

# Valve Disease in Heart Failure

## Secondary but Not Irrelevant



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### KEYWORDS

- Secondary mitral regurgitation • Secondary tricuspid regurgitation • Valvular heart failure
- Mechanism • Treatment

### KEY POINTS

- Secondary (functional) mitral regurgitation is a common and insidious complication of heart failure patients with ischemic or idiopathic systolic left ventricular dysfunction.
- Secondary (functional) tricuspid regurgitation has long been neglected and regarded as a surrogate of a more fundamental condition (left-sided valvular lesions, pulmonary hypertension, or atrial fibrillation).
- When present, secondary mitral or tricuspid regurgitation may exhibit a broad range of severity. Any degree of secondary mitral or tricuspid regurgitation conveys an adverse prognosis, with a graded relationship between severity of regurgitation and reduced survival.
- Imaging and more specifically echocardiography plays a central role in diagnosis and serial assessment of secondary regurgitation as well as for timing the intervention and guiding the procedure.
- By convention, secondary mitral or tricuspid regurgitation is graded into mild, moderate, and severe. For tricuspid regurgitation, massive and torrential regurgitation are to be considered.

### INTRODUCTION

Valve disease caused by the remodeling of cardiac chambers may complicate heart failure, worsening both symptoms and prognosis. This type of valve disease involves the atrioventricular valves because of their intricate structure and function with the adjacent cardiac chambers, and it is the result of dilatation of the annulus of the valve and of distortion of the subvalvular apparatus. Affecting the valves indirectly, because of changes in size, shape, and function of the ventricles and/or of the atria, it is named secondary or functional

valve disease. By comparison, primary valve disease affects the valves directly, causing changes of the leaflets or cusps.

Secondary valve disease may complicate both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).<sup>1</sup> In HFrEF, the secondary mitral regurgitation (MR) is predominantly ventricular-secondary, due to remodeling (increased tethering force) and dysfunction (reduced closing force) of the left ventricle as a result of ischemic or nonischemic myocardial disease.<sup>2</sup> In HFpEF, the secondary MR is predominantly atrial-secondary, due to

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dilatation of the left atrium as a result of diastolic dysfunction with increased left atrial pressure (increased pushing force) and/or atrial fibrillation. Similarly, secondary tricuspid regurgitation (TR) can be ventricular-secondary or atrial-secondary.

Ventricular-secondary valve disease evolves with the progression of heart failure and varies in severity with the response of heart failure to medical treatment<sup>3</sup> (Fig. 1). Ventricular-secondary MR may worsen as a result of systolic dyssynchrony due to left bundle branch block, improving with cardiac resynchronization therapy.<sup>4</sup> There seems to be a certain threshold, a stage of no return, when secondary valve disease stops responding to heart failure treatment and drives the worsening of heart failure.<sup>5,6</sup> This threshold signals development of valvular heart failure.<sup>6</sup> It also signals the need for valve-specific management, valve repair; however, further evidence is needed regarding timing of valve repair before or after reaching this threshold.

Atrial-secondary valve disease responds to diuretics and, in the case of atrial fibrillation, it responds to the specific treatment<sup>7</sup>: rate control, cardioversion, or ablation.

## HEMODYNAMICS OF MITRAL REGURGITATION

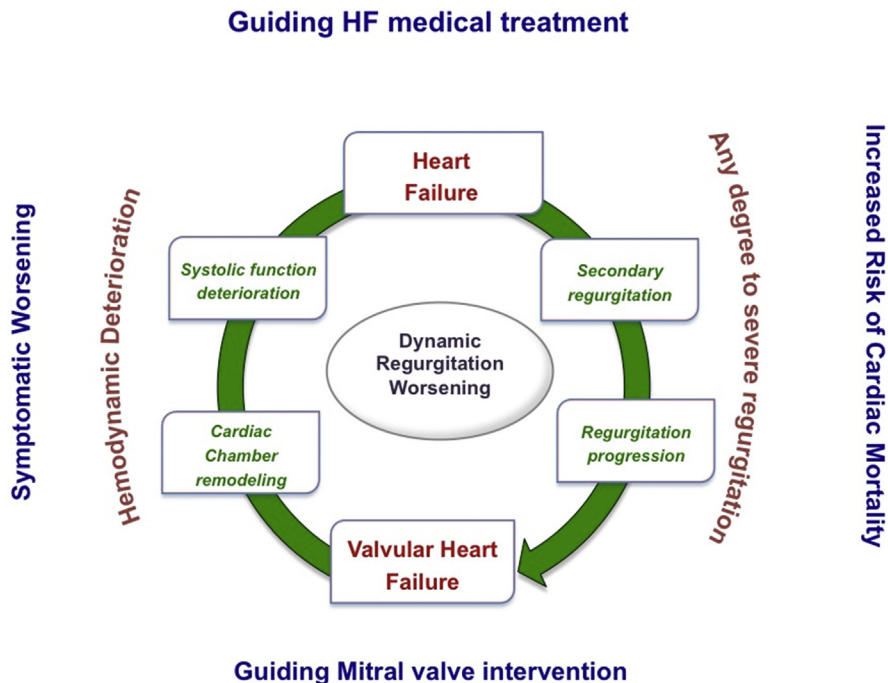
MR creates a volume overload state. The duration and severity of MR are the main determinants of

