Section Editors: Lindsey Lyle and Wendy H. Vogel

Carcinoid Heart Disease

NICOLE KUHNLY,[1] MS, ACNPC-AG, JESSICA SHANK COVIELLO,[2] DNP, APRN, ANP-BC, CATHERINE A. KOBZA,[3] MSN, AGACNP-BC, DEVESH A. PATEL,[4] DO, JACQUELINE S. LAGOY,[4] MD, and MARY-ANN L. CYR,[5] DNP, APRN, ACNP-BC

From [1]Memorial Sloan Kettering Cancer Center, New York, New York; [2]Cizik School of Nursing, University of Texas, Houston, Texas; [3]NYU Langone Hospital Long Island, Mineola, New York; [4]University of Connecticut Department of Anesthesiology, Hartford, Connecticut; [5]Yale University School of Nursing, Hartford Healthcare CTICU, Hartford, Connecticut

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Jessica Shank Coviello, DNP, APRN, ANP-BC, 6901 Bertner Ave, Houston, TX 77030
E-mail: jessica.s.coviello@uth.tmc.edu

https://doi.org/10.6004/jadpro.2024.15.6.3

Abstract

Carcinoid heart disease (CHD) is a rare cardiac complication that occurs most commonly in patients with advanced neuroendocrine tumors and is a known sequela of carcinoid syndrome. Neuroendocrine tumors most widely associated with CHD include tumors in the small bowel, followed by lung, large bowel, pancreatic, appendiceal, and ovarian neoplasms. Carcinoid syndrome is a paraneoplastic syndrome caused by the release of serotonin and other substances from neuroendocrine tumors. It results in a spectrum of symptoms, including diarrhea, flushing, bronchospasm, and symptoms of congestive heart failure. Without treatment and for patients with advanced heart failure, the prognosis of CHD can be less than a year. Management of CHD is often challenging as patients typically present late, and the disease can progress rapidly. Therefore, optimal management of these patients requires close collaboration among various specialties to quantify disease burden, delay the progression of valvular disease, and determine the most effective surgical and medical management strategies depending on the cardiac manifestations to improve quality of life and reduce mortality. This involves a collaborative team, including cardiology and oncology, and often involves many other disciplines, including hepatobiliary and cardiovascular surgeons, endocrinologists, anesthesiologists, and gastroenterologists.

Neuroendocrine tumors are rare solid tumors with an estimated incidence of 6 per 100,000 persons. They can occur in any part of the body and have a broad spectrum of diseases ranging from slow growing to highly aggressive malignancies (Jin et al., 2021). Carcinoid syndrome is a paraneoplastic syndrome caused by the release of serotonin and other substances from neuroendocrine tumors and results in a spectrum of symptoms, including diarrhea, flushing, bronchospasm, and symptoms of congestive heart failure (Hassan et al., 2019; Jin et al., 2021). Approximately 20% to 30% of patients with neuroendocrine tumors develop carcinoid syndrome (Uema et al., 2019). While carcinoid syndrome most commonly occurs in patients with liver metastases, it can occur in more localized disease (Jin

J Adv Pract Oncol 2024;15(6):378–386

et al., 2021). Carcinoid heart disease (CHD) is a rare cardiac complication that occurs most commonly in patients with advanced neuroendocrine tumors and is a known sequela of carcinoid syndrome (Grozinsky-Glasburg et al., 2022; Hassan et al., 2019; Laskaratos et al., 2021; Uema et al., 2019). Neuroendocrine tumors most associated with CHD include tumors in the small bowel (4%), followed by lung (4%), large bowel (4%), pancreatic (1%), appendiceal (1%) and ovarian neoplasms (1%–3%; Laskaratos et al., 2021).

Carcinoid heart disease is characterized by plaque-like deposits on fibrous tissues, primarily occurring on heart valves, but can also involve other cardiac structures, including the cardiac chambers, pulmonary arteries, and coronary sinus (Hassan et al., 2019; Rubin de Celis Ferrari et al., 2018). This is related to the secretion of vasoactive substances released into systemic circulation by neuroendocrine tumors that results in tissue fibrosis, most commonly on right-sided heart valves, causing regurgitation and/or stenosis and subsequent right ventricular dilatation and dysfunction (Grozinsky-Glasburg et al., 2022; Laskaratos et al., 2021; Steeds et al., 2019; Uema et al.; 2019). While CHD most commonly includes right heart involvement, approximately 5% to 10% of cases result in left heart involvement, with these cases most often associated with lung neuroendocrine tumors, patent foramen ovale, or diffuse liver metastases (Uema et al., 2019).

