Carcinoid Heart Disease: Pathophysiology, Pathology, Clinical Manifestations, and Management

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Abstract

Carcinoid heart disease (CHD) is a rare and potentially lethal manifestation of an advanced carcinoid (neuroendocrine) tumor. The pathophysiology of CHD is related to vasoactive substances secreted by the tumor, of which serotonin is most prominent in the pathophysiology of CHD. Serotonin stimulates fibroblast growth and fibrogenesis, which can lead to cardiac valvular fibrosis. CHD primarily affects right heart valves, causing tricuspid and pulmonic regurgitation and less frequently stenosis of these valves. Left heart valves are usually spared because vasoactive substances such as serotonin are enzymatically inactivated in the lung vasculature. The pathology of CHD is characterized by plaque-like deposition of fibrous tissue on valvular cusps, leaflets, papillary muscles, chordae, and ventricular walls. Symptomatic CHD usually presents between 50 and 70 years of age, initially as dyspnea and fatigue. Echocardiography is the mainstay of imaging and demonstrates thickened right heart

valves with limited mobility and regurgitation. Treatment focuses on control of the underlying carcinoid syndrome, targeting subsequent valvular heart disease and managing consequent heart failure. Surgical valve replacement and catheter-directed valve procedures may be effective for selected patients with CHD.

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Introduction

Carcinoid syndrome is a rare endocrine disorder related to the effects of vasoactive substances produced by carcinoid tumors, the most prominent of which is serotonin (5-hydroxytryptamine) [1–4]. Serotonin stimulates intestinal secretion and motility and inhibits intestinal absorption [4]. These neoplasms primarily arise from enterochromaffin cells of endocrine and nervous system origin; the great majority of the tumors is benign, and <10% are malignant [3, 5, 6]. The incidence of carcinoid tumors in the general population is approximately 1–5/100,000 persons [1, 3, 7, 8]. Carcinoid tumors are most commonly located in the gastrointestinal tract (midgut carcinoid),

Table 1. Types of carcinoid disease

Type	Characteristics	Biomarker profile
Carcinoid tumor (NET)	Location: GI, bronchus and GU tract	↑ Serum 5-HT and ↑ 24-h urine 5-HIAA levels
Carcinoid syndrome	NET with metastasis, mainly to liver	↑↑ Serum 5-HT and ↑↑ 24-h urine 5-HIAA levels + systemic manifestations
Carcinoid heart disease	Carcinoid syndrome + cardiac involvement	Same as carcinoid syndrome + ↑NT-pro-BNP ¹

↑, elevated; ↑↑, markedly elevated; NET, neuroendocrine tumor; GI, gastrointestinal; GU, genitourinary; 5-HT, serotonin (5-hydroxytryptamine); 5-HIAA, 5-hydroxy indole acetic acid; NT-proBNP, N-terminal pro-brain natriuretic peptide. ¹ In heart failure.

Table 2. Carcinoid heart disease pathology

Cardiac involvement	Pathology	Symptoms and signs
Tricuspid valve (TV)	Fibrosis; thickened and fused commissures, ↑ Mobility Regurgitation/stenosis	Exertional dyspnea, fatigue, and symptoms of RHF; edema, ascites, pleural effusion; ↑ JVP, prominent V waves and pan-systolic murmur of TR; less frequently, diastolic murmur of TS
Pulmonic valve	Same as TV	Early diastolic murmur of PR; less frequently, systolic murmur of PS
Aortic valve (<10% of cases)	Same as TV, 2° to atrial R → L shunt	Murmur of AS/AI
Mitral valve (<10% of cases)	Same as TV, 2° to atrial R → L shunt	Murmur of MS/MR
Myocardium (<5% of cases)	Carcinoid metastases to myocardium (ventricles and septum)	Heart failure due to restrictive cardiomyopathy

↑, elevated; RHF, right heart failure; JVP, jugular venous pulse; R, right; L, left; AS, aortic stenosis; AI, aortic incompetence; MS, mitral stenosis; MR, mitral regurgitation; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis.

