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ORIGINAL ARTICLE

Carcinoid heart disease: outcomes after surgical valve replacement

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Abstract

OBJECTIVES: To describe the early and late outcomes of carcinoid patients undergoing surgical heart valve replacement.

METHODS: In a retrospective study, records of patients with symptomatic carcinoid heart disease referred for valve surgery between 1993 and 2010 at two academic centres were reviewed. The perioperative and postoperative outcomes were analysed.

RESULTS: Nineteen patients, with a mean age of 56 ± 9.6 years, underwent cardiac surgery for carcinoid syndrome. Sixteen patients underwent implantation of one or more mechanical bileaflet valve prosthesis and three patients had one or more bioprosthetic valves implanted. Survival after 1 and 5 years was 71 and 43%, respectively. Six out of nine survivors were at last follow-up in New York Heart Association class I. Valve-related events such as valve thrombosis or bleeding complications were not registered. Echocardiography showed improvement of right ventricular dilatation in 80% of patients.

CONCLUSIONS: Despite advanced cardiac morbidity at the time of operation, early postoperative survival was 90%. Long-term survival of patients with carcinoid heart disease undergoing valve replacement is determined by carcinoid progression. The surviving patients had a persistent improvement in functional capacity without valve-related complications of the mechanical prosthesis.

Keywords: Carcinoid syndrome • Carcinoid heart disease • Survival • Valve surgery • Valvular disease

INTRODUCTION

Carcinoid syndrome is a rare disorder, with an incidence of 1–2 per 100 000 people. The appendix and the terminal ileum are the most common sites for the primary carcinoid tumour [1–4]. These neuroendocrine tumours derived from enterochromaffin cells in the gastrointestinal tract produce vasoactive substances, including serotonin, which is the most prominent one [1–7]. The tumour products released in the portal circulation are inactivated by the liver. However, when liver metastases occur, these vasoactive substances can reach the right side of the heart without being inactivated by the first-pass metabolism in the liver and carcinoid heart disease might evolve [1, 8, 9]. Forty percent of patients with the carcinoid syndrome develop carcinoid heart disease, in different grades of severity. Twenty percent of these patients present with carcinoid heart disease as the primary symptom of metastatic carcinoids [10]. Characteristic for this type of heart disease are plaque deposits. Endocardial thickening due to these plaques leads to retraction and fixation of the valves especially on the right side of the heart, which is predominantly involved. The left side of the heart is rarely affected (<10%), due to inactivation of the vasoactive substances by the lungs [1, 6, 8, 9, 11–13].

The major cause of morbidity and mortality in patients with carcinoid syndrome is heart disease [4, 8, 12, 14, 15]. This typically results in progressive dysfunction of the tricuspid valve and pulmonary valve as well as right-sided heart failure [8, 14–17]. At the time when right heart failure symptoms emerge, the expected survival decreases dramatically. The 5-year survival rate of patients without cardiac involvement ranges from 70 to 80% for all carcinoid tumours [18]. Surgical valve replacement is the only effective treatment for carcinoid heart disease [6, 14, 16, 19]. The long-term outcome of valve surgery has seldom been reported. In addition to the perioperative risk, the risk of thromboembolic complications in mechanical valves in tricuspid and pulmonic positions may be elevated. The possibility of the right heart to recover or remain restrained by the plaque deposits is also unknown.

The purpose of this study was to present the early and late outcomes of valve surgery in patients with carcinoid heart disease in our specialized centres and to assess the prognostic factors. In addition, the incidence of complications including thromboembolic events and bleeding events and bleeding complications regarding the carcinoid tumour was assessed.

METHODS

All patients undergoing surgical valve replacement at the Erasmus University Medical Centre, Rotterdam, and at the University Medical Centre, Utrecht, The Netherlands, with symptomatic carcinoid heart disease between 1993 and 2010 were included in this study.

Clinical characteristics

Demographic data, laboratory measurements, electrocardiography (ECG), echocardiography and details of surgery and the prosthetic type were obtained from the chart.

Electrocardiography

For each patient, preoperative ECG was analysed. Micro-voltage was defined as QRS amplitude <5 mm in the limb leads and <10 mm in the precordial leads.

Echocardiography

Cardiac carcinoid involvement was identified by the presence of characteristic thickened, immobile valves in the absence of other aetiologies.