The development of CHD occurs in about 19% to 50% of patients with carcinoid syndrome (Grozinsky-Glasburg et al., 2022; Rubin de Celis Ferrari et al., 2018). This wide range in incidence is likely related to variance in patient population, access to somatostatin analogs, how CHD is defined, and methods used for diagnosis (Rubin de Celis Ferrari et al., 2018). Risk factors for the development of CHD include elevated levels of serotonin and urinary 5-hydroxyindoleacetic acid (5-HIAA), in addition to high liver tumor burden and prior cardiovascular disease (Alves et al., 2018).

The development of CHD is a poor prognostic factor in patients with neuroendocrine tumors, with reduced overall survival at 3 years of 31% in patients with CHD, in comparison to 69% in patients without CHD (Grozinsky-Glasburg et al., 2022). Without treatment and for patients with advanced heart failure, the prognosis of CHD has a median survival of 11 months (Hassan et al., 2019).

The management of CHD is often challenging, as patients typically present late, and the disease can progress rapidly (Hassan et al., 2019; Steeds et al., 2019). Therefore, optimal management of these patients requires close collaboration among various specialties to quantify disease burden, delay the progression of valvular disease, and determine the most effective surgical and/or medical management strategies depending on the cardiac manifestations in order to improve quality of life and reduce mortality (Hassan et al., 2019).

SIGNS AND SYMPTOMS

The presentation of patients with CHD varies, although most patients are initially asymptomatic. Isolated tricuspid valve regurgitation is seen, and most patients exhibit pulmonic valve regurgitation or stenosis. These valvular dysfunctions lead to right-sided heart failure, which generally presents with lower extremity edema (Ram et al., 2019). In patients with nonocclusive coronary artery disease, coronary artery vasospasm can be associated with CHD. The presence of vasospasm is associated with serotonin-inducing vasoconstriction in diseased endothelium (such as in patients with atherosclerotic disease). Less commonly, patients may experience arrhythmias, in which serotonin incites paroxysmal ventricular tachycardias and atrial arrhythmias (Ram et al., 2019). Patients diagnosed with CHD often experience dyspnea, fatigue, a systolic murmur heard best along the sternal border and increased with inspiration, jugular venous pressure elevation with prominent V wave, ascites, peripheral edema, and pleural effusions (Davar et al., 2017).

PATHOPHYSIOLOGY

The pathophysiologic patterns of CHD are complex and not entirely understood. Ultimately, they create a cascade of physiologic events that lead to fibrosis of cardiac structures, mostly of the right heart. Fibrosis is the primary driver influenced by the interaction of serotonin, growth factors, kinins, and peptides (Bober et al., 2020).

The principal contributor of carcinoid syndrome is serotonin (5-hydroxytryptamine; 5-HT), but there are over 40 other vasoactive substances

that are also responsible (Table 1). Predominant are the tachykinins (neurokinin A, neuropeptide K, and substance P), prostaglandins, histamine, transforming growth factor β, and bradykinin. These peptides are secreted by neuroendocrine tumor cells and do not act independently of each other but by way of pathway crosstalk that ultimately leads to fibrosis of cardiac tissue (Baron et al., 2021; Subash et al., 2022; Figure 1).

Table 1. Vasoactive Peptides Associated With Fibrogenesis in Neuroendocrine Tumors

- Serotonin receptor type 5-HT_{2b}
- Bradykinin A
- Neuropeptide K
- Prostaglandins
- Substance P
- Transforming growth factor β

The serotonin receptor is most abundant in the heart. The stimulation of these receptors increases the mitogenic cell activity of cardiomyocytes and fibroblasts, resulting in the release of proinflammatory cytokines and transforming growth factor β. Fibrosis occurs on the endocardial surfaces of valve leaflets and can cause fused and shortened chordae tendineae and thickened papillary muscle. These are both characteristics of CHD. These deposits are comprised of fibrosed tissue. The left heart is involved only when a high burden of vasoactive agents exceeds the degradation of this substance, primarily in the liver or lung, where these bioactively secreted substances are metabolized and inactivated. Carcinoid syndrome only occurs if the active metabolite 5-HT makes it to the systemic circulation, bypassing these two pathways usually because of organ metastasis or exceedingly high levels of these vasoactive agents. Examples include retroperitoneal metastasis and bronchial carcinoids that are associated with carcinoid syndrome because vasoactive agents have been released into the systemic circulation via the inferior vena cava to the right heart or, in the case of retroperitoneal metastasis, into the renal vein leading to the inferior vena cava bypassing inactivation in the liver. In the case of lung metastasis or the rare instance of primary pulmonary tumor location, the left heart is exposed to the pathologic changes associated with CHD (Bober et al., 2020; Laskaratos et al., 2021; Subash et al., 2022).

