# Carcinoid Syndrome with Involvement of Tricuspid and Pulmonary Valves: Findings on Three-Dimensional Echocardiography

*Eduardo Menti, Renata Patrícia Moreira Camargo, Marcia Castilhos Puchalski, Felipe Gropelli Crochemore, Fabio Moreira Cañelas*

*Complexo Hospitalar Santa Casa de Porto Alegre, Centro Histórico, Porto Alegre, RS – Brazil*

## Introduction

Carcinoid tumors are rare neuroendocrine neoplasms with a prevalence of 1.2 to 2.1 cases per 100,000 inhabitants.[1] In a historical overview, the first description of a carcinoid tumor was attributed to Ranson in 1890. The term "karzinoid" was used by Oberndorfer in 1907 to describe adenocarcinomas with indolent evolution. The tumor was classified as a neuroendocrine tumor in 1928 through the identification of enterocromaffin cells and Page et al. described high levels of 5-hydroxy indoleacetic acid in the urine of patients with carcinoid syndrome in 1955.[2] These tumors originate in the gastrointestinal tract and in the tracheobronchopulmonary system in 75% and 25% of the cases, respectively. In the gastrointestinal tract, the small intestine is the most common primary site followed by the cecal appendix and rectum. Indolent growth determines that 20% to 30% of patients present disseminated disease upon diagnosis.[1-3]

Carcinoid syndrome is present in only 5% to 7% of the tumors. It consists of a set of signs and symptoms generated by the release of vasoactive substances in the systemic circulation mainly from liver metastases, as they deviate first pass liver metabolism. The most common clinical manifestations are flushing, secretory diarrhea and dyspnea. Cardiac involvement occurs in 50% of patients and heart failure is the main cause of mortality.[4]

Echocardiography is the initial diagnostic method for evaluating patients with suspected cardiac involvement in carcinoid syndrome, since it is a simple noninvasive inexpensive test that is widely available. Through echocardiography, it is possible to evaluate the valvular involvement and its hemodynamic consequences. Three-dimensional echocardiographic analysis delivers a clearer picture of the valvular involvement and may be an important tool in the therapeutic planning of these patients with increased knowledge and experience in the treatment of the disease.

## Keywords

Carcinoid Heart Disease; Carcinoid Tumor; Tricuspid Valve/dysfunction; Pulmonary Valve/dysfunction; Echocardiography, Three-Dimensional.

**Mailing Address: Eduardo Menti** •
Rua Regente, 245, Sl504. Postal Code 90470-170, Porto Alegre, RS - Brazil
E-mail: eduardomenti@gmail.com
Manuscript received March 20, 2017; revised April 12, 2017; accepted April 12, 2017

**DOI:** 10.5935/2318-8219.20170022

### Case Report

A 37-year-old male patient complained of diarrhea, facial flushing and dyspnea. On physical examination, besides erythema on the face, bilateral jugular turgence, painful hepatomegaly, severe lower limb edema and systolic murmur in tricuspid focus were observed. Abdominal tomography revealed hepatomegaly with heterogeneous parenchyma at the cost of multiple nodular lesions with predominantly arterial and venous enhancement, lobed contours and poorly defined borders, and a 2.6 cm nodular lesion with contrast enhancement near the distal ileum loop in the right iliac fossa, probably corresponding to the primary lesion. Diagnosis of low-grade neuroendocrine neoplasia was confirmed by intestinal lesion-positive chromogranin A immunohistochemistry. Elevation of 5-hydroxindoleacetic acid in 24-hour urine confirmed the suspicion of carcinoid syndrome. Transthoracic echocardiography revealed adequate left ventricular systolic dysfunction and severe enlargement of the right chambers with preserved right ventricular contractility. The tricuspid valve presented diffuse thickening of the leaflets and subvalvar apparatus, determining severe chordae retraction and restricted mobility of the cusps with severe regurgitant flow on Doppler (Figures 1, 2 and 3). The pulmonary valve presented thickened leaflets with severe mobility restriction, systolic flow with increased 3.6 m/s velocity and maximum systolic gradient of 53 mmHg and mean systolic gradient of 32 mmHg (Figure 4). Therapy with monthly doses of long-acting somatostatin analogue (octreotide) was initiated, then followed by progressive symptomatic worsening. The patient was submitted to liver transplantation without previous correction of the valvular diseases. This was followed by hemodynamic instability and death.

