Improving outcome of valve replacement for carcinoid heart disease

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ABSTRACT

Objective: Carcinoid heart disease is characterized by tricuspid valve regurgitation and varying degrees of pulmonary valve regurgitation or stenosis. Valve replacement procedures may be complicated by systemic effects of carcinoid syndrome, as well as hepatic dysfunction and right heart failure. This study was performed to identify factors that might be associated with improving early mortality rates and late outcomes.

Methods: Between November 1985 and January 2018, 240 adult patients underwent surgery for carcinoid heart disease at the Mayo Clinic. We analyzed the association of multiple clinical and echocardiographic variables on early mortality and late survival.

Results: The median (interquartile range) age of patients was 63 years (55-69), and 117 patients (49%) were male. Before operation, 157 patients (70%) had New York Heart Association class III or IV limitation. Somatostatin analogs were used in 221 patients (92%), and long-acting somatostatins were used in 130 patients (54%). Loop diuretic therapy was used preoperatively in 125 patients (52%). Early mortality rate was 29% (9/22) between 1985 and 1994, but decreased to 7% (6/81) during 1995 to 2004, and to 5% (7/128) from 2005 onward. Overall survival estimates at 1, 3, and 5 years were 69%, 48%, and 34%, respectively. Older age, advanced New York Heart Association class, and a nonlinear effect of creatinine were independently associated with overall mortality.

Conclusions: Valve replacement for carcinoid heart disease has acceptable short-term mortality, and early risk has decreased in the current era. Earlier intervention may improve overall survival. (J Thorac Cardiovasc Surg 2019;158:99-107)

Survival by preoperative NYHA class.

Central Message

Valve surgery for patients with carcinoid heart disease has acceptable operative mortality. Early operation on patients with lower NYHA class may improve short- and long-term outcomes.

Perspective

In patients with carcinoid heart disease and symptoms of right-sided heart failure, valve surgery improves functional outcomes. Early operative mortality has decreased significantly over the last decades, but late survival is limited by carcinoid tumor progression. Reintervention due to carcinoid involvement of bioprostheses is rare.

See Commentary on page 108.

Carcinoid tumors are malignancies of the neuroendocrine system. These tumors secrete high levels of vasoactive substances, including serotonin, and typically arise from

the terminal ileum or appendix. Carcinoid syndrome is characterized by facial flushing, bronchoconstriction, and secretory diarrhea and may occur in patients with invasive carcinoid tumors or metastases. Cardiac involvement (carcinoid heart disease) occurs in approximately 20% to 50% of patients with carcinoid syndrome. Carcinoid heart disease leads to fibrosis and endocardial thickening of the heart valves and is thought to occur as the result of chronic exposure of valve tissue to high levels of serotonin.¹⁻⁴

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Abbreviations and Acronyms

CI	= confidence interval
NYHA	= New York Heart Association
OR	= odds ratio

Patients with carcinoid heart disease typically present with right heart failure and associated right heart enlargement (Figure 1, A) caused by tricuspid and pulmonary valve regurgitation; the tricuspid valve leaflets are thickened and retracted with shortening of subvalvular attachments (Figure 1, B). Carcinoid involvement of the pulmonary valve leads to thickening and retraction of the cusps, and there may be additional scarring and constriction of the pulmonary valve annulus leading to mild stenosis.⁵ In addition, the left-sided heart valves can be affected (<10% of patients).^{6,7} Cardiac involvement dramatically reduces survival of patients with carcinoid syndrome and metastatic disease, and heart failure contributes to poor quality of life in these patients who have limited life expectancy.

In patients with severe tricuspid and pulmonary valve regurgitation and symptoms of heart failure, valve replacement can improve functional capacity and may allow more aggressive treatment of hepatic metastases.^{8,9} However, operation in patients with carcinoid heart disease may be challenging because of systemic effects of carcinoid syndrome, especially those with impaired hepatic function. Careful preoperative planning and intraoperative and postoperative management are particularly important in these patients.¹⁰

Despite these clinical challenges, previous reports from our institution have highlighted the feasibility of surgical valve replacement in patients with carcinoid heart disease.^{8,11} In the present study, we describe our surgical experience with management of carcinoid heart disease and analyzed preoperative factors associated with early (<30 day) mortality. Furthermore, we aimed to describe predictors of long-term mortality in patients with carcinoid heart disease.

