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CARCINOID HEART DISEASE

A cardiologist's viewpoint

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Abstract

In patients with malignant midgut carcinoid tumors, characteristic cardiac abnormalities can be demonstrated by cardiac ultrasound in 60–70%. These ultrasound findings include morphological and functional changes of the tricuspid and pulmonary valves, enlargement of the right heart cavities and paradoxical septal contraction pattern. In patients with severe carcinoid heart disease leading to right ventricular failure, reconstructive valvular surgery is of obvious beneficial value and should be considered when the malignant disease is under control and clinical signs of right heart failure cannot be managed medically. The pathognomonic carcinoid lesions are mainly located on the right side of the heart and consists microscopically of fibrous tissue superimposed on mural and valvular endocardium. Infiltration into underlying endocardium and myocardium has been demonstrated. The etiology of carcinoid heart disease remains obscure. The extent of the cardiac disease seems related to circulating tumor-released substances such as serotonin and tachykinins.

Key words: Carcinoid tumor, carcinoid heart disease, echocardiography, heart valve surgery.

Background

Cardiac abnormalities in patients with malignant carcinoid tumors were first described in 1930 by Cassidy (1). The association between the tumor and the typical cardiac lesions—the carcinoid heart disease—was independently reported two decades later by three research groups (2–4). The pathogenetic link between the carcinoid tumor and this characteristic cardiac disease, however, still remains a subject of controversy. There seems to be no relation between the severity of cardiac disease and of other tumor parameters such as flush, diarrhea, or duration and extent of the tumor disease (5–6). Several substances known to be released from carcinoid tumors have been proposed as possible mediators of the cardiac pathology in carcinoid heart disease, e.g. vasoactive substances such as serotonin and bradykinin, but no causal relationship has yet been found. In a study of 68 consecutive patients with metastatic carcinoid tumors we found significantly higher urinary excretion of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and higher plasma levels of the tachykinins neurokinin A (NKA) and substance P (SP) in those with the most extensive carcinoid heart disease (6).

New treatment regimens of the carcinoid tumor disease have dramatically improved the quality of life and prognosis for these patients (7). Since the associated cardiac disease is one of the major causes of morbidity and mortality in these patients (8), it is necessary to efficiently investigate and treat also the carcinoid heart disease, in addition to the tumor disease.

Morphology of the carcinoid heart lesions

Macroscopic anatomy and distribution. The carcinoid heart lesions are plaque-like or diffuse endocardial thickenings measuring up to 2 mm in thickness. They are almost invariably found on the right side of the heart, located on mural as well as valvular endocardium. The tricuspid and pulmonary leaflets are thickened, retracted and immobilized. Affection of the tricuspid papillary muscles and chordae frequently occur, which further immobilizes the leaflets, often in a semiopen position resulting in tricuspid invompetence more frequently than stenosis. Carcinoid

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lesions also occur on the intima of the venae cavae, the pulmonary trunk, the coronary sinus and the cardiac veins. Simultaneous appearance of carcinoid lesions on the right and left side of the heart has been observed in approximately 30% of autopsy cases. The left-sided lesions are less extensive than the right sided ones and most frequently located on the mitral valve. Lesions on the left ventricular walls, aortic leaflets, ascending aorta, and coronary arteries have been described (5, 9–14).

Microscopic anatomy. The microscopic appearance of the carcinoid lesions are uniform. They are superimposed on normal endocardium and covered by a single layer of endothelium. Although the lesions on most locations are delineated by an intact internal elastic membrane, tissue indistinguishable from typical carcinoid lesions on several locations extends through this membrane into the underlying myocardium (15). Small- to medium-sized vessels can be demonstrated in the lesions.

The carcinoid heart lesions are mainly composed by a stroma rich in acid mucopolysaccharides, reticulum fibers and collagen, but are typically devoid of elastic components. The number of cells in the carcinoid lesions is small and their proliferation rate low. The majority of cells, which have characteristics of smooth muscle cells as well as fibroblasts, have been characterized as myofibroblasts (14, 16–18).

