

CARCINOID HEART DISEASE: MEDICAL AND SURGICAL CONSIDERATIONS

Heidi M. Connolly, MD

From the Cardiovascular Division at the Mayo Clinic, Rochester, Minnesota.

Introduction and Diagnosis

Carcinoid tumors are rare, arising in 1.2-2.1 per 100,000 people in the general population per year.¹ In 20%-30% of patients, the initial presentation occurs as a result of peptide production, ie, carcinoid syndrome. The malignant carcinoid syndrome consists of flushing, gastrointestinal hypermotility (secretory diarrhea), bronchospasm, and carcinoid heart disease. The syndrome is caused by the release of the vasoactive substances 5-hydroxytryptamine (serotonin), 5-hydroxytryptophan, histamine, bradykinins, tachykinins, and prostaglandins. The diagnosis of carcinoid syndrome is usually suspected by clinical features and confirmed by elevation of the byproduct of serotonin metabolism, 5-hydroxy indole acetic acid (5-HIAA). The urinary 5-HIAA (24-hour collection) is a specific and reproducible test that provides a reliable biological marker for the assessment of tumor activity and the response to intervention.² Measurement of circulating plasma chromogranin A, a protein produced by neuroendocrine cells, has also become a useful marker for carcinoid tumor diagnosis and follow-up.^{3,4}

Systemic and Regional Therapy for Metastatic Carcinoid Disease

During the past decade, progress in the management of malignant carcinoid tumors and carcinoid syndrome has resulted

in better patient survival. Octreotide acetate (Sandostatin), the somatostatin analog, is a synthetic octapeptide that binds to subtypes of the somatostatin receptors and inhibits the secretion of bioactive substances that cause the carcinoid syndrome. Treatment with the somatostatin analog relieves symptoms in more than 70% of patients.^{5,6} Somatostatin analog is now available as a long-acting release, once-a-month intramuscular injection, Sandostatin LAR Depot. This microencapsulated depot formulation provides longer steady-state levels, thus improving quality of life by providing similar therapeutic benefits with less discomfort and inconvenience.⁷

Patients may present with bulky disease in the liver and no other metastatic carcinoid disease. These patients are candidates for surgical debulking (partial hepatectomy).⁸ Tumors that cannot be debulked with surgery may be debulked by catheter-based hepatic artery embolization. This procedure is usually followed by the use of somatostatin analog, which has a static effect on the tumor. Aggressive medical and interventional therapy for patients with carcinoid disease and syndrome has resulted in improved prognosis. Carcinoid heart disease remains a major cause of morbidity and mortality among patients with carcinoid syndrome.

Carcinoid Heart Disease

Carcinoid heart disease, which was first described in 1952,⁹ even-

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tually occurs in more than 50% of patients with carcinoid syndrome.¹⁰ Symptoms of carcinoid heart disease may be the initial presentation of carcinoid disease in as many as 20% of patients.

In carcinoid heart disease, deposition of a matrix-like material is present on the valves and endocardium of the right side of the heart (Fig 1). Retraction and fixation of the tricuspid leaflets result in reduced motion and lack of central coaptation. These changes characteristically cause severe tricuspid valve regurgitation and, less commonly, tricuspid valve stenosis. The pulmonary valve is also commonly affected in carcinoid heart disease and may be regurgitant or stenotic. Also, right-sided endocardial disease may be present in patients with advanced carcinoid heart disease. Patients often present with symptoms of right heart failure.

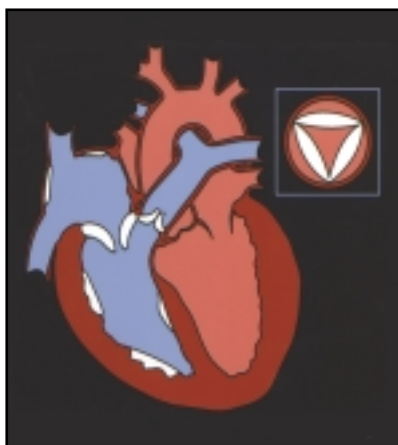


Fig 1. — Schematic demonstrating tricuspid and pulmonary valve disease as well as endocardial plaque deposition in carcinoid heart disease. Insert is a cross-sectional image of the pulmonary valve affected by carcinoid heart disease.

