Functional Tricuspid Regurgitation and Atrial Fibrillation: Which Comes First, the Chicken or the Egg?

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INTRODUCTION

Long-standing atrial fibrillation (AF) has been associated with functional tricuspid regurgitation (FTR) despite normal right ventricular geometry and function.[1-3] The pathophysiology of FTR in AF patients involves the interplay among tricuspid annulus (TA) remodeling, right atrium (RA) dilatation, and loss of function.[4] However, the temporal relationship between FTR and AF remains to be clarified. Accordingly, we report two cases of severe FTR in patients with AF that may help to address this issue.

CASE PRESENTATIONS

Case 1

A 61-year-old female patient was admitted in the emergency department for dyspnea at mild effort and signs of peripheral congestion. Her past medical history was remarkable for class III thyroid goiter with Graves's disease. She did not report any cardiovascular risk factor or previous cardiovascular disease. Electrocardiogram (ECG) showed AF (150 bpm) with normal QRS morphology. Her CHA(2)DS(2)-VASc score was 2. Transthoracic echocardiography (Figure 1, Videos 1 and 2) showed massive FTR (tricuspid regurgitation vena contracta = 10 mm) with a wide leaflet coaptation gap (12 mm), severely dilated RA (maximal volume = 172 mL) in the presence of a normally sized right ventricle (end-diastolic area = 25 cm^2; end-systolic area = 18 cm^2; fractional area change = 28%). Her TA diameter was 47 mm.

After a complete evaluation, she was diagnosed with thyrotoxicosis (thyroid stimulating hormone = 0.01 MIU/L; fT3 = 18.92 pmol/L; fT4 = 24.8 pmol/L; Ab anti TPO = 6,500 UI/mL; AB ant thyroid stimulating hormone receptor = 21.9 UI/L). One month later, she underwent thyroidectomy with replacement therapy, and euthyroidism was restored. At 3-month follow-up, she was completely asymptomatic. An ECG showed sinus rhythm and normal QRS morphology. Transthoracic echocardiography (Figure 2, Videos 3-6) revealed only mild FTR (tricuspid regurgitation vena contracta = 2 mm) with normal tricuspid valve leaflet coaptation. Both the RA volume (maximal volume = 96 mL) and TA dimension (39 mm) were significantly reduced, with no change in right ventricular size (end-diastolic area = 26 cm^2; end-systolic area = 14 cm^2). Right ventricular function was significantly improved (fractional area change = 46%).

Case 2

A 77-year-old woman was admitted to the emergency department for dyspnea at mild effort (New York Heart Association class III) and signs of peripheral venous congestion. Medical history was remarkable for hypertension and dyslipidemia. She had complained of palpitations for 2 years. One month prior to admission, she was diagnosed with AF and started oral anticoagulation. Her usual treatment consisted of digoxin 0.125 mg once daily (OD), bisoprolol 3.75 mg OD, ramipril 2.5 mg twice a day, furosemide 25 mg OD, atorvastatin 40 mg OD, pantoprazole 40 mg OD, and acenocoumarine with a target international normalized ratio of 2-3.

At admission, she was tachypneic. Her peripheral oxygen saturation was 97% while breathing room air. The blood pressure was 102/74 mm Hg, and heart rate 110 bpm, irregular. Physical examination revealed clear lungs, jugular venous distension, and bilateral ankle edema. At cardiac auscultation, she was irregularly irregular, and a 3/6 holosystolic murmur was detected at the left lower sternal border. Electrocardiography showed AF and a right bundle branch block. Blood tests revealed high brain natriuretic peptide levels (959 ng/L), congestive hepatopathy (aspartate transaminase 51 U/L, alanine transaminase 83U/L, gamma-glutamyl transpeptidase 298 U/L), and moderately impaired renal function (creatinine 1.27, estimated glomerular filtration rate 41 mL/min/1.73 m^2 Chronic Kidney Disease Epidemiology Collaboration equation). All the other blood tests were normal. Her CHA(2)DS(2)-VASc score was 5.