## Discussion

Carcinoid syndrome is a rare late manifestation of a neuroendocrine tumor. Carcinoid tumors can secrete a large amount of vasoactive substances, which are largely inactivated by the liver. When tumor cells metastasize to the liver, vasoactive substances are able to reach the systemic circulation and determine the clinical manifestations that are typical of the carcinoid syndrome. These vasoactive substances will cause structural changes in the endocardium of the right heart chambers, with plaque deposits of fibrous tissue on the valvar and subvalvular surfaces. In patients with echocardiographic evidence of carcinoid heart disease, survival over a three-year period is 31% versus 68% in those without cardiac involvement.[5]

Carcinoid heart disease typically involves the tricuspid and pulmonary valves, causing right heart failure. Involvement of the aortic and mitral valves is rarely reported.[4,5] Echocardiography is the main diagnostic modality for evaluating cardiac involvement. The echocardiographic characteristics of the cardiac carcinoid disease are thickening of the cusps and the subvalvar apparatus of the pulmonary and tricuspid valves, determining coaptation failure or restricted opening of the valvular cusps. Tricuspid valve with severe regurgitation appears in 90% of the cases; pulmonary valve with stenosis in 53%; and regurgitation in 81%.[6] Pulmonary stenosis may aggravate tricuspid regurgitation and, inversely, the severity of pulmonary stenosis may be underestimated because of low cardiac output and large tricuspid regurgitant volume. Diffuse thickening of the valves and subvalvar apparatus is less severe in the aortic and mitral valves compared to the right side, because vasoactive substances are inactivated in the pulmonary parenchyma. When the involvement of the left side is observed, the presence of patent foramen ovale, atrial septal defect, bronchogenic carcinoid tumor or high circulating levels of vasoactive substances should be investigated. Contrast-enhanced transesophageal echocardiography is a method to check for right-left flow through patent foramen ovale, which may be present in 41% of the patients.[7]

Three-dimensional (3D) echocardiography represents a major breakthrough in cardiovascular diagnosis and allows the representation of cardiac structures from any spatial point of view. Evaluation of the tricuspid valve through the 3D echocardiography presents an incremental diagnostic value on two-dimensional (2D) echocardiography, favoring the identification of the cusps and location of valve involvement. As for the pulmonary valve, 2D echocardiography, 3D transthoracic echocardiography and 3D transesophageal echocardiography do not present any significant differences in their capacity to diagnose pulmonary valve lesions. In this case, real-time 3D echocardiography was important in demonstrating the valve origin of pulmonary stenosis and made clear the role of valve retraction and thickening in tricuspid valvular dysfunction.

Although some cases present good control of symptoms with the use of somastotin analogs, evolution into heart failure is expected. Valve replacement surgery should be an option in some cases. Prognosis is still limited. In the past decades, an increase in survival averaging 4.4 years has been observed. Early surgical indication in asymptomatic patients may be the factor involved in this improvement, although there is insufficient evidence in the literature to define changes in the natural history of the disease.[8] The therapeutic approach to the heart disease is complex, and careful evaluation with complementary imaging tests is critical for proper recognition of the disease patterns.[9,10]

## Authors' contributions

Data acquisition: Menti E, Camargo RPM, Puchalski MC, Crochemore FG; Manuscript drafting: Menti E, Camargo RPM, Crochemore FG; Critical revision of the manuscript as for important intellectual content: Menti E, Camargo RPM, Puchalski MC, Crochemore FG, Cañelas FM.

