

# Successful Double Bioprosthetic Valve Replacement in a 64-Year-Old Man with Carcinoid Syndrome and Bipolar Disorder: Case Report

Sarah S. Tang<sup>1</sup>, Michael Y. Henein<sup>1,2</sup>, Anthony De Souza<sup>1</sup>

<sup>1</sup>Department of Cardiac Surgery, Royal Brompton Hospital, <sup>2</sup>National Heart and Lung Institute, Imperial College London, London, UK

The case is described of a 64-year-old man with bipolar disorder and severe carcinoid heart disease who required a double valve replacement. Multi-disciplinary team involvement and extensive preoperative investigations resulted in a successful regimen which prevented reactivation of carcinoid syndrome and avoided the serious side effects of

lanreotide and lithium therapy. In addition, two bioprosthetic valves were used, thereby avoiding the potential complications of anticoagulation in a patient with known hepatic metastases.

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In healthy individuals without comorbidities, a double valve replacement requires careful perioperative management. However, the additional history of carcinoid syndrome and bipolar disorder presents an unusual challenge requiring multidisciplinary team involvement and extensive preoperative investigations.

## Case report

A 64-year-old man presented with diarrhea, flushing and weight loss four years previously. His past medical history included bipolar disorder since 1978, but this had been controlled with lithium (800 mg/day). Laboratory measurements revealed abnormal liver function, and further investigations, including 24-h urinary 5-hydroxy-indole-acetic acid (HIAA) excretion, ultrasound, computed tomography (CT) and endoscopy, confirmed a diagnosis of carcinoid syndrome with lesions confined to the liver, though no primary site was identified. The patient had good resolution of symptoms when prescribed lanreotide. Side effects included initial instability of glycemic control, but this resolved spontaneously. More recently, he began to complain of exertional dyspnea, but denied wheeze.

Physical examination revealed a well-looking man with no respiratory distress at rest. There were prominent pulsations in both carotid regions. He was in

sinus rhythm (82 beats/min), and his blood pressure was 120/75 mmHg. Auscultation revealed quiet heart sounds and a loud split P2. There were no signs of right-sided heart failure, and the abdominal examination was normal.

Transthoracic echocardiography (TTE) performed to investigate the dyspnea revealed severe tricuspid regurgitation (TR) and severe pulmonary regurgitation (PR), without stenosis. The valves were thickened, shortened, and retracted (Fig. 1).

The patient was reviewed over a period of one year, during which time his symptoms clearly worsened. He had increasing difficulty climbing stairs and found it difficult to work as a teacher. In view of the severity of his heart disease, impending right heart failure and, given the insidious course of his carcinoid syndrome and estimated life expectancy of more than two years, the patient was accepted for surgery.

The preoperative assessment was extensive. Cardiac MRI confirmed severe TR and severe PR, a grossly dilated right atrium (end-diastolic dimension 58 mm) and ventricle (end-diastolic dimension 62 mm (normal <45 mm), end-diastolic volume 330 ml (normal 88-227 ml)) which were compressing on the left heart (Fig. 2). The left ventricular size was therefore small (end-diastolic dimension 44 mm, end-diastolic volume 107 ml), with function at the lower limit of normal (stroke volume 63 ml). The right ventricular output was impaired due to PR and TR (ejection fraction 56%; normal 47-74%).

Formal lung function studies indicated minimal hyperinflation with a normal gas transfer coefficient and spirometric indices. Arterial oxygen saturation was 95% on air.

Laboratory measurements were normal, with the exception of a marginally elevated bilirubin (26

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Address for correspondence:  
Sarah Tang, 24 Heathfield Road, Acton, London W3 8EL, UK  
e-mail: stang@doctors.org.uk

