Carcinoid Heart Disease

Sanjeev Bhattacharyya, MB, ChB, MRCP; Joseph Davar, MD, PhD; Gilles Dreyfus, MD, FRCS; Martyn E. Caplin, BSc (Hons), DM, FRCP

Carcinoid tumors are relatively rare neuroendocrine malignancies most commonly originating from enterochromaffin cells in the gastrointestinal tract. The incidence is ~1 in 100,000 of the general population. They usually grow slowly over years, commonly causing no symptoms at all until they become large or have metastasized. Carcinoid tumors of midgut origin may secrete large amounts of vasoactive substances, including 5-hydroxytryptamine (5-HT), tachykinins, and prostaglandins. These are largely inactivated by the liver. Carcinoid syndrome occurs when tumor cells metastasize to the liver as the vasoactive substances produced are able to reach the systemic circulation via the hepatic vein. Clinically, this is characterized by flushing, diarrhea, and bronchospasm.

Over the past decade, several new therapies for carcinoid tumors have emerged to reduce symptoms and cause tumor regression. Most notably, the development of somatostatin analogs, which inhibit the release of various biogenic amines and peptides, including serotonin, has resulted in a marked regression. Most notably, the development of somatostatin analogs and other antitumor therapies designed to reduce the tumor load and the production of tumor secretory products. Exceptionally, CHD may present in carcinoid tumors without liver metastases or in primary ovarian carcinoid tumors in which 5-HT is thought to reach the systemic circulation directly, bypassing portal circulation and the liver.

Presentations

Up to 20% of patients with carcinoid syndrome present with CHD at diagnosis. CHD is remarkably well tolerated initially. Patients may be in functional New York Heart Association class I despite severe right-sided valve lesions. Eventually, the signs and symptoms of right heart failure, including shortness of breath on exertion, ankle edema, and fatigue, develop as CHD progresses. Case reports have demonstrated presentations resulting from pericardial effusions, restrictive cardiomyopathy, constrictive pericarditis, and patent foramen ovale presenting with cyanosis and hypoxia secondary to a combination of right heart disease and interatrial shunts.

Clinical Examination

Initially, clinical examination reveals prominent CV waves of tricuspid regurgitation; a right ventricular heave can be palpated; and auscultation reveals the pansystolic murmur of tricuspid regurgitation, early diastolic murmur of pulmonary regurgitation, and systolic murmur of pulmonary stenosis at the left sternal edge. Murmurs may be difficult to detect because velocities in the right heart are low. Peripheral edema, ascites, and pulsatile hepatomegaly develop as the disease progresses.

Biochemical Markers and Pathogenesis of CHD

The pathogenesis of CHD and the development of carcinoid plaques remain incompletely understood, although a growing body of evidence points toward serotonin (5-HT) playing a key role.

Evidence for 5-HT–induced valvulopathy has arisen from a variety of sources. The appetite suppressants fenfluramine and phentermine have been withdrawn from the market because of the development of valve pathology with changes similar to those seen in carcinoid patients. These drugs display a serotonergic action on human tissue.
Carcinoid heart valves demonstrate accumulation of tissue growth factor-β latency--associated peptide and latent binding protein.\textsuperscript{15} 5-HT has been shown to increase synthesis and upregulate tissue growth factor-β, as well as stimulating collagen synthesis by heart valve interstitial cells.\textsuperscript{16} These findings may contribute to the pathophysiology of carcinoid heart valve involvement because 5-HT receptors are present in human heart valves.