Clinical presentation

Physical examination. The most characteristic clinical sign of carcinoid heart disease is the presence of a systolic precordial murmur representing valvular pulmonary stenosis, tricuspid incompetence, or both. Diastolic murmurs due to tricuspid stenosis or pulmonary regurgitation are less frequently heard. A precordial lift and a systolic thrill are sometimes palpable in these patients. The superficial jugular veins are often distended in the upright position and the presence of pulsatile jugular veins and a pulsating liver strongly suggest tricuspid regurgitation. Hepatomegaly, pleural effusion, ascites and edema of the legs may be consequences both of the tumor disease and of congestive phenomena due to right ventricular failure (4, 5, 10, 13, 17, 19). Electrocardiogram (ECG) and chest roentgenographic findings seem to be unspecific and of limited diagnostic value in these patients (5, 10, 17, 20).

Cardiac ultrasound characteristics. Cardiac ultrasound has greatly improved the diagnostic possibilities in carcinoid patients (21–24). Transthoracic cross-sectional (two-dimensional) echocardiographic images, in particular, frequently demonstrate abnormalities of the right side of the heart, in our material of 68 consecutive patients in 66% (6). Morphological and functional abnormalities of the tricuspid valve are the most commonly observed pathologic cardiac findings in carcinoid patients. These abnormalities include increased thickness and reduced motion amplitude of the tricuspid leaflets and Doppler findings of tricuspid incompetence. Although the pulmonary valve leaflets are less frequently visualized than those of the tricuspid valve, Doppler ultrasound recordings often show signs of pulmonary stenosis as well as incompetence. The size of the right atrium was increased in 53% of our patients and the right ventricle was enlarged in 30%. In severe cases signs of right ventricular volume/pressure overload with abnormal septal contraction pattern was observed (26%). The echocardiographic findings of the left side of the heart are usually normal. With transesophageal cardiac ultrasound the proximity of the transesophageal transducer to the heart generates images which often show the details of cardiac morphology better than transthoracic images. In an investigation of 31 consecutive carcinoid patients the thickened tricuspid leaflets and their often club-like edges were clearly visualized, and tricuspid incompetence was actually detected more frequently than with the transthoracic technique. Presence of a normally thin inner wall layer of both atria could be demonstrated. The mean thickness of this wall layer of the right atria in the carcinoid patients was significantly thicker ($p < 0.001$) than that of healthy controls (25).

Hemodynamic characteristics. Increased right atrial and ventricular pressures with prominent v-waves in the atrial and central venous pressure curves have frequently been recorded indicating tricuspid incompetence and volume/pressure overload of the right heart cavities. Pulmonary artery pressures are almost invariably found to be normal, as are left heart pressure tracings. Simultaneous or pull back pressure tracings and angiographic investigations often demonstrate pulmonary valvular stenosis, while tricuspid stenosis has been observed less frequently (13, 19, 26–28). Pressure curves of the dip-plateau type, suggesting restrictivity of the right heart chambers, have been reported (29–30). Cardiac output is often found to be normal or moderately reduced in patients with carcinoid heart disease. During episodes of flushing, however, an increase in cardiac output has been observed (31).

Management of patients with carcinoid heart disease

Clinical and echocardiographical investigations should be performed regularly in all patients with malignant carcinoid tumor disease in order to detect and follow the characteristic cardiac abnormalities. Right ventricular failure due to severe carcinoid heart disease is a serious prognostic sign, which ought to bring about consideration of valvular surgery, especially when the clinical signs of right ventricular failure cannot be controlled medically. Determination of the plasma levels of atrial natriuretic peptide (ANP) can provide guidance in making this decision (32). Valvular surgery has been reported in 32 cases in the literature and a number of reports have documented gratifying long-term palliation by valvular surgery in many