the adaptive cardiac changes in response to volume overload. The regurgitant volume reflects the sum of regurgitant flow throughout systole and is determined by the MR orifice area, the left ventricle/left atrial pressure gradient, and the duration of the systole. It is typically lower in secondary than in primary MR. Secondary MR has a different physiology as compared with primary MR, because it is the consequence of an initial ventricular disease. The left ventricle and left atrial dilatation are in excess to the degree of MR. The left atrial pressure is often elevated despite lower regurgitant volume than in primary MR. Furthermore, the consequences of regurgitation on the left ventricular and left atrial volumes and function provide indirect signs on the chronicity and severity of the regurgitation. The excess regurgitant blood entering in the left atrium may induce a progressive increase in pulmonary arterial pressure and a significant right atrial and tricuspid annulus dilatation, contributing to TR development.

## Imaging Assessment of Secondary Mitral Regurgitation

### The role of echocardiography

Echocardiography plays a central role in diagnosis and serial assessment of secondary MR as well as for timing the intervention and guiding the procedure.<sup>2,8-12</sup> The assessment begins with the left



**Fig. 1.** Vicious cycle associated with secondary regurgitation in heart failure (HF). Secondary regurgitation progression contributes to a cascade of events progressing to poor prognosis. At each point of this cycle, imaging, and, in particular, echocardiography, plays a major role.

ventricle (Fig. 2) and the left atrium, to define the specific secondary MR mechanism.

In nonischemic cardiomyopathy, dilatation of the left ventricle with spherical remodeling and displacement of the papillary muscles away from the mitral valve annulus results in symmetric tethering of the mitral valve leaflets (Fig. 3), restricting their descent toward the closure plane. Consequently, the coaptation point is displaced toward the apex of the left ventricle, and the coaptation length is reduced or the leaflets fail to coapt. Concomitantly, the mitral valve annulus may be dilated as a result of dilatation of the left ventricle, with or without dilatation of the left atrium as well. The mitral valve leaflets' failure to coapt all throughout systole causes an anatomic regurgitation orifice parallel with the coaptation line, semi-lunar in shape, having a large dimension in the bicommissural view and small dimensions in all other views (Fig. 4). Therefore, the vena contracta of the regurgitant jet in color-flow Doppler imaging is larger in a bicommissural 2-chamber view, and smaller in the other views (Fig. 5). The proximal iso-velocity surface area (PISA) method of MR quantification assumes a circular regurgitant orifice, thus being likely invalid in ventricular-secondary MR. However, the effective regurgitant orifice area (EROA) can be directly measured using 3-dimensional echocardiography-guided planimetry.

In ischemic cardiomyopathy, the mechanism of ventricular-secondary MR may be similar with the mechanism in nonischemic cardiomyopathy, in case scar involves the distal myocardial segments and in the absence of scar. Myocardial scar involving basal and midmyocardial segments, causing eccentric expansion of the left ventricular wall, results in asymmetric tethering of one of the mitral valve leaflets. The MR orifice shape depends

on the extent of the scar circularly, on the perimeter of the mitral valve annulus, to involve a small segment, a scallop or a larger proportion of the leaflet of the mitral valve. The jet resembles that of MR due to mitral valve prolapse of the opposite leaflet. This is because asymmetric tethering and restriction of one of the mitral valve leaflets results in relative prolapse of the opposite leaflet that has free excursion toward the mitral valve annulus in systole; however, this relative prolapse does not result in mitral valve leaflet systolic excursion beyond the mitral valve annulus, within the left atrium.

