CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Carcinoid heart disease: The heart is part of the whole body

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Carcinoid tumours are rare neoplasms that have unique and challenging cardiovascular manifestations. The incidence of carcinoid tumours is about 1.5/100,000 in the general population and it is estimated that about 30% of affected individuals go on to develop carcinoid syndrome.[1] Cardiac manifestations are thought to occur in about half of these patients. The purpose of this issue of *Cardiology Rounds* is to discuss the history, biology, pathology, clinical presentation, and management of patients with the cardiac carcinoid syndrome.

History of carcinoid disease

Lubrasch first described carcinoid tumours over 100 years ago after autopsies on two patients.[2] Both had tumours in the terminal ileum. It was not until 1907, however, that Oberndorf ascribed the term "Karzinoide" to describe the tumours.[3] In 1952, the first case of cardiac involvement associated with these characteristic tumours was described in a young man.[4]

Biology

Carcinoid tumour cells are thought to arise from neuroendocrine cells known as the amine precursor uptake and decarboxylation (APUD) cells. They contain neurosecretory granules capable of releasing a variety of physiologically active hormones and biogenic amines. The best known and studied of these substances are serotonin (5-hydroxytryptamine [5-HT]) and histamine (5-hydroxytryptophan), but includes bradykinins, tachykinins, and prostaglandins as well. The specific release of any one or a combination of these products determines the clinical picture.

Serotonin is the best characterized of these substances and has received the greatest attention. The carcinoid cells take up tryptophan that is hydroxylated and decarboxylated within the cells by the enzymes tryptophan dehydroxygenase and dopa-carboxylase, respectively, ultimately producing serotonin. Serotonin is then secreted into the circulation where it is metabolized to 5-hydroxyindole acetic acid (5-HIAA), which is excreted in the urine (Figure 1).

The physiologic actions of serotonin are numerous and complex. It functions as a CNS neurotransmitter, a melanin precursor, and a promoter of platelet aggregation. Its cardiovascular effects are exerted through a variety of receptors. Activation of the receptors 5-HT1 and 5-HT4 produces vasoconstriction. Potentiation of angiotensin II adds to its vasoconstricting properties. The 5-HT1 receptor has many subtypes, and depending on which subtype is activated, serotonin can cause paradoxical vasodilatation, while activation of other subtypes exert positive chronotropic and inotropic effects on cardiac muscle.

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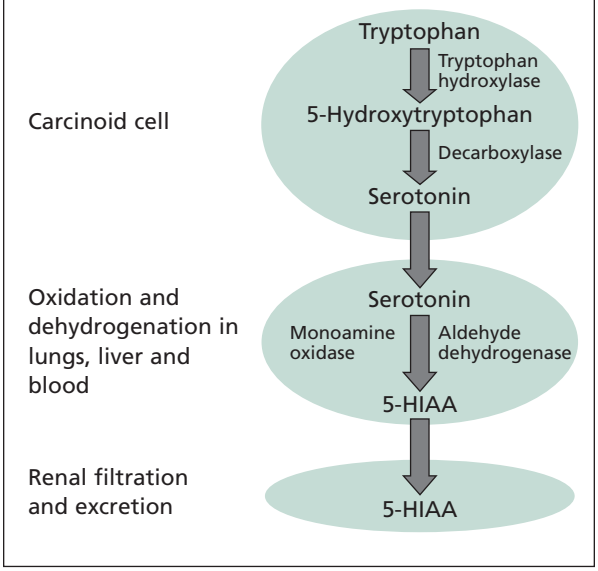
Figure 1: Synthesis and metabolism of serotonin



Clinical presentation

Carcinoid tumours produce a classic constellation of clinical features called the "carcinoid syndrome." This syndrome includes cutaneous flushing, secretory diarrhea, wheezing, cutaneous telangiectasia, and cardiac abnormalities. Cardiac involvement occurs in only about half of carcinoid syndrome cases and is seen predominately in patients with hepatic metastases or in those with ovarian carcinoid. The predilection for right-sided cardiac involvement is thought to be due to the release of mediators into the venous circulation.

The cardiovascular manifestations of carcinoid tumours can be divided into structural and hemodynamic effects. Structural abnormalities predominately involve the valves. Tricuspid regurgitation is the most common valvular lesion, followed by pulmonary stenosis. Pulmonary regurgitation is exceedingly rare, as are left-sided valvular lesions. The presence of the latter should raise the suspicion of an intracardiac shunt or a bronchial carcinoid.

