

# Echocardiographic diagnosis in carcinoid heart disease

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## ABSTRACT

In this case report the typical echocardiographic features of carcinoid heart disease are presented. Newer treatments such as the use of a somatostatin analogue, interferon and hepatic de-arterialisation have improved the prognosis in patients with carcinoid syndrome. Nevertheless this syndrome portends a poor prognosis in patients with cardiac involvement. Cardiac lesions are mainly located in the right side of the heart. Regurgitation and stenosis of the tricuspid and pulmonary valve, leading to right heart failure, are the most common cardiac manifestations of the disease. Elevated levels of serotonin are probably responsible for the development of these cardiac lesions. Despite treatment resulting in significant reductions of urinary levels of 5-HIAA, regression of the cardiac manifestations in carcinoid syndrome has not been observed. Two-dimensional and Doppler echocardiography are the main tools to establish the diagnosis and severity of carcinoid heart disease. Cardiac surgery for carcinoid heart disease might improve symptoms and longevity, but the scarce data report on early mortality of over 35%.

## INTRODUCTION

In 1907 Oberndorfer introduced the term 'Karzinoide' (meaning similar to carcinoma) to describe indolent but malignant tumours arising from the enterochromaffin cells (Kulchitsky cells), in particular from Kulchitsky cells situated in the gastrointestinal tract and the bronchi. These cells produce various biologically active amines or polypeptide hormones, including serotonin (5-hydroxytrypta-

mine) which, when reaching the circulation, are held responsible for the occurrence of the characteristic symptoms. The classical syndrome, occurring in only 4% of the patients with a carcinoid tumour, is characterised by dermal flushing, diarrhoea, bronchospasm (wheezing) and right-sided valvular heart disease.<sup>1,2</sup> In the majority (95%) of patients, the carcinoid tumour arises from the gastrointestinal tract and only causes the syndrome in the presence of hepatic metastases. Serotonin is metabolised to 5-HIAA (5-hydroxyindoleacetic acid) by the monoamine oxidase enzyme in the endothelium of lung and liver vasculature. The amount of serotonin can be measured both in serum and in thrombocytes. The amount of 5-HIAA is measured in the urine.

During the past decade, several new treatments have emerged for patients with malignant carcinoid syndrome in order to eliminate systemic symptoms. Somatostatin inhibits the release of numerous peptides, such as growth hormone, insulin, glucagon and gut peptide. Because of the short half-life of the native somatostatin compound, the somatostatin analogue sandostatin (SMS 201-995) was developed and proved to be more potent and longer acting in its inhibitory effects. It has resulted in marked symptomatic improvement and improved survival in patients with the carcinoid syndrome. Hepatic de-arterialisation by ligation or occlusion has also been effective in relieving the symptoms by inducing rapid tumour shrinkage in patients with hepatic metastases. Despite the alleviation of systemic symptoms by these measures, patients in whom carcinoid cardiac involvement has already developed continue to experience progressive symptoms of right-sided heart failure and mortality from cardiac causes. Treatment

involving only medications for the relief of symptoms of heart failure results in a high mortality rate from progressive right heart failure. To improve the long-term outlook for these patients, severe haemodynamic consequences of the valvular abnormalities of carcinoid heart disease can be corrected by means of valvular surgery. It is therefore important to follow up the patients regularly and consider surgical intervention when cardiac symptoms become severe, albeit with a significant risk of perioperative mortality. Cardiovascular involvement occurs in over half of the patients with carcinoid disease. The severity of cardiac involvement does not seem to be related to the duration of carcinoid disease, but more to the extent of the disease, i.e. higher plasma levels of serotonin and tachykinins. Cardiac lesions are pathognomonic and in over 50% of patients the cause of death.<sup>3</sup> Because two-dimensional echocardiography can assess cardiac anatomy and valvular motion and Doppler examination can assess the severity of valvular stenosis and regurgitation, these procedures appear ideally suited for analysing and following the progression of carcinoid heart disease.

## CASE REPORT

A 65-year-old man from the Caribbean (Dutch Antilles), who was known to have hypertension, underwent a resection of the coecum in 1985. A carcinoid tumour was diagnosed on the histology findings. Small metastases in the liver were present. In 1993 flushing, diarrhoea and oedema of the legs became manifest.

On admission to our hospital in 1996, his blood pressure was 160/100 mmHg. The jugular veins were distended. On auscultation an S<sub>3</sub> gallop was noted; first and second heart sounds were normal. A mid frequent, holosystolic murmur accompanied by a mid frequent, decrescendo diastolic murmur, both grade 2/6, were present. No right ventricle impulse was detected. The lung fields were clear, without the presence of wheezing. The liver was palpable about 5 cm below the xiphoid process and the right costal margin. Expansive pulsations of the liver and pitting oedema on the lower legs were present.

