Carcinoid Heart Disease
Clinical and Echocardiographic Spectrum in 74 Patients

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Background. The carcinoid syndrome is a rare cause of acquired valvular heart disease. Although the typical echocardiographic features of carcinoid heart disease are well recognized, this large series provides new information about unusual manifestations of the disease as well as the role of Doppler echocardiography.

Methods and Results. Between 1980 and 1989, 132 patients with carcinoid syndrome underwent echocardiographic study. The echocardiographic, Doppler, and clinical features of the 74 patients (56%) with echocardiographic evidence of carcinoid heart disease are described. Among these patients, 97% had shortening, thickened tricuspid leaflets. Tricuspid regurgitation was present in all 69 patients with carcinoid heart disease who underwent Doppler examination, and it was of moderate or severe degree in 62 patients (90%). Severe tricuspid regurgitation was characterized by a dagger-shaped Doppler spectral profile with an early peak pressure and rapid decline. The pressure half-time was prolonged (mean, 116 msec), which is consistent with associated tricuspid stenosis. The pulmonary valve appeared thickened, retracted, and immobile in 36 patients (49%) and was diminutive to the extent of not being visualized in an additional 29 patients (39%). Among the 47 patients who underwent Doppler evaluation of the pulmonary valve, regurgitation was present in 81%, and stenosis was present in 53%. Left-sided valvular involvement was present in five patients (7%), four of whom had patent foramen ovale or carcinoid tumor involving the lung. Previously undescribed myocardial metastases were present in three patients (4%) and were confirmed by biopsy in each case. Small pericardial effusions were present in 10 patients (14%). Patients with and without echocardiographic evidence of carcinoid heart disease did not differ with regard to sex, age, location of the primary tumor, duration of diagnosis, or duration of symptoms of carcinoid syndrome. However, the mean pretreatment level of urinary 5-hydroxyindoleacetic acid was higher in patients with carcinoid heart disease than in patients without carcinoid heart disease (270 versus 131 mg/24 hrs, p < 0.001). The symptom of dyspnea was more prevalent among patients with carcinoid heart disease than in patients without the disease (54% versus 27%, p = 0.003); as expected, heart murmurs were also noted more frequently in patients with disease (92% versus 43%, p < 0.0001). Treatment regimens and response to therapy were similar in the two groups. Survival of patients with echocardiographic evidence of carcinoid heart disease was reduced compared with those without cardiac involvement (p = 0.0003). ECG and chest roentgenographic findings in patients with carcinoid heart disease were nonspecific.

Conclusions. The broad spectrum of carcinoid heart disease is detailed in this large series. This includes not only right-sided valvular lesions but also left-sided involvement, pericardial effusion, and myocardial metastases. (Circulation 1993;87:1188–1196)

Key Words • carcinoid syndrome • valvular heart disease • tricuspid stenosis • regurgitation • pulmonary stenosis • patent foramen ovale • myocardial metastasis

The carcinoid syndrome is a rare cause of acquired valvular heart disease. However, cardiac involvement has been recognized in more than half the patients with this syndrome,1 and it may be the cause of death in this condition.

Two-dimensional echocardiography has been useful in recognizing the characteristic morphological changes of the tricuspid and pulmonary valves.2,3 Doppler echocardiography and color flow imaging permit more precise evaluation of valvular dysfunction and complement two-dimensional echocardiography in assessing patients with carcinoid heart disease.

In the present report, we describe the clinical characteristics of 74 patients with two-dimensional echocardiographic evidence of carcinoid heart disease evaluated at our institution during the past decade. Both typical and unusual manifestations of cardiac involvement are described. Furthermore, we detail the Doppler features of carcinoid valvular heart disease.

Methods

Study Group

Between January 1980 and December 1989, 132 patients with carcinoid syndrome underwent echocar-

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Received February 13, 1992; revision accepted December 15, 1992.
diagnostic study at our institution either as a baseline screening test or because cardiac involvement was suspected. All patients had one or more of the symptoms typical of carcinoid syndrome, including flushing, diarrhea, or wheezing. All had histologically demonstrated carcinoid and elevated 5-hydroxyindoleacetic acid (5-HIAA) levels. The mean age was 58±11 years (range, 23–81 years). There were 80 men and 53 women (ratio of men to women, 1.5:1). The duration of symptoms of carcinoid syndrome, duration from histological diagnosis of carcinoid, clinical cardiac diagnosis, findings on chest roentgenogram and ECG, and the mean pretreatment levels of 5-HIAA were obtained by review of the patient’s clinical records.