MATERIALS AND METHODS**Study Population**

This study was approved by the Mayo Clinic Institutional Review Board. Between November 1985 and January 2018, 240 patients underwent cardiac surgery for carcinoid heart disease. We collected patient data from a prospectively maintained database, which records information on all patients undergoing cardiac surgery at the Mayo Clinic and supplemented this with data obtained by chart review. Follow-up information was collected through questionnaires that are sent to all cardiac surgery patients at 1, 3, 5, 10, 15, and 20 years after operation. Vital status was determined using Accurant (LexisNexis, New York City, NY).

Preoperative Assessment and Operative Planning

All patients included in this study were cared for by a multidisciplinary team with special interest in carcinoid heart disease. Preoperative

assessment included transthoracic echocardiography, and cardiac computed tomography or cardiac magnetic resonance imaging was performed as necessary. All patients underwent assessment of renal and liver function, and coagulation testing before surgery.

Perioperative management of patients with carcinoid heart disease is important to avoid triggering a carcinoid crisis, which is a life-threatening complication that may be exacerbated by general anesthesia and trauma of surgery. A carcinoid crisis is characterized by sudden onset of hypotension (or labile blood pressure), tachycardia, flushing, and bronchoconstriction. To prevent this complication, all patients receive somatostatin analogs preoperatively, which, in current practice, include the long-acting formulation.^{12,13} Patients with very active disease despite outpatient somatostatin therapy are hospitalized preoperatively for intravenous infusion of octreotide (100-200 μ g/h, 12 hours preoperatively). The infusion is continued during and after the procedure. If the patient experiences signs and symptoms suggestive of carcinoid crisis, a 1000 μ g bolus of octreotide is administered with intravenous fluids.⁴

Operative Methods

Almost all patients with carcinoid heart disease have some degree of tricuspid valve regurgitation, and tricuspid valve replacement is performed in the majority of patients.¹⁴ In our earlier experience, the pulmonary valve was frequently excised at the time of tricuspid valve replacement. Although pulmonary valve regurgitation was tolerated well early postoperatively, longitudinal follow-up of patients who had pulmonary valvectomy showed increased risk of progressive right ventricular enlargement.¹⁵ Therefore, it is our practice to replace the pulmonary valve in patients with pulmonary valve regurgitation.

After median sternotomy, we use bicaval cannulation with direct cannulation of the superior vena cava for cardiopulmonary bypass (Video 1). The heart is arrested using cold blood cardioplegia. After snaring the caval cannulas to isolate the right atrium, we make a longitudinal atriotomy and inspect the septum for a defect or patent foramen ovale, which is then closed. Next, the anterior and posterior tricuspid valve leaflets are excised, and the septal leaflet and chordal attachments are left in place. After calibrating the annulus, valve sutures are placed through leaflet tissue remnants in the area of the penetrating bundle of His, and the crossclamp is removed and sinus rhythm restored to allow the heart to beat during the remainder of the procedure.

For pulmonary valve replacement, an incision in the pulmonary artery begins 3 to 4 cm distal to the valve annulus and is carried across the valve onto the right ventricular outflow tract. Remnants of pulmonary valve cusps are excised, and a large oval autologous pericardial patch is sewn to the pulmonary arteriotomy with 4-0 polypropylene suture. The augmented valve annulus is calibrated, and the appropriate size prosthesis is secured with running 3-0 polypropylene suture that anchors the valve to the native annulus posteriorly and to the pericardial patch anteriorly. The remainder of the pericardial patch is then used to close the ventriculotomy.

Postoperative Management

The intravenous octreotide infusion is continued in the early postoperative phase until the patient is stable. Anticoagulation with warfarin is instituted in all patients with a target international normalized ratio of 2.5 (range, 2-3)¹⁶ and is continued for 3 to 6 months for those with biological tissue valves and indefinitely for those receiving mechanical prostheses. Patients should undergo continued surveillance by an experienced cardiology team, with frequent echocardiographic assessment every 3 to 12 months after operation.⁴

Statistical Analysis

Categorical data are presented as frequencies and percentages, and continuous variables are expressed as medians and interquartile range. Unadjusted survival time was estimated by Kaplan-Meier analysis, with differences determined using log-rank test. In the subset of patients with follow-up of 30 days or more, cumulative incidence of reintervention

FIGURE 1. Intraoperative photographs of carcinoid heart disease. A, Enlargement of the right atrium. B, Carcinoid fibrosis of the tricuspid valve. C and D, Carcinoid metastases.

was estimated in a competing risk analysis in which death before reoperation was treated as a competing event. Prespecified preoperative variables were assessed as potential predictors of long-term mortality with multivariable Cox proportional hazards regression. Logistic regression analysis was used to analyze the association of the same factors with early mortality, although the number of 30-day deaths was too small to support a multivariable analysis. In all models, continuous predictors were expanded into multiple terms using restricted cubic splines to allow for nonlinear effects. All statistical analyses were carried out using SAS software (Version 9.4; SAS Institute Inc, Cary, NC).

