Carcinoid Heart Disease: Diagnosis by Two-dimensional Echocardiography

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SUMMARY We prospectively studied 14 patients with the carcinoid syndrome to determine if two-dimensional echocardiography could detect the nature and extent of valvular abnormalities. Eight of the 14 patients had definite abnormalities of the right-sided cardiac valves. The tricuspid valve had a characteristic appearance, similar to previously described pathologic findings. The leaflets appeared diffusely thickened, shortened and stiff without evidence of commissural fusion. Saline contrast studies demonstrated tricuspid regurgitation, which corresponded to the severity of the tricuspid valve involvement. The pulmonary valve could only be adequately assessed in seven of 14 patients, and morphologic abnormalities similar to those in the tricuspid valve were found. Follow-up studies have shown progression of cardiac disease in six of eight patients.

We conclude that two-dimensional echocardiography can detect the characteristic cardiac abnormalities in the carcinoid syndrome and may be a useful tool for following their progression.

IN 1954, Thorssen et al.1 established malignant carcinoid heart disease as part of a clinical and pathologic syndrome. They identified the complete carcinoid syndrome as consisting of right-sided valvular dysfunction, facial flushing, abdominal pain, diarrhea and telangiectasia in patients with malignant carcinoid of the small intestine and hepatic metastases. In 1964, Roberts and Sjoerdsmab reported the clinical and pathologic features of nine patients with carcinoid heart disease. Distinctive fibrous plaques involved the tricuspid and pulmonary valves and restricted leaflet motion, causing valvular stenosis or regurgitation. In 1972, Graham-Smith3 described a serial progression of cardiac symptoms and clinical findings. He noted that carcinoid tumor growth was variable and patients often lived for years despite multiple liver metastases. In addition, the cardiac lesions often developed slowly, but could result in congestive heart failure and death.2,3 Cardiac involvement and its severity have usually been confirmed pathologically,4-7 with isolated reports of hemodynamic abnormalities.8-10

In 1979, Okada et al.11 reported the M-mode echocardiographic findings in a young patient with severe carcinoid involvement of the tricuspid and pulmonary valves. However, the findings were nonspecific and did not help in the assessment of severity. Because two-dimensional echocardiography can assess cardiac anatomy and valvular motion, it appears ideally suited for analyzing and serially following the progression of carcinoid heart disease. In this report, we describe the two-dimensional echocardiographic findings in 14 patients with the carcinoid syndrome and demonstrate how this noninvasive technique can define and monitor the degree of cardiac involvement.

Methods

Patients

The study group consisted of 14 patients with histologically proved gastrointestinal carcinoid tumors. There were six males and eight females, ages 22–68 years. Their symptoms included flushing, diarrhea, abdominal pain, dyspnea, chest pain, ankle edema, palpitations and wheezing (table 1). Cardiac examination revealed evidence of tricuspid regurgitation in seven patients. Three of these seven patients had evidence of right-sided volume overload and one had a diastolic rumble and slow jugular venous "Y" descent, suggestive of tricuspid stenosis. Four patients had systolic ejection murmurs, thought to represent pulmonary valve disease. Two other patients had the typical middle-to-late systolic murmur of mitral valve prolapse. Chest radiographs did not demonstrate cardiac abnormalities in any patient. The ECGs were usually normal; one patient had nonspecific T-wave abnormalities, another had inferolateral T-wave inversions, and a third had right bundle branch block.

Echocardiography

Each patient underwent two-dimensional echocardiography. Varian V-3000 or V-3400 phased-array ultrasonograph with a 2.25-MHz fixed-field-focus transducer was used. Standard parasternal long- and short-axis views from the left sternal border, as well as apical four-chamber and long-axis views were obtained.12 In addition, a right ventricular long-axis view was attempted by angling the transducer medially from the parasternal left ventricular long-axis position. Contrast studies, as described by Lieppe et al.,13 were carried out in all patients after 10 ml of saline solution were injected into a peripheral vein. We carefully viewed the tricuspid valve and inferior vena cava for evidence of systolic tricuspid regurgitation. Severe tricuspid regurgitation was defined as the presence of continuous systolic reflux of microbubbles into the inferior vena cava and hepatic veins. Mild tricuspid regurgitation was defined as microbubbles passing back and forth across the tricuspid valve and appearing

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in the inferior vena cava on not more than two successive beats. Moderate tricuspid regurgitation was defined as intermediate between mild and severe.