Echocardiography, Doppler, and Color Flow Imaging

Two-dimensional echocardiography, pulsed and continuous-wave Doppler, and color flow imaging were performed using previously described techniques. Two-dimensional echocardiography was performed in all patients. Doppler echocardiography was performed in 121 patients (92%). Color flow examinations were performed in 99 patients (75%). Contrast echocardiographic studies were performed only in those patients in whom left-sided involvement was suspected. The presence and degree of chamber enlargement were based on the visual estimate of an experienced staff echocardiologist.

Initial echocardiograms showed findings consistent with carcinoid valvular heart disease in 65 patients (49%). This included abnormal right-sided valves with thickening or retraction of the tricuspid or pulmonary valve. One patient presented with a myocardial mass but no evidence of valvular involvement. Seven patients (5%) had mild thickening of the tricuspid valve that was suggestive (but not diagnostic) of early carcinoid heart disease. Two of these patients underwent follow-up echocardiography. In one patient, there were no changes in echocardiographic findings at 55 months. Another patient had typical features of carcinoid heart disease at 12 months. Fifty-nine patients (45%) had no evidence of carcinoid heart disease on the initial examination. Twenty-nine of these patients (45%) underwent a follow-up study at a mean of 27±19 months from the initial study. During this period, seven of 29 patients (24%) developed echocardiographic findings typical of carcinoid heart disease. In one patient (3%), mild abnormalities detected on subsequent examinations were suggestive of early carcinoid heart disease. Thus, during the study period, 74 patients (56%) had echocardiographic findings characteristic of carcinoid heart disease either at the initial examination or at subsequent examination, and 51 patients (39%) had no evidence of carcinoid heart disease.

Statistical Methods

Data are expressed as mean±SD. Baseline differences between patients with and without echocardiographic evidence of carcinoid heart disease were evaluated using a two-sample t test or a χ2 analysis for equality of proportions. A value of p<0.05 was considered statistically significant.

Results

Clinical Characteristics of Patients With Carcinoid Heart Disease

Among the 74 patients with carcinoid heart disease, the mean age was 59±11 years; 44 were men (ratio of men to women, 1.5:1). The mean duration of symptoms of carcinoid syndrome was 57±53 months (range, 0–276 months). The mean time from histological diagnosis of carcinoid to echocardiographic diagnosis of cardiac involvement was 49±70 months (range, 0–346 months). The site of primary carcinoid lesion was small bowel in 53 patients (72%), lung in three patients (4%), cecum or large bowel in three patients (4%), pancreas in one patient (1%), and appendix in one patient (1%). The site could not be determined in 13 patients (18%). Hepatic metastases were present in all patients. Levels of urinary 5-HIAA were elevated in all patients (mean, 270±154 mg/24 hrs; normal, 0–6 mg/24 hrs). Exertional dyspnea was present in 40 patients (54%).

The patients with carcinoid heart disease and those with no evidence of cardiac involvement did not differ significantly with regard to age, sex, location of primary tumor, duration of symptoms, or duration of diagnosis (Table 1). However, the mean level of 5-HIAA was significantly higher among patients with carcinoid heart disease (p<0.001). Dyspnea was significantly more prevalent among patients with cardiac involvement (p=0.003). As expected, heart murmurs were heard significantly more frequently in patients with cardiac involvement (p<0.0001). A murmur of tricuspid regurgitation was noted in 57 of 74 patients (77%). A murmur of pulmonic stenosis was noted in 24 patients (32%). A diastolic murmur of pulmonary regurgitation was heard in 23 patients (31%). No murmurs were heard in six patients (8%) with carcinoid heart disease. One of these patients had myocardial metastases without evidence of valvular involvement. The remaining five patients had echocardiographic evidence of carcinoid involvement confined to the tricuspid valve. Murmurs of mitral regurgitation and aortic stenosis were described in two patients (3%) and one (1%) patient, respectively.

