

Chapter 8

Right Heart Failure from Carcinoid Syndrome



Melissa A. Lyle and Heidi M. Connolly

Case

A 64-year old female with a history of a neuroendocrine tumor presents with exertional dyspnea and progressive lower extremity edema. Four years prior she presented with frequent diarrhea and abdominal pain. Abdominal computed tomography revealed a cecal mass and multiple hepatic lesions. Colonoscopy identified the mass located at the ileocecal valve, and biopsy revealed a well-differentiated neuroendocrine tumor. Liver biopsy was consistent with metastatic neuroendocrine tumor, and monthly octreotide injections were started. Despite octreotide injections, she continued to experience flushing and severe diarrhea, with greater than ten bowel movements per day.

Progressive lower extremity edema, exertional dyspnea, and fatigue raised the concern for carcinoid heart disease (CHD). Physical exam illustrated an elevated jugular venous pressure around 15 cm of water, with a prominent “V” wave and a parasternal impulse. Auscultation revealed single first and second heart sounds, grade 2 systolic and grade 2 diastolic murmurs, best heard at the left sternal border, with an

M. A. Lyle · H. M. Connolly (✉)

The Department of Cardiovascular Medicine, Mayo Clinic,
Rochester, MN, USA

e-mail: Connolly.heidi@mayo.edu

© Springer Nature Switzerland AG 2020

L. Tsao, M. E. Afari (eds.), *Clinical Cases in Right Heart Failure*, Clinical Cases in Cardiology,

https://doi.org/10.1007/978-3-030-38662-7_8

171

increase in intensity with inspiration. A transthoracic echocardiogram was ordered to evaluate for CHD.

8.1 What Is the Initial Approach to Evaluating Right-Sided Valvular Disease?

When a patient present with signs of right-sided heart failure, including increasing dyspnea, lower extremity edema, and ascites, the initial evaluation should include a physical examination (see Chap. 2). And if physical exam confirms suspicion of right-sided valvular disease, then a transthoracic echocardiogram should be performed to further elucidate pathology. Cardiac magnetic resonance imaging and computed tomography can serve as valuable adjuncts for the assessment of right-sided valvular disease in select cases.

8.2 Discuss the Pathophysiology of Carcinoid Heart Disease

Neuroendocrine tumors are rare, with an incidence ranging from 2.5 to 5 per 100,000 people [1]. These tumors arise from enterochromaffin cells; they can occur anywhere in the body, but have a predilection for the gastrointestinal tract. Gastrointestinal neuroendocrine tumors were originally described as “carcinoids,” with the “midgut carcinoid,” originating from the distal small intestine to the proximal colon [2]. Primary midgut carcinoid tumors can metastasize to the liver and regional lymph nodes. Thirty to forty percent of patients with carcinoid tumors present with carcinoid syndrome, and the most common manifestations are vasomotor changes such as flushing and hypotension, gastrointestinal hypermotility with diarrhea, and bronchospasm. Carcinoid tumors release vasoactive substances, such as serotonin (5-hydroxytryptamine), 5-hydroxytryptophan, histamine, bradykinin, and prostaglandins, responsible for the

vasomotor changes. Carcinoid syndrome frequently occurs in the setting of primary midgut carcinoid tumor metastases to the liver because the vasoactive substances reach the systemic circulation quickly via the hepatic vein [3].

CHD occurs in over 50% of patients with carcinoid syndrome and [4, 5] is characterized by plaque-like depositions on the endocardial surface of heart valves, most frequently the right-sided valves, the subvalvular apparatus, cardiac chambers, and even occasionally the intima of pulmonary arteries and aorta [6, 7]. The pathogenesis of CHD is still not completely understood. It is speculated that the vasoactive substances, particular serotonin (5-HT), secreted by the neuroendocrine tumor induce proliferative effects on fibroblasts, upregulate transforming growth factor- β 1, and activate inflammatory cytokines by activating the 5-HT receptors. The 5-HT_{2B} receptors are most prevalent on heart valves. The resulting plaque-like deposits are comprised of myofibroblasts, smooth muscle cells, and an extracellular matrix composed of collagen, microfibrils, and mucopolysaccharides [7]. In approximately 90% of CHD cases, the right-sided valves are primarily affected [3]. It is thought that the left-sided valves are often spared because of the inactivation of vasoactive substances by the lungs. When left-sided valve pathology occurs, it is often associated with an atrial level right-to-left shunt [5], which allows the vasoactive substances to reach the left sided cardiac chambers without undergoing inactivation in the pulmonary capillaries. Recent investigations have also revealed that bronchopulmonary carcinoid is not associated with left-sided involvement in the absence of a patent foramen ovale as previously suspected [8].

The affected right-sided valves have a typical thickened white appearance. The carcinoid plaques typically deposit on the ventricular aspect of the tricuspid valve leaflets, resulting in leaflet thickening, reduced mobility, and thickening of the subvalvular apparatus and papillary muscles. In severe cases, there is reduced excursion and the leaflets become retracted and do not coapt. This is associated with severe tricuspid valve regurgitation, with a classic dagger-shaped profile on Doppler echocardiography, and occasionally mild tricuspid stenosis [1, 3, 9].