Transthoracic echocardiography revealed dilated RA, normal right ventricular size and function, and severe tricuspid regurgitation with loss of leaflets coaptation. Potential reversible etiologies of AF were excluded during hospitalization. Transesophageal echocardiography excluded the presence of left atrial thrombi, and she underwent electrical cardioversion to sinus rhythm. Amiodarone was recommended for long-term sinus rhythm maintenance.

The day after the cardioversion in sinus rhythm, the patient underwent a comprehensive two- and three-dimensional transthoracic echocardiography (Figures 3 and 4, Videos 7-10) that showed mildly enlarged right ventricular basal diameter (43 mm) but normal right ventricular volumes (end-diastolic volume = 101 mL, end-systolic volume = 47 mL) and function (ejection fraction 53%). Both the RA (maximal volume = 50 mL/m^2) and the TA (linear diameter = 35 mm or 25 mm/m^2, area = 10.1 cm^2 or 7.2 cm^2/m^2)

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Keywords: Functional tricuspid regurgitation, Three-dimensional echocardiography, Atrial fibrillation, Tricuspid annulus, Right atrium, Right ventricle

Conflicts of interest: The authors reported no actual or potential conflicts of interest relative to this document.

2468-6441

https://doi.org/10.1016/j.case.2020.04.011

VIDEO HIGHLIGHTS

Video 1: Two-dimensional apical 4-chamber view recorded in the emergency room during rapid atrial fibrillation.
Video 2: Two-dimensional apical 4-chamber view with color Doppler showing severe tricuspid regurgitation.
Video 3: Two-dimensional apical 4-chamber view recorded 2 months after cardioversion in sinus rhythm showing significant reduction of right atrial size and normal coaptation of tricuspid leaflets.
Video 4: Two-dimensional apical 4-chamber view with color Doppler showing mild tricuspid regurgitation.
Video 5: Two-dimensional right ventricular inflow parasternal view with color Doppler showing mild tricuspid regurgitation.
Video 6: Three-dimensional echocardiography, multislice display of a color Doppler dataset showing a small vena contracta area of the tricuspid regurgitation jet.
Video 7: Two-dimensional right ventricular focused apical 4-chamber view recorded during high rate atrial fibrillation.
Video 8: Three-dimensional echocardiography. En-face volume rendering of the tricuspid valve from the right ventricular perspective showing a large coaptation gap among the tricuspid valve leaflets.
Video 9: Two-dimensional right ventricular inflow parasternal view with color Doppler showing massive tricuspid regurgitation.
Video 10: Three-dimensional echocardiography, multislice display of a color Doppler dataset showing a very large vena contracta area of the tricuspid regurgitation jet.
Video 11: Two-dimensional right ventricular focused apical 4-chamber view recorded 1 year after restoring the sinus rhythm.
Video 12: Three-dimensional echocardiography. En-face volume rendering of the tricuspid valve from the right ventricular perspective 1 year after restoring the sinus rhythm and showing normal coaptation of tricuspid valve leaflets.
Video 13: Two-dimensional apical 4-chamber view with color Doppler showing massive tricuspid regurgitation.
Video 14: Two-dimensional right ventricular inflow parasternal view with color Doppler showing massive tricuspid regurgitation.

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were severely dilated. The RA function measured using three-dimensional longitudinal strain was severely reduced (reservoir function = 12% and contractile function = −2%). There was a large leaflet coaptation gap (1.2 mm or 0.8 cm^2), and FTR was massive. The width of the regurgitant jet vena contracta was 8 mm in the apical four-chamber view and 7 mm in the parasternal long-axis view. A vena contracta area of 3.4 cm^2 was measured using three-dimensional color Doppler echocardiography.