ECGs obtained at the time of echocardiograms were available for 68 patients (Table 2). The ECGs were normal in 21 patients (31%). The most common abnormality was nonspecific ST-T wave changes in 24% of the patients. Sinus tachycardia was present in 13%, low anterior forces in 12%, low voltage in 10%, and first-degree atrioventricular block in 9%. Right axis devia-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Present (n=74)</th>
<th>Absent (n=51)</th>
<th>p</th>
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<tbody>
<tr>
<td>Carcinoid heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>59</td>
<td>61</td>
<td>NS</td>
</tr>
<tr>
<td>Age (mean, years)</td>
<td>59±11</td>
<td>56±12</td>
<td>NS</td>
</tr>
<tr>
<td>Primary tumor location in small bowel (%)</td>
<td>87</td>
<td>72</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of symptoms (mean, months)</td>
<td>57±53</td>
<td>61±64</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of diagnosis (mean, months)</td>
<td>49±70</td>
<td>43±56</td>
<td>NS</td>
</tr>
<tr>
<td>Dyspnea present (%)</td>
<td>54</td>
<td>27</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart murmurs noted (%)</td>
<td>92</td>
<td>43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean urinary 5-HIAA (mg/24 hrs)</td>
<td>270±154</td>
<td>131±149</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival (median, years)</td>
<td>1.6</td>
<td>4.6</td>
<td>0.0003</td>
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5-HIAA, 5-hydroxyindoleacetic acid.
TABLE 2. Electrocardiographic Findings in Patients With Carcinoid Heart Disease

<table>
<thead>
<tr>
<th>Findings</th>
<th>Patients (n=68)</th>
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<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Normal</td>
<td>21</td>
</tr>
<tr>
<td>ST-T wave abnormality</td>
<td>16</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>9</td>
</tr>
<tr>
<td>Low anterior forces</td>
<td>8</td>
</tr>
<tr>
<td>Low voltage</td>
<td>7</td>
</tr>
<tr>
<td>Right axis deviation</td>
<td>6</td>
</tr>
<tr>
<td>1st Atrioventricular block</td>
<td>6</td>
</tr>
<tr>
<td>Right atrial enlargement</td>
<td>5</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>4</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>3</td>
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</tbody>
</table>

Atrial premature contractions, sinus arrhythmia, ventricular premature contractions, sinus bradycardia, interventricular conduction delay, left ventricular hypertrophy, left bundle branch block, left atrial enlargement, left axis deviation, or delta waves occurred in 1–3% of patients.

The treatment regimens for the two groups were similar (Table 4). The most common therapy used for both groups was a somatostatin analogue, Sandostatin. Patients with carcinoid heart disease showed a mean maximum reduction of 5-HIAA levels of 53% with this therapy, whereas those patients without evidence of carcinoid heart disease had a similar mean reduction of 58%. Hepatic artery ligation or occlusion (alone or sequentially with combination chemotherapy) was also a frequently used protocol. With this procedure, the groups had almost equal results: nine of 11 evaluable patients with carcinoid heart disease exhibited a >50% reduction in urinary 5-HIAA levels, and eight of 11 carcinoid patients without cardiac involvement showed the same >50% reduction. Finally, resection of hepatic metastases, previously described by McEntee et al., was performed on four patients in each group.

Follow-up data were available for 130 of 132 patients (98%). Three-year survival for patients with carcinoid heart disease was 31% compared with 68% for those without echocardiographic evidence of cardiac involvement (p=0.0003) (Figure 1). The duration of follow-up ranged from 8 to 75 months in the seven patients who initially had no echocardiographic evidence of carcinoid heart disease but in whom the disease later developed. The characteristics of this group are shown in Table 5. Five of the seven patients presented with new heart murmurs. Two had no signs or symptoms to suggest the development of carcinoid heart disease. Six patients showed an increase in levels of urinary 5-HIAA during the period of follow-up. In one patient, cardiac involvement developed despite treatment with somatostatin (500 mg t.i.d.) and reduction in levels of 5-HIAA.

Thirty-four of the 74 patients (46%) with carcinoid heart disease underwent a follow-up echocardiographic study (4–67 months after the initial study) that demonstrated carcinoid heart disease. In no patient was regression of carcinoid heart disease noted.

Echocardiographic Findings

Right atrium and right ventricle. The right atrium was enlarged in 67 of 74 patients (91%) and was moderately to severely enlarged in 40 patients (54%). The right ventricle was enlarged in 65 patients (88%) and moderately to severely enlarged in 40 patients (54%).