In atrial-secondary MR,<sup>13</sup> the systolic excursion of the mitral valve leaflets toward the closure plane is not restricted. The leaflets are fully unfolded and stretched, attempting but failing to cover the systolic valve area, enlarged because of annular dilatation with or without loss of posterior annulus systolic sphincter mechanism.<sup>14</sup>

### The role of stress echocardiography

Exercise echocardiography with supine bicycle exercise can be used for the assessment of secondary MR to explain symptoms or to establish prognosis.<sup>15–17</sup>

In nonischemic cardiomyopathy, exertion-induced increase in myocardial contractility with consequent decrease in left ventricular cavity size may result in MR severity decrease, predictive of response to medical treatment and good prognosis. The severity of MR can increase on exertion, particularly in the case of exertion-induced systolic dyssynchrony.<sup>15,16</sup>

In ischemic cardiomyopathy, the severity of MR can increase on exertion because of induced ischemia or simply because of change in balance of tethering forces of the valve as a result of an

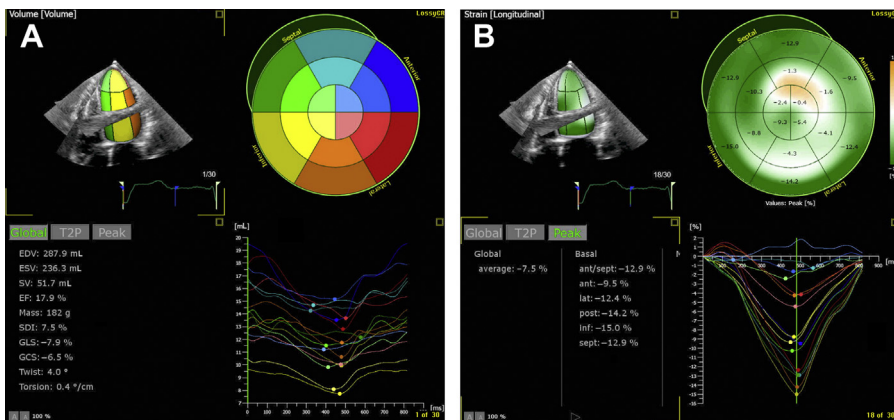
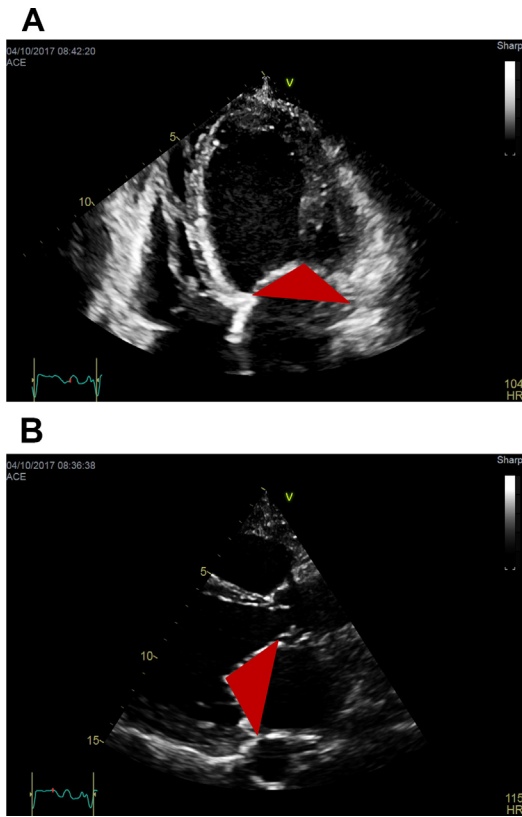


Fig. 2. Assessment of the left ventricle: (A) 3-dimensional echo-based assessment of volumes, ejection fraction, systolic dyssynchrony; (B) 3-dimensional echo-based assessment of Global Longitudinal Strain and systolic dyssynchrony based on peak strain.