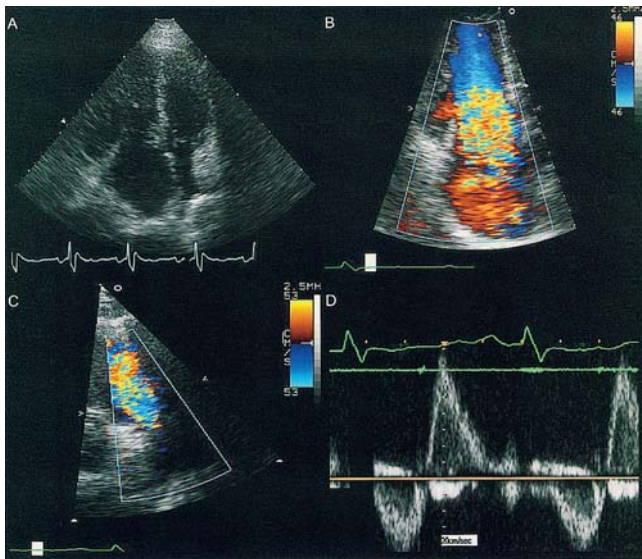


Figure 1: A) Two-dimensional image of the tricuspid valve from the apical four-chamber view in diastole, showing failure of the leaflets to coapt as a result of leaflet fibrosis and shortage. Note the relative enlargement of the right heart size compared to the left. B) Color flow Doppler across the tricuspid valve, demonstrating severe valve regurgitation (vena contracta 30 mm). C) Color flow Doppler across the pulmonary valve, demonstrating severe valve regurgitation (vena contracta 19 mm) (taken from the short-axis parasternal view of the right ventricular outflow tract). D) Pulsed-wave Doppler of the pulmonary valve, demonstrating laminar flow of the forward and backward flow across the valve consistent with severe pulmonary regurgitation. Note the pressure equalization between the pulmonary artery and right ventricle in mid diastole (vertical scale 20 cm/s velocity).

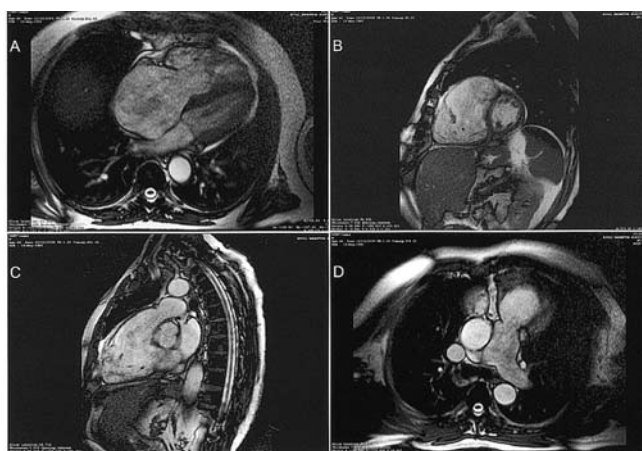


Figure 2: Magnetic resonance images. A) Four-chamber view showing a markedly dilated right heart and shrunken and immobile tricuspid valve leaflets, allowing free regurgitation. B) Short-axis view showing a dilated right ventricle and compression of the left ventricle. C) Right ventricular outflow tract. D) Fibrotic and shrunken pulmonary valve leaflets, allowing free regurgitation.

$\mu\text{mol/l}$ ) and creatinine ( $138 \mu\text{mol/l}$ ). These abnormalities were thought to be a result of lanreotide-induced hepatic congestion and lithium-induced renal impairment. Thus, the lithium therapy was stopped during the perioperative period.

An ultrasound study of the renal tract was performed to exclude other causes of renal impairment; this showed normal-sized kidneys with thin cortices and no evidence of hydronephrosis. Both CT and ultrasound confirmed multiple liver metastases, but the biliary tree was normal and there was no evidence of gallstones (also a side effect of lanreotide therapy).

Because of the risk of reactivating the carcinoid syndrome by diaphragmatic manipulation and liver disturbance, the case was discussed in detail with a consultant gastroenterologist and the following regimens were instigated: (i) antihistamine was commenced on the day before surgery (cytoheptadine 4 mg, tds); (ii) intravenous octreotide was commenced on the day of surgery (1.6 mg in 48 ml normal saline, infusion rate 6 ml/h) and continued for 24 h; this was followed by the patient's normal oral regimen; (iii) intravenous aprotinin on weaning off cardiopulmonary bypass (CPB); and (iv) intravenous methylprednisolone (1 g) on induction.

Surgery was carried out through a median sternotomy. The heart was exposed and the ventricle thought to be enlarged but contracting moderately well. CPB was instituted from a bicaval cannula to the ascending aorta, with subsequent cooling to  $34^{\circ}\text{C}$ . With the heart beating and the cava snug, the pulmonary artery was opened and the pulmonary valve inspected. The leaflets were shriveled and thickened. The valve was excised and replaced with a 25-mm Perimount pericardial tissue valve (Edwards Lifesciences, Irvine, CA, USA), after which the pulmonary artery was closed. The right atrium was opened and tricuspid valve inspected. The leaflets were so fibrotic and shrunk that there was little tissue to excise. A second, 33-mm, Perimount pericardial tissue valve was inserted and the right atrium closed. The patient was weaned off CPB with norepinephrine, milrinone, and nitric oxide. The sternum was closed in routine manner and the patient transferred to the intensive care unit in a stable condition.