Surgical management

The operation was performed on extracorporeal circulation with moderate hypothermia and under cardioplegic arrest. The tricuspid valve prosthesis was inserted with everting u-stitches on Teflon felt without resection of the fibrous deformed valve. In some cases, the anterior leaflet had to be incised to accommodate a sufficiently large prosthesis. In 12 patients, the pulmonary valve was replaced by prosthesis after a longitudinal incision in the pulmonary artery, through the stenosed annulus into the right ventricular outflow tract. The defect was closed with an autologous pericardial patch relieving the pulmonary valve stenosis and allowing implantation of valve prosthesis of sufficient size for the body surface area. The valve was implanted with a running suture. The valves used were St. Jude® bileaflet mechanical valves and Perimount Bio valves.

Data collection

Follow-up information was obtained from the hospital electronic medical record system. Mortality was determined by chart review and by enquiry of the national death registry. Last follow-up was obtained in 2010.

Statistical analysis

The average preoperative and 1-year postoperative results of ECG, echocardiography, laboratory and New York Heart Association (NYHA) class were compared using the Student's paired *t*-test and Wilcoxon signed rank test, respectively. For all tests, a two-sided *P*-value of <0.05 was considered significant. Statistical software SPSS for Windows version 17 (SPSS, Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Patient characteristics

Nineteen patients (eight males) with a mean age of 56 ± 9.6 years were included. Carcinoid heart disease as well as liver metastases were present in all patients, and the mean preoperative NYHA class was III (±0.3). Patient characteristics at baseline and at operation are shown in Table 1. The mean interval from diagnosis of carcinoid syndrome to heart valve replacement was 2.2 ± 1.8 years. The preoperative ECG and echocardiography results are shown in Tables 2 and 3, respectively. All patients were in sinus rhythm preoperatively. Severe valvular dysfunction with symptomatic right heart failure was the indication for surgery in all patients.

Congestive heart failure was present in 17 of the patients before surgery. Patients with carcinoid syndrome were treated with radioactive-labelled lutetium octreotate.

Perioperative outcomes

Of the 19 patients, 14 underwent tricuspid and pulmonic valve replacement. In four patients, only the tricuspid valve was replaced and in one patient both the tricuspid and aortic valve were replaced. Only one patient had involvement of the aortic valve and there were no other patients with left-sided heart

Table 1: Baseline clinical characteristics of carcinoid heart disease patients before and at the time of operation[a]

Variable	Value
Male (%)	42
Age at diagnosis of carcinoid syndrome (years)	53 ± 11 (21–70)
NYHA class	3 ± 0.32 (2–3)
Body mass index (kg/m^2)	23 ± 3.0 (18–28)
5-HIAA (μmol/24 h)	953 ± 547 (250–2649)
Creatinine (μmol/l)	93 ± 15 (71–125)
Age at operation (years)	56 ± 9.6 (28–73)
Length of hospital stay (days)	17 ± 11 (10–59)
St. Jude (%)	
PVR and TVR	68
TVR	11
TVR and AVR	5
Perimount Bio (%)	
PVR and TVR	5
TVR	11

NYHA: New York Heart Association; 5-HIAA: 5-hydroxyindolacetic acid; PVR: pulmonic valve replacement; TVR: tricuspid valve replacement.
[a]Data are presented as mean ± standard deviation (range) unless stated otherwise.

Table 2: ECG findings of carcinoid heart disease patients at baseline[a]

Variable	Value
Axis	
Normal (%)	16
Intermediate (%)	47
Right (%)	21
Left (%)	11
Extreme (%)	5
QRS duration (ms)	99 ± 21 (74–160)
Morphology	
Normal (%)	47
Right bundle branch block (%)	11
Right atrium overload (%)	22
Intraventricular conduction delay, right atrium overload (%)	5
First-degree atrioventricular block (%)	5
First-degree atrioventricular block, right atrium overload (%)	5
Left and right atrium overload, left bundle branch block (%)	5
QRS duration (ms)	
Heart rate (beats/minute)	77 ± 17 (52–111)
Micro-voltages (%)	61

[a]Data are presented as mean ± standard deviation (range) unless stated otherwise.

