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Tricuspid regurgitation, right ventricular function, and renal congestion: a cardiorenal triangle

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There is a growing interest in the evaluation of tricuspid regurgitation due to its increasing prevalence and detrimental impact on clinical outcomes. Historically, it has been coined the "forgotten" defect in the field of valvular heart disease due to the lack of effective treatments to improve prognosis. However, the development of percutaneous treatment techniques has led to a new era in its management, with promising results and diminished complication risk. In spite of these advances, a comprehensive exploration of the pathophysiological mechanisms is essential to establish clear indications and optimal timing for medical and percutaneous intervention. This review will address the most important aspects related to the diagnosis, pathophysiology and treatment of tricuspid regurgitation from a cardiorenal perspective, with a special emphasis on the interaction between right ventricular dysfunction and the development of hepatorenal congestion.

1. Introduction

Tricuspid regurgitation (TR) is a common condition most commonly associated with degenerative and left-sided heart disease (1, 2). Right-sided cardiac chambers and TR have been historically overlooked and mostly become relevant during the surgical evaluation of left valvular heart disease.

TR can lead to dysfunction of the right ventricle (RV) due to increased preload and progressive remodeling. This consequently results in signs and symptoms of heart failure (HF) and subsequently contributes to a spectrum of liver and kidney impairment (3–5) primarily attributable to persistent right-sided congestion. The interplay between the cardiovascular and renal systems becomes evident in the context of cardiorenal syndrome, wherein chronic abnormalities in heart function leads to kidney dysfunction (6).

TR has long been considered a relatively benign entity resulting in the underutilization of diagnostic and therapeutic resources. The underestimation of the clinical impact of TR has led to a pattern of care delaying intervention until very advanced stages of disease where the risks of treatment become excessively elevated (7). While surgical treatment of TR, even in early stages, has been associated with poor outcomes, innovative percutaneous techniques

have emerged as a potential alternative. These percutaneous techniques have expanded their scope beyond the conventional surgical indications, encompassing high-risk patients previously excluded from surgical studies (8). In addition to mechanical treatments decongestion management in TR is of paramount importance, so the cardiorenal interaction is a key factor. Hemodynamic profiling of patients and the assessment of right ventricular function and systemic congestion are crucial to determine optimal timing and indications for percutaneous interventions along with identifying who would not derive any benefit from further interventions.

2. Tricuspid regurgitation: prevalence, prognosis, and diagnosis

TR is frequently encountered in the echocardiography laboratory. While mild TR may not have significant consequences, advanced degrees of TR are associated with factors such as advanced age, female sex, and left sided heart disease. Moderate to severe TR is present in 4%–6.6% of patients older than 75 years and is associated with increased mortality and morbidity independent of RV dysfunction and pulmonary hypertension (1, 2).

Primary TR is the least prevalent etiology, representing only 8%–10% of all TR cases and is mainly related to pathologies affecting the tricuspid apparatus (papillary muscles, chordae and annulus) and tricuspid valve (TV) leaflets. Causes of primary TR include carcinoid syndrome, rheumatic heart disease, congenital abnormality of TV, iatrogenic valve damage and endocarditis. Lead impingements from cardiac implantable electronic devices are a leading cause of primary TR, as it has been reported to occur in up to 38% of patients following implant (9–11).

Secondary TR can arise as a consequence of various factors, including RV dilatation due to volume overload or increased pulmonary pressures. It may also result from dilatation of the right atrium or tricuspid annulus as occurs in atrial fibrillation. Additionally left heart or valvular diseases can contribute to the development of secondary TR. Interestingly, 8% of cases of secondary TR can occur in isolation (1). In the setting of left-sided heart pathology, TR is a late event indicating a more advanced disease, higher pulmonary pressures, extensive ventricular remodeling, and worse prognosis (12). Without appropriate intervention, TR perpetuates a vicious pathophysiological cycle that leads to further adverse remodeling of the ventricles, atria, tricuspid annulus, with increasing TR severity and subsequent irreversible RV dysfunction leading to unfavorable outcomes (7, 13).