During hospitalization, volume status was optimized using intravenous diuretic therapy. Amiodarone was recommended for long-term sinus rhythm maintenance. Right heart cardiac catheterization documented normal pulmonary artery pressures at rest (mean pulmonary pressure = 21 mm Hg and mean pulmonary artery wedge pressure = 13 mm Hg). The echocardiography study recorded at discharge (fifth day) was unchanged compared to the one described above. The patient was considered for surgical tricuspid valve repair. However, due to the thickening of the tricuspid valve leaflets, the workup to exclude carcinoid syndrome was also started.

At 12-month follow-up the patient was asymptomatic, and ECG showed sinus rhythm with right bundle branch block. There was no evidence of carcinoid disease. Her chronic treatment included amiodarone 200 mg OD, bisoprolol 2.5 mg OD, ramipril 5 mg twice a day, furosemide 25 mg OD, atorvastatin 40 mg OD, and apixaban 5 mg twice a day. Transthoracic echocardiography showed a mild decrease of right ventricular size (basal diameter = 38 mm, end-diastolic volume = 91 mL, end-systolic volume = 35 mL) with improved function (ejection fraction 62%; Figures 5 and 6, Videos 11-14). There was a significant reverse remodeling of the RA size (maximal volume = 22 mL/m^2) and recovery of its function demonstrated using three-dimensional longitudinal strain measurement (reservoir function = 47% and contractile function = −51%). The TA also remodeled in a favorable way (linear diameter = 27 mm or 19 mm/m^2, area = 7.3 cm^2 or 4.8 cm^2/m^2), and the tricuspid regurgitation was remarkably reduced (mild). The width of the vena contracta of the tricuspid regurgitation jet was 1 mm in the apical four-chamber view and 3 mm in the parasternal short-axis view.

DISCUSSION

Atrial fibrillation is the most common arrhythmia. The estimate prevalence of AF is 0.4%-1% in the general population, increasing with age, and accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances.[5] Interestingly, the prevalence of FTR in the general population is similar (0.55%) and follows the same epidemiologic pattern.[6]

Previous studies have found associations between chronic AF with RA and TA dilation,[1-3] and the role of the RA volume as a main

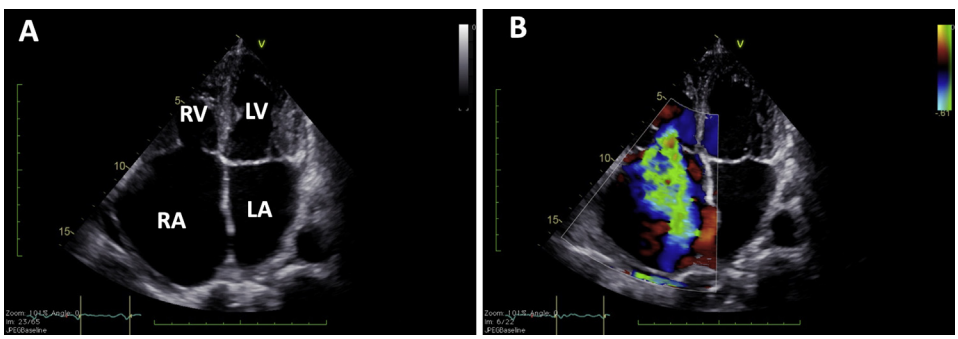

Figure 1 Transthoracic echocardiography study recorded in the emergency room at patient admission. **(A)** Apical four-chamber view showing a severely enlarged RA, mildly enlarged left atrium, with normally sized and functioning ventricles. There is a wide leaflet coaptation gap. **(B)** Color Doppler flow mapping showing severe tricuspid regurgitation. *LA*, Left atrium; *LV*, left ventricle; *RV*, right ventricle.