The carcinoid plaques frequently affect the arterial aspect of the pulmonary valve cusps. In a similar pattern to the tricuspid valve, the pulmonary valve cusps can become diffusely thickened in CHD. This progressive thickening results in straightening of the cusps, leading to retraction and severe pulmonary valve regurgitation [3]. Pulmonary annular stenosis is also associated with CHD, and can be visualized by 2D echocardiography and may cause increased velocities noted on continuous wave Doppler echocardiography in the right ventricular outflow tract.

8.3 What Are the Clinical Manifestations of Carcinoid Heart Disease?

The clinical manifestations of CHD include features of right-sided heart failure. Early symptoms may include progressive fatigue and dyspnea on exertion. As the right-sided heart failure progresses, patients can present with increasing dyspnea, ascites, early satiety, and lower extremity edema. Physical exam will frequently illustrate elevated jugular venous pressure, with a prominent “V” wave in the setting of severe tricuspid valve regurgitation. On palpation, a right ventricular heave is often noted, and a pulsatile liver can be felt in the setting of severe tricuspid valve regurgitation. Auscultation will reveal the holosystolic murmur of tricuspid valve regurgitation and the diastolic murmur of pulmonary regurgitation, and occasionally the diastolic murmur of tricuspid stenosis and the systolic pulmonary stenosis murmur. The valve murmurs are often subtle due to the low pressure right-sided system.

8.4 What Is the Diagnostic Work Up?

The initial diagnostic work-up includes a detailed history and physical exam. Chest radiography may illustrate enlargement of the right-sided chambers, with right ventricular enlargement often indicated by a decreased retrosternal space noted on the lateral view. An electrocardiogram often illustrates

ST-T wave abnormalities and some demonstrate low voltage QRS, but most electrocardiograms in patients with CHD demonstrate nonspecific findings.

Laboratory evaluation, specifically biomarkers, can aid in the initial diagnosis of CHD. The most useful biomarker is N-terminal pro-B-type natriuretic (NT-proBNP), which does have diagnostic and prognostic importance [10]. In the absence of known CHD, it is recommended that yearly NT-proBNP levels be obtained in patients with carcinoid syndrome to monitor for CHD. Urinary 5-hydroxyindoleacetic acid (5-HIAA), the result of serotonin metabolism by monoamine oxidases in the liver, also serves as a biomarker for CHD [11]. Plasma and urinary 5-HIAA levels are elevated in patients with CHD, and higher levels are associated with an increased risk of progression of disease [12]. Finally, chromogranin A (CgA) is a glycoprotein released by the neuroendocrine tumor and is increased in a majority of patients with CHD. This biomarker is quite sensitive, up to 100% for detection of CHD, but only 30% specific. Therefore, CgA levels are more helpful for detection of recurrence of the neuroendocrine tumor rather than initial screening for CHD [10, 13].

Transthoracic echocardiography (TTE) remains the gold standard for diagnosis and evaluation of CHD. Frequently, TTE can illustrate characteristic features, such as the thickened and retracted tricuspid valve with associated severe regurgitation, as well as the immobility of the pulmonary valve cusps and pulmonary annular constriction, resulting in pulmonary valve regurgitation and outflow tract obstruction. However, when the pulmonary valve cusps are severely thickened and retracted, it may be difficult to visualize them by standard TTE, and 3D echocardiography can enhance visualization of the cusps. 3D echocardiography can also aid in right ventricular volume and function assessment [14]. Several echocardiographic scoring systems have been created in an attempt to further define prognostic features in CHD, and it was determined that the scoring system that focuses mainly on tricuspid valve anatomy and regurgitation is best for screening, with more complex scoring systems reserved for monitoring pro-

gression of disease in patients with established heart disease [15]. An agitated saline shunt study should be performed during the initial echocardiogram for CHD to identify any potential right-to-left atrial level shunt, given the risk of left-sided valve involvement in patients with a patent foramen ovale or atrial level right-to-left shunt.

Multimodality imaging echocardiography (as shown in Chap. 3) is often utilized to refine the diagnostic assessment of CHD, and can be complimentary to initial echocardiography. Cardiac magnetic resonance (CMR) imaging can further define CHD, particularly assisting in delineating the degree of pulmonary valvular involvement and right ventricular volume and function assessment. CMR can also further define other morphologic features of CHD, such as myocardial metastases [3, 16]. Cardiac computed tomography (CT) is a valuable tool for assessing the degree of valvular pathology in CHD, and aids in evaluation of right ventricular size and function [17], similar to CMR. Cardiac CT can also provide a pre-operative assessment of coronary artery anatomy.

Functional imaging with radiolabeled somatostatin analogues, such as gallium-68-DOTATOC/DOTATATE positron emission tomography CT scanning, can help localize the primary tumor, and occasionally this type of functional imaging can be useful in the assessment of carcinoid cardiac metastases to the pericardium and myocardium. However, in general, cross-sectional imaging of the heart, in the form of echocardiography, CMR, and cardiac CT, are the optimal modalities to assess right-sided valvular pathology and right ventricular size and function [3].

