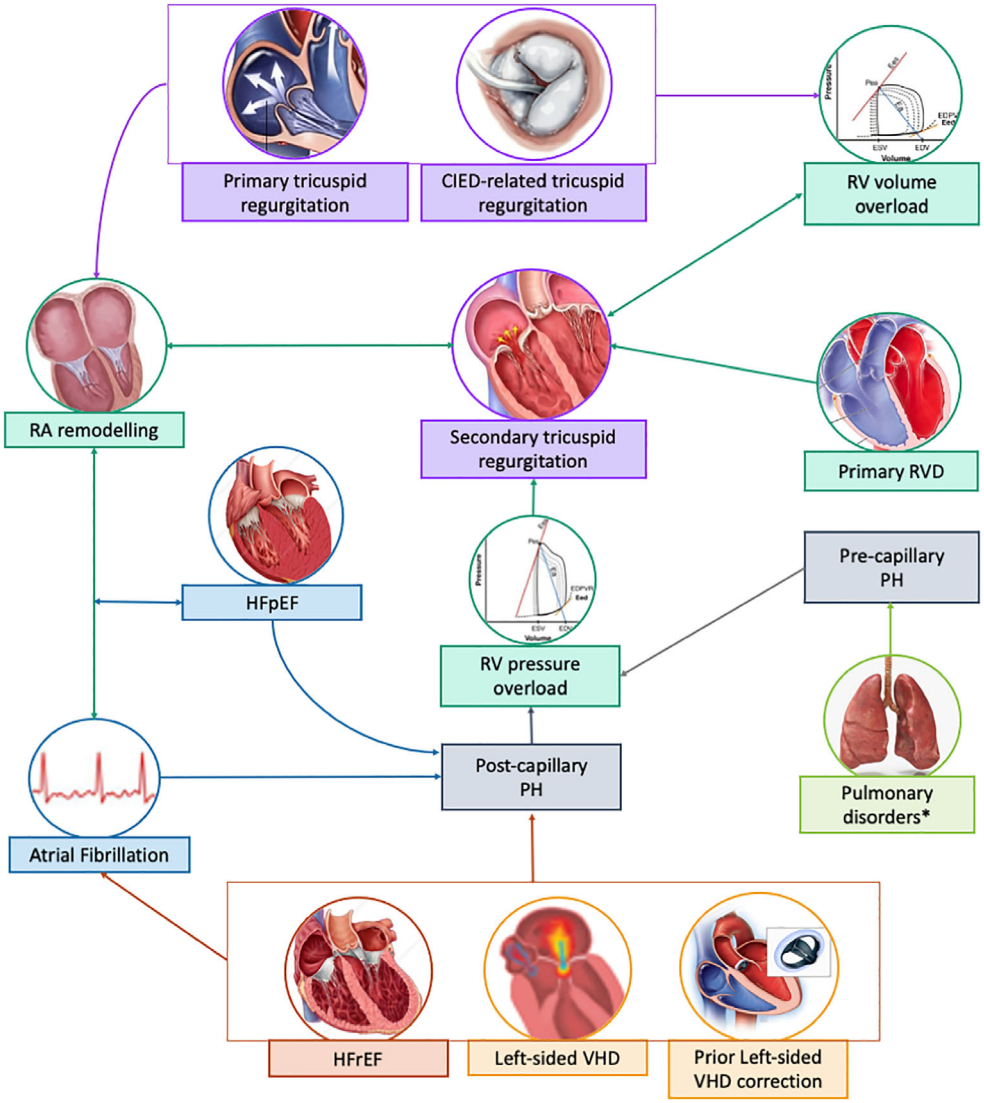

Figure 1 Aetiopathogenesis and mechanisms of right-sided heart failure and tricuspid regurgitation. CIED, cardiac implantable electronic device; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PH, pulmonary hypertension; RA, right atrial; RV, right ventricular; RVD, right ventricular dysfunction; VHD, valvular heart disease. *Pulmonary disorders include parenchymal diseases, chronic obstructive pulmonary disease and restrictive disorders as well as pulmonary artery hypertension and pulmonary thromboembolism.

and preserved LVEF. Prognosis of patients with atrial secondary TR has been recently reported to be better than that of patients with ventricular secondary TR.[36,37]

Notably, different phenotypes of RHF (i.e. RVD, right atrial remodelling) and TR (primary, CIED-related, secondary) can coexist. Pathophysiological interplays between RHF and TR are reported in *Figure 1*.

Clinical presentation and course

Right HF and TR are debilitating conditions strongly affecting quality of life, hospitalization rates and survival.[38] They can be considered as parts of a multi-organ syndrome involving cardiac (i.e. right heart chambers, TV apparatus) and extra-cardiac structures (i.e. liver, kidneys, bowels, lungs, brain, muscles). Systemic congestion, involving splanchnic organs, is the first pathophysiological consequence of both RHF and TR.[22,24] Moreover, at the later stages, decrease in cardiac output leads to cerebral and peripheral hypoperfusion, and ventricular interdependence leads to pulmonary congestion[13,30] (*Figure 2*).

