What do we know about carcinoid heart disease in the present era?

Mariola Pęczkowska[1], Sonia J Konsek-Komorowska[2], Agnieszka D Kolasińska-Ćwikła[3], Marek Konka[4], Ilona Michałowska[5], Jarosław B Ćwikła[2]

[1]Department of Hypertension, National Institute of Cardiology, Warszawa, Poland
[2]Department of Cardiology and Internal Medicine, School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland
[3]Maria Sklodowska-Curie National Research Institute of Oncology, Warszawa, Poland
[4]Department of Congenital Cardiac Defects, National Institute of Cardiology, Warszawa, Poland
[5]Department of Radiology, National Institute of Cardiology, Warszawa, Poland

Correspondence to:
Mariola Pęczkowska, MD, PhD, Department of Hypertension, National Institute of Cardiology, Alpejska 42, 04–628 Warszawa, Poland,
phone: +48 22 343 43 39,
e-mail: mpeczkowska@ikard.pl

DOI: 10.33963/KP.a2022.0222

Received:
March 31, 2022

Accepted:
June 17, 2022

Early publication date:
September 22, 2022

ABSTRACT

Carcinoid heart disease (CHD) is a severe complication of carcinoid syndrome (CS) found primarily in patients with small intestine neuroendocrine neoplasms (SI-NENs). Patients who develop CHD have significantly worse morbidity and mortality outcomes, highlighting the importance of clinical practice recommendations for CHD screening, diagnosis, and treatment that are both consistent and practical. CHD is characterized by white plaque-like deposits on the endocardial surface of heart structures, generally affecting the right heart valves, causing tricuspid and pulmonary regurgitation and, less commonly, valve stenosis. Cardiac imaging is essential for both the diagnosis and management of CHD. Previously, imaging for CHD was mostly achieved by echocardiography, but more recently, imaging has become multimodal. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and 5-hydroxyindoleacetic acid in the urine (u5-HIAA) are currently the most effective markers used in screening CS patients and evaluating CHD severity. Managing patients with CHD is challenging since both systemic malignant disease and cardiac involvement must be treated concurrently. Early diagnosis and surgical intervention when required are critical to patient prognosis, especially in those without primary tumor resection. Valve replacement surgery is the most effective treatment for patients with advanced carcinoid heart disease for alleviating cardiac symptoms and contributing to survival outcomes. To deliver effective patient treatment, multidisciplinary team collaboration is needed. This review summarizes current research findings on CHD pathogenesis, clinical and epidemiological features, useful biomarkers and imaging modalities, and treatment strategies.

Key words: carcinoid heart disease, carcinoid syndrome, neuroendocrine neoplasms of the small intestine

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a group of tumors that most commonly arise from the gastrointestinal tract and bronchopulmonary system. The incidence is estimated to be 6.9 cases per 100 000 people [1]. Gastro-entero-pancreatic neuroendocrine neoplasms/tumors (GEP NENs/NETs) derive from diffuse endocrine system (DES) cells located in the gastrointestinal tract and pancreas [2]. Neuroendocrine neoplasms of the small intestine (SI-NENs) originate in the midgut and are the third most common subtype of NENs in the gastroenteropancreatic system [3, 4]. GEP NETs are becoming more common across the world, particularly in North America, Asia, and Europe, with North America seeing the largest rise [5].

GEP NENs may be hormonally productive or not release enough hormones and/or biogenic amines. Non-functional neuroendocrine neoplasms are difficult to diagnose since they do not cause clinical symptoms of the disease.

Carcinoid syndrome (CS) is the most frequent paraneoplastic syndrome with a reported prevalence of approximately 19% in the NET patient population [1]. It is characterized by signs and symptoms linked to the hormonal activity of small intestine NENs. Increased synthesis and secretion to the systemic cir-

culation of 5-hydroxytryptamine (5-HT, serotonin) and/or other biologically active substances such as histamine, kallikrein, prostaglandins, and tachykinin lead to the development of the main clinical manifestations of carcinoid syndrome [4, 6]. Circulating hormones can be inactivated by the liver and lungs. However, in patients with liver metastases, production escapes the metabolism [7].

Carcinoid heart disease (CHD) is the most severe consequence of carcinoid syndrome, characterized by fibrotic valve degeneration, particularly in the right heart chambers. Isolated tricuspid valve regurgitation is found in up to 90% of patients; it causes progressive right heart failure and leads to a worsening of the patient's oncological prognosis [8–10]. CHD is observed in around 40% of patients with carcinoid syndrome [8].

The development of CHD is related to increased morbidity and mortality [11]. Patients with cardiac involvement have a markedly poorer long-term prognosis, with a 3-year survival rate of 31%, which is half that of patients who do not have cardiac involvement [9, 12–14]. Valvular carcinoid heart disease has a short life expectancy without treatment, with median overall survival (OS) of only 11 months in patients with advanced heart failure [15, 16].

All these facts indicate that, in the present era, focusing on accurate patient diagnosis, treatment, and management under the supervision of a multidisciplinary team, are essential to lengthen OS of patients with CHD. In this review article, we present a detailed description of the pathogenesis, clinical and epidemiological aspects, useful biomarkers and imaging modalities, as well as CHD management methods.

EPIDEMIOLOGY

CHD prevalence estimated in patients with carcinoid syndrome varies from 3% to 66% [8, 17–20], but in recent studies, has tended to be lower [17]. This might be due to an increase in somatostatin analogs usage and their impact on circulating serotonin levels, as well as improvements in diagnostic and surgical techniques [21–23].

Pellikka et al. [24] reported that the majority of CHD cases are associated with SI-NENs (72%), followed by lung, large bowel, pancreatic, and appendiceal neoplasms [24]. According to recent Mayo Clinic research, CHD is rare in individuals with bronchopulmonary NENs (1%) [25].

PATHOPHYSIOLOGY

CHD is characterized by formation of endocardial plaques on the surfaces of valve leaflets, chordae, papillary muscles, heart chambers, and in rare cases, the intima of the pulmonary arteries, and aorta [1, 26]. The plaque is formed as a result of dysregulated inflammatory and remodeling processes, which result in an inappropriate extracellular matrix formation, fibrosis, angiogenesis, and calcification, finally leading to structural valve deformation [1, 27].

The pathophysiology of fibrosis in NENs is still unknown, and few advances have been made in recent years toward a better understanding of the underlying processes of fibrogenesis. The effects of serotonin, growth factors, and other peptides released by neuroendocrine tumor cells are hypothesized to cause NEN-associated fibrosis although these substances do not act alone, and pathway crosstalk is critical in the pathophysiology of the fibrotic process [28]. Several growth factors, including transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF2), and connective tissue growth factor (CTGF or CCN2), stimulate fibroblasts both directly and indirectly [7].

Serotonin activity appears to be critical in the development of valvular carcinoid heart disease [15, 28]. Several animal studies have shown that 5-HT can promote cardiac fibrosis and valvulopathy, indicating that it may play an important role in the development of CHD [29–34]. In cardiac valve tissues, various subtypes of serotonergic 5-HT1 and 5-HT2 receptors are present, with subtype 5-HT2B receptors being the most common and playing a crucial role in valve pathology [35, 36]. Activation of the 5-HT2B receptor causes the release of inflammatory cytokines, increases the expression of TGF-β, and has mitogenic effects on fibroblasts and smooth muscle cells [1]. TGF is a serotonin downstream mediator and a big contributor to fibrosis [37].

There is also some evidence that serotoninergic pathways can cause oxidative stress, which can induce fibrosis in heart valves [38].

DIAGNOSIS

Clinical presentation

Cardiac symptoms are commonly subtle until CHD progresses [39]. This frequently leads to a delay in the diagnosis of CHD [11]. Early in the disease course, symptoms such as fatigue and exertional dyspnea may appear [40]. Valve disease does not always progress in a predictable manner, and valves can quickly deteriorate over several months [1]. According to a report by Bhattacharyya et al. [41], only around 57 percent of patients with moderate to severe tricuspid regurgitation will have no or mild symptoms [41].

Typical and common symptoms of right-sided heart failure, such as fatigue, peripheral edema, exertional dyspnea, and cardiac cachexia can occur as a result of progressive CHD. Left-sided cardiac failure occurs in approximately 10% of patients because vasoactive hormones are inactivated in the pulmonary vasculature and do not have a chance to reach the left-sided cardiac components [11, 24]. Patients with right-to-left shunts (patent foramen ovale and atrial septal defects), a poorly controlled disease with high levels of circulating hormones, or bronchopulmonary carcinoid disease are more likely to develop left-sided heart disease due to higher levels of vasoactive hormones reaching the left side of the heart [42].