TABLE 3. Chest Roentgenographic Findings in Patients With Carcinoid Heart Disease

<table>
<thead>
<tr>
<th>Findings</th>
<th>Patients (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Normal</td>
<td>34</td>
</tr>
<tr>
<td>Cardiac enlargement</td>
<td>13</td>
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<tr>
<td>Pleural effusion</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary nodules</td>
<td>8</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>4</td>
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<tr>
<td>Blunting of costophrenic angles</td>
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Hilar or pulmonary masses, fibrosis at bases, interstitial edema, elevation of hemidiaphragm, tracheal deviation, or prior thoracotomy occurred in 1–4% of patients.
normal motion of the ventricular septum was noted in 33 patients (45%). A flattened curvature of the ventricular septum or D-shaped left ventricle, consistent with right ventricular pressure overload, was present in six patients (8%). The right ventricle was described as dilated and hypokinetic in four patients (5%).

Tricuspid valve. Two-dimensional echocardiography revealed abnormalities of the tricuspid valve in 72 of the 74 patients (97%) with carcinoid heart disease. The valve leaflets were thickened, shortened, retracted, and hypomobile, resulting in incomplete coaptation (Figure 2A). In most patients, the leaflets were rigid and fixed in a semipenopen position, resulting in a fixed orifice. These abnormalities most prominently involved the septal and anterior leaflets. Diving of the tricuspid valve was not observed in any patients with carcinoid heart disease. In the two patients in whom the tricuspid valve appeared normal, the diagnosis of carcinoid heart disease was based on the presence of pulmonic stenosis in one patient and the presence of myocardial metastases in the other patient.

Tricuspid regurgitation was present in all 69 patients with carcinoid heart disease who underwent Doppler examination (100%), and it was of moderate or severe degree in 62 patients (90%) (Figure 2B). Follow-up Doppler examination in 34 patients again confirmed these findings. Severe tricuspid regurgitation was characterized by a dagger-shaped spectral profile on continuous-wave Doppler examination (Figure 3), with an early peak pressure and rapid decline; this was consistent with severe regurgitation and rapid equalization of right atrial and ventricular pressures. The tricuspid regurgitant velocity was increased in many patients (mean, 2.6±0.5 m/sec; range, 1.5–4.0 m/sec). This finding reflects the increased right ventricular pressure imposed by the pulmonary stenosis that was commonly

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Site of primary tumor</th>
<th>Duration of follow-up (months)</th>
<th>New signs or symptoms</th>
<th>Initial 5-HIAA (mg/24 hrs)</th>
<th>Change in 5-HIAA (mg/24 hrs)</th>
<th>Treatment</th>
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<tr>
<td>67</td>
<td>M</td>
<td>Appendix</td>
<td>8</td>
<td></td>
<td>40</td>
<td>+17</td>
<td>Resection, low-dose somatostatin</td>
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<td>46</td>
<td>M</td>
<td>Colon</td>
<td>20</td>
<td>New murmur, dyspnea</td>
<td>331</td>
<td>−208</td>
<td>Resection, high-dose somatostatin</td>
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<td>48</td>
<td>F</td>
<td>Ileum</td>
<td>25</td>
<td></td>
<td>104</td>
<td>+45</td>
<td>Resection and chemotherapy*</td>
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<tr>
<td>61</td>
<td>F</td>
<td>Ileum</td>
<td>36</td>
<td>New murmur</td>
<td>268</td>
<td>+5</td>
<td>Resection</td>
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<tr>
<td>63</td>
<td>M</td>
<td>Jejunum</td>
<td>42</td>
<td>New murmur</td>
<td>18</td>
<td>+82</td>
<td>Resection</td>
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<tr>
<td>71</td>
<td>F</td>
<td>Ileum</td>
<td>61</td>
<td>New murmur</td>
<td>147</td>
<td>+46</td>
<td>Resection</td>
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<tr>
<td>54</td>
<td>F</td>
<td>Ileum</td>
<td>75</td>
<td>New murmur, edema, dyspnea</td>
<td>20</td>
<td>+220</td>
<td>Resection and 5-fluorouracil</td>
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</table>

5-HIAA, 5-hydroxyindoleacetic acid.
*Adriamycin, dacarbazine, streptozotocin, 5-fluorouracil.