A graphical description of the clinical course and presentation of RHF and TR is shown in *Figure 3*. Despite the dramatic picture of end-stage RHF, the initial clinical course, even in presence of severe TR, may be sub-clinical with unspecific and mild symptoms and signs. Peripheral oedema is often the most prominent

Table 2 Classification of tricuspid regurgitation

Type of TR	Causes	Mechanisms	Main echocardiographic findings
Primary TR	Prolapse/myxomatous disease Rheumatic heart disease Congenital TV abnormalities Infective endocarditis Traumatic or iatrogenic (biopsy, drugs) Carcinoid syndrome Endomyocardial fibrosis Radiation therapy Cardiac tumors	Intrinsic structural abnormalities of the TV apparatus (due to degenerative, congenital or acquired TV disease) leading to restricted or excessive leaflet mobility or leaflet perforation	Abnormal leaflet structure (defining TR aetiology) Variable leaflet mobility (according to the specific aetiology) RA dilatation and annular dilatation are frequently observed, RV dilatation/dysfunction may be present
CIED-related TR	PM ICD CRT	Direct interaction of the CIED lead on the TV apparatus: leaflet impingement, leaflet adherence, leaflet laceration or perforation, leaflet/chordal entanglement, leaflet avulsion (after lead extraction), chordal rupture	Normal or abnormal leaflet structure Variable leaflet mobility (frequent restricted leaflet mobility in systole/diastole, frequent leaflet tethering) RA dilatation, annular dilatation and RV dilatation/dysfunction are frequently observed
Secondary TR			
Atrial TR	Atrial myopathy Atrial fibrillation HFpEF	Isolated annular dilatation (due to RA dilatation and dysfunction) with morphologically normal leaflets	Normal leaflet structure Marked annular dilatation and RA dilatation (key findings) Normal leaflet mobility, no or minimal leaflet tethering RV dilatation/dysfunction may be present (but RV volume is usually normal)
Ventricular TR	Pulmonary hypertension Left-sided heart disease RV cardiomyopathy RV dysfunction from any other cause	Displacement of the papillary muscles, leaflet tethering and annular dilatation (due to RV dilatation and dysfunction) with morphologically normal leaflets	Normal leaflet structure Marked leaflet tethering (key finding) Restricted leaflet mobility in systole Marked RV dilatation and RV dysfunction are frequently observed RA dilatation and annular dilatation are frequently observed

CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardiac defibrillator; PM, pacemaker; RA, right atrial; RV, right ventricular; TR, tricuspid regurgitation; TV, tricuspid valve.

clinical feature in patients with chronic RHF. Also, patients can complain of fatigue, abdominal distension, dyspepsia, anorexia and/or early satiety due to hepato-splanchnic congestion and gut oedema (*Figure 2*). Patients typically show elevated jugular venous pressure and have, at an earlier stage, a positive abdominojugular reflux test. A low-amplitude holosystolic murmur of TR may be present. Atrial tachyarrhythmias are common in the setting of elevated right atrial pressure and may lead to haemodynamic decompensation. More rarely, chest discomfort can occur, due to elevated intracardiac pressures, reduction in coronary perfusion and subendocardial ischaemia. As RV function worsens, the reduction in cardiac output and ventricular interdependence lead to progressive exercise intolerance and dyspnoea, while persistence of systemic congestion leads to hepatomegaly, ascites, and lower extremity or presacral oedema.

Notably, the increase in central venous pressure and consequent rise in renal vein pressure, even in the absence of decreased cardiac output, may cause worsening renal function, reduction in urine output, refractory fluid retention, and increase in diuretic requirements. Notably, moderate or severe TR was found to be a strong risk factor for cardiorenal syndrome in patients with HF.[39,40] Diuretic resistance and irreversible kidney dysfunction may occur as a consequence of the increased renal venous pressure and kidney hypoperfusion. Laboratory abnormalities include increased blood urea nitrogen and creatinine.

Hepatic dysfunction is another possible consequence of systemic congestion with or without hypoperfusion. It can lead to the development of cardiac cirrhosis. The most prominent laboratory abnormalities include markers of cholestasis (i.e. elevated bilirubin, γ-glutamyl transpeptidase, and alkaline phosphatase) and altered synthetic function (prolonged prothrombin time). These laboratory abnormalities are more commonly encountered than elevations in transaminases.[41,42]

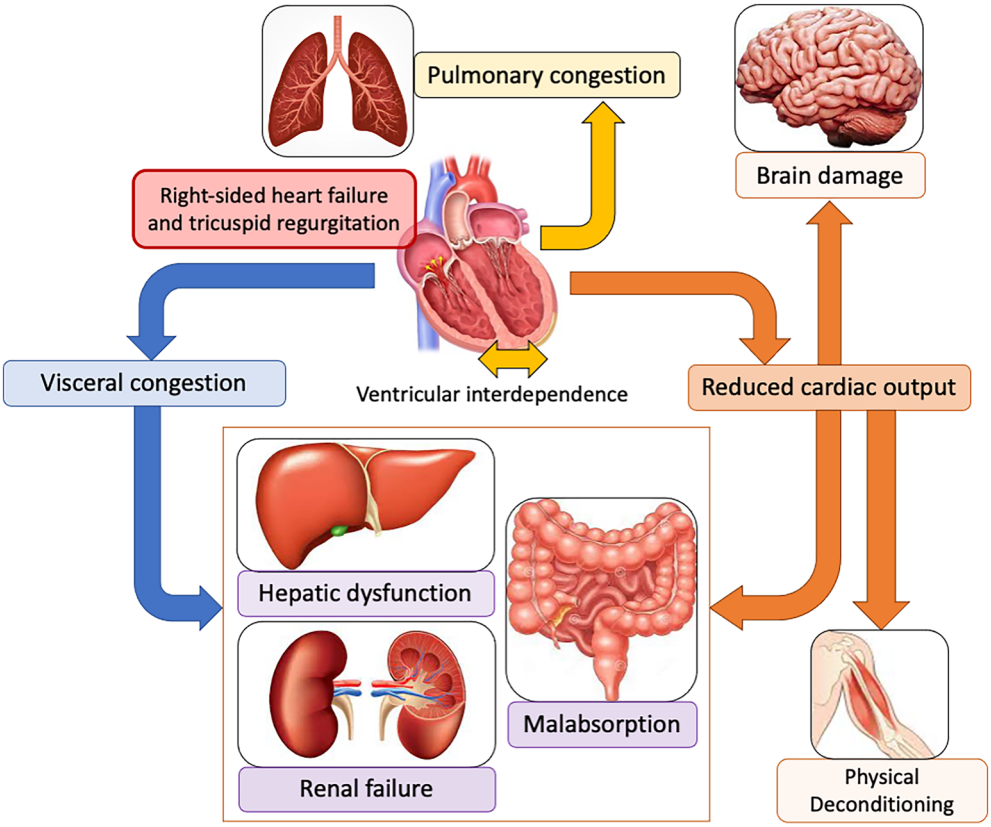

Figure 2 Pathophysiology and extracardiac consequences of right-sided heart failure and tricuspid regurgitation.