A physical examination may reveal symptoms of right heart failure, such as increased jugular venous pressure,

a palpable right ventricular impulse, peripheral edema, hepatomegaly, and ascites. For cardiac auscultation, murmurs of tricuspid and pulmonary valve regurgitation are common although a systolic murmur of pulmonary stenosis or a diastolic murmur of tricuspid stenosis are seldom observed [23, 41].

CHD is also linked to coronary artery vasospasm, which is rare but may occur in patients with non-occlusive coronary artery disease [43, 44]. Serotonin can stimulate either vasodilatory or constrictive responses depending on endothelial conditions. 5-HT can promote vasoconstriction in dysfunctional endothelium, for example, in individuals with atherosclerotic disease, due to the superiority of vasoconstriction-inducing 5-hydroxytryptamine2 (5-HT2) receptors and lack of 5-HT1 receptors that mediate vasodilation [44–46]. Patients experiencing symptoms of acute coronary syndrome and with a history of carcinoid disease should be evaluated for possible coronary vasospasm [9].

Unfortunately, in CS patients, screening or routine assessment for CHD is commonly missed, resulting in late diagnosis when the disease is already advanced [47]. The proposed screening algorithm for carcinoid heart disease in all patients with NEN (especially SI-NEN) is presented in Figure 1.

Electrocardiogram

In 50% of patients, the electrocardiogram (ECG) is normal or may indicate nonspecific abnormalities including low-voltage QRS complexes and right bundle branch block [11]. Arrhythmias have been described occasionally in the setting of CHD [9]. In the literature, a single patient without ischemic heart disease, presented with carcinoid-induced ventricular tachycardia [48], which was controlled with the use of metoprolol, and two other identified cases were associated with CHD atrial arrhythmias [49, 50]. Serotonin has been linked to paroxysmal ventricular tachycardias and atrial arrhythmias in canine investigations [51]. The possible mechanism is assumed to be enhanced sympathetic activity caused by a vasoactive substance, resulting in cardiac excitation and tachyarrhythmias [48]. Serotonin-induced coronary vasospasm might result in ST-segment elevation [43].

Biomarkers

Many studies have investigated the usefulness of biochemical markers in monitoring cardiac function, CS activity, and oncologic disease state in CHD patients [17, 52–59].

Natriuretic peptides

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is currently the most effective marker used in echocardiographic screening of CS patients and evaluating CHD severity [8]. NT-proBNP is a neurohormone produced by cardiomyocytes in response to increased ventricular wall stress [54]. NT-proBNP at cutoff values of 235–260 pg/ml revealed sensitivity and specificity of 87%–92% and 80%–89%, respectively, for CHD detection. Levels of NT-proBNP are associated with the severity of CS symptoms, the New York Heart Association functional class, and overall mortality [55, 56].

Although plasma levels of atrial natriuretic peptide (ANP) are significantly elevated in individuals with CHD and indicative of cardiac dysfunction and heart failure, this biomarker is not employed in clinical practice [28, 57].

5-hydroxyindoleacetic acid in the urine

Platelet serotonin and, specifically, levels of the urinary catabolite 5-hydroxyindoleacetic acid (u5-HIAA) have been shown to have a high diagnostic and prognostic value in patients with CS. However, the clinical picture of CS may not correlate with u5-HIAA levels, possibly related to the tumor's inconsistent hormone release or the synthesis of other biologically active substances [60]. Studies demonstrate that the majority of patients with CHD have greater levels of u5-HIAA than those without [17, 57]. In individuals with worsening CS symptoms, defined as a >50% increase in the frequency of bowel movements or flushing, there was a positive correlation between higher u5-HIAA levels and echocardiographic findings of CHD advancement. In patients with CS, u5-HIAA levels of more than 300 mmol/24 hours indicate a 2- to 3-fold increase in the risk of developing or progressing carcinoid heart disease [52].

Chromogranin-A

Chromogranin A (CgA) is a glycoprotein that NET cells secrete [42]. CgA is a useful biomarker in the diagnosis of NEN since it is affordable and easy to measure using a blood sample for an immunological assay [61]. Modlin et al. [62] reported that CgA did not only reflect tumor burden but appears to be associated with tumor progression or response to treatment [62].

In a report by Tran et al. [63] increased CgA level before SI-NEN-related surgery was associated with lower overall survival (median 87.8 months vs. not reached; $P = 0.01$) [63]. These data suggest that sequential CgA concentration measurement is effective in both predicting and monitoring progression to CS, as well as progression from CS to CHD [61, 63].

Unfortunately, CgA has only 30% specificity for detecting severe carcinoid heart disease [42] and has therefore a limited value in CHD diagnosis and monitoring [53].

Activin A

Activin A is a TGF family member found to be an independent predictor of CHD although no statistically significant difference in activin A levels is found between patients with early and advanced disease. CHD was detected with 87% sensitivity and 57% specificity when activin A levels were less than 0.34 ng/ml [58].

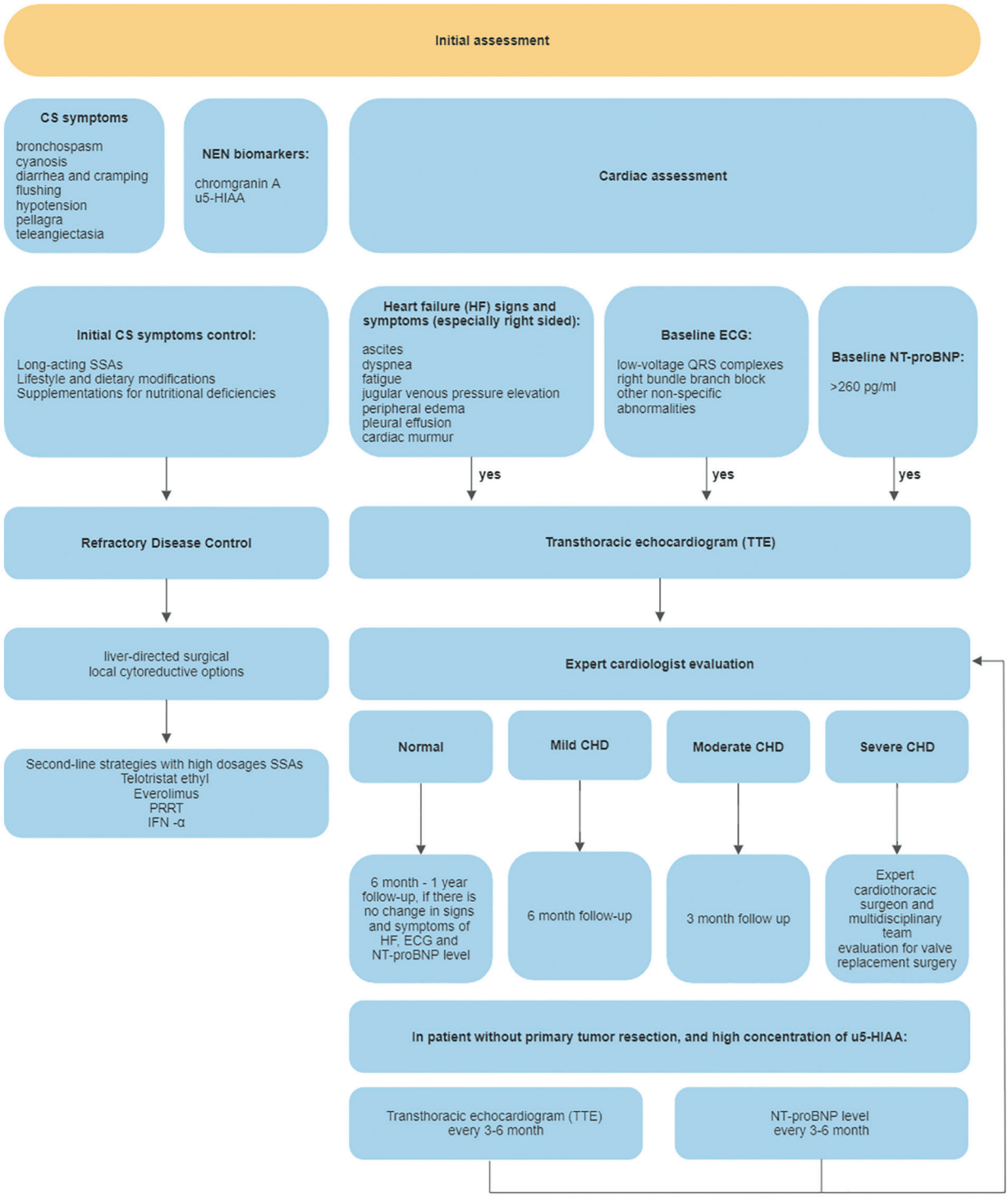

Figure 1. Proposed screening algorithm for carcinoid heart disease in all patients with NEN (especially SI-NEN) [1–3]

Abbreviations: CHD, carcinoid heart disease; CS, carcinoid syndrome; ECG, electrocardiogram; IFN-α, interferon-alpha; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PRRT, peptide receptor radionuclide therapy; SI-NEN, small intestine neuroendocrine neoplasms; u5-HIAA, 5-hydroxyindoleacetic acid in the urine

Chest radiography (X-ray)

Chest radiography is typically inefficient in CHD patients, as 50% of cases appear normal, and abnormalities are commonly non-specific [11]. However, the cardiothoracic ratio could be increased [64].