FIGURE 2. Carcinoid involvement of the tricuspid valve. Panel A: Two-dimensional echocardiogram shows retraction and thickening of septal and anterior leaflets that fail to coapt in systole. Panel B: Color flow imaging shows severe tricuspid regurgitation with the regurgitant jet nearly filling the dilated right atrium. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TV, tricuspid valve; TR, tricuspid regurgitation.
present. The Doppler pressure half-time was prolonged, averaging 116±43 msec (range, 45–200 msec); this was consistent with associated tricuspid stenosis secondary to a fixed semilunar orifice. The mean gradient across the tricuspid valve was increased at 4.9±1.4 mm Hg (range, 2.4–7 mm Hg), consistent with the combination of stenosis and regurgitation.

**Pulmonary valve.** The pulmonary valve appeared thickened and retracted or stenotic, with narrowing of the annulus in 36 patients (49%) (Figure 4A); it appeared to be normal in nine patients (12%) and diminutive to the extent of not being visualized in 29 patients (39%). Thus, the pulmonary valve was abnormal in 88% of cases. Among patients in whom Doppler evaluation of the pulmonary valve was performed, pulmonary regurgitation was present in 36 of 47 (76%) (Figure 4B). Pulmonary stenosis was present in 25 of 47 patients (53%), with peak velocities ranging from 1.7 to 3.6 m/sec (mean, 2.2±0.5 m/sec) and mean gradients from 7 to 37 mm Hg (mean, 14±9 mm Hg) (Figures 4C and 4D). Doppler examination revealed pulmonary valve involvement in 11 patients in whom the valve could not be visualized by echocardiography (stenosis in 10, regurgitation in one).

**Left-sided valvular involvement.** Left-sided valvular involvement was present in five patients (7%) (Figure 5). The mitral valve was involved in all of these patients, and the involvement was characterized by diffuse thickening and mild reduction of excursion. On flow imaging, mitral regurgitation was severe in three patients (grade 4/4) and moderate in two patients (grade 2/4). Two patients, ages 48 and 57 years, also had diffusely thickened aortic cusps consistent with carcinoid involvement of the aortic valve. The extent of cusp thickening was greater than would be expected for age-related changes. Aortic regurgitation was severe in one patient and mild in the other. Carcinoid tumor involved the lung in one of the five patients with left-sided valvular involvement. In three patients, a patent foramen ovale was present, with right-to-left shunt demonstrated on contrast echo.

One patient had neither lung involvement nor a shunt at contrast echocardiography. This patient had been symptomatic for nearly 5 years before the diagnosis of carcinoid syndrome was made. The 24-hour urinary level of 5-HIAA was markedly increased at 416 ng/mL at the time of diagnosis of carcinoid syndrome. Carcinoid involvement of all four cardiac valves was detected by echocardiography at the time of diagnosis. The patient subsequently underwent replacement of four valves. All five patients had the characteristic echocardiographic features of right-sided valve involvement as well.

Left ventricular size and systolic function were normal in 71 patients (96%). Three had reduced systolic function (global in two, regional in one). Doppler evaluation of mitral inflow did not reveal the presence of restrictive cardiomyopathy in any patient.

**Myocardial metastases.** Myocardial metastases were present in three patients (4%) (Figure 6). Pathological confirmation was obtained in each case. In one case, a 3×1.5-cm mass was present in the left ventricular wall, and a biopsy specimen was studied at the time of coronary artery bypass grafting. Mild carcinoid involvement of the tricuspid and pulmonary valves was present (Figure 6A). In another patient, a 3.6-cm mass was detected in the right ventricular free wall (Figures 6B and 6C). This patient had no other echocardiographic evidence of carcinoid valvular heart disease. At the time of surgical exploration, the large tumor in the right ventricular wall was excised, and five additional small carcinoid myocardial tumors were resected, including lesions in the ventricular septum and left ventricular myocardium. During 5 years of follow-up of this patient, there has been no recurrence of metastases or any evidence of development of carcinoid valve disease. In another patient, echocardiography demonstrated a 3-cm tumor mass in the left ventricular myocardium and a 2.5-cm nodule in the right ventricular myocardium, in addition to typical carcinoid involvement of the tricuspid and pulmonary valves (Figure 6D). At the time of tricuspid valve replacement and pulmonary valvectomy, a total of three tumors were visualized. Biopsy of the right ventricular mass confirmed that it was a carcinoid tumor involving the myocardium.

