Carcinoid Heart Disease
A Review

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KEYWORDS

• Carcinoid heart disease • Carcinoid syndrome • Neuroendocrine tumor

KEY POINTS

- Carcinoid heart disease remains a major cause of morbidity and mortality among patients with carcinoid syndrome and metastatic neuroendocrine tumours.
- Screening of all patients with NT-proBNP and transthoracic echocardiogram is critical for early detection as early symptoms and signs have low sensitivity for the disease.
- Cardiac surgery, in appropriate cases, is the only definitive therapy for advanced carcinoid heart disease and it improves patient symptoms and survival.
- Management of carcinoid heart disease is complex and multidisciplinary assessment of cardiac status, hormonal syndrome and tumour burden is critical in guiding optimal timing of surgery.

INTRODUCTION

Although progress in the medical and surgical management of patients with metastatic neuroendocrine tumors (NETs) has resulted in improved symptoms and survival, carcinoid heart disease (CHD) remains a major cause of morbidity and mortality among patients with carcinoid syndrome. CHD has been previously described in up to 50% of patients with carcinoid syndrome,[1,2] although recent studies suggest the prevalence has fallen to approximately 20%,[3,4] perhaps secondary to the more widespread use of somatostatin analog therapy. It is reported to occur most frequently in patients with primary small bowel NETs (72%), followed by NETs arising from the lung, large bowel, pancreas, appendix, and ovaries.[1] A slight male predominance has been reported (approximately 60%), with a mean age at diagnosis 59 (± 11) years.[1]

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Without treatment, the prognosis of CHD is poor, with 3-year survival as low as 31% (compared with 68% in patients with NETs but without CHD).[1] CHD with advanced symptoms (New York Heart Association [NYHA] functional class III or IV) carries a particularly poor prognosis, with median survival only 11 months.[5] Over the past few decades, however, the prognosis of patients with CHD has improved. In a retrospective series of 200 patients with carcinoid syndrome and CHD,[6] the median survival improved from 1.5 years in the 1980s to 4.4 years in the late 1990s, with the data suggesting this improvement is related to increased rates of cardiac surgery and the use of somatostatin analogs.

PATHOPHYSIOLOGY

The pathogenesis of CHD is thought to be multifactorial and is not completely understood. A variety of vasoactive substances secreted by the tumor, including serotonin, prostaglandins, histamine, bradykinin, and other substances with fibroblast proliferative properties, such as tachykinins (substance P, neurokinin A, neuropeptide K) or transforming growth factor-beta, are thought to be involved in the disease pathogenesis.[7]

The Role of Serotonin

There is a growing body of evidence that suggests serotonin plays a major role in the pathogenesis of CHD. It is well known that urinary 5-hydroxyindoleacetic acid (5-HIAA), the serotonin metabolite, is significantly higher in patients with CHD compared with those without cardiac involvement.[1,2,8,9] Other support for the pathophysiological role of serotonin arises from the observation that serotoninergic drugs, such as the ergot-alkaloid derivatives (eg, ergotamine and methysergide used for treatment of migraine; pergolide and cabergoline used for treatment of Parkinson disease) or the anorectic drugs (eg, fenfluramine, alone or in combination with phentermine, and dexfenfluramine), cause valvular fibrosis similar to that seen in CHD.[10,11] These agents are full or partial 5-HT2B receptor agonists, suggesting that activation of this receptor is involved in the pathologic process that leads to plaque development.[12,13] Furthermore, in cell culture studies, serotonin has been shown to promote cell proliferation in valvular subendocardial cells,[14] and human heart valves have been demonstrated to express the serotonin receptors 5-HT1B, 1D, 2A, and 2B.[13,15] In addition, preliminary animal studies, using Sprague-Dawley rats and cynomolgus monkeys, have demonstrated that long-term exposure to elevated levels of serotonin induces carcinoid-like plaques on cardiac valves, as well as echocardiogram findings similar to those seen in humans with CHD.[16–18] Furthermore, the concomitant administration of the ergoline terguride (transdihydrolisuride), a 5-HT2B/2C receptor antagonist, inhibited these changes.[19] Nevertheless, despite the growing evidence that serotonin plays a major role in the development of CHD, it is likely that other biochemical mediators are also significant and may act as cofactors in the fibrotic process.[20–22]