RIGHT-SIDED HEART FAILURE

Carcinoid heart disease may remain clinically undetectable until advanced pathology has occurred. A first presentation with symptoms of advanced right-sided heart failure may account for the association between CHD and poor long-term prognosis (Alizadehasl et al., 2021; Ram et al., 2019). Several presenting right-sided heart failure symptoms are directly related to right ventricular dilation in response to the increasing volume load imposed by valvular dysfunction. Volume pressure transferred back to the venous system manifests in peripheral edema, jugular vein distention, pleural effusions, and weight gain. Congestive hepatopathy produces pulsatile hepatomegaly, elevated liver enzymes, coagulopathy, bleeding risk, and ascites (Francis, 2022). Stomach and intestinal congestion exacerbate abdominal distension, discomfort, early satiety, malnutrition, and cardiac cachexia. Pleural effusions, ascites, and peripheral edema without right-sided heart failure may be related to liver insufficiency, malnutrition, or tumorous venous obstruction (Bober et al., 2020).

Mechanisms contributing to decreased right ventricular output and left ventricular filling culminate in dyspnea on exertion and fatigue. 3D echocardiogram confirms early right ventricular contractile impairment independent of, yet later worsened by, valvular dysfunction (Khay et al., 2018; Lyon et al., 2022). Contractility may also be negatively impacted by right ventricular ischemia in the setting of underlying coronary artery disease, as CHD produces vulnerability of diseased endothelium to vasoconstriction and coronary stents to stenosis (Alizadehasl et al., 2021; Jin et al., 2021; Ram et al., 2019). Right ventricular contractility is initially preserved at rest while the contractile reserve for increased activity progressively declines.

Typically, pericardial restraint assures a limit to the cross-sectional expansion of the right and left ventricles, creating diastolic ventricular interdependence. As CHD progresses, this interdependence becomes exaggerated during exercise, compromising left ventricular filling (Bigler et al., 2020). Diastolic left ventricular filling is initially maintained as the dilating right ventricular is matched with a gradual stretching of the pericardium. As volume overload progresses to a