VIDEO 1. Intraoperative video of a patient with carcinoid heart disease who underwent tricuspid and pulmonary valve replacement. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32526-1/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32526-1/fulltext).

RESULTS

Baseline Characteristics and Preoperative Echocardiography

The baseline characteristics of the study population are shown in Table 1. For these 240 patients, the median (interquartile range) age was 63 years (55-69), and 117 (49%) were male. New York Heart Association (NYHA) class III or IV dyspnea was present in 157 patients (70%). Loop diuretic therapy to control edema was used in 125 patients (52%). Somatostatin analog therapy was used in 221 patients (92%); 108 patients (45%) received short-acting somatostatins, and from 1999 onward, when long-acting somatostatins became available, 130 (72%) of 180 patients had long-acting somatostatin therapy. Markers of renal and hepatic function were normal in most patients.

Preoperative left ventricular ejection fraction was 61% (56-66). Tricuspid valve regurgitation was present in almost all patients, and 231 patients (97%) had severe valve regurgitation on preoperative echocardiography. Severe pulmonary valve regurgitation was seen in 157 patients (66%). Left-sided valves were less commonly affected, and severe regurgitation of the mitral or aortic valve was present in 15 patients (6%) and 17 patients (7%), respectively.

TABLE 1. Baseline characteristics

Variable	Median or n	IQR or percentage
Age (y)	63	(55-69)
Male	117	49%
BMI (kg/m ²)	24	(22-27)
BSA (m ²)	1.8	(1.7-2.0)
Smoker	90	38%
Diabetes	24	10%
NYHA class		
I	7	3%
II	59	26%
III	122	55%
IV	35	16%
Chemotherapy	61	25%
Loop diuretics	125	52%
Dose of loop diuretics (mg)	40	(20-60)
Somatostatin therapy	221	92%
Short-acting somatostatins	108	45%
Long-acting somatostatins	130/180	72%
Creatinine (mg/dL)	1.2	(1.0-1.4)
AST (IU/L)	30	(23-38)
ALP (IU/L)	209	(134-355)
Total bilirubin (mg/dL)	1.0	(0.7-1.5)
INR	1.2	(1.1-1.3)
Year of surgery	2005	(1999-2011)

IQR, Interquartile range; BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; AST, aspartate transaminase; ALP, alkaline phosphatase; INR, international normalized ratio.

Operative Details and Postoperative Complications

As shown in Table 2, tricuspid valve replacement was performed in 237 patients (99%) and bioprosthetic valves were used in 201 patients (85%). Pulmonary valve operation was performed in 202 patients (84%). Operation on left-sided valves was performed in 38 patients (16%), and in 30 of these patients (79%), the mitral or aortic valve dysfunction was due to carcinoid plaque. In these 38 patients with left-sided valve surgery, the atrial septum was intact in 25 (66%). Median crossclamp time was 11 (7-34) minutes.

Among the 26 patients (11%) who underwent concomitant mitral valve operations, prosthetic replacement was performed in 17 patients (65%) who had carcinoid involvement of leaflet tissue. Mitral regurgitation was thought to be due to degenerative etiologies in 9 patients (35%) who had repair. Likewise, 25 patients (10%) required aortic valve intervention, of whom 19 (76%) had valve replacements. Most patients (n = 175; 73%) required double valve surgery, but triple and quadruple valve surgery were performed as necessary in 24 patients (10%) and 9 patients (4%), respectively. At the time of surgery, an atrial septal defect or patent foramen

TABLE 2. Operative details and postoperative complications

Variable	n (%)
Tricuspid valve replacement	237 (99)
Mechanical valve	36 (15)
Tissue valve	201 (85)
Pulmonary valve operation	202 (84)
Excision	59 (29)
Valve replacement	143 (71)
Mitral valve operation	26 (11)
Repair	9 (35)
Replacement	17 (65)
Aortic valve operation	25 (10)
Repair	6 (24)
Replacement	19 (76)
Left-sided operation (mitral or aortic valve)	38 (16)
No. of valves operated on	
Single	32 (13)
Double	175 (73)
Triple	24 (10)
Quadruple	9 (4)
ASD/PFO closure	57 (24)
Tumor excision	6 (3)
Reoperation	27 (11)
Reoperation due to bleeding	18 (8)
Postoperative permanent pacemaker implantation	14 (6)
Early (30-d) mortality	22 (9)

ASD, Atrial septal defect; PFO, patent foramen ovale.

ovale was closed in 57 patients (24%). Cardiac metastases were excised in 6 patients (3%) (Figure 1, C and D).