Pathologic Findings

CHD is characterized by plaque-like deposits on the endocardium of valvular cusps, leaflets, chordae, and papillary muscles and cardiac chambers, and occasionally within the intima of the pulmonary arteries or aorta.[23–25] The deposits are composed of myofibroblasts and smooth muscle cells surrounded by extracellular matrix components (collagen and myxoid matrix) and covered by an endothelial cell layer.[23,26] The valves and endocardium of the right side of the heart are most frequently affected and this is usually due to the presence of hepatic metastases that secrete large quantities

of vasoactive peptides that subsequently reach the right heart without being inactivated.[27,28] The plaque is usually deposited on the ventricular aspect of the tricuspid valve leaflet and the pulmonary arterial aspect of the pulmonary valve cusps.[24,29] In the pulmonary valve, this leads to adherence of the leaflets to the pulmonary artery endothelium with consequent regurgitation, stenosis, or both. In contrast, regurgitation tends to predominate with tricuspid valve disease due to retraction of leaflets.

The left-sided valves are less commonly affected, and it is hypothesized that they are spared because of inactivation of the vasoactive hormones by the pulmonary circulation.[1,30] Involvement of the left-sided valves is usually associated with a patent foramen ovale and right-to-left atrial shunt allowing serotonin-rich blood to enter the left heart chambers without passing through the pulmonary circulation.[1,4,29] In a study by Bhattacharyya and colleagues,[4] 52 (21%) of 252 patients with carcinoid syndrome were found to have CHD. Of those patients with CHD, 15 (29%) had left-sided carcinoid valve involvement and of those patients with left-sided involvement, 13 (87%) of 15 had a patent foramen ovale. Left-sided valve disease can also occur in patients with bronchial carcinoids and in patients with high levels of circulating serotonin due to severe, refractory carcinoid syndrome.[31] CHD affecting the aortic or mitral valve usually manifests as valve regurgitation rather than valve stenosis.[4,23,30]

Intramyocardial metastases from carcinoid tumors are rare and are seen in approximately 4% of patients.[4,31]

CLINICAL MANIFESTATIONS

Symptoms

Early valvular changes of CHD can be well tolerated for protracted periods, and hence the initial clinical manifestations can be subtle or absent leading to delay in diagnosis. Early symptoms of isolated, severe tricuspid regurgitation include fatigue and exertional dyspnea due to low cardiac output.[32] Peripheral edema with hepatic congestion and consequent anorexia can also occur with elevated right atrial pressure.[32] Atrial arrhythmias also are common in the setting of right atrial enlargement. Without treatment, progressive right heart failure typically ensues with ascites and anasarca.[32]

Physical Examination

The earliest finding of severe tricuspid regurgitation is often jugular venous distension with prominent systolic “v” wave, although its presence varies between 35% and 75% of patients.[33–35] Other findings may include a palpable right ventricular impulse and murmurs of tricuspid and pulmonary regurgitation. Less frequently, a systolic murmur of pulmonary stenosis or a diastolic murmur of tricuspid stenosis may be audible, although findings on auscultation may be subtle due to the low pressure in the pulmonary circulation.[36] As the valvular disease progresses, and right ventricular enlargement and dysfunction develop, peripheral edema, ascites, and pulsatile hepatomegaly may become evident.