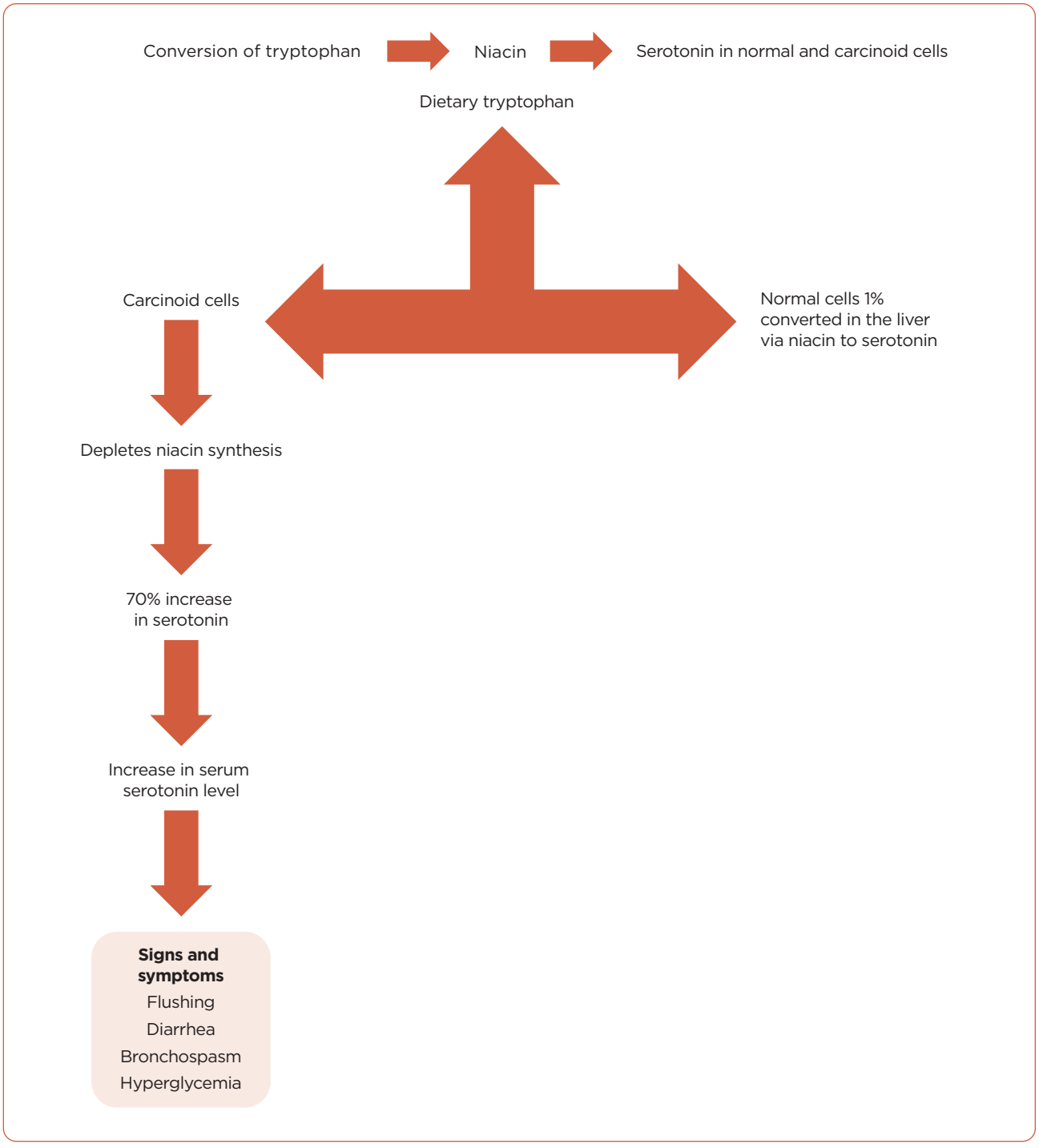

Figure 1. Pathophysiologic pathways leading to symptoms.

critical point, pericardial restraint will dramatically increase with the acute increase in venous return accompanying exercise (Reddy, 2021). This, along with septal bowing into the left ventricular, significantly compromises left ventricular filling, stroke volume, and cardiac output when needed. Fatigue with decreasing activity levels becomes evident.

Additionally, metaboreceptor stimulation of the respiratory center in inadequate tissue oxygen delivery produces dyspnea on exertion. Dyspnea

on exertion is further exacerbated by lung congestion resulting from the reflection of increased left heart pressure exerted by a growing pericardial restraint during exercise into the pulmonary capillaries (Reddy, 2021).

Although valve replacement does not consistently improve right ventricular function, decreased right ventricular size has been observed following both tricuspid valve and pulmonary valve replacement (Connolly et al., 2002). This size reduction alleviates most symptoms of right-sided heart failure despite unchanged function. In the past, medical treatment to palliate right-sided heart failure symptoms was recommended. Surgical valve replacement was reserved for severely symptomatic patients. With the knowledge that perioperative mortality increases with the severity of preoperative right-sided heart failure and the safety of improved valve replacement techniques, early intervention has become preferable, although guidelines for the timing of surgery have not been established (Alizadehasl et al., 2021; Balanescu et al., 2018; Bober et al., 2020; Luthra et al., 2020; Lyon et al., 2022; Sanchez-Nadales et al., 2020).

SCREENING AND DIAGNOSTICS

Most often, patients undergo workup for CHD after presenting to the hospital with signs of right-sided heart failure. In addition, patients with the noncardiac symptoms of carcinoid syndrome, including flushing, wheezing, diarrhea, and abdominal pain, undergo workups. The workup includes plasma level and/or urinary excretion of 5-HIAA, serum level of glycoprotein chromogranin A (CgA), and natriuretic peptides. Echocardiography remains the mainstay for diagnosis of CHD. Evaluation of the tricuspid and pulmonary valve involvement, right ventricular size and function of left-sided valves, presence of patent foramen ovale, and any cardiac metastases is imperative to evaluate the extent of CHD (Baron et al., 2021; Lyon et al., 2022). Of note, the electrocardiogram is often performed in patients, although it yields little diagnostic support as it often demonstrates sinus tachycardia and nonspecific ST-T abnormalities (Ram et al., 2019).

Completing a urine analysis and serum analysis for 5-HIAA levels is necessary for diagnosis and follow-up of carcinoid syndrome. Carcinoid tumors release 5-HT and metabolize in the liver, lungs, and brain to 5-HIAA. In patients with carcinoid syndrome, levels of 5-HT are elevated and often accompanied by diarrhea. In patients who have no symptoms of carcinoid syndrome, rarely are the urinary 5-HIAA levels markedly high, but instead may have slightly increased levels. Plasma and urinary levels are significantly higher in patients with CHD compared with those without cardiac involvement. While studies show that 5-HIAA is a significant predictor of CHD, sampling can be technically challenging. Urinary 5-HIAA levels require complete 24-hour sampling. Certain foods rich in tryptophan can skew the results by causing an elevation in urinary excretion of 5-HIAA and lead to a false negative. Drugs may also increase these levels, including acetaminophen, ephedrine, and diazepam, among others.

Conversely, particular drugs may lead to false negative results, including aspirin and levodopa. More recently, plasma analysis for 5-HIAA has been utilized, as it is more convenient for the patients and simpler to collect. Studies have shown similar associations between CHD progression and elevated 5-HIAA levels (Davar et al., 2017).