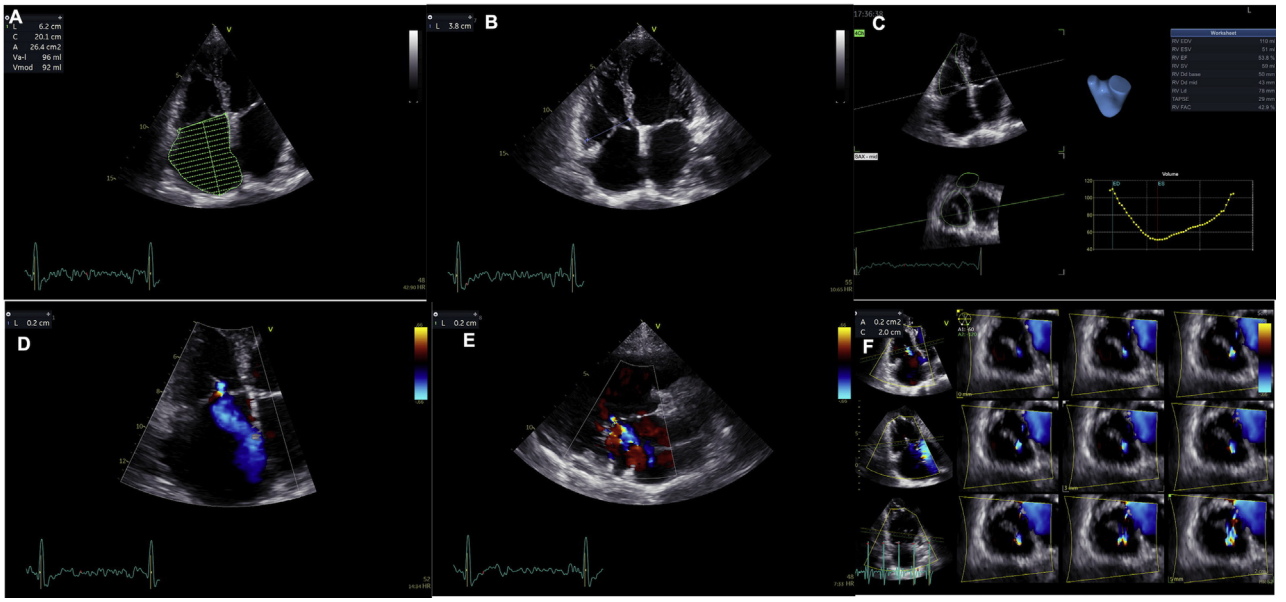

Figure 2 Transthoracic echocardiography 3 months after thyroidectomy and 2 months after sinus rhythm restoration. **(A)** Apical four-chamber view showing significantly reduced right atrial maximal volume; **(B)** coaptation of tricuspid leaflets was normal; **(C)** three-dimensional echocardiography assessment of the right ventricle showed normal volumes and function; **(D, E)** TV flow interrogation using color Doppler showing mild FTR with a vena contracta of 2 mm in both the apical four-chamber view and the parasternal right ventricular inflow view; **(F)** three-dimensional echocardiography color Doppler assessment of FTR with a measured vena contracta area of 0.2 cm^2, compatible with mild regurgitation. *VCA*, Vena contracta area; *VCW*, vena contracta width.

determinant of TA size was reported many years ago.[7] However, the mechanism by which AF leads to TA dilation and regurgitation is still uncertain and variably reported as a consequence of right ventricular dysfunction, RA dilation and/or dysfunction, or "degenerative" alteration of TA, or it was simply labeled as "idiopathic annular dilation" in the form of "isolated/idiopathic FTR."[1,2,8] The role of the remodeling of the RA in the pathophysiology of TA dilation and development of FTR has been largely neglected until recently.[4,9] Contemporary three-dimensional echocardiography allows a comprehensive assessment of the tricuspid valve,[10,11] the RA,[12] and the right ventricle[13] to clarify the pathophysiology of FTR. However, it remains to be clarified whether it is a preexisting FTR that, through a dilation of the RA, triggers the AF onset or, conversely, whether it is the chronic AF that, through the dilation of the RA, causes the dilation of the TA and leads to FTR. Our cases demonstrate that RA dilatation is the major determinant of TA remodeling, which leads to FTR in AF patients.[4] Even more, persistent restoration of the sinus rhythm can lead to RA and TA reverse remodeling with significant reduction in RA volume and TA area and improvement of FTR.