It should be noted, however, that early symptoms and physical signs have low sensitivity for the presence of CHD, and screening with N-terminal pro-B-type natriuretic peptide (NT-proBNP), even in those patients who are asymptomatic, is paramount for early CHD detection (**Fig. 1**). In a series by Bhattacharyya and colleagues,[3] 8 (27%) of 30 patients with CHD had moderate to severe carcinoid valve disease but were in NYHA functional class I, whilst 11 patients (37%) had no physical signs.

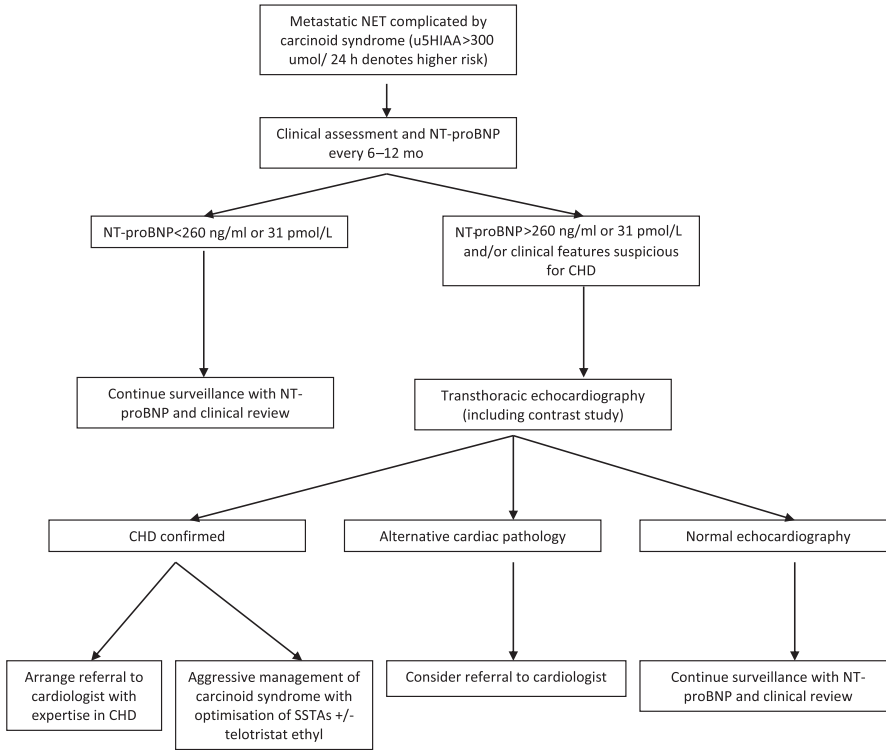

Fig. 1. Screening and evaluation of CHD. u5HIAA, urinary 5-hydroxyindoleacetic. (*Adapted from* Davar J, Connolly HM, Caplin ME, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumours. J Am Coll Cardiol 2017;69(10):1296; with permission.)

Biomarkers

Urinary 5- hydroxyindoleacetic acid

Patients with neuroendocrine tumors and CHD have been shown to have significantly higher (two-fold to four-fold) levels of serum serotonin, platelet serotonin, and urinary 5-HIAA compared with those without CHD.[8] In addition, elevated urinary 5-HIAA levels have been demonstrated to positively correlate with progression of CHD.[9,37–39] In a retrospective series of 71 patients with carcinoid syndrome who underwent serial echocardiographic studies performed more than 1 year apart, peak urinary 5-HIAA levels were significantly higher (median 265 mg/24 hours vs 189 mg/24 hours; $P = .004$) in patients with progressive CHD and in patients with severe symptomatic disease who were referred directly for cardiac surgery.[38]

Chromogranin A

Chromogranin A is a secretory protein found in the large dense-core vesicles of neuroendocrine cells. Despite a number of limitations, it remains a valuable tumor marker, usually of neuroendocrine tumor burden. Chromogranin A is also a sensitive biomarker for CHD but is not specific for the detection of severe CHD (specificity 0.30).[40]

