Surgical Management of Left-Sided Carcinoid Heart Disease

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Background—Carcinoid involvement of left-sided heart valves has been reported in patients with a patent foramen ovale, carcinoid tumor of the lung, and active carcinoid syndrome with high levels of serotonin. The present study details the clinical features and surgical management of patients with carcinoid heart disease affecting both left- and right-sided valves.

Methods and Results—Eleven patients (7 men, 4 women) with symptomatic carcinoid heart disease underwent surgery for left- and right-sided valve disease between 1989 and 1999. Mean age was 57 ± 9 years, and median preoperative NYHA class was 3. All patients had metastatic carcinoid tumors and were on somatostatin analog. Of 11 patients, 5 (45%) had a patent foramen ovale; 1 of these also had a primary lung carcinoid tumor. Surgery included tricuspid valve replacement in all patients, pulmonary valve replacement in 3 and valvectomy in 7, mitral valve replacement in 6 and repair in 1, aortic valve replacement in 4 and repair in 2, CABG in 2, and patent foramen ovale closure in 5. One myocardial metastatic carcinoid tumor was removed. There were 2 perioperative deaths. At a mean follow-up of 41 months, 4 additional patients were dead. All but 1 surgical survivor initially improved ≥ 1 functional class. No patient required reoperation.

Conclusions—Carcinoid heart disease may affect left- and right-sided valves and occurred without intracardiac shunting in 55% of this surgical series. Despite metastatic disease that limits longevity, operative survivors had improvement in functional capacity. Cardiac surgery should be considered for select patients with carcinoid heart disease affecting left- and right-sided valves. (Circulation. 2001;104[suppl I]:I-36-I-40.)

Key Words: valves ■ surgery ■ carcinoid

Carcinoid tumors are rare, arising in 1.2 to 2.1 per 100 000 people in the general population per year. In 20% to 30% of patients, the initial presentation occurs as a result of carcinoid syndrome. The malignant carcinoid syndrome consists of flushing, gastrointestinal hypermotility (secretory diarrhea), bronchospasm, and carcinoid heart disease. The syndrome is caused by the release of the vasoactive substances 5-hydroxytryptamine (serotonin), 5-hydroxytryptophan, histamine, bradykinins, tachykinins, and prostaglandins. The diagnosis of carcinoid syndrome is confirmed by elevation of the byproduct of serotonin metabolism, 5-hydroxy indole acetic acid (5-HIAA). The urinary 5-HIAA (24-hour collection) provides a reliable biological marker for the assessment of tumor activity and the response to intervention.

During the past decade, progress in the management of malignant carcinoid tumors and carcinoid syndrome has resulted in better patient survival. The somatostatin analog, octreotide acetate (Sandostatin), is a synthetic octapeptide that binds to subtypes of the somatostatin receptors and inhibits the secretion of bioactive substances that cause the carcinoid syndrome. Treatment with the somatostatin analog relieves symptoms in >70% of patients. Carcinoid heart disease remains a major source of morbidity and mortality for patients with carcinoid syndrome. Typically, carcinoid heart disease involves the tricuspid and pulmonary valves, and patients often present with symptoms of right heart failure. Left-sided valve disease is reported infrequently in patients with carcinoid heart disease. However, in our experience, it may have important hemodynamic consequences that necessitate valve replacement or repair. In the present study, we analyzed the characteristics of surgical patients with carcinoid heart disease affecting both the left- and right-sided valves and describe the outcome of cardiac surgery in this population.

Methods
The protocol for this study was reviewed and approved by the Mayo Clinic Institutional Review Board.

Selection of Patients
From 1989 through 1999, 11 patients underwent surgical treatment of carcinoid heart disease involving both left- and right-sided valves. This group comprised 15% (11 of 75) of the surgical carcinoid patient population who underwent valve surgery at our institution during this interval.
Diagnosis and Surgical Procedures in 11 Patients With Carcinoid Heart Disease Affecting Right- and Left-Sided Valves

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Operation, y</th>
<th>NYHA Class</th>
<th>Carcinoid Diagnosis to Surgery Interval, mo</th>
<th>Diagnosis</th>
<th>Echocardiographic Findings</th>
<th>Catheterization Findings</th>
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TR indicates tricuspid valve regurgitation; MR, mitral valve regurgitation; PS, pulmonary valve stenosis; PR, pulmonary valve regurgitation; EF, ejection fraction; PFO, patent foramen ovale; CAD, coronary artery disease; AR, aortic valve regurgitation; and met, myocardial carcinoid metastasis. Regurgitation scale: grade 0 = none; 1 = mild, 2 = moderate, 3 = moderately severe, 4 = severe.

