Carcinoid Heart Disease

Successful Repair of the Valvular Lesions under Cardiopulmonary Bypass

By Julian M. Aboesty, M.D., James A. DeWeese, M.D., Marvin J. Hoffman, M.D., and Paul N. Yu, M.D.

The carcinoid tumor is a slow growing malignant lesion capable of distant metastases. Frequently, patients afflicted with this tumor develop a pathognomonic fibrosis of valves and endocardium involving primarily the right side of the heart. Although only 50% of the patients with metastatic disease survive for 3 years, these patients usually succumb from intractable congestive heart failure. Recently, a patient was seen at the University of Rochester Medical Center with severe congestive heart failure due to carcinoid heart disease. This patient experienced dramatic improvement following corrective open-heart surgery of both tricuspid and pulmonic valves. To the best of our knowledge, this represents the first patient with carcinoid heart disease successfully treated by surgery.

Report of Case

I.G. (SMH no. 52-54-07), a 50-year-old, white man had been in excellent health until 1950 (at age 35) when he began to note episodes of crampy abdominal pain. Five years later at laparotomy performed for intermittent intestinal obstruction, he was found to have a malignant carcinoid in the terminal ileum with involvement of the regional lymph nodes but no evidence of hepatic metastases. The tumor was resected without difficulty. Immediately following surgery, the patient noted episodic diarrhea and facial flushing. In 1958, a grade-III/VI ejection systolic murmur was heard at the second left sternal border. Over the ensuing 4 years, he became progressively incapacitated with exertional dyspnea, ankle edema, and fatigue. Cardiomegaly was found on a routine chest roentgenogram. In February 1963 cardiac catheterization was performed. The findings were consistent with moderately severe pulmonic and tricuspid stenosis, mild tricuspid insufficiency, and systemic hypertension with a low cardiac output (table 1).

Gradually, progressive cardiomegaly, hepatic enlargement, ankle edema, ascites, distended neck veins, and exertional dyspnea developed. These were initially treated with diuretics with only minimal amelioration. In January 1965 the patient had an episode of atrial flutter but the heart reverted to sinus rhythm after treatment with digitalis. At this time there was a marked increase in ascites and he was given 6.0 g of 5-fluorouracil intravenously over a 2-week period. Paracenteses were performed five times over the following 6-week period. After two of the paracenteses, thio-tepa was instilled into the peritoneal cavity (total dose 90 mg), and the patient received 15 mg of thio-tepa per day for 4 days. Cytological examination was made on each of the five samples of ascitic fluid, and all were negative for malignant cells. However, the ascitic fluid reaccumulated rapidly. In order to determine whether or not the ascites was primarily cardiac in origin, the patient was readmitted for repeat cardiac catheterization in April 1965.

Physical examination at this time revealed a chronically and acutely ill, wasted, white male with violaceous colored cheeks. The blood pressure was 135/85, and the pulse was regular at 75 per minute. The jugular veins were markedly distended with a prominent v wave. The lungs were clear to percussion and auscultation, but the diaphragm was high and moved poorly with respiration. A moderately prominent parasternal lift and a mild apical thrust were present. There was a systolic thrill at the left upper sternal border. The left border of cardiac dullness was percussed at the anterior axillary line. The first heart sound and aortic second sound were much diminished, and the pulmonic second sound was absent. Four murmurs were present: a grade-
Table 1

Hemodynamic Changes

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th></th>
<th>Postoperative</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of blood flow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.1</td>
<td>1.6</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Arteriovenous O₂-difference (ml/L)</td>
<td>69</td>
<td>83</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Pressures (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrium (a/v, m)</td>
<td>20/24, 17</td>
<td>23/35, 21</td>
<td>12/12, 10</td>
<td></td>
</tr>
<tr>
<td>Right ventricle (S/D)</td>
<td>46/8</td>
<td>70/11</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery (S/D, m)</td>
<td>15/9, 12</td>
<td>22/10, 14</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pulmonary wedge (m)</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Left atrium (m)</td>
<td></td>
<td>6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Systemic artery (S/D, m)</td>
<td>105/100</td>
<td>120</td>
<td>125/87, 100</td>
<td>125/75, 95</td>
</tr>
<tr>
<td>Resistances (dyne·cm·sec⁻³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total systemic</td>
<td>2540</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total pulmonary</td>
<td>254</td>
<td>386</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular</td>
<td>60</td>
<td>140</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Calculated valve area (cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonic</td>
<td>0.6</td>
<td>0.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tricuspid*</td>
<td>1.3</td>
<td>1.0</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: a = a wave, v = v wave, S = systolic, D = diastolic, m = mean.

Because of the presence of tricuspid regurgitation, there may be significant errors in this calculation.