### Potential Conflicts of Interest

There are no relevant conflicts of interest.

### Sources of Funding

This study had no external funding sources.

### Academic Association

This study is not associated with any graduate program.

# Case Report

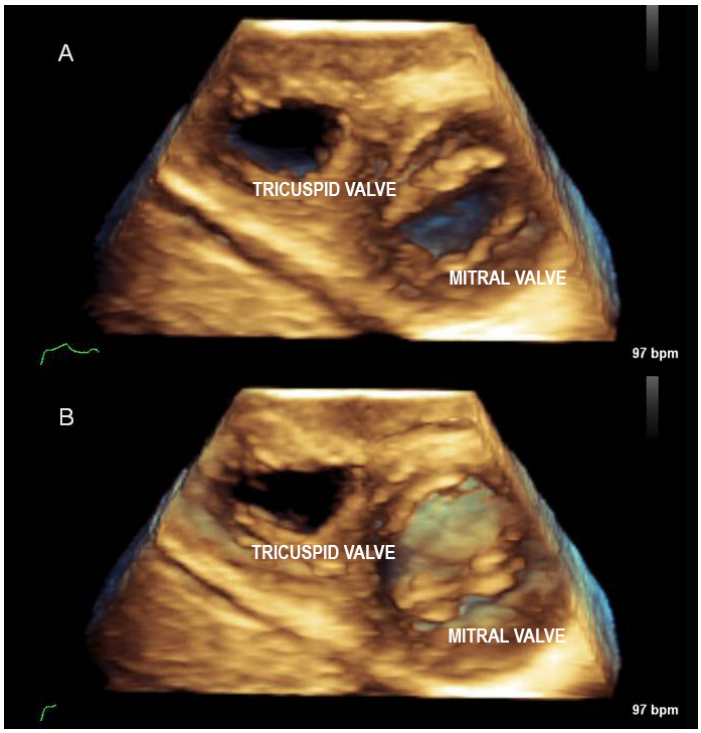


**Figure 1 –** *Real-time three-dimensional transthoracic echocardiography. A: View of atrioventricular valves in their ventricular face during diastole, showing the open valves; B: The same plane during systole, showing the closed mitral valve and the fixed tricuspid valve.*

