

Carcinoid Heart Disease: From Pathophysiology to Treatment – ‘Something in the Way It Moves’

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Key Words

Carcinoid · Neuroendocrine · Heart · Valve · Tricuspid · Serotonin · 5-Hydroxyindoleacetic acid

Abstract

Carcinoid heart disease (CHD) is a rare cardiac manifestation occurring in patients with advanced neuroendocrine tumours and the carcinoid syndrome, usually involving the right-sided heart valves and eventually leading to right heart failure. The pathophysiology of CHD is still obscure and believed to be multifactorial, as a variety of vasoactive substances secreted by the tumour appear to be involved. The management of patients with CHD is complex, as both the systemic malignant disease and the heart involvement have to be addressed. Timely diagnosis and early surgical treatment in appropriately selected patients are of outmost importance, as CHD is associated with increased morbidity and mortality. Valve replacement surgery alleviates right heart failure and may also contribute to improved survival. In the present study we have comprehensively reviewed the existing literature to date, mainly focusing on the pathophysiology of CHD. Other aspects of CHD (such as the clinical presentation, diagnostic tools and therapeutic approach) are addressed in brief.

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Introduction

Neuroendocrine tumours (NETs), previously known as carcinoid tumours, are rare malignancies, with an incidence of 5.1/100,000/year, occurring mainly in the gastrointestinal tract (67.5%) followed by the bronchopulmonary system (25.3%) [1, 2]. However, they may develop everywhere in the body, either from various endocrine glands (the pituitary, the parathyroid or the adrenal medulla), from endocrine cells within secretory organs (thyroid C-cell and pancreas islets of Langerhans), but mainly from neuroendocrine cells distributed between exocrine cells throughout the digestive and respiratory tracts [1, 2]. NETs may present with a diversity of morphological and behavioural characteristics, the vast majority being relatively slow-growing tumours (well-differentiated NETs), whereas some of them may present with a highly malignant phenotype (poorly differentiated neuroendocrine carcinoma). NETs may be ‘functioning’ or ‘non-functioning’ based on the presence or the absence of clinical symptoms of hormonal hypersecretion; however, non-functioning tumours may well show immunohistochemical positivity for hormones, neuropeptides or neurotransmitters, and this distinction may to some extent be artificial [3, 4].

NETs may secrete as many as 40 secretory products (vasoactive substances), the most prominent being 5-hy-

droxytryptamine (5-HT, serotonin) but also tachykinins, kallikrein or prostaglandins. These tumour products are usually inactivated by the liver [5–9]. In approximately 30–40% of NET patients, when hepatic spread from a primary gastrointestinal NET results in hormonally active tumour products exceeding the hepatic capacity for degradation, the classical carcinoid syndrome (CS) ensues [10–12]. Rarely, CS may appear without pre-existing liver metastases in patients with extensive retroperitoneal lymph node metastases and drainage bypassing the liver via the thoracic duct and retroperitoneal venous collaterals or when the tumour products drain directly into the systemic circulation such as in the rare case of ovarian NETs [13, 14]. The classical (typical) CS is usually characterized by cutaneous flushing, gut hypermotility with diarrhoea and bronchospasm with wheezing and shortness of breath [15]. The atypical CS is rare, mainly occurring in the context of lung NETs. It is characterized by extended episodes of flushing, headache, shortness of breath and, in rare cases, lacrimation [16].

Carcinoid heart disease (CHD, Hedinger syndrome), a rare and unique manifestation, has been described in up to 60% of patients with both NETs and CS, typically inducing abnormalities of the right side of the heart [17]. CHD occurs most frequently in patients with NETs originating in the small bowel (72%) followed by NETs of the lung, large bowel, pancreas, appendix, or ovarian origin. However, in approximately 18% of cases the primary tumour site cannot be determined [18]. A slight male preponderance (~60%) has been reported, with a mean age at diagnosis of 56–63 years.

CHD is diagnosed approximately 1.5 years after the initial diagnosis of NET and CS [19]. However, diagnosis at the earliest stage possible is essential as the development of right ventricular dysfunction portends a poor prognosis and represents a major cause of morbidity and mortality, with death as a result of cardiac decompensation in as high as 43% in untreated patients [20–23].