Structural valvular lesions are characterized by the presence of the hallmark of carcinoid heart disease – the cardiac plaque. These form a whitish-coloured layer over the surfaces of the tricuspid and pulmonic valves. Histologically, they are composed of smooth muscle cells, myofibroblasts, and an overlying endothelial layer. Early studies suggested that cardiac plaques were void of elastic tissues, normally seen in the cardiac muscle.[5] This point of view has, however, been recently challenged by Simula et al who recently reported on 139 valves from 75 patients with carcinoid heart disease. He found that up to 20% of valves did indeed contain elastic fibers.[6]

The tricuspid valve is commonly affected in carcinoid heart disease with resultant concomitant tricuspid regurgitation and stenosis. This is a consequence of asymmetrical deformation of the valve and the partial fusion and rigidity of the valve leaflets.[5,6] The pulmonary valve is stiff, with a reduction of the opening, resulting in stenosis. However, pulmonary regurgitation is uncommon. Left-sided cardiac involvement is also uncommon and when seen, is usually limited to the mitral valve. Aortic valve involvement is exceedingly rare. Plaques seen on the mitral valve are identical to those seen on the right side, but are less severe. The plaques, irrespective of location, are confined to the endocardium and subendocardium.[6]

The pathogenesis of these plaques remains unknown. Animal studies have suggested a link to serotonin and/or tryptophan or niacin deficiency. Interest in this hypothesis was fuelled by the use of anorectic drugs, fenfluramine and dexfenfluramine, that were found to be associated with valvular lesions identical to those seen in carcinoid patients. These drugs are known to exert their effects via interference in normal serotonin metabolism.[7]

Diagnosis

Conclusive diagnosis of carcinoid heart disease is made by the demonstration of the classic cardiac plaque. Biochemical evidence of the diagnosis is demonstrated by elevated 5-HIAA urinary levels. Consideration of the patient's consumption of foods rich in tryptophan (ie, nuts, banana, pineapple, kiwi, or avocados) should be made when interpreting elevated levels. Other common diagnostic cardiac tests include an electrocardiogram (ECG) that can reveal right atrial and right ventricular enlargement, right axis deviation, and right bundle branch block. A chest x-ray is less helpful, since it is normal in nearly half of cases (Table 1).

The diagnostic test of choice, however, is the echocardiogram. Typical echocardiogram features include marked, diffuse, thickening and shortening of the tricuspid valve leaflets. The shortened leaflets are unable to coapt com-

Table 1: Frequency of ECG, chest X-ray and echo findings in patients with carcinoid heart disease

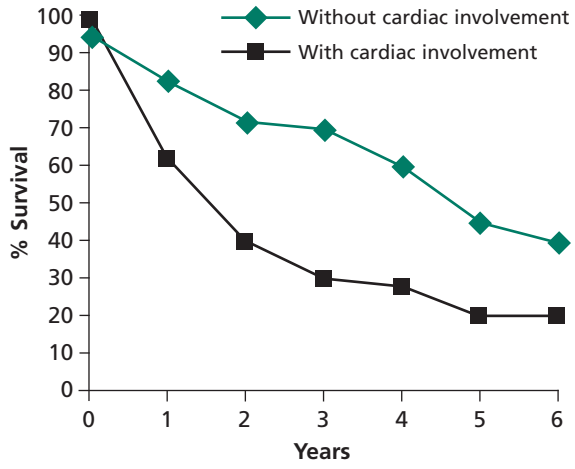
Abnormality	% with Finding
ECG	
Normal	31
ST-T wave abnormality	24
Sinus tachycardia	13
Low anterior forces	12
Low voltage	10
Right axis deviation	9
First degree AV block	9
Right atrial enlargement	7
Left axis deviation	6
RBBB	4
Chest X-ray findings	
Normal	46
Cardiac enlargement	18
Pleural effusion	11
Pulmonary nodules	11
Hepatomegaly	5
Blunting of costophrenic angles	5
Echocardiogram	
Tricuspid regurgitation	100
Pulmonary stenosis	49
RA/RV enlargement	91
Left-sided valvular lesion	7

pletely, resulting in tricuspid regurgitation. In severe cases, the leaflets are stiff and move in a "board-like fashion," resulting in classic stenosis and regurgitation. Typically, the pulmonary valve shows the same abnormalities, although it is less commonly involved. Other structural abnormalities include enlargement of the right-sided chambers. Although infrequent, left-sided involvement of the mitral valve should be (Table 1) sought. If, in fact, the left side of the heart is found to be involved, the possibility of an intra-cardiac shunt or pulmonary carcinoid should be considered.[10,11]