In each of these three cases, the atrial septum was intact, and no evidence of pulmonary disease was present. The ileum was the primary source of tumor in each patient (all of whom were men). These three patients were indistinguishable from others with carcinoid heart disease with respect to age, duration of symptoms, duration of diagnosis, or mean levels of 5-HIAA.

**Other findings.** Small pericardial effusions were present in 10 patients (14%) (Figure 5). Patent foramen ovale was demonstrated in five patients (7%) by color flow or contrast echo. Small right-to-left shunts were present in four of the five patients with left-sided cardiac involvement.

**Pathological Correlations**

Pathological confirmation of myocardial metastases was obtained by biopsy for each of the three patients in whom they were noted. In two patients, myocardial metastases were multiple and at the time of surgery were greater in number than had been appreciated.
FIGURE 4. Panel A: Echocardiogram shows carcinoid involvement of the pulmonary valve. The pulmonary valve is diminutive to the extent of being poorly visualized. The annulus is narrowed. Panel B: Color flow examination shows severe pulmonary regurgitation. Panel C: Color flow examination shows jet of pulmonary stenosis. Panel D: Continuous-wave Doppler examination of the pulmonary valve shows pulmonary stenosis (peak velocity, 2 m/sec) and regurgitation with a short deceleration time, consistent with severe regurgitation. Ao, aorta; PA, pulmonary artery; PR, pulmonary regurgitation; PS, pulmonary stenosis; PV, pulmonary valve; RVOT, right ventricular outflow tract.

echocardiographically. Fourteen patients underwent valve replacement, including tricuspid valve replacement and pulmonary valve resection in 11 patients, tricuspid and mitral valve replacement, pulmonary valve resection with pericardial patch enlargement of the pulmonary valve annulus, and suture closure of a patent foramen ovale in one patient, four-valve replacement in one patient, and tricuspid valve replacement, pulmonary valve resection, and biopsy of myocardial metastasis in one patient. In each case, intraoperative findings of carcinoid valvular heart disease closely resembled those noted echocardiographically, with thickening, retraction, and immobility of valve leaflets, a lesion consistent with combined stenosis and regurgitation. In addition, the pulmonary valve annulus was narrowed, as noted echocardiographically. Histological examination demonstrated carcinoid plaques, the pathognomonic mounds of smooth muscle proliferation, involving all valves resected.

One patient with advanced carcinoid disease underwent postmortem examination. This demonstrated fibrous plaques involving the endocardium of the right heart as well as all four valves, with severe retraction of the tricuspid and pulmonary valves. Echocardiography had demonstrated marked involvement of the tricuspid valve; the pulmonary valve could not be visualized because of severe retraction.

Discussion

This large series of patients with carcinoid heart disease documents a broad spectrum of cardiac involvement, including not only right-sided valvular lesions but also left-sided involvement in 7% of patients, myocardial metastases in 4% (the only manifestation of carcinoid heart disease in one patient), and pericardial effusions in 14%. Anatomic correlation was available for 17 patients (23%), including surgery in 16 patients and autopsy in one patient. Carcinoid involvement of all valves resected was demonstrated, and biopsy of myocardial metastases in three patients revealed carcinoid tumor. Carcinoid tumor presenting as a right atrial mass has been reported previously; however, to our knowl-
edge, carcinoid myocardial metastases have not been described previously. Although pathological confirmation of pericardial involvement was not obtained in any of our patients, metastatic carcinoid tumor involving the pericardium has been described.8

Cardiac involvement has been recognized in more than 50% of patients with carcinoid heart disease. Cardiac complications, including intractable right ventricular failure secondary to tricuspid and pulmonary valvular disease, may be fatal. Preliminary experience suggests that favorable results with aggressive surgical treatment may be beneficial in some patients with carcinoid heart disease.9-12

The definitive diagnosis of carcinoid heart disease is difficult, and cardiac symptoms do not appear until the late stages of the disease. In this retrospective study, patients with cardiac involvement could not be distinguished on the basis of duration of carcinoid syndrome or duration of histological diagnosis. However, heart murmurs and the symptom of dyspnea were noted more frequently among patients with carcinoid heart disease. The ECG and chest roentgenogram at presentation were nonspecific; changes showing evidence of cardiac enlargement with these tests may not occur until late in the course of cardiac involvement. Mean urinary levels of 5-HIAA (a serotonin metabolite) were significantly higher in patients with carcinoid heart disease; however, the range was quite broad (24–866 mg/24 hrs in patients with cardiac involvement versus 11–687 mg/24 hrs for those without cardiac involvement).