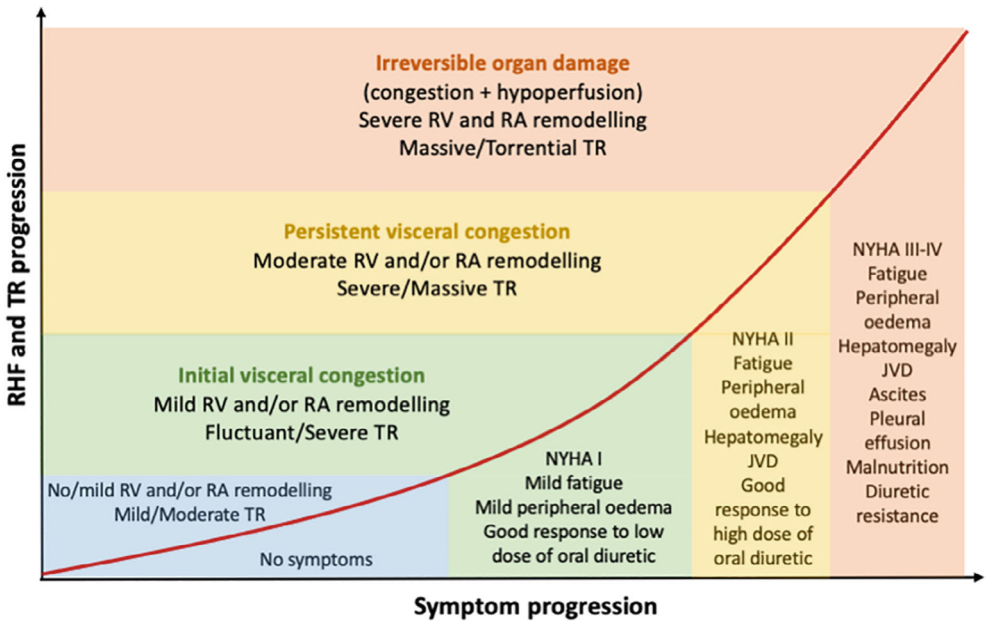

Figure 3 Clinical course and progression of right-sided heart failure and tricuspid regurgitation. JVD, jugular vein distention; NYHA, New York Heart Association; RA, right atrial; RHF, right heart failure; RV, right ventricular; TR, tricuspid regurgitation.

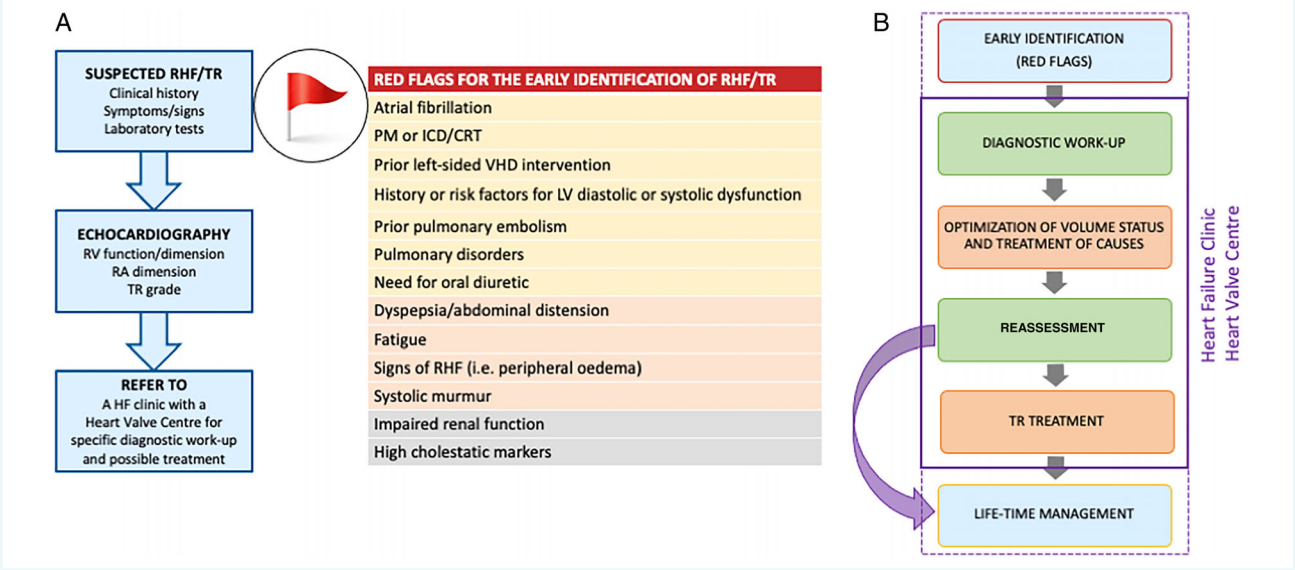

Figure 4 Step-by-step management of patients with right-sided heart failure and tricuspid regurgitation. Identification includes clinical and laboratory assessment (red flags) and transthoracic echocardiography (Panel A) and is not necessarily performed at a Heart Failure Clinic or Heart Valve Centre. Diagnostic confirmation, treatment optimization, reassessment and possible tricuspid intervention should be performed at a Heart Failure Clinic with a Heart Valve Centre. Life-time management (i.e. follow-up timing and modalities) varies according to patient characteristics (Panel B). CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; HF, heart failure; LV, left ventricular; PM, pacemaker; RA, right atrial; RHF, right heart failure; RV, right ventricular; TR, tricuspid regurgitation; VHD, valvular heart disease.

