Carcinoid Heart Disease: Review of Current Knowledge

Carcinoid heart disease is the collective term for all cardiac manifestations in patients who have carcinoid syndrome. Carcinoid heart disease has a multifactorial pathophysiology, and the right side of the heart is usually involved. Symptoms and signs vary depending upon the affected cardiac components; most typical is right-sided heart failure secondary to diseased tricuspid and pulmonary valves. Despite no single ideal diagnostic test, strong suspicion, coupled with serologic and imaging results, usually enables diagnosis. Advances in imaging, such as speckle-tracking echocardiography and cardiac magnetic resonance, have improved the diagnostic yield. Treatment is challenging, warrants a multidisciplinary approach, and can be medical or surgical depending on the cardiac manifestations. Investigators are exploring the therapeutic use of monoclonal antibodies and new somatostatin analogues. In this review, we cover current knowledge about the pathophysiology, diagnosis, and treatment of carcinoid heart disease. (Tex Heart Inst J 2019;46(1):21-7)

Carcinoid tumors are neuroendocrine neoplasms that typically arise from the gastrointestinal tract and bronchopulmonary system. Approximately 2 in 100,000 people are affected annually. Carcinoid tumors, which are typically indolent, secrete myriad vasoactive substances, serotonin chief among them. Patients are often asymptomatic until these tumors metastasize to the liver, which cannot then inactivate the vasoactive substances. Rarely, ovarian and retroperitoneal metastasis occurs when the vasoactive substances bypass the liver and enter the systemic circulation through the caval system, a process that causes the classic symptoms of flushing and diarrhea.

Carcinoid tumors involve the heart in up to 60% of patients. Cardiac involvement is associated with a poor long-term prognosis: the estimated 3-year survival rate of 31% is half that of patients without cardiac involvement.

In this review, we discuss current knowledge about cardiac carcinoid tumors.

Pathophysiology

Carcinoid heart disease (HD) occurs when large amounts of vasoactive substances such as serotonin, tachykinins, and prostaglandins reach the right side of the heart, consequent to reduced hepatic metabolism from extensive metastatic liver involvement of the carcinoid tumor. Generally, the left side of the heart is spared because the lungs metabolize the vasoactive substances; the rare exceptions are associated with patent foramen ovale and primary bronchopulmonary carcinoid disease.

In cardiac involvement, the carcinoid tumor releases the vasoactive substances, as well as transforming growth factor-β. After the initial endocardial injury, plaque is deposited at the endocardial surfaces of the right-sided heart valves, papillary muscles, and chordae tendineae. The plaque, composed of fibroblasts, smooth muscle cells, and extracellular matrix, is usually found downstream, at the ventricular aspect of the tricuspid valve (TV) and the pulmonary arterial side of the pulmonic valve (PV). Fibrosis may be induced by serotonin, evidenced by high levels of serotonin metabolites found in the urine of patients with carcinoid heart involvement, in addition to serotonin receptors in their cardiac valves. Moreover, serotonergic drugs and fenfluramine (a weight-loss medication that targets serotonin receptors) have caused valvular changes similar to those associated with carcinoid HD. Conversely, some patients seemingly do not benefit from lower serotonin levels and experience progressive carcinoid HD. This observation suggests the important role that other vasoactive chemical mediators play in the disease progression.
Manifestations
The presentation of cardiac carcinoid HD (also called Hedinger syndrome) is usually insidious and subtle. Most patients are initially asymptomatic, and clinical features appear along with right-sided heart involvement (Fig. 1).

Valvular Heart Disease. In carcinoid HD, valvular involvement—specifically isolated TV regurgitation—is seen most often. In one series, all patients with carcinoid HD had TV regurgitation on echocardiograms; the valve leaflets were thickened, shortened, and retracted, with incomplete coaptation. In most patients, the leaflets were also fixed in a half-open position, which led to TV stenosis. Up to 80% of patients have had PV regurgitation or stenosis. These structural and valvular lesions eventually lead to right-sided heart failure with symptoms such as lower-extremity edema and early satiety. New York Heart Association functional class III/IV symptoms and right ventricular (RV) dysfunction were important predictors of outcome in these patients.

