PATHOPHYSIOLOGY AND NATURAL HISTORY

CARCINOID HEART DISEASE

Circadin heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities

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ABSTRACT Cardiac ultrasound investigation of 68 prospectively studied patients with histologically proven midgut carcinoid tumors showed right heart disease in 66%. The abnormal findings included morphologic and functional aberrations of the tricuspid valve in 52% and 83%, respectively, right atrial and ventricular enlargement in 53% and 30%, and paradoxical systolic septal contractions in 19%. The patients with the most pronounced right heart disease had significantly higher (p<.01) plasma levels of the tachykinins neuropeptide K and substance P as well as higher (p<.001) urinary excretion of the serotonin metabolite 5-hydroxyindoleacetic acid. These patients also had the most extensive tumor disease. The occurrence of echocardiographic abnormalities of the left heart was similar to that in healthy individuals of the same age, but abnormalities were less frequent among the patients with severe right heart disease. Electrocardiographic changes were nonspecific. Right heart disease thus seems to be present more often than previously reported in patients with malignant midgut carcinoid tumors. The severity of cardiac involvement does not seem to be related to the duration of carcinoid disease but more to the extent of the disease, i.e., higher plasma levels of serotonin and tachykinins.


PATIENTS with carcinoid syndrome often develop a characteristic heart disease previously reported to occur in 19% to 53% of cases.1–6 In a majority of the patients the endocardial fibrous lesions considered to be pathognomonic of carcinoid heart disease2,7–10 involve the cavities and valves of the right heart. Only a small number of cases with typical changes of the left heart have been reported.11–13 In many patients with carcinoid heart disease, the predominant terminal symptoms and death may be attributed directly to the cardiac disease.1,14–17 The pathogenesis of carcinoid heart lesions has not yet been elucidated. Investigators have postulated etiologic agents released from the tumor, such as serotonin, kallikrein, bradykinin, histamine, gastrin, ACTH, and prostaglandins.13 However, none of these substances has been found responsible for the characteristic cardiac lesions.

The present study was designed to investigate prospectively the extent of cardiac disease in patients with carcinoid tumors by means of ultrasound investigation. In an effort to study possible etiologic agents the urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) and the plasma levels of the tachykinins neuropeptide K (NPK) and substance P (SP) were compared in patients with midgut carcinoid tumors and different degrees of carcinoid heart disease.

Methods

Study population. Cardiac ultrasound studies were performed in 68 consecutive patients (36 women and 32 men) with a midgut type of malignant carcinoid tumor admitted to the Department of Internal Medicine, University Hospital, Uppsala, Sweden, over a 6 year period (1979–1985). The diagnosis of a carcinoid tumor was histologically proven by the Grimelius and Mason silver-staining technique18,19 on tumor tissue obtained at biopsy or operation. The patients median age was 64 years (range 38 to 83) and at the time of the cardiac investigation, carcinoid symptoms had been present for a median period of 4.5 years (range 0.5 to 27). The initial complaints were facial flushing (n = 27), diarrhea (n = 23), ileus (n = 17), abdominal pain (n = 7), and blood in the stool (n = 1). At the time of investigation 58 patients had flush, 59 had diarrhea, and 50 individuals presented with the carcinoid syndrome, i.e., flush, diarrhea, and elevated urinary 5-HIAA excretion.
**Methods.** Standard 12-lead electrocardiograms were recorded in all patients at a paper speed of 50 mm/sec and were classified according to the Minnesota code. In the first eight patients only M mode echocardiography was performed by means of an Irex Mark I system, while in the remaining 60 patients, M mode and two-dimensional echocardiography were performed with a Hewlett-Packard ultrasound system 77020A (upgrade version D). The M mode tracings were obtained at a paper speed of 50 mm/sec. Distance measurements were made to the nearest millimeter. The two-dimensional registrations were recorded on videotape. Left atrial and ventricular end-diastolic diameters and ventricular septal and posterior wall thickness were measured according to the recommendations of the American Society of Echocardiography.20 Left ventricular and end-systolic diameter was measured at the peak anterior movement of the left ventricular posterior wall. Fractional shortening of the left ventricular diameter was calculated according to Kronik et al.21 in order to estimate the global left ventricular function. The largest right atrial superior-inferior and mediolateral diameters were measured on the video recordings in a carefully optimized horizontal plane in the apical four-chamber view and values above the mean +2 SDs reported by Weyman22 were considered abnormal. Right ventricular size was evaluated in the same horizontal plane and considered increased when the maximal mediolateral diameter exceeded that of the left ventricle and grossly increased when this dimension was exceeded by more than 50%.