Finally, the gastrointestinal tract function can be impaired by RHF as a consequence of increased central venous pressure and, possible reduced cardiac output, leading to reduced absorption and malnutrition. Splanchnic venous congestion with deficient abdominal lymphatic drainage causes interstitial oedema with a consequent increases in intra-abdominal pressure and impairment of the barrier function of the intestine.[13]

Early identification

The suspicion of RHF and TR is based on clinical history, clinical presentation and laboratory exams. Red flags for early identification of patients with RHF and TR are shown in *Figure 4*.

Clinical history includes all the possible causes of RHF and TR (*Figures 1* and *4*). As mentioned above, clinical presentation is not specific, at least at the early stages, and thus, requires particular attention. Mild fatigue, peripheral oedema and dyspepsia should increase the suspicion of RHD and TR, especially in presence of a suggestive clinical history. Laboratory exams can show initial renal and hepatic injury with a slight increase in serum creatinine and cholestasis markers. Antigen carbohydrate 125, in addition to N-terminal pro-B-type natriuretic peptide, may help in the detection of systemic congestion, especially in presence of significant TR.[43–45] In presence of these risk factors, a transthoracic echocardiography (TTE) can confirm the diagnosis of RHF and TR (*Figure 4*).

In presence of RHF and moderate or severe TR, a diagnostic work-up to confirm the diagnosis and identify the cause/phenotype of RHF and TR is needed preferably to be performed at a HF clinic with a multidisciplinary HF team and Heart Valve Centre.[9,46]

Diagnostic work-up

First-line exam for diagnostic confirmation is transthoracic echocardiography (TTE). It should be performed by an expert/dedicated operator at a HF clinic with a Heart Valve Centre.[9] Additional imaging tools (i.e. transoesophageal echocardiography, cardiac magnetic resonance) are important to support the diagnosis and/or identify the cause/phenotype of RHF and TR. Right heart catheterization (RHC) has a key role to confirm or exclude pulmonary hypertension, to differentiate pre- from post-capillary phenotypes, and to define the haemodynamic impact of TR. All these examinations need to be performed after volume status optimization, i.e. with fluid overload reduced as much as possible. Importantly, conditions identified as having a cause–effect relationship with RHF and TR need to be treated (*Figures 4* and *5*) and severity of RHF and TR then reassessed.

Imaging

A detailed description of the assessment of RV and right atrial function and TR by imaging is given in other reviews and position statements and goes beyond the aims of the present document.[1,6,33,47–51] We only provide in the following paragraph a brief overview of the main imaging tools that can be adopted for the assessment of right heart chambers and TV in patients with HF.

Right heart chambers

Non-invasive assessment of the right ventricle is a challenging task due to its complex anatomy and location in the chest. Therefore, a

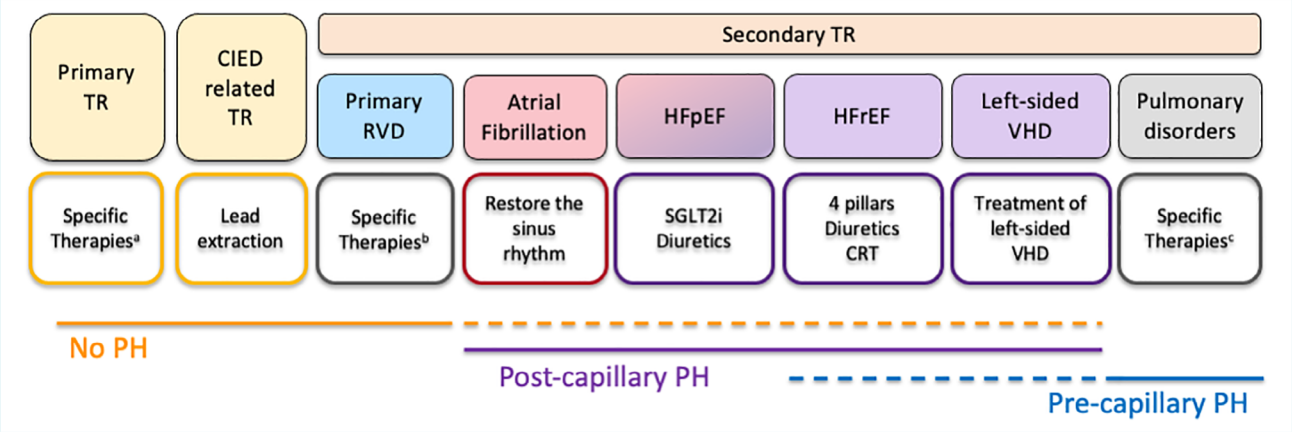

Figure 5 Aetiologies, hemodynamic profiles and first-line treatments of right-sided heart failure and tricuspid regurgitation. CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PH, pulmonary hypertension; RVD, right ventricular dysfunction; SGLT2i, sodium–glucose cotransporter 2 inhibitor; TR, tricuspid regurgitation; VHD, valvular heart disease. [a]Antibiotics in case of endocarditis. [b]Revascularization in case of right coronary artery disease causing right ventricular failure, treatment of specific cardiomyopathies (i.e. amyloidosis, sarcoidosis). [c]Specific treatment for parenchymal diseases, chronic obstructive pulmonary disease and restrictive disorders as well as pulmonary arterial hypertension and pulmonary thromboembolism.

systematic and thorough evaluation of RV size, shape, and function should be performed by using, in a complementary fashion, the different imaging modalities available, knowing their strengths and weaknesses.