In animal models, both long-term 5-HT administration and the deficiency of 5-hydroxyindoleacetic acid (5-HIAA) transporter gene can induce morphological and echocardiographic changes consistent with cardiac fibrosis and valvulopathy similar to those seen in human CHD.\textsuperscript{17,18}

5-HT is metabolized to urinary 5-HIAA by monoamine oxidases in the liver. Mean 5-HIAA level has a high sensitivity (100%) but a very low specificity for the development of CHD. Therefore, it has been postulated that although 5-HT is important, other factors combined with serotonin must be required for the development of CHD.\textsuperscript{19} The tachykinins neuropeptide K and substance P have been shown to be elevated in CHD and may be an important part of the pathogenesis of CHD.\textsuperscript{6} Peak 5-HIAA is a significant predictor of the progression of CHD.\textsuperscript{20}

N-terminal brain natriuretic peptides are released by the atria and ventricles of the heart in response to wall stress.\textsuperscript{21} Brain natriuretic peptide is released in a variety of valvular lesions and ventricular dysfunction. Significantly greater median levels of N-terminal brain natriuretic peptides are found in patients with CHD than in those without CHD. A high sensitivity may allow accurate differentiation between those with and without CHD and its use as a possible screening test for CHD.\textsuperscript{7}

**Morphological and Histological Features of CHD**

The carcinoid plaque, composed of smooth muscle cells, myofibroblasts, and elastic tissue, forms a white fibrous layer lining the endocardial surface of cardiac valves superficial to normal valve tissue. Native, underlying valve morphology is unharmed.\textsuperscript{22} Plaques develop on the endocardium of the right ventricle and atrium, the valve leaflets, and the subvalvular apparatus, including chordae and papillary muscle. Deposition of plaques has been found in the vena cava, pulmonary artery, coronary sinus, and coronary arteries.\textsuperscript{23} The tricuspid valve plaques have a preponderance to develop on the ventricular side of the leaflets, causing adherence to mural endocardium and creating a substrate for regurgitation of blood volume. Fibrous tissue at the valve annulus causes constriction at the ring, resulting in a degree of valvular stenosis. For the pulmonary valve, the predominant lesion is stenosis because plaques develop at the pulmonic root, causing constriction of the root and diminishing an already small orifice.\textsuperscript{24}

**Investigations**

**ECG and Chest X-Ray**

The ECG and chest x-ray may provide clues to the diagnosis of CHD. The cardiothoracic ratio may be enlarged. The ECG in patients with CHD has a higher frequency of low-voltage QRS complexes in CHD patients than those without; however, they are not sensitive.\textsuperscript{5,24}

**Cardiac Imaging in CHD**

**Echocardiography**

The echocardiographic features of CHD are well described.\textsuperscript{3,25} Appearances are pathognomonic in the absence of exposure to the appetite suppressants fenfluramine and phentermine, ergot-derived dopamine agonists, and ergot alkaloid agents such as methysergide and ergotamine.\textsuperscript{13,26}

Multiple views of each valve should be obtained for optimal evaluation of right-sided heart valves. The tricuspid valve is visualized in the parasternal long-axis view of the right ventricular inflow tract, parasternal short-axis view, apical 4-chamber view, and subcostal long-axis view. The pulmonary valve is visualized in the parasternal long-axis view of the right ventricular outflow tract, parasternal short-axis view, and subcostal short-axis view.\textsuperscript{27}

Classically, both tricuspid and pulmonary valve leaflets and their corresponding subvalvular apparatus are thickened. Excursion of the leaflets is reduced. Eventually, valve leaflets become retracted, fixed, and noncoapting, leading to the valve remaining in a semiopen position. Functionally, a combination of valvular regurgitation and stenosis occurs (Figures 1 and 2). A “dagger-shaped” continuous-wave Doppler profile, resulting from severe tricuspid regurgitation that causes early peak pressure and rapid decline and representing equalization of right atrial and ventricular pressures, is seen in severe disease. The tricuspid valve, with or without pulmonary valve involvement, is involved in most cases of CHD. Indeed, it is the combination of these that creates the most hemodynamic disturbance. Pulmonary stenosis is thought to worsen the severity of tricuspid regurgitation; conversely, the severity of pulmonary stenosis may be underestimated because of low cardiac output and severe tricuspid regurgitation.