Case Continued

A transthoracic echocardiogram was obtained for our patient, and this revealed features of classic CHD. She was found to have a severely thickened tricuspid valve with immobile leaflets (Fig. 8.1a). There was lack of tricuspid leaflet coaptation with severe tricuspid valve regurgitation (Fig. 8.1b). Continuous wave (CW) Doppler echocardiography illustrated a dagger-shaped

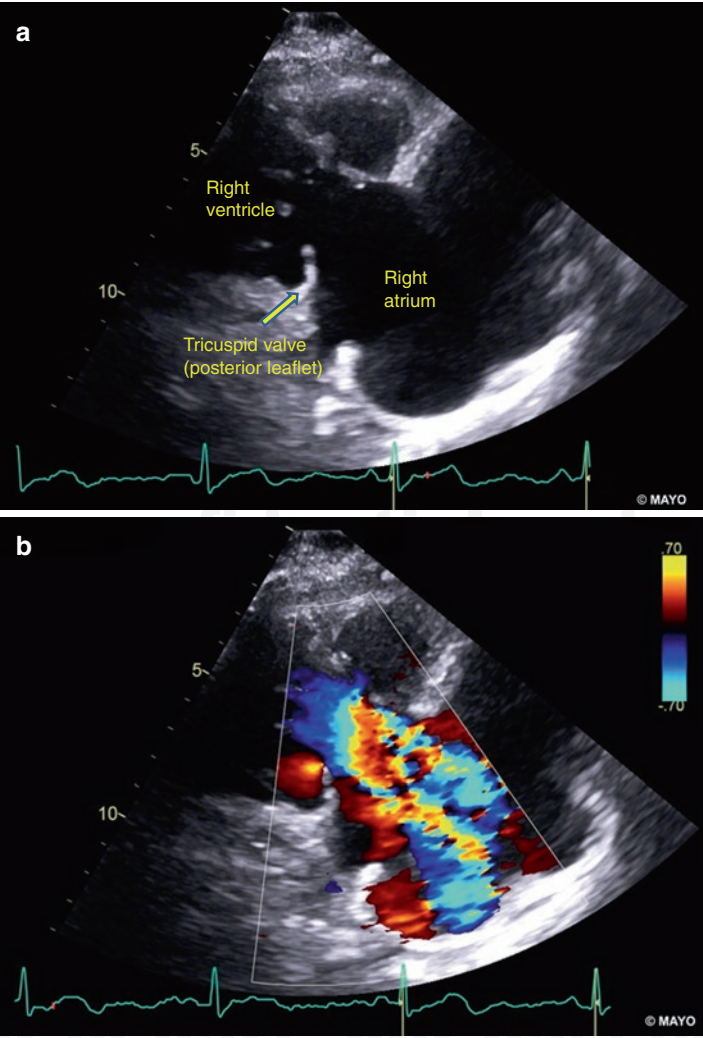


FIGURE 8.1 (a) Right ventricular inflow view illustrating thickened and retracted tricuspid valve leaflets. (b) Right ventricular inflow view illustrating severe tricuspid valve regurgitation

profile, consistent with severe tricuspid valve regurgitation. The tricuspid valve regurgitant velocity jet was only 2.4 m/s, which is in the setting of rapid equalization of pressures between the right atrium and right ventricle (Fig. 8.2). The inferior vena cava was dilated and non-collapsible, consistent with severely elevated central venous pressures. Systolic flow reversals were visualized in the hepatic veins in the setting of severe tricuspid valve regurgitation (Fig. 8.3). The pulmonary valve cusps were not well visualized by TTE, which is suspicious for severe pulmonary pathology (Fig. 8.4). Color flow imaging illustrated flow acceleration through the pulmonary valve (Fig. 8.5a) and also was suggestive of severe pulmonary valve regurgitation (Fig. 8.5b). There was also a rapid deceleration of the CW Doppler regurgitant signal with termination of flow in mid-diastole (Fig. 8.6). The right ventricle was severely enlarged, with a basal right ventricular diameter of 54 mm (upper normal 42 mm) and a mid-right ventricular diameter of 51 mm (upper normal 35 mm). There was mild-moderate dysfunction based on quantitative and qualitative assessment (Figs. 8.7 and 8.8).

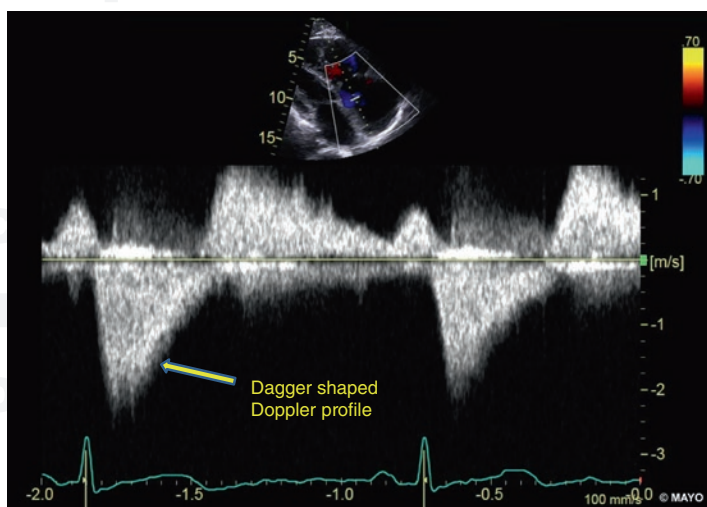


FIGURE 8.2 Continuous wave Doppler demonstrating severe tricuspid valve regurgitation with a dagger shaped Doppler profile, consistent with rapid equalization of pressures between the right atrium and right ventricle