bronchus (foregut carcinoid), and genitourinary tract (hindgut carcinoid) [3, 7]. The term “carcinoid” was coined in 1907 by the German pathologist, Siegfried Oberndorfer, who discovered and named the tumor “karzinoid” or “carcinoma-like,” to describe the unique behavior of a benign tumor despite a malignant microscopic appearance [3, 7]. The World Health Organization re-defined “carcinoid” in 2000 with the preferred term: neuroendocrine tumor (NET; Table 1).

Carcinoid syndrome (Table 1) is most common in patients with tumor metastases to the liver, but it can also occur in localized disease [1, 3]. Carcinoid heart disease (CHD; Table 1) is an uncommon presentation of carcinoid syndrome, but it does eventually occur in a majority of patients with the syndrome, and it is the major cause of morbidity and mortality in these patients [2, 3, 6]. During the past 20 years, advances in diagnosis and treatment

have provided improved therapeutic approaches with the potential to decrease the toll of death and disability from CHD [6, 8].

Pathology and Pathophysiology

Carcinoid tumors of midgut origin usually present as classic carcinoid syndrome, whereas the syndrome is rare in tumors of hindgut and foregut origin [3, 9]. CHD primarily affects the right heart valves with tricuspid and pulmonic regurgitation and stenosis, because vasoactive substances such as serotonin are enzymatically inactivated in the lung vasculature preventing transport to the left heart (Table 2). Therefore, left-sided disease occurs in <10% of patients and is almost always associated with a right-to-left intracardiac shunt at the atrial level [2, 6]. In

the rare cases in which shunts are not a factor, the underlying etiology is often primary bronchopulmonary carcinoid disease or high serotonin levels due to poorly controlled carcinoid syndrome [10].

The symptoms of carcinoid syndrome are caused by excessive secretion of vasoactive substances produced by NETs, of which serotonin is the primary agent [2–4]. Other neurotransmitters play variable pathophysiologic roles and include prostaglandins, histamine, tachykinin, and kallikrein [6, 11–13]. Serotonin is a monoamine neurotransmitter derived from tryptophan. It is found in enterochromaffin cells in the gastrointestinal tract, where it regulates intestinal smooth muscle function, and in neurons of the central nervous system, where it influences mood and sleep [4, 5]. The NET is typically located in the gastrointestinal tract; because serotonin undergoes degradation in the liver by hepatic monoamine oxidase, symptoms do not develop until metastases to the liver have significantly impaired hepatic function [11, 13]. Rarely, primary ovarian carcinoid tumors can also cause CHD, in which serotonin is thought to reach the systemic circulation directly, bypassing the portal circulation and liver via the ovarian veins [5, 11]. Enzymatic inactivation of serotonin by pulmonary monoamine oxidase in lung vasculature protects left-sided cardiac structures [6, 13].

Serotonin can stimulate fibroblast growth and fibrogenesis, which may lead to cardiac valvular fibrosis (Table 2) and peritoneal fibrosis [5, 6, 12]. The valvular lesions produced by high circulating serotonin levels are similar to those of ergot-alkaloid derivatives or (dex)fenfluramine [12–14]. The role of serotonin in the development of CHD is supported by markedly elevated levels (2- to 4-fold above normal) of circulating serotonin in those with the disease. Additionally, urinary 5-hydroxyindole acetic acid (5-HIAA), the major metabolite of serotonin, is also elevated in patients with CHD compared to carcinoid patients without cardiac involvement (Table 1) [6, 7]. A high level of circulating serotonin is associated with increased transforming growth factor- β latency-associated peptide and latent binding protein in the tissue of an involved heart valve, both of which promote fibrosis [12, 15, 16]. Serotonin receptors are present on heart valves and participate in collagen synthesis in valvular interstitial cells [16, 17]. In experimental animal studies, long-term serotonin administration can produce morphologic and echocardiographic valvular alterations similar to those in human CHD [16, 18].