In the present study we have comprehensively reviewed the existing literature to date, mainly focusing on the pathophysiology of CHD. Other aspects of CHD (such as the clinical presentation, diagnostic tools and therapeutic approach) are addressed in brief.

Pathophysiology

The precise mechanisms responsible for the development of CHD remain obscure. The disease is thought to be multifactorial and mediated by a variety of vasoactive

substances secreted by the tumour, including 5-HT (serotonin), prostaglandins, histamine, bradykinin, and other substances with fibroblast proliferative properties such as tachykinins (substance P, neurokinin A, neuro-peptide K) or transforming growth factor- β (TGF- β), which finally lead to the deposition of plaques on the endocardial surfaces of valve leaflets, subvalvular apparatus (chordae and papillary muscles) and cardiac chambers and occasionally within the intima of the pulmonary arteries and the aorta. These plaque-like deposits are composed of myofibroblasts, smooth muscle cells, extracellular matrix (ECM) components (collagen and myxoid ground substance), and an endocardial cell layer [17, 24]. These deposits usually involve primarily the right side of the heart (in ~90% of cases), specifically the downstream side of the valve leaflets, i.e. the ventricular aspect of the tricuspid valve and the pulmonary arterial side of the pulmonary valve [5]. Simultaneous involvement of both the tricuspid and pulmonary valves strongly suggests CHD as the likely diagnosis, demonstrating a pathognomonic appearance. In the pulmonary valve the plaques are deposited on the leaflets, leading to the adherence of pulmonic leaflets to the pulmonary arterial endocardium and resulting in a mixture of valvular stenosis and regurgitation, whereas in the tricuspid valve regurgitation tends to be predominant as the plaques involve mainly the subvalvular apparatus [18, 24, 25]. Compared with the right side of the heart, the left-sided valves are rarely affected because of the pulmonary metabolism and deactivation of the hormonal substances [18]. However, left-sided involvement is more frequent in patients with patent foramen ovale (76–88%) [26], which appears to be more common in patients with CS and CHD compared with the general population (up to 41% in patients with CS and up to 59% in those with CHD) [27].

The complex mechanism of cardiac plaque formation in CHD is considered to be multifactorial. Initial animal studies postulated that the variety of vasoactive substances secreted by the NET may exert paraneoplastic effects [28]. For example, bradykinin has been reported to induce endocardial injury, the resulting fibrosis representing a healing response of the endocardium. Moreover, tachykinin was described as a pro-proliferative agent for the endocardial fibroblasts, thereby inducing plaque formation [29].

Nowadays, there is a strong body of evidence implying that serotonin plays a major role in stimulating fibroblast growth and fibrogenesis [28]. It is well known that urinary 5-hydroxyindoleacetic acid (5-HIAA), the serotonin metabolite which reflects the amount of serotonin pro-

duction, is significantly higher in patients with CHD compared with those without cardiac involvement [17, 30].

Serotonin and Serotonin Receptors

Serotonin (5-HT), synthesized from the amino acid tryptophan subsequent to hydroxylation and decarboxylation, is a well-known neurotransmitter found in neurons located along the raphe nuclei of the brainstem. Outside the central nervous system, serotonin is produced mainly by the enterochromaffin (or Kulchitsky) cells, dispersed throughout the gastrointestinal and bronchopulmonary system, being involved in cell motility, fluid secretion and regional blood circulation [31, 32].

Serotonin actions are mediated by interaction with seven serotonin receptor classes [33] located on the cell membrane of neurons and of many other cells in the body [34, 35]. There are six types of serotonin G protein-coupled receptors (5-HTR 1, 2, 4, 5, 6, 7); the seventh type of 5-HTR, 5-HTR₃, is unique as it is a ligand-gated ion channel [36, 37]. The 5-HT₂ receptors are among the most frequently targeted [34, 38]. Specifically, 5-HT_{2B} receptors have been found to be present, particularly, in the cardiovascular system, gastrointestinal tract, bone, and CNS, with similar tissue distribution and pharmacological properties in both rodents and humans, thereby facilitating extrapolation of rodent studies to humans [39–42].