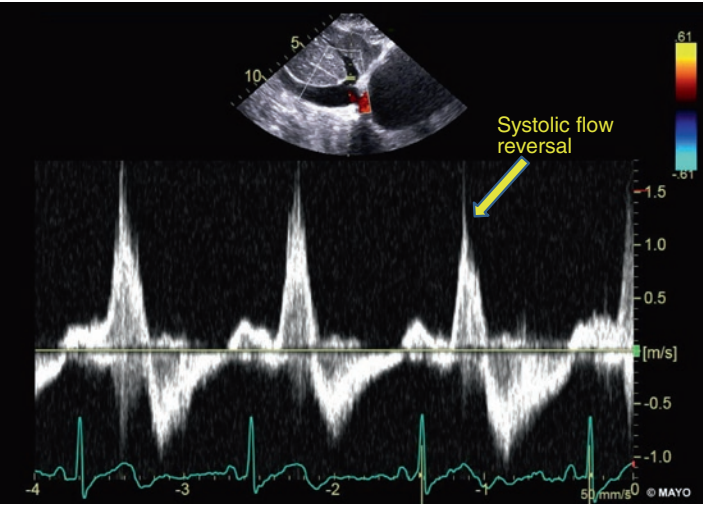


FIGURE 8.3 Hepatic vein pulsed wave Doppler with systolic flow reversals in the setting of severe tricuspid valve regurgitation and elevated right atrial pressure