Doppler ultrasound investigation was performed in 23 individuals with either a Pedof 2.0 MHz or an Alfred 2.0 MHz pulsed and continuous-wave system (Vingmed, Norway) without simultaneous two-dimensional imaging. The signals were analyzed on a Daisy spectral analyzer (Vingmed, Norway) and the recordings were presented on a paper speed of 50 mm/sec.

Urinary 5-HIAA excretion was determined according to a method described earlier23 as an average of two 24 hr samples (reference range < 80 μmol/24 hr). The plasma NPK and SP concentrations were analyzed by means of radioimmunoassay technique24, 25 (reference ranges: NPK <12 pmol/liter, SP <16 pmol/liter). The presence and extent of hepatic metastases were estimated by abdominal computed tomography.

**Statistical analysis.** The median and interquartile ranges are used as measures of central tendency and variation throughout the study. The chi-square test or the Kruskal-Wallis nonparametric analysis of variance for independent samples and multiple comparisons was used to compare data from groups of patients with different degrees of heart disease.26

**Results**

Right heart abnormalities were present in 45 of the 68 patients studied (66%) (table 1). Morphologic signs of tricuspid valve disease and/or tricuspid incompetence on Doppler investigation were demonstrated in 60% of the patients. The morphologic valve abnormalities were thickening of the cusps and/or abnormal motion patterns mostly of stenotic appearance. In a few cases a typical doming of the cusps could be observed. Tricuspid incompetence on Doppler investigation was considered significant only when the registrations displayed a pansystolic backward flow into the right atrium on both continuous and pulsed-wave Doppler images. Right atrial enlargement was present in 53% and right ventricular enlargement in 30% of patients. The right ventricle was grossly increased in size in 13% of the patients and 26% had signs of severe right-sided heart disease as judged from the presence of paradoxical systolic septal motion, i.e., systolic concentrations in the direction of the right ventricle. Right ventricular wall thickness was increased in 19%. In 20 patients in whom visual inspection of the pulmonic valve was possible, four (20%) displayed reduced motion amplitude and/or thickened cusps. The lack of simultaneous two-dimensional and Doppler images resulted in a very low number of accurate registrations of pulmonary flow and therefore these were not subjected to further analysis. The ultrasound cardiac investigation of the right heart was considered normal in 34% of the patients.

To classify the patients with respect to the degree of right heart disease three subgroups were formed. Individuals in whom results concerning the right heart (n = 23) were normal constituted group I. The patients with gross disease of the tricuspid valve, increased right atrial and ventricular size, and paradoxical septal contractions were considered to have advanced right-sided heart disease. These 18 patients formed group III. The remaining 27 patients, who demonstrated tricuspid valve abnormalities and/or increased size of the right atrium and/or ventricle, formed group II.

ECG examination of the left heart showed minor abnormalities in 34% of the patients (table 2). The majority of these abnormalities consisted of slight sclerosis or the thickening of the aortic cusps found in 18 of 67 patients (27%). Six patients displayed a left atrial diameter exceeding 40 mm, the upper normal limit for our laboratory, and eight patients had lower than normal left ventricular systolic function, i.e., fractional shortening below 0.28. The presence of left-sided abnormalities was less common (p<.001) in group III (table 2).

ECG examination exposed the presence of 34 abnormalities in 26 patients, including atrial fibrillation (n = 2), ectopic atrial rhythm (n = 1), fré-

| TABLE 1 |
|-----------------|---------|---------|
| **Frequency of abnormalities of the right heart on ultrasound investigation of 68 consecutive patients with malignant midgut carcinoid tumors** | | |
| Tricuspid valve abnormalities | 60% | 38/63 |
| Thickness increased | 48% | 30/62 |
| Motion decreased | 30% | 18/61 |
| Incompetence by Doppler | 83% | 19/23 |
| Right atrial enlargement | 53% | 32/60 |
| Right ventricular enlargement | 30% | 20/67 |
| Massive enlargement | 13% | 9/67 |
| Right ventricular wall thickness increased | 19% | 12/63 |
| Paradoxical septal motion | 26% | 18/67 |
| Any right-sided pathologic finding | 66% | 45/68 |
| Normal | 34% | 23/68 |

