Features of Carcinoid Heart Disease Identified by 2- and 3-Dimensional Echocardiography and Cardiac MRI

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Background—Carcinoid heart disease is a rare form of valvular heart disease. We sought to describe the spectrum of carcinoid heart disease identified by echocardiography and cardiac MRI.

Method and Results—Two hundred fifty-two patients with carcinoid syndrome underwent a range of investigations including 2D transthoracic echocardiography, 3D transthoracic echocardiography and transesophageal echocardiography, and cardiac MRI. Fifty-two patients had evidence of carcinoid heart disease. Involvement of the tricuspid, pulmonary, mitral, and aortic valves were found in 47 (90%), 36 (69%), 15 (29%), and 14 (27%), respectively. Myocardial metastases were found in 2 (3.8%) patients. Several patterns of disease were identified depending on the extent and severity to which each leaflet and its associated subvalvular apparatus was affected. Thirteen of 15 (87%) patients with left-sided carcinoid involvement had a patent foramen ovale. Three patients with severe degree of shunting had severe valvular regurgitation. Patients with mild/moderate degree of shunting had mild or moderate valvular regurgitation. Three-dimensional transthoracic echocardiography/transesophageal echocardiography provided detailed anatomic information particularly for the tricuspid and pulmonary valves. Cardiac MRI allowed complementary assessment of valvular heart disease and delineation of myocardial metastases. Gallium-68 octreotide positron emission tomography identified neuroendocrine metastases.

Conclusions—Carcinoid heart disease is a heterogeneous disease with a wide spectrum of echocardiographic findings. A multimodality approach is needed in patients with this complex pathology. 

Key Words: valves ■ heart disease ■ carcinoid

Carcinoid tumors occur in between 2.5 and 5 cases per 100 000 of the population. Carcinoid syndrome is thought to occur when the tumor metastases to the liver allowing high levels of 5-hydroxytryptamine (5-HT) to reach the systemic circulation. Manifestations of the syndrome include flushing, diarrhea, bronchospasm, and the development of carcinoid heart disease. 

Clinical Perspective on p 111

5-HT is thought to promote deposition of plaques composed of myofibrocytes onto the endocardial surfaces of the heart. Cardiac involvement is commonly manifested by the development of right-sided valvular dysfunction. Characteristic changes include thickening of valve leaflets/cusps that become retracted and eventually immobile, resulting in a combination of valvular regurgitation and stenosis. 

Significant advances in echocardiography, including the development of transesophageal TEE and 3D echocardiography, have allowed greater understanding and assessment of valve pathology. Second, newer imaging modalities such as cardiac MRI (CMR) have emerged, which may allow complementary assessment of cardiac pathology.

The purpose of this study is to describe the echocardiographic features of carcinoid heart disease identifying features of both early and advanced disease and to ascertain the value of advanced echocardiographic techniques and other imaging modalities.

Methods

Patients

Patients with carcinoid syndrome were consecutively and prospectively enrolled between April 2006 and December 2008. The diagnosis of carcinoid tumor was based on histological examination of either primary tumor or liver metastases biopsy. The protocol was approved by the institution’s ethics committee. All patients gave written informed consent.

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103
Echocardiography
All patients underwent comprehensive 2D transthoracic echocardiography (TTE). Additional 3D TTE was performed after the 2D study from 2008 onward. Three-dimensional TEE was performed where transthoracic windows were not suitable for full evaluation of heart valves, and there was clinical suspicion of valvular heart disease or as part of preoperative assessment before valve surgery.

2D Echocardiography
Two-dimensional TTE was performed in all patients using commercially available echocardiography machines (Siemens Acuson CS12 and Philips iE33). Valve morphology and function was evaluated in several views. Valve regurgitation severity and quantification were assessed and graded according to the American Society of Echocardiography (ASE) guidelines. Valve stenosis was quantified according to the American College of Cardiology Guidelines. Pulmonary stenosis was graded (according to peak gradient across valve) as mild (<25 mm Hg), moderate (25 to 50 mm Hg), or severe (>50 mm Hg). Tricuspid stenosis was graded (mean gradient across valve) as mild (1 to 5 mm Hg), moderate (5 to 8 mm Hg), or severe (>8 mm Hg). Right and left ventricular function and sizes were assessed and calculated according to ASE guidelines.