Although the RA myocardial wall is thinner than the left atrial wall, it includes muscle structures such as the crista terminalis and pectinate muscles. Moreover, the RA vestibule (a smooth muscular rim that anchors the pectinate muscles) surrounds the tricuspid valve orifice, and its thin musculature fibers insert into the leaflet hinges. The muscular fibers of RA vestibule are involved in the atrial flutter circuit and contribute to the "sphincteric-like" contraction of TA. In contrast to

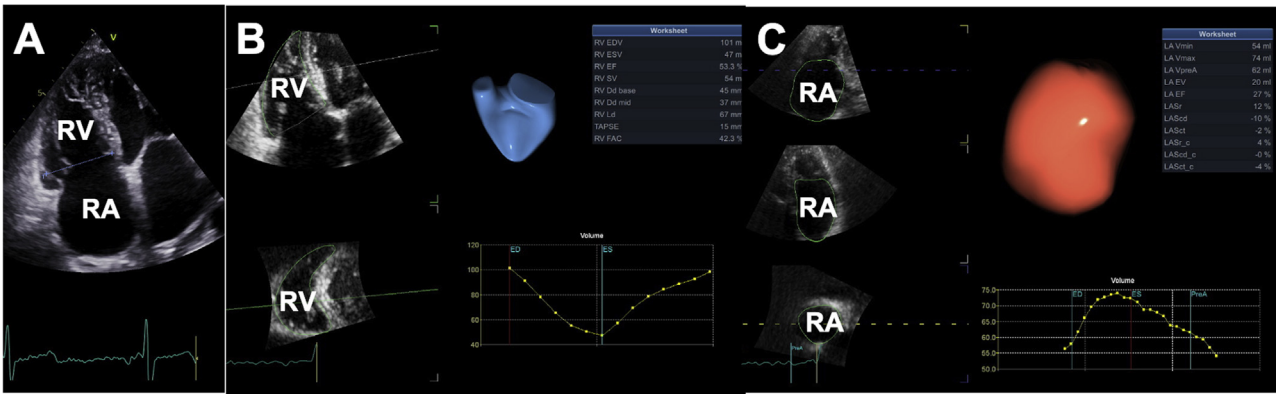

Figure 3 Right heart chamber geometry and function evaluated by transthoracic echocardiography the day after the cardioversion in sinus rhythm. **(A)** Two-dimensional apical four-chamber view showing mildly increased right ventricular basal diameter; **(B)** three-dimensional echocardiography assessment of right ventricular geometry and function showing normal size and function; **(C)** three-dimensional echocardiography assessment of right atrial size and function showing a severely dilated and dysfunctional RA.