N-terminal pro-B-type natriuretic peptide

Natriuretic peptides belong to the neurohormone family and are produced primarily within the heart and released into the circulation due to increased wall stress.[41] In a

study of 200 patients with carcinoid syndrome,[42] NT-proBNP was found to be significantly higher in those with CHD (1149 pg/mL) compared with those without CHD (101 pg/mL, $P<.001$). At a cutoff level of 260 pg/mL for detection of CHD, the sensitivity and specificity of NT-proBNP was 0.92 and 0.91, respectively. It was also found to positively correlate with severity of carcinoid symptoms ($r = 0.81$, $P<.001$) and NYHA functional class ($P<.001$). The negative and positive predictive values were 98% and 71%, respectively. The high negative predictive value allows NT-proBNP to serve as a good screening test for CHD in the NET population.

The role of NT-proBNP paired with chromogranin A to predict prognosis has also been studied. In a retrospective study by Korse and colleagues[40] (n = 102), levels of chromogranin A and NT-proBNP were independently associated with CHD and overall mortality. Five-year survival was 81% in patients with normal chromogranin A levels, 44% in those with elevated chromogranin A but normal NT-proBNP, and 16% in those with elevations of both chromogranin A and NT-proBNP.

Activin A

Plasma activin A, a growth factor with fibrogenic properties and a cytokine member of the transforming growth factor-beta superfamily, has also been demonstrated to be an independent predictor for the presence of CHD in patients with NETs. Plasma activin A levels were found to be significantly higher in patients with NETs and CHD compared with those patients without CHD ($P = .005$), and a positive correlation was also found between plasma activin A and urinary 5-HIAA ($r = 0.31$, $P = .02$).[22] A cutoff value of 0.34 ng/mL for activin A had a high negative predictive value (94%) but a weak positive predictive value (sensitivity 87%, specificity 57%) and is another potential biomarker that may serve as a screening test for CHD in the NET population.[22] Interestingly, in contrast to NT-proBNP, activin A was found to be elevated in patients with early CHD but without right heart dilatation.[22]

Imaging Modalities

Echocardiography is the gold standard for the diagnosis of CHD and reveals a wide spectrum of CHD findings.[4] A multimodality approach, including 2-dimensional (2D) transthoracic echocardiography (TTE), 3-dimensional (3D) TTE, transoesophageal echocardiography (TOE), cardiac computed tomography (CT) and MRI can help to comprehensively assess different aspects of CHD (eg, valve pathology, presence of patent foramen ovale, ventricular and atrial volumes, coronary anatomy, presence of cardiac metastases and their relationship to coronary arteries).[4,43]

Echocardiography

TTE is the main modality to diagnose and evaluate CHD, as it allows assessment of valvular disease as well as right heart chamber size and function. Advanced techniques including 3D TTE and 3D TOE may help diagnose and assess valve pathology, especially in the tricuspid and pulmonary valves, as all leaflets may not be visualized on 2D TTE. Moreover, 3D echocardiography allows detailed assessment of the subvalvular apparatus and assessment of the relationship between valve leaflets to each other and surrounding structures. Agitated saline contrast echocardiography (*bubble study*) should also be performed at the time of initial echocardiogram to assess for a patent foramen ovale.

Typical echocardiographic appearances of advanced tricuspid valve involvement include thickening and retraction of the leaflets that are fixed and do not coapt.[4] This is typically associated with severe tricuspid regurgitation, a “dagger-shaped” doppler profile and mild to moderate tricuspid stenosis.[4]

Early tricuspid valve carcinoid involvement includes thickening of the valve leaflets and subvalvular apparatus leading to loss of the normal concave curvature of the leaflets and a stiffer "board-like" dynamic motion during diastole rather than the normal undulating motion.[4] Only trivial or mild, centrally directed tricuspid regurgitation is noted at this stage. Thickening of the valve leaflets may be associated with thickening of the chordae and papillary muscles, which results in greater retraction and reduction excursion of the valve cusps.[4]