There is an emerging body of evidence for the key role of serotonin in the development of CHD, as follows:

- 1 Serotonergic drugs used in the treatment of obesity, migraine and Parkinson's disease have been demonstrated to cause valvular fibrosis [10] similar to that seen in patients with CHD. The current hypotheses came about as a result of inadvertent targeting of the 5-HT_{2B} receptors with the 'fen-phen' anorexigen combination [43]. Fenfluramine, but mainly its active metabolite norfenfluramine, are known to be potent agonists of the 5-HT_{2B} receptors, which are abundantly expressed on human cardiac valves. It is believed that the repeated stimulation of 5-HT_{2B} receptors induces uncontrolled valve cell division [41, 44]. Moreover, the administration of different dopamine agonists in patients with Parkinson's disease (such as pergolide or cabergoline) has also been associated with the occurrence of similar valvular changes [45, 46].
- 2 Studies on cell cultures have shown that serotonin has mitogenic effects on fibroblasts [47], smooth muscle cells [48], osteoblasts [49, 50], renal mesangial cells [51], and endothelial cells [52].

- 3 Preliminary animal studies using Sprague-Dawley rats and cynomolgus monkeys demonstrated that long-term exposure to high levels of serotonin induces morphological (shortened and thickened aortic cusps and carcinoid like plaques made of myofibroblasts within an ECM of collagen ground substance) as well as echocardiographic changes similar to those seen in human CHD [53–55]. It has been demonstrated that the overexpression of 5-HT_{2B} receptors in hearts of transgenic mice resulted in cardiac hypertrophy and decreased ventricular function due to enhanced ECM deposition and remodelling [56], whereas genetic deletion of 5-HT_{2B} receptors has been shown to lead to ventricular dilatation and incomplete cardiac development [57].

The signal transduction effects induced by the 5-HT_{2B} receptor activation in different cells and tissues are complex and may include the following:

- 1 Stimulation of phospholipase C and phospholipase A2 [58, 59].
- 2 Stimulation of nitric oxide synthase [60].
- 3 Mitosis initiation [41, 61], together with the increase in the secretion of inflammatory cytokines such as TNF- α and ECM components [62, 63].
- 4 Activation of MAPK (mitogen-activated protein kinase) [64].
- 5 Phosphorylation of the cytoplasmic tyrosine kinase Src and activation of ERK (extracellular-regulated kinase) [61, 65].
- 6 Phosphorylation of retinoblastoma protein (Rb-P) and cell cycle progression [66].
- 7 Overexpression of TGF- β 1: the 5-HT_{2B} receptor works in concert with the angiotensin II type 1 receptor (AT1R) to mediate hypertrophic signalling in cardiac fibroblasts [63]. The agonist signalling of these receptors has been shown to induce an increase in the synthesis and upregulation of the cytokine TGF- β 1 [67, 68], known to stimulate fibroblasts to produce ECM proteins; TGF- β 1 is overexpressed in CHD lesions and seems to be a major mediator in the tissue changes related to the valvular disease [69, 70] (fig. 1).

Despite the growing body of evidence showing the major involvement of serotonin in the development of CHD, more than 50% of patients with elevated circulating serotonin levels do not develop CHD [9], implying therefore that other biochemical mediators are also significant; activin A [13] and connective tissue growth factor (CTGF) [71] have been associated with the development of the disease in these patients. Activin A, a cytokine member of the TGF- β superfamily with fibrogenic properties, was found to be expressed in the fibrotic plaques of CHD le-