Early Mortality and Morbidity

Early mortality, defined as death within 30 days of operation, was 9% (22 patients) over the course of the study. Early mortality decreased as time progressed and as operative experience increased (Figure 2). For operations

FIGURE 2. Trend in early operative mortality over study period.

performed in our earlier experience (1985 to 1994), early mortality was 29% (9/22). However, the rate decreased to 7% (6/81) over the next 10 years (1995 to 2004) and to 5% (7/128) from 2005 onward. A more recent year of surgery correlated with older patient age (Spearman's correlation $r_s = 0.20$, $P = .002$) and with lower baseline levels of total bilirubin ($r_s = -0.19$, $P = .004$) and creatinine ($r_s = -0.17$, $P = .01$).

On univariate analysis (Table E1), older age and higher NYHA class were associated with early mortality (odds ratio [OR], 2.31, 95% confidence interval [CI], 1.30-4.11, $P = .008$ and OR, 2.67, 95% CI, 1.31-5.45, $P = .007$, respectively). Use of long-acting somatostatins appeared to have some protective effects on early mortality, although this result was not statistically significant (OR, 0.45; 95% CI, 0.18-1.12; $P = .085$). The number of valves involved and presence of left-sided valve disease did not influence early mortality.

Eighteen patients (8%) had to be taken back to the operating room because of postoperative bleeding. Fourteen patients (6%) required permanent pacemaker insertion for complete heart block ($n = 12$) or sustained sinus bradycardia ($n = 2$).

Late Survival and Functional Outcomes

Figure 3 shows survival over time for the entire study population, with survival estimates at 1, 3, and 5 years of 69%, 48%, and 34%, respectively. Survival was significantly better in patients with lower preoperative NYHA class ($P < .001$). On univariate analysis, older age, higher NYHA class, and a nonlinear effect of creatinine were associated with increased overall mortality. In a multivariable model, these factors remained independently predictive of mortality (Table 3). Use of short- or long-acting somatostatins was not associated with overall mortality. Among the late deaths in which cause was known, 80% died of noncardiac conditions, primarily tumor progression.

Early functional outcomes were assessed at a median follow-up of 0.5 (0.3, 0.9) years after surgery in 107 patients. Subanalysis of these patients showed that preoperative NYHA class III or IV symptoms were present in 64%. Postoperatively, only 15% had NYHA class III limitation with no patients reporting NYHA class IV dyspnea (Figure E1).

During early follow-up, hepatic operation was performed in 21 patients (9%). Eighteen patients had resection of hepatic metastases, and 3 patients had liver transplant.

Cardiac Reintervention

Cardiac reintervention was necessary in 20 patients (8%) (Table E2). Figure 4 shows the cumulative incidence of cardiac valve reintervention in the presence of the competing risk of death. Reasons for reintervention were

FIGURE 3. A, Overall survival curve. B, Survival stratified by preoperative NYHA class. NYHA, New York Heart Association.

native or prosthetic valve dysfunction in 16 patients and pericardiectomy for constrictive pericarditis in 4 patients. Of the 16 late valve interventions, 3 were percutaneous procedures, 1 was balloon dilatation, 1 was insertion of a Melody valve (Medtronic, Minneapolis, Minn) in the pulmonary bioprosthesis, and 1 was insertion of Melody valves in dysfunctional tricuspid and pulmonary valves. Among the patients who underwent late valve operations, 2 developed carcinoid involvement of native mitral or aortic valves. Late prosthetic valve dysfunction was due to carcinoid involvement of the bioprosthesis in 3 patients. All patients with valve thrombosis had tissue bioprostheses implanted at the time of initial surgery.

DISCUSSION

This study updates and expands our surgical experience with carcinoid heart disease over a 33-year period.⁸ Early mortality declined in the 240 patients who underwent surgical valve replacement during this time frame, and

TABLE 3. Predictors of overall mortality on univariate and multivariable analysis