Transthoracic echocardiography (TTE) is the preferred diagnostic method for TR, allowing TV visualization as well as RV function (10). Despite its widespread use, TTE has limitations in TV assessment, since only two leaflets can be visualized simultaneously. 3D echocardiography, an extension of TTE, provides simultaneous visualization of the three leaflets and surrounding structures including a complete visualization of the annulus, providing a better characterization of TV. The addition of color flow Doppler allows to quantify the severity of TR by analyzing the effective regurgitant orifice size, regurgitant volume, the TR jet, and the vena contracta width. Of note, transesophageal echocardiography (TEE) is no more effective in providing optimal views of the TV than TTE (10, 14).

3. Tricuspid regurgitation and right ventricle

The impact of TR on the RV varies on a number of factors including the underlying cause, degree of anatomical alteration, presence of pulmonary hypertension, left valvular heart disease or presence of atrial fibrillation (AF) (15, 16). Several phenotypical classifications have been used to predict outcomes. Deitz et al. describe four RV remodeling patterns based on RV dilatation and dysfunction in patients with secondary moderate to severe TR: (1) normal RV size with normal function, (2) dilated RV with normal function, (3) normal RV size with reduced function, and (4) dilated RV with reduced function. The 4th pattern is common in patients with severe TR, accounting for 43%. Any degree of RV dysfunction (patterns 3 and 4) is associated with decreased survival when compared to patients with normal RV function (17). Two additional phenotypes of functional TR have been described: atrial functional TR (A-FTR) and ventricular functional TR (V-FTR). A-FTR refers to TR associated with AF leading to a progressive dilatation and enlargement of the tricuspid annulus associated with right atrial enlargement (18, 19). In this group, the RV changes its shape into a conical remodeling pattern with annular enlargement and dilatation of the RV basal segments despite a normal RV length (20). In contrast, in V-FTR [as seen in left-sided heart disease, RV dysfunction or pulmonary hypertension (PH)], the RV takes on a spherical or elliptical pattern as a consequence of a longitudinal remodeling with valvular tethering, while tricuspid annulus enlargement is only mild (18, 19, 21, 22). Patients with V-FTR have worse survival compared with patients with A-FTR, especially in the PH subgroup (23). RV function is the main prognostic factor in HF and in TR. Therefore, its evaluation is essential for risk stratification (7, 24).

As in the case of TR, TTE remains the primary imaging modality for RV assessment, for practical reasons. Conventional TTE parameters such as tricuspid annular systolic excursion (TAPSE), tissue Doppler velocity at the lateral tricuspid annulus and fractional area change rely on geometric assumptions and are load and angle-dependent leading to an overestimation of RV function in severe TR (25). Other parameters, such as free wall longitudinal strain, can provide a more accurate assessment of RV function (26). TAPSE/SPAP (systolic pulmonary arterial pressure), a parameter of ventricular arterial coupling, which assesses the relationship between RV contractility and afterload, has proven to be a valuable prognostic parameter in this context (27, 28). In general, multimodality imaging would be the preferred approach for RV assessment in the context of severe TR, with cardiac magnetic resonance as the gold standard for evaluating RV volumes and function (29–31).

4. Right ventricular failure and abdominal congestion: renal, hepatic and intestinal consequences

TR causes an elevation of RV preload leading to a decrease in cardiac output, and an increase in venous congestion. Consequently, signs and symptoms of right heart failure (RHF) include an elevated jugular venous pressure, edema, ascites, hepatomegaly and, in advanced stages, renal and hepatic failure with malnutrition (32). Congestion is one of the main manifestations of RV dysfunction and it is associated with worse quality of life, frequent admissions, and increased mortality. As the disease progresses, a shift in the clinical phenotype can be seen: with a low cardiac output state can advance towards a high cardiac output state secondary to hepatic failure and portal hypertension. Decreased splanchnic wash-out of vasoactive substances often leads to vasoplegia and high and a hyperdynamic state resulting in hepatorenal failure. End stage RV failure is associated with a poor response to percutaneous treatment of TR (33).