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TABLE 2
Frequency of left heart abnormalities on ultrasound investigation related to the degree of right heart disease in 68 patients with malignant carcinoid tumors

<table>
<thead>
<tr>
<th>Heart disease group</th>
<th>All patients</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve sclerosis</td>
<td>27% 18/67</td>
<td>27% 6/22</td>
<td>31% 8/26</td>
<td>22% 4/18</td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>9% 6/67</td>
<td>4% 1/23</td>
<td>19% 5/27</td>
<td>0 0/17</td>
</tr>
<tr>
<td>LV function decreased</td>
<td>13% 8/64</td>
<td>18% 4/22</td>
<td>12% 3/26</td>
<td>6% 1/16</td>
</tr>
<tr>
<td>Any left-sided abnormality</td>
<td>34% 23/68</td>
<td>35% 8/23</td>
<td>41% 11/27</td>
<td>22% 4/18</td>
</tr>
</tbody>
</table>

LV = left ventricular.

quent ventricular extrasystoles (n = 1), atrioventricular block I (n = 3), intraventricular conduction disturbances (n = 8), abnormal electrical axis deviation (n = 3), left ventricular myocardial infarction (n = 1), high voltage (n = 2), and nonspecific abnormal T waves in left precordial leads.\textsuperscript{13} Seventy-one percent of the patients in group III had some kind of electrocardiographic abnormality, while the corresponding figures in the groups I and II were 23% and 30%, respectively. Patients in group III showed a higher frequency of electrical axis deviation and conduction disturbances than those in groups I and II. The axis deviation and the conduction abnormalities in group III were, however, not uniform. There was no relationship between the left heart findings and any distinct electrocardiographic abnormality.

The urinary 5-HIAA excretion was pathologically increased in 61 patients (89%) and the median value was 363 \( \mu \text{mol}/24 \text{ hr} \) (range 30 to 2700). Group III had significantly higher (p<.001) urinary 5-HIAA excretion than group I or II (figure 1). Plasma NPK was found elevated in 58 of the patients (85%), median concentration 34 pmol/liter (range 8 to 222). The plasma levels of NPK were significantly higher in group III than in groups I (p<.01) and II (p<.001). Median plasma SP was 25 pmol/l in the patient material (range

![FIGURE 1. Urinary 5-HIAA excretion and plasma concentrations of NPK and SP in patients with malignant carcinoid tumors grouped with respect to degree of heart disease. Median levels are indicated with a horizontal bar. The heart disease groups (I, II, III) are defined in the text.](http://circ.ahajournals.org/)

266 CIRCULATION
12 to 1050) and was higher than normal in 68% (18/56). Group III displayed significant higher (p<.01) median concentration than did group I or II. There were no significant differences between groups I and II in any of the three biochemical variables.

Patients with left heart abnormalities had higher median urinary 5-HIAA excretion and serum NPK levels than patients with normal left hearts on ultrasound investigation. The values did not differ statistically, however. Plasma SP levels were similar in patients with and without left-sided abnormalities.

Flush was present in 88% of the patients and the median duration of flush at the time of investigation was 3.0 years. No significant differences in the presence or duration of flushing was found in patients with and without cardiac abnormalities of the right heart (table 3). Liver metastases were found in 91% of the patients and the majority had multiple metastases as demonstrated in table 3. The proportion of patients with metastases in the three groups did not differ statistically, although the patients with advanced right heart disease were all found to have liver metastases.

**Discussion**

Failure of the right heart is a serious complication to malignant carcinoid tumors.1, 2, 12, 13, 16 By means of a prospective cardiac ultrasound investigation performed in patients with malignant carcinoid disease, we found lesions of the right heart in 66%. The echocardiographic abnormalities observed, which are exemplified in figure 2, were similar to those previously described,3-6, 27-29 and included tricuspid valve aberrations, dilatation of the right heart cavities, and abnormal motion of the interventricular septum. In a smaller number of patients investigated by means of Doppler ultrasound, a significant tricuspid incompetence was evident with still higher frequency (83%). The development of more sensitive investigational methods has led to the realization that cardiac lesions are probably present more often in patients with malignant carcinoid tumors than previously believed.1-6