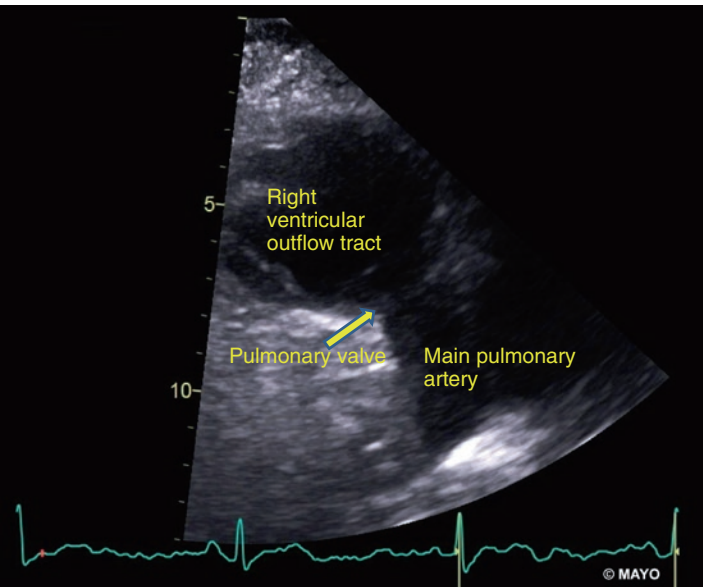


FIGURE 8.4 Right ventricular outflow view

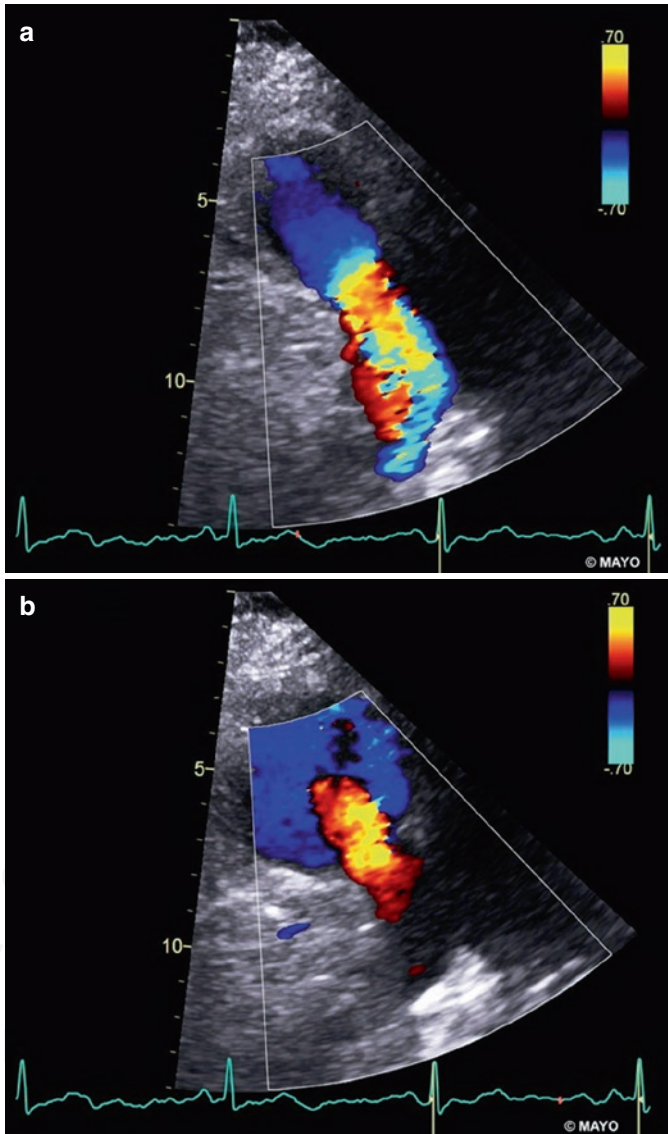


FIGURE 8.5 (a) Right ventricular outflow view illustrating flow acceleration through the pulmonary valve. (b) Right ventricular outflow view illustrating severe pulmonary valve regurgitation

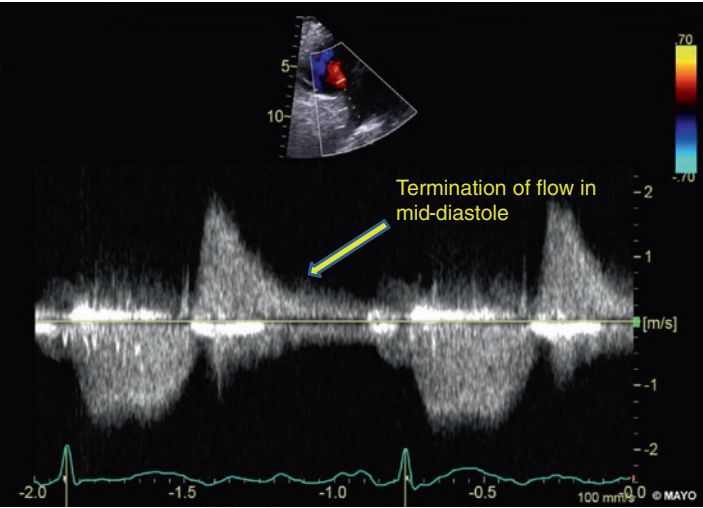


FIGURE 8.6 Continuous wave Doppler through the pulmonary valve, illustrating severe pulmonary valve regurgitation with a rapid deceleration time and termination of flow in mid-diastole

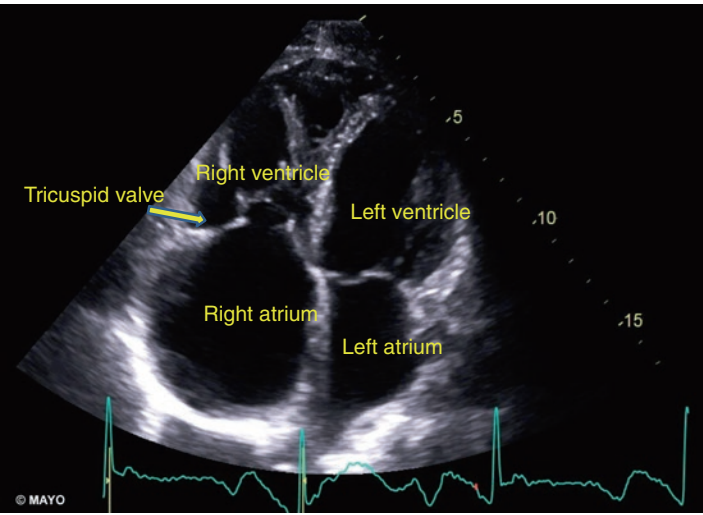


FIGURE 8.7 Apical four chamber view demonstrating right atrial and ventricular enlargement

This document is copyright of the original publisher. This document is strictly private, confidential and personal to its recipients and should not be copied, distributed or reproduced in whole or in part, nor passed to any third party.

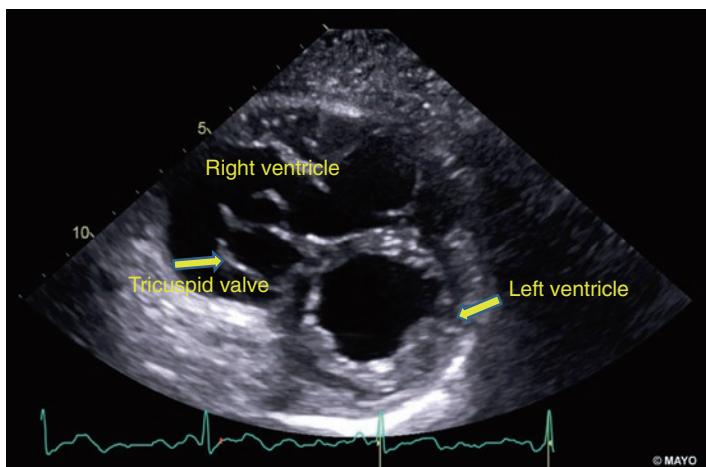


FIGURE 8.8 Short axis view illustrating right ventricular enlargement and lack of coaptation of tricuspid leaflets

Following the echocardiogram, a cardiopulmonary exercise test was completed to assess functional capacity. She exercised for only 4 min and had a low peak VO_2 (11.9 mL/(min kg), 55% predicted), despite maximal effort. These findings were consistent with cardiac output impairment in the setting of her CHD. She also underwent a PET DOTATATE scan, which illustrated extensive metastatic disease with progression, despite long-term therapy with a somatostatin analogue. Peptide Receptor Radionuclide Therapy (PRRT) is planned to slow the progression of her metastatic disease.