4.1. Congestive nephropathy

Observational studies have consistently highlighted the strong association between TR and renal dysfunction. These studies have underscored the adverse effects of TR on clinical outcomes. In fact, less than 18% of the patients with functional TR have a normal renal function, defined by an eGFR greater than 90 ml/min/1.73 m^2 (5). The persistent elevation of central venous pressure is the main determinant of kidney dysfunction.

The glomerulus has the remarkable ability to maintain relatively stable glomerular filtration despite reduced renal plasma flow by regulating the vascular tone of intraglomerular vessels. Activation of the renin angiotensin system causes vasoconstriction predominantly of the efferent arteriole, increasing intraglomerular pressure and filtration fraction (5, 34, 35). Severe TR leads to renal venous hypertension in peritubular, interstitium and tubular lumen which counteracts intraglomerular pressure and deteriorates GFR (glomerular filtration rate).

Another critical aspect of kidney damage is the presence of diuretic resistance related to the presence of tubular dysfunction and increased sodium avidity (36). Neurohormonal activation and hemodynamics perturbance increase active sodium and water reabsorption in the renal tubules, perpetuating congestion and a diminished diuretic response (5, 34).

4.2. Congestive hepatopathy

Passive chronic congestion from TR leads to an increase in hepatic venous pressure and, thus, to sinusoidal hypertension. Over time, this causes hepatocyte atrophy and apoptosis, sinusoidal thrombosis and centrilobular fibrosis, which can eventually lead to cardiac cirrhosis. The coexistence of reduced cardiac output and decreased hepatic perfusion may aggravate the problem. Liver damage caused by congestion may be subclinical with primary evidence from alterations in hepatocellular laboratory tests including mild hyperbilirubinemia and elevation of cholestasis markers (alkaline phosphatase and gamma-glutamyl transferase). If liver damage progresses, increased serum aminotransferase, hypoalbuminemia and coagulopathy can be seen. Liver disease can become as clinically relevant with progressive cardiac disease which further complicates its management (37–39).

4.3. Intestinal congestion

The relationship between HF and the gastrointestinal system is complex and not yet fully understood. RV dysfunction has been linked with malabsorption, loss of appetite and weight loss, often culminating in the development of cardiac cachexia. Splanchnic congestion, a hallmark of RV dysfunction, exerts changes on gut morphology, permeability, and function. These alterations can result in changes in the composition of the gut microbiota, potentially impacting processes like bacterial translocation and activation of inflammatory pathways (40).

5. Multi-parametric approach to congestion in TR

When evaluating congestion in TR, it is crucial to employ diverse diagnostic methods. These may encompass clinical scoring systems, imaging techniques, bioimpedance measurements, hemodynamic tests, and analysis of circulating biomarkers.

5.1. Venous excess ultrasound score (VExUS)

The Venous Excess Ultrasound Score (VExUS) is a valuable tool for assessing a patient's volume status through point-of-care ultrasound (41, 42). The scoring system assesses congestion by evaluating the diameter of the inferior vena cava (IVC) and the Doppler waveform patterns of hepatic, portal, and intrarenal veins. VExUS offers a practical and effective means of gauging congestion in a clinical setting (43).

While ultrasound volume assessment is at times considered less informative in patients with TR due to its association with elevated right atrial pressure, it is important to recognize that patients with TR can still experience clinical overload, even without absolute excess volume. Therefore, severity indicators identified through ultrasound warrant careful consideration, especially those unaffected by right atrial pressure, such as the Doppler portal vein pulsatility index and the intrarenal veins waveform, as they reflect right-sided heart hemodynamics. It is worth noting that while portal Doppler remains unaffected by right atrial pressure, a false negative interpretation can occur in the setting of liver

cirrhosis due to centrilobular fibrosis. Therefore, a scenario of a seemingly normal pattern (pulsatility <30%) can mask hepatic congestion (44). In TR, key intrarenal waveform findings include an elevated x-descent and a significant increase in the v-wave.