Transthoracic echocardiography

Echocardiography should be conducted in all patients with carcinoid syndrome and high suspicion of CHD, according to an expert statement released by the American College of Cardiology on the diagnosis and management of CHD.

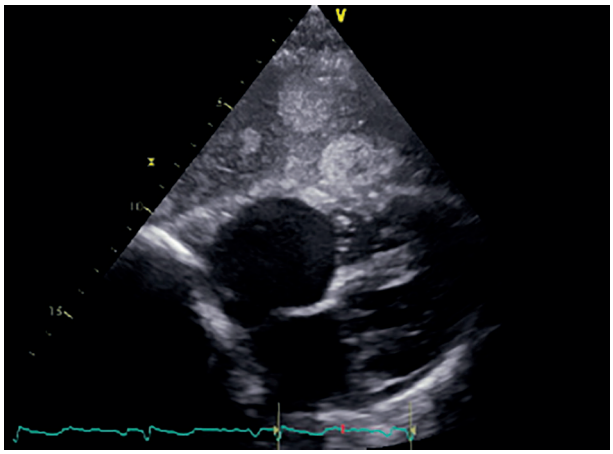

Figure 2. Transthoracic echocardiography (TTE): a 51-year-old patient with carcinoid heart disease and severe tricuspid regurgitation. Subcostal view: huge enlargement of the right atrium and liver metastases

Transthoracic echocardiography (TTE) should be performed in patients with known CHD every 3–6 months or if there is a change in clinical status [8]. In contrast, the European Neuroendocrine Tumor Society (ENETS) recommends TTE screening for patients with CS – once or twice a year for patients with or without cardiac involvement, respectively [9, 65]. Patients with CS should also be screened with TTE if their 5-hydroxyindoleacetic acid levels are markedly increased according to the ENETS recommendations. The severity of CHD can be determined by the constellation of abnormalities observed on TTE [66]. There have been several scoring systems based on echocardiographic findings, including the first (and possibly the most well-known) scoring system based on tricuspid valve morphology, tricuspid regurgitation severity, pulmonary stenosis severity, and pulmonary regurgitation severity [20].

Two-dimensional TTE is the most common imaging modality used in CHD evaluation because it can examine both, morphological and functional, components of the heart (Figure 2). Valvular involvement can range from mild thickening of a single valve leaflet with no major functional impairment to severe thickening, retraction, and immobility of several valves in advanced conditions. Tricuspid regurgitation is the most common right-sided valve abnormality, followed by pulmonary regurgitation and/or pulmonary stenosis. On 2D TTE, initial fibrous deposition of the tricuspid and/or pulmonary valve leaflets typically shows up as a thickening [67]. Fibrous deposition may also damage the chordae and papillae, causing further abnormal function of the valve. The leaflets become retracted and locked in a semi-open position as the condition progresses, resulting in stenosis and regurgitation [66]. When tricuspid regurgitation is present in CHD patients, the Doppler profile usually shows a typical "dagger-shaped" spectrum (early peak pressure rise with a subsequent rapid decline).

To determine the existence of a patent foramen ovale (PFO), a TTE with a "microbubble" contrast can be conducted [66].

CHD may have an impact on ventricular strain due to valvular anomalies. In one study, right ventricular (RV) strain was found to be lower in CHD patients than in controls (a mean of 20.6 versus 26.9). Patients with carcinoid syndrome showed identical RV strain regardless of whether they had evident valvular involvement, suggesting that abnormal RV strain might be a sensitive and early predictor of CHD before apparent valvular abnormalities occur. In addition to RV strain, patients with CHD have slightly decreased global left ventricular (LV) strain as compared to healthy individuals [68].

When compared to 2D TTE, three-dimensional TTE (3D TTE) has several notable advantages. In the case of the tricuspid and pulmonary valves, 3D TTE allows for simultaneous visualization of all valve leaflets. 3D TTE also provides a comprehensive image of subvalvular structures including chordae and papillary muscles, which might be affected by carcinoid "plaque". In advanced stages of CHD, 3D TTE can in addition detect abnormalities of neighboring structures, for example, poststenotic dilatation of the pulmonary artery. In comparison to 2D TTE, 3D TTE enables the detection of myocardial metastasis with a better ability to differentiate their borders from surrounding structures, allowing for a more precise estimation of the real dimensions and mass effects. 3D TTE may have value in operation planning in patients who are prepared for surgical valve repair [69].

Transesophageal echocardiography (TEE) offers better imaging of the pulmonary valve than TTE and may reveal minor tricuspid valve anomalies when TTE is ambiguous.

2D TTE is a useful tool for screening asymptomatic CS patients and monitoring established disease development with excellent sensitivity and specificity [70].

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) is becoming a useful technique for detecting CHD, particularly when echocardiographic findings are ambiguous [71], and is beneficial when echocardiography cannot offer good images of the pulmonary valve [69]. Late gadolinium enhancement of the tricuspid and/or pulmonary valves may show evidence of CHD when valvular anomalies are not visible on TEE. This is not specific and can occur in a variety of cardiovascular conditions [66]. When compared to echocardiography, CMR gives a better estimation of RV size and function with reduced interobserver variability [72].

CMR can be used for more accurate assessment of RV volumes, LV volumes, and cardiac index following a tricuspid valve replacement, in addition to predicting regurgitant volumes after surgical intervention [73]. CMR has various disadvantages, including a higher cost as compared to echocardiography, and the probable requirement for contrast [66].

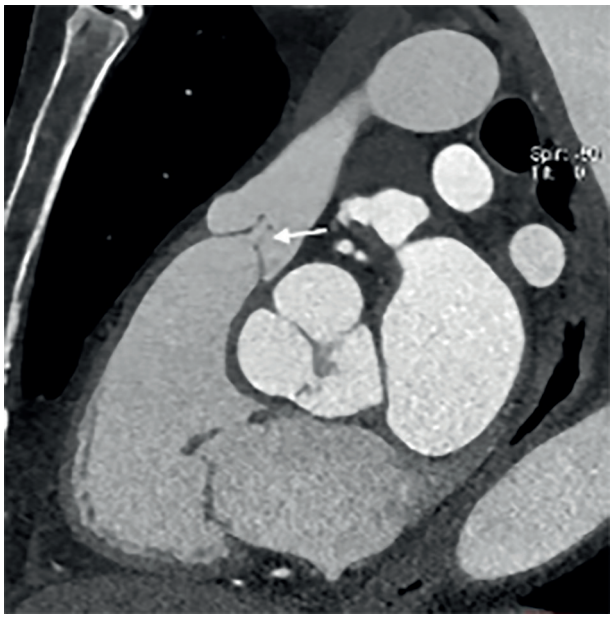

Figure 3. Cardiac computed tomography: multiplanar reconstructions at diastole, views centered on the pulmonary valve, severe thickening of the leaflets of the pulmonary valve with incomplete coaptation during diastole (the arrow)

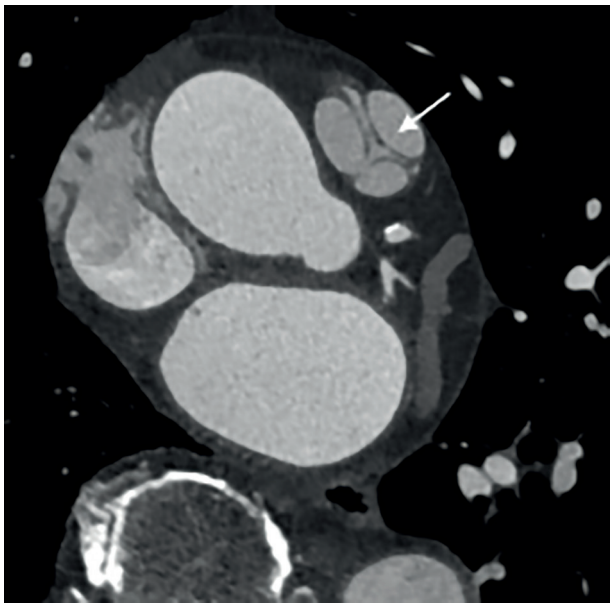

Figure 4. Cardiac computed tomography: multiplanar reconstruction, four-chamber view at diastole; enlargement of the right-sided chambers and thickening of the tricuspid valve and subvalvular apparatus (the arrow)

Cardiac computed tomography scanning

Cardiac computed tomography (CT) can also be used to assess the degree of valve damage, particularly in cases of severe calcification, as well as to quantify RV diameters, evaluate coronary arteries [66], and assess pulmonary post-surgical prosthetic valve thrombosis (Figures 3 and 4).