IV/VI, ejection systolic murmur at the left upper sternal border extending to the left infraclavicular area; a grade-IV/VI, regurgitant systolic murmur at the left lower sternal border that increased in intensity with inspiration; an apical and left para-sternal, long, low-pitched, rumbling, diastolic murmur that was accentuated with inspiration; and a short, low pitched, early, diastolic murmur along the left sternal border in the third interspace. There was marked ascites as well as 3+ pitting edema of the legs. A firm, nontender, pulsating liver was palpable 5 cm below the right costal margin, and the spleen was felt 0.5 cm below the left costal margin.

Laboratory Data

A complete blood count was normal. Urinalysis was negative except for 1+ albuminuria, and the stool was negative for occult blood. The values for blood urea nitrogen, creatinine, sodium, potassium, chloride, CO₂, calcium, phosphorus and fasting blood glucose were all within normal limits. Total serum protein was 7.0 g%, with an albumin of 3.5 g%. The alkaline phosphatase measured 9 Bodansky units, and serum glutamic oxaloacetic transaminase (SGOT) 25 Karmen units. The prothrombin time was 80% of normal, icteric index 7, and sulfobromophthalein (BSP) retention 36% at 45 minutes. The serum uric acid was 9.3 mg%. The protein in the ascitic fluid was 3.4 g%. A 24-hour specimen of urine contained 100 mg of 5-hydroxyindole acetic acid. The persistent electrocardiographic changes included low voltage, first degree heart block, and poor R wave progression from leads V₁ through V₃ (fig. 1). There was marked cardiomegaly with clear lung fields by roentgenogram (fig. 2A). Results of an upper gastrointestinal series, including examination of the small intestine, was entirely within normal limits. Cardiac catheterization and angiocardiography were performed. These studies demonstrated progression of the patient's cardiac disease with markedly reduced cardiac output and aggravation of pulmonary stenosis and tricuspid regurgitation (table 1, figs. 3 and 4).

Since the patient's major disability seemed to be cardiac in origin, it was decided to repair his valvular lesions under cardiopulmonary bypass. On May 19, 1965, open-heart surgery was performed. The heart was exposed through a median sternotomy and longitudinal incision of the pericardium. The right atrium was hypertrophied, markedly dilated, and tense. A Kay-Cross rotating disk oxygenator was used for cardiopulmonary bypass, with a constant flow of 3900 cc per minute (60 cc/kg/min) and a perfusion pressure of about 90 mm Hg. The patient was cooled to 31°C.

The markedly deformed pulmonic valve was exposed through a longitudinal incision in the pulmonary artery. There was fusion of all three commissures, leaving an orifice of approximately 1.5 cm in diameter. The valve cusps appeared thickened by a moderately firm white material.
CARCINOID HEART DISEASE

Serial electrocardiograms: In 1955 and 1960, the tracings were normal. By 1963, however, there was diminution of the T wave in leads I, aVf, and V4 through V6. In 1965 there was low voltage in the standard leads and inversion of the T waves in leads V1 through V4. No R wave was demonstrable in leads V1 through V6 and first degree heart block was observed. Postoperatively, a complete right bundle-branch block pattern appeared.

A longitudinal incision was made in the right atrium. The right atrial wall was markedly thickened and there appeared to be an inner layer of a white, moderately firm material. This material completely covered the septal and inferior leaflets of the tricuspid valve, the thickened chordae tendineae and papillary muscles, resulting in immobile inferior and septal leaflets of the tricuspid valve and marked tricuspid regurgitation (fig. 5B). The anterior leaflet was slightly immobile but was also covered with this thick layer of white fibrotic material. The anterior and posterior papillary muscles were divided and all three valve leaflets were excised, leaving a margin of approximately 5 mm. A number 3 Starr-Edwards mitral ball valve prosthesis* was sutured into place. The right atriotomy was closed in the usual manner and cardiopulmonary bypass was discontinued after a period of 1 hour and 55 minutes. An elective tracheostomy was performed at the end of this procedure. The patient had an uneventful post-

*Manufactured by Edwards Laboratories, Inc., Santa Ana, California.
operative course, and he was placed on long-term anticoagulant therapy.

Over the 6-month period since cardiac surgery, the patient experienced a marked improvement in exertional dyspnea and fatigue and has returned to work. However, there has been no change in the frequency of his flushing attacks. At the time of this writing, the patient has normal venous pressure with a normal jugular venous pulse. The lungs are clear to percussion and aus-

Figure 2

Standard posteroanterior chest roentgenograms taken in 1965. (A) Prior to operation (B) Three months after operation.

Figure 3

Simultaneous recording of the right atrial and right ventricular pressures during preoperative cardiac catheterization in 1965. There were prominent $a$ and $v$ waves in the right atrial pressure tracing and a diastolic pressure gradient of 10 mm Hg across the tricuspid valve.

Figure 4

Intravenous angiocardiogram following the preoperative cardiac catheterization in 1965. The patient was supine and rotated 45° in the left posterior oblique position. Contrast media (75% sodium diatrizoate) was injected through a catheter in the right atrium. The marked thickening of both tricuspid and pulmonic valves is indicated by the arrows.