Outcome

Only a handful of small studies have examined outcomes in patients with cardiac carcinoid. They have consistently shown a poor prognosis. Pellikka et al identified

Figure 2: Survival of patients with or without cardiac carcinoid



132 patients with carcinoid disease during the decade 1980-1989 and compared the outcomes of those with, and without, cardiac involvement. The 3-year survival was significantly lower in those with cardiac involvement (31%) compared to those without cardiac involvement (68%; Figure 2). Mean life expectancy was reduced from 4.6 years to 1.6 years.[10]

Lundin et al examined 68 patients with histologically-proven, mid-gut, malignant carcinoid tumours and examined the characteristics of three groups:

- patients with normal right hearts;
- patients with tricuspid regurgitation and mild chamber abnormalities;
- patients with tricuspid regurgitation and severe chamber abnormalities.

The latter group had significantly higher urinary 5-HIAA levels, plasma levels of neuropeptide k, and plasma substance P. No such differences were found between those without cardiac involvement and those with only tricuspid regurgitation without chamber involvement.[10] This suggests that, based on the best evidence in the literature, the presence of cardiac involvement in patients with carcinoid tumours carries a worse prognosis.

Medical therapy (Table 2)

Chemotherapy forms the basis of medical therapy for carcinoid disease, regardless of the presence or absence of cardiac involvement. Treatment with streptomycin, 5-fluo-

Table 2: Medical therapy for carcinoid disease

Chemotherapy to help control disease

- Streptomycin
- 5-fluorouracil
- Cyclophosphamide
- Doxorubicin
- Alpha-interferon

Combination chemotherapy + hepatic artery ligation

(shows promise in improving survival)

Drugs for symptomatic relief

- Somatostatin
- Octreotide

Other medications for specific conditions

- Ketanserin (to manage hypertensive crisis refractory to vasodilators)
- Theophylline, steroids (for bronchoconstriction)
- Diphenhydramine, ranitidine, cyproheptadine (to control histamine-related symptoms)

rouracil, cyclophosphamide, doxorubicin, and alpha-interferon have been successful in controlling metastatic disease, but none have been shown, alone or in combination, to induce a sustained remission or a cure. The combination of chemotherapy and hepatic artery ligation has shown promise of improving survival.[13,14]

For symptomatic relief, the best-studied drugs are somatostatin and octreotide. Somatostatin binds to the cell-surface receptors of the carcinoid cell and inhibits the release of serotonin. The half-life of somatostatin is only minutes, limiting its use; therefore, octreotide, a related drug with a longer half-life has received greater clinical attention. Octreotide has been shown to be effective in reducing flushing by 87%, diarrhea in 77%, and urinary 5-HIAA levels by 77%.[14,15]

Other medications used in specific conditions include ketanserin, a selective serotonin receptor antagonist with alpha-blocking properties, that is useful in the management of a hypertensive crisis refractory to vasodilators.[16] Clinically, ketanserin is used most often intra-operatively during valve replacement. Prolongation of the QT interval and precipitation of torsade de pointes in the setting of hypomagnesemia or hypokalemia have been documented. For bronchoconstriction, theophylline and steroids have been used successfully. Various antihistamines such as diphenhydramine, ranitidine, and cyproheptadine, have been used successfully to control histamine-related symptoms of flushing and urticaria, as well as in the preoperative setting.

Surgical therapy

Surgical considerations in the management of patients with carcinoid disease include:

- tumour debulking in patients with metastatic disease
- resection of nonmetastatic primary tumours that may result in a potential cure
- cardiac valve surgery in patients with cardiac involvement.