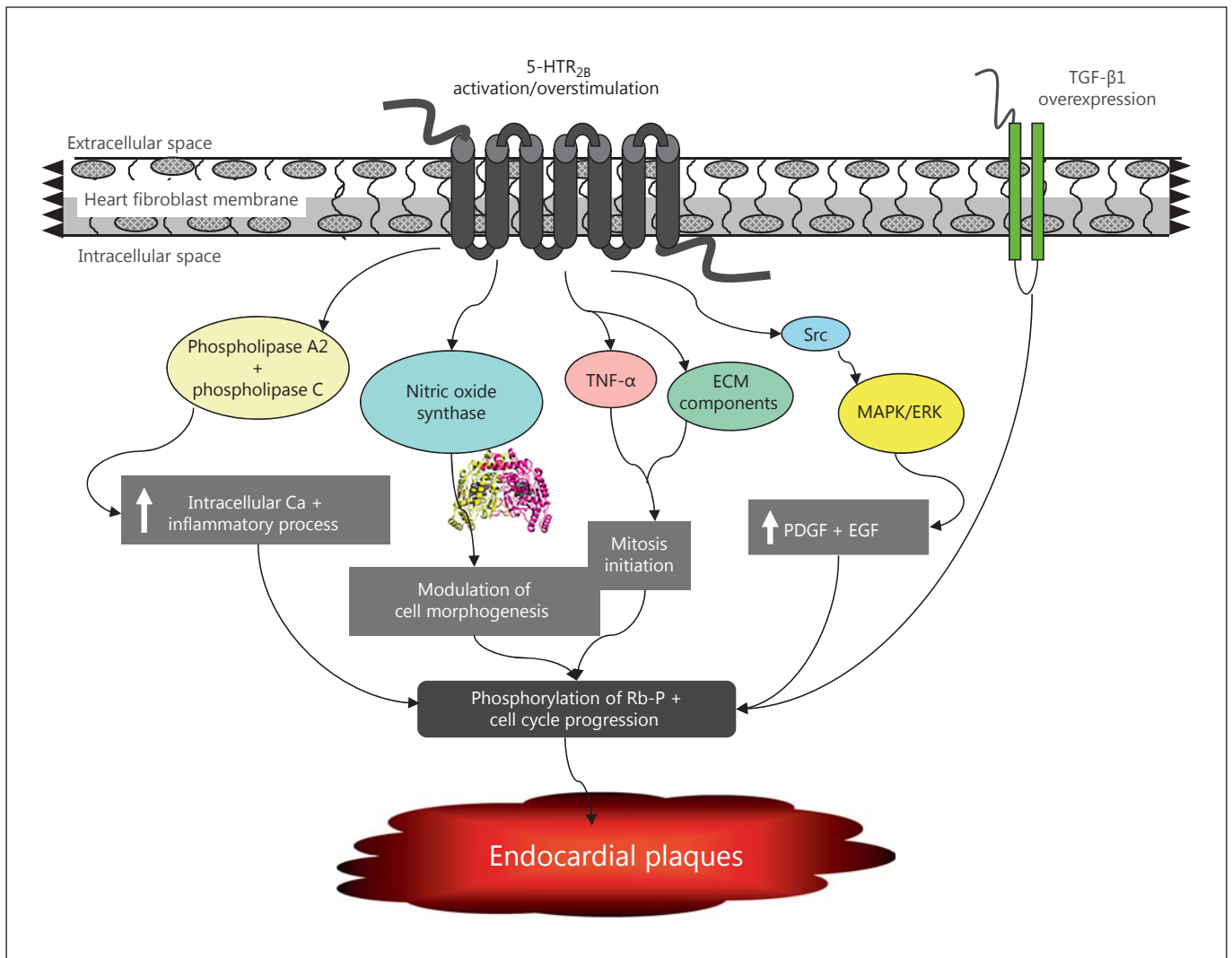


Fig. 1. The signal transduction effects induced by the 5-HT_{2B} receptor activation. PDGF = Platelet-derived growth factor; EGF = epidermal growth factor; Rb-P = phosphorylated of retinoblastoma protein.

sions [72]. Intestinal NETs overexpress CTGF and TGF-β1 mRNA and synthesize CTGF and TGF-β1 proteins, which act in concert to drive the overproduction of collagen, contributing to the initiation and maintenance of the fibrotic process [73, 74].

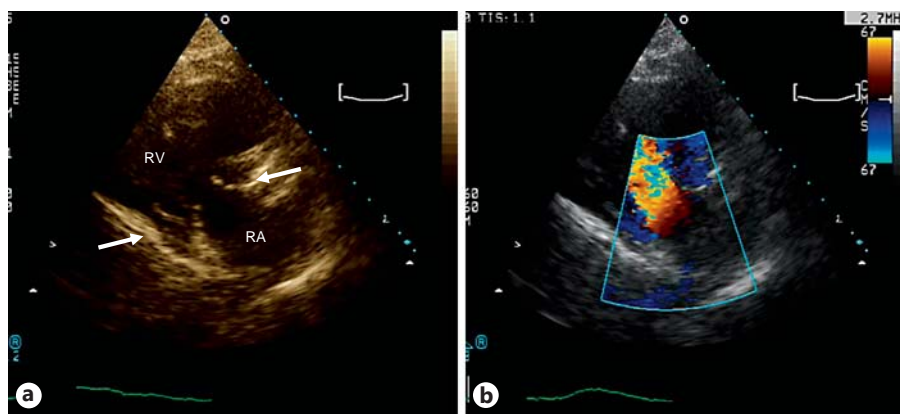
Clinical Features of CHD Patients

Early in the course of the disease the clinical manifestations of CHD are often subtle, as tricuspid and pulmonary valve disease of various degrees may be well tolerated for long periods of time and difficult to detect be-