Echocardiography represents the first-line imaging modality for the assessment of RV function in most patients.[1] Conventional M-mode and two-dimensional echocardiography provide very limited and quite inaccurate assessment of both RV size and function, particularly in pathologic conditions. The advent of myocardial deformation imaging and three-dimensional echocardiography has improved the accuracy of echocardiography to assess RV geometry and function, and prognostic stratification of patients.[1,50,52–56] Echocardiographic cut-offs for the definition of RVD are highly debated, especially in presence of TR. A comprehensive classification have been recently proposed (online supplementary *Table S2*).[57]

Cardiac magnetic resonance (CMR), although considered the reference imaging modality for RV dimension and function assessment, is often limited by time, costs, availability, and presence of CIED but should be performed particularly when echocardiographic image quality is poor and the findings are not conclusive, when detailed anatomical information (such as in congenital heart disease) is necessary, and when tissue characterization is required.[48]

Assessment of the RV function by cardiac computed tomography (CCT) has been validated in multiple studies using CMR as the reference standard showing that volumes are slightly overestimated and, consequently, LVEF and stroke volume are underestimated. Limitations for CCT include need for contrast and radiation exposure and low temporal resolution for functional assessments.[58]

Right atrial size is commonly assessed with standard two-dimensional echocardiography by acquiring dedicated apical four-chamber views focused on the right heart. Besides the standard evaluation of right atrial dilatation, advanced three-dimensional assessment of right atrial volumes and different volumetric, Doppler or strain parameters of right atrial function have been developed to better define right atrial impairment.[59,60] Beyond its role in discriminating atrial versus ventricular secondary TR,[61] isolated or disproportionate right atrial enlargement may also identify patients at increased risk of TR progression.[62]

Tricuspid valve

Due to increasing interest in TR, relevant advances in understanding TV anatomy and imaging have been done in the last years.[6,33,49] The TV is usually composed by three leaflets (named as anterior, posterior and septal), but anatomical variants with a different number of leaflets are frequently observed.[49] In order to uniformly classify TV anatomy and optimize pre-procedural planning and intra-procedural management, a novel nomenclature has recently been proposed that identified four major classes of TV morphologies based on the number of leaflets.[51] In parallel, TR classification has been updated (*Figure 1* and *Table 2*) and a new TR grading scheme, including the 'massive' and 'torrential' grade beyond severe, has been proposed and adopted in clinical trials on transcatheter TV intervention (TTVI).[63–66] Of note, an incremental prognostic impact of massive and torrential versus severe TR has been reported.[67,68]

Transthoracic echocardiography represents the first-line and key imaging modality to assess TV anatomy and quantify TR. Notably, a transoesophageal echocardiography (TOE) is needed when mechanisms and/or quantification of TR are not conclusive after TTE assessment, and for anatomical suitability of transcatheter or surgical interventions. A comprehensive assessment including different qualitative, semi-quantitative and

quantitative methods is fundamental to evaluate TR severity, integrating data obtained from two-dimensional and Doppler echocardiography.[33,69] Relevant parameters include vena contracta width, effective regurgitant orifice area, regurgitant volume and regurgitant fraction.[33] However, due to the large regurgitant orifice, the frequent tethering of the leaflets, and the low atrio-ventricular pressure gradient usually associated with significant secondary TR, the conventional proximal isovelocity surface area Doppler method grossly underestimates the severity of moderate or severe secondary TR in about 30% of patients.[70,71] In this context, three-dimensional parameters may be particularly useful for TR quantification, especially three-dimensional colour Doppler planimetry of the vena contracta area obtained by both TTE or TOE.[69,72,73]

The importance of a novel, multimodality approach to TV imaging is increasingly recognized.[33] Beyond echocardiography, cross-sectional imaging with CMR and CCT has an additive role in the assessment of TV disease and gives complementary information.[74] CMR allows to quantify TR regurgitant volume and regurgitation fraction.[75,76] CCT provides detailed anatomic assessment of the tricuspid annulus, explores vascular structures such as superior and inferior caval veins, and characterizes anatomic relationships with relevant surrounding structures such as the right coronary artery.[9] Of note, CCT is emerging as a key examination in the pre-procedural planning of patients evaluated for percutaneous TV interventions beyond transcatheter edge-to-edge TV repair (including annuloplasty or replacement devices).[77]

Right heart catheterization

Right heart catheterization is an important diagnostic tool for pulmonary hypertension assessment since in presence of severe TR and RHF, echocardiography can misestimate pulmonary pressures.[78,79] RHC enables to evaluate severity of pulmonary hypertension and distinguish between pre- and post-capillary phenotypes. Pre-capillary pulmonary hypertension is currently defined as the concomitant presence of mean pulmonary pressure >20 mmHg, pulmonary wedge pressure ≤15 mmHg and pulmonary vascular resistance >2 Wood units. Post-capillary pulmonary hypertension, defined as pulmonary pressure >20 mmHg and pulmonary wedge pressure >15 mmHg, can be isolated or combined according to pulmonary vascular resistance value.[80] All these phenotypes can cause RHF and TR; however, a careful distinction is paramount to provide specific treatments (Figure 5). In a previous retrospective study, isolated pre-capillary pulmonary hypertension, defined as mean pulmonary pressure >30 mmHg and trans-pulmonary gradient >17 mmHg, was associated with a poorer prognosis among patients undergoing TTVI.[81]