The right atrium and ventricle are typically enlarged. As the ventricle becomes volume overloaded, paradoxical motion of the interventricular septum occurs. Right ventricular function seemingly remains intact until quite late in the disease course. The increasing elevation in right ventricular pressure and increasing size of the right atrium may lead to reopening of patent foramen ovale in severe CHD.\textsuperscript{28}

Left-sided lesions occur in up to 15% of all cases.\textsuperscript{5,29} Involvement is characterized by diffuse thickening of valve leaflets and is usually less severe than right-sided valvular lesions (Figure 3). Serotonin is thought to be inactivated as it passes through lung parenchyma.\textsuperscript{30} Involvement of left-sided valves is thought to be due to the presence of a patent foramen ovale with a right-to-left shunt, bronchial carcinoid, or high levels of circulating vasoactive substances. Small pericardial effusions are present in up to 10% of cases. Myocardial metastases are rare.\textsuperscript{31} When transthoracic echocardiography cannot adequately visualize structures, transesophageal echocardiography should be undertaken.\textsuperscript{32}

**Cardiac Magnetic Resonance Imaging/64-Slice Computed Tomography**

Cardiac magnetic resonance imaging has been shown to provide clear anatomic and functional information on both
the pulmonary and tricuspid valve in CHD. This can be of use, particularly in evaluating the pulmonary valve when it is difficult to visualize by echocardiography and when limited ultrasound acoustic windows provide sparse echocardiographic data or in providing accurate data of right ventricular function.33,34 Recently, 64-slice coronary angiography has demonstrated similar anatomic information.34

Management
Without intervention, CHD patients may develop progressively worsening symptomatic right heart failure. Life expectancy is significantly reduced. The Mayo Clinic showed a mean life expectancy of 1.6 years for those with cardiac disease compared with 4.6 years for those without cardiac disease in patients with metastatic midgut carcinoid tumors.5 Recent improvements in medical and surgical therapy over the past decade may have improved the prognosis.

Medical
Treatment of carcinoid disease rarely achieves cure. However, with modern antitumor therapy, its progression can be substantially slowed. Many patients survive for many years.


Figure 2. Carcinoid involvement of tricuspid valve (TV). A, Right ventricular inflow view. Fixed, retracted, and thickening of tricuspid valve leaflets and associated chordae. B, Continuous-wave Doppler showing dagger-shaped profile of tricuspid regurgitation (TR). C, Apical 4-chamber view showing dilated right ventricle with tricuspid valve leaflets failing to coapt resulting in constant semiopen position. D, Color Doppler demonstrating severe tricuspid regurgitation into a dilated right atrium.
after resection of a primary carcinoid tumor or palliative treatment of metastatic disease. Therefore, cardiac intervention should be considered in CHD to offer symptomatic palliation.

Medical management consists of relieving symptoms of right heart failure with a combination of loop and thiazide diuretic therapy. The use of digoxin may play a role, but no convincing data for the right ventricle are available. Intuitively, optimizing somatostatin analog therapy should reduce circulating vasoactive substances and carcinoid syndrome and therefore may stabilize CHD.

In patients not suitable for cardiac valve surgery, the use of balloon valvuloplasty has been reported. Identification of suitable patients, with predominantly stenotic valvular lesions, will be problematic in that most patients with CHD also have significant valvular regurgitation. Success of the procedure has been very limited. Although a couple reports have shown some functional and hemodynamic benefit, others have noted either a lack of symptomatic benefit or a rapid relapse of symptoms and valvular stenosis when initial benefit did occur.