5.2. Biomarkers

In patients with right heart failure (RHF), particularly those with significant TR, natriuretic peptides may not provide additional prognostic information as their levels tend to be lower than in patients with reduced left ventricular ejection fraction. Alternatively, CA-125, a glycoprotein synthetized by serous epithelial cells, has been found to better reflect right heart function and may have a stronger predictive value in RV failure and venous congestion. CA-125 concentrations are not influenced by factors like renal function, age, or weight (45–47). Another biomarker, bio-adrenomedullin (bioADM), has been shown to have an association with various signs of right-sided cardiac dysfunction such as peripheral edema, hepatomegaly, and ascites (48). Soluble ST2 has been linked to echocardiographic signs of RHF and central venous pressure, and it can serve as an indicator of diuretic resistance (49, 50). Urinary albumin level is a reliable indicator of the severity of RHF, with higher levels associated with a more advanced functional class and symptoms of congestion. Moreover, urinary albumin has been closely associated with other congestion biomarkers (51). Another intriguing urinary biomarker is sodium excretion:low levels of natriuresis following a furosemide stress test suggest a greater likelihood of inadequate diuretic response and improper decongestion (52).

6. Treatment strategies

6.1. Congestion treatment in RV failure

The evidence for guideline-directed medical therapy for TR is lacking. There is a limited armamentarium in treatment options beyond addressing the underlying causes of secondary tricuspid regurgitation and diuretics (Class IIa indication in the 2022 European guidelines) (53). Loop diuretics, such as furosemide, torasemide, and bumetanide, are commonly used, with varying oral bioavailability and efficacy in patients with RHF. When loop diuretics are insufficient, a sequential nephron tubular blockade treatment may be necessary, combining thiazides, acetazolamide, iSGLT2 or even vaptanes. A more in-deep review in that sense has been previously published by our group (54). In cases of refractory congestion secondary to severe TR, the diuretic response can be impaired both in acute and chronic phases. Therefore, extracorporeal ultrafiltration may need to be considered. Hemodialysis, hemodiafiltration and ultrafiltration can be used according to the specific situation. Of note, in some severe cases of TR and refractory congestion, peritoneal dialysis (PD) has been shown to be beneficial as a chronic treatment, even in patients with mildly impaired glomerular filtrate, as strategy to optimize RV filling pressures, resulting in an

improvement in quality of life, reduced hospitalizations, and enhanced renal and cardiac function (55–60).

6.2. Inotropes and other cardiovascular drugs

In contrast to left-sided HF, the evidence supporting the use of standard HF medications other than diuretics for the right side is not well established and may vary according to the underlying cause and the acute or chronic presentation. Inotropes can be used to support RV function and optimize left ventricular filling pressures. Levosimendan and milrinone may be of particular interest due to their pulmonary vasodilatation properties, that would diminish RV afterload (61), but careful monitoring of systemic perfusion pressures needs to be considered. Digoxin may also be beneficial considering its potential inotropic effect over the RV, although the available evidence in this specific situation is limited and heterogeneous, with no conclusive data on potential improvements in RV ejection fraction or NYHA class (62). In the case of RV failure with normal left ejection fraction, beta-blockers may be deleterious due to their negative inotropic and chronotropic effect (63, 64).

6.3. Percutaneous treatment for TR: techniques and clinical implications

Isolated surgery for severe TR has a class IIa indication in symptomatic patients, however, it is limited by its high in-hospital mortality rate. As an alternative, percutaneous interventions have emerged for inoperable or very high-risk patients, with a Class IIb indication in the recent European guidelines (53).