Right heart catheterization can also provide information on RV function. Pulmonary artery pulsatility index (PAPi), defined as the ratio between the differential pulmonary artery pressure (systolic − diastolic) and the right atrial pressure, assessed by RHC, was found to be useful in prognostic stratification of patients with chronic RHF,[82,83] but not in those with severe TR undergoing TTVI.[81] Non-invasive assessment of PAPi was recently reported as associated with outcome in patients with TR.[84] However, the more comprehensive way to assess RV function is to take into account its adaptation to the afterload. The gold standard measurements of RV contractility and afterload are end-systolic elastance (Ees) and arterial elastance (Ea), respectively.[85] Notably, measurements of Ees and Ea require expensive conductance catheter technology and expert catheterization laboratory environment. Of note, non-invasive assessment of RV to pulmonary artery coupling was validated in HF populations[86,87] and it seems to be a prognostic predictor of outcome also in medically or percutaneously treated patients with TR.[88,89]

Cardiac output assessment is mandatory during RHF evaluation because it provides information on cardiac function and also allows, in relationship with pulmonary and capillary wedge pressures, to calculate pulmonary vascular resistance. The Fick method (indirect or, when feasible, direct) for cardiac output assessment is preferable. The role of the thermodilution method is still debated since it may underestimate cardiac output when TR is severe.[78,90,91] Low (<1.7 ml/min/m^2) and high (>2.6 ml/min/m^2) cardiac output values were associated with a lower survival as compared to intermediate cardiac output status among patients undergoing TTVI.[92] Hyperdynamic circulation due to hepatic damage may explain the negative role of a high cardiac output as a marker of advanced disease.

Integration of RHC and echocardiographic data is mandatory in the pre-procedural evaluation of candidates to TR intervention. Discordance between echocardiographic and invasive assessment of pulmonary artery pressure is related with poor outcomes in patients undergoing TTVI, probably because of greater TR grade.[79]

Management

Specific treatments according to aetiology

Strategies aiming to treat the predominant cause of RHF and TR represent the first-line approach (Figure 5). Therefore, treatment of chronic HF is recommended according to current guidelines.[93]

In case of severe left-sided VHD and severe TR, or mild/moderate TR with dilated TV annulus, concomitant TV treatment during surgery for mitral and/or aortic valve is indicated.[94] However, patients with combined VHD may undergo transcatheter procedures[95] because of an increased surgical risk due to age, frailty and comorbidities, as well as RHF. Severe TR is observed in about 3% of patients undergoing transcatheter aortic valve implantation[96] and in up to 20% of patients undergoing mitral transcatheter edge-to-edge repair (TEER).[97,98] About 40–50% of patients improve their TR grade early after transcatheter correction of the left-sided

VHD.[99,100] However, long-term follow-up data about TR changes in this setting are lacking and persistance of significant TR after left-sided VHD treatment is associated with adverse outcome.[99]

Treatment of AF, including catheter ablation, can be advised when AF is the direct cause, and not a consequence, of TR. A recent study showed an improvement in atrio-ventricular regurgitation severity when a durable conversion to sinus rhythm was obtained at 12 months.[101] Long-standing AF is likely less associated with this positive response.

Pulmonary disorders must be treated with specific therapies. The role of TR treatment in this setting is unsettled. Specifically, patients with pulmonary arterial hypertension should receive pulmonary vasodilators according to the most recent guidelines[80]; patients with chronic thromboembolic pulmonary hypertension should receive oral anticoagulant, specific medications, surgical endarterectomy or percutaneous angioplasty; those with lung disease should receive bronchodilators and/or ventilatory support.[80]

In patients with CIED-related TR, lead extraction can be advised in selected cases of recent implantation (i.e. <3 months) taking into account that the procedure can be ineffective when the lead has no direct influence on valve dysfunction and can even worsen TR in case of leaflet laceration.[102]

Medical therapies

We refer here to the cases where no clear treatable cause of RHF and TR can be addressed, and to those where RHF and TR persist despite treatment of the predominant cause. In these cases, optimization of volume status remains the mainstay of treatment. Diuretics are needed to treat congestion, regardless of LVEF.[93] In patients with TR and RHF with signs and symptoms of systemic congestion and possible malabsorption of oral diuretics due to gut congestion, hospitalization may be needed for intravenous diuretic treatment and to monitor the diuretic response (i.e. diuresis and natriuresis).[93,103] In case of diuretic resistance and/or insufficient diuretic response, combined diuretic therapy may be necessary as well as inotropic agents and vasopressors, in case of peripheral hypoperfusion.[93]

Notably, there are no specific drugs (i.e. neurohormonal modulators) shown to have beneficial effects on the symptoms, clinical course and prognosis of patients with RHF and TR. A small observational study showed a possible association between sacubitril/valsartan and improvement in RV function[104] and some experimental studies reported a possible impact of mineralocorticoid receptor antagonists in reducing RV afterload.[105,106] Moreover, in a small randomized controlled trial including patients with HFrEF, sodium–glucose cotransporter 2 inhibitors in addition to other HF drugs, were found to be more effective in improving RV function as compared to other HF drugs alone.[107] Indeed, current guidelines clearly state that medical therapy (i.e. diuretics) should not delay TR intervention when indicated.[94] Nevertheless, clinical reassessment, complete echocardiography and RHC should be performed under an euvolaemic status before considering any possible TR intervention.