The pathology of right-sided CHD is characterized by plaque-like deposition of fibrous tissue on valvular cusps,

leaflets, papillary muscles, chordae, ventricular walls, and occasionally on the intima of pulmonary arteries [5, 6, 14, 19] (Table 2). Tricuspid valve chordae are focally thickened and commissures often mildly fused, thus mimicking the pathology of chronic rheumatic valve disease. The downstream aspect of the pulmonary cusps and surfaces of the tricuspid leaflets are the most prominent sites of plaque formation. Plaques usually present a “stuck-on” pattern without compromising the underlying valve architecture [6, 19]. The composition of the plaque comprises myofibroblasts, lymphocytes, mast cells, extracellular matrix (collagen, myxoid matrix, and elastin), and an overlying endothelial layer. Over 95% of those with valvular involvement have tricuspid valve disease, and approximately 90% display moderate or severe tricuspid regurgitation. In the 85% of patients with pulmonary valve disease, about 80% had regurgitation while stenosis was present in 50% [2].

It has been reported that serotonin has a vasospastic effect on predisposed atherosclerotic coronary arteries [20, 21]. The spasm displays a biphasic dose-dependent result causing vasoconstriction of the diseased coronary arteries and dilatation of the normal vessels. The coronary vasospastic effect can manifest clinically as variant (Prinzmetal) angina with chest pain at rest in the absence of occlusive coronary lesions. Additionally, serotonin may also reach the coronary circulation via shunting through a patent foramen ovale. Given the role of serotonin as a potent platelet activator, it may consequently induce stent thrombosis [22].

CHD may also develop as a direct result of metastases to cardiac muscle itself. One case series reported a 3.8% incidence of metastases, with most tumors found on the ventricular septum [23]. The location of metastases dictates the presenting symptoms; solitary atrial masses may remain asymptomatic, while ventricular septal masses can result in outflow tract obstruction [24]. Ultimately, direct cardiac metastases correlate with greater tumor burden, necessitating even more stringent workup when these characteristics are found.

Presentation and Physical Examination

The typical clinical manifestations of carcinoid syndrome are the triad of cutaneous flushing, diarrhea, and bronchospasm [5–7, 12, 13]. Less frequently, cardiac valvulopathy, restrictive cardiomyopathy, and emesis occur. CHD is relatively frequent in patients with carcinoid syndrome and is responsible for considerable morbidity and

mortality [5–7]. Onset of CHD symptoms is usually between 50 and 70 years of age and is often subtle, initially including mild exertional dyspnea and fatigue [25, 26]. With disease progression, symptoms and signs of right-sided heart failure such as edema, ascites, pleural effusions, and cardiac cachexia may ensue. Major physical findings of CHD reflect regurgitation and stenosis of the tricuspid and pulmonic valves (Table 2). These include right ventricular failure, elevated jugular venous pulse with prominent V waves (related to tricuspid regurgitation), a pan-systolic murmur of tricuspid regurgitation accented on inspiration, early diastolic murmur of pulmonary regurgitation, pleural effusions, ascites, and edema. Less frequently, a systolic murmur of pulmonic valve stenosis or a diastolic murmur of tricuspid stenosis are audible (Table 2).

While arrhythmias are a rare presenting feature of CHD, it is necessary to consider them in patients with CHD. As a vasoactive substance, serotonin may increase sympathetic discharge and thereby cardiac excitation, resulting in multiple tachyarrhythmias [27]. This concept was supported by experimental studies, as sudden release of serotonin was associated with paroxysmal ventricular tachycardias and atrial arrhythmias [28].