Positron emission tomography

Functional imaging with radiolabeled somatostatin analogs (typically Gallium-68-DOTATOC/DOTATATE positron emission tomography [PET]/CT) may help to detect carcinoid cardiac metastases (myocardial and/or pericardial) [66]. For the detection of metastatic neuroendocrine neoplasms, this approach has been shown to be >97% sensitive and 92% specific [74].

TREATMENT

The treatment of patients with CHD is multifaceted because of the need to treat both systemic cancer disease and cardiac pathology at the same time [75]. The aim of CHD management is symptom alleviation and increased survival rather than definitive treatment and cure, requiring a multidisciplinary approach involving both medical and surgical therapies for optimal care [76]. This multidisciplinary approach should be used to design a treatment strategy based on symptoms, histological grade, overall performance status, as well as nutritional status, NEN stage (stable disease, progressive, or metastatic disease), the function of major organs (mainly kidney and liver), and the impact of CHD on the proceedings of the underlying NEN [75, 76].

Pharmacotherapy for heart failure

To date, the standard of treatment for asymptomatic patients is to wait for symptoms to appear. On the contrary, loop or thiazide diuretics and aldosterone antagonists are recommended for treatment in individuals who develop signs of right-sided heart failure, particularly peripheral edema. However, because these drugs might cause intravascular volume depletion and decreased cardiac output, they should be used with caution. Other drugs, such as digoxin or angiotensin-converting enzyme inhibitors, have been used, but their benefit in CHD patients has yet to be established [77]. Improvement in heart failure symptoms with medication should not be seen as reassurance that management is adequate and sufficient, but rather as a window to optimize and assess the patient for consideration of valve surgery if required [39].

Cardiac surgery

In patients with well-controlled systemic disease, cardiac valve replacement remains the most effective treatment in severe stages of CHD [77]. Patients with symptomatic right heart failure or ventricular dysfunction, as well as at least 12 months of predicted survival due to their oncologic disease status, are usually candidates for a cardiac procedure [78]. Valve surgery has been shown to enhance long-term prognosis in CHD patients by reducing right heart failure, increasing functional capacity, allowing for more aggressive oncological treatment, and decreasing right heart failure. A multidisciplinary assessment of total operability in relation to oncological status and cardiac function should be used to decide whether to replace a valve [79]. Advances

in surgical techniques, better patient selection, anticancer and hormonal control treatments have resulted in tolerable early mortality rates and survival benefits [78].

The Mayo Clinic's 30-year study by Nguyen et al. [80] involving 240 CHD-operated patients, represents the largest study investigating the relationship between several clinical and echocardiographic factors and early mortality and late survival. Between 1985 and 1994, the early mortality rate was 29% but fell to 7% from 1995 to 2004, and 5% from 2005 onwards. Overall survival rates were 69%, 48%, and 34% after one, three, and five years, respectively [80]. According to the mortality rates reported, valve surgery for carcinoid heart disease is a high risk procedure, but may be beneficial to some patients due to symptomatic relief [81].

Preoperative preparation should mainly focus on optimizing patient status and symptoms with appropriate medical therapy. The severity of tricuspid valve disease, right ventricular dysfunction, right atrial dilatation, pulmonary hypertension, and high central venous pressures are significant risk factors [78]. Preoperative nutritional optimization and somatostatin analog treatment for carcinoid hormonal activity are critical parts of surgical planning [79]. Intravascular volume depletion and electrolyte disturbances are typical in CHD patients and must be treated. Patients with CS are at risk of developing a possibly life-threatening carcinoid crisis, which can be triggered by surgery or any invasive intervention, so therapies aimed at lowering high u5-HIAA levels, such as dose escalation with somatostatin analogs and add-on therapy with telotristat ethyl, should be used. Carcinoid crisis is characterized by hemodynamic instability, with predominant hypotension, tachycardia, arrhythmias, bronchoconstriction, and flushing caused by the release of biologically active substances. The administration of octreotide infusion at a dosage of 50 µg/h administered 12 hours before the procedure and continued throughout the operation and until the patient is hemodynamically stable and off inotropes is the primary preventative therapy aimed at reducing the occurrence of carcinoid crisis. The dosage can be increased to 100–200 µg/h if necessary [82]. Depending on the patient's recovery, the octreotide infusion should be progressively reduced postoperatively [78].

The type of valve selected for use (biological or mechanical valve prosthesis) is a complex matter that should be based on a particular patient's risk of bleeding, tumor-related life expectancy, and possible future therapeutic interventions [81, 83]. According to research by Albåge et al. [79], surgery of the left-sided valves is not linked to poorer outcomes and ought to be conducted concomitantly with right-sided valve surgery if needed [79].

Bioprosthetic valves are mostly favored when CHD patients have an enhanced bleeding risk due to significant liver disease and hepatic dysfunction, but still, thrombus formation on the tricuspid bioprosthesis is the most prevalent cause of valve dysfunction in right-sided valve replacements [98]. Postoperative right ventricular failure, an overall reduced flow condition on the right side of the heart, and a hypercoagulable state with high serotonin levels acting as a stimulus for platelet activation all seem to be risk factors for valve thrombosis [78]. Patients with bioprosthetic valves in sinus rhythm should begin and continue warfarin anticoagulation for 6 months, but patients with mechanical valve prosthesis or with atrial fibrillation and bioprosthetic valves should continue anticoagulation permanently [82].

TTE should be conducted as soon as possible after surgery [84]. In uncomplicated conditions during follow-up, TTE should be performed every 3 to 12 months, depending on comorbidities [8].

It should be highlighted that, despite medical and surgical developments, valve surgery in subjects with CHD is always challenging and associated with significant risk. In high-risk patients with severe CHD for whom open-heart surgery is hazardous, transcutaneous catheter-based interventions represent a minimally invasive option [84, 85].

In addition, the recent introduction of percutaneous valve-in-valve technology in subjects with a failing bioprosthetic valve has broadened treatment selections for less invasive procedures, and a transcatheter heart valve placed in the inferior vena cava may decrease carcinoid hormone levels and relieve symptoms in patients with severe carcinoid syndrome symptoms [86, 87].

Primary tumor resection

Primary tumor resection with metastatic disease (resectable and unresectable) has been shown to improve survival in all patients with SI-NENs (with and without CHD) [14]. This may relate to decreased synthesis of vasoactive substances [12], as well as a reduction in potentially fatal complications such as intestinal obstruction caused by tumor growth and blockage [14]. Uema et al. [88] found that removing the primary tumor reduced mortality in 139 patients with advanced disease, carcinoid symptoms, and/or elevated u5-HIAA [88].

Polcz et al. [89] recently published significant findings from a retrospective cohort analysis of 4076 patients with metastatic SI-NETs, with 2025 (61%) receiving primary tumor resection (PTR). Patients who were more likely to have PTR were younger, had been diagnosed sooner, and had lower-grade small intestine primary tumors. Patients who had PTR had longer median overall survival than those who did not (71 months vs. 29 months, $P = 0.001$). According to the findings of Polcz et al. [89], patients treated in an academic or research facility were, likewise, less likely to have PTR, and primary resection has become less common over time. One possible explanation is the increasing use of somatostatin analogs as first-line treatment for metastatic disease, which gives both excellent symptom alleviation and inhibition of tumor progression. Although these findings were also associated with improved survival, it should be noted that they apply to the entire group of SI-NET patients — both with and without CHD — and that, despite proven benefits in progression-free survival, no OS benefit with somatostatin analogs has been demonstrated

to date [89], which indicates that primary tumors should be removed when possible.