Surgical
Cardiac surgery offers definitive therapy for symptoms. Marked symptomatic improvement, of >1 New York Heart Association class, occurs after valve replacement. There also may be survival benefit with cardiac surgery, although this is difficult to prove, given the other morbidities of this patient group. Median survival of 6 years with the greatest at 11 years after cardiac valve replacement compares very favorably with medically treated patients. Several series report high perioperative mortality, although the operative risk has declined from >20% in the 1980s to <10% more recently. The main perioperative complications are bleeding and right ventricular failure. Despite some patients having relatively mild pulmonary valve disease, pulmonary valve replacement in addition to tricuspid valve replacement has been shown to reduce right ventricular size after surgery compared with patients with isolated tricuspid valve replacement. Right ventricular dysfunction may not recover postoperatively. The optimal timing of surgery in relation to the severity of valve dysfunction and symptoms has not been identified. However, on the basis of these data, cardiac surgery at the onset of either symptoms or right ventricular dysfunction with pulmonary valve replacement in addition to replacement of the tricuspid valve may be considered prudent.

More controversial is the choice of valve prosthesis. No large series have compared the choice of valve prosthesis. Initial reports favored the use of mechanical prosthesis on the basis of the assumption of damage to a bioprosthetic valve with vasoactive substances. There have been several case reports of bioprosthetic valve degeneration. Carcinoid plaques have caused pulmonary valve allograft failure as early as 3 months after implantation and tricuspid biological graft dysfunction after as little as 4 years. However, the advent of somatostatin analogs and other antitumor therapies may theoretically protect the valve from deposition of further carcinoid plaques. Tissue valves have the advantage of not requiring anticoagulation and consequently lower the risk of bleeding in patients with hepatic dysfunction, reduce the risk of valve thrombosis (mechanical valve thrombosis is 4% per year), and allow further procedures such as hepatic dearterialization to proceed at a later date. Therefore, choice of prosthesis should be tailored to individual patient risk of bleeding, life expectancy, and future interventions.

There have been several reports of patients presenting with dyspnea, hypoxia, and cyanosis. Interatrial shunts via patent foramen ovale associated with valvular disease were described. Surgical closure of patent foramen ovale and percutaneous transcatheter closure devices in patients at high surgical risk have produced dramatic relief of symptoms. Elevated right atrial pressure secondary to valvular disease may have contributed to stretching of the foramen ovale and development of a right-to-left shunt.

Perioperative Anesthetic Management
Carcinoid crises characterized by hypotension, bronchospasm, and flushing can be precipitated by surgery and by drugs that release catecholamine and histamines. During the perioperative period, it can be difficult to differentiate between carcinoid crisis and hypotension secondary to myocardial dysfunction. Perioperative octreotide, aimed at reducing serotonin release, is the most efficacious treatment for preventing crises during surgery and is the mainstay treatment of carcinoid crisis. Intravenous octreotide (50 to 100 μg/h) should be started at least 2 hours before surgery. The infusion should continue for 48 hours after surgery. Patients may then require subcutaneous octreotide, depending on previous somatostatin analog requirements and current control of carcinoid syndrome. Avoiding or minimizing the use of drugs

known to precipitate mediator release such as opioids, the neuromuscular relaxant atracurium, and catecholamine producers like dopamine and epinephrine may reduce the risk of carcinoid crisis.48,49

Conclusions
Although carcinoid tumors are rare malignancies, cardiac involvement is relatively common. Despite severe disease, patients may possess relatively few signs or symptoms in the early stages. Echocardiography is the investigation of choice, revealing a unique valvular appearance. Gradual decline in right ventricular function and increasing severity of valvular disease lead to right heart failure and a poor outlook if treated medically. In view of the increasing longevity of patients with carcinoid tumors as a result of better control of carcinoid symptoms and treatment of metastatic disease, patients should be considered for surgical therapy to relieve cardiac symptoms. A multidisciplinary team experienced in dealing with these complex patients is required to provide informed decisions on optimal patient management.

Disclosures
None.

References


**KEY WORDS:** carcinoid heart disease / heart diseases / valves
Carcinoid Heart Disease
Sanjeev Bhattacharyya, Joseph Davar, Gilles Dreyfus and Martyn E. Caplin

Circulation. 2007;116:2860-2865
doi: 10.1161/CIRCULATIONAHA.107.701367
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/116/24/2860

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/