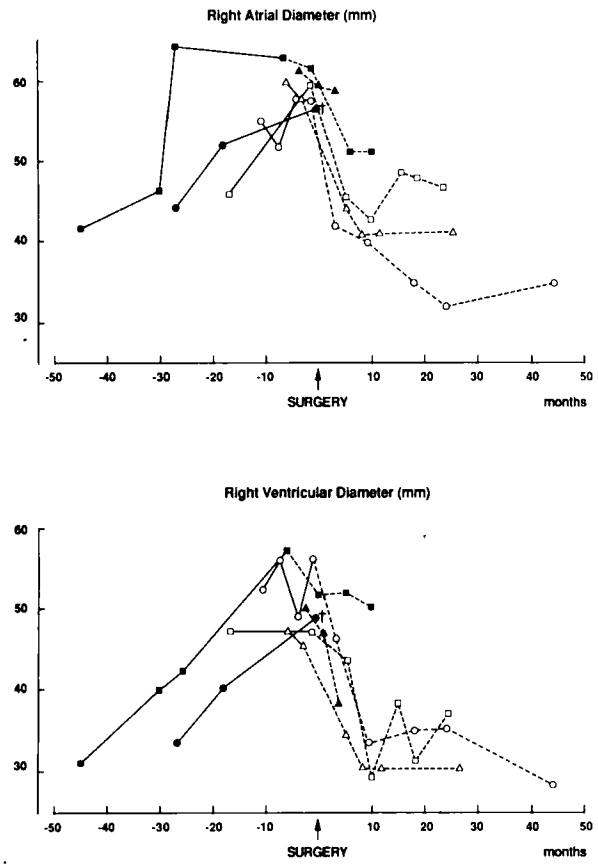

Figure. Mean right atrial and maximal medial-lateral right ventricular diameter measures by two-dimensional echocardiography before and after valve replacement surgery in 6 patients with severe carcinoid heart disease; —— = preoperatively, - - - = postoperatively, † = died postoperatively.

cases despite heavy burden of metastatic disease (33). One carcinoid patient with tricuspid stenosis has recently been reported to have undergone tricuspid valvuloplasty (34). Although angina pectoris may not be present, coronary angiography might be recommended preoperatively in order to reveal any stenotic carcinoid lesions in coronary arteries as well as common atherosclerotic changes.

Due to progressive right heart failure, six of our patients have been subjected to tricuspid and pulmonary valve replacement surgery. The postoperative course was prolonged in the first patient because of peripheral carcinoid manifestations (flushing, hyperperistalsis, bronchoconstriction), which promptly disappeared on treatment with a long-acting somatostatin analogue (Sandostatin™). Probably on account of the prophylactic treatment with this substance, the remaining 5 patients did not suffer from carcinoid symptoms of this kind. After an immediate circulatory improvement, one of the patients died on the fifth postoperative day in multiorgan failure and septicemia. The five patients successfully operated on experienced a rapid improvement with disappearance of symptoms and signs of cardiac decompensation within 2–4 months. Medical decompensation treatment has been decreased or withdrawn. At the most recent follow-up 48, 28, 26, 12 and 6 months postoperatively all patients reported a stable circulatory improvement. The preoperatively increased right atrium and ventricle showed a steady decrease in size as measured echocardiographically (Figure).

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REFERENCES

1. Cassidy MA. Abdominal carcinomatosis, with probable adrenal involvement. Proc R Soc Med 1930; 24: 139–41.
2. Isler P, Hedinger C. Metastasierendes Dünndarm-carcinoid mit schweren, vorwiegend das rechte Herz betreffenden Klappenfehlern und Pulmonalstenose—ein eigenartiger Symptomenkomplex? Schweiz Med Wochenschr 1953; 83: 4–7.
3. Rosenbaum FF, Santer DG, Claudon DB. Essential telangiectasia, pulmonic and tricuspid stenosis, and neoplastic liver disease. A possible new clinical syndrome. J Lab Clin Med 1953; 42: 941–2.
4. Thorson Å, Biörck G, Björkman G, Waldenström J. Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation with septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis. Am Heart J 1954; 47: 795–817.
5. Ross EM, Roberts WC. The carcinoid syndrome: Comparison of 21 necropsy subjects with carcinoid heart disease to 15 subjects without carcinoid heart disease. Am J Med 1985; 79: 339–54.
6. Lundin L, Norheim I, Landelius J, Öberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound detectable cardiac abnormalities. Circulation 1988; 77: 264–9.
7. Öberg K, Persson UM, Alm G, Eriksson B. Long-term treatment with alpha interferons of patients with malignant carcinoid tumors—The six year experience. In: Kawade Y, Kobayashi S, eds. The biology of the interferon system 1988. Tokyo: Kodansha Sci Ltd 1989: 219–25.
8. Norheim I, Öberg K, Theodorsson-Norheim E, et al. Malignant carcinoid tumors. An analysis of 103 patients with regard to tumor localization, hormone production, and survival. Ann Surg 1987; 206: 115–25.
9. Cosh J, Cates JE, Pugh DW. Carcinoid heart disease. Br Heart J 1959; 21: 369–80.
10. Roberts WC, Sjoerdsma A. The cardiac disease associated with the carcinoid syndrome (carcinoid heart disease). Am J Med 1964; 36: 5–34.
11. Wolinsky H, VanderBel J, Cohen L, Runniger K, Glagov S. Cinical pathologic conference. Am Heart J 1968; 75: 799–808.
12. Ludwig J. Cardiac vein involvement in carcinoid syndrome: Possible evidence of retrograde blood flow in cardiac veins in tricuspid insufficiency. Am J Clin Pathol 1971; 55: 617–23.
13. Trell E, Rausing A, Ripa J, Torp A, Waldenström J. Carcinoid heart disease. Clinicopathologic findings and follow-up in 11 cases. Am J Med 1973; 54: 433–44.
14. Ferrans VJ, Roberts WC. The carcinoid endocardial plaque. An ultrastructural study. Hum Pathol 1976; 7: 387–408.
15. Lundin L, Funa K, Hansson HE, Wilander E, Öberg K. Histochemical and immunohistochemical morphology of carincoid heart disease. Pathol Res Pract 1991; 187: 73–7.