All echocardiograms were reviewed by 2 cardiologists experienced in echocardiography (S.B., J.D.). The abnormalities described are based on the consensus of the 2 reviewers. Carcinoid heart disease was defined as the presence of characteristic thickening, reduced excursion or retraction of valvular leaflets (with associated evidence of valvular stenosis or regurgitation), or the presence of myocardial metastases, in the absence of other etiologies.

Contrast Echocardiography
All patients were assessed for the presence of a patent foramen ovale using “microbubble” contrast at rest and with cough and Valsalva maneuver. The presence of patent foramen ovale was defined as the presence of at least 3 microbubbles in the left atrium within 3 cardiac cycles of contrast visualization in right atrium. The degree of shunting was classified as mild if 3 to 9 microbubbles appeared, moderate if 10 to 30 microbubbles appeared, and large if more than 30 microbubbles appeared.

Three-Dimensional TTE
Three-dimensional TTE was performed using Philips iE33 equipped with X3–1 transducer (Philips Medical Systems, Andover, Mass) after 2D examination was complete. Full-volume, 3D zoom, and live data sets were obtained from parasternal, apical, and subcostal views. Full-volume acquisition was performed over 5 cardiac cycles with breath-hold. Image rendering was performed after the procedure. Pyramidal data sets were cropped along x, y, z axes or manually using the cropping plane of choice. Gain settings, smoothing, and brightness were adjusted to optimize visualization of valve and valvular apparatus.

Transesophageal Echocardiography
TEE was performed using Philips iE33 equipped with a X7–2t transducer. Multiplane 2D TEE evaluation was completed followed by acquisition of a 3D data set. A live 3D zoom and full-volume data set was obtained. Images were rendered in the same way as for transthoracic echocardiography.

Cardiac MRI
CMR was undertaken using commercially available 1.5-T MR scanners. Steady-state–free precession and gradient echo pulse sequences were used to assess valve morphology and ventricular function and to detect valvular regurgitation. By using phase contrast sequences, the forward and regurgitant volumes were calculated from phase-encoded velocity maps. Delayed enhancement gadolinium images were acquired to assess myocardial involvement.

Table. Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Carcinoid Heart Disease</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Present (n=52)</td>
<td>Absent (n=200)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64 (55–69)</td>
<td>64 (58–71)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>28 (54)</td>
<td>98 (49)</td>
</tr>
<tr>
<td>Duration of diagnosis, mo</td>
<td>5 (1–6)</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>48 (92)</td>
<td>194 (97)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4 (8)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Presence of liver metastases</td>
<td>50 (96)</td>
<td>171 (86)</td>
</tr>
<tr>
<td>Chromogranin A, pmol/L</td>
<td>1000 (655–1000)</td>
<td>140 (56–484)</td>
</tr>
<tr>
<td>Urinary 5-hydroxyindolacetic acid, μmol/24 h</td>
<td>800 (399–1490)</td>
<td>42 (0–205)</td>
</tr>
<tr>
<td>Therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatostatin analog</td>
<td>48 (92)</td>
<td>161 (81)</td>
</tr>
<tr>
<td>Interferon</td>
<td>2 (4)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6 (12)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Surgery</td>
<td>19 (37)</td>
<td>98 (49)</td>
</tr>
<tr>
<td>Targeted radionuclide</td>
<td>18 (35)</td>
<td>52 (26)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or n (%).

Statistical Analysis
Data are expressed as either median and (first to third quartile) or number and percentage. The Mann-Whitney U test was used to compare continuous variables between groups. The χ² test was used to compare groups regarding categorical variables; when a cell frequency was <5, the Fisher exact test was used. All tests of significance were two sided. A probability value (P) of <0.05 was considered statistically significant. Statistical analysis was performed using StatsDirect Version 2.5.7 (StatsDirect, Altrincham, United Kingdom).