Tricuspid valve interventions

A thorough discussion of TV surgery, as well as of right-sided mechanical circulatory supports, goes beyond the aims of the present article. Briefly, in the 2021 European Society of Cardiology (ESC) guidelines for the management of patients with VHD, TV surgery is recommended in patients with primary severe TR without severe RVD, as well as in those with secondary severe TR undergoing left-sided VHD and it should be considered in patients with severe TR without severe RVD and/or severe LV dysfunction and/or severe pulmonary hypertension. On the other hand, transcatheter therapies may be considered in patients with secondary and symptomatic TR deemed inoperable.[94]

The benefit of TR correction during left-sided VHD surgery has been demonstrated.[108–110] On the other hand, in patients with multiple VHD and high or prohibitive surgical risk undergoing transcatheter interventions, the role of concomitant treatment of left-sided lesions and TV is still unclear.[111,112] As mentioned above, persistence of severe TR after transcatheter left-sided VHD correction is associated with a poorer outcome.[99] Also, RVD was found to be a strong predictor of poor prognosis in patients undergoing transcatheter left-sided VHD intervention[113,114] as well as in those receiving TTVI.[115]

With regard to isolated TR without left-sided VHD), patients are largely undertreated.[116] Reluctance to perform an isolated TR surgery can be explained on the one hand by the lack of evidence that surgical TR correction improves outcomes compared to medical management and the falsely benign reputation of TR, and on the other hand, by a high in-hospital mortality of isolated TR surgery, up to 10%, mostly related to the late presentation of these patients.[10,11]

In a large single centre retrospective study, operative mortality for isolated TR was 0% in patients at early stages of the disease and 16% at the late stages, once more confirming the importance of timely intervention and correct risk stratification.[117] Recently, a dedicated risk model, the TRI-SCORE, was proposed to estimate in-hospital mortality in patients undergoing isolated TR surgery. Notably, most of the variables included in this model (age ≥70 years, NYHA functional class III–IV, right-sided HF signs, daily dose of furosemide ≥125 mg, glomerular filtration rate <30 ml/min, elevated total bilirubin, LVEF <60%, moderate/severe RVD) are HF- and congestion-related confirming the prognostic importance of HF stage and presentation.[11] In most Heart Valve Centres, surgery for isolated TR is conducted in a minimally invasive, beating heart approach to reduce the risk of the procedure.

Transcatheter TV interventions are emerging as possible treatment options in patients with severe TR. Several devices are currently available or under evaluation with different design and functioning (online supplementary *Table S3*).[9,118,119] TEER is the most widely used because of ease of use and high safety profile.[120] In a small single-arm study, transcatheter annuloplasty seemed effective in reducing TR grade and was associated with an improvement in symptoms and quality of life[121] Heterotopic devices showed improvement in cardiac systemic congestion and functional status,[122] but do not increase cardiac output.[123] Orthotopic

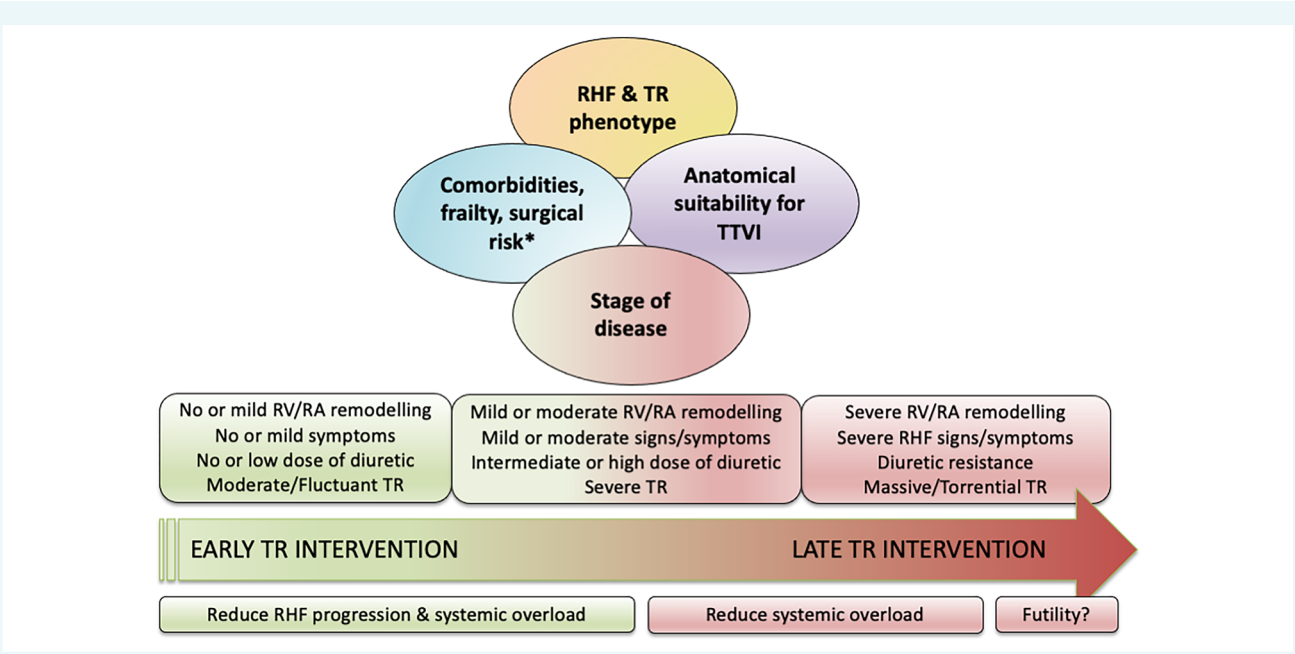

Figure 6 Comprehensive evaluation of patients with right-sided heart failure and tricuspid regurgitation for possible intervention. HF, heart failure; RA, right atrial; RHF, right heart failure; RV, right ventricular; TR, tricuspid regurgitation; TTVI, transcatheter tricuspid valve intervention. *TRI-SCORE (Dreyfus *et al.*[11]).

implantation is also available with promising preliminary results.[124] Limited data on RV reverse remodelling after TTVI were recently reported.[125–127]

Most of the available data on TTVI come from observational registries. A large multicentre observational retrospective study showed a possible benefit of TTVI compared to conservative management in reducing mortality and HF hospitalization of patients with severe TR regardless of demographic and clinical features, but with larger effects in patients with a moderate impairment of RV function (vs. no or severe RVD).[128–130]

Single arm observational retrospective studies identified several predictors of poorer outcomes among patients undergoing TTVI: pre-capillary pulmonary hypertension,[81] discordance between RHC and echocardiography in assessing pulmonary hypertension,[79] massive and torrential versus severe TR,[67] severe RVD assessed by global parameters,[115] organ damage (i.e. renal failure and liver dysfunction).[131] These findings may suggest that TR treatment in late stages of RHF might not lead to a prognostic benefit. Accordingly, even if the optimal timing for TR intervention is unknown, efforts for an early identification of these patients may improve selection and results.