Variable	Comparison [‡]	Univariate analysis		Multivariable analysis	
		HR (95% CI)	P value	Adjusted HR (95% CI) [§]	P value
Age*	69:55	1.37 (1.10-1.69)	.002	1.55 (1.22-1.97)	<.001
Sex	Male:Female	1.22 (0.92-1.63)	.171	1.12 (0.77-1.64)	.548
BMI*	26.5:21.7	0.87 (0.72-1.05)	.305	0.90 (0.71-1.15)	.556
Short-acting somatostatin	Yes:No	1.04 (0.78-1.40)	.774	1.57 (1.00-2.49)	.052
Long-acting somatostatin	Yes:No	1.17 (0.87-1.58)	.305	1.57 (0.97-2.56)	.069
Loop diuretics	Yes:No	1.22 (0.91-1.63)	.177	1.13 (0.80-1.57)	.489
No. of valves operated on [†]	4:1	1.60 (0.77-3.33)	.210	1.06 (0.34-3.38)	.916
Left-sided operation	Yes:No	1.29 (0.88-1.90)	.195	1.52 (0.81-2.85)	.190
NYHA class [†]	III:II	1.48 (1.18-1.85)	.001	1.53 (1.15-2.03)	.004
AST*	37.5:23	0.98 (0.75-1.28)	.185	1.15 (0.84-1.55)	.196
Total bilirubin*	1.5:0.7	1.09 (0.82-1.45)	.833	1.05 (0.76-1.46)	.892
Creatinine*	1.4:1.0	0.98 (0.79-1.22)	<.001	0.81 (0.63-1.06)	.013

HR, Hazard ratio; CI, confidence interval; BMI, body mass index; NYHA, New York Heart Association; AST, aspartate transaminase. *Continuous variables were expanded into multiple terms using restricted cubic splines (using 3 knots) to allow for nonlinear effects and assessed for general association based on a 2 d.f. test. [†]Because of data discreteness, a linear relationship was assumed for numeric variable (1 d.f. test). [‡]Effects of predictor variables were estimated with unadjusted and adjusted hazard ratios (and 95% confidence limits) from univariable and multivariable models, respectively. Unless noted otherwise, continuous variables are reported as interquartile range hazard ratios (comparing the 75th percentile with the 25th percentile of the predictor). Because these variables are modeled nonlinearly, confidence limits of the hazard ratio are not necessarily consistent with general tests of association. That is, inclusion of 1.0 in the interval does not imply nonsignificance, and conversely, it is possible to have intervals excluding 1.0 without having evidence of an overall association. [§]A multivariable Cox regression model was fitted for all-cause mortality on n = 214 who had complete data for predictor variables shown in the table.

risk of perioperative death was associated with older age and more advanced heart failure (higher NYHA class); although not significant, long-acting somatostatins may have some protective effect on early mortality. The study adds important information on durability of valve prostheses in patients with carcinoid heart disease.

In previous reports, operative mortality for valve replacement in patients with carcinoid heart disease has ranged from 18% to 63%, but most of these series were small with fewer than 50 patients.¹⁷ In the present series between 1985 and 1994, early mortality was 29%; this risk decreased to 7% between 1995 and 2004, and has been 5% in the 128 patients undergoing operation since 2005 (Figure 2). Recent studies have reported similar early risks, 5% to 10%.^{18,19} Indeed, in current practice, multiple valve replacement for carcinoid heart disease has an operative risk similar to that for multiple valve disease of other etiologies (8%-13%).²⁰ It is notable that the number of valves replaced was not predictive of mortality in this surgical cohort.

Decreasing early mortality may be due to multiple factors, including refinement in patient selection and improved overall surgical care. These measures, especially improved perioperative management, are difficult to quantify and were not captured in our database.

However, increased early mortality was associated with older age and higher NYHA class at presentation (Table E1), suggesting that patients with carcinoid heart disease may benefit from earlier surgical intervention. Indeed, in our more recent experience, patients with

carcinoid heart disease had less severe symptoms, and this accounts, in part, for better outcome. Some clinicians argue that operation should be performed before onset of significant functional impairment, and Bhattacharyya and colleagues^{3,21} reported NYHA class I or II symptoms in 55% of 22 patients with carcinoid heart disease who underwent cardiac surgery at their institution. Nevertheless, optimal timing of surgery may be difficult to determine in these complex patients whose symptoms occur in combination with gastrointestinal/hepatic impairment. For example, it is often challenging to determine to what degree right heart failure is contributing to functional decline and ascites in a patient with carcinoid syndrome and extensive hepatic metastases.

In our cohort, survival at 3 years was 48%, but was significantly better in patients with NYHA class I or II symptoms preoperatively (Figure 3). Overall survival of our surgical patients compares favorably to medically managed patients with carcinoid heart disease, in whom 3-year survival estimates of 31% have been reported.¹ In most patients, late survival after valve replacement for carcinoid heart disease is limited by tumor progression. Despite limitations of overall survival in patients undergoing valve surgery for carcinoid heart disease, early functional outcomes were excellent (Figure E1). Symptoms from right-sided heart failure were greatly improved in the majority of patients, and enhanced quality of life should be considered in these patients with limited life expectancy.