**Fig. 3.** Symmetric tenting (enclosed red area *arrow head*) of the mitral valve leaflets in dilated cardiomyopathy: (A) 4-chamber view; (B) parasternal long-axis view.

increase in contractility in areas with no scar, whereas areas with scar remain akinetic or become dyskinetic.<sup>18</sup>

Exertion-induced dynamic MR was also associated with HFpEF, related to increase in left ventricular filling pressures.<sup>19</sup>

#### **The role of cardiac magnetic resonance**

The role of cardiac magnetic resonance in the assessment of secondary MR is still to be defined based on evidence.<sup>8</sup> There are limited outcome data and also limited data on regurgitant volume and regurgitant fraction thresholds for severity grading. However, cardiac magnetic resonance provides gold-standard assessment of volumes and ejection fraction of the left ventricle, assessment of the myocardial scar, and assessment of the left atrial volume. Furthermore, the quantification of MR severity based on regurgitant volume and regurgitant fraction does not depend on the shape of the regurgitant orifice or on existence of multiple jets.<sup>8</sup>

#### **Grading mitral regurgitation severity**

By convention, MR is graded into mild, moderate, and severe. When present, secondary MR may

exhibit a broad range of severity. Any degree of secondary MR conveys an adverse prognosis, with a graded relationship between severity of regurgitation and reduced survival. In the American guidelines, on the basis of the criteria used for determination of severe MR in randomized controlled trials of surgical intervention, both primary and secondary MR are considered severe if EROA is  $\geq 40$  mm<sup>2</sup>, regurgitant volume is  $\geq 60$  mL, and regurgitant fraction is  $\geq 50\%$ .<sup>8</sup> In the European Society of Cardiology guidelines, the corresponding thresholds of severity for secondary MR, which are of prognostic value, are 20 mm<sup>2</sup> and 30 mL, respectively (Table 1).<sup>9</sup> These differences in the definition of severe secondary MR are generating considerable controversy within the cardiology community. Noteworthy, in secondary MR, a concomitant increase in MR severity (EROA  $\geq 13$  mm<sup>2</sup>) and in pulmonary arterial pressure ( $>60$  mm Hg of systolic arterial pressure) identifies a subset of patients with moderate MR at high risk of cardiac-related death.<sup>17</sup>

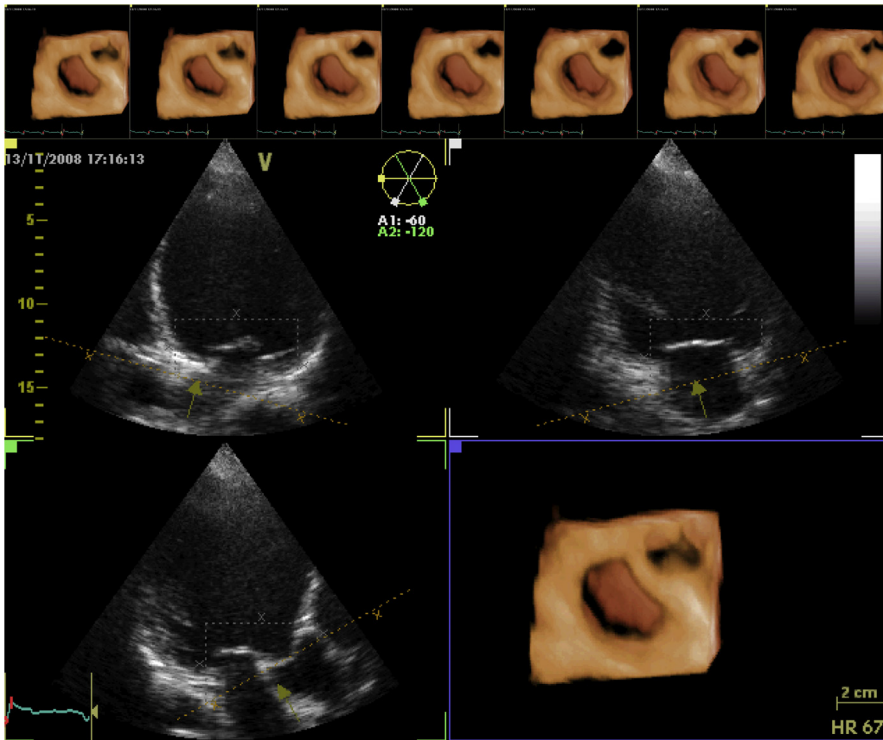
#### **HEMODYNAMICS OF TRICUSPID REGURGITATION**

As for secondary MR, secondary TR begets TR. Indeed, TR itself leads to further RV dilation and dysfunction, right atrial enlargement, more tricuspid annular dilatation and tethering, and worsening TR. With increasing TR, the right ventricle dilates and eventually fails, causing increased right ventricular diastolic pressure and, in advanced situation, a shift of the interventricular septum toward the left ventricle. Such ventricular interdependence might reduce the left ventricular cavity size (pure compression), causing restricted left ventricular filling and increased left ventricular diastolic and pulmonary artery pressure. The resulting increase in left and right atrial pressures may promote atrial fibrillation and precipitate symptom onset.