Coronary Artery Involvement. Coronary artery vasospasm is also associated with carcinoid HD, usually in patients who have nonocclusive coronary artery disease. Depending on endothelial conditions, serotonin can stimulate vasodilatory or constrictive responses. Serotonin can cause vasoconstriction in diseased endothelium (such as in patients with atherosclerotic disease) because of the predominance of vasoconstriction-provoking 5-hydroxytryptamine_2 (5-HT_2) receptors and the loss of 5-HT_1 receptors that mediate vasodilation. This response explains the finding of carcinoid-induced coronary vasospasm in patients who have nonocclusive coronary disease.

In addition, serotonin sometimes reaches the coronary circulation by means of shunting through a patent foramen ovale; as a known platelet activator, it might also contribute to stent thrombosis. Possible coronary vasospasm should be considered when patients present with acute coronary syndrome and a history of carcinoid disease. Therapeutic decisions include whether to use vasodilators such as calcium channel blockers, serotonin antagonists, or somatostatin analogues.

Arrhythmias. Arrhythmias have rarely been reported in the presence of carcinoid HD. In a patient without ischemic HD, carcinoid-induced ventricular tachycardia was controlled with the use of metoprolol; 2 other cases involved associated atrial arrhythmias. In canine studies, serotonin was implicated in paroxysmal ventricular tachycardias and atrial arrhythmias. The underlying mechanism is thought to be increased sympathetic discharge induced by a vasoactive substance, leading to cardiac excitation and tachyarrhythmias.

Direct Myocardial Involvement. A fourth manifestation of carcinoid HD is tumor metastasis directly to the cardiac muscle. In one series (incidence of metastasis, 3.8%), most of the tumors were on either ventricle (including the ventricular septum), and all were circumscribed, homogeneous, and noninfiltrative on echocardiograms. Lesions smaller than 1 cm are usually not detectable on echocardiograms, and positron-emission tomography/computed tomography (PET/CT) may prove more useful. Of note, the presence of carcinoid metastasis did not correlate with the usual echocardiographic findings of carcinoid HD, such as right-sided valvular involvement; however, metastasis to the heart did correlate with higher tumor burden. This finding suggests different pathophysiologic mechanisms related to different manifestations of a single disease. Cardiac carcinoid metastasis can be asymptomatic, such as when it presents as a solitary atrial mass, or it can cause ventricular outflow tract obstruction. These tumors are usually well-circumscribed and noninvasive, so excision may be beneficial.

Prognostic Factors
Some prognostic factors for carcinoid HD have been studied. Increases in carcinoid-related symptoms may indicate disease progression in affected patients; however, the disease in asymptomatic patients appears to remain stable. Radiographic progression does not seem to correlate with disease progression. On the other hand, biochemical markers—specifically increased urinary and serum levels of 5-hydroxyindoleacetic acid (5-HIAA), a product of serotonin metabolism—correlate well with progression. This last finding has substantial implications for therapeutic approaches.

Diagnosis
The diagnosis of carcinoid HD depends upon strong clinical suspicion, biomarker levels, cardiac imaging results, and possibly the use of cardiac nuclear medicine.
**Electrocardiography.** Electrocardiograms provide little diagnostic support. Sinus tachycardia and nonspecific ST-T abnormalities may be seen. In advanced disease, low-voltage QRS complexes have been detected.10,51

**Biomarker Levels.** In the presence of carcinoid syndrome, increased urinary 5-HIAA levels and chromogranin A are useful in evaluating cardiac involvement and disease progression.52,53 An even stronger biomarker, N-terminal pro-brain-type natriuretic peptide (NT-proBNP), has both diagnostic and prognostic significance.52

The cardiac hormone NT-proBNP is released by the atria and ventricles in response to stretching from volume or pressure overload. Levels of NT-proBNP can be elevated for various reasons; however, in one series of patients, NT-proBNP had a sensitivity of 92% and a specificity of 91% for carcinoid HD.52 Therefore, it is a good screening test for heart involvement. Furthermore, higher NT-proBNP levels correlate strongly with worsening symptoms and poor survival prospects.53,54