An important consideration for patients undergoing valve replacement is the choice of valve prosthesis. At the Mayo

FIGURE 4. Cumulative risk of cardiac valve reintervention.

Clinic, we have generally preferred tissue valves for patients with carcinoid heart disease; bioprostheses were implanted in more than 80% of patients. Tissue valves are appropriate for most patients with carcinoid heart disease who have limited life expectancy. Exceptions to this practice include patients who require anticoagulation with warfarin for other reasons or patients with ovarian carcinoid tumors who have a favorable outlook after valve surgery and oophorectomy.²² However, as seen in the present review, tissue bioprostheses were not free of risk from thrombosis; 3 patients required surgical reintervention because of thrombosis of a bioprosthetic valve. Thus, anticoagulation is advised for patients receiving tissue bioprostheses, and we suggest using warfarin for 3 to 6 months for patients in sinus rhythm and indefinitely for those with atrial fibrillation.^{4,23,24}

Recurrent carcinoid fibrosis of bioprostheses is another concern for patients undergoing valve replacement with tissue valves. In our series, this was documented by pathologic examination of valves from 3 patients (Table E2). Carcinoid recurrence seems to be a rare complication, but has been reported by van Rijswijk and colleagues.²⁵ In the present series, carcinoid involvement of bioprostheses occurred between 3 and 8 years after initial surgery, but cause(s) of recurrence could not be ascertained from our data. Two of these 3 patients were treated with somatostatin preoperatively and remained on this medication after surgery; 24-hour urinary 5-hydroxyindoleacetic acid levels were elevated before reoperation in 1 of these patients. The other patient had no systemic symptoms from his metastatic carcinoid tumor and did not receive somatostatin therapy preoperatively or postoperatively. It is important to note that valve thrombosis and carcinoid recurrence occurred only in patients who received tissue bioprostheses, and thus mechanical heart valves may be appropriate for some patients, such as young patients in whom further surgical treatment of primary or metastatic tumor is not planned.⁹

In the present series, left-sided heart valves were replaced or repaired in 16% of patients. However, presence of

left-sided disease did not appear to be associated with intracardiac shunts because 66% of these patients had an intact atrial septum. This result is consistent with those reported by Connolly and colleagues,⁶ who observed left-sided heart disease without shunts in 55% of their study population. Furthermore, presence of left-sided heart disease was not associated with early or overall mortality in our cohort. In our experience, surgery in patients with associated aortic or mitral valve regurgitation is safe and should be performed if clinically indicated.

Study Limitations

This is a retrospective study from a single center and may be influenced by referral bias. These surgical results also reflect the importance of an experienced team specializing in carcinoid heart disease and may not be replicable at other institutions.

CONCLUSIONS

Operation on patients with carcinoid valvular disease leads to excellent improvement in symptoms during early follow-up and has acceptable short-term mortality and complication rates. Early mortality has improved in recent experience, but overall survival is limited by tumor progression. Bioprostheses are appropriate for most patients because structural valve deterioration due to carcinoid involvement is rare.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: carcinoid heart disease, tricuspid valve, surgery

Discussion

Dr Anita Nguyen (Rochester, Minn). Good morning. My name is Anita Nguyen, and I'm a research fellow at Mayo Clinic. Today I am presenting our study on improving outcomes of valve replacement for patients with carcinoid heart disease. We have no disclosures, but would like to acknowledge the very generous support of the Paul and Ruby Tsai family.

Carcinoid heart disease occurs in patients with carcinoid tumors, which are neuroendocrine malignancies secreting high levels of serotonin. This affects 20% to 50% of patients with carcinoid syndrome and can cause symptoms of right-sided heart failure and fibrosis, mainly affecting the tricuspid and pulmonary valves. In patients with right-sided heart failure symptoms, surgical valve replacement may be indicated. At the Mayo Clinic, we have operated on 240 patients with carcinoid heart disease over a 33-year period. The median age of patients was 63 years, and approximately half of our patients were male. Preoperatively, approximately 75% were in NYHA class III or IV.

Loop diuretic therapy was necessary in approximately half of our patients, and the majority of patients required somatostatin analogue therapy. Hepatic metastases are common in patients with carcinoid heart disease, but despite this, our patients had normal renal and liver function. This table shows the operative details. The majority of patients underwent tricuspid valve replacement, and 84% had tissue valves. Left-sided heart valves are less commonly affected by carcinoid heart disease, and 16% required operation on the aortic or mitral valve. Concomitant atrial septal defect or patent foramen ovale closure was necessary in 24% of patients. We excised cardiac tumors, which were a rare complication of carcinoid heart disease in 6 patients.