8.5 Discuss Medical Management

With regard to medical therapy for carcinoid syndrome, somatostatin analogues are the treatment of choice, and are even used in asymptomatic patients in an attempt to prevent or slow the progression of CHD [18, 19]. By decreasing the circulating serotonin levels, there could be added benefit of

somatostatin analogues for reducing risk of development and progression of CHD. Interferon alpha can be used in conjunction with somatostatin analogues for refractory carcinoid syndrome or in patients who do not tolerate somatostatin analogues [20]. In patients with advanced disease with limited response to somatostatin analogues, peptide receptor radionuclide therapy can be utilized in an attempt to control tumor growth. Finally, transcatheter arterial embolization (TAE) and surgical debulking have both served as effective treatments of advanced disease with predominant liver metastases. Embolization can be effective at reducing symptoms in 50–100% of patients with hepatic lesions [21]. Other studies have shown that patients with CHD who undergo liver resection have reduced risk of progression and an overall improved prognosis [22]. However, in patients with severe heart disease, it is important to exercise caution before undergoing hepatic resection, given the significant increased bleeding risk at the time of surgery. In patients with severe CHD with significant right-sided valvular pathology, right heart dysfunction, and elevated right atrial pressure, it may be prudent to address the right-sided valves prior to undergoing surgical intervention for hepatic metastases.

In regard to CHD, the first step in medical management is the treatment of right-sided failure. Unfortunately, medical therapy is mostly limited to loop diuretic therapy, which can improve lower extremity edema, ascites and shortness of breath, but may further decrease cardiac output by decreasing preload, leading to increased fatigue. The mainstay of therapy for severe right-sided valvular disease in the setting of CHD remains surgical intervention.

8.6 What Are the Indications for Tricuspid Valve Replacement?

Cardiovascular surgery with valve replacement is still the most effective treatment for advanced CHD and severe right-sided valvular pathology, most frequently severe regurgita-

tion. Valve surgery can dramatically improve symptoms in patients with severe CHD [23] and is the only treatment that improves survival [24]. Without surgical intervention, there is only an estimated 10% survival at 2 years once patients develop New York Heart Association (NYHA) functional Class III/IV symptoms [23, 25]. Tricuspid valve regurgitation is typically the main lesion in CHD, and therefore patients with CHD and severe tricuspid valve regurgitation are frequently evaluated for tricuspid valve replacement [26].

With severe pulmonary valve regurgitation occurring in conjunction with the tricuspid valve disease, it is preferable to proceed with pulmonary valve replacement rather than resection [27]. Given there is an association with pulmonary annular stenosis, a patch enlargement of the right ventricular outflow tract is often performed to alleviate any right ventricular outflow tract obstruction. Balloon valvuloplasty is not recommended for treatment of the pulmonary annular stenosis given the frequent presence of concomitant pulmonary regurgitation. If a patent foramen ovale is present, it should be closed at the time of surgery.

Two questions that surround the surgical treatment in CHD are the optimal timing of surgery and the choice of prosthesis type. Timing of surgery is difficult, and should involve a multidisciplinary approach. Patients with severe tricuspid and/or pulmonary valve regurgitation who develop cardiac symptoms and do not respond to medical therapy, should be referred for surgical consideration if the metastatic carcinoid disease is controlled. When observation rather than operation is chosen, it is important to continue monitoring patients for evidence of right ventricular dysfunction, and multimodality imaging can be helpful for further assessment of right ventricular size and function. Valve replacement should be considered for medication refractory right-sided heart failure. A final indication for cardiac valve replacement is prior to consideration of liver metastasis resection or liver transplantation to avoid excessive bleeding risk at the time of hepatic intervention [3].

There still remains some controversy regarding the choice of valve prosthesis, but the decision should always include shared

decision making. One disadvantage of mechanical valves is the need for continued systemic anticoagulation, which can be cumbersome when additional surgical interventions may be warranted. Another disadvantage is the known increased risk of thrombosis associated with mechanical valves in the tricuspid and pulmonic position, which approaches 4% per year [26, 28]. Bioprosthetic valves are usually preferred for patients with CHD, although there have been concerns for premature degeneration of the valve prostheses, thought to be hastened by the carcinoid syndrome [29, 30]. However, improvements in the treatment of carcinoid syndrome, with focus on optimization before and after surgery, may help protect the bioprosthetic valves from premature degeneration secondary to vasoactive substances [23]. Recent investigations have also shown that structural valve deterioration secondary to the carcinoid process is in fact rare. Another concern is bioprosthetic valve dysfunction secondary to thrombosis [25, 31]. Therefore, we recommended continued systemic anticoagulation for at least 3–6 months after bioprosthesis implantation.