Results
Two hundred fifty-two patients were recruited over the study period and underwent 2D TTE. Fifty-two patients were found to have abnormalities consistent with carcinoid heart disease; 100 patients (40 patients with carcinoid heart disease) underwent additional 3D TTE; 22 patients with carcinoid heart disease underwent 3D TEE; and 10 patients with carcinoid heart disease had a CMR study.

There were no significant differences in age, sex, tumor characteristics, or treatments received between those patients with or without carcinoid heart disease. Significantly higher levels of urinary 5-hydroxyindolacetic acid and plasma Chromogranin A were found in patients with carcinoid heart disease (Table).

Right Ventricle, Atrium, and Tricuspid Valve
Abnormalities of the tricuspid valve were found in 47 (90%) patients with carcinoid heart disease. The mildest changes were thickening of the valve leaflets and subvalvular appa-
The normal concave curvature of the leaflets was diminished causing them to become straightened. The dynamic motion of the leaflet during diastole was altered. The leaflets moved in a stiff “board-like” fashion rather than the normal undulating motion. Only trivial or mild centrally directed tricuspid regurgitation was noted.

Thickening of the valve leaflets was associated with thickening of the chordae and papillary muscles. Chordae may become fused and shortened. This was associated with greater degrees of retraction and reduction excursion of the valve cusps. The extent to which each leaflet and subvalvular apparatus was affected was variable and produced several patterns of disease (Figure 1).

In the most severe cases, leaflets were fixed, retracted, and did not coapt. This was associated with severe tricuspid regurgitation with a characteristic “dagger-shaped Doppler” profile and mild or moderate tricuspid stenosis (median gradient, 3.5 mm Hg; interquartile range, 2.9 to 4.3 mm Hg).

The right ventricle was dilated in 28 (93%) patients with severe tricuspid regurgitation (median, 3.9 cm; interquartile range, 3.6 to 4.2 cm). The right atrium was enlarged in all patients with severe tricuspid regurgitation (median, 26 cm²; interquartile range, 22 to 27 cm²) (Figure 1).

Three-dimensional TTE visualization of the tricuspid valve allowed an en face view of the valve from either atrial or ventricular side to be obtained. In 22 patients, all 3 leaflets were thickened and fixed in a semiopen position. This caused a large area of noncoaptation. Detailed delineation of subvalvular structures was obtained. Gross thickening and shortening and fusion of chordae together with papillary muscles was observed (Figure 2). The ability to visualize all 3 leaflets simultaneously allowed comparison between leaflets. Three patients had involvement of an isolated septal leaflet. This leaflet was thickened, retracted, and fixed with preservation of mobility of anterior and posterior leaflets. This caused malcoaptation of the cusps. Typically, the tip of unaffected

Figure 1. Two-dimensional transthoracic echocardiogram is shown: Right atrium (RA), right ventricle (RV), right ventricular outflow tract (RVOT), and pulmonary artery (PA). A, Diffuse thickening of septal and anterior tricuspid valve (TV) leaflets (arrow) and chordae. Leaflets are “stiffened” and “board-like” and lose their normal curvature. Good excursion of the leaflets was present. Trivial/mild tricuspid regurgitation was present. B, Fixed, thickened septal leaflet of tricuspid valve tethered to ventricular endocardium (arrow). Anterior leaflet, although thickened, had good excursion (dashed arrow). The tip of anterior leaflet meets body of septal leaflet in diastole causing an eccentric jet of moderate tricuspid regurgitation. C, Tricuspid valve (TV) leaflets (arrow) are thickened, fixed, and retracted. This patient had “free-flowing” severe tricuspid regurgitation. Both right atrium and right ventricle are dilated. D, Mild thickening of pulmonary valve cusps. The cusps are “straightened” and lose their normal curvature. E, Grossly thickened, fixed, and retracted pulmonary valve (PV) cusps (arrow) do not coapt. F, Continuous-wave Doppler demonstrating pulmonary stenosis (PS) with a peak gradient of 58 mm Hg and peak velocity of 3.8 m/s and the steep deceleration slope of severe pulmonary regurgitation (PR).
leaflet met the body of the affected leaflet. This was associated with a moderate, eccentrically directed jet of tricuspid regurgitation.