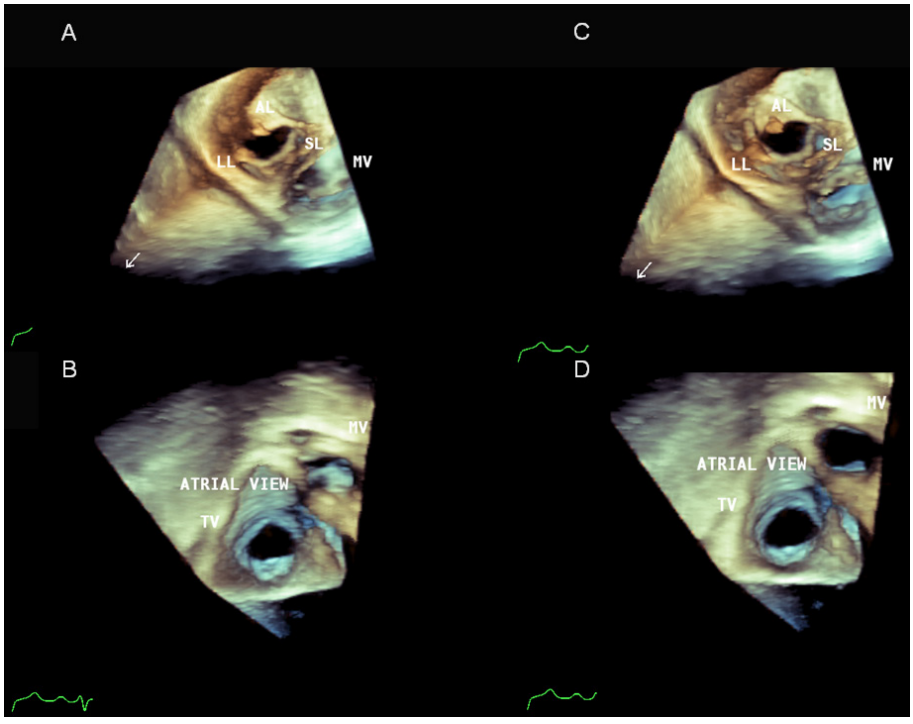


**Figure 2 –** *Three-dimensional transthoracic echocardiography after reconstruction, showing the tricuspid valve with diffuse thickening of leaflets, shortening of chordae and apical traction with systolic coaptation deficit. A and C: Ventricular view showing the tricuspid and mitral valves during diastole; B and D: Atrial view showing the tricuspid and mitral valves during systole.*

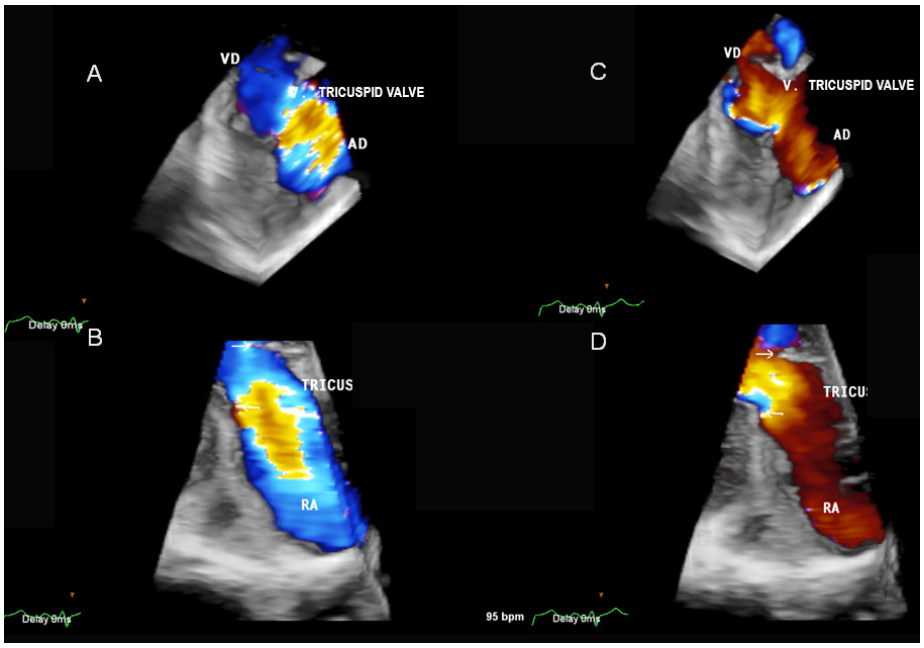


**Figure 3 –** *Real-time three-dimensional transthoracic echocardiography with tricuspid valve flow mapping with color Doppler showing fixed leaflets (arrows) and laminar flow during systole (A and B) and during diastole (C and D). Severe grade tricuspid regurgitation without stenotic component.*