### Results

#### Tricuspid Valve

At the initial study, five patients had nonrheumatic tricuspid valve disease and nine appeared normal. The abnormal valves had a characteristic appearance, and their mobility and morphology were abnormal. The most severely involved valves were virtually immobile and frozen partly open, resulting in both stenosis and regurgitation (fig. 1). In valves less severely involved, the leaflets were abnormal, particularly in early diastole. Instead of the normal undulating motion, the leaflets appeared stiff and straightened, moved in a board-like fashion and opened and closed slowly; total excursion was decreased (fig. 2). Morphologically, the striking abnormality was thickened, foreshortened leaflets. The thickening was diffuse, extending from the tips to the base; the foreshortening was in direct proportion to the degree of thickening and often prevented systolic coaptation of the leaflets (figs. 1 and 2).

Saline contrast studies demonstrated tricuspid regurgitation in eight of 14 patients. The regurgitation was judged severe in two patients, moderate in three and mild in three. The five patients with moderate or severe echocardiographic tricuspid regurgitation had clinical findings of significant tricuspid regurgitation. However, the three patients with mild echocardiographic tricuspid regurgitation had either subtle or no clinical findings.

In some patients with tricuspid regurgitation, the inferior vena cava was not enlarged (systolic diameter less than 2.0 cm/m²). Figure 3A, from patient 7, shows a normal-sized inferior vena cava and hepatic vein, even though severe, chronic tricuspid regurgitation was present. For comparison, figure 3B shows the very dilated inferior vena cava and hepatic vein from a patient with a similar degree of severe, chronic tricuspid regurgitation that was due to rheumatic heart disease.

In one patient with severe tricuspid valve involvement, the right ventricular papillary muscles were more highly reflective of ultrasound than normal. We interpreted this finding as endocardial coating of the papillary muscles by carcinoid-related fibrous plaque (fig. 4). Our interpretation was confirmed at autopsy.

#### Pulmonic Valve

The pulmonic valve could be adequately visualized in seven of 14 patients. This difficulty was remarkable because we could usually obtain clear views of the right ventricular outflow tract and proximal main pulmonary artery. Five of the seven visualized pulmonary valves were normal. The two abnormal valves were shortened, highly reflective, and exhibited decreased systolic motion (fig. 5). These abnormalities were similar to those in the affected tricuspid valves. Pulmonary regurgitation was suspected in one patient from

### Table 1. Patient Data

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Abbreviations: FL = flushing; DIA = diarrhea; PN = abdominal pain; N = normal; TV = tricuspid valve; PV = pulmonary valve; N/A = not available; SEM = systolic ejection murmur; RV = right ventricle; NV = not visualized; TR = tricuspid regurgitation; PI = pulmonic insufficiency; PS = pulmonic stenosis; CXR = chest radiograph; LSB = left sternal border; † = increased; ‡ = decreased.
### TABLE 1. (Continued)

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**FIGURE 1.** Stop-action echocardiographic frames with the echocardiographic transducer in the parasternal position oriented toward the right ventricular long axis. (A) Ventricular systole; (B) diastole. (C and D) Diagrams of panels A and B, respectively. The tricuspid leaflets are thickened, shortened and frozen partly open. RV = right ventricle; RA = right atrium; A = anterior; P = posterior; R = right; L = left.

**FIGURE 2.** (A and B) Echocardiographic frames in the apical four-chamber view at end-diastole and end-systole with attention directed to the tricuspid valve. (C and D) The respective line diagrams. The tricuspid valve leaflets appear highly reflective and foreshortened, but are more mobile than those seen in figure 1. Panel B shows the absence of systolic coaptation. LV = left ventricle; LA = left atrium; other abbreviations as in figure 1.

Diastolic reflux of saline microbubbles across the pulmonary valve.

**Other Abnormalities**

There were no carcinoid-related abnormalities of left-heart valves. One patient had a small atrial septal defect and pulmonary hypertension. Hemodynamic monitoring revealed worsening of the right-to-left shunt during flushing spells and systemic oxygen desaturation. Saline contrast echocardiography showed right-to-left shunting at the atrial level (fig. 4). Several abnormalities probably not related to the carcinoid syndrome were also seen, including mitral valve prolapse in two patients, left ventricular hypertrophy probably due to systemic hypertension in two patients and mild congestive cardiomyopathy in a patient with a history of ethanol abuse.

**Follow-up**

Eight patients have had at least one follow-up study, 3 months to 3 years (average 23 months) after the initial assessment. Five patients have shown evidence of increasing tricuspid involvement and three remain unchanged (table 1). The patients with right-heart failure have been treated with diuretics and digoxin. Eight of 14 patients have died. Three deaths were due to small bowel obstruction or perforation, one death was...
due to hepatic failure and one to myocardial infarction; three deaths were due to unknown causes.