Because of the known poor prognosis of patients with symptomatic carcinoid heart disease, patients were referred for cardiac surgery if they met the following criteria: (1) systemic carcinoid symptoms well controlled with somatostatin or hepatic dearterialization (embolization or ligation of arterial supply to hepatic metastases), (2) symptoms of right (and/or left) heart failure caused by carcinoid valvular involvement, (3) hemodynamically severe valvular regurgitation, and (4) no other serious concurrent major medical illnesses. Eleven carcinoid patients with left- and right-sided valve disease met these criteria and were referred for valvular surgery (7 men, 4 women; mean age, 57 years; range, 35 to 65 years).

Clinical and Laboratory Findings
The preoperative evaluation included a complete history and physical examination, ECG, chest radiography, and determination of the urinary 5-HIAA levels in all patients. Comprehensive 2D and Doppler echocardiographic examination was performed preoperatively in all patients. Coronary angiography was also performed in all patients. Hemodynamic cardiac catheterization, ventriculography, and aortic root angiography were used selectively to evaluate associated left-sided valve disease (the Table).

Surgical Management
The surgical procedure performed on each patient was individualized and determined by patient characteristics and clinical judgment. Follow-up was obtained in all patients by review of medical records. Perioperative mortality included death within 30 days of surgery or during the same hospitalization. Anesthetic management involved the use of a high-dose narcotic technique with fentanyl (9 patients) or sufentanil (2 patients), together with a volatile inhalational anesthetic, isoflurane (9 patients) or enflurane (2 patients). Invasive hemodynamic monitoring included the use of a pulmonary artery catheter (5 patients) or a central venous catheter (6 patients). Octreotide acetate was used liberally by intravenous administration any time the patient demonstrated a flushing reaction, unexplained hemodynamic lability, or sudden volume loss during the period of cardiopulmonary bypass. In all patients, transesophageal echocardiography was used to evaluate the results of the surgical procedure and to monitor ventricular and valve function.

Pathological Findings
The surgical pathology reports were reviewed to assess the gross and microscopic pathology. Microscopic slides were prepared with hematoxin-eosin, Masson’s trichrome, and Verhoff-van Gieson stains.

Statistical Analysis
Data are expressed as mean±SD. Comparison of group characteristics was performed by Fisher’s t test for nominal data. A value of P<0.05 was considered significant.

Follow-Up Data
Follow-up data were collected from the patients’ records, and survival was calculated from the date of operation.

Results
Clinical and Diagnostic Data
All patients had the carcinoid syndrome with associated symptomatic valvular heart disease, median NYHA class 3 (range, 2 to 4). Ten patients had primary carcinoid disease in the intestine. One patient had primary lung carcinoid. All had hepatic metastases. The mean interval from the diagnosis of carcinoid syndrome to the diagnosis of carcinoid heart disease was 49 months. The interval from diagnosis of carcinoid syndrome to cardiac operation was 64 months (range, 3 to 282 months). All patients were on somatostatin before surgical intervention. The usual initial dose was 150 µg administered subcutaneously every 8 hours or 20 mg Sandostatin LAR administered every 28 days. Increased dosages were administered for breakthrough symptoms or for the development of tachyphylaxis. The mean somatostatin dose at the time of cardiac operation was 664 µg/d (range, 450 to 1500 µg/d) for 8 patients on short-acting therapy. The long-acting (Sandostatin LAR) dose ranged from 20 mg/28 d (2 patients) to 30 mg/28 d (1 patient).

At the time of preoperative diagnostic evaluation, all patients had severe tricuspid regurgitation determined by echocardiography. The mean diastolic tricuspid gradient was 6±2 mm Hg (range, 4 to 10 mm Hg). Pulmonary regurgitation was considered moderate or greater in all patients by echocardiography. The average pulmonary valve peak gradient measured by echocardiography was 16±6 mm Hg (range, 7 to 29 mm Hg); all pulmonary valves appeared to have intrinsic pulmonary stenosis.
Aortic valve regurgitation was noted to be moderate or greater by preoperative or intraoperative echocardiography or aortic root angiography in the 6 patients who underwent aortic valve surgery. There were no cases of aortic stenosis; however, 1 patient had a bicuspid aortic valve with associated regurgitation.

Mitral valve regurgitation was noted to be moderate to severe by preoperative or intraoperative echocardiography or left ventriculography in all 7 patients who underwent mitral valve replacement or repair. No patient had mitral stenosis.

Of the 11 patients, 5 (45%) had a patent foramen ovale detected by preoperative transthoracic or intraoperative transesophageal echocardiography, and intra-atrial communications resulted in bidirectional or right-to-left shunting. One patient with a patent foramen ovale had primary endobronchial carcinoid. In the other 6 patients (55%), surgical exploration confirmed an intact atrial septum.