Pulmonary valve carcinoid disease has a similar appearance to that of tricuspid valve pathology. Mild involvement produces diffusely thickened valve cusps, which causes them to become straightened.[4] As the disease progresses, varying degrees of retraction and reduction in excursion of the valve cusps occurs, and in severe cases valves appear fixed, retracted, and thickened and are associated with severe pulmonary regurgitation.[4] In severe disease, pulmonary annular constriction may also occur, resulting in predominant outflow obstruction and pulmonary stenosis.[4]

Cardiac MRI and computed tomography

Cardiac CT or MRI can complement echocardiography when incomplete data are obtained or when structures (eg, the pulmonary valve) are poorly visualized. CT or MRI allows delineation of valve pathology, assessment of valve regurgitation and stenosis, and may be particularly helpful for quantification of ventricular volumes.[4] MRI also allows assessment of myocardial metastases, including measurement of size and extracardiac invasion that cannot be assessed on echocardiography.[4] Furthermore, cardiac CT can delineate coronary artery anatomy and the relationship to myocardial metastases if present.

^{68}Gallium DOTA-somatostatin analog PET/computed tomography

^{68}Gallium DOTA-somatostatin analog PET/CT is more specific than CT or MRI in detecting metastatic, well-differentiated NETs[44] and may enhance the detection of rare intramyocardial metastases.

MANAGEMENT

Management Approach

The management of patients with metastatic NETs complicated by carcinoid syndrome and CHD is complex and referral to a specialist center and multidisciplinary team with CHD experience is critical.

Medical Management of Right Heart Failure

Loop diuretic therapy, fluid and salt restriction, and compression stockings may provide temporary relief by reducing symptoms of edema; however, they must be used judiciously, as depletion of intravascular volume may further reduce cardiac output and, in turn, lead to worsening fatigue and breathlessness.[36] In selected cases, ultrafiltration could be useful.

Control of Carcinoid Syndrome

Given the strong body of evidence that suggest serotonin, or its metabolites, plays a major role in the pathogenesis of CHD, it is likely that somatostatin analogs, telotristat ethyl (a novel serotonin synthesis inhibitor), liver-directed or cytoreductive therapies, and systemic therapies (eg, peptide receptor radionuclide therapy) that reduce circulating levels of serotonin may reduce the risk of developing CHD. Optimal doses of somatostatin analogs to appropriately reduce urinary 5-HIAA levels may be of importance. In an observational cohort study by Bhattacharyya and colleagues,[39]

urinary 5-HIAA levels greater than 300 μmol/24 hours conferred a two-fold to three-fold risk for the development or progression of CHD and reducing urinary 5-HIAA to below this level may be an important therapeutic strategy. There is no evidence, however, that reducing urinary 5-HIAA can reverse established carcinoid valvular lesions.

Telotristat ethyl is a peripheral tryptophan hydroxylase inhibitor and reduces the production of serotonin. It has recently been approved in the United States and Europe, in combination with somatostatin analog therapy, for control of diarrhea associated with refractory carcinoid syndrome. In a post hoc analysis of a phase III study (n = 135),[45] telotristat ethyl reduced urinary 5-HIAA levels by ≥30% in 78% (n = 25) and 87% (n = 26) of patients in the 250 mg and 500 mg (3 times a day) treatment arms, respectively, compared with 10% (n = 3) in the placebo group. It may be reasonable to consider telotristat therapy in patients at higher risk of CHD (eg, urinary 5-HIAA >300 μmol/24 hours despite optimal doses of somatostatin analogs); however, as yet, there is no evidence that telotristat ethyl can prevent the development or progression of CHD.

Surgical Valve Replacement

Cardiac valve replacement is the only definitive therapy for advanced CHD, and it improves patient symptoms and survival.[6,46] CHD may progress rapidly[39] and, therefore, early diagnosis and careful cardiac monitoring are pivotal to identify those patients likely to benefit from surgery.