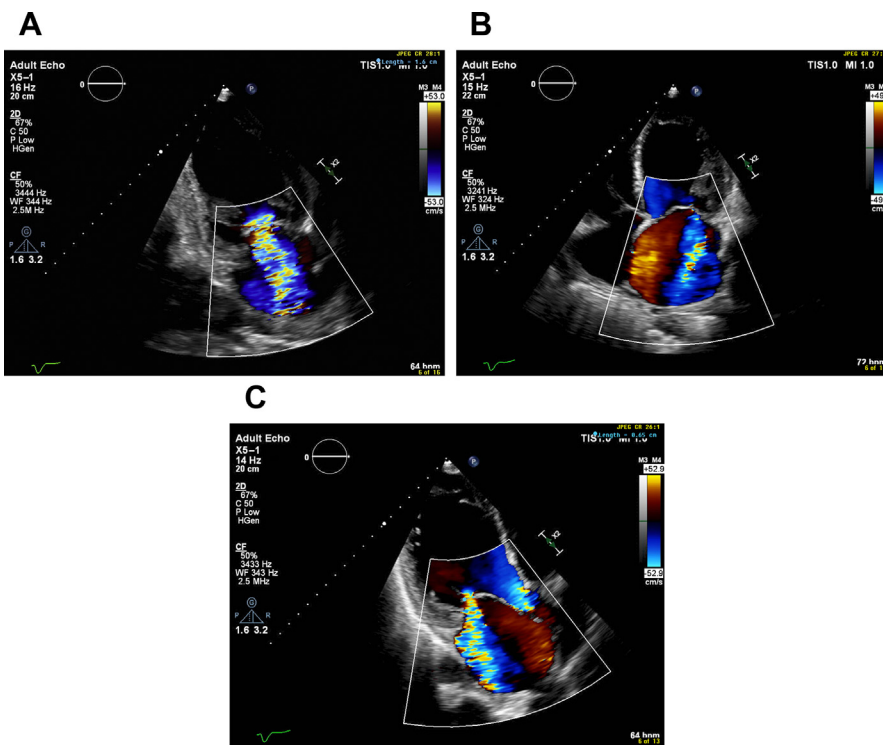
#### **Imaging Assessment of Secondary Tricuspid Regurgitation**

##### **The role of echocardiography**

As for MR, echocardiography plays a central role in the assessment of secondary TR for diagnosis, follow-up, timing of intervention, and procedure guiding.<sup>8–11,20,21</sup> The morphology of the tricuspid valve is more complex, and the diagnosis of secondary TR is more difficult to make. Three-dimensional echocardiography is essential, because 2-dimensional echocardiography is a poor assessment tool for identification of the 3 valve leaflets and detection of the regurgitation



**Fig. 4.** Failure of mitral valve leaflets to coapt all throughout systole (illustrated with the help of 3-dimensional echo surgical view, in all the systolic frames) causing an anatomic regurgitant orifice parallel with the coaptation line.



**Fig. 5.** Color-flow Doppler demonstrating large vena contracta in the bicommissural 2-chamber view (A) and smaller vena contracta in 4-chamber (B) and 3-chamber (apical long-axis) view (C) in ventricular-secondary MR.