Prior reports of operative mortality for valve replacement in CHD have ranged from 18 to 63% [32]. Recent studies have shown that early operative mortality has improved to approximately 5% in patients undergoing surgery at an experienced center since 2005 [33]. Overall, early mortality in cardiovascular surgery for CHD has improved, and it remains the most effective treatment to provide symptomatic improvement. However, overall survival for these patients still depends on tumor progression and their underlying neuroendocrine tumor prognosis [33].

8.7 Which Interventional Percutaneous Strategies Are Available?

While surgical valve replacement remains the gold standard for treatment of severe, symptomatic CHD, transcatheter valve replacement may become an attractive option for patients considered too high risk for cardiac surgery [34].

There have been case reports describing percutaneous pulmonary valve implantation in patients with native CHD [35], but experience appears to be more robust with transcatheter valve-in-valve replacement [36], with case reports describing valve-in-valve replacements in both the pulmonary and tricuspid positions [37]. Currently, percutaneous valve prostheses are not clinically available in the United States for treatment of native tricuspid valve disease.

Case Conclusion

Given overall survival still depends on tumor progression, the decision was made to initially treat our patient's metastatic carcinoid disease with PRRT. Following PRRT, she will complete a surgical evaluation, with potential tricuspid and pulmonary valve bioprosthetic replacements. In the interim, symptoms of right-sided heart failure will be palliated with loop diuretic therapy.

Clinical Pearls

1. Patients with carcinoid heart disease (CHD), which is characterized by plaque-like depositions on the endocardial surface of heart valves, most frequently right-sided valves, often present with symptoms of right-sided heart failure, including progressive dyspnea on exertion and fatigue.
2. Physical exam findings include elevated jugular venous pressure with a prominent "V" wave in the setting of severe tricuspid valve regurgitation, right ventricular heave on palpation, and the holosystolic murmur of tricuspid valve regurgitation and diastolic murmur of pulmonary regurgitation.
3. Transthoracic echocardiography can illustrate characteristic features, such as the thickened and retracted tricuspid valve with associated severe regurgitation, as well as the retracted pulmonary valve cusps and pulmonary annular constriction, resulting in pulmonary valve regurgitation and outflow tract obstruction. Multimodality imaging with CT and MRI can help further define valvular pathology and assess right ventricular enlargement and function.

4. Somatostatin analogues are the main medical treatment for carcinoid disease, but medical therapy for right sided heart failure in the context of CHD is limited to loop diuretic therapy.
5. Cardiovascular surgery with valve replacement is the gold standard treatment for advanced CHD and severe right-sided valvular pathology, most frequently for severe tricuspid regurgitation.

References

1. Bhattacharyya S, Toumpanakis C, Burke M, Taylor AM, Caplin ME, Davar J. Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI. *Circ Cardiovasc Imaging*. 2010;3:103–11.
2. Askew JW, Connolly HM. Carcinoid valve disease. *Curr Treat Options Cardiovasc Med*. 2013;15:544–55.
3. Davar J, Connolly HM, Caplin ME, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. *J Am Coll Cardiol*. 2017;69:1288–304.
4. Lundin L, Norheim I, Landelius J, Oberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. *Circulation*. 1988;77:264–9.
5. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation*. 1993;87:1188–96.
6. Pandya UH, Pellikka PA, Enriquez-Sarano M, Edwards WD, Schaff HV, Connolly HM. Metastatic carcinoid tumor to the heart: echocardiographic-pathologic study of 11 patients. *J Am Coll Cardiol*. 2002;40:1328–32.
7. Simula DV, Edwards WD, Tazelaar HD, Connolly HM, Schaff HV. Surgical pathology of carcinoid heart disease: a study of 139 valves from 75 patients spanning 20 years. *Mayo Clin Proc*. 2002;77:139–47.
8. De Jesus T, Luis SA, Ryu JH, et al. Carcinoid heart disease in patients with bronchopulmonary carcinoid. *J Thorac Oncol*. 2018;13:1602–5.