5-HIAA is the final product of serotonin metabolism and is almost exclusively excreted in the urine. Thus, measurement of 24-h urinary excretion of 5-HIAA is a useful initial diagnostic test for carcinoid syndrome because of its association with carcinoid tumor [26, 29, 30]; a urinary 5-HIAA level >300 mmol/24 h helps identify individuals at risk for CHD [26, 31]. However, certain medications and foods such as plantain, pineapple, and banana can produce false-positive results in 24-h urinary excretion of 5-HIAA and thus should be avoided prior to testing [29, 32]. Only posttreatment 5-HIAA levels independently predicted development or progression of CHD based on serial echocardiography, with a threshold of 100 mg/24 h (normal <25 mg/24 h) [33]. False-negative serum tests for serotonin can result from use of selective serotonin reuptake inhibitors, which deplete platelet stores of the neurotransmitter [21, 34], whereas false-positive tests are caused by ingestion of tryptophan/serotonin-rich foods [31–33]. Because of its lower sensitivity and specificity compared to urinary 5-HIAA, serum serotonin level is not a standard diagnostic test for carcinoid syndrome [7].

In patients with carcinoid syndrome, N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is a sensitive and specific marker for the presence of CHD in the absence of other cardiac disease [31, 35]. NT-pro-BNP (blood) cor-

related moderately well with the severity of CHD while 5-HIAA (blood) correlated only weakly, based on an echocardiographic score evaluating the severity of valvulopathies [36]. It is uniformly recommended that all patients with carcinoid syndrome undergo 6- to 12-monthly clinical evaluations for symptoms and signs of valvular disease or heart failure by measurement of serum NT-pro-BNP (Table 1) [31, 36]. Chromogranin A is an additional biomarker, albeit one with poor screening utility (sensitivity 60–90% and specificity 10–35%) [37, 38]. It is best employed as a follow-up indicator for carcinoid recurrence, as it possesses a sensitivity of 100% for CHD [39].

Electrocardiogram and Chest Radiograph

In patients with CHD, the electrocardiogram (ECG) usually has nonspecific findings such as ST-T changes, but low voltage QRS complexes may be evident in patients with advanced CHD [26, 31, 40]. ST segment elevation can occur in the setting of serotonin-induced coronary vasospasm [20]. Additional ECG findings include PR prolongation and sinus tachycardia [26, 31]. The chest radiograph may reveal cardiomegaly with prominent right-sided chambers in 50% of patients [25, 41].

Imaging Studies

Echocardiography

Transthoracic two-dimensional echocardiography is the mainstay of imaging for CHD [6, 31]. Tricuspid regurgitation is typical in almost all patients with CHD and is characterized by thickened tricuspid valve leaflets, reduced mobility, and occasional immobility of tricuspid right-sided valve leaflets (Fig. 1) [25, 41, 42]. These findings are reflected in a series of 74 patients with CHD: all had tricuspid regurgitation, more than half had tricuspid valve stenosis, four-fifths had pulmonic valve regurgitation, and only 5% had left heart involvement [2]. Right ventricular volume overload and increased right heart filling pressures occur in late-stage disease. Metastatic carcinoid tumor to the heart is rare (<5%) but occurs at a wide variety of sites, including the right ventricle, left ventricle, interventricular septum, and myocardial walls [2, 6, 19]. On echocardiography, cardiac metastases appear as homogenous, well-circumscribed, noninfiltrative masses [13, 23].

Compared to two-dimensional echocardiography, three-dimensional echocardiography provides more de-

Fig. 1. Two-dimensional echocardiogram, parasternal long axis right ventricle (RV) inflow view. The tricuspid valve (TV) septal posterior leaflets (arrows) are thickened and rigid; the posterior leaflet (identified by the lower arrow) is fixed in the open position during systole (**a**) and diastole (**b**). RA, right atrium.

tailed en face visualization of valvular and subvalvular structures, and may be important in the diagnosis and evaluation of cardiac pathology, especially of pulmonic valve disease [31, 41]. Additionally, ventricular strain determined by echocardiographic speckle tracking has demonstrated reduced ventricular function that is predictably associated with a more advanced disease state [43].