cause of the low pressure in the pulmonary circulation [19, 25]. Early symptoms usually include fatigue and dyspnoea, mainly on exertion. Then, in parallel with tumour progression and the increased levels of serotonin, progressive right-sided heart failure with worsening dyspnoea, anasarca and cardiac cachexia eventually occurs. However, in a substantial proportion of patients with cardiac involvement no symptoms or signs suggesting CHD are found; in these patients a high degree of awareness is necessary to establish a timely diagnosis [75].

On physical examination, elevated jugular venous pressure and a palpable right ventricular impulse may be found. Murmurs of tricuspid and pulmonary valve regur-

Fig. 2. Transthoracic echocardiogram of the tricuspid valve in CHD. RA = Right atrium; RV = right ventricle. **a** Right ventricular inflow view demonstrating thickened and retracted anterior and posterior leaflets of the tricuspid valve, resulting in malcoaptation at end-systole (arrows). **b** Colour flow Doppler image showing severe tricuspid regurgitation as a result of malcoaptation.



gitation are frequent on heart auscultation, whereas a systolic murmur of pulmonary stenosis or a diastolic murmur of tricuspid stenosis is rarely described. As the valve disease progresses, peripheral oedema, ascites and pulsatile hepatomegaly develop [21, 75]. Clinical assessment, including New York Heart Association (NYHA) classification and physical examination, to identify signs of valvular disease is rarely sufficient to make the diagnosis [76].

Biochemical Evaluation of Patients with CHD

- NET patients with CHD have been shown to have 2- to 4-fold higher values of serum serotonin, platelet serotonin and urinary 5-HIAA levels than those without CHD [30]. Elevated 5-HIAA urinary levels have been correlated with an increased risk of CHD progression, as well as with worsening of the echocardiographic findings [77–79].
- Chromogranin A has also been suggested as a sensitive marker for patients with NETs and CHD [80].
- N-terminal pro-brain natriuretic peptide (NT-pro-BNP) belongs to a neurohormone family released by the atria and ventricles in response to the increase in wall stress in response to both volume and pressure overload and may act as an antifibrotic agent in the myocardium [81, 82]. To date, NT-proBNP has been considered extremely useful in the evaluation of CHD severity and prognosis, as its median levels appear to be significantly higher in patients with CHD than in those without [83]. Moreover, NT-proBNP has a high sensitivity and specificity (87 and 80%, respectively) in predicting CHD in NETs and correlates with patient survival [80]. Therefore, this marker is highly recom-

mended by the UK and Ireland NET Society (UKI NETS) guidelines as a screening tool for CHD in patients with intestinal NETs, with or without hepatic metastases, and in all patients with CS [83, 84].

- Plasma activin A levels were reported to be significantly higher in NET patients with CHD compared with those without. Activin A was defined as an independent predictor for the presence of CHD, with 87% sensitivity and 57% specificity for detecting CHD at plasma levels of ≥ 0.34 ng/ml [72]. As plasma activin A levels were increased in both the early and the advanced stages of CHD, it was suggested that its assessment may be indicative of early CHD compared with elevated circulating levels of neuropeptide K, substance P and atrial natriuretic peptide, which were considered as markers of advanced CHD in earlier studies [20, 85]. Moreover, in contrast with NT-pro-BNP, increased activin A levels were also found in CHD patients without right heart dilatation [72].
- Elevated CTGF levels were reported to represent an independent predictor factor of reduced right ventricular function, with 88% sensitivity and 69% specificity in NET patients with CHD [86].

Imaging Modalities for CHD

The principal imaging modality used in the assessment of CHD is echocardiography (fig. 2). On a 2-dimensional transthoracic echocardiogram, the affected tricuspid valve typically appears thickened. Then, in parallel with disease progression, the leaflets become fixed and retracted in a half-open position, resulting in regurgitation with some degree of stenosis [87, 88]. Colour flow Doppler may help further characterize the degree of tricuspid regurgitation.