The recent TRILUMINATE Pivotal trial[66] is the first prospective randomized controlled trial comparing a TR correction strategy (TEER with TriClip) to medical therapy in patients with at least severe TR. The primary endpoint was a hierarchical composite that included death from any cause or tricuspid-valve surgery, HF hospitalization, and an improvement in quality of life assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), with an improvement defined as an increase of at least 15 points at the 1-year follow-up. The primary endpoint was met due to a relevant improvement in quality of life (mean KCCQ change 12.3 ± 1.8 points in the TEER group and 0.6 ± 1.8 points in the control group). However, no differences were found between the two groups of treatment with regard to mortality and HF hospitalization. In absence of a sham comparator, the interpretation of quality of life changes is limited, but the improvement in KCCQ was significantly correlated with the degree of TR reduction, suggesting a causative rather than placebo effect. Importantly, the safety profile of TEER was confirmed to be very high with 98.3% of the patients who underwent the procedure free from major adverse events at 30 days.

Notably, the TRILUMINATE population was at low risk (i.e. preserved LVEF, no severe RHF, HF hospitalization in the year preceding inclusion in only 25% of patients), had short follow-up (i.e. 1 year), and the trial was underpowered for hard endpoints since the observed event rates were much lower than expected.

The results of the TRISCEND II trial, a randomized controlled trial comparing transcatheter TV implantation with the EVOQUE system and medical therapy, based on the first 150 patients enrolled in the study, were recently presented with promising results (major adverse events lower than expected, TR reduction and improvement in quality of life), but not published yet.

Despite the rapid advances in technologies, further randomized controlled studies, including more symptomatic patients and correctly powered for hard endpoints and with long follow-up are urgently needed to clearly understand whether TR correction may improve prognosis in these patients in addition to the benefit in quality of life.

Palliative care

According to the World Health Organization palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of symptoms and, physical, psychosocial and spiritual problems. Such an approach has a major role in patients with RHF and TR. Notably, clinicians should not wait with thinking about symptom relief and improving quality of life or palliative care as a last option. Indeed, palliative care can go hand in hand with curative care and be an integral part of HF management.[132] A patient centred approach should be used in all treatment decisions with the aim of improving quality of life of patients.

Multidisciplinary approach: from detection of right-sided heart failure and tricuspid regurgitation to lifetime management

A step-by-step approach in the management of patients with RHF and TR is reported in *Figure 4*.

Identification of patients with RHF and TR can involve different specialists including general practitioners, nephrologists, hepatologists, gastroenterologists, internal medicine specialists, geriatrics, electrophysiology specialists, HF specialists, specialists in cardiac imaging, interventional cardiologists and surgeons. Awareness of RHF and TR is paramount to enable early identification and treatment. A multidisciplinary approach is needed since different phenotypes can overlap requiring the involvement of different specialists. After early identification of RHF and TR and confirmation by TTE, a further evaluation at a HF clinic, preferentially with a Heart Valve Centre, is needed for a complete work-up including diagnostic confirmation and identification of the RHF and TR phenotype. Specific treatments are required as soon as the cause is identified. Also, congestion and hypoperfusion have to be treated, in a hospital environment if needed. Clinical and echocardiographic reassessment have to be performed after treatment optimization, and if there is persistence of severe TR that may benefit from an intervention, a RHC has to be performed or repeate. In the evaluation for the possible TR treatment many aspects need to be considered (*Figure 6*). First, the TR phenotype, since some phenotypes, such as pulmonary vascular disorders causing isolated pre-capillary pulmonary hypertension, may represent a contraindication to TR correction, and other phenotypes, such as HFrEF, may benefit from specific treatments before considering TR intervention. Second, the surgical risk, that can be evaluated by means of dedicated risk models (i.e. TRI-SCORE in case of isolated TR), as well as assessment of comorbidities and patient's frailty. Third, the anatomical suitability for TTVI, that requires TEE and/or CCT performed by expert operators, since specific criteria are needed for each specific device. Finally, the RHF stage, including RVD severity, TR severity and organ damage, has to be considered as strongly related with prognosis (*Figure 6*).

In high-risk patients with RHF and/or severe TR and left-sided VHD requiring intervention, a clinical and echocardiographic reassessment at 1–3 months after percutaneous treatment of aortic and/or mitral valve disease is needed to evaluate the possible persistence of RHF symptoms and/or severe TR and need for TR intervention.

Patients with RHF undergoing TR intervention, as well as those managed with medical treatment, need to be followed up by HF specialists. Periodic reassessment of congestion and optimization of medical therapies is the major tool to prevent HF hospitalizations. Timing of follow-up has to be tailored based on phenotype, stage of disease and risk of HF readmission. In patients with moderate TR without RHF, regular follow-up including clinical evaluation, laboratory exams and TTE is advised to be performed every 6 months with referring to HF clinic in case of RHF onset and/or worsening of HF and/or worsening of TR.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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