

## Bioprosthetic Valve Thrombosis in Carcinoid Heart Disease

### Abstract

Tricuspid regurgitation in carcinoid syndrome leads to significant morbidity and mortality that may warrant a tricuspid valve replacement. However, for patients with high serotonin levels and known hypercoagulable risks, the optimum timing for surgery and postoperative anticoagulation approaches remain unclear. High serotonin-triggered hypercoagulability makes prosthetic valves susceptible to thrombosis. Despite appropriate management with a somatostatin analog, some patients continue to have high markers of serotonin that causes platelet aggregation and rapid clot formation. In severely symptomatic patients who require valve surgery, it may not be feasible to postpone surgery until these metabolites are normalized, which may add a substantial risk for postoperative valve thrombosis to an otherwise uneventful procedure. In some, there is a significant need to predict and prevent bioprosthetic valve thrombosis in carcinoid heart disease and to identify best anticoagulation practices across a spectrum of its complex coagulation dynamics and clinical presentation.

**Keywords:** Carcinoid heart disease, heart valve prosthesis, serotonin, thrombosis

### Introduction

Tricuspid regurgitation in carcinoid syndrome leads to significant morbidity and mortality that may warrant a tricuspid valve replacement.<sup>[1,2]</sup> However, for patients with high serotonin levels and associated hypercoagulable risks, the optimum timing for surgery and postoperative anticoagulation approaches remain unclear.<sup>[2,3]</sup> Herein, we present a patient with carcinoid heart disease who developed immediate valve thrombosis after bioprosthetic tricuspid valve replacement, which ultimately required a reoperation to declot the valve and lifelong anticoagulation therapy.

### Case Report

A 59-year-old male with a history of metastatic small bowel carcinoid tumor and severe tricuspid regurgitation presented for surgical valve replacement. His carcinoid syndrome was managed preoperatively by a multidisciplinary team including oncology, endocrinology, and cardiac surgery to optimize him medically. Over a 4-month period, the patient received lanreotide depot injections (Ipsen Biopharmaceuticals, Basking Ridge, NJ, USA) with improvement in serum serotonin

from 2100 to 1200 ng/mL (reference range: 56–244 ng/mL) and chromogranin from 215 to 22 ng/mL (reference range <15 ng/mL). He had overall improvement in his energy levels and diarrhea; however, he continued to have New York Heart Association Class II symptoms with exertional dyspnea and lower extremity edema and was, therefore, referred for cardiac surgery. Preoperative transthoracic echocardiogram (TTE) showed moderate tricuspid stenosis and severe tricuspid regurgitation with restricted leaflet motion and dilated annulus, no pulmonary valve stenosis or regurgitation, mildly dilated right ventricle with preserved function, and preserved left ventricular function.

The patient underwent an uncomplicated tricuspid valve replacement with a 29 mm Hancock porcine tissue valve (Medtronic, Minneapolis, MN, USA). Intraoperative transesophageal echocardiography (TEE) before cardiopulmonary bypass demonstrated a dilated right ventricle with normal systolic function (tricuspid annular plane excursion measured 2 cm) and retracted tricuspid leaflets with severe tricuspid regurgitation, consistent with the preoperative TTE findings [Figures 1 and 2]. TEE immediately after bypass demonstrated a dilated right heart with otherwise normal systolic function and a well-functioning tricuspid valve with no

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tricuspid regurgitation nor stenosis [Figure 3]. However, postoperatively over the next 24 h, he was unable to wean from supplemental oxygen and inotropic support as would otherwise be expected. Although carcinoid crisis was on the differential diagnosis, his carcinoid treatment was unaltered since he was only receiving monthly injections, and a serum serotonin level postoperatively was 171 ng/ml, well below his preoperative level and within normal range. After 24 h, when the patient did not demonstrate expected clinical improvement, further investigation was initiated with a noninvasive TTE on postoperative day 2 that showed a well-seated valve with mean gradient 5 mmHg. While being unable to wean from vasoactive medications over the next several days, serial echocardiograms were performed that showed preserved right and left ventricular function, no pericardial effusion, or signs of hypovolemia. However, one repeat TTE showed tricuspid stenosis with mean gradient 10 mmHg.