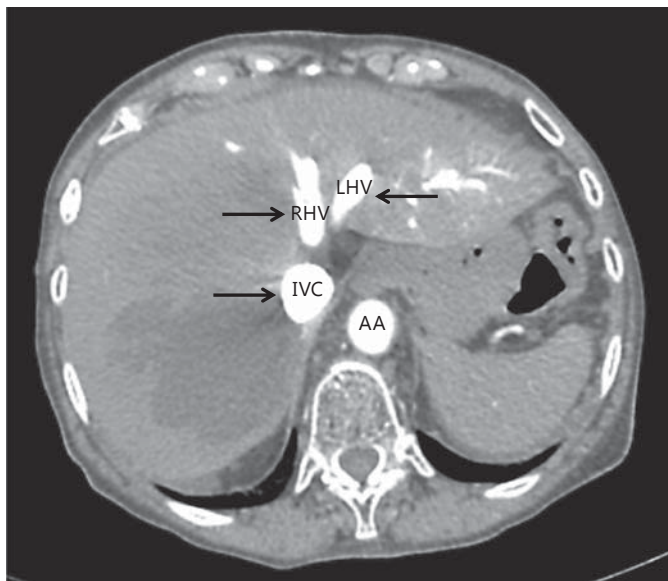


Fig. 3. High-resolution CT of the abdomen (axial image) in a patient with NET, CS and CHD. IVC = Inferior vena cava; RHV = right hepatic vein; LHV = left hepatic vein; AA = abdominal aorta. Reflux of contrast material into inferior vena cava and hepatic veins during arterial phase of CT study can be seen (arrows), which is highly indicative of severe tricuspid valve regurgitation and right heart failure.

Involvement of the pulmonic valve may also lead to a thickened appearance with reduced movement. As a consequence of valvular disease, the right-sided cardiac chambers may become progressively dilated and hypokinetic: 3-dimensional transthoracic echocardiography/transoesophageal echocardiography provides detailed anatomic information, particularly for the tricuspid and pulmonary valves, enhancing the ability to detect the involvement of chordae and papillary muscles [87]. Several echocardiographic scoring systems have been developed to assess the progression of CHD. However, the clinical relevance of these scoring systems is uncertain, and it has been shown that they are comparable in their discriminatory ability for the detection of cardiac involvement and correlate with the biomarkers of CHD [89].

Other imaging modalities may be valuable in the assessment of disease severity. Cardiac MRI [90, 91] overcomes the issue of suboptimal visualization of the right-sided heart valves and enables accurate quantification of regurgitant volumes and right ventricular ejection fraction, which is pivotal to the long-term management of the patients [75]. Occasionally, CHD is diagnosed by the radiologist on contrast-enhanced CT, where reflux of con-

trast from the right atrium to the inferior vena cava and hepatic veins is noted (fig. 3). Positron emission tomography, using synthetic radiolabelled octreotide with radio-nuclide tracers such as ^{68}Ga and ^{18}F -dihydroxy-phenyl-alanine, can also identify cardiac metastases [87, 92].

Consensus European Neuroendocrine Tumor Society (ENETS) guidelines recommended that annual echocardiography be mandatory as part of the routine surveillance of CHD patients [93–95]. Importantly, in the early stages of the disease, subtle thickening of the tricuspid valve leaflets and subvalvular apparatus with mild tricuspid regurgitation may appear as a non-specific finding. These patients should be therefore screened regularly, and comparisons should be made with previous echocardiograms to assess valvular disease progression. Echocardiography should be performed by an experienced echocardiographer with considerable personal experience (at least 200 examinations/year) [96].

Stepwise Therapeutic Approach in Patients with CHD

Patients with the rare diagnosis of CHD developing in the context of a metastatic NET and the CS should be treated in specialized centres by a multidisciplinary team including endocrinologists, oncologists, cardiologists, pathologists, and surgeons with experience in the treatment of this complex condition [75]. Without a timely intervention, NET patients with CHD will eventually develop progressive right heart failure in parallel with a significant decrease in their life expectancy compared with those NET patients without CHD [18] (fig. 4).