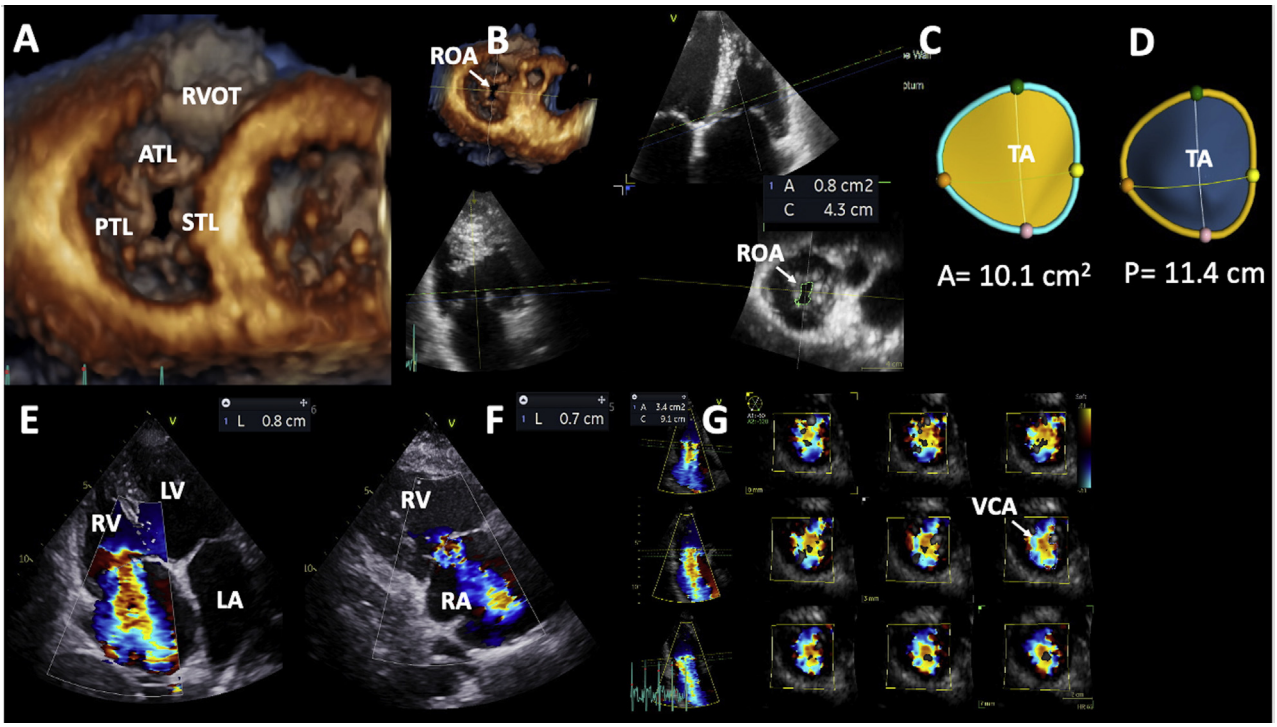

Figure 4 Tricuspid valve geometry and severity of tricuspid regurgitation evaluated by transthoracic echocardiography the day after the cardioversion in sinus rhythm. **(A)** Volume rendering of the tricuspid valve from the right ventricular perspective showing normal morphology of the leaflets and a large anatomical regurgitant orifice; **(B)** planimetry of the anatomical regurgitant orifice area using the Flexi-slice tool (EchoPac Software only v204, GE Vingmed, Horten, Norway) to align the cropping plane at the level of the tip of the tricuspid valve leaflets and oriented perpendicular to the opening axis of the valve; **(C, D)** measurement of TA area and perimeter using 4D Auto TVQ software package (EchoPac Software only, v204) showing dilated tricuspid annulus; **(E, F)** tricuspid flow interrogation using color Doppler showing massive tricuspid regurgitation in both the apical four-chamber view and the parasternal right ventricular inflow view; **(G)** three-dimensional color Doppler planimetry of the vena contracta area by slicing the proximal part of the regurgitant jet. *ATL*, Anterior tricuspid leaflet; *PTL*, posterior tricuspid leaflet; *ROA*, regurgitant orifice area; *RVOT*, right ventricular outflow tract; *STL*, septal tricuspid leaflet; *VCA*, vena contracta area.

the mitral annulus, which is disconnected from the myocardium across the base of the anterior mitral leaflet between both fibrous trigones, the TA has only a single right fibrous trigone. Therefore, the TA is in contact with RA myocardium over the largest part of its circumference. The lower extent of fibrotic tissue might explain why the TA is more prone to dilate along with the remodeling of the adjacent chamber than the mitral annulus. Moreover, only 40% dilatation of TA is required to result in significant tricuspid regurgitation, whereas a 75% dilation of the mitral annulus is required for significant mitral regurgitation to occur.[14] These differences may provide a