Given the unclear etiology of tricuspid stenosis and the patient's clinical deterioration, a redo sternotomy was performed 2 weeks after the initial operation. Intraoperative TEE showed an immobile septal leaflet with a hyperechoic density encasing the valve reminiscent of a thrombus preventing its free motion, with normal right ventricular function [Figure 4]. This finding was confirmed upon surgical reopening, wherein the valve was found to have a significant thrombus cast within the belly of the leaflet in the septal position. The valve was declotted, and normal valve indices were measured on TEE thereafter. Given his procoagulant profile and rapid valve thrombus formation in <2 weeks, the patient was started on systemic

anticoagulation immediately postoperatively once surgical bleeding was stable. Successively, the patient was weaned off vasoactive medications and supplemental oxygen and was discharged home on lifelong anticoagulation with warfarin. With the patient's significant symptomatic improvement after heart surgery and given the extensive metastatic liver disease, the patient did not undergo subsequent liver resection. He continued to improve symptomatically remaining on lanreotide depot injections and warfarin for the 6-month follow-up period.

### Discussion

Patients with carcinoid heart disease often require right-sided valve replacement; however, high serotonin-triggered hypercoagulability makes prosthetic valves susceptible to thrombosis. In right-sided valve replacements, there are multiple risk factors for valve thrombosis including postoperative right ventricular failure and the overall lower flow state on the right side of the heart. In addition, in our patient with preoperative serotonin levels almost five times the upper limit of normal, with serotonin being a stimulus for platelet activation, there is likely a hypercoagulable state. The lower flow state in the right heart causing a relative stasis, in addition to a hypercoagulable state seen in carcinoid syndrome, are two pillars of Virchow's triad that lead to thrombosis, and these were likely contributing factors to thrombosis in our case.

In a retrospective study of 195 patients with carcinoid heart disease who underwent valve replacement, thrombus formation on the tricuspid bioprosthesis was the most common cause of valve dysfunction. Out of eight patients who developed recurrent tricuspid valve disease requiring reoperation, four patients had bioprosthetic valve thrombosis as the cause compared to only one patient having carcinoid plaque deposition as the cause.<sup>[4]</sup> As a comparison, in all patients, in general, the incidence of prosthetic valve thrombosis in the tricuspid position is 1%–4% in the setting of appropriate anticoagulation, which is similar to the incidence in this study of patients with carcinoid disease.<sup>[5]</sup> This finding of valve thrombosis as a frequent cause of bioprosthesis dysfunction led the study authors to recommend postoperative anticoagulation

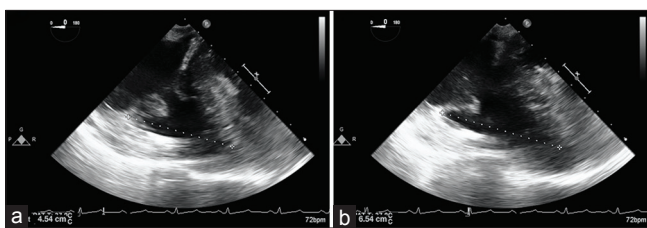


Figure 1: Tricuspid annular plane excursion measurement, measuring distance between lateral tricuspid annulus and right ventricular apex during systole (a) and diastole (b). The tricuspid annular plane excursion measures 2 cm, suggestive of normal right ventricular systolic function

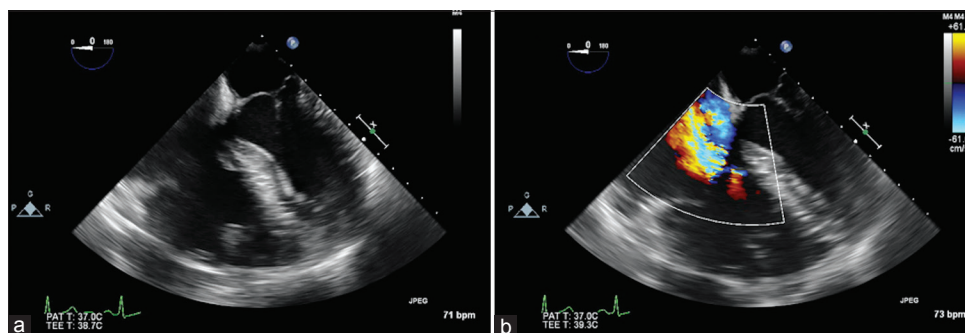
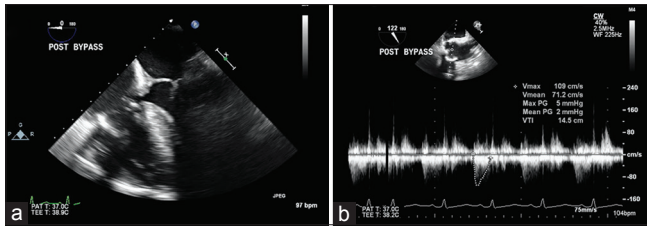


Figure 2: (a) Mid-esophageal view showing a dilated right ventricle with retracted tricuspid leaflets. (b) Color flow Doppler showing severe tricuspid regurgitation