Percutaneous intervention for TR includes a range of devices:

1) Coaptation devices: these include leaflet approximation with tricuspid transcatheter edge-to-edge repair (T-TEER) or spacers devices, whose objective is to increase leaflet coaptation. Initial experience with T-TEER systems have shown potential benefits in observational trials, including a decrease in hospitalizations for HF (65), increase in cardiac output, improved liver enzymes (66), reverse RV remodeling (67) and improved nutritional status (32). The recently published TRILUMINATE trial, randomly assigned 350 symptomatic severe TR patients to T-TEER or placebo, showing an improvement in quality-of-life questionnaires with no differences in mortality or HF hospitalization rates (68).

2) Percutaneous annuloplasty: this involves procedures to reduce the diameter of the tricuspid annulus. The Cardioband (Edwards Lifesciences, Irvine, CA, USA) system facilitates a percutaneous annuloplasty, reducing the diameter of the tricuspid anulus to facilitate leaflet coaptation. It was evaluated in the TriBAND study ($n = 61$) and showed a sustained reduction of TR (69% grade II or lower), reduction in annular diameter, inferior vena cava diameter and early evidence of right heart remodeling 1 month after implantation (69).
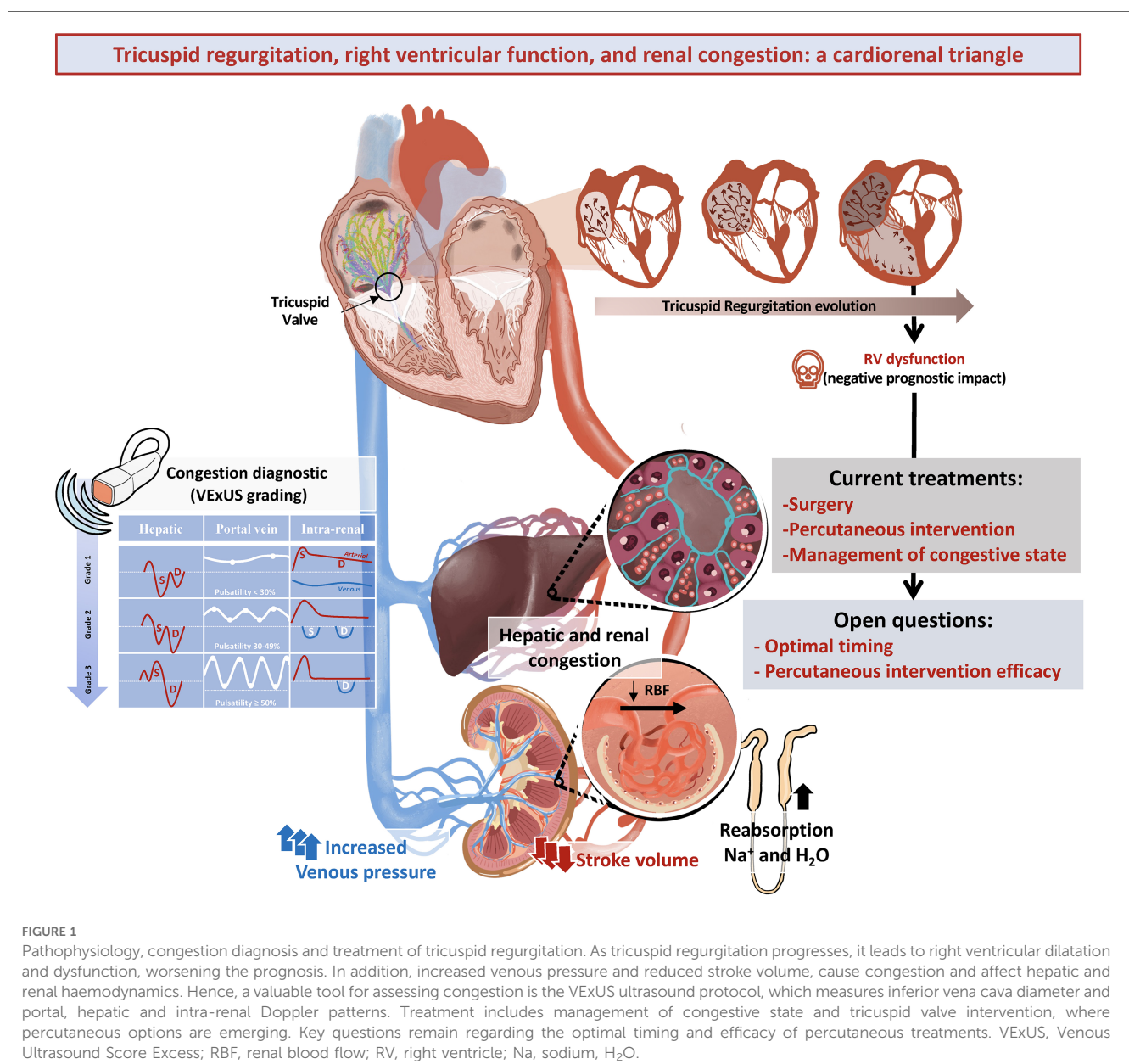
3) Heterotopic caval valve implantation: this approach aims to reduce retrograde cava flow and hepato-renal congestion in patients with unacceptable surgical risk who are refractory to medical treatment and unsuitable for T-TEER with initially promising results (70).