9. Callahan JA, Wroblewski EM, Reeder GS, Edwards WD, Seward JB, Tajik AJ. Echocardiographic features of carcinoid heart disease. *Am J Cardiol.* 1982;50:762–8.
10. Korse CM, Taal BG, de Groot CA, Bakker RH, Bonfrer JM. Chromogranin-A and N-terminal pro-brain natriuretic peptide: an excellent pair of biomarkers for diagnostics in patients with neuroendocrine tumor. *J Clin Oncol.* 2009;27:4293–9.
11. Maroun J, Kocha W, Kvols L, et al. Guidelines for the diagnosis and management of carcinoid tumours. Part 1: the gastrointestinal tract. A statement from a Canadian National Carcinoid Expert Group. *Curr Oncol.* 2006;13:67–76.
12. Bhattacharyya S, Toumpanakis C, Chilkunda D, Caplin ME, Davar J. Risk factors for the development and progression of carcinoid heart disease. *Am J Cardiol.* 2011;107:1221–6.
13. Bhattacharyya S, Gujral DM, Toumpanakis C, et al. A stepwise approach to the management of metastatic midgut carcinoid tumor. *Nat Rev Clin Oncol.* 2009;6:429–33.
14. Knight DS, Grasso AE, Quail MA, et al. Accuracy and reproducibility of right ventricular quantification in patients with pressure and volume overload using single-beat three-dimensional echocardiography. *J Am Soc Echocardiogr.* 2015;28:363–74.
15. Dobson R, Cuthbertson DJ, Jones J, et al. Determination of the optimal echocardiographic scoring system to quantify carcinoid heart disease. *Neuroendocrinology.* 2014;99:85–93.
16. Bastarrika G, Cao MG, Cano D, Barba J, de Buruaga JD. Magnetic resonance imaging diagnosis of carcinoid heart disease. *J Comput Assist Tomogr.* 2005;29:756–9.
17. Mollet NR, Dymarkowski S, Bogaert J. MRI and CT revealing carcinoid heart disease. *Eur Radiol.* 2003;13(Suppl 4):L14–8.
18. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *New Engl J Med.* 2014;371:224–33.
19. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J Clin Oncol.* 2009;27:4656–63.
20. Oberg K. Interferon in the management of neuroendocrine GEP-tumors: a review. *Digestion.* 2000;62(Suppl 1):92–7.
21. Toumpanakis C, Meyer T, Caplin ME. Cytotoxic treatment including embolization/chemoembolization for neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab.* 2007;21:131–44.

22. Bernheim AM, Connolly HM, Rubin J, et al. Role of hepatic resection for patients with carcinoid heart disease. *Mayo Clin Proc.* 2008;83:143–50.
23. Connolly HM, Nishimura RA, Smith HC, Pellikka PA, Mullany CJ, Kvals LK. Outcome of cardiac surgery for carcinoid heart disease. *J Am Coll Cardiol.* 1995;25:410–6.
24. Moller JE, Pellikka PA, Bernheim AM, Schaff HV, Rubin J, Connolly HM. Prognosis of carcinoid heart disease - analysis of 200 cases over two decades. *Circulation.* 2005;112:3320–7.
25. Connolly HM, Schaff HV, Abel MD, et al. Early and late outcomes of surgical treatment in carcinoid heart disease. *J Am Coll Cardiol.* 2015;66:2189–96.
26. Raja SG, Bhattacharyya S, Davar J, Dreyfus GD. Surgery for carcinoid heart disease: current outcomes, concerns and controversies. *Futur Cardiol.* 2010;6:647–55.
27. Connolly HM, Schaff HV, Mullany CJ, Abel MD, Pellikka PA. Carcinoid heart disease: impact of pulmonary valve replacement in right ventricular function and remodeling. *Circulation.* 2002;106:151–6.
28. Thorburn CW, Morgan JJ, Shanahan MX, Chang VP. Long-term results of tricuspid-valve replacement and the problem of prosthetic valve thrombosis. *Am J Cardiol.* 1983;51:1128–32.
29. DiSesa VJ, Mills RM Jr, Collins JJ Jr. Surgical management of carcinoid heart disease. *Chest.* 1985;88:789–91.
30. Ridker PM, Chertow GM, Karlson EW, Neish AS, Schoen FJ. Bioprosthetic tricuspid valve stenosis associated with extensive plaque deposition in carcinoid heart disease. *Am Heart J.* 1991;121:1835–8.
31. Pislaru SV, Hussain I, Pellikka PA, et al. Misconceptions, diagnostic challenges and treatment opportunities in bioprosthetic valve thrombosis: lessons from a case series. *Eur J Cardiothorac Surg.* 2015;47:725–32.
32. Castillo JG, Milla F, Adams DH. Surgical management of carcinoid heart valve disease. *Semin Thorac Cardiovasc Surg.* 2012;24:254–60.
33. Nguyen A, Schaff HV, Abel MD, et al. Improving outcome of valve replacement for carcinoid heart disease. *J Thorac Cardiovasc Surg.* 2019;158(1):99–107.e2.
34. Laule M, Pschowski R, Pape UF, et al. Staged catheter-based valve treatment of severe carcinoid heart disease. *Neuroendocrinology.* 2016;103:259–62.

35. Heidecker B, Moore P, Bergsland EK, Merrick SH, Rao RK. Transcatheter pulmonic valve replacement in carcinoid heart disease. *Eur Heart J Cardiovasc Imaging*. 2015;16:1046.
36. Conradi L, Schaefer A, Mueller GC, et al. Carcinoid heart valve disease: transcatheter pulmonary valve-in-valve implantation in failing biological xenografts. *J Heart Valve Dis*. 2015;24:110–4.
37. De Rosa R, Schranz D, Zeiher A, et al. Again, two melodies in concert: transcatheter double valve replacement in Hedinger syndrome. *Ann Thorac Surg*. 2017;104:61–3.

original publisher.

This document is

strictly private,

confidential and

personal to its

recipients and

should not be

copied, distributed or

reproduced in whole

or in part, nor passed

to any third party.