In the largest retrospective series to date of surgical patients with CHD (n = 195), symptomatic improvement was seen in 69 (75%) of 92 patients with significant preoperative symptoms (NYHA functional class III or IV).[46] Survival for the entire cohort at 1, 5, and 10 years was 69%, 35%, and 24%, respectively,[46] which is a marked improvement compared with medically managed historical control subjects with NYHA functional class symptoms greater than II, only 10% of whom survive 2.5 years.[5,6]

All patients with severe tricuspid valve regurgitation should be carefully considered for valve replacement surgery. In the past, patients with pulmonary valve disease underwent pulmonary valvectomy with outflow tract enlargement, given that many patients tolerate some degree of pulmonary regurgitation.[46] However, severe pulmonary valve regurgitation, which can occur after valvectomy, has been demonstrated to adversely impair right ventricular remodeling[47] and replacement of the pulmonary valve when involved by CHD is now preferred. In addition, homografts are sometimes used to replace the pulmonary valve, although some centers report premature valve dysfunction related to constriction of the homograft and, alternatively, prefer placement of a large stented bioprosthesis facilitated with patch enlargement of the pulmonary valve annulus and right ventricular outflow tract.[46] When the mitral and/or aortic valves are affected, valve repair or replacement may be performed depending on the severity of carcinoid involvement.[48] Other procedures may include closure of a patent foramen ovale and, rarely, excision of intramyocardial metastases in selected cases.[48]

Timing of Surgery

The most optimal time for valve replacement surgery in CHD has not been determined, but generally patients with well-controlled carcinoid syndrome and a life expectancy of at least 12 months are referred once they develop progressive symptoms and right-sided heart failure or asymptomatic/minimally symptomatic patients who develop progressive right ventricular dilatation or dysfunction.[46,48] Rarely, asymptomatic patients with CHD and increased right atrial pressure require valve replacement surgery to enable cytoreductive hepatic resection.[32]

Due to the previous high perioperative mortality risk, valve replacement surgery has historically been performed relatively late in the natural history of the disease and on patients with advanced right-sided heart failure.[49,50] However, more recent series demonstrate a significant improvement in perioperative outcomes, probably secondary to a combination of improved patient selection, experience of the multidisciplinary team, improved perioperative management of carcinoid syndrome, and possible advances in surgical and valve technology.[46] In 1995, Connolly and colleagues[5] published on the initial Mayo Clinic experience and reported an overall early perioperative mortality of 35%. In a recent update, however, the overall 30-day mortality rate was 10%.[46] Furthermore, the surgical deaths were not equally distributed over the 27 year study period. Of the 20 perioperative deaths, 12 occurred in the first 71 patients (before 2000; 17%). Since 2000, 8 (6%) perioperative deaths occurred in 124 patients: 7 (7.2%) of 97 occurred between 2000 to 2009 and 1 (3.7%) of 27 occurred between 2010 and 2012. On multivariate analysis, perioperative mortality was not only independently related to the era of operation but also the need for preoperative intravenous diuretic therapy, suggesting that patients with advanced right heart failure have worse perioperative survival.

The significant improvement in perioperative outcomes and survival will likely impact surgical referral patterns in the imminent future. Further data, however, are needed to determine if there is survival benefit with presymptomatic surgical intervention. Based on current data, presymptomatic intervention is not associated with late survival benefit.[46]

Choice of Valve Prosthesis

The choice of valve prosthesis remains controversial, as the literature is limited to retrospective, non-randomized studies. Historically, mechanical valve prostheses were preferred for tricuspid valve replacement due to the risk of premature degeneration of bioprostheses secondary to persistent circulating vasoactive peptides.[51] However, the literature has progressively supported the use of bioprostheses because of (1) the improved management of carcinoid syndrome, (2) the low rates of carcinoid involvement in recent pathologic series of explanted bioprostheses, (3) the favorable short-term outcomes, (4) the likelihood that the longevity of newer generation bioprosthetic valves will succeed the medium to long-term survival of the patient, (5) the inherent bleeding risk in patients with liver metastases and hepatic dysfunction, and (6) the likelihood of oncological surgery or chemotherapy in the future for which long-term anticoagulation may represent additional risk.[46] Furthermore, the recent development of transcutaneous therapies could facilitate “valve-in-valve” replacement in patients with implanted bioprostheses.