A valuable biomarker of CHD is N-terminal pro-B-type natriuretic peptide (NT-proBNP) using a cutoff level of 250 pg/mL. Bhattacharyya and colleagues (2007) showed that levels were significantly higher in patients with CHD (median 1,149 pg/mL) than in carcinoid patients without heart disease (median 101 pg/mL). NT-proBNP carries a sensitivity rate of 92% and a specificity rate of 91%. There was also an association between high levels of NT-proBNP and patients experiencing worse symptoms (Davar et al., 2017; Lyon et al., 2022). Chromogranin A is an established biomarker for neuroendocrine tumors. It is a glycoprotein released by neuroendocrine tumor cells and is elevated in more than 80% of patients with advanced carcinoid tumors. Chromogranin A carries a high sensitivity value (up to 100%) but specificity of only 30% to predict severe CHD. Therefore, it is indicated to assess for neuroendocrine tumor recurrence or tumor progression and not recommended as a screening test for CHD. It can, however, be helpful in prognostication as it can be useful in assessing mortality. Elevated levels of both NT-proBNP and CgA are associated with higher mortality.

Patients with CHD with elevated CgA levels and normal NT-proBNP had a survival probability of 44% after 5 years. In contrast, patients with elevated levels of both had only a 16% survival probability (Davar et al., 2017). Research surrounding other biomarkers, including activin A, is ongoing and may lead to updates in the clinical practice guidelines for patients with CHD.

Abnormalities seen on echocardiography in a patient with CHD vary depending on the level of cardiac involvement. On evaluating the tricuspid valve in a patient with CHD, it is typical to see a dilated annulus and diffusely thickened, retracted leaflets with a loss of pliability. Chordae may also be thickened and shortened, which may have some effect on papillary muscles at times. It may also reveal severe tricuspid regurgitation and, very rarely, tricuspid stenosis (Baron et al., 2021). Evaluation of the pulmonary valve may reveal leaflet thickening, retraction, and restricted mobility in CHD with combined pulmonic regurgitation and stenosis. The right ventricle may appear dilated, with diastolic septal flattening, right ventricular remodeling, and initially increased systolic function, followed by a decline due to right ventricular failure over time. Evaluation for a patent foramen ovale is critical, as right-to-left shunting may occur in this setting, enabling the active substances to affect the left-sided valves by bypassing the pulmonary passage deactivation process. Aortic and/or mitral regurgitation is seen chiefly in cases involving the left-sided valves, but it is mostly not severe (Baron et al., 2021). Transthoracic echocardiography is an efficacious imaging modality, although some patients may require transesophageal imaging. This poses a potential problem, as a carcinoid crisis may be triggered during transesophageal echocardiography.

The use of cardiac MRI is increasing in the diagnostic workup of patients with CHD. Typically, it is utilized in patients with insufficient or inconclusive echocardiography results. It allows for accurate quantification of valvular regurgitation and provides better data than echocardiography in this respect. Cardiac MRI also provides the ability to characterize the cardiac muscle tissue and identify cardiac metastases (Baron et al., 2021).

Davar and colleagues (2017) proposed a screening algorithm for patients with metastatic neuroendocrine tumors to investigate the presence of CHD. It involves a clinical assessment and measurement of NT-proBNP every 6 months. In cases in which clinical features suggest CHD and/or NT-proBNP levels are greater than 250 ng/mL, it is recommended to perform transthoracic echocardiography (preferably with contrast bubble study to evaluate for patent foramen ovale). If the transthoracic echocardiogram is normal, the patient will return to every-6-month screenings. If it is diagnostic of CHD, the patient should be referred to a cardiologist with a background in treating it. If the echocardiogram reveals abnormal pathology but does not suggest CHD, the patient should be referred to a cardiologist. Following a screening algorithm is essential in early diagnosis and prompt treatment (Davar et al., 2017; Lyon et al., 2022).

MANAGEMENT

The treatment of advanced metastatic carcinoid includes agents that block the biologically active mediators, cytotoxic treatment in highly proliferative tumors, somatostatin receptor–based peptide radionuclide therapy, and transcatheter embolization and/or surgical removal of the tumors (Baron et al., 2021). Typically, there is a multifaceted approach to managing CHD. This management involves a collaborative team, including cardiology and oncology, and often involves many other disciplines, including hepatobiliary and cardiovascular surgeons, endocrinologists, anesthesiologists, and gastroenterologists. The treatment of carcinoid syndrome involves somatostatin analogs, such as long-acting octreotide and lanreotide autogel (Laskarato et al., 2021). If further treatment is required, there are other options. These include interferon alfa, telotristat ethyl to reduce serotonin secretion, peptide receptor radionuclide therapy, transarterial embolization, and surgical cytoreduction. These treatments remain the mainstay and adjunct options for carcinoid syndrome. This review will focus on the treatments specific to CHD, involving surgery and perioperative management.

In valvular disease and heart failure from CHD, treatment typically follows American College of Cardiology/American Heart Association guidelines for heart failure, which include guideline-directed medical therapy involving blood pressure management with angiotensin-

converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), diabetes control, healthy lifestyle habits, beta-blockers, and statin therapy (Heidenreich et al., 2022). In patients with carcinoid-induced ventricular tachycardia, beta-blockers may be helpful. Diuretics must be used cautiously to minimize the reduction in cardiac output in patients with right-sided dysfunction. Blood pressure management involving ACE inhibitors, ARB, renin inhibitors, and spironolactone is typically discontinued prior to surgical intervention to mitigate hemodynamic instability in the perioperative setting (Jin et al., 2021).