The patient spent two days in the intensive care unit, during which time he developed nephrogenic diabetes insipidus secondary to preoperative lithium therapy (urine osmolality 250, plasma osmolality 327). DDAVP (a synthetic antidiuretic hormone;  $1 \mu\text{g}$ ) therapy was commenced, fluids containing sodium were eliminated from the fluid regimen, and lithium was recommenced at a much lower dose (200 mg). The patient was weaned off milrinone and octreotide and transferred to the ward-based high-dependency unit on postoperative day 3.

Further recovery was complicated only by a brief episode of atrial fibrillation which was successfully treated with DC cardioversion. Postoperative TTE

showed satisfactory bioprosthetic pulmonary and tricuspid valve function, with peak gradients of 12 mmHg and 4 mmHg, respectively. As the patient's lithium levels approached therapeutic range, he was discharged home on postoperative day 10.

## Discussion

Carcinoid tumors are rare neuroendocrine lesions that arise from amine precursor uptake and decarboxylation (APUD) cells. These cells exist throughout the gastrointestinal tract, lungs, biliary tree, pancreas and gonads, and are responsible for producing a wide range of hormones (e.g., serotonin, histamine, dopamine, tachykinins, prostaglandin) which have profound effects on the circulatory system, the gastrointestinal tract and the lungs.

In the UK, the annual incidence of carcinoid is estimated at three per 100,000 of the population (1), with 90% occurring in the gastrointestinal tract (most commonly the appendix and terminal ileum). The majority of tumors are slow-growing, with 10% diagnosed at post-mortem examination (1). Other tumors present as a palpable mass, rectal bleeding, weight loss, or as carcinoid syndrome. Carcinoid syndrome occurs in 10% of patients with metastatic disease or primary lung disease. When not metabolized by the liver or the lungs, large quantities of vasoactive products reach the systemic circulation, and this results in a characteristic syndrome of flushing, wheeze, and diarrhea.

Approximately 50% of patients develop cardiac disease (2); this is the result of large quantities of vasoactive tumor products reaching the right side of the heart without being inactivated by the liver. This paraneoplastic syndrome is typified by the formation of endocardial plaques of fibrous tissue on structures within or connected to the right heart. This in turn results in distortion of the valves, leading to either stenosis, regurgitation, or both. Typically, lesions are limited to the tricuspid valve, and combined lesions of the tricuspid and pulmonary valves are rare (3). The natural history is progression to right-sided heart failure and death. The inactivation of tumor products by the lungs reduces the incidence of left-sided lesions to only 5-10% (4). In these cases, extensive liver metastases, bronchial carcinoid or a patent foramen ovale should be investigated (4).

Valve surgery remains the definitive treatment in right-sided heart failure, and has been shown to extend life expectancy and improve symptoms in survivors (5). However, the perioperative mortality is high, with one study quoting a surgical mortality of 63% (6). A more recent case series of 11 patients quoted a mortality of 20%, with the reduction in mortality attributed to good preoperative control of carcinoid symptoms and meticulous perioperative anesthetic and surgical care (7). Perioperative regimens include

the use of octreotide boluses or infusions to reduce intraoperative hypotension, antihistamines prior to surgery to prevent flushing and bronchospasm, and corticosteroids to reduce bradykinin production. In the present case, the additional history of lithium therapy to treat bipolar disorder created an additional challenge to the patient's perioperative management. Despite stopping lithium preoperatively, he required treatment for lithium-induced nephrogenic diabetes insipidus, and the postoperative reintroduction of lithium was carefully titrated to serum levels.

Traditionally, it is thought that circulating vasoactive products damage bioprosthetic valves, with the result that mechanical valves have been more commonly used (5,6). However, improved therapies for managing carcinoid syndrome with the emergence of superior somatostatin analogues may potentially protect biological valves from the adverse effects of serotonin and other vasoactive peptides. A recent case study reported the first successful treatment of carcinoid heart disease using two bioprostheses. After two years, both valves are functioning well (as shown by echocardiography) (8). The avoidance of formal anticoagulation with bioprosthetic valves eliminates well-recognized bleeding complications which may be further exacerbated by liver metastases.

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