All patients had urinary 5-HIAA measured before surgery. The mean immediate preoperative 5-HIAA value for the 11 patients was 182±125 mg/24 h (range, 48 to 468 mg/24 h; normal, 0 to 6.0 mg/24 h). The highest preoperative urinary 5-HIAA value for the 11 patients was 258±147 mg/24 h. Carcinoid intervention (hepatic artery ligation or embolization) resulted in a reduction in 5-HIAA in 4 patients preoperatively. The highest mean preoperative 5-HIAA level among 5 patients with a patent foramen ovale was 131±79 versus 328±144 mg/24 h among 6 patients with no patent foramen ovale (P=0.02). Significant coronary artery disease (stenosis ≥50% diameter) was present in 2 patients preoperatively.

**Surgical Management**

The surgical procedures performed for valvular heart disease are shown in the Table. All patients had tricuspid valve replacement because of severe tricuspid valve regurgitation (7 bioprosthetic, 4 mechanical). A pulmonary valve procedure was performed in 10 of the 11 patients for relief of right ventricular outflow tract obstruction and or management of pulmonary valve regurgitation. Pulmonary valvectomy was performed in 7 patients and pulmonary valve replacement in 3 (1 homograft, 1 bioprosthetic, 1 mechanical). The pulmonary valve annulus was enlarged with pericardial patch to relieve annular narrowing in 4 patients. Mitral valve replacement was performed in 6 patients (4 bioprosthetic, 2 mechanical), and 2 patients underwent aortic valve repair. Two patients had all 4 valves replaced. Simultaneous CABG surgery was performed in 2 patients; 1 had undergone prior CABG surgery at another institution. An intramyocardial carcinoid metastasis was removed from 1 patient. The 5 patients with a patent foramen ovale underwent suture closure. The average cardiopulmonary bypass time was 117±36 minutes (range, 72 to 173 minutes).

Large doses of somatostatin were often required in the perioperative and postoperative periods. The average somatostatin dose administered during cardiac surgery among these 11 patients was 3321±3105 μg (range 486 to 10 000 μg).

**Surgical Outcome**

Results of operation are summarized in Figure 2. The 2 perioperative deaths (18%) were due to cardiovascular causes. One death (patient 7, the Table) was due to bradycardia and pacemaker failure, which occurred on postoperative day 7. In this patient, the early postoperative period was complicated by acute renal failure requiring dialysis and hemodynamic instability requiring inotropic support and intra-aortic balloon counterpulsation. The second perioperative death (patient 4, the Table) occurred in a patient who developed bradycardia and hypotension after induction of
anesthesia. After sternotomy, spontaneous ventricular fibrillation required urgent resuscitation and institution of cardiopulmonary bypass. After operation, inotropic support and intra-aortic balloon counterpulsation were necessary, but the patient had persistent low cardiac output syndrome and died of ventricular fibrillation on postoperative day 3.

The preoperative NYHA functional class of the 9 surgical survivors was similar to that of the 2 patients who did not survive surgery at 3 compared with 3.5 respectively. The mean hospital stay among the 9 patients who survived operation was 8.6 days. One patient required permanent pacemaker implantation for persistent postoperative heart block.

Valve Pathology
Pathological examination of the 11 tricuspid valves, 10 pulmonary valves, 6 mitral valves, and 5 aortic valves demonstrated gross thickening but no calcification except for the 1 aortic valve that was congenitally bicuspid. On microscopy, there was carcinoid plaque involving the tricuspid valve leaflets in all patients; in most patients, the tendinous cords and papillary muscles of the tricuspid valve also exhibited carcinoid plaque. All 6 mitral valve specimens showed carcinoid plaque involvement of both the leaflets and the tendinous cords (Figure 3). In addition, 3 showed involvement of the papillary muscles. Carcinoid plaques were identified in all cusps of excised pulmonary and aortic valves, including the bicuspid aortic valve.

Follow-Up Data
Of the 9 surgical survivors, 8 had functional improvement after surgery. One patient (patient 9, the Table) had no functional improvement after valve surgery. Five patients were alive and had a mean follow-up of 41 months (range, 6 months to 9.5 years). Four patients died after hospital dismissal at 4, 22, 25, and 38 months postoperatively (patients 10, 11, 5, and 1; the Table). All late deaths were related to progressive metastatic carcinoid disease. The death at 4 months was due to acute hyperkalemia.

There was substantial improvement in symptoms of patients who survived operation (median NYHA functional class 3 versus 2, $P=0.003$). The decline in functional status in the 3 patients who subsequently died was related to progression of metastatic carcinoid disease. As shown in Figure 4, the preoperative and postoperative functional class of the 5 patients alive at follow-up was significantly improved (NYHA functional class 3 versus 2; $P=0.01$). None of the patients in this series has required reoperation for complications of prosthetic valves.