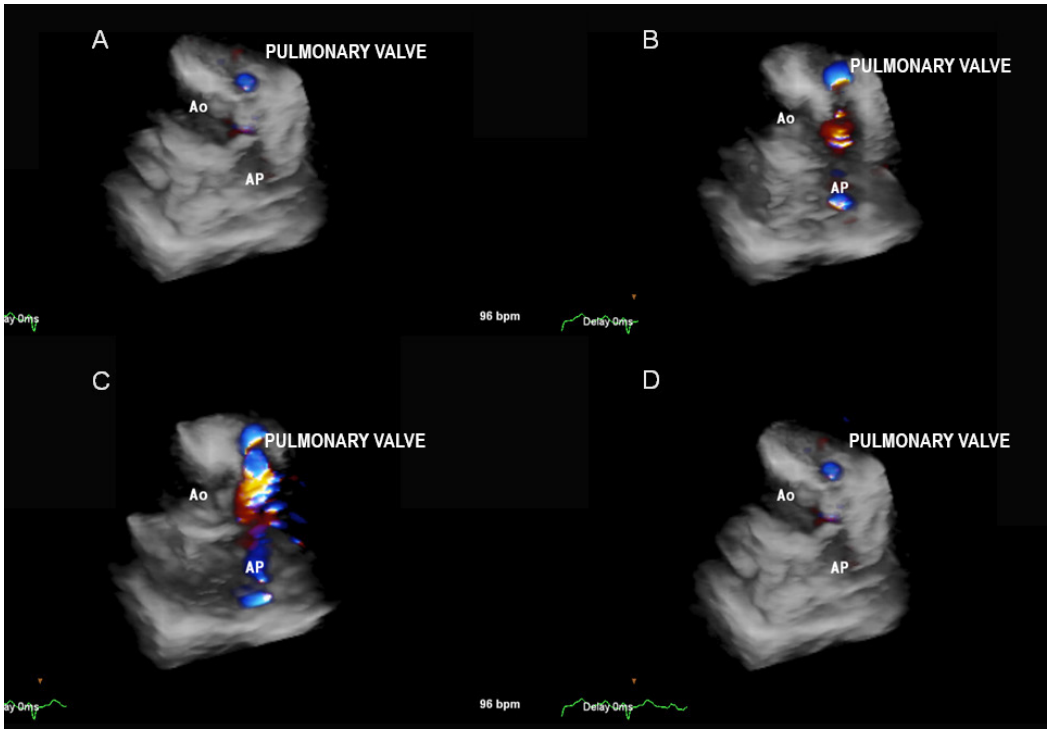


**Figure 4 –** *Real-time three-dimensional transthoracic echocardiography with right ventricular outflow tract mapping and pulmonary valve in four moments of the cardiac cycle, showing valve stenosis with slight valvar regurgitation associated. A: late diastole; B: pulmonary valve opening; C: systolic peak; D: early diastole.*

## References

1. Modlin, IM, Sandor, A. An analysis of 8305 cases of carcinoid tumors. Cancer. 1997;79(4):813-29.
2. Schnirer II, Yao JC, Ajani JA. Carcinoid: a comprehensive review. Acta Oncol. 2003;42(7):672-92.
3. Bhattacharyya S, Davar J, Dreyfus G, Caplin ME. Carcinoid heart disease. Circulation. 2007;116(24):2860-5.
4. Connolly HM, Schaff HV, Mullany CJ, Rubin J, Abel MD, Pellikka PA. Surgical management of left-sided carcinoid heart disease. Circulation. 2001;104(12 Suppl 1):I36-40.
5. Pellikka PA, Tajik AJ, Khandheria BK, Seward JB, Callaham JA, Pitot HC, et al. Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. Circulation. 1993;87(4):1188-96.
6. Moerman VM, Dewilde D, Hermans K. Carcinoid heart disease: typical findings on echocardiography and cardiac magnetic resonance. Acta Cardiol. 2012;67(2):245-8.
7. Mansencal N, Mitry E, Pillière R, et al. Prevalence of patent foramen ovale and usefulness of percutaneous closure device in carcinoid heart disease. Am J Cardiol. 2008;101(7):1035-8.
8. Møller JE, Pellikka PA, Bernheim AM, Schaff HV, Rubin J, Connolly HM. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. Circulation. 2005;112(21):3320-7.
9. Gustafsson BI, Hauso O, Drozdov I, Kidd M, Modlin IM. Carcinoid heart disease. Int J Cardiol. 2008;129(3):318-24.
10. Moller JE, Connolly HM, Rubin, J, Seward JB, ModestoK, Pellikka PA. Factors associated with progression of carcinoid heart disease. N Engl J Med. 2003; 348(11):1005-15.