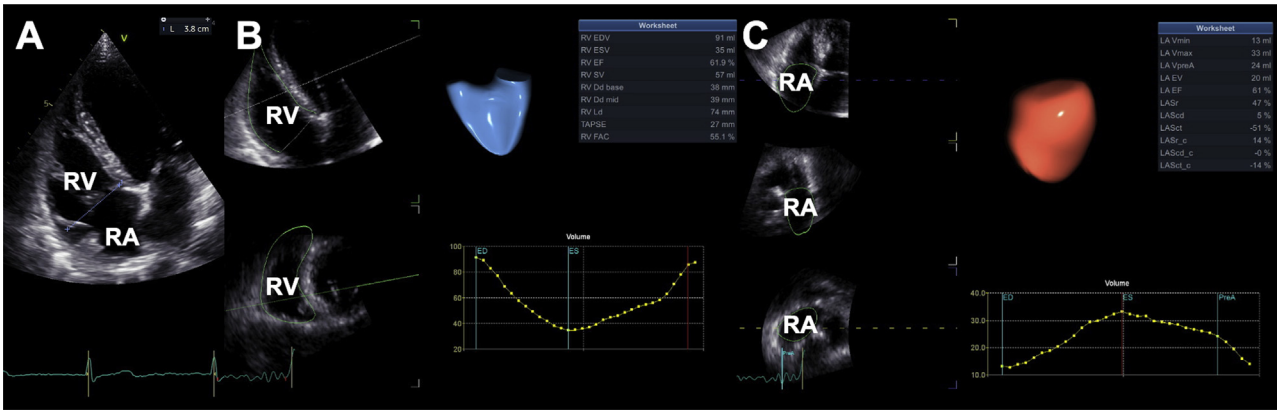

Figure 5 Right heart chamber geometry and function evaluated by transthoracic echocardiography 1 year after the cardioversion in sinus rhythm. **(A)** Two-dimensional apical four-chamber view showing mildly increased right ventricular basal diameter; **(B)** three-dimensional echocardiography assessment of right ventricular geometry and function showing normal size and function; **(C)** three-dimensional echocardiography assessment of right atrial size and function showing a normally sized and normally functioning RA.