Circulation, Volume XXXIV, July 1966
CARCINOID HEART DISEASE

9.8 mg%. The 24-hour urinary excretion of 5-hydroxyindole acetic acid is 90 mg.

Limited right heart catheterization was performed on August 2, 1965, and only slightly elevated right atrial pressure and slightly reduced cardiac output were found (table 1).

Discussion

The pathognomonic cardiac lesion of carcinoid syndrome is an unusual fibrotic plaquing on the pulmonary valve, tricuspid valve, and the endocardium of the right heart. Approximately one third of the patients with carcinoid heart disease have lesions on the left side of the heart, but usually these are not hemodynamically significant unless the primary tumor arises from a bronchus. Usually, plaque formation in the right atrium is more severe than that in the right ventricle. These fibrous plaques are laid down on normal endocardium and valve tissue and result in a rigid, immobile valve with constriction of the valve ring. Hemodynamically, this results in predominant tricuspid regurgitation and pulmonic stenosis with associated tricuspid stenosis and pulmonic regurgitation.

The clinical diagnosis of valvular lesions in these patients may be difficult since dependent edema and ascites may be due to metastatic lesions in the liver. Nevertheless, the occurrence of distended neck veins with prominent a or v waves, pulmonic and tricuspid valvular murmurs, hepatomegaly with or without pulsation, ascites, and a marked increase in dependent edema should alert the physician to a careful search for carcinoid heart disease.

Although cardiac failure is the leading cause of death in patients with the carcinoid syndrome, cardiac decompensation has been observed occasionally in these patients without evidence of significant valvular, myocardial, or coronary artery disease at subsequent postmortem examination. Even in patients with congestive heart failure, the cardiac lesions often did not seem severe enough to account for the degree of demonstrable cardiac decompensation. Flament has described a patient with carcinoid heart disease who had a loud systolic murmur, radiologic

Figure 5

Artist’s drawings. (A) Appearance of the pulmonic valve at the time of cardiopulmonary bypass. The incision was made in the main pulmonary artery. The valve leaflets were covered with thick white plaques and there was fusion of the commissures. (B) Appearance of the right atrium and tricuspid valve at the time of cardiopulmonary bypass. The incision was made into the right atrium. The leaflets of the tricuspid valve were covered with the white fibrotic material which extends down over the papillary muscles. Circumscribed plaques of this material were also present in the right atrium.
evidence of cardiomegaly, and the manifestations of right-sided congestive heart failure but no valve lesions at autopsy. We believe, therefore, that the evaluation of carcinoid heart disease should include cardiac catheterization and angiocardiography before cardiac surgery is seriously considered.

Surgical repair of the valvular lesions in carcinoid heart disease has been attempted previously in a patient with predominant tricuspid insufficiency and mild pulmonic stenosis. At operation under cardiopulmonary bypass, pulmonary valvotomy and tricuspid annuloplasty were performed. Unfortunately, the patient died in the early postoperative period. Generally, plastic procedures on the tricuspid valve for lesions other than those of carcinoid heart disease have been unsuccessful. Furthermore, because of the nature of this disease, annuloplasty may be followed rapidly by recurrent plaques. It is hoped, however, that the insertion of a valve prosthesis will overcome this difficulty.

Summary
A patient with carcinoid syndrome with both tricuspid and pulmonic valvular lesions has been described. Successful repair of the valvular lesions was performed under cardiopulmonary bypass. The operation consisted of pulmonic valvotomy with the excision of a single pulmonic valve cusp, and replacement of the tricuspid valve by a Starr-Edwards prosthesis. Postoperatively, the patient noted marked improvement in symptomatology, and there was a concomitant improvement in serial hemodynamic studies.

The development of the signs of tricuspid regurgitation and pulmonic stenosis in patients with metastatic carcinoid tumor should alert the physician to the possible presence of carcinoid heart disease. If hemodynamic and angiocardiographic studies confirm the presence of significant valvular lesions, corrective cardiac surgery should be performed in selected patients.

Acknowledgment
The authors wish to express their thanks to the following individuals who assisted in the care and study of this patient: Carl Oshrain, M.D., Bernard F. Schreiner, Jr., M.D., Gerald W. Murphy, M.D., Jules Cohen, M.D., Elliot O. Lipchik, M.D., and Eric A. Schenk, M.D. The authors are also grateful to Mrs. Bonnie Sollie and Miss Sharon Frederick for their secretarial assistance in the preparation of this manuscript.

References
Carcinoid Heart Disease: Successful Repair of the Valvular Lesions under Cardiopulmonary Bypass
JULIAN M. AROESTY, JAMES A. DEWEESE, MARVIN J. HOFFMAN and PAUL N. YU

Circulation. 1966;34:105-110
doi: 10.1161/01.CIR.34.1.105
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/34/1/105

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/