4) Transcatheter orthotopic valve implantation: this involves replacing the TV with a transcatheter valve. Preliminary data of the TRISCEND trial has been published regarding the EVOQUE system (Edwards Lifesciences, Irvine, CA, USA), a transcatheter valve that replaces the TV:TR was reduced to mild or less in 98% of the patients and there was a significant improvement in symptoms 30 days after the procedure (71).

While device therapy is rapidly evolving, more randomized trials are needed to allow us to select the right population and optimal timing for each device.

7. Conclusions and future directions

TR is highly prevalent, particularly when associated with left heart disease and among vulnerable populations such as women and the elderly. Although it has been historically overlooked, TR is associated with a 65% increase in hospitalizations and death, a risk that is even higher in patients with RV dysfunction. Diagnosis is made by TTE (2D and 3D). RV assessment by TTE is more challenging in the presence of severe TR.

Clinical manifestations of TR revolve around signs of abdominal congestion, which bear prognostic implications even when mild (72). A comprehensive approach to diagnose and manage congestion includes abdominal ultrasound and biomarkers in addition to clinical evaluation. Renal, hepatic, and intestinal involvement are key findings that may perpetuate a cycle of refractory congestion and hemodynamic abnormalities. Treatment

FIGURE 1

Pathophysiology, congestion diagnosis and treatment of tricuspid regurgitation. As tricuspid regurgitation progresses, it leads to right ventricular dilatation and dysfunction, worsening the prognosis. In addition, increased venous pressure and reduced stroke volume, cause congestion and affect hepatic and renal haemodynamics. Hence, a valuable tool for assessing congestion is the VExUS ultrasound protocol, which measures inferior vena cava diameter and portal, hepatic and intra-renal Doppler patterns. Treatment includes management of congestive state and tricuspid valve intervention, where percutaneous options are emerging. Key questions remain regarding the optimal timing and efficacy of percutaneous treatments. VExUS, Venous Ultrasound Score Excess; RBF, renal blood flow; RV, right ventricle; Na, sodium, H_2O.

strategies are based on combination of diuretics and renal replacement techniques in refractory patients. RV failure often coexists with severe TR and represents a significant prognostic factor although there is no evidence-based medical treatment available (**Figure 1**).

In the recent years, several percutaneous treatment techniques have emerged, with different mechanistic approaches, showing promising safety profiles. However, there remains limited evidence regarding their clinical and prognostic impact, and more importantly their appropriate indications. More advanced patients may benefit less from the therapy, therefore identifying optimal timing for these interventions becomes a crucial element (73). Further refinement of clinical, laboratory and echocardiographic assessment are needed to establish ideal timing and preferred technique for percutaneous TR interventions. Additionally, understanding how these procedures can improve RV function combined with medical therapy to enhance decongestive effects and protect against end-organ failure is an important area for future research. This is an exciting time as emerging TR innovations hold promise to improve outcomes and quality of life in patients facing this challenging yet common condition.

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