SURGICAL INDICATIONS AND ANESTHESIA MANAGEMENT

The recommendation to undergo cardiac surgery should be based on the goals of prolonging survival and improving a patient's quality of life (Davar et al., 2017). Surgery is indicated for severe valvular dysfunction, symptomatic right ventricular failure, and to reduce systemic venous pressure elevation in preparation for hepatic resection of carcinoid tumor. The recommended procedures may include tricuspid or pulmonic valve replacement, and less commonly, aortic or mitral valve replacement, patent foramen ovale closure, or metastatic tumor excision (Davar et al., 2017). These open-heart surgeries are traditionally performed through a full median sternotomy, requiring cardiopulmonary bypass.

Tricuspid valve replacement with or without pulmonic valve replacement is the most commonly indicated surgery. Albåge and Montibello (2020) note that pulmonic valve regurgitation and stenosis may be underestimated in the presence of severe tricuspid regurgitation, and severe pulmonic valve disease may be unmasked following isolated tricuspid valve replacement. Therefore, pulmonic valve intervention should be considered during tricuspid valve replacement. For 10% to 15% of patients, left heart involvement may necessitate the replacement of the mitral and/or aortic valves (Albåge & Montibello, 2020).

Once the decision is made to perform surgical valve replacement, the choice of mechanical vs. bioprosthetic valve must be considered. Mechanical valves resist degeneration but necessitate life-long systemic anticoagulation to prevent valve thrombosis. The risk of valve thrombosis is greater in the right heart than in the left heart, possibly because of lower pressures. Due to the high prevalence of liver dysfunction in this patient population, anticoagulation medications may introduce an unacceptable bleeding risk. These patients also frequently require invasive procedures, which may be complicated by the need to maintain anticoagulation (Sabet et al., 2020). Bioprosthetic valves do not require lifelong anticoagulation but are susceptible to the degenerative fibrotic deposits associated with progressive carcinoid disease (Jin et al., 2020).

A newer alternative, percutaneous transcatheter valve replacement, has successfully been used to treat tricuspid bioprosthetic and pulmonic valve disease in patients with CHD (Luthra et al., 2020). These transcatheter techniques may be offered to patients who might not otherwise have been surgical candidates. In patients who have previously undergone sternotomy surgery and present with bioprosthetic valve degeneration or pulmonic valve disease, this technique can be offered to avoid the increased risk of a redo sternotomy.

Preoperative preparation must include recognition and management of right heart dysfunction, often with the administration of inotropic and diuretic medications. Cardiology should optimize the treatment of patients with right heart disease. Preoperative optimization also includes limiting vasoactive mediator release. Clinical manifestations of neuroendocrine release include facial flushing, fluctuating blood pressure, tachycardia, bronchospasm, and diarrhea. These symptoms should be managed with the administration of octreotide, which blocks the release of serotonin and other vasoactive mediators. An octreotide infusion of 50 to 100 µg/hr should be initiated 12 hours before surgery (Castillo et al., 2018). Dehydration, electrolyte derangements associated with diarrhea, and poor nutrition are common and will likely require guided fluid and electrolyte replacement, nutritional support, and blood glucose control.

A goal of anesthesia management is the prevention, early diagnosis, and treatment of life-threatening carcinoid crises. Such a crisis is a result of an uncontrolled release of vasoactive mediators that can potentially end in cardiovascular collapse. Fluctuations in blood pressure

and tumor manipulation can trigger the release of vasoactive substances (Iglesias-Gonzalez et al., 2022). Common triggers include anxiety, hypothermia, and hypercapnia (Castillo et al., 2018). Intraoperative carcinoid crisis can be mitigated by hemodynamic optimization and the limitation of neuroendocrine production of vasoactive mediators throughout the preoperative, intraoperative, and postoperative phases of care.

During cardiac surgery, the priority is to avoid triggers of carcinoid crisis, including hemodynamic fluctuations. Therefore, anesthetic induction, endotracheal intubation, and initiation of cardiopulmonary bypass require careful management. Medications that enhance histamine release, such as atracurium, meperidine, morphine, and hydromorphone, should be avoided. Fentanyl, remifentanil, desflurane, isoflurane, and sevoflurane can be used (Wiederholt et al., 2022). The octreotide infusion, if continued intraoperatively, can be increased to 300 μg/hr. Bolus administration (50–100 μg) is used to prevent or treat symptoms suggestive of carcinoid crisis. The infusion can be continued postoperatively. Perioperative hypotension should be managed with phenylephrine and vasopressin as opposed to sympathomimetics epinephrine, norepinephrine, dopamine, and ketamine (Wiederholt et al., 2022). Histamine receptor antagonists (H_1 and H_2 or H_1 alone) are also recommended (Castillo et al., 2018; Wiederholt et al., 2022).