The mechanism of valve injury in carcinoid heart disease is not completely understood. Circulating serotonin levels are higher among patients with carcinoid heart disease compared to carcinoid patients without cardiac involvement. This implies that serotonin contributes to the development of cardiac involvement.^{11,12} Hepatic metastases allow large quantities of tumor products such as serotonin to reach the right heart without being inactivated.^{13,14} Rarely, patients with a primary ovarian carcinoid may develop carcinoid heart disease in the absence of hepatic metastases. This occurs as a result of the direct venous drainage of the ovary into the inferior vena cava.¹⁵

The preferential right-sided valve involvement in carcinoid heart disease is likely related to inactivation of the humoral substances by the lung. Left-sided valvular pathology occurs in 10%-15% of carcinoid patients with cardiac involvement^{16,17} and is most commonly found among patients with an intracardiac shunt, which allows the serotonin-rich blood to enter the left heart chambers without passing through the lungs initially. Left-sided valve disease in carcinoid syndrome may also occur in the presence of a primary bronchial carcinoid and, less commonly, in patients with severe, poorly controlled carcinoid syndrome with associated high levels of circulating serotonin. Left-sided carcinoid valve disease is characterized by valve regurgitation rather than valve stenosis.

Clinical Features of Carcinoid Heart Disease

The clinical features of carcinoid heart disease are often subtle early in the disease course. Severe tricuspid and pulmonary valve disease may be well tolerated for many months. Early symptoms of right-sided valvular heart disease include fatigue and dyspnea on exertion. These symptoms may initially be attributed to the primary carcinoid disease. Right-sided heart failure with worsening dyspnea, edema, ascites, and eventual cardiac cachexia occur with progressive cardiac disease. Carcinoid heart disease with advanced symptoms (New York Heart Association [NYHA] class III or IV) portends a poor prognosis. Without treatment, the median duration of survival with malignant carcinoid syndrome is 38 months from the onset of systemic symptoms. Clinical evidence of carcinoid heart disease with NYHA class III or IV symptoms is associated with a median survival duration of only 11 months.¹⁸ Rarely, patients may present with symptomatic left-sided valvular lesions, restrictive cardiomyopathy,¹⁹ pericardial effusion,²⁰ or cyanosis.²¹

The physical findings among patients with carcinoid heart disease may be subtle early in the course of the disease. The murmurs of tricuspid and pulmonary valve disease may be difficult to detect due to the low pressure in the pulmonary circulation. Elevation of the jugular venous pressure with a prominent V wave is often the earliest finding on physical examination. Peripheral edema, ascites, and pul-

satile hepatomegaly occur as the valve disease progresses. Cardiac findings include a palpable right ventricular impulse and murmurs of tricuspid and pulmonary valve regurgitation. Less frequently, a systolic murmur of pulmonary stenosis and a diastolic murmur of tricuspid stenosis may be audible. Right-sided cardiac murmurs are accentuated by inspiration.

The electrocardiogram in advanced carcinoid heart disease demonstrates low-voltage QRS complex. The cause of the low voltage is not clear but may be related to decreased conduction of the electrical signal to the body surface. The chest radiograph demonstrates cardiomegaly with prominence of the right-sided cardiac chambers in the setting of advanced cardiac valve disease. Pleural effusions and metastatic pleural plaque formation occur late in the course of the disease.