Several authors have suggested that it is the exposure of the endocardium to elevated levels of serotonin that might lead to the development of heart lesions.13,14 Although several hypotheses have been proposed—including serotonin-induced endocardial damage with subsequent reparative fibroblastic activity or serotonin effects on cardiac lymphatics15—the exact etiology of the cardiac plaques remains obscure. Despite treatment that resulted in significant reductions of urinary levels of 5-HIAA, we did not observe regression of the carcinoid heart lesions in any of the patients in this large study.

In our series, overall survival was significantly worse for patients with cardiac involvement (Figure 1); median survival was only 1.6 years. Himelman and Schiller15 also noted similar shortened survival. Thus, detection of cardiac involvement carries important prognostic implications, and two-dimensional echocardiography is the technique of choice to establish the diagnosis of carcinoid heart disease.

Doppler Features of Carcinoid Valvular Heart Disease

We have expanded our clinical experience to a total of 69 patients since our earlier description of Doppler findings in carcinoid valvular heart disease.16 Tricuspid regurgitation was present in all patients and was characterized by a dagger-shaped spectral profile on continuous-wave Doppler examination, indicative of a severe degree of regurgitation with a large right atrial "V" wave. Tricuspid stenosis was diagnosed by Doppler with prolongation of Doppler pressure half-times (mean, 116±43 msec). The mean gradient across the tricuspid valve was increased (mean, 4.9±1.4 mm Hg), consistent with the combination of stenosis and regurgitation.

The relatively infrequent finding of pulmonary valvular stenosis in comparison to tricuspid regurgitation has been described by others from both autopsy17 and two-dimensional echocardiographic studies.18 However, in our study, the pulmonary valve was inadequately visualized in 39% of patients. Difficulty in visualizing the pulmonary valve is secondary to the disease process itself, which results in retraction of the valve leaflets. Inadequate visualization, however, did not preclude Doppler examination. Pulmonary stenosis was present in 53% of patients in whom Doppler examination was possible (mean gradient, 14±9 mm Hg). In addition, pulmonary regurgitation appears to be a common functional abnormality and was present in 81% of patients who underwent Doppler assessment.

Conclusions

This large series describes the broad spectrum of cardiac involvement in carcinoid heart disease. The typical right-sided valvular lesion appears to be one of combined stenosis and regurgitation. A dagger-shaped spectral profile characteristic of severe tricuspid regurgitation is noted by Doppler. Left-sided valvular lesions, myocardial metastases, and pericardial effusion are other manifestations of the disease. Given the rarity of the carcinoid syndrome, the findings of this study are not likely to be duplicated.

Echocardiography permits demonstration of cardiac involvement in carcinoid syndrome. Because of the important clinical implications of cardiac involvement, we recommend a comprehensive two-dimensional echocardiographic and Doppler examination when evaluating patients with metastatic carcinoid syndrome to aid in the detection of cardiac involvement and assessment of the severity of valvular stenosis and regurgitation. Serial examinations may also be indicated, as several patients (seven of 29; 24%) developed typical features of carcinoid heart disease during follow-up.
FIGURE 6. Panel A: Echocardiogram shows myocardial metastasis in the left ventricular wall of a 61-year-old man who also had carcinoid involvement of the tricuspid and pulmonary valves. LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; M, myocardial metastases; RV, right ventricle. Panel B: This sagittal view obtained with magnetic resonance imaging demonstrates a tumor (arrows) in the free wall of the right ventricle in a 59-year-old man. Panel C: Gross specimen resected from right ventricular free wall (same patient as in panel B). Panel D: Myocardial metastasis in the right ventricular wall of a 52-year-old man, two-dimensional echocardiographic subcostal view. M, metastasis; RA, right atrium.
Acknowledgment

The authors appreciate the assistance of Kent R. Bailey, PhD, Section of Biostatistics.

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Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients.

Circulation. 1993;87:1188-1196
doi: 10.1161/01.CIR.87.4.1188

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