In the latter case, little is known about the timing and outcome of patients undergoing valve surgery. Connolly et al compared significant outcomes of cardiac surgery in patients with carcinoid heart disease; 26 patients had valvular surgery and 40 patients were managed medically. The 30-day mortality in the surgical group was 35%, predominately from bleeding complications. At 6 months, however, there was favourable trend for the surgical group. By 2 years, this difference was significant, with 40% survival in the surgical group, compared to 8% in the medically-managed group. At 3 years, none of the medically-managed patients had survived.[17]

Summary

Carcinoid heart disease is a rare condition that may become even more so with time. Interestingly, it is so rare that experienced cardiologists and gastroenterologists at St.Michael's Hospital were unable, recently, to readily identify cases of carcinoid heart disease in their clinical practices. Possibly one reason for the increasingly rare occurrence of this disease is

that the more aggressive screening programs for colon cancer are able to detect and treat carcinoid tumours before metastases and cardiac involvement have occurred. Despite this, carcinoid tumours and carcinoid heart disease remain an important diagnosis to consider in patients presenting with primarily right-sided valvular pathology. The patient evaluation includes documenting elevated urinary 5-HIAA levels and an echocardiographic assessment of the extent of valvular involvement. Patient management involves the aggressive management of heart failure, specifically, the use of chemotherapy and octreotide for symptomatic benefit. In severe cases, consideration should be given to surgical replacement of the valves.

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References

1. Basson MD, Ahlman H, Wangberg B, Modlin IM. Biology and management of the midgut carcinoid. *Am J Surg* 1993;165:288-297.
2. Lubarsch O. Ueber den primaren Krebs des Ileum, nebst Bemerkungen uber das gleichzeitige Vorkommen von Krebs und Tuberkolose. *Virchows Arch* 1888;111:280-317.
3. Orbendorfer S. Karzinoide Tumoren des Dunndarms. *Frankf Z Pathol* 1907;1:425-429.
4. Mason RA, Steane PA. Carcinoid syndrome; its relevance to the anesthetist. *Anaesthesia* 1976;31:228-242.
5. Ferrans VJ, Roberts WC. The carcinoid endocardial plaque; an ultrasructural study. *Hum Pathol* 1976;7:387-409.
6. Simula DV, Edwards WD, Tazelaar HD, Connolly HM, Schaff HV. Surgical pathology of carcinoid heart disease: a study of 139 valves from 75 patients spanning 20 years. *Mayo Clin Proc* 2002;77:139-147.
7. Connolly HD, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997;337(9):581-588.
8. Conlon JM, Deacon CF, Richter G, Stockmann F, Creutzfeldt W. Circulating tachykinins (substance P, neurokinin A, neuropeptide K) and the carcinoid flush. *Scand J Gastroeneterol* 1987;22:97-105.
9. Kvols LK. Metastatic carcinoid tumors and the malignant carcinoid syndrome. *Ann NY Acad Sci* 1994;733:464-470.
10. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation* 1993;87:1188-1198.
11. Howard RJ, Drobac M, Rider WD, et al. Carcinoid heart disease: diagnosis by two-dimensional echocardiography. *Circulation* 1995;66(5):1059-1065.
12. Lundin L, Norheim I, Landelius J, Oberg K, Theodorsson-Norheim E. Carcinoid heart disease; relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. *Circulation* 1988;77(2):264-269.
13. Janson ET, Oberg K. Long term management of the carcinoid syndrome. *Acta Oncologica* 1993;32:225-229.
14. Kvols LK. Metastatic carcinoid tumors and the malignant carcinoid syndrome. *Ann N Y Acad Sci* 1994;733:464-470.
15. Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, HahnRG. Treatment of the malignant carcinoid syndrome: evaluation of long-acting somatostatin analogue. *N Engl J Med* 1986;315:663-666.
16. Houghton K, Carter JA. Perioperative management of carcinoid syndrome using ketanserin. *Anaesthesia* 1986;41:596-599.
17. Connolly HM, Nishimura RA, Smith HC, Pellikka PA, Mullany CJ, Kvols LK. Outcome of cardiac surgery for carcinoid heart disease. *J Am Coll Cardiol* 1995;32:225-229.
18. Kulke MH, Mayer RJ. Carcinoid Tumors. *N Engl J Med* 1999;340(11):858-868.
19. Strickman NE, Rossi PA, Massumkhani GA, Hall RJ. Carcinoid heart disease: a clinical, pathologic and therapeutic update. *Curr Probl Cardiol* 1982;6(11):1-42.
20. Robiolio PA, Rigolin VH, Wilson JS, et al. Carcinoid heart disease: Correlation of high serotonin levels with vavlular abnormalities detected by cardiac catheterization and echocardiography. *Circulation* 1995;92(4):790-795.
21. Propst JW, Siegel LC, Stover EP. Anesthetic considerations for valve replacement surgery in a patient with carcinoid syndrome. *J Cardiothorac Vasc Anesth* 1994;8:209-212.