Echocardiographic Features of Carcinoid Heart Disease

Thickening and retraction of immobile tricuspid valve leaflets with associated severe tricuspid valve regurgitation are characteristic echocardiographic features of advanced carcinoid heart disease (Fig 2). Tricuspid valve stenosis is noted less often. Pulmonary valve involvement usually coexists when tricuspid valve disease is noted. Characteristic pulmonary valve involvement includes immobility of the pulmonary valve leaflets (Fig 3). The pulmonary valve leaflets

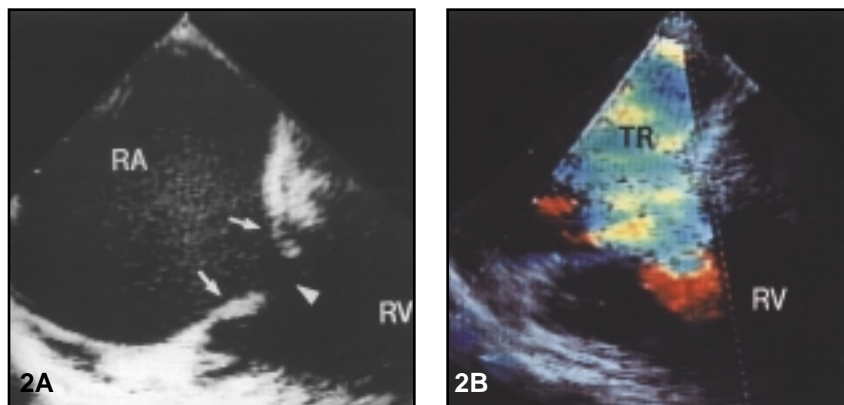


Fig 2. — Transesophageal echocardiographic right ventricular inflow view in the transverse plane demonstrating advanced carcinoid tricuspid valve disease. (A) The septal and anterior tricuspid leaflets (arrows) are severely thickened and retracted and are fixed in a semiopen position, resulting in marked deficiency of central systolic coaptation (arrowhead). (B) Color-flow Doppler imaging demonstrates severe central tricuspid valve regurgitation passing through the fixed open tricuspid orifice. RA indicates right atrium; RV, right ventricle; and TR, tricuspid regurgitation. From Olson LJ, Freeman W, Enriquez-Sarano M, et al. Transesophageal echocardiographic evaluation of native valvular heart disease. In: Freeman WK, Seward JB, Khandheria BK, et al, eds. *Transesophageal Echocardiography*. Boston, Mass: Little, Brown; 1994:231. Reprinted with permission. <http://lww.com>