CT and MRI

These techniques can provide additional anatomic evaluation such as demonstration of right heart dilatation due to volume overload with more details than conventional imaging methods [31, 41]. Cardiovascular MRI is a useful adjunct for accurate assessment of right ventricular systolic function and detection of myocardial metastases [23, 31].

Treatment

The goal of management for carcinoid syndrome and CHD is symptomatic relief and improved survival rather than definitive therapy and cure. A multidisciplinary approach should be employed to implement a treatment plan based on symptoms, stage of carcinoid tumor, histological grade, and clinical status (Fig. 2).

The somatostatin analogues, octreotide and lanreotide, have been effective in controlling symptoms of carcinoid syndrome [3, 26, 31]. Both agents are synthetic octo-amino acid peptides that bind to the somatostatin receptor subtypes 2 and 5, inhibit serotonin release, and reduce secretion of gastrointestinal hormones, such as

gastrin, secretin, and cholecystokinin. Somatostatin receptors are present in NET tissue and platelets [44–46], and somatostatin analogues can thereby decrease serotonin levels. Telotristat ethyl is an oral tryptophan hydroxylase inhibitor used in combination with a somatostatin analogue for patients with inadequate response to initial management of carcinoid syndrome with a somatostatin analogue alone [47, 48]. Recent trials have also demonstrated that everolimus can enhance progression-free survival in patients with progressive carcinoid tumor [49, 50]. However, deaths related to pulmonary or cardiac failure were observed more frequently in patients treated with everolimus [51].

Liver-directed therapies include surgical resection, cytoreductive therapy, radiofrequency ablation, and hepatic embolization. In a study of 42 patients, these methods were associated with a symptom-free 5-year survival of 61% in 14 patients with carcinoid syndrome and liver-predominant disease with CHD. The latter outcome compared favorably with the 44% survival in 28 patients with carcinoid syndrome and liver-predominant disease without CHD [52].

Treatment of valvular disease and heart failure from CHD follows current guidelines [53, 54]. Carcinoid-induced ventricular tachycardia has been successfully managed with metoprolol [27]. Diuretics must be used judiciously because of the potential to reduce cardiac output in patients with right ventricular dysfunction and valve disease. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, renin inhibitors, and spironolactone are discontinued prior to surgical valve intervention to avert intraoperative blood pressure instability. Early valvular intervention before significant

Fig. 2. Diagnostic and treatment algorithm for carcinoid heart disease.

right-sided heart failure may enhance survival [26, 55]. Therefore, regular follow-up is mandatory with identification of patients likely to benefit from this approach.

Although there is evidence suggesting a close association between serotonin levels and presence of CHD, there is no indication that reduction of these levels can prevent or delay CHD progression [56, 57]. Only post-treatment urinary 5-HIAA levels have independently predicted development or progression of CHD based on serial echocardiography. Thus, persistent elevations in urinary 5-HIAA levels (>100 mg/24 h despite therapy) have been independently associated with development or progression of CHD [26, 30, 57–59]. In addition, somatostatin analogue, hepatic dearterialization, and chemotherapy were not associated with delay of CHD progression [8, 16, 57].

Without proper management intervention, progressive right heart failure is inevitable. The median survival of advanced carcinoid syndrome is 12–30 months [26, 29, 60]. The presence of CHD with heart failure is associated with a poor prognosis and median survival of 11 months; without treatment, most patients succumb within 1 year because of progressive heart failure [26, 29, 60]. In a pooled analysis of 10 retrospective studies with a total of 193 patients, valvular surgery, largely comprising tricuspid valve replacement, was associated with improved prognosis; median postoperative survival was 58 months (28–80 months) with significant symptomatic relief in a majority of patients [61]. Operative risk was high as reflected by an average 30-day mortality of 17% (range 1–63%). Valvular replacement surgery (usually of the tricuspid valve) has been the only approach that prolongs

survival; mortality is generally related to tumor progression [31, 61].