Two-dimensional and 3D TEE assessment of the tricuspid valve allowed visualization of valve leaflets in all patients who had poor transthoracic windows. Eighteen (90%) of patients with carcinoid heart disease who underwent TEE had thickened right ventricular endocardium with probable deposition of carcinoid plaque (Figure 2).

Pulmonary Valve

Abnormalities of the pulmonary valve were found in 36 (69%) of patients with carcinoid heart disease. Changes in valve morphology were similar to the tricuspid valve. With mild involvement, valve cusps were diffusely thickened, which caused them to become straightened. With more severe disease varying degrees of retraction and reduction in excursion of valve cusps was seen. In severe cases valve cusps were fixed, retracted, and thickened with severe pulmonary regurgitation. The characteristic sharp deceleration slope of severe pulmonary regurgitation was seen. The peak velocity through the pulmonary valve ranged from 1.6 to 3.8 m/s (Figure 1).

Three-dimensional TTE allowed identification of all 3 pulmonary valve cusps simultaneously. In 2 patients, 3D TTE demonstrated marked thickening of a single cusp of the pulmonary valve (demonstrating probable carcinoid plaque deposition), with the other 2 cusps unaffected (Figure 3). These abnormalities were not on identified on 2D images. Additionally, 3D TTE allowed the anatomic relationship between all 3 leaflets and endocardial surfaces as well as the degree of coaptation of the cusps to be assessed. In patients with severe disease, 3D TTE demonstrated constriction of the pulmonary valve annulus with thickened, partially retracted, and fixed pulmonary cusps causing noncoaptation of the cusps and significant stenosis. Poststenotic dilation of the pulmonary artery was seen. In 3 patients, the arterial surfaces of the pulmonary valve cusps were grossly thickened to the extent that they completely filled the valve sinus. This made it difficult to demarcate the valve cusps from underlying endocardium (Figure 3).

Three-dimensional TEE provided anatomic information regarding relationship of the all 3 pulmonary valve cusps...
including the relationship of cusps to the ventricular walls, mobility, and thickness as well as allowing assessment of pulmonary valve annulus constriction and visualization of right ventricular outflow tract and pulmonary artery.

Left-Sided Heart Valves and Foramen Ovale
Fifteen (29%) patients had left-sided valvular involvement. Thirteen (87%) of these were associated with a patent foramen ovale. The 2 patients with left-sided disease but without patent foramen ovale both had multiple bronchial carcinoid metastases. Three patients with a severe degree of shunting on their bubble contrast had severe mitral and/or aortic valve regurgitation. The remaining 10 patients with mild or moderate degree of shunting had mild or moderate mitral or aortic regurgitation.

Aortic Valve
Aortic valve involvement was seen in 14 (27%) cases of carcinoid heart disease. Diffuse thickening of valve cusps was identified together with mild aortic regurgitation. One patient had gross thickening of the noncoronary cusp with mild thickening of right coronary cusp. Two patients had severe aortic regurgitation. Visualization of the valve cusps was poor on 2D TTE, but they were clearly thickened. On 2D TEE, gross thickening and retraction of all 3 leaflets, which were almost fixed leading to noncoaptation of the leaflets, was found (Figure 4).

Mitrail Valve
Mitrail valve involvement was seen in 15 (29%) patients with carcinoid heart disease. Similar to the aortic valve, patients
had diffuse thickening of both leaflets, although 1 patient had a node-like involvement. Trivial or mild mitral regurgitation was present.

Three patients had grossly thickened papillary muscles and shortened chordae. This caused tenting of the mitral valve leaflets and associated severe mitral regurgitation. Although leaflet mobility was restricted, no significant stenosis was seen. Two- and 3-dimensional TEE enabled detailed assessment of the subvalvular apparatus and visualize valve anatomy (Figure 4).