The electrocardiogram revealed normal sinus rhythm with a left bundle branch block.

Laboratory results showed a serotonin level of 60.0 nmol/10<sup>9</sup> (normal: 2.8-5.4) in the thrombocytes. Urine (24 h collection): creatinine 9.9 mmol total (normal: 8.9-16.0), HIAA: 1865 mmol total (normal: 0-50). HIAA/creatinine: 188.4 mmol creatinine (normal: 0-4.4).

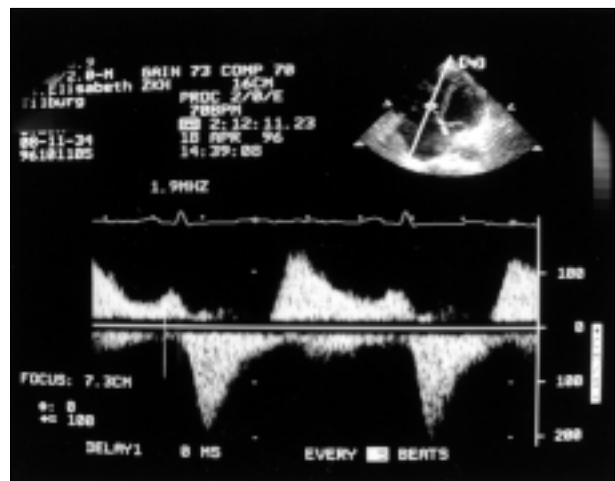
CT scan of the abdomen demonstrated pathological lesions in the right liver quadrant.

Transthoracic echocardiography revealed normal dimensions and wall thickness of the left ventricle with an ejection

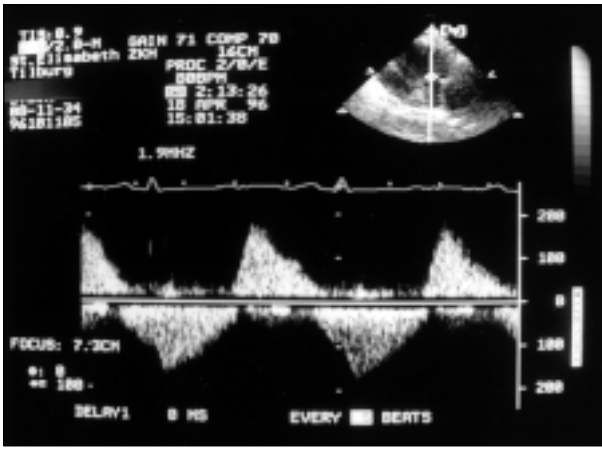
fraction of 70%. The aortic and mitral valves were normal. Both the right ventricle and right atrium were dilated. The tricuspid valve showed retraction and shortening of thickened anterior and septal cusps, leading to an immobile valve in a semi-open position. The pulmonary valve showed similar features. With colour Doppler, severe regurgitation of both the tricuspid and pulmonary valves could be demonstrated (jet area >40%). The continuous-wave (CW) Doppler signal showed tricuspid regurgitation, without severe stenosis: a characteristic 'dagger-shaped' regurgitation signal with max velocity 194 cm/sec, demonstrating rapid decline in pressure difference between RV and RA, indicating severe tricuspid regurgitation, and mild tricuspid stenosis with a mean pressure gradient of 2.4 mmHg and a pressure half-time of 128 m/sec (figure 1). CW Doppler of the pulmonary valve revealed severe regurgitation and mild stenosis (max velocity 167 cm/sec and a short deceleration time), indicating severe regurgitation (figure 2). No pericardial effusion or features of myocardial fibrosis were noted. Transoesophageal echocardiography highlighted the typical findings on the tricuspid and pulmonary valve as seen on transthoracic echocardiography (figures 3 and 4). No shunt could be demonstrated. No findings suggestive of myocardial metastases or endocardial fibrosis were noted.

## DISCUSSION

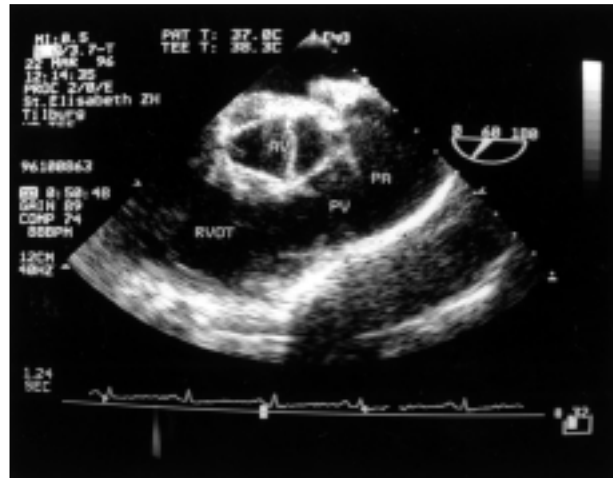
Carcinoid heart disease, first described by Thorssen *et al.* in 1954,<sup>2</sup> has a prevalence of 57-77% in patients diagnosed