Autopsy Findings

Six patients were autopsied. However, three autopsies were done at other hospitals, and because the hearts were not adequately examined, we could not be certain of cardiac involvement. Patient 12 had no evidence of cardiac involvement by clinical or two-dimensional echocardiographic examination. The lack of cardiac involvement was confirmed by postmortem examination. Patients 1 and 10 had clinical and two-dimensional echocardiographic findings consistent with valve dysfunction that were confirmed at autopsy. For illustration, the pathologic findings in patient 1 are described in detail.

Patient 1 had a carcinoid tumor of the ileum with metastases to the liver and abdominal lymph nodes. On gross examination of the heart, the right atrium was moderately dilated and the right ventricle hypertrophied. The foramen ovale was patent and was consid-
tered to represent a functional atrial septal defect. The tricuspid valve leaflets were shortened and had numerous yellow-white plaques on their atrial surfaces. There was no commissural fusion, but the free edges were thickened and indurated by fibrous tissue. The chordae tendineae attached to the anterior leaflet were markedly thickened, fused and shortened (fig. 6). Whitish plaques were seen on the posterior wall and anterior papillary muscle of the right ventricle; the largest plaque was about 1 cm in diameter. The pulmonary valve was diffusely thickened and indurated. The free edges were rounded and the cusps were contracted. There was minimal commissural fusion.

Figure 4 shows two-dimensional echocardiographic images of the tricuspid valve in patient 1. Panel A shows the abnormal tricuspid valve and the highly reflective right ventricular papillary muscles. Panels B and C show the microbubbles of agitated saline crossing the patent foramen ovale. The morphology was very similar to that in the gross specimen shown in figure 6.

Discussion

Valvular Heart Disease

Carcinoid heart disease is a rare but interesting disorder that predominantly causes right-sided valvular dysfunction. It is speculated that hepatic metastases from carcinoid tumors release vasoactive substances that chronically bathe and damage the tricuspid and pulmonary valves. These substances appear to be inactivated by the liver; therefore, liver metastases are a prerequisite for cardiac involvement. The only exception to this rule appears to be ovarian carcinoid, since both ovaries drain directly into the inferior vena cava, bypassing the liver.

Roberts and Sjoerdsma described the distinctive cardiac pathology of carcinoid disease as consisting of focal or diffuse collections of a peculiar type of fibrous tissue, which is free of elastic fibers and is deposited on the endocardium of the valvular cusp, on the endocardium of the cardiac chambers, and on the intima of the great veins, coronary sinus and occasionally great arteries. The valvular cusps per se remain normal as does the mural endocardium, and each is clearly separated from the fibrosing process by the internal elastic membrane. Electron microscopic findings indicate that the carcinoid plaques are composed of a material which is consistent in its features with young collagen.

They also noted that the right-sided involvement with fibrous plaques predominates; involvement progresses from the right ventricular inflow area and tricuspid valve to the outflow area and pulmonary valve. Only very rarely is the left side of the heart involved.

The pathologic description of thickened, immobile, and shortened leaflets with markedly restricted mobility in severe cases is exactly what we saw on two-dimensional echocardiograms (figs. 1 and 2). The tricuspid leaflets are thickened uniformly from the base to the tips. In severe cases, they are frozen partly open and move little between systole and diastole, which produces both stenosis and incompetence. With lesser degrees of involvement, the valves exhibited less thickening or shortening and more mobility, but the pattern of stiff motion appeared characteristic. In patients with trivial involvement, no abnormalities of valvular motion or structure could be detected. However, saline contrast studies demonstrated microbubbles moving back and forth across the tricuspid valve, and there was systolic reflux into the inferior vena cava and hepatic veins, which indicates tricuspid regurgitation.

The major differential diagnosis in patients with stenosed valves is rheumatic tricuspid valve disease. Figure 7 shows a tricuspid valve damaged by rheumatic valvulitis resulting in stenosis. Typically increased reflectance is visible at the tips of the valve leaflets, and there is also commissural fusion. The body of the leaflet initially remains relatively thin and pliable, resulting in marked bowing of the leaflets through diastole. This is in striking contrast to the carcinoid-affected leaflets where diffusely increased reflectance and lack of commissural fusion are seen. Moreover, rheumatic tricuspid disease is virtually always associated with more severe mitral valve disease, while carcinoid is only rarely associated with mitral disease, which is always trivial.

Pathologically, carcinoid affects the pulmonary valve exactly as it does the tricuspid valve (fig. 5). Unfortunately, the pulmonary valve is much more difficult to visualize by two-dimensional echocardiography than the tricuspid valve, and often only one pulmonary cusp can be recorded. However, in two patients we detected leaflets with diffusely increased reflectance and decreased mobility. We found it difficult to view the pulmonary valve in some patients, even though we could clearly identify the right ventricular outflow tract and main pulmonary artery. The reduced motion of the pulmonary valve when involved by carcinoid appears to increase the difficulty of locating the valve markedly.