Management of carcinoid syndrome

Considering the significance of 5-HT in the sequence of events that leads to the development of CHD, controlling serotonin synthesis from the tumor is critical. This can be accomplished by either medical or surgical intervention methods. Long-acting somatostatin analogs, peptide receptor radionuclide therapy (PRRT), and the new drug telotristat ethyl are among the available medical treatments. Transcatheter arterial embolization (TAE) or chemoembolization (TACE), as well as surgical debulking of hepatic metastases, are interventional alternatives [8].

Long-acting somatostatin analogs

Long-acting somatostatin analogs (SSAs), synthetic octo-amino acid peptides, which primarily act on the somatostatin receptor subtype 2, are recommended for first-line antiproliferative therapy in advanced NETs due to their proven effectiveness in controlling symptoms of carcinoid syndrome [28, 75–77, 90]. The somatostatin analogs octreotide and lanreotide improved symptoms in 65%–72% of patients and had a biochemical response in 45%–46%. In 72%–84% of patients, increasing the dose or frequency or switching classes resulted in a decrease in flushes and/or diarrhea [90].

Long-acting somatostatin analogs extended time-to-tumor progression (TTP) in patients with metastatic well-differentiated, predominantly G1, midgut neuroendocrine tumors compared to placebo (NET; octreotide LAR: PROMID study) [91]. Progression-free survival (PFS) was as well enhanced in individuals with advanced, non-functioning enteropancreatic NETs of grade 1 or 2 with confirmed progression of the disease (lanreotide autogel: CLARINET study) [92].

Although the optimal levels of u5-HIAA used to reduce the development of CHD are yet to be determined, long-acting SSAs are unquestionably important in CHD patient management [78].

In CS patients, infusion of short-acting octreotides should begin in the perioperative setting to avoid the onset of carcinoid crisis. Furthermore, in patients with recurrent CS symptoms, short-acting octreotide (half-life 1.5 to 2 hours) may be administered as a rescue drug in addition to the long-acting formulations [78].

Telotristat ethyl

Telotristat, an oral inhibitor of peripheral 5-HT synthesis, was recently approved by the Food and Drug Administration for the treatment of symptomatic CS-related diarrhea that has not responded to SSAs therapy. Telotristat ethyl is converted to its active metabolite, telotristat, which inhibits tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin production. Two double-blind, randomized phase 3 clinical trials (TELESTAR and TELECAST) found that telotristat ethyl reduced bowel movement in 40%–44% of patients treated, compared to 0–20% of patients who received a placebo [78, 93]. After three months, there was a substantial decrease in urinary 5-HIAA. The findings of this study supported the safety and effectiveness of telotristat when combined with somatostatin analog treatment in individuals with CS. The impact on the development of carcinoid heart disease and mesenteric fibrosis residues is unidentified because this endpoint has not been adequately powered in clinical studies [94].

Everolimus

Everolimus is a small molecule oral inhibitor of the serine/threonine protein kinase mammalian target of rapamycin (mTOR), which promotes cancer cell growth and survival in a variety of malignancies, including NETs [78]. Pavel et al. [95] reported that everolimus plus octreotide LAR increased progression-free survival in patients with advanced neuroendocrine tumors associated with carcinoid syndrome when compared to placebo plus octreotide LAR [95]. Due to everolimus-related adverse effects including infections, edema, and diarrhea, patients with CHD should be treated with caution [8, 78].

Interferon-alpha

For refractory CS and negative somatostatin receptor NETs, interferon-alpha (IFN-α) is a supplementary treatment to SSAs. However, usage of this drug is limited due to its adverse effects (e.g., flu-like symptoms, chronic fatigue, liver and bone marrow toxicity) [78]. The reported response rates of IFN monotherapy in CS patients ranged from 0% to 90% for clinical control and 50%–80% for biochemical control [90].

Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) is primarily used to inhibit growth in progressive NETs with high somatostatin receptor expression [96]. It has been shown to improve quality of life and symptoms such as diarrhea in patients with midgut NETs [97]. Due to the requirement for simultaneous amino acid and fluid infusions in patients with CHD and heart failure, caution is advised [8, 78].

Transcatheter arterial embolization, chemoembolization, selective internal radiotherapy, radiofrequency ablation

Transcatheter arterial embolization (TAE), local administration of high doses of chemotherapy (TACE), and selective internal radiotherapy (SIRT) employing Yttrium-90 microspheres are examples of vascularly accessed interventional methods that provide diverse treatment modalities [78].

TAE and TACE are implemented to minimize tumor burden and have been shown to be effective in the treatment of NET, particularly in individuals with liver involvement. Circulating hormone levels drop as tumor burden decreases, resulting in symptom control in 50%–100% of

patients with NET and liver metastasis [98]. Patients with severe CHD and/or a significant hepatic tumor burden may have serious treatment complications such as hemorrhage or even liver failure, and as such, loco-regional therapies must be used with extreme caution. TAE and TACE are relatively contraindicated in patients with total portal vein occlusion, poor performance status, or underlying hepatic impairment [77]. TAE, TACE, and SIRT radiological response rates were estimated to be 25%–92%, 22%–100%, and 22%–63%, respectively [78].

Radiofrequency ablation and microwave ablation, done either percutaneously or in association with surgical resection, have also been shown to improve symptom management [78].

Surgical debulking of hepatic metastases

Surgical debulking (cytoreductive surgery) of liver tumor burden has been shown to be a significant advancement in the management of NETs in recent years [77]. Bernheim et al. [99] reported that patients with CHD who undergo hepatic resection had delayed progression of the disease and a better prognosis [99]. This method may be risky in individuals with severe CHD since it is associated with significant morbidity and mortality. There is also a greater risk of preoperative hemorrhage due to elevated right atrial pressure and a pulsatile liver. In selected individuals, liver surgery may be an option following heart valve replacement and cardiac function restoration to lower circulating serotonin, relieve carcinoid symptoms, and avoid recurrence of CHD [8, 77].

Kinney et al. [100] presented peri-operative findings of 169 patients who had partial hepatic resection due to metastatic NETs at Mayo Clinic Rochester. The most prevalent adverse events were persistent tachycardia (8.9%), followed by hypotension (5.3%), flushing, cardiac conduction abnormalities, and acidosis with pH 7.2, with an occurrence of less than 1%. There were no incidents of carcinoid crises [100].

CONCLUSIONS

All patients with SI-NENs, particularly those without primary tumor resection and high concentration of u5-HIAA require a cyclic assessment of clinical status and TTE performance every 3-6 months to detect the onset of CHD. The therapeutic methods include pharmacotherapy for symptomatic management, as well as medications and interventional approaches, for successful control of serotonin excess, most notably somatostatin analogs.

Despite medical and surgical improvements, carcinoid heart disease remains a significant challenge. Valve surgery for carcinoid heart disease is a high-risk intervention, given the mortality rates, although it may be beneficial for patients with symptomatic severe right heart valve disease who have a 12-month survival prognosis owing to symptomatic improvement. It should be emphasized that early risk linked to valve surgery has decreased in the present era. A multidisciplinary team should be involved in patient selection for valve surgery, adequate preoperative planning, and perioperative treatment procedures.

Article information

Conflict of interest: None declared.

Funding: None.