After surgery, early mortality, which we defined as death within 30 days of operation, occurred in 9% of patients. Before 2000, our early operative mortality was 17%, and after 2000, this decreased to 6%. On univariate analysis, higher NYHA class and older age was predictive of early mortality. Higher aspartate transaminase levels, which are associated with liver dysfunction, were somewhat predictive. This graph shows the overall survival of our study population. Of note, most of the late deaths occurred as the result of tumor progression. We grouped our patients by NYHA class and noticed that patients with NYHA class 1 or 2 had significantly better survival.

We then conducted univariate and multivariable analyses and noticed that older age and higher NYHA class were independently predictive of overall mortality. These graphs show the association between log relative hazard and age and NYHA class. The association was linear for both age and NYHA, which means that the higher the age or the higher the NYHA class, the higher the risk of overall mortality. Twenty patients required cardiac reintervention, and 16 patients required valve reintervention at a mean follow-up of 6 years. Only 3 patients required valve reintervention because of recurrence of carcinoid heart disease, and pericardiectomy for constrictive pericarditis was necessary in 4 patients. This graph shows patients alive without reintervention in dark blue and the cumulative incidence of reintervention in light blue. We assessed functional outcomes at 1 year in 107 patients and noticed that preoperatively, more than 65% were in NYHA class 3 or 4, and

postoperatively, this number decreased to less than 15%.

Patients with carcinoid heart disease who undergo valve surgery have improved early mortality, late survival is limited by tumor progression, the majority of patients experience symptomatic improvement, carcinoid involvement of bioprosthesis is rare, and earlier operation may decrease operative mortality and increase overall survival.

Questioner. Can you tell us how many patients still had tumor burden after the surgery and whether they ever received complete resection of the primary?

Dr Nguyen. The primary indication for performing the surgery was that most patients already had hepatic metastases at presentation, and we operated on the valves in view of future resection of the metastases, but it's rare for patients who are disease free to be completely disease free. This is only something that occurs with certain types of carcinoid tumors, such as ovarian cancers.

Questioner. What is your valve of choice, and if it's a bioprosthesis, is there any special novel therapy that you're doing to try to prevent carcinoid to involve a bioprosthetic valve?

Dr Nguyen. The valve of choice in this series was a bioprosthesis, and 84% of patients had a bioprosthesis. There is nothing specific that we can recommend to decrease the risk of carcinoid heart involvement in the future; however, the risk in this series was small, 3 of 240 patients.

Questioner. When you compare your historical mortality, that is pre-2000, it is 17% versus 6%. What other things did you change and do you think that might reflect just better management of the right ventricle? As I reflect upon this, I would have to assume that age and NYHA class are robust risk factor predictors, but perhaps it was better management of right ventricular dysfunction perioperatively that led to the better results. Is this true?

Dr Nguyen. Yes, we tried to ascertain the causes of the decrease in early mortality, and it was difficult for us to really pinpoint what exactly was causing the decrease in early mortality. We think it's a combination of better patient selection and improvement in general management of carcinoid heart disease with newer medical therapies.

Dr Joseph Cleveland (*Aurora, Colo.*)

Are you using valve-in-valve transcatheter aortic valve replacement technology to salvage some of the recurrent disease in the right-sided heart valves?

Dr Nguyen. We performed 2 percutaneous right-sided reinterventions.

Dr Cleveland. Hartzell?

Dr Hartzell Schaff (*Rochester, Minn.*)

Just to clarify a point that Anita made about the treatment of patients afterward with bioprosthesis. We don't know for certain but would advise continued use of somatostatins that might have an influence on reducing the risk of carcinoid development on the bioprosthesis.

The perioperative deaths are not related necessarily to right heart failure, and in fact, that's an uncommon cause of death. Most of the deaths are due to hepatic and renal failure, and liver function tests don't really predict who's going to have hepatic insufficiency after operation, so that's a challenge. Your last question had to do with how many of these patients were disease free. All of the patients had hepatic metastases except for 2 or 3 patients who had ovarian carcinoid tumors, who have serotonin going directly into the heart. So all of the patients had metastatic disease at the time we operated on them and afterward.

FIGURE E1. Functional outcomes of 107 patients at median follow-up of 0.5 (0.3-0.9) years. *NYHA*, New York Heart Association.