When a carcinoid tumor metabolizes tryptophan, the resulting serotonin then breaks down into 5-HIAA, which is entirely excreted in the urine. Patients with cardiac carcinoid involvement have elevated levels of serum and urinary 5-HIAA.22 This acid is also correlated with disease progression, but less strongly than is NT-proBNP.49

Chromogranin A, another marker released by neuroendocrine tumors, screens poorly for those tumors in general (sensitivity, 60%–90%; specificity, 10%–35%) and is better used during follow-up evaluation for recurrent malignancy.55,56 It has a sensitivity approaching 100% but only 30% specificity for carcinoid HD.53,57 Taken together, chromogranin A and NT-proBNP levels correlate well with carcinoid HD progression and overall mortality rates.53

New and potentially superior techniques for measuring biomarkers are emerging. A polymerase chain reaction-based 51-marker peripheral blood test had good sensitivity (85%–98%) and specificity (93%–97%) in diagnosing carcinoid tumors.54 Results of further studies will indicate whether the diagnostic value of these tests justifies their financial cost.

**Imaging.** Currently available imaging methods can be used in the diagnosis of carcinoid HD.

Chest radiographs in patients with carcinoid HD usually show normal findings but may also reveal nonspecific right-sided heart enlargement, pulmonary nodules, or pleural effusions.10

Given the facility of 2-dimensional (2D) transthoracic echocardiography (TTE) to characterize RV, TV, and PV function,9 it is the chief diagnostic tool for carcinoid HD, and the North American Neuroendocrine Tumor Society recommends its use.48 The European Neuroendocrine Tumor Society (ENTS) recommends TTE screening for patients diagnosed with carcinoid syndrome, annually for patients with no cardiac involvement and semiannually for those with it.44 In addition, TTE can reveal intracardiac carcinoid metastases (present in approximately 4% of cases of carcinoid syndrome).43 Color-flow Doppler evaluation and agitated saline solution are routinely used to rule out intra-atrial communication, a finding that suggests left-sided cardiac carcinoid involvement.62

Initial TV and PV involvement can be minimal, presenting with mild leaflet thickening. At advanced stages, thick, retracted, immobile TV leaflets cause mild-to-moderate tricuspid regurgitation, and the chordae tendineae and papillary muscle can become thick and short.10,40 A thickened PV causes pulmonary regurgitation or, less frequently, pulmonary stenosis.10,40

Three-dimensional (3D) TTE usefully characterizes right-sided heart structure and function,40 including the pathologic valvular conditions in carcinoid HD, although more studies are warranted.40 Investigators of aortic valve carcinoid involvement (a rare condition) preferred 3D TTE over 2D TTE.44

Speckle-tracking TTE enables the use of ventricular strain to stratify risk in patients who have carcinoid HD.49 Reduced myocardial function, as measured by using speckle-tracking strain, is associated with more advanced disease stages and with death.46

Whereas 2D TTE is superior to multidetector cardiac CT in measuring hemodynamic status, the latter helps to characterize cardiac metastases, RV structure and dysfunction, and PV and TV compromise.57,58

Cardiac magnetic resonance enables functional, volumetric, and structural characterizations of the right-sided heart valves—specifically, PV involvement—that 2D TTE cannot readily reveal.59,60 Cardiac carcinoid metastases and structural infiltration appear clearly. The ENTS recommends using cardiac magnetic resonance to evaluate PV involvement, RV function, and metastasis in carcinoid HD.71 This imaging method is an excellent alternative when suboptimal TTE images are obtained or when quantifying regurgitant jets on 2D TTE is difficult.40,60

Cardiac carcinoid metastases can be revealed by PET/CT and radionuclide tracer. The tracer, a somatostatin analogue, binds the somatostatin receptors on the carcinoid tumor that is affecting the heart (of note, the tracer is not useful in the presence of nonmetastatic carcinoid HD). 18F-dihydroxyphenylalanine, gallium-68 octreotide, and indium-111 octreotide have been used as tracers.72,73 But new ones such as iobenguane I-123 might have better sensitivity and specificity for neuroendocrine tumors in general and necessitate less radiation.76

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**Disease Management**

The management of carcinoid HD necessitates multidisciplinary control of progressive heart failure, treat-
ment of systemic malignancy and neuroendocrine derangements, and surgical correction of right-sided valvular involvement. Of note for all practitioners, bacterial endocarditis prophylaxis is not indicated in patients who have carcinoid HD.