**Table 1**  
**Mitral and tricuspid regurgitation grading**

	MR	TR		
	Severe	Severe	Massive	Torrential
<b>Qualitative</b>				
Morphology	Abnormal/flail/large coaptation defect			
Color Doppler of regurgitant jet	Very large central jet or eccentric wall impinging jet			
Continuous wave signal of regurgitant jet	Dense/triangular with early peaking	Dense/triangular with early peaking	Peak TR velocity <2 m/s	—
<b>Semiquantitative</b>				
Vena contracta width (mm)	≥7 (>8 for biplane)	7–13.9	14–20	>21
PISA radius (mm)	Large flow convergence zone	>9	—	—
Venous flow (pulmonary/hepatic)	Systolic vein flow reversal			
Inflow	Mitral E-wave dominant (>1.2–1.5)	Tricuspid E-wave dominant (≥1 cm/s)		
<b>Quantitative</b>				
EROA (mm <sup>2</sup> ) by PISA	≥20 (EACVI) ≥40 (ASE) (may be lower in secondary MR with elliptical EROA)	40–59	60–79	≥80
EROA (mm <sup>2</sup> ) by 3-dimensional	≥41	75–94	95–114	≥115
R Vol (mL) by PISA	≥30 (EACVI) ≥60 (ASE) (may be lower in low flow conditions)	45–59	60–74	≥75

*Abbreviations:* ASE, American Society of Echocardiography; EACVI, European Association of Echocardiography; R Vol, regurgitant volume.



mechanism. Furthermore, primary TR is often complicated by a secondary mechanism, because of the susceptibility of the right ventricle to dilatation, as a result of volume overload.

The assessment should begin with the right ventricle (Fig. 6) and the right atrium. Dilatation of the right ventricle may occur as a result of systolic dysfunction due to myocardial disease or pressure overload; it may also occur as a result of volume overload due to a pathologic intercavitary communication (usually atrial septal defect) or as a result of primary TR or primary pulmonary valve regurgitation. The dilatation of the right ventricle causes dilatation of the tricuspid valve annulus and distortion of the subvalvular apparatus restricting the systolic excursion of the leaflets. As for secondary MR, the annulus can be dilated purely because of dilatation of the right atrium, usually due to chronic atrial fibrillation. In the process of dilatation, the annulus takes a more circular shape (Fig. 7), because the increase in dimensions occurs mainly in the direction less supported by the atrioventricular junction fibrous skeleton (Fig. 8).

The same quantification methods as for MR can be applied; however, it is supported by less

evidence.<sup>8</sup> Systolic flow reversal in the hepatic veins is present with severe TR. Lack of coaptation of the tricuspid valve leaflets creating an anatomic regurgitant orifice defines free (massive) TR; in this case, the right atrial pressure is very high and the TR jet velocity is very low, regardless of the pulmonary artery pressure, being no longer useful for the estimation of systolic pulmonary artery pressure.

#### The role of stress echocardiography

The role of stress echocardiography in the assessment of TR, particularly secondary TR, is less well defined. However, increased contractility of the right ventricle may result in reduction in TR severity in the case of ventricular-secondary TR due to right ventricle myocardial disease. In the case of TR secondary to pulmonary hypertension and consequent right ventricular pressure overload, further increase in systolic pulmonary artery pressure on exertion may result in an increase in TR severity.

#### The role of cardiac magnetic resonance

Cardiac magnetic resonance is less established for the assessment of TR severity; however, it is