Discussion
Left-sided valvular pathology occurs in <10% of carcinoid patients with cardiac involvement and is characterized by valve regurgitation rather than valve stenosis. Patients with carcinoid heart disease usually present with symptoms of right-sided heart failure (hepatomegaly, edema, ascites, fatigue, and low cardiac output). Clinical evidence of carcinoid heart disease with NYHA class 3 or 4 symptoms is associated with median survival duration of only 11 months.

The pathological characteristics of carcinoid heart disease include diffuse collections of thick, pearly white plaque that are composed of smooth muscle cells called myofibroblasts. These plaques are deposited on the endocardial surface of the valves on the right side of the heart, resulting in characteristic pathological and echocardiographic features, which include thickening and immobility of the tricuspid valve and pulmonary valve leaflets. Hepatic metastases allow large quantities of tumor products such as serotonin to reach the right side of the heart without being inactivated. The preferential right-sided valve involvement in carcinoid heart disease is likely related to inactivation of the humoral substances by the lung. The mechanism of valve injury in carcinoid heart disease is not completely understood. Circulating serotonin levels are higher among patients with carcinoid heart disease compared...
with carcinoid patients without cardiac involvement. This implies that serotonin contributes to the development of cardiac involvement.\textsuperscript{11,12}

**Present Study**

The present study affirms the clinical benefit of valve replacement and repair among patients with carcinoid heart disease affecting left- and right-sided valves and demonstrates several important points. First, significant left-sided carcinoid heart disease occurred in the absence of atrial communication in more than half of the patients referred to surgery. The patients with left-sided valve disease occurring in the absence of a patent foramen ovale had significantly higher levels of urinary 5-HIAA, suggesting increased disease activity. Second, the perioperative mortality for patients with multivalve disease related to carcinoid syndrome was acceptable. As might be expected, early operative mortality in these patients with multivalvular involvement and advanced metastatic tumor is higher than that expected for the usual patient having valve replacement or repair but is comparable to other series of cardiac surgery in carcinoid heart disease.\textsuperscript{13}

Third, despite the presence of left-sided valve disease, the patients in this series presented primarily with right heart failure. Fourth, prolonged survival and functional improvement were noted in most of the surgical survivors. Two patients in this series survived >10 years after valve replacement. Marked symptomatic improvement was noted in most patients at a mean follow-up of 3.7 years. This is dramatically different than the survival of patients with symptomatic carcinoid heart disease managed medically.\textsuperscript{6} Lastly, either bioprosthetic or mechanical valves may be selected for valve replacement, because reoperation was not required for bioprosthetic valve degeneration in any of the patients included in this small series.

Surgical reports have largely recommended tricuspid valve replacement with a mechanical prosthesis for patients with carcinoid heart disease. This recommendation was based on the assumed damage to the bioprosthetic valve from vasoactive tumor substances but has not been well established.\textsuperscript{14–16} In addition, this recommendation was made before the introduction of synthetic somatostatin and hepatic artery interruption, both of which potentially protect prosthetic valve tissue from the adverse effects of vasoactive peptides by decreasing the carcinoid activity. The choice of prosthetic valve type should be individualized.

The timing of cardiac operation for carcinoid heart disease remains difficult. No definitive guidelines could be established from this small series. Our current practice includes clinical assessment, echocardiography, and functional evaluation by exercise testing to provide objective assessment of the functional status. Patients with carcinoid heart disease currently are referred for cardiac operation when they develop symptoms or ventricular dysfunction, and rarely in anticipation of hepatic surgery.

Preoperative control of carcinoid activity by administration of somatostatin helps the perioperative hemodynamic management of carcinoid patients undergoing surgical procedures. Meticulous anesthetic care is required during cardiac surgery in the management of patients with carcinoid heart disease to prevent a life-threatening carcinoid crisis or to institute early therapy should a crisis occur intraoperatively.\textsuperscript{17} The complexity of intraoperative management has been moderated and the hemodynamic and fluid management have been simplified with the advent of somatostatin therapy.

**Conclusions**

Carcinoid heart disease is an uncommon and complex form of valvular heart disease that may affect left-sided and right-sided valves. Cardiac involvement is a major cause of morbidity and mortality, and cardiac operation is the only definitive treatment. Despite metastatic disease that limits longevity, operative survivors in this series had functional improvement after valve surgery for carcinoid heart disease. Cardiac surgical intervention should be considered for patients with symptomatic carcinoid valvar heart disease.

**References**

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Circulation. 2001;104:I-36-I-40
doi: 10.1161/hc37t1.094898

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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