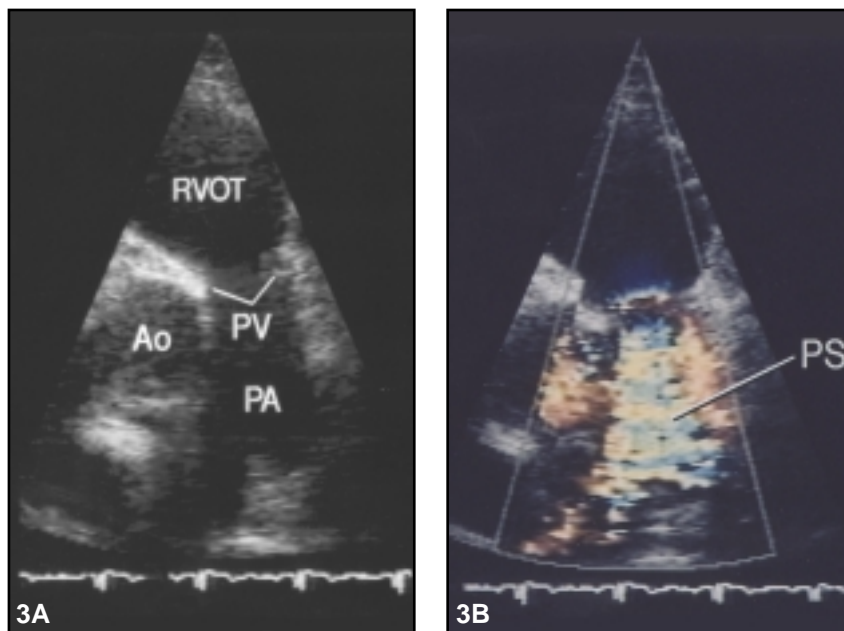


Fig 3. — A: Transthoracic echocardiogram demonstrating carcinoid involvement of the pulmonary valve. The pulmonary valve is difficult to visualize which is characteristic of carcinoid pulmonary valve involvement. The pulmonary annulus is narrowed. B: Color-flow examination demonstrating a jet of pulmonary stenosis. From Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. *Circulation*. 1993;87:1188-1196. Reprinted with permission. <http://lww.com>

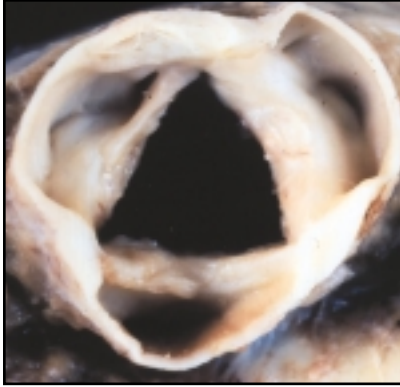


Fig 4. — Gross pathologic specimen of the pulmonary valve in a patient with carcinoid heart disease. The pulmonic valve leaflets are thickened, retracted, and shortened, with a fixed opening.

may be difficult to visualize by echocardiography due to leaflet retraction. Pulmonary annular constriction may also occur, resulting in predominant pulmonary outflow tract obstruction.

Long-standing tricuspid and pulmonary valve disease results in progressive right ventricular volume overload and right ventricular diastolic pressure elevation.¹⁶ Less frequent echocardiographic findings among patients with carcinoid heart disease include left-sided valvular pathology occurring in 10%-15%¹⁷ and myocardial metastases in less than 5%.²² Pericardial effusions are commonly noted by echocardiography; however, these are rarely hemodynamically significant.

Pathology of Carcinoid Valve Disease

The affected cardiac valves in carcinoid heart disease have a white appearance with thick

leaflets and chordal structures (Fig 4). Microscopic evaluation demonstrates deposits of fibrous tissue. The carcinoid plaque is composed of smooth muscle cells, myofibroblasts, and an overlying endothelial cell layer. Smooth muscle cells and myofibroblasts are surrounded by an extracellular matrix composed of microfibrils, acid mucopolysaccharides, basement membrane, and collagen fibers (Fig 5). The morphology of the valve leaflet is not disrupted, and the carcinoid plaque generally affects the ventricular aspect of the tricuspid valve leaflets and the arterial aspect of the pulmonic valve cusps.²³

Management of Carcinoid Heart Disease

Limited medical therapeutic options are available for patients

with symptomatic right heart failure related to carcinoid heart disease. Diuretic therapy temporarily improves symptoms of edema but may result in further reduction in left-sided cardiac output, which in turn may worsen the symptoms of fatigue and dyspnea.

Cardiac surgery is the only effective treatment for carcinoid heart disease and should be considered for symptomatic patients whose metastatic carcinoid disease and symptoms of carcinoid syndrome are well controlled. The timing of cardiac operation for carcinoid heart disease remains difficult. No definitive guidelines can be established from the published series to date. Current practice at our institute includes annual screening of carcinoid patients with echocardiography to identify carcinoid heart disease. When car-