**Myocardial Metastases**

Myocardial metastases were detected in 2 (3.8%) of patients with carcinoid heart disease. One patient with valvular involvement had a 1.2×10 cm metastasis in the right atrium and 1 patient without valvular involvement had multiple metastases in the inferior (3.3×2.2 cm) and anterior walls (4.1×2.9 cm and 3.4×5.6 cm) as well as basal septum of the left ventricle. Two-dimensional TTE and TEE allowed visualization of the cardiac masses. However, only an estimate of their diameter could be obtained as it was difficult to demarcate the mass from surrounding myocardium. Three-dimensional TTE demonstrated better delineation of the mass to adjacent structures. CMR allowed identification of location, number, size, and relationship of cardiac metastases to surrounding structures. Gallium-68 octreotide positron emission tomography (PET) demonstrated avid focal uptake in the 2 masses, suggesting metastatic spread (Figure 5).

**Cardiac MRI**

Ten patients with carcinoid heart disease underwent CMR (Figure 6). Eight patients had dilated right ventricle and 2 patients had impaired right ventricular function. CMR demonstrated thick, fixed, retracted leaflets that did not coapt in all 10 patients. Quantification of tricuspid regurgitation was severe in all cases. One patient had mild tricuspid stenosis.

Eight of 10 patients had thickened pulmonary valve cusps with restricted motion. All of these patients had either mild or moderate pulmonary stenosis. Five of these patients had mild pulmonary regurgitation and 3 had moderate pulmonary regurgitation. No patient demonstrated myocardial involvement on late gadolinium enhancement imaging.

**Pathological Correlation**

Twenty-one patients with carcinoid heart disease underwent cardiac valve replacement surgery. Gross morphological and
histological examination of the excised valves was performed in all patients. The identification of carcinoid heart disease in individual valves by echocardiography correlated with findings at pathological examination.

In 1 patient with severe right-sided valvular dysfunction, echocardiography demonstrated diffuse thickening of mitral valve leaflets and chordae with trivial regurgitation (Figure 4, C and D). At the time of surgery, visual inspection identified

Figure 5. A, Transesophageal echocardiogram demonstrating large mass in mid to distal inferior wall of the left ventricle (arrow). B, 3D TTE showing well-demarcated, rounded mass (arrow) in the posterior wall of left ventricle (LV). C, CMR demonstrating 2 well-demarcated masses in the mid infero-lateral wall extending to the apex (dashed arrow). Masses are limited to myocardium with no extra cardiac extension. D, Gallium-68 octreotide PET demonstrating focal avid uptake of tracer in the region of the 2 masses (arrow), suggesting metastatic carcinoid tumor.

Figure 6. Cine CMR. A, Four-chamber view (systole): Dilated right atrium and ventricle is shown. Thickened, fixed, and retracted tricuspid valve leaflets (arrow) with associated subvalvular involvement (dashed arrow). B, Thickening, retraction, and reduced excursion of the pulmonary valve leaflets (arrow). C, Phase contrast flow map (short-axis view in systole). Severe tricuspid regurgitation is demonstrated by black retrograde jet (arrow).
features of carcinoid heart disease in this valve, therefore mitral valve replacement was performed in addition to tricuspid and pulmonary valve replacement. Histological examination confirmed the diagnosis. In 1 patient (with bronchial in addition to liver metastases) with severe left-sided valvular dysfunction, echocardiography demonstrated mild thickening and retraction of the tricuspid and pulmonary valves. This was associated with mild pulmonary stenosis and moderate tricuspid regurgitation. The patient underwent replacement of all 4 valves. Histological examination confirmed carcinoid involvement of all valves.

Discussion
This study describes the features of carcinoid heart disease encompassing the spectrum of disease from early to advanced disease and encompassing both 2D and 3D echocardiography as well as CMR and PET imaging.

Echocardiography remains pivotal in the investigation of patients with carcinoid syndrome and suspected carcinoid heart disease. The classic features of advanced carcinoid heart disease typically involving the tricuspid valve and pulmonary valve have been well described. However, the spectrum of disease is wide.