TABLE E1. Predictors of early mortality on univariate analysis

Variable	Comparison [‡]	OR (95% CI)	P value
Age*	69:25	2.31 (1.30-4.11)	.008
Sex	Male:Female	0.86 (0.36-2.08)	.746
BMI*	26.5:21.7	1.04 (0.60-1.78)	.826
Short-acting somatostatins	Yes:No	1.87 (0.77-4.56)	.169
Long-acting somatostatins	Yes:No	0.45 (0.18-1.12)	.085
Loop diuretics	Yes:No	1.69 (0.68-4.18)	.259
No. of valves operated on [†]	1-level increase	1.01 (0.50-2.05)	.976
Left-sided operation	Yes:No	0.83 (0.23-2.94)	.767
NYHA class [†]	1-level increase	2.67 (1.31-5.45)	.007
AST*	38:23	1.87 (1.06-3.30)	.067
Total bilirubin*	1.5:0.7	1.15 (0.47-2.80)	.559
Creatinine*	1.4:1.0	1.14 (0.58-2.25)	.906

OR, Odds ratio; CI, confidence interval; BMI, body mass index; NYHA, New York Heart Association; AST, aspartate transaminase. *Continuous variables were expanded into multiple terms using restricted cubic splines (using 3 knots) to allow for nonlinear effects, and assessed for general association based on a 2 d.f. test. [†]Because of data discreteness, a linear relationship was assumed for the numeric variable (1 d.f. test). [‡]Effects are estimated as unadjusted ORs (and 95% CIs) from univariable logistic regression models. Unless noted otherwise, continuous variables are reported as IQR ORs (comparing the 75th percentile with the 25th percentile of the predictor). Because these variables are modeled nonlinearly, CIs of the ORs will not be entirely consistent with general tests of association, unlike the case with linear effects. That is, inclusion of 1.0 in the interval does not imply nonsignificance, and conversely, it is possible to have intervals excluding 1.0 without having evidence of a significant association.

TABLE E2. Details of cardiac valve reintervention

Patient	Year of initial surgery	Time to reintervention (y)	Initial procedure on the valve requiring reintervention	Reintervention procedure	Additional details
1	1992	0.9	Pulmonary homograft	Percutaneous balloon dilatation of pulmonary valve	Pulmonary artery rupture after percutaneous procedure
2	1994	2.6	Tricuspid bioprosthesis	Tricuspid valve replacement	Carcinoid recurrence of tricuspid bioprosthesis
3	1995	0.5	Tricuspid and pulmonary bioprostheses	Tricuspid and pulmonary valve replacement	Thrombosis of both bioprostheses
4	1996	0.9	Tricuspid bioprosthesis, pulmonary homograft	Tricuspid and pulmonary valve replacement	Tricuspid valve thrombosis, pulmonary homograft stenosis
5	1997	14.5	Native mitral valve, tricuspid mechanical prosthesis	Mitral and tricuspid valve replacement	Mitral valve stenosis (late carcinoid involvement)
6	1997	12.7	Pulmonary valvectomy	Pulmonary valve replacement	Severe pulmonary valve regurgitation (s/p valvectomy)
7	1997	5.0	Native aortic valve, pulmonary valvectomy	Aortic and pulmonary valve replacement	Aortic valve regurgitation (late carcinoid involvement), severe pulmonary valve regurgitation (s/p valvectomy)
8	1997	13.6	Tricuspid bioprosthesis, pulmonary valvectomy	Tricuspid and pulmonary valve replacement	Thrombosis of tricuspid bioprosthesis, severe pulmonary valve regurgitation (s/p valvectomy)
9	2001	8.6	Tricuspid and pulmonary bioprostheses	Tricuspid and pulmonary valve replacement	Carcinoid recurrence of both bioprostheses
10	2001	7.8	Tricuspid and pulmonary bioprostheses	Tricuspid and pulmonary valve replacement	Carcinoid recurrence of both bioprostheses
11	2002	10.2	Tricuspid and pulmonary bioprostheses	Tricuspid and pulmonary valve replacement	Unknown etiology, reintervention at outside hospital
12	2004	8.2	Pulmonary bioprosthesis	Percutaneous pulmonary valve replacement	Severe pulmonary valve regurgitation
13	2004	4.0	Tricuspid bioprosthesis	Tricuspid valve replacement	Thrombosis of tricuspid bioprosthesis
14	2007	5.7	Tricuspid and pulmonary bioprostheses	Percutaneous tricuspid and pulmonary valve replacement	Severe tricuspid and pulmonary valve regurgitation
15	2009	1.9	Tricuspid bioprosthesis	Tricuspid valve replacement	Pannus overgrowth of tricuspid bioprosthesis cusps
16	2015	2.0	Tricuspid and pulmonary bioprostheses	Tricuspid and pulmonary valve replacement	Structural valve deterioration due to infective endocarditis