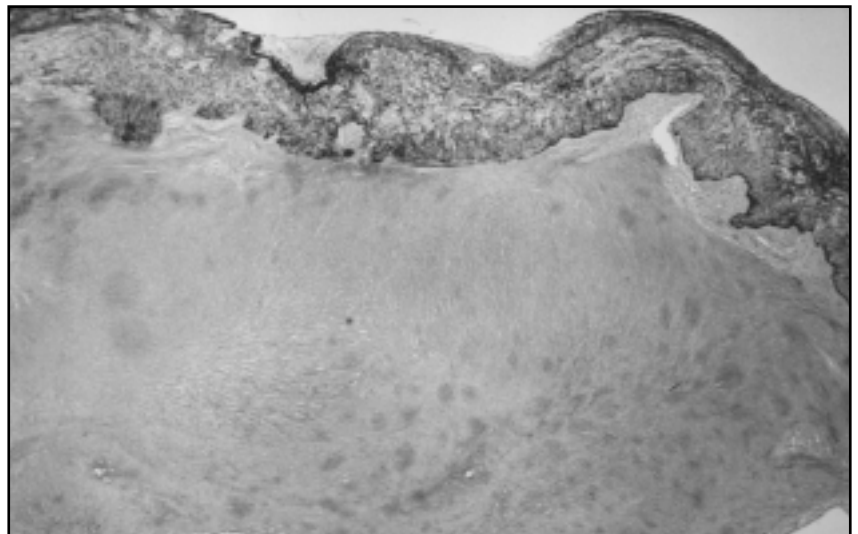


Fig 5. — Photomicrograph of carcinoid involvement of the tricuspid valve. Carcinoid plaque is adherent to valvular endocardium but does not produce destruction of the adjacent leaflet tissue (elastic Van Gieson, $\times 36$). From Hauck AJ, Freeman DP, Ackermann DM, et al. Surgical pathology of the tricuspid valve: a study of 363 cases spanning 25 years. *Mayo Clin Proc.* 1988;63:851-863. Reprinted with permission.

cinoid heart disease is established by echocardiography, clinical cardiovascular assessment and functional evaluation by exercise testing are recommended to provide objective assessment of the functional status. This information helps to identify the most appropriate timing of cardiac surgery. At our institute, patients with carcinoid heart disease are referred for cardiac operation when they develop symptoms of right heart failure, right ventricular dysfunction or, rarely, in anticipation of hepatic surgery, as long as the metastatic carcinoid disease and syndrome are controlled. Patients with severe, unoperated carcinoid cardiac disease are not candidates for hepatic surgery due to the risk of hepatic hemorrhage at the time of surgery as a result of high right atrial pressure.

At our institution, patients with carcinoid heart disease who remain asymptomatic or minimally symptomatic are followed clinically on a biannual basis. Cardiovascular follow-up includes clinical examination, echocardiography, and selective exercise testing. Patients are referred for cardiac surgery when they meet the criteria outlined above.

Cardiac surgery has been successful in reducing or relieving the cardiac symptoms of many patients with carcinoid heart disease. However, review of a small surgical series from our institution suggests a high surgical mortality and incomplete symptom resolution among surgical survivors.¹⁸ In this early series, cardiac surgery

was performed primarily on patients with advanced right heart failure manifest by edema and ascites. Despite the high surgical mortality, the survival among surgically treated patients was better than the survival among patients with similar symptoms related to carcinoid heart disease who were treated medically (Fig 6). Subsequent data suggest that early and regular cardiac evaluation of patients with metastatic carcinoid syndrome and cardiac surgical intervention prior to the development of advanced right heart failure may result in a reduction in surgical mortality, currently less than 10%.²⁴ Marked symptomatic improvement was noted in most patients after valve surgery. This is dramatically different than the survival of patients with symptomatic carcinoid heart disease managed medically.¹⁸

Choice of Valve Prosthesis

Surgical reports have largely recommended tricuspid valve replacement with a mechanical prosthesis for patients with carcinoid heart disease. This recommendation was based on the assumed damage to the bioprosthetic valve from vasoactive tumor substances, but this has not been well established.²⁵⁻²⁷ In addition, this recommendation was largely made before the introduction of synthetic somatostatin and hepatic artery interruption by embolization or ligation, both of which may potentially protect prosthetic valve tissue from the adverse effects of serotonin and other vasoactive peptides by decreasing the carcinoid activity.