**Figure 6.** Postmortem photograph of the tricuspid valve and right atrium from patient 1. The right atrium is above and the right ventricle below. The white arrow points to a thickened chorda tendineae attached to a thickened, foreshortened tricuspid leaflet. The black arrow points to an 8-mm patent foramen ovale.
marked infiltration of the liver by carcinoid tumor may result in compression of the hepatic vein and inferior vena cava which would prevent the gross dilatation seen in other patients with severe, chronic tricuspid regurgitation (fig. 3).

Clinical Course

Investigators have followed the clinical course of carcinoid patients and noted the development and later the worsening of cardiac failure.3 Clearly, patients with the carcinoid syndrome may become severely symptomatic or even die from cardiac decompensation. Cardiac surgery may occasionally be required, and there are several case reports in the literature of successful operations.14-21 In addition, with advances in chemotherapy, the prognosis may be further improved, and valve replacement may become more important.

We performed repeat echocardiographic studies in eight of the 14 patients. The six other patients died. Six of these eight have shown deterioration and increasing evidence of valvular involvement. However, we have not been able to correlate progression of disease with other variables, such as duration of disease and tumor size. In the pathologic series of Roberts and Sjoerdsma,2 three of the nine patients with cardiac involvement probably died from their heart disease. Although several of our patients have had significant cardiac involvement, none of our patients has died as a direct result of carcinoid heart disease.

The pathophysiology of the fibrous plaques that characterize carcinoid heart disease is still unknown, nor is it understood why cardiac involvement is more severe and progresses more rapidly in some patients. Therefore, we suggest that these patients should be followed with serial two-dimensional echocardiography where possible. This would not only assist in formulating their medical therapy, but also might help identify those who might benefit from tricuspid valve replacement.

Conclusions

Two-dimensional echocardiography is valuable in diagnosing carcinoid heart disease. The valvular lesions are characteristic and easily differentiated from those caused by rheumatic valvular disease. Two-dimensional echocardiography is particularly useful in identifying abnormalities of the tricuspid and pulmonary valves and assessing the severity of lesions; it may also detect subclinical involvement. Serial two-dimensional echocardiographic studies can be used to follow the progression of the disease and may be useful in assessing the efficacy of therapy.

References

Congenital Aneurysms of the Left Atrium: Recognition by Cross-sectional Echocardiography

RODNEY A. FOALE, M.R.C.P., THOMAS C. GIBSON, F.R.C.P., DAVID E. GUYER, M.D.
LINDA GILLAM, M.D., MARY ETTA KING, M.D., AND ARTHUR E. WEYMAN, M.D.

SUMMARY The two-dimensional echocardiographic features of three patients with congenital aneurysms of the left atrium are described. The aneurysm arose from the left atrial appendage in two patients and from the posterior left atrial wall in one. The aneurysms were characterized by their origin from an otherwise normal left atrium, a well-defined neck, their position within the pericardial space, and distortion of the left ventricular free wall by the aneurysmal body. The differentiation of these structures from other abnormalities of the left atrium are also discussed. Two-dimensional echocardiography is a safe and reliable method for diagnosing congenital aneurysm of the left atrium, and such studies should be considered in any patient with an otherwise unexplained abnormality on the chest radiograph.

CONGENITAL ANEURYSMS of the left atrium are rare but clinically important disorders. These aneurysms, which are considered to arise from focal areas of developmental weakness of the atrial wall,1 most frequently involve the atrial appendage,2–15 but may also arise from the body of the left atrium.2, 16–21 Although congenital, they do not usually become clinically apparent until the fourth decade or later, when complications such as cardiac arrhythmias and systemic embolization may occur.15 Because of these major complications, early diagnosis and surgical excision is mandatory. An abnormal cardiac silhouette on the chest radiograph may suggest the anomaly, but is often mistaken for a cardiac tumor or pericardial cyst.19 Angiography is the established mode of diagnosis, the aneurysm is visualized by direct injection of contrast into the left atrium or by left-heart follow-through of contrast from a pulmonary arteriogram. In some cases, however, angiography has been misleading, and the correct diagnosis has been established only at thoracotomy or at postmortem examination.5, 11, 15–20

In this report, we describe cross-sectional echocardiographic findings in three patients with aneurysmal dilatation of the left atrial wall. In two patients, the diagnosis was confirmed at surgery, and in one the echocardiographic findings were definitive. Criteria for the diagnosis of this uncommon but potentially correctable condition are described.

Patients and Echocardiographic Findings

Patient 1

A 43-year-old woman was admitted to hospital with sudden onset of left hemiparesis, dysarthria and dysphasia. She had atrial fibrillation at a mean heart rate of 100 beats/min. There were no other abnormal physical findings, apart from the neurologic signs associated with her presenting symptoms. The chest radiograph
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