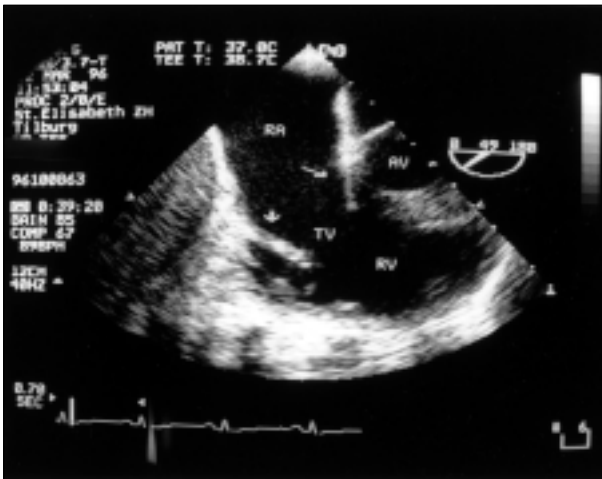
**Figure 1**  
*Continuous-wave Doppler of the tricuspid valve*  
The characteristic 'dagger-shaped' regurgitation signal (max velocity, 194 cm/sec) demonstrating rapid decline in pressure difference between RV and RA, due to severe tricuspid regurgitation, and only mild tricuspid stenosis with a mean pressure gradient of 2.4 mmHg and a pressure half-time of 128 m/sec.



**Figure 2**  
*Continuous-wave Doppler signal of the pulmonary valve*  
This suggests minor pulmonary stenosis (max. velocity 167 cm/sec). The short deceleration time indicates severe regurgitation.



**Figure 4**  
*Transoesophageal echocardiogram with multiplane transducer (60°) of the outflow tract of the right ventricle*  
The thickened and shortened pulmonary valve without coaptation is barely visualised.  
RVOT = right ventricle outflow tract, PV = pulmonary valve, PA = pulmonary artery, AV = aortic valve.



**Figure 3**  
*Transoesophageal echocardiogram of the right side of the heart with multiplane transducer (49°)*  
Dilated right atrium and right ventricle. In carcinoid heart disease, the tricuspid valve shows typical lesions of retraction and thickening of the anterior and septal cusp, which remain in an immobile, semi-open position. RA = right atrium, RV = right ventricle, TV = tricuspid valve, AV = aortic valve.

with a carcinoid tumour.<sup>3,4</sup> Histological investigation of the carcinoid lesions in the heart demonstrates white, plaque-like endocardial thickening measuring up to 2 mm. The preponderance of lesions in the right side of the heart suggests that carcinoid heart disease is related to factors secreted into the hepatic vein due to liver metastases.<sup>5</sup> Both the tricuspid valve and the pulmonary valve thicken and retract, then become immobile and remain in a permanent semi-open position. Tricuspid regurgitation and pulmonary regurgitation are the result, and stenosis may also occur. These very characteristic valvular lesions eventually lead to

right-sided heart failure.<sup>1-4</sup> Apart from the valves, similar formation of fibrosis can be seen in the intima of the great vessels, in the pleura, pericardium and retroperitoneum in carcinoid disease. Myocardial metastases have been described in the left and right ventricle as well as pericardial effusions and restrictive cardiomyopathy. Abnormalities of the valves of the left side of the heart were described in patients who had a carcinoid tumour primarily located in the lungs and in patients who had a right-to-left shunt at the level of the fossa ovalis. The largest series of patients with carcinoid syndrome published so far is from the Mayo Clinic.<sup>3</sup> In this retrospective study, patients with carcinoid heart disease did not differ from patients without carcinoid heart disease regarding duration of histological diagnosis of carcinoid syndrome, age or sex, as was reported earlier.<sup>1,3,6,7</sup> ECG and chest X-ray abnormalities appeared to be non-specific. Repeated echocardiographic examination is essential for the diagnosis of carcinoid heart disease. Denny *et al.* suggested an echocardiographic scoring system to monitor carcinoid heart disease development and progression quantitatively.<sup>8</sup> Mean 5-HIAA urinary levels were significantly higher in patients with carcinoid heart disease. Despite treatment resulting in significant reductions of 5-HIAA urinary levels, regression of carcinoid heart disease has never been observed at follow-up echocardiography. With the same treatment regimens for both groups, the three-year survival for patients with carcinoid heart disease was 31%, and 68% for patients without carcinoid heart disease. The mean duration of survival in carcinoid heart disease was 1.6 years, which is in agreement with other studies.<sup>1</sup>