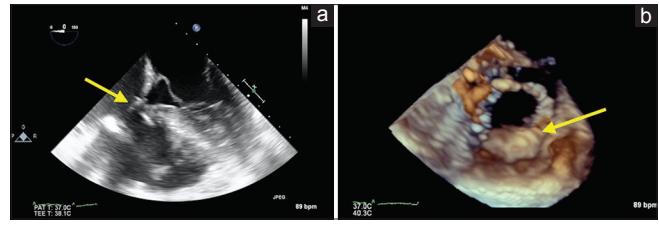
**Figure 3: (a) Well-seated bioprosthetic valve in the tricuspid position. (b) Mean gradient through tricuspid prosthesis is 2 mmHg, demonstrating no stenosis**

for 3 months. Furthermore, the 2017 expert statement on carcinoid heart disease recommends anticoagulation for 3 to 6 months postoperatively for patients having a bioprosthetic tricuspid valve replacement.<sup>[6]</sup> In our patient, the initial surgery was not followed with anticoagulation given the risk of coagulopathy with his extensive liver metastases and that his carcinoid syndrome was controlled. However, after the second surgery and valve thrombosis, the risk-benefit assessment shifted and anticoagulation was started.

There are also examples of recurrent carcinoid plaque formation and bioprosthetic valve dysfunction resulting from the vasoactive mediators in carcinoid disease. Two case reports describe recurrent carcinoid plaque deposition over a period of months to years, in which one patient previously had a bioprosthetic tricuspid valve replacement and another had a pulmonary allograft.<sup>[7,8]</sup> In a study of 22 patients with carcinoid heart disease who underwent valve surgery, two patients developed bioprosthetic valve degeneration.<sup>[1]</sup> Thus, carcinoid syndrome should be expertly managed after cardiac surgery to minimize the effect of the vasoactive mediators on bioprosthetic valve dysfunction.<sup>[2,6]</sup>

Although bioprosthetic valve thrombosis in carcinoid syndrome has been reported in the literature, this case demonstrates clot formation in a rapid interval, less than a week, of the original operation that is deemed unusually rare. Of the 31 patients who developed bioprosthetic valve thrombosis, the peak incidence was 13–24 months after valve implantation.<sup>[9]</sup> This study included all patients at a single institution with bioprosthetic valve thrombosis over a period of 16 years. Only a minority of patients had risk factors for thromboembolism, including atrial fibrillation, hypercoagulable state, and severe left ventricular dysfunction. For anticoagulation, these patients were managed with either a Vitamin K antagonist or aspirin. However, in the patient with carcinoid syndrome who has a known hypercoagulable risk due to serotonin, this acute thrombus formation is more probable and should be recognized as a likely complication.

The coagulopathies associated with carcinoid heart disease are complex. While the serotonergic activities lead to procoagulant effects, these patients often have



**Figure 4: (a) Mid-esophageal four-chamber view showing an immobile septal leaflet (arrow) not opening during diastole. (b) Three-dimensional image demonstrating thrombus (arrow) on a tricuspid valve leaflet**

concurrent liver abnormalities with metastatic carcinoid disease that leads to increased bleeding risks whereby an anticoagulation therapy could potentially be unsafe.<sup>[3]</sup> Given this complex balance of clotting and bleeding, coagulation tests may be useful in guiding postoperative management in carcinoid heart disease. One may consider performing thromboelastography or rotational thromboelastometry preoperatively and monitoring these tests intraoperatively pre- and postbypass and postoperatively in the intensive care unit. Future research could address the application of appropriate tests to determine the dynamic underlying coagulation profile of these patients. However, published consensus guidelines to date have only made allusions to coagulation tests and risk stratification of valve thrombosis rather than to formally recommend management strategies.

Although controversy still exists regarding timing of surgery in carcinoid heart disease, the general agreement is to perform valve surgery when patients become symptomatic or have evidence of ventricular dysfunction in those with stable carcinoid tumor.<sup>[1,2,3,6,10]</sup> Despite appropriate management with a somatostatin analog, some patients continue to have high markers of serotonin that causes platelet aggregation and clot formation. While it seems prudent to postpone surgery until these metabolites are normalized, with no current literature suggesting optimal serotonin levels before surgery, such delays may not always be feasible in symptomatic patients as seen in our case. Hence, predicting bioprosthetic valve thrombosis in carcinoid patients is challenging but critical to individualize anticoagulation strategies to avert subsequent postoperative valve thrombosis and reoperation.

#### **Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

#### **Conflicts of interest**

There are no conflicts of interest.

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