In the Mayo Clinic series,[46] tricuspid valve replacement involved bioprostheses in 159 patients and mechanical valves in 36 patients. Of note, there was no significant difference in survival or reoperation rate in relation to type of prosthesis. Pathologic review of explanted bioprostheses demonstrated carcinoid involvement in only one explanted valve, with thrombus being the most frequent alternative cause of tricuspid bioprosthesis dysfunction. For this reason, vitamin K antagonist anticoagulation is recommended for 3 to 6 months after bioprostheses insertion, followed by serial echocardiography thereafter. Importantly, the reversal of bioprosthesis dysfunction has been reported with reinitiation of vitamin K antagonist anticoagulation.

Anesthesia Management

Patients with carcinoid syndrome represent a high-risk surgical cohort because of potentially life-threatening carcinoid crisis that can cause hemodynamic lability

characterized by profound peripheral vasodilation and hypotension, tachycardia, arrhythmias, and bronchoconstriction.[32,48] Carcinoid crisis can be precipitated directly by the surgery or when receiving anesthetic and other perioperative pharmacologic agents, including vasopressors and opioids.[48]

Meticulous preoperative planning and perioperative care are required. In the perioperative setting, continuous intravenous somatostatin analog (octreotide) infusion should be commenced at least 12 hours before surgery and continued for 48 hours afterwards, with slow tapering of the infusion before discontinuation (commenced at 50–100 μg/h and titrated up to 200 μg/h should signs or symptoms occur).[7,48]

SUMMARY AND RECOMMENDATIONS

- CHD remains a major cause of morbidity and mortality among patients with carcinoid syndrome.
- Recent studies suggest the prevalence of CHD among patients with carcinoid syndrome to be approximately 20%.
- CHD with advanced symptoms of right heart failure carries a particularly poor prognosis with median survival of only 11 months.
- Early symptoms and physical signs have low sensitivity for the presence of CHD, and screening, even in those patients who are asymptomatic, is critical for early CHD detection. NT-proBNP appears to be the best biomarker for CHD screening to date.
- Transthoracic echocardiography is the gold standard for the diagnosis of CHD and should be performed in all patients with suspicious symptoms or elevated NT-proBNP and/or urinary 5-HIAA.
- Measurement of urinary 5-HIAA is important in all patients with NETs and a level greater than 300 μmol/24 hours may denote increased risk of developing CHD.
- It is essential to aggressively treat patients at every stage of CHD. Optimal doses of somatostatin analogs to appropriately reduce urinary 5-HIAA levels may be of importance.
- Cardiac surgery, in appropriate cases, is the only definitive therapy for advanced, symptomatic CHD and it improves patient symptoms and survival.
- In recent decades, there has been significant improvement in perioperative outcomes and survival of patients with CHD.
- The most optimal time for valve replacement surgery in CHD has not been determined. Patients with well-controlled carcinoid syndrome and a life expectancy of at least 12 months are often referred once they develop progressive symptoms of right-sided heart failure or asymptomatic/minimally symptomatic patients who develop progressive right ventricular dilatation or dysfunction.
- The management of patients with metastatic NETs complicated by carcinoid syndrome and CHD is complex, and comprehensive multidisciplinary assessment of cardiac status, hormonal syndrome, and tumor burden is critical in guiding optimal timing of surgery.

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