References

1. Oleinikov K, Korach A, Planer D, et al. Update in carcinoid heart disease - the heart of the matter. Rev Endocr Metab Disord. 2021; 22(3): 553–561, doi: 10.1007/s11154-020-09624-y, indexed in Pubmed: 33443717.
2. Kos-Kudła B, Blicharz-Dorniak J, Strzelczyk J, et al. Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours). Endokrynol Pol. 2017; 68(2): 79–110, doi: 10.5603/EP.2017.0015, indexed in Pubmed: 28597909.
3. Kos-Kudła B, Blicharz-Dorniak J, Strzelczyk J, et al. Neuroendocrine neoplasms of the small intestine and the appendix - management guidelines (recommended by the Polish Network of Neuroendocrine Tumours). Endokrynol Pol. 2013; 64(6): 480–493, doi: 10.5603/EP.2013.0029, indexed in Pubmed: 24431119.
4. Niederle B, Pape UF, Costa F, et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. Neuroendocrinology. 2016; 103(2): 125–138, doi: 10.1159/000443170, indexed in Pubmed: 26758972.
5. Das S, Dasari A. Epidemiology, Incidence, and Prevalence of Neuroendocrine Neoplasms: Are There Global Differences? Curr Oncol Rep. 2021; 23(4): 43, doi: 10.1007/s11912-021-01029-7, indexed in Pubmed: 33719003.
6. Gut P, Czarnywojtek A, Sawicka-Gutaj N, et al. Assessment of serotonin concentration in patients with a small-intestine neuroendocrine neoplasm and carcinoid syndrome treated with somatostatin analogues. Pol Arch Intern Med. 2020; 130(10): 903–905, doi: 10.20452/pamw.15504, indexed in Pubmed: 32643913.
7. Clement D, Ramage J, Srirajaskanthan R. Update on pathophysiology, treatment, and complications of carcinoid syndrome. J Oncol. 2020; 2020: 8341426, doi: 10.1155/2020/8341426, indexed in Pubmed: 32322270.
8. 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(10): 1288–1304, doi: 10.1016/j.jacc.2016.12.030, indexed in Pubmed: 28279296.
9. Ram P, Penalver JL, Lo KB, et al. Carcinoid heart disease: review of current knowledge. Tex Heart Inst J. 2019; 46(1): 21–27, doi: 10.14503/THIJ-17-6562, indexed in Pubmed: 30833833.
10. Mota JM, Sousa LG, Riechelmann RP. Complications from carcinoid syndrome: review of the current evidence. Ecancermedicalscience. 2016; 10: 662, doi: 10.3332/ecancer.2016.662, indexed in Pubmed: 27594907.
11. Gustafsson BI, Hauso O, Drozdov I, et al. Carcinoid heart disease. Int J Cardiol. 2008; 129(3): 318–324, doi: 10.1016/j.ijcard.2008.02.019, indexed in Pubmed: 18571250.
12. Westberg G, Wängberg B, Ahlman H, et al. Prediction of prognosis by echocardiography in patients with midgut carcinoid syndrome. Br J Surg. 2001; 88(6): 865–872, doi: 10.1046/j.0007-1323.2001.01798.x, indexed in Pubmed: 11412260.
13. Møller JE, Pellikka PA, Bernheim AM, et al. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. Circulation. 2005; 112(21):

3320–3327, doi: 10.1161/CIRCULATIONAHA.105.553750, indexed in Pubmed: 16286584.
14. Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. Heart. 2004; 90(10): 1224–1228, doi: 10.1136/hrt.2004.040329, indexed in Pubmed: 15367531.
15. Hassan SA, Palaskas NL, Agha AM, et al. Carcinoid heart disease: a comprehensive review. Curr Cardiol Rep. 2019; 21(11): 140, doi: 10.1007/s11886-019-1207-8, indexed in Pubmed: 31745664.
16. Connolly HM, Schaff HV, Abel MD, et al. Outcome of cardiac surgery for carcinoid heart disease. J Am Coll Cardiol. 1995; 25(2): 410–416, doi: 10.1016/0735-1097(94)00374-y, indexed in Pubmed: 7829795.
17. Buchanan-Hughes A, Pashley A, Feuilly M, et al. Carcinoid heart disease: prognostic value of 5-hydroxyindoleacetic acid levels and impact on survival: a systematic literature review. Neuroendocrinology. 2021; 111(1-2): 1–15, doi: 10.1159/000506744, indexed in Pubmed: 32097914.
18. Mansencal N, Mitry E, Bachet JB, et al. Echocardiographic follow-up of treated patients with carcinoid syndrome. Am J Cardiol. 2010; 105(11): 1588–1591, doi: 10.1016/j.amjcard.2010.01.017, indexed in Pubmed: 20494667.
19. Baron E, Szymanski C, Hergault H, et al. Progression of carcinoid heart disease in the modern management era. J Am Heart Assoc. 2021; 10(23): e020475, doi: 10.1161/JAHA.120.020475, indexed in Pubmed: 34816734.
20. Denney W, Kemp W, Anthony L, et al. Echocardiographic and biochemical evaluation of the development and progression of carcinoid heart disease. J Am Coll Cardiol. 1998; 32(4): 1017–1022, doi: 10.1016/s0735-1097(98)00354-4.
21. Norlén O, Stålberg P, Öberg K, et al. Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. World J Surg. 2012; 36(6): 1419–1431, doi: 10.1007/s00268-011-1296-z, indexed in Pubmed: 21984144.
22. Hayes AR, Davar J, Caplin ME. Carcinoid heart disease: a review. Endocrinol Metab Clin North Am. 2018; 47(3): 671–682, doi: 10.1016/j.ecl.2018.04.012, indexed in Pubmed: 30098723.
23. Dobson R, Burgess MI, Valle JW, et al. Serial surveillance of carcinoid heart disease: factors associated with echocardiographic progression and mortality. Br J Cancer. 2014; 111(9): 1703–1709, doi: 10.1038/bjc.2014.468, indexed in Pubmed: 25211656.
24. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. Circulation. 1993; 87(4): 1188–1196, doi: 10.1161/01.cir.87.4.1188, indexed in Pubmed: 7681733.
25. De Jesus T, Luis SA, Ryu JH, et al. Carcinoid heart disease in patients with bronchopulmonary carcinoid. J Thorac Oncol. 2018; 13(10): 1602–1605, doi: 10.1016/j.jtho.2018.06.023, indexed in Pubmed: 30251640.
26. Simula DV, Edwards WD, Tazelaar HD, et al. Surgical pathology of carcinoid heart disease: a study of 139 valves from 75 patients spanning 20 years. Mayo Clin Proc. 2002; 77(2): 139–147, doi: 10.4065/77.2.139, indexed in Pubmed: 11838647.
27. Ayme-Dietrich E, Aubertin-Kirch G, Maroteaux L, et al. Cardiovascular remodeling and the peripheral serotonergic system. Arch Cardiovasc Dis. 2017; 110(1): 51–59, doi: 10.1016/j.acvd.2016.08.002, indexed in Pubmed: 28017279.
28. Laskaratos FM, Rombouts K, Caplin M, et al. Neuroendocrine tumors and fibrosis: An unsolved mystery? Cancer. 2017; 123(24): 4770–4790, doi: 10.1002/cncr.31079, indexed in Pubmed: 29112233.
29. Jackson LN, Chen LA, Larson SD, et al. Development and characterization of a novel in vivo model of carcinoid syndrome. Clin Cancer Res. 2009; 15(8): 2747–2755, doi: 10.1158/1078-0432.CCR-08-2346, indexed in Pubmed: 19336516.
30. Gustafsson BI, Tømmerås K, Nordrum I, et al. Long-term serotonin administration induces heart valve disease in rats. Circulation. 2005; 111(12): 1517–1522, doi: 10.1161/01.CIR.0000159356.42064.48, indexed in Pubmed: 15781732.
31. Musunuru S, Carpenter JE, Sippel RS, et al. A mouse model of carcinoid syndrome and heart disease. J Surg Res. 2005; 126(1): 102–105, doi: 10.1016/j.jss.2005.01.003, indexed in Pubmed: 15916982.
32. Mekontso-Dessap A, Brouri F, Pascal O, et al. Deficiency of the 5-hydroxytryptamine transporter gene leads to cardiac fibrosis and valvulopathy in mice. Circulation. 2006; 113(1): 81–89, doi: 10.1161/CIRCULATIONAHA.105.554667, indexed in Pubmed: 16380550.
33. Lancellotti P, Nchimi A, Hego A, et al. High-dose oral intake of serotonin induces valvular heart disease in rabbits. Int J Cardiol. 2015; 197: 72–75, doi: 10.1016/j.ijcard.2015.06.035, indexed in Pubmed: 26114494.
34. Janssen W, Schymura Y, Novoyatleva T, et al. 5-HT2B receptor antagonists inhibit fibrosis and protect from RV heart failure. Biomed Res Int. 2015; 2015: 438403, doi: 10.1155/2015/438403, indexed in Pubmed: 25667920.
35. Ayme-Dietrich E, Lawson R, Da-Silva S, et al. Serotonin contribution to cardiac valve degeneration: new insights for novel therapies? Pharmacol Res. 2019; 140: 33–42, doi: 10.1016/j.phrs.2018.09.009, indexed in Pubmed: 30208338.
36. Hutcheson JD, Setola V, Roth BL, et al. Serotonin receptors and heart valve disease--it was meant 2B. Pharmacol Ther. 2011; 132(2): 146–157, doi: 10.1016/j.pharmthera.2011.03.008, indexed in Pubmed: 21440001.
37. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. Nat Rev Nephrol. 2016; 12(6): 325–338, doi: 10.1038/nrneph.2016.48, indexed in Pubmed: 27108839.
38. Peña-Silva RA, Miller JD, Chu Yi, et al. Serotonin produces monoamine oxidase-dependent oxidative stress in human heart valves. Am J Physiol Heart Circ Physiol. 2009; 297(4): H1354–H1360, doi: 10.1152/ajpheart.00570.2009, indexed in Pubmed: 19666839.
39. Steeds R, Sagar V, Shetty S, et al. Multidisciplinary team management of carcinoid heart disease. Endocr Connect. 2019; 8(12): R184–R199, doi: 10.1530/EC-19-0413, indexed in Pubmed: 31751305.
40. Dobson R, Burgess MI, Pritchard DM, et al. The clinical presentation and management of carcinoid heart disease. Int J Cardiol. 2014; 173(1): 29–32, doi: 10.1016/j.ijcard.2014.02.037, indexed in Pubmed: 24636550.
41. Bhattacharyya S, Toumpanakis C, Caplin ME, et al. Analysis of 150 patients with carcinoid syndrome seen in a single year at one institution in the first decade of the twenty-first century. Am J Cardiol. 2008; 101(3): 378–381, doi: 10.1016/j.amjcard.2007.08.045, indexed in Pubmed: 18237604.
42. Perry D, Hayek SS. Carcinoid heart disease: a guide for clinicians. Cardiol Clin. 2019; 37(4): 497–503, doi: 10.1016/j.ccl.2019.07.014, indexed in Pubmed: 31587790.
43. Eapen DJ, Clements S, et al. Jr, Block P, Metastatic carcinoid disease inducing coronary vasospasm. Tex Heart Inst J. 2012; 39(1): 76–78, indexed in Pubmed: 22412234.
44. Bourgault C, Bergeron S, Bogaty P, et al. A most unusual acute coronary syndrome. Can J Cardiol. 2006; 22(5): 429–432, doi: 10.1016/s0828-282x(06)70930-8, indexed in Pubmed: 16639480.
45. Frishman WH, Grewall P. Serotonin and the heart. Ann Med. 2000; 32(3): 195–209, doi: 10.3109/07853890008998827, indexed in Pubmed: 10821327.
46. McFadden EP, Clarke JG, Davies GJ, et al. Effect of intracoronary serotonin on coronary vessels in patients with stable angina and patients with variant angina. N Engl J Med. 1991; 324(10): 648–654, doi: 10.1056/NEJM199103073241002, indexed in Pubmed: 1994247.
47. Dobson R, Valle JW, Burgess MI, et al. Variation in cardiac screening and management of carcinoid heart disease in the UK and republic of ireland. Clin Oncol (R Coll Radiol). 2015; 27(12): 741–746, doi: 10.1016/j.clon.2015.06.016, indexed in Pubmed: 26170123.
48. Rupp AB, Ahmadjee A, Morshedzadeh JH, et al. Carcinoid syndrome-induced ventricular tachycardia. Case Rep Cardiol. 2016; 2016: 9142598, doi: 10.1155/2016/9142598, indexed in Pubmed: 27088017.
49. Kuczma JA, Grzywa M. Broncho-pulmonary carcinoid with the cardiac arrhythmia manifestation [in Polish]. Pol Arch Med Wewn. 2006; 116(4): 971–973, doi: 18416299.
50. Langer C, Piper C, Vogt J, et al. Atrial fibrillation in carcinoid heart disease: The role of serotonin. A review of the literature. Clin Res Cardiol. 2007; 96(2): 114–118, doi: 10.1007/s00392-006-0463-y, indexed in Pubmed: 17115326.
51. Kuruvilla A, Aiman R. Influence of 5-hydroxytryptamine on experimentally induced atrial arrhythmias in dogs. Indian J Physiol Pharmacol. 1973; 17(2): 111–116, indexed in Pubmed: 4128954.
52. Bhattacharyya S, Toumpanakis C, Chilkunda D, et al. Risk factors for the development and progression of carcinoid heart disease. Am J Cardiol. 2011; 107(8): 1221–1226, doi: 10.1016/j.amjcard.2010.12.025, indexed in Pubmed: 21296329.
53. Dobson R, Burgess MI, Banks M, et al. The association of a panel of biomarkers with the presence and severity of carcinoid heart disease:

a cross-sectional study. PLoS One. 2013; 8(9): e73679, doi: 10.1371/journal.pone.0073679, indexed in Pubmed: 24069222.
54. Zuetenhorst JM, Korse CM, Bonfrer JMG, et al. Role of natriuretic peptides in the diagnosis and treatment of patients with carcinoid heart disease. Br J Cancer. 2004; 90(11): 2073–2079, doi: 10.1038/sj.bjc.6601816, indexed in Pubmed: 15150565.
55. Bhattacharyya S, Toumpanakis C, Caplin ME, et al. Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease. Am J Cardiol. 2008; 102(7): 938–942, doi: 10.1016/j.amjcard.2008.05.047, indexed in Pubmed: 18805126.
56. Korse CM, Taal BG, de Groot CA, et al. 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(26): 4293–4299, doi: 10.1200/JCO.2008.18.7047, indexed in Pubmed: 19667278.
57. Zuetenhorst JM, Bonfrer JM, Korse CM, et al. Carcinoid heart disease: the role of urinary 5-hydroxyindoleacetic acid excretion and plasma levels of atrial natriuretic peptide, transforming growth factor-beta and fibroblast growth factor. Cancer. 2003; 97(7): 1609–1615, doi: 10.1002/cncr.11226, indexed in Pubmed: 12655516.
58. Bergestuen DS, Edvardsen T, Aakhus S, et al. Activin A in carcinoid heart disease: a possible role in diagnosis and pathogenesis. Neuroendocrinology. 2010; 92(3): 168–177, doi: 10.1159/000318014, indexed in Pubmed: 20720391.
59. Zahid W, Bergestuen D, Haugaa KH, et al. Myocardial function by two-dimensional speckle tracking echocardiography and activin a may predict mortality in patients with carcinoid intestinal disease. Cardiology. 2015; 132(2): 81–90, doi: 10.1159/000431076, indexed in Pubmed: 26111973.
60. Fanciulli G, Ruggeri RM, Grossrubatscher E, et al. NIKE. Serotonin pathway in carcinoid syndrome: Clinical, diagnostic, prognostic and therapeutic implications. Rev Endocr Metab Disord. 2020; 21(4): 599–612, doi: 10.1007/s11154-020-09547-8, indexed in Pubmed: 32152781.
61. Konsek-Komorowska SJ, Pęczkowska M, Kolasińska-Ćwikła AD, et al. Chromogranin A (CgA) as a biomarker in carcinoid heart disease and NETG1/G2 neuroendocrine neoplasms of the small intestine (SI-NENs) related carcinoid syndrome. Med Clin (Barc). 2021 [Epub ahead of print], doi: 10.1016/j.medcli.2021.06.029, indexed in Pubmed: 34736622.
62. Modlin IM, Gustafsson BI, Moss SF, et al. Chromogranin A--biological function and clinical utility in neuro endocrine tumor disease. Ann Surg Oncol. 2010; 17(9): 2427–2443, doi: 10.1245/s10434-010-1006-3, indexed in Pubmed: 20217257.
63. Tran CG, Sherman SK, Scott AT, et al. It is time to rethink biomarkers for surveillance of small bowel neuroendocrine tumors. Ann Surg Oncol. 2021; 28(2): 732–741, doi: 10.1245/s10434-020-08784-0, indexed in Pubmed: 32656719.
64. Bhattacharyya S, Davar J, Dreyfus G, et al. Carcinoid heart disease. Circulation. 2007; 116(24): 2860–2865, doi: 10.1161/CIRCULATIONAHA.107.701367, indexed in Pubmed: 18071089.
65. Arnold R, Chen YJ, Costa F, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: follow-up and documentation. Neuroendocrinology. 2009; 90(2): 227–233, doi: 10.1159/000225952, indexed in Pubmed: 19713715.
66. Agha AM, Lopez-Mattei J, Donisan T, et al. Multimodality imaging in carcinoid heart disease. Open Heart. 2019; 6(1): e001060, doi: 10.1136/openhrt-2019-001060, indexed in Pubmed: 31245014.
67. Edwards NC, Yuan M, Nolan O, et al. Effect of valvular surgery in carcinoid heart disease: an observational cohort study. J Clin Endocrinol Metab. 2016; 101(1): 183–190, doi: 10.1210/jc.2015-3295, indexed in Pubmed: 26580239.
68. Haugaa KH, Bergestuen DS, Sahakyan LG, et al. Evaluation of right ventricular dysfunction by myocardial strain echocardiography in patients with intestinal carcinoid disease. J Am Soc Echocardiogr. 2011; 24(6): 644–650, doi: 10.1016/j.echo.2011.02.009, indexed in Pubmed: 21440415.
69. Bhattacharyya S, Toumpanakis C, Burke M, et al. Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI. Circ Cardiovasc Imaging. 2010; 3(1): 103–111, doi: 10.1161/CIRCIMAGING.109.886846, indexed in Pubmed: 19920029.
70. Castillo JG, Naib T, Zacks JS, et al. Echocardiography in functional midgut neuroendocrine tumors: When and how often. Rev Endocr Metab Disord. 2017; 18(4): 411–421, doi: 10.1007/s11154-017-9434-z, indexed in Pubmed: 29080935.
71. Franzen D, Boldt A, Raute-Kreinsen U, et al. Magnetic resonance imaging of carcinoid heart disease. Clin Cardiol. 2009; 32(6): E92–E93, doi: 10.1002/clc.20260, indexed in Pubmed: 19382278.
72. Puchalski MD, Williams RV, Askovich B, et al. Assessment of right ventricular size and function: echo versus magnetic resonance imaging. Congenit Heart Dis. 2007; 2(1): 27–31, doi: 10.1111/j.1747-0803.2007.00068.x, indexed in Pubmed: 18377513.
73. Kim HK, Kim YJ, Park EA, et al. Assessment of haemodynamic effects of surgical correction for severe functional tricuspid regurgitation: cardiac magnetic resonance imaging study. Eur Heart J. 2010; 31(12): 1520–1528, doi: 10.1093/eurheartj/ehq063, indexed in Pubmed: 20233787.
74. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med. 2007; 48(4): 508–518, doi: 10.2967/jnumed.106.035667, indexed in Pubmed: 17401086.
75. Bober B, Saracyn M, Kołodziej M, et al. Carcinoid heart disease: how to diagnose and treat in 2020? Clin Med Insights Cardiol. 2020; 14: 1179546820968101, doi: 10.1177/1179546820968101, indexed in Pubmed: 33192110.
76. Jin C, Sharma AN, Thevakumar B, et al. Carcinoid heart disease: pathophysiology, pathology, clinical manifestations, and management. Cardiology. 2021; 146(1): 65–73, doi: 10.1159/000507847, indexed in Pubmed: 33070143.
77. Koffas A, Toumpanakis C. Managing carcinoid heart disease in patients with neuroendocrine tumors. Ann Endocrinol (Paris). 2021; 82(3-4): 187–192, doi: 10.1016/j.ando.2020.12.007, indexed in Pubmed: 33321109.
78. Oleinikov K, Korach A, Planer D, et al. Update in carcinoid heart disease — the heart of the matter. Rev Endocr Metab Disord. 2021; 22(3): 553–561, doi: 10.1007/s11154-020-09624-y, indexed in Pubmed: 33443717.
79. Albåge A, Montibello M. Surgical aspects of valve replacement in carcinoid heart disease. J Card Surg. 2021; 36(1): 290–294, doi: 10.1111/jocs.15169, indexed in Pubmed: 33124055.
80. 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, doi: 10.1016/j.jtcvs.2018.09.025, indexed in Pubmed: 30527716.
81. Konsek-Komorowska SJ, Kolasińska-Ćwikła AD, Różański J, et al. Outcomes of cardiac surgical treatment for carcinoid heart disease. Kardiol Pol. 2022; 80(2): 202–204, doi: 10.33963/KP.a2021.0189, indexed in Pubmed: 34939659.
82. Laskaratos FM, Davar J, Toumpanakis C. Carcinoid heart disease: a review. Curr Oncol Rep. 2021; 23(4): 48, doi: 10.1007/s11912-021-01031-z, indexed in Pubmed: 33725214.
83. Florczak E, Pęczkowska M, Konka M, et al. A 51-year-old patient with carcinoid heart disease and severe tricuspid regurgitation. Kardiol Pol. 2017; 75(2): 183, doi: 10.5603/KP.2017.0027, indexed in Pubmed: 28205198.
84. Rdzanek A, Szymański P, Gackowski A, et al. Percutaneous tricuspid edge-to-edge repair - patient selection, imaging considerations, and the procedural technique. Expert opinion of the Working Group on Echocardiography and Association of CardioVascular Interventions of the Polish Cardiac Society. Kardiol Pol. 2021; 79(10): 1178–1191, doi: 10.33963/KP.a2021.0125, indexed in Pubmed: 34611879.
85. De Rosa R, Schranz D, Zeiher AM, et al. Again, two melodies in concert: transcatheter double valve replacement in hedinger syndrome. Ann Thorac Surg. 2017; 104(1): e61–e63, doi: 10.1016/j.athoracsur.2017.01.063, indexed in Pubmed: 28633265.
86. Luthra S, Olevano C, Richens T, et al. Percutaneous transcatheter valve-in-valve pulmonary and tricuspid replacement in carcinoid heart disease. JACC Case Rep. 2020; 2(4): 533–536, doi: 10.1016/j.jaccas.2019.11.089, indexed in Pubmed: 34317287.
87. Sagar VM, Steeds RP, Doshi SN, et al. Transcatheter valve implantation to inferior vena cava to control carcinoid symptoms. BMJ Case Rep. 2017; 2017, doi: 10.1136/bcr-2017-220888, indexed in Pubmed: 29066637.
88. Uema D, Alves C, Mesquita M, et al. Carcinoid heart disease and decreased overall survival among patients with neuroendocrine tumors: a retrospective multicenter latin american cohort study. J Clin Med. 2019; 8(3), doi: 10.3390/jcm8030405, indexed in Pubmed: 30909590.
89. Polcz M, Schlegel C, Edwards GC, et al. Primary tumor resection offers survival benefit in patients with metastatic midgut neuroendocrine