CONCLUSIONS

Carcinoid syndrome is a rare cause of acquired valve disease occurring mainly with the right heart valves, although left-sided involvement can also be seen. Survival has improved in patients with carcinoid tumors with the use of somatostatin analogues and surgical and transcatheter interventions. The management of CHD is often challenging as patients can present late with rapidly progressing disease. Poor access to medical care has also been reported as an added reason for delay (Sharma et al., 2023). Considering social determinants of health is an important part of the initial assessment for the advanced practice provider. An awareness of the disease is essential in the early diagnosis as is the need for close collaboration among various specialties to quantify disease burden, delay the progression of valvular disease, and determine the most effective surgical and/or medical management strategies to improve quality of life and reduce mortality. Future research is needed to better define the best therapeutic options.

Disclosure

Ms. Nicole Kuhnly is supported, in part, by the Core Grant (P30 CA008748) and the Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, New York. The authors have no conflicts of interest to disclose.

References

Albåge, A., & Montibello, M. (2021). Surgical aspects of valve replacement in carcinoid heart disease. *Journal of Cardiac Surgery, 36*(1), 290–294. https://doi.org/10.1111/jocs.15169

Alves, C., Mesquita, M., Silva, C., Soeiro, M., Hajjar, L., & Riechelmann, R. P. (2018). High tumour burden, delayed diagnosis and history of cardiovascular disease may be associated with carcinoid heart disease. *Ecancermedicalscience, 12*, 879. https://doi.org/10.3332/ecancer.2018.879

Alizadehasl, A., Galeshi, B., Peighambari, M., Pouraliakbar, H., Moradian, M., & Hashemi, A. (2021). A forgotten diagnosis in right heart failure: A case report and literature review. *Clinical Case Reports, 9*(4), 2040–2047. https://doi.org/10.1002/ccr3.3938

Balanescu, D. V., Donisan, T., Lopez-Mattei, J., Hassan, S., Kim, P., Dasari, D.,...Iliescu, C. (2019). The 1, 2, 3, 4 of carcinoid heart disease: Comprehensive cardiovascular imaging is the mainstay of complex surgical treatment. *Oncology Letters, 17*(5), 4126–4132. https://doi.org/10.3892/ol.2018.9732

Baron, T., Bergsten, J., Albåge, A., Lundin, L., Sörensen, J., Öberg, K., & Flachskampf, F. A. (2021). Cardiac imaging in carcinoid heart disease. *JACC. Cardiovascular Imaging, 14*(11), 2240–2253. https://doi.org/10.1016/j.jcmg.2020.12.030

Bhattacharyya, S., Davar, J., Dreyfus, G., & Caplin, M. E. (2007). Carcinoid heart disease. *Circulation, 116*(24), 2860–2865. https://doi.org/10.1161/circulationaha.107.701367

Bigler, M. R., Hunziker, L., Fausto de Marchi, S., Pilgrim, T., Windecker, C., & Seiler, S. C. (2020). Pulmonary artery pressure ventricularization in a patient with carcinoid heart disease. *Journal of the American College of Cardiology: Case Reports, 2*(8), 1200–1204. https://doi.org/10.1016/j.jaccas.2020.05.057

Bober, B., Saracyn, M., Kołodziej, M., Kowalski, K., Deptula-Krawcyk, E., Kapusta, W.,...Bil, J. (2020). Carcinoid heart disease: How to diagnose and treat in 2020? *Clinical Medicine Insights: Cardiology, 14*, 1–10. https://doi.org/10.1177/1179546820968101

Castillo, J., Silvay, G., & Weiner, M. (2018). Anesthetic management of patients with carcinoid syndrome and carci-

noid heart disease: The Mount Sinai Algorithm. *Journal of Cardiothoracic and Vascular Anesthesia, 32*(2), 1023–1031. https://doi.org/10.1053/j.jvca.2017.11.027

Connolly, H. M., Hartzell, V., Schaff, H. V., Mullany, C. J., Abel, M. D., & Pellikka, P. A. (2002). Carcinoid heart disease: Impact of pulmonary valve replacement in right ventricular function and remodeling. *Circulation, 106*(12), I51–I56. https://doi.org/10.1161/01.cir.0000032884.55215.87

Davar, J., Connolly, H. M., Caplin, M. E., Pavel, M., Zacks, J., Bhattacharyya, S.,...Toumpanakis, C. (2017). Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: An Expert Statement. *Journal of the American College of Cardiology, 69*(10), 1288–1304. https://doi.org/10.1016/j.jacc.2016.12.030

Francis, J. (2022). Carcinoid heart disease [Lecture with powerpoint slides]. *BMH Medical Journal*. https://johnsonfrancis.org/professional/carcinoid-heart-disease/