**Medical Therapy**

Tricuspid regurgitation and right-sided heart failure lead to progressive heart failure. Loop and thiazide diuretic agents should be carefully administered to control fluid status without risking volume depletion, which causes fatigue and low cardiac output.

The somatostatin analogues octreotide and lanreotide inhibit tumoral serotonin secretion and lower the resultant 5-HIAA levels, thus relieving symptoms of carcinoid syndrome. However, these medications neither reverse the progression of the carcinoid cardiac involvement nor improve survival prospects. Somatostatin analogues control carcinoid-syndrome crises that can lead to preoperative hemodynamic instability. To prevent the tumor from releasing vasoactive metabolites, patients should not be given drugs such as dopamine, opioids, or epinephrine before undergoing cardiac surgery. Antihistamines may be given preoperatively to prevent flushing and bronchospasm.

Telotristat etiprate, a peripheral 5-HT synthesis inhibitor, is approved in the United States for diarrhea treatment. Antihistamines may be given preoperatively to opioids, or epinephrine before undergoing cardiac surgery. Interferon-alpha may be given to patients who have carcinoid HD from progressing.

Another new somatostatin analogue, pasireotide, has helped symptomatic patients whose carcinoid syndrome is refractory to octreotide therapy. However, results of a phase-3 clinical trial showed no statistically significant difference between pasireotide and octreotide in symptom control upon 6-month follow-up evaluation.

Interferon-alpha may be given to patients who have uncontrolled carcinoid syndrome resistant to somatostatin; however, its side effects may cause patients to discontinue therapy.

Monoclonal antibody therapy and other chemotherapeutic agents have been studied in a phase-I clinical trial. Paclitaxel and trastuzumab in combination with interleukin-12 may be suitable therapy for human epidermal growth factor receptor 2/neu-expressing malignancies, including carcinoid tumors.

**Surgical Treatment**

Surgical correction of carcinoid valvular disease is the only definitive way to alleviate symptoms. Indications for valve replacement are symptomatic valvular disease and RV dysfunction. To correct tricuspid regurgitation, TV replacement is most appropriate. In PV disease, valve replacement with patch enlargement of the RV outflow tract is preferred over valve resection.

Balloon valvuloplasty of the PV has been performed in poor surgical candidates; however, recurrent valvular disease and the risk of coexistent TV and PV regurgitation limit its use. The replacement of both valves has been described. Median survival times of 6 to 11 years after valve replacement have been reported. Replacement of a diseased TV when the PV was not severely involved was associated with a low risk of subsequent PV dysfunction and the need for further surgical intervention.

Biological or mechanical prostheses may be implanted. Bioprosthetic valves can degenerate early because of graft failure and carcinoid-guided fibrosis; however, this can be avoided through postoperative control of neuroendocrine effects. Despite possible thrombosis in bioprosthetic valves, lifelong anticoagulation is rarely indicated (in general, 3–6 mo of anticoagulation is prescribed). Mechanical valves, although durable, warrant anticoagulation after insertion, which increases the risk of bleeding and the need for reoperation.

Investigators have performed 3D printing of 3D echocardiographic images to better characterize left-sided valvular disease and RV cardiac tumors; we do not know if this has been done before right-sided valvular repair in carcinoid HD. In patients with left-sided carcinoid valvular involvement from presumed interatrial shunts, surgical shunt closure has enabled symptom control.

**Conclusion**

The diagnosis and management of carcinoid HD are complex. Patients with right-sided heart failure may have a poorer prognosis. Advances in diagnostic techniques have improved the detection of cardiac carcinoid involvement. Symptom control and longer-term survival are possible through appropriate medical therapy and surgical treatment. Results of ongoing clinical trials may reveal further improvements in diagnosis and treatment.

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