In this study, we have identified several patients with diffuse thickening of valve leaflets or isolated thickening of a single valve leaflet without significant reduction in leaflet mobility or the development of valvular regurgitation. Histological examination in 2 of these patients demonstrated changes typical of carcinoid heart disease. Therefore, these findings may represent the early stages of carcinoid heart disease.

We have demonstrated greater involvement of the subvalvular apparatus and valve leaflets can lead to a wide heterogeneous array of appearances and functional consequences. These findings are in keeping with previous necropsy studies, in which the location, extent, and pattern of “plaque” deposition on valvular and subvalvular structures is highly variable with both focal and diffuse patterns of plaque deposition described.

Advanced techniques such as 3D TTE or 3D TEE are helpful in identifying and assessing valve pathology, particularly in the pulmonary and tricuspid valves, because all leaflets may not be visualized on 2D echocardiography. The ability to crop images and change the plane of view allowed detailed assessment of the subvalvular apparatus and delineation of the relationship between valve leaflets to each other and surrounding structures and the endocardium.

CMR can be a valuable adjunct in the investigation of these patients, particularly where echocardiographic windows are poor or structures such as the pulmonary valve are difficult to visualize. Morphological features of severe carcinoid heart disease can be delineated with assessment of valvular regurgitation, stenosis, and quantification of ventricular volumes. CMR enables measurement of size of metastases and is able to offer information regarding extension into extracardiac structures, which is not available on echocardiographic techniques.

Cardiac metastases from carcinoid tumor are rare. In this study, 4% of patents had cardiac metastases. Although echocardiographic and CMR techniques may be able to accurately identify and characterize the mass, they are not able to elucidate whether it is a carcinoid metastases or another primary cardiac tumor. Carcinoid tumors express several somatostatin receptors, particularly receptors 2 and 5. Gallium-68 octreotide PET uses a somatostatin analogue labeled with gallium-68 tracer. Neuroendocrine tumor cells will take up the somatostatin analogue, and this will be visible on PET as it is labeled with Gallium-68. Recent data suggest >97% sensitivity and 92% specificity of Gallium-68 octreotide PET for metastatic deposits in patients with neuroendocrine tumors.

A limitation of the present study is that pathological correlation was not available in all patients. This was because patients with mild abnormalities or those with progressive carcinoid tumor would not undergo valve replacement surgery. The number of patient studies may seem relatively small; however, given the relative rarity of the condition, this represents one of the largest cohorts of carcinoid patients studied, and a full range of pathology has been described.

Conclusion
Carcinoid heart disease is a heterogeneous disease with a wide spectrum of echocardiographic findings. An integrated approach using multiple modalities should be adopted in patients at risk of carcinoid heart disease to identify pathology and assess severity of disease.

Disclosures
None.

References
Carcinoid heart disease is a common complication and a major cause of morbidity in patients with carcinoid syndrome. The classic echocardiographic features of tricuspid and pulmonary valvular dysfunction are well recognized. The role of newer imaging modalities including 3D echocardiography and cardiac MRI has not been established. The current study prospectively assessed a large cohort of patients with carcinoid syndrome for features of carcinoid heart disease using a variety of imaging modalities, including both 2D and 3D transthoracic and transesophageal echocardiography as well as cardiac MRI. A spectrum of disease from early to advanced disease was identified. The extent and severity to which each valve leaflet or cusp and its associated subvalvular apparatus was affected was highly variable, producing a wide range of appearances. Three-dimensional transthoracic and transesophageal echocardiography are particularly useful in identifying pathology in the pulmonary and tricuspid valve, as all leaflets may not be visualized on 2D echocardiography. Cardiac MRI allowed quantification of the size of cardiac metastases and the extent of their invasion into the myocardium. Positron emission tomography imaging allowed functional assessment of metastases. The study recommends an integrated approach using multiple modalities in patients at risk of carcinoid heart disease to identify pathology and assess severity of disease.
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