Medical Therapy and Tumour Debulking

Treatment with somatostatin analogues is based on NET cell ability to express specific somatostatin receptors on their surface membrane, a characteristic being of great value for both tumour imaging and staging as well as for the treatment of these tumours [97]. Treatment with somatostatin analogues and/or tumour debulking techniques (hepatic artery embolization, palliative hepatic cytoreductive surgery, etc.) may improve the symptoms of the CS [98, 99] as well as the negative haemodynamic impact of tumour vasoactive agents on CHD and on the development of heart failure [100]. However, to date, there is no current evidence suggesting that these interventions are beneficial in terms of CHD progression [77]. Moreover, bacterial endocarditis prophylaxis is not indicated in patients with CHD [101].

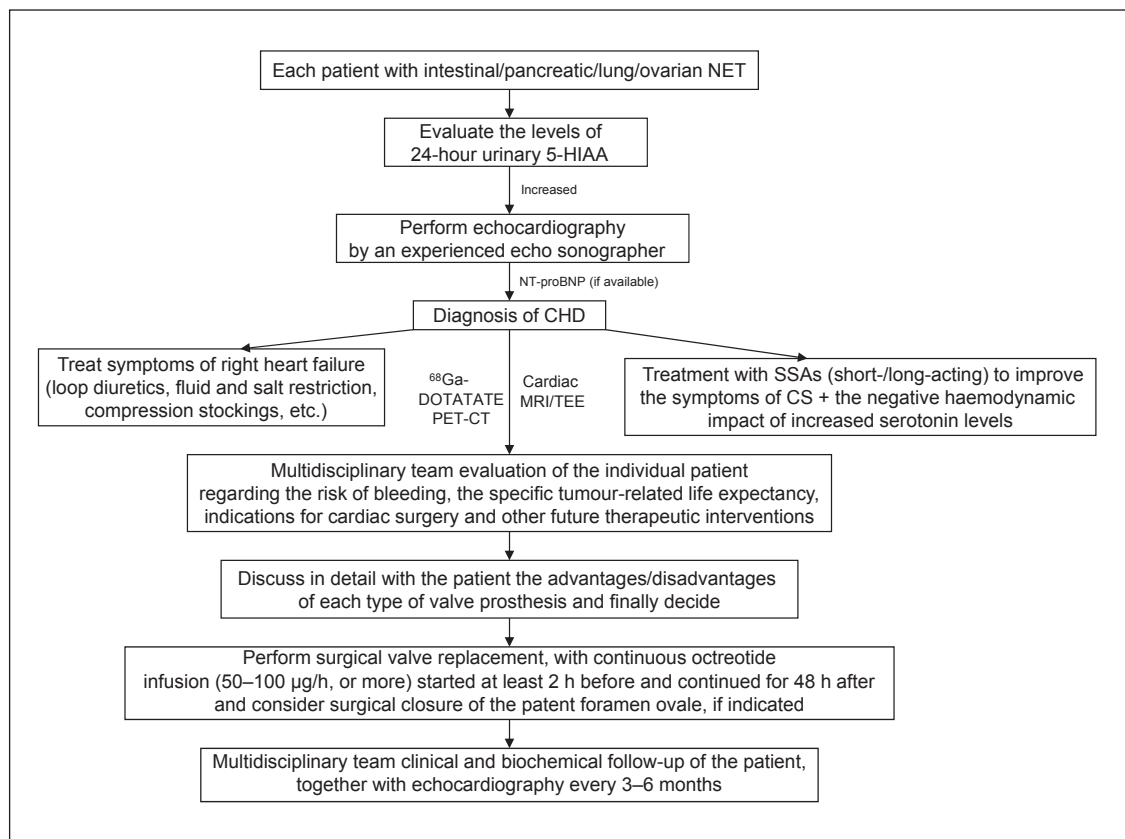


Fig. 4. Stepwise therapeutic approach in patients with CHD. ^{68}Ga -DOTATATE PET-CT = Positron emission tomography using synthetic radiolabeled octreotide with ^{68}Ga ; TEE = transesophageal echocardiography; SSAs = somatostatin analogues.