The choice of valve prosthesis requires meticulous discussion

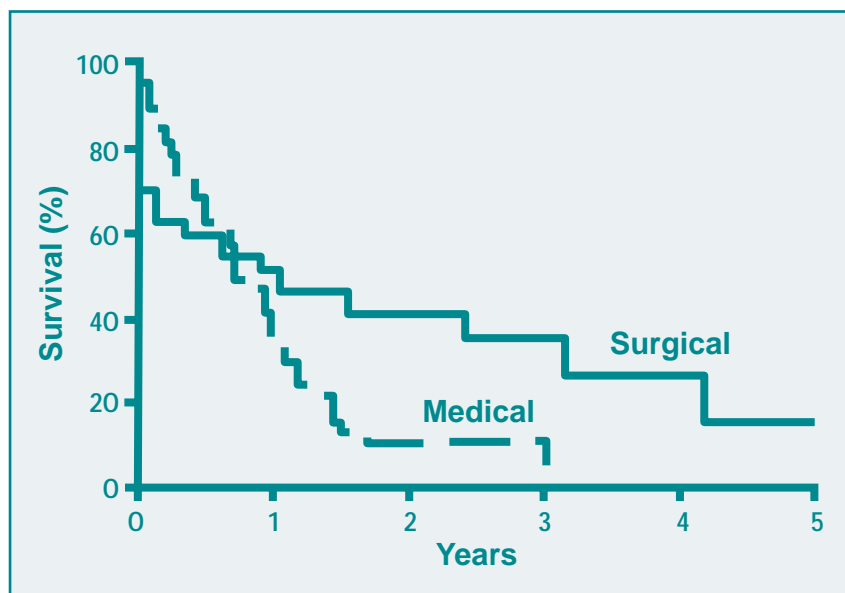


Fig 6. — Medical versus surgical survival among 40 medically and 26 surgically treated patients with class III or IV symptoms related to carcinoid heart disease. Reprinted with permission from the American College of Cardiology (*J Am Coll Cardiol.* 1995;25:410-416).

and individual selection in carcinoid patients. Premature bioprosthesis degeneration may occur among carcinoid patients.^{25,28,29} This premature degeneration may be related to damage of the bioprosthesis by the carcinoid process. The risk of bioprosthetic valve degeneration may be offset by aggressive carcinoid tumor intervention and somatostatin therapy.¹⁸ Mechanical prostheses are not ideal for patients with carcinoid heart disease as subsequent surgical procedures for tumor control are often required and are complicated by anticoagulation management. In addition, the risk of mechanical tricuspid prosthesis thrombosis is approximately 4% per year.³⁰ The most appropriate management is to individualize prosthesis selection.

Anesthetic Management

Preoperative control of carcinoid activity by administration of octreotide analogue helps the perioperative hemodynamic management of carcinoid patients undergoing surgical procedures. Meticulous anesthetic care is required during cardiac surgery in the management of patients with carcinoid heart disease to prevent a life-threatening carcinoid crisis or to institute early therapy should a crisis occur intraoperatively. Large doses of somatostatin are often required in the perioperative and postoperative periods.³¹ The complexity of intraoperative management has been moderated and the hemodynamic and fluid management have been simplified due to the routine use of somatostatin.

Conclusions

Carcinoid heart disease is an uncommon and complex form of valvular heart disease. New treatment modalities for patients with metastatic carcinoid syndrome have resulted in improvement in symptoms and survival. Cardiac involvement is common and leads to increased morbidity and mortality. In carcinoid patients with controlled systemic symptoms but severe cardiac symptoms, cardiac valve replacement surgery may reduce the short-term mortality rate and alleviate otherwise intractable symptoms. An experienced medical, surgical, and anesthetic team approach to the patient with carcinoid heart disease is critical to provide state-of-the-art management for these patients with complex cardiovascular disease.

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