16. MacDonald RA, Robbins SL. Pathology of the heart in the carcinoid syndrome. AMA Arch Pathol 1957; 63: 103–12.
17. Amoury RA. Heart disease and the malignant carcinoid syndrome. A case report and review of pathophysiologic and pathogenetic mechanisms. Am J Surg 1970; 119: 585–94.
18. Müller HG, Siebenmann RE. Ultrastructur der Endokardveränderungen beim Carcinoidsyndrom. Virchows Arch [A] 1981; 391: 33–44.
19. Strickman NE, Rossi PA, Massumkhani GA, Hall RJ. Carcinoid heart disease: A clinical, pathologic, and therapeutic update. Curr Probl Cardiol 1982; 6: 1–42.
20. Thorvinger B, Lundstedt C, Mårtensson H. Chest radiography in the carcinoid syndrome. Acta Radiol 1987; 28: 49–51.
21. Howard RJ, Drobac M, Rider WD, et al. Carcinoid heart disease: Diagnosis by two-dimensional echocardiography. Circulation 1982; 66: 1059–65.
22. Callahan JA, Wroblewski EM, Reeder GS, Edwards WD, Seward JB, Tajik AJ. echocardiographic features of carcinoid heart disease. Am J Cardiol 1982; 50: 762–8.
23. Reid CL, Chandraratna PAN, Kawanishi DT, Pitha JV, Rahimtoola SH. Echocadiographic features of carcinoid heart disease. Am Heart J 1984; 107: 801–2.
24. Forman MB, Byrd BF, Oates JA, Robertson RM. Two-dimensional echocardiography in the diagnosis of carcinoid heart disease. Am Heart J 1984; 107: 492–6.
25. Lundin L, Landelius J, Andrén B, Öberg K. Transesophageal echocardiography improves the value of cardiac ultrasound in patients with carcinoid heart disease. Br Heart J 1990; 64: 190–4.
26. Charms BL, Kohn P, Applebaum HI, Geller J. Hemodynamic studies in a case of carcinoid cardiovascular syndrome. Circulation 1959; 20: 208–14.
27. Lancaster JF, Leon DF, Leonard JJ. Carcinoid heart disease with tricuspid stenosis and pulmonic insufficiency. Am J Cardiol 1966; 17: 265–8.
28. Shariff M, Gould L. Carcinoid heart disease. Importance of cardiac catheterization. J Cardiovasc Surg 1969; 10: 400–3.
29. Roberts WC, Mason DT, Wright LD. The nondistensable right atrium of carcinoid disease of the heart. Am J Clin Pathol 1965; 44: 627–31.
30. McGuire MR, Pugh DM, Dunn MI. Carcinoid heart disease. Restrictive cardiomyopathy as a late complication. J Kansas Med Soc 1978; 79: 661–2.
31. Schwaber JR, Lukas DS. Hyperkinemia and cardiac failure in the carcinoid syndrome. Am J Med 1962; 32: 846–53.
32. Lundin L, Öberg K, Landelius J, Hansson HE, Wilander E, Theodorsson E. Plasma atrial natriuretic peptide in carcinoid heart disease. Am J Cardiol 1989; 63: 969–72.
33. Lundin L, Hansson HE, Landelius J, Öberg K. Surgical treatment of carcinoid heart disease. J Thorac Cardiovasc Surg 1990; 100: 553–61.
34. Mullins PA, Hall JA, Shapiro LM. Balloon dilatation of tricuspid stenosis caused by carcinoid heart disease. Br Heart J 1990; 63: 249–50.