In the perioperative setting, continuous somatostatin analogue (octreotide) infusion (50–100 µg/h, or more) is of utmost importance [102]; it should be started at least 2 h before surgery and continued for 48 h afterwards, with a slow tapering down before treatment discontinuation [103]. The octreotide infusion is aimed at reducing serotonin release, optimizing surgical outcome by reducing perioperative complications such as hypotension, carcinoid crisis and death [104]. Antihistamines may also be used before surgery to prevent flushing and bronchospasm, whereas corticosteroids can be used to reduce bradykinin production [17]. In the perioperative setting, minimizing the use of specific drugs known to precipitate vasoactive products released by the tumour (such as opioids, the neuromuscular relaxant atracurium, dopamine, or adrenaline/epinephrine) is strongly advised to reduce the risk of carcinoid crisis [105].

Recently, telotristat etiprate, a novel serotonin synthesis inhibitor, has been reported as being highly effective

for alleviating diarrhoea in patients with CS inadequately controlled by octreotide alone. As a biochemical response ($\geq 50\%$ reduction or normalization in 24 h of urinary 5-HIAA levels) has been reported in most of the patients, this new drug may be promising for patients with CHD with intractably elevated levels of serotonin [106].

The use of loop diuretics, together with fluid and salt restriction and compression stockings, may initially relieve the symptoms of right heart failure. However, in advanced right ventricular failure these measures become ineffective and even deleterious due to the depletion of intravascular volume, further reducing of the cardiac output [17].

Balloon Valvuloplasty

In patients not suitable for cardiac valve surgery, balloon valvuloplasty has been used to treat stenotic pulmonary or tricuspid valves [107]. Although some short-lasting functional and haemodynamic benefit has been re-

ported, the rapid relapse of valvular disease renders the use of this technique of limited value [108].

Surgical Valve Replacement in CHD

Patients with CHD usually die as a result of severe tricuspid regurgitation [109] rather than carcinomatosis. Whereas previously undertaken only in severely symptomatic patients with advanced cardiac disease, surgical valve replacement is now performed earlier because of the increased perioperative mortality in patients with severe heart failure and improvements in cardiac surgery [23, 28]. As valvular surgery offers definitive therapy for CHD-related symptoms, marked symptomatic improvement usually occurs after valve replacement [109, 110]. The reports on median survival after cardiac valve replacement vary between 6 and 11 years [19]. The improved survival of patients with CHD in recent years may reflect the increasing surgical expertise in this field and better perioperative management of the patient with octreotide [75].

The choice of the type of valve prosthesis (biological vs. mechanical) is controversial as the literature is limited to small, retrospective series or case reports [111]. On the one hand, biological prosthetic valve degeneration with valve allograft failure has been reported to occur as early as 3 months after implantation, being the result of intractable high levels of NET vasoactive products inducing carcinoid plaque reformation [112–114]; on the other hand, the use of mechanical prosthesis requires life-time anticoagulation in these patients who have an already increased risk of bleeding due to hepatic dysfunction, together with an increased risk of valve thrombosis [115, 116].

The decision on the type of prosthesis is complex and should be individually tailored based on the individual patient risk of bleeding, the specific tumour-related life expectancy and possible future therapeutic interventions. The advantages and disadvantages of both valve types should be discussed in detail with the patient as part of the decision-making process. A recent overview on the outcome of CHD patients following valvular surgery suggested that surgical intervention can lead to improved prognosis and should therefore be considered for symptomatic palliation in carefully selected individuals [117]. Moreover, a recent paper aimed at identifying outcomes, risks and complications related to valve surgery for CHD patients suggested that surgical valvular replacement presented a higher risk compared with most other forms of valvular surgery. However, in patients surviving the operation, a significant improvement in functional class

could be observed, whereas most long-term complications were related to the tumour itself and not to the cardiac procedure [118].

In the rare patients with left-heart valvular involvement due to interatrial shunts via a patent foramen ovale, surgical closure of the patent foramen ovale is advised, inducing a dramatic relief of symptoms [119].

Conclusions

CHD is a rare and severe complication of advanced NETs and is associated with increased morbidity and mortality. The biological basis for the development of CHD remains obscure, despite the emerging evidence indicating that serotonin plays a main role in the pathological process of valve destruction and dysfunction. Early recognition and surgical intervention, before advanced heart failure has occurred, may improve the outcome of these patients. A better understanding of the molecular mechanisms underlying the progression of fibrosis in CHD may lead to the development of appropriate targets for targeted molecular therapy. Finally, the management of patients with CHD is extremely complex and requires a multidisciplinary approach involving specialists with broad experience in the field.

Disclosure Statement

The authors have no conflicts of interest to declare.

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