## THERAPEUTIC OPTIONS

Surgery is the best treatment for localised carcinoid tumours, although a complete cure is difficult to obtain. It can be used for liver involvement to reduce the bulk of the tumour and to reduce the symptoms. Surgical resection of liver metastases is a treatment in patients with limited hepatic disease; it will give relief of symptoms and a longer survival. Another option for liver metastases is selective embolisation of the hepatic artery, but this can be accompanied by complications, such as massive necrosis of the liver and increasing symptoms due to release of 5-HT. The duration of the endocrine response after this treatment is short.

Cytotoxic chemotherapy should be considered for patients with rapidly progressive tumours, for those with urinary excretion of 5-HIAA greater than 150 mg/24h, and for those with carcinoid-induced valvular heart disease, but it has shown only a modest benefit. The most effective options are fluorouracil and streptozocin, in monotherapy or in combination, but they also have a minimal effect.

Remission varies from 13-26%.

Using interferon in patients with a metastatic carcinoid tumour decreases the urinary 5-HIAA in about 40% of patients; the effect in tumour regression is 15-20%. It has the greatest effect in controlling the symptoms, but this medication has many side effects (fever, fatigue, nausea and anorexia). Because of this and the high costs it is of limited use.

Primary tumour or metastases can take up meta-iodobenzyl guanidine (MIBG). In such cases, MIBG in therapeutic dose may be used as a palliative treatment. There is a minimal effect on tumour regression.

As for medical treatment, somatostatin and analogues play an important part in the medical treatment of metastatic carcinoid tumours. Palliation of the symptoms of carcinoid syndrome is best achieved with the long-acting analogue of somatostatin, octreotide, which can be given subcutaneously. The use of octreotide is a major advance in the management of carcinoid tumours. It also decreases the urinary 5-HIAA production. This treatment is successful in almost 80% of the patients.<sup>5,9-11</sup>

Therapeutic options in patients with carcinoid heart disease are limited. Whenever medical therapy of right-sided heart failure fails, surgical intervention can be considered.<sup>5,8,12</sup> Connolly *et al.* presented the results of the largest cardiac surgery series of patients with carcinoid heart disease studied to date.<sup>7</sup> In their series, 26 patients with severe symptoms of right ventricular failure were operated between 1985 and 1992. Later on, several other small studies reported on the clinical benefit of surgical intervention with valvuloplasty or valve replacement to improve right heart valvular function. Since 1966, at least 38 cases of valvular surgery for carcinoid heart disease have been

reported (American Cancer Society 1997). Connolly *et al.* concluded that, even though the procedure is carried out by experienced surgeons, the perioperative mortality is extremely high (35%, mainly because of extensive pleural or pericardial plaques present at operation leading to uncontrollable bleeding). Progression of the malignancy and hepatic dysfunction due to liver metastases adds to a high short-term mortality postoperatively. The eight (30%) survivors, however, experienced a marked symptomatic improvement during follow-up (more than two years). The timing of cardiac operation for carcinoid heart disease remains difficult and guidelines are not available as such. In our patient, sandostatin treatment was started in 1993. Until 1997 he was doing fairly well, only complaining of diarrhoea and flushing. From 1997 up to his death in 2000, he slowly deteriorated due to progressive right-sided heart failure. The echocardiogram did not show dramatic changes. Our patient refused surgery because of the high procedural risk.

## CONCLUSION

Cardiac involvement in carcinoid syndrome, often combined with hepatic metastases, is nowadays diagnosed by echocardiography in over 50% of patients with this syndrome. In the last decade newer therapeutic options, such as the use of medical therapy with somatostatin analogues and interferon, embolisation of liver metastases and surgery, have improved survival in carcinoid disease. The presence of cardiac involvement in this syndrome worsens the prognosis and contributes significantly to morbidity and mortality. Right heart failure as a consequence of regurgitation and stenosis due to (sub)endocardial fibrous plaques covering the endocardium of the tricuspid and pulmonary valves is clinically most relevant. Elevation of serum serotonin levels is most likely responsible for this phenomenon. Regression of cardiac lesions by reducing the serotonin levels has not been observed. Regular echocardiographic examination is the best diagnostic tool to detect and evaluate cardiac involvement. The therapeutic options in the case of cardiac involvement are limited. If right-sided heart failure is severe, surgical intervention with valve replacement can be considered. Even in experienced centres, surgery carries a high risk, with a perioperative short-term mortality (within two years) of 70% all together.

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