Abstracts of Interest

Carcinoid tumour

KINOVA S, DURIS I. BRATISLAVA, SLOVAKIA.

Carcinoid tumours are slow growing malignancies which occur most frequently in the gastrointestinal tract (about 74%). They can also be found in the bronchus, ovary, lung, thymus, kidney or thyroid gland. Carcinoid tumours are usually identified histologically by their affinity to silver salts, or more specifically by immunocytochemistry using antibodies against their specific cellular products. Survival rates depend on the location of primary tumour, extent of locoregional and metastatic disease, functional status of the tumor and the feasibility of complete surgical extirpation. Clinical manifestations are often vague or absent. Nevertheless, tumours secrete bioactive mediators which may in approximately of 10% of patients engender various elements of characteristics of carcinoid syndrome. Patients with advanced carcinoid disease should be treated with aggressive medical and surgical therapies.

Bratisl Lek Listy 2001;102(11):495-504

Carcinoid heart disease: a case report and literature review

BOTERO M, FUCHS R, PAULUS DA, LIND DS. GAINESVILLE, FL

We report a patient who presented for elective exploratory laparotomy, and resection of a pelvic mass, which was thought to be ovarian carcinoma. Intraoperative transesophageal echocardiography demonstrated right-sided valvular heart lesions, which suggested the diagnosis of carcinoid syndrome before a pathologic confirmation was obtained. This article discusses the classical presentation and anesthetic management of patients with carcinoid syndrome and emphasizes the importance of proper preoperative diagnosis and careful planning if the incidence and severity of the symptoms that this condition can provoke are to be reduced.

J Clin Anesth 2002;14(1):57-63

Surgical pathology of carcinoid heart disease: a study of 139 valves from 75 patients spanning 20 years

SIMULA DV, EDWARDS WD, TAZELAAR HD, CONNOLLY HM, SCHAFF HV. MAYO CLINIC, ROCHESTER, MINN

OBJECTIVE: To quantitate the pathologic features of carcinoid plaques in a relatively large number of surgical specimens from a single institution.

PATIENTS AND METHODS: Medical records, operative reports, and surgical specimens were reviewed from all patients with carcinoid heart disease who underwent cardiac valvular surgery at Mayo Clinic, Rochester, Minn, between 1980 and 2000.

RESULTS: The study group included 75 patients (45 men, 30 women) who ranged in age from 26 to 78 years (mean, 59 years). From these 75 patients, 139 valves had been excised surgically (73 tricuspid, 55 pulmonary, 6 mitral, 5 aortic). Pure regurgitation was the most common dysfunctional state of the tricuspid valve (80% [60/75]), mitral valve (97% [32/33]), and aortic valve (96% [23/24]). The pulmonary valve was more often both stenotic and insufficient (52% [37/71]) than purely regurgitant (30% [21/71]). In all cases, valve dysfunction was attributed to the presence of carcinoid plaques, which caused both thickening and retraction. Thickening was the result of both cellular proliferation and deposition of extracellular matrix. Proliferation of myofibroblasts was observed in all plaques and was mild in 49% (68/139) and moderate or severe in 51% (71/139). Extracellular matrix included collagen (in 99% of the 139 valves), myxoid ground substance (98% [136/139]), and elastin (20% [28/139]). Carcinoid plaques were also involved by neovascularization (94% [131/139]), chronic inflammation (94% [131/139]), and mast cell infiltration (64% [89/139]). Severe thickening was attributable primarily to collagen deposition in tricuspid valves and to myofibroblast proliferation and myxoid matrix in pulmonary valves.

CONCLUSIONS: Among patients undergoing valvular surgery for carcinoid heart disease, tricuspid and pulmonary valves represented 92% of the excised valves (128/ 139). Although numerous cellular and extracellular features were common to the carcinoid plaques, variability in their relative expression produced appreciable differences in the histologic appearance among the plaques.

Mayo Clin Proc 2002;77(2):139-47

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