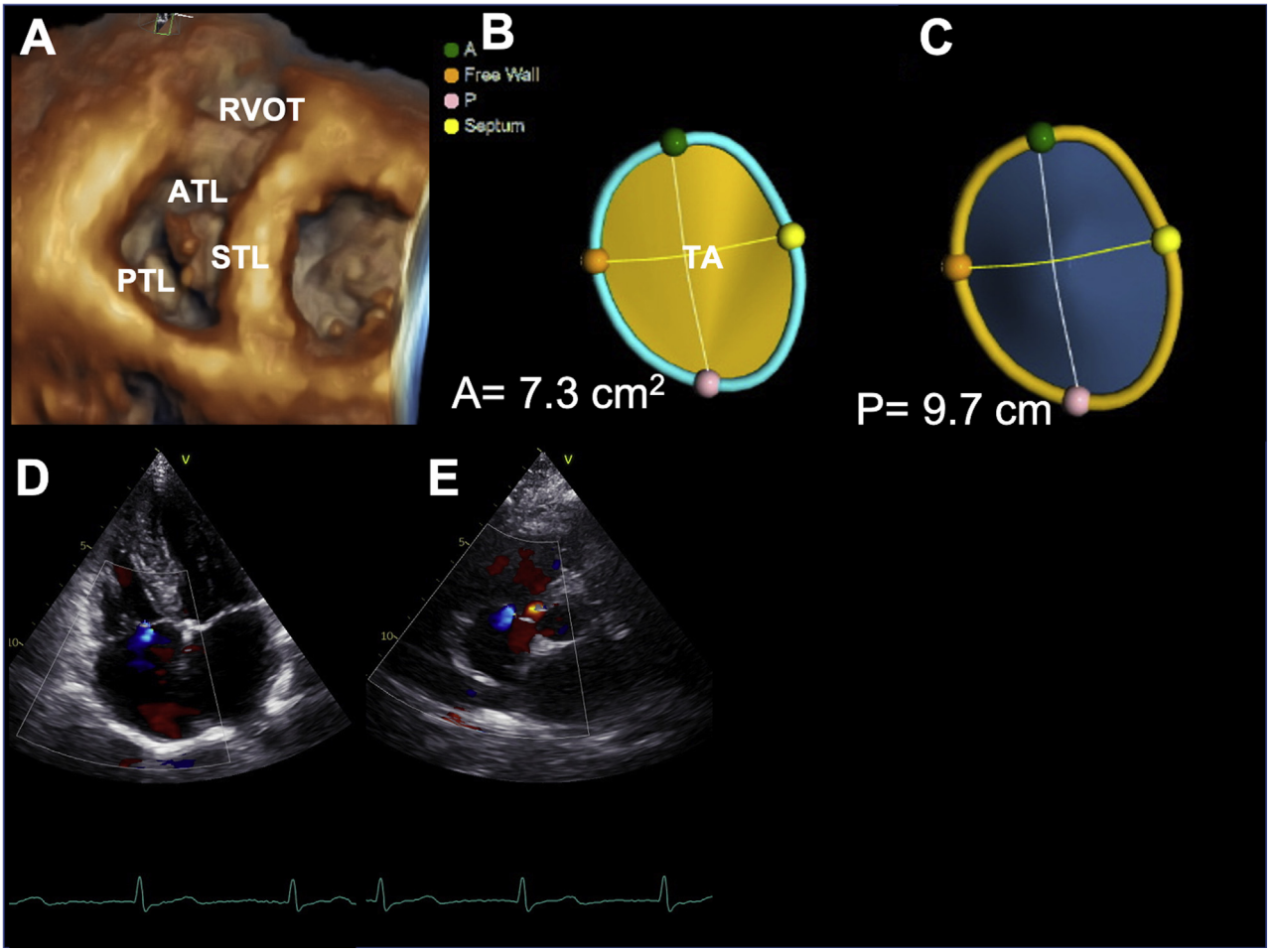

Figure 6 Tricuspid valve geometry and severity of tricuspid regurgitation evaluated by transthoracic echocardiography 1 year after the cardioversion in sinus rhythm. **(A)** Volume rendering of the tricuspid valve from the right ventricular perspective showing normal morphology and normal coaptation of the leaflets. **(B, C)** measurement of TA area and perimeter using 4D Auto TVQ software package (EchoPac Software only, v204) showing normal TA geometry; **(D, E)** tricuspid flow interrogation using color Doppler showing mild tricuspid regurgitation in both the apical four-chamber view and the parasternal right ventricular inflow view.

pathophysiologic basis for the higher prevalence of FTR compared with functional mitral regurgitation reported in lone AF.[15]

CONCLUSION

Atrial fibrillation may be the primary cause of the onset and/or worsening of FTR through RA and TA remodeling. Our cases reinforce the concept of the atriogenic FTR.[4] In addition, we showed that, in some patients, restoring the normal sinus rhythm is associated with reverse remodeling of both the RA and the TA with improvement of the FTR severity. This finding has important clinical implications since aggressive rhythm control strategies in patients with AF seem to be beneficial not only for symptom relief but also to prevent RA and TA remodeling.

ACKNOWLEDGMENTS

Dr. A.C.G. was supported by an educational grant (POCU/380/6/13/125245 no. 36 482/May 23, 2019) funded by the project "Excellence in interdisciplinary Ph.D. and post-PhD research, career alternatives through entrepreneurial initiative (EXCIA)". Dr. D.M. was supported by a training grant funded by the European Association of Cardiovascular Imaging.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2020.04.011.

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