Prior to surgery, symptoms and serum serotonin level must be well controlled. Carcinoid crisis is a life-threatening event that may be triggered by tumor manipulation during biopsy, surgery, embolization, and anesthesia that results in sudden release of an overwhelming amount of vasoactive substances. It manifests as flushing, extreme fluctuation of blood pressure, bronchoconstriction, arrhythmias, and altered mental status. Perioperative intravenous octreotide (50–100 µg/h) should be started 2 h before surgery and continued for 48 h postoperatively to prevent these crises [5, 16, 31]. Medications such as opioids, atracurium, and catecholamines (dopamine and epinephrine) should be avoided or dose limited during the perioperative period [16, 60].

Tricuspid and pulmonic valve replacement entail open heart surgery, and valve replacement is generally preferred over repair [62, 63]. In some patients, tricuspid and pulmonic valve replacements have been undertaken simultaneously [31, 60, 62]. In patients with both left- and right-sided CHD, triple or even quadruple valve replacement (tricuspid, pulmonary, mitral, and/or aortic) has been performed [62]. Both mechanical and bioprosthetic valves are used for these procedures, and both types are associated with value and limitations. Mechanical valves benefit from increased durability but require strict anticoagulation, increasing the risk of bleeding and reoperation [16]. Conversely, bioprosthetic valves rarely require long-term anticoagulation, but they tend to degenerate earlier due to graft failure or carcinoid-induced fibrosis [64]. For high-risk patients who are not surgical candidates, transcatheter replacement of the pulmonic and tricuspid valves has been utilized [65, 66]. Valve-in-valve transcatheter replacement has also been employed for patients with a degenerated bioprosthetic valve.

The options for nonsurgical medical therapy have also increased. Combination therapy of paclitaxel, trastuzumab, and interleukin-12 has displayed promise in malignancies positive for human epidermal growth factor receptor 2/neu expression, including carcinoid disease [67]. New therapies, specifically pasireotide, a somatostatin analogue, have helped control symptoms as efficaciously as classic octreotide treatment [68]. In patients with disease resistant to somatostatin, interferon-α and lutetium dotate have both reduced severity of disease as part of octreotide combination therapy [69, 70]. Lastly, in the case of unresectable metastases from NETs such as carcinoid syndrome, yttrium-90 radioembolization of the liver has been successful in improving survival rate and tumor response [71].

CHD is a distinct yet rare form of carcinoid disease that has potentially lethal manifestations. Stemming from serotonin-induced fibroblast growth and fibrogenesis, CHD is characterized by severe valvular abnormalities and diagnosed by echocardiography. CHD most often presents between 50 and 70 years of age as severe dyspnea and fatigue. Treatment should rely on controlling the underlying carcinoid syndrome and managing subsequent valvular abnormalities and heart failure. The advent of novel nonsurgical medical therapies for the condition afford potentially promising approaches for CHD treatment.

Statement of Ethics

Ethical approval was not required given this was a review article that did not include human subjects.

Conflict of Interest Statement

None of the authors has any conflict of interest related to this work.

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Author Contributions

C.J.: primary author of the 1st submission and acquired the majority of references. A.N.S.: primary author of responses to reviewer comments on 1st submission, edited throughout resubmitted manuscript, and added key references and text. B.T.: proofed manuscript, designed tables, added references, made corrections to Discussion. M.M.: co-designed tables, added key references, and corrections to Introduction and Discussion of original and resubmitted manuscripts. S.A.C.: contributed references, wrote section on coronary spasm, and made corrections to original submission. N.T.: detailed proofing of all aspects of original manuscript and made important corrections to original submission text. A.T.: added important references and text to original and resubmitted manuscripts. A.D.A.: added important elements to Discussion section of original and resubmitted manuscript. N.B.: wrote several sections of original and resubmitted manuscripts. E.A.A.: conceived and directed project, rewrote multiple sections of original and resubmitted manuscript, and delegated work distribution of co-authors.

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