tumors. Ann Surg Oncol. 2020; 27(8): 2795–2803, doi: 10.1245/s10434-020-08602-7, indexed in Pubmed: 32430752.
90. Hofland J, Herrera-Martínez AD, Zandee WT, et al. Management of carcinoid syndrome: a systematic review and meta-analysis. Endocr Relat Cancer. 2019; 26(3): R145–R156, doi: 10.1530/ERC-18-0495, indexed in Pubmed: 30608900.
91. Rinke A, Müller 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(28): 4656–4663, doi: 10.1200/JCO.2009.22.8510, indexed in Pubmed: 19704057.
92. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014; 371(3): 224–233, doi: 10.1056/NEJMoa1316158, indexed in Pubmed: 25014687.
93. Kulke MH, Hörsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. J Clin Oncol. 2017; 35(1): 14–23, doi: 10.1200/JCO.2016.69.2780, indexed in Pubmed: 27918724.
94. Lamarca A, Barriuso J, McNamara MG, et al. Telotristat ethyl: a new option for the management of carcinoid syndrome. Expert Opin Pharmacother. 2016; 17(18): 2487–2498, doi: 10.1080/14656566.2016.1254191, indexed in Pubmed: 27817224.
95. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011; 378(9808): 2005–2012, doi: 10.1016/S0140-6736(11)61742-X, indexed in Pubmed: 22119496.
96. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017; 376(2): 125–135, doi: 10.1056/NEJMoa1607427, indexed in Pubmed: 28076709.
97. Strosberg J, Wolin E, Chasen B, et al. Health-Related quality of life in patients with progressive midgut neuroendocrine tumors treated with lu-dotatate in the phase III NETTER-1 trial. J Clin Oncol. 2018; 36(25): 2578–2584, doi: 10.1200/JCO.2018.78.5865, indexed in Pubmed: 29878866.
98. Gupta S. Intra-arterial liver-directed therapies for neuroendocrine hepatic metastases. Semin Intervent Radiol. 2013; 30(1): 28–38, doi: 10.1055/s-0033-1333651, indexed in Pubmed: 24436515.
99. Bernheim AM, Connolly HM, Rubin J, et al. Role of hepatic resection for patients with carcinoid heart disease. Mayo Clin Proc. 2008; 83(2): 143–150, doi: 10.4065/83.2.143, indexed in Pubmed: 18241623.
100. Kinney MAO, Nagorney DM, Clark DF, et al. Partial hepatic resections for metastatic neuroendocrine tumors: perioperative outcomes. J Clin Anesth. 2018; 51: 93–96, doi: 10.1016/j.jclinane.2018.08.005, indexed in Pubmed: 30098573.