Table 3: Echocardiography findings of carcinoid heart disease patients before surgery[a]

Variable	Value
LVED (mm)	41 ± 6.5 (28–54)
LVES (mm)	27 ± 6.5 (18–42)
LVFS (%)	33 ± 8.6 (22–49)
La (mm)	35 ± 8.2 (24–50)
Peak velocity (m/s)	
TV	1.2 ± 0.54 (0.7–2.5)
PV	1.8 ± 0.60 (1.0–2.7)
Regurgitation (m/s)	
TV	
Velocity	2.3 ± 0.71 (0.7–3.4)
Grade	4 ± 0.60 (2–4)
PV	
Velocity	1.7 ± 0.32 (1.2–2.1)
Grade	3 ± 0.83 (1–4)
Dilatation (%)	
Right atrium and right ventricle	79
Right atrium	5
Right ventricle	5
Absent	11
RVF (%)	
Normal	46
Mildly impaired	39
Moderately impaired	15

LVED: left ventricular end-diastolic volume; LVES: left ventricular end-systolic volume; LVFS: left ventricular fractional shortening; La: left atrium; TV: tricuspid valve; PV: pulmonic valve; RVF: right ventricular function.
[a]Data are presented as mean ± standard deviation (range) unless stated otherwise.

involvement. All patients underwent coronary angiography before valve surgery. No significant coronary artery disease was discovered, except in one patient. All patients were treated with intravenous octreotide preoperatively to prevent carcinoid crisis. One perioperative death occurred due to postoperative infection with *Enterococcus faecalis*, leading to sepsis. A concomitant procedure during the valve surgery was performed in five patients: one coronary artery bypass graft surgery, two atrial septal defect or open foramen ovale and two right ventricular outflow tract reconstructions. One other patient required a resternotomy for cardiac tamponade. The mean postoperative length of hospital stay was 17 days (±11.3). All patients were treated with therapeutic anticoagulant therapy after operation.

Follow-up

Of the 18 hospital survivals, 9 died after a mean follow-up of 2.3 ± 2.3 years. Fig. 1 shows the Kaplan–Meier survival curve. The cause of death was progression of carcinoid syndrome in six and a combination of both carcinoid syndrome and cardiac involvement in one patient. The remaining two patients died suddenly, 0.3 and 4.4 years after valve replacement and no additional information on cause of death could be obtained. No autopsy was performed. During follow-up, cardioversion was necessary in three patients for atrial fibrillation or atrial tachycardia. Five patients needed an abdominal procedure for carcinoid disease. No thromboembolic events or bleeding complications occurred in our study population.

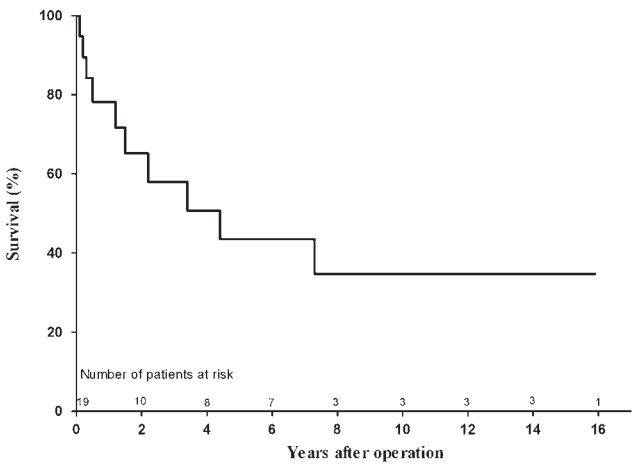

Figure 1: Kaplan–Meier survival curve of patients with carcinoid syndrome undergoing valve replacement.

Follow-up 1 year after the operation

Twelve patients were alive 1 year after the operation. Results are presented in Table 4. Functional capacity improved significantly from NYHA class III preoperatively to I, at 1 year follow-up (Fig. 2). Congestive heart failure improved significantly after valve surgery ($P = 0.001$).

Table 4: Comparison of preoperative and postoperative results in patients with carcinoid heart disease undergoing valve replacement

Variable	Preoperative	1–3 years postoperative	*P*-value (paired *t*-test)	*P*-value (Wilcoxon signed rank test)
NYHA class[a] (*n* = 12)	3 (2–3)	1 (1–2)	–	0.002
Laboratory[b] (*n* = 11)				
5-HIAA (μmol/24 h)	1050 ± 618	894 ± 712	0.2	–
ECG[b]				
QRS duration (*n