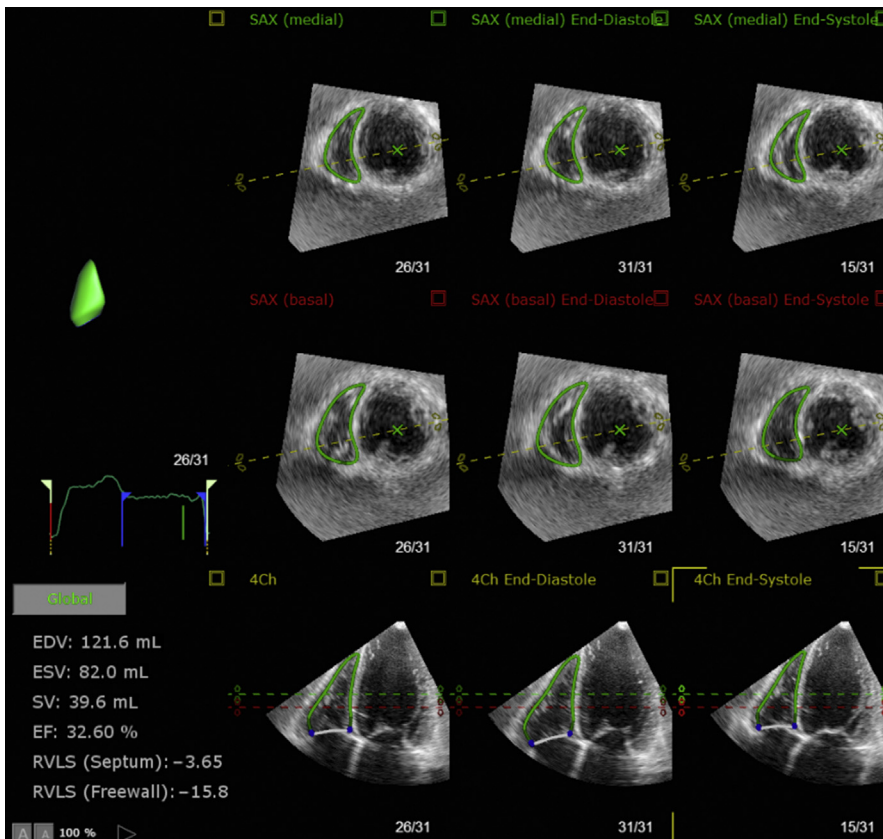
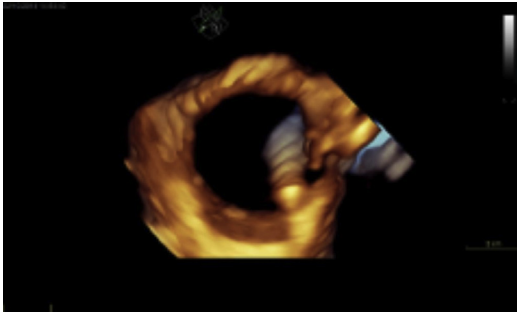


Fig. 6. Assessment of right ventricular volumes and ejection fraction using 3D transthoracic echocardiography.

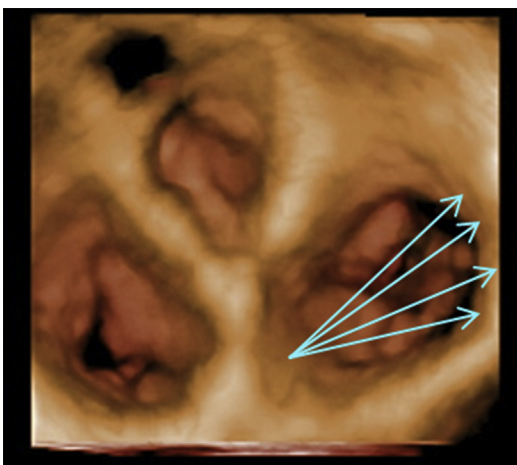


**Fig. 7.** Dilated tricuspid valve annulus, circular in shape.

the gold standard for the assessment of the right ventricular volumes and ejection fraction, and derived quantification techniques can be used.<sup>8</sup>

#### **Grading tricuspid regurgitation severity**

Traditionally, TR is graded into mild, moderate, and severe, following the severity grading conventions that also apply to mitral, aortic, and pulmonary valves. Severe TR is defined quantitatively as an EROA of  $\geq 40$  mm<sup>2</sup> and a regurgitant volume of  $\geq 45$  mL according to both the European and the American recommendations.<sup>8,22</sup> Massive TR is referred to as TR that is beyond severe, and it is associated with a low TR jet velocity of less than 2 m/s because there is near equalization of right ventricular and right atrial pressures. Expansion of TR severity grading to include massive (EROA 60–79 mm<sup>2</sup>) and torrential (EROA  $\geq 80$  mm<sup>2</sup>) TR, based on quantitative assessment, has been recently proposed.<sup>23</sup> Natural history studies have



**Fig. 8.** Three-dimensional echocardiography image obtained with oblique rendering of the base of the heart to visualize the annuli of both atrioventricular valves. The arrows show the direction of maximal dilatation of the tricuspid valve annulus, explaining why the annulus acquires a more circular shape.

shown that patients' prognosis worsened as the severity of TR increases, supporting the case for grading TR beyond severe to reflect the differential outcomes.<sup>24</sup>

#### **SUMMARY**

Secondary regurgitation caused by the remodeling and dysfunction of left or right heart chamber may complicate heart failure, worsening both symptoms and prognosis. Outcome studies have shown that patients' prognosis worsened as the severity of secondary regurgitation increases. Imaging and more specifically echocardiography plays a central role for diagnosis and serial assessment of secondary regurgitation as well as for timing the intervention and guiding the procedure.

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