Grozinsky-Glasberg, S., Davar, J., Hofland, J., Dobson, R., Prasad, V., Pascher, A.,...Toumpanakis, C. (2022). European Neuroendocrine Tumor Society (ENETS) 2022 Guidance Paper for Carcinoid Syndrome and Carcinoid Heart Disease. *Journal of Neuroendocrinology, 34*(7), e13146. https://doi.org/10.1111/jne.13146

Hassan, S. A., Palaskas, N. L., Agha, A. M., Iliescu, C., Lopez-Mattei, J., Chen, C.,...Yusuf, S. W. (2019). Carcinoid heart disease: A comprehensive review. *Current Cardiology Reports, 21*(11), 140. https://doi.org/10.1007/s11886-019-1207-8

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M.,...Yancy, C. W. (2022). 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation, 145*(18). https://doi.org/10.1161/cir.0000000000001063

Jin, C., Sharma, A. N., Thevakumar, B., Majid, M., Al Chalaby, S., Takahashi, N.,...Amsterdam, E. A. (2021). Carcinoid heart disease: Pathophysiology, pathology, clinical manifestations, and management. *Cardiology, 146*(1), 65–73. https://doi.org/10.1159/000507847

Khay, K., Arous, S., Bentaoune, T., Drighil, A., & Habbal, R. (2018). Carcinoid heart disease revealed by cyanosis with both right and left valvular involvement: A case report. *Journal of Medical Case Reports, 12*(23), 1–5. https://doi.org/10.1186/s13256-018-1574-6

Laskaratos, F. M., Davar, J., & Toumpanakis, C. (2021). Carcinoid heart disease: A review. *Current oncology reports, 23*(4), 48. https://doi.org/10.1007/s11912-021-01031-z

Luthra, S., Olevano, C., Richens, T., Tsang, G. M. (2020). Percutaneous transcatheter valve-in-valve pulmonary and tricuspid replacement in carcinoid heart disease. *Journal of the American College of Cardiology: Case Reports, 2*(4), 533–536. https://doi.org/10.1016/j.jaccas.2019.11.089

Lyon, A. R., López-Fernández, T., Couch, L. S., Asteggiano, R., Aznar, M. C., Bergler-Klein, J.,...Moslehi, J. (2022). 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *European Heart Journal, 43*(41), 4229–4361. https://doi.org/10.1093/eurheartj/ehac244

Ram, P., Penalver, J. L., Lo, K. B. U., Rangaswami, J., & Pressman, G. S. (2019). Carcinoid heart disease: Review of current knowledge. *Texas Heart Institute Journal, 46*(1), 21–27. https://doi.org/10.14503/thij-17-6562

Reddy, Y. (2021). The hemodynamics of pericardial restraint in heart failure. *Journal of the American College of Cardiology*. https://www.acc.org/latest-in-cardiology/articles/2021/05/04/19/07/the-hemodynamics-of-pericardial-restraint-in-heart-failure

Rubin de Celis Ferrari, A. C., Glasberg, J., & Riechelmann, R. P. (2018). Carcinoid syndrome: Update on the pathophysiology and treatment. *Clinics (Sao Paulo, Brazil), 73*(suppl 1), e490s. https://doi.org/10.6061/clinics/2018/e490s

Sanchez-Nadales, A., Celis-Barreto, V., Anampa-Guzman, A., Salazar-Leon, M., & Contreras-Cavez, P. (2020). Carcinoid right heart disease. *Journal of Medical Cases, 11*(3), 73–76. https://doi.org/10.14740/jmc3452

Sharma, A., Fierro, M. E., Pak, S., Thallapureddy, K., Awoajo, M., & Otchere, P. (2023). Late stage diagnosis of carcinoid heart disease due to lack of access to health care. *Cardiooncology, 9*(28). https://doi.org/10.1186/s40959-023-00176-z

Steeds, R., Sagar, V., Shetty, S., Oelofse, T., Singh, H., Ahmad, R.,...Shah, T. (2019). Multidisciplinary team management of carcinoid heart disease. *Endocrine Connections, 8*(12), R184–R199. https://doi.org/10.1530/EC-19-0413

Subash, N., Papali, M. M., Bahadur, K. P., Avanthika, C., Jhaveri, S., Thannir, S.,...Valisekka, S. S. (2022). Recent advances in the diagnosis and management of carcinoid syndrome. *Disease-a-month: DM, 68*(7), 101304. https://doi.org/10.1016/j.disamonth.2021.101304

Uema, D., Alves, C., Mesquita, M., Nuñez, J. E., Siepmann, T., Angel, M.,...Riechelmann, R. P. (2019). Carcinoid heart disease and decreased overall survival among patients with neuroendocrine tumors: A retrospective multicenter Latin American cohort study. *Journal of Clinical Medicine, 8*(3), 405. https://doi.org/10.3390/jcm8030405