Malignant midgut (jejunum, ileum and proximal colon) carcinoid tumors release vasoactive substances such as serotonin, histamine, bradykinin, kallikrein, prostaglandins, and tachykinins.30-34 Some of these have been suggested as possible etiologic agents for the carcinoid heart disease. This study of 68 well-characterized patients with malignant midgut carcinoid tumors reveals a significantly higher urinary 5-HIAA excretion in patients with severe carcinoid heart disease than in those without or with a lesser degree of right heart abnormalities. The mean plasma concentrations of NPK and SP were also found to be significantly higher in this group of patients. These results indicate that vasoactive substances like serotonin, NPK, and SP might be involved in the development of carcinoid cardiac lesions. Tachykinins such as SP and neurokinin A are known to stimulate fibroblast proliferation in vitro.35 The increased fibrosis in patients with carcinoid heart disease thus might be the result of continuous exposure of the right heart valves and endocardium to tachykinins. Patients with cardiac involvement also had more severe tumor disease with multiple liver metastases and a higher urinary excretion of 5-HIAA compared with those with a smaller total tumor mass. The duration of carcinoid symptoms did not seem to be related to the development of heart lesions, indicating that a long duration of disease in itself does not explain the frequency of cardiac involvement.

Carcinoid lesions localized to the left heart have been demonstrated in a small number of patients in the absence of a cardiac shunt or in the presence of a bronchial carcinoid.2 Aortic valve sclerosis is nonspecific and the frequency with which it is found in patients with carcinoid heart disease is almost that expected in healthy individuals of the same age. The fact that the frequency of left heart abnormalities found in our patients with carcinoid tumors was significantly lower

<table>
<thead>
<tr>
<th>TABLE 3</th>
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<td>Median duration of symptoms and flush and the number of liver metastases related to the degree of right heart disease in 68 patients with carcinoid tumors</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart disease group</th>
<th>All patients</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms (years)</td>
<td>5.0 (2.8-7.2)</td>
<td>5.0 (2.0-6.5)</td>
<td>5.0 (2.0-7.5)</td>
<td>5.0 (3.3-8.8)</td>
</tr>
<tr>
<td>Duration of flush (years)</td>
<td>3.0 (1-5)</td>
<td>3.0 (1.8-5.3)</td>
<td>1.5 (0.9-5.3)</td>
<td>4.0 (1.0-5.0)</td>
</tr>
<tr>
<td>Presence of flush</td>
<td>85% 58/68</td>
<td>87% 20/23</td>
<td>77% 21/27</td>
<td>94% 17/18</td>
</tr>
<tr>
<td>Liver metastases not found</td>
<td>9% 6/68</td>
<td>17% 4/23</td>
<td>7% 2/27</td>
<td>0</td>
</tr>
<tr>
<td>Solitary liver metastases</td>
<td>22% 15/68</td>
<td>26% 6/23</td>
<td>26% 7/27</td>
<td>11% 2/18</td>
</tr>
<tr>
<td>Multiple liver metastases</td>
<td>69% 47/68</td>
<td>57% 13/23</td>
<td>67% 18/27</td>
<td>89% 16/18</td>
</tr>
</tbody>
</table>

The interquartile ranges are given in parentheses.
FIGURE 2. Echocardiographic apical four-chamber view of a patient with carcinoid heart disease. 

Top. Diastolic frame. 

Bottom. Systolic frame. Note prominent enlargement of right heart cavities and pronounced immobility of tricuspid valve leaflets as compared with the mitral leaflets. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.
in patients with severe right-sided lesions combined with a lack of signs of cardiac shunting rather contradiacts the suggestion that left heart lesions are related to carcinoid disease, although this possibility cannot be excluded in a minority of patients. The electrocardiographic changes in these patients were nonspecific and did not seem to be related to the presence of carcinoid heart disease.

In conclusion, right heart disease seems to present more often than previously reported in patients with malignant midgut carcinoid tumors. The severity of cardiac involvement does not seem to be related to the duration of carcinoid disease or to the extent of liver metastases. The correlation we observed between the degree of carcinoid heart disease and levels of circulating vasoactive substances suggests an etiologic relationship.

References
Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities.
L Lundin, I Norheim, J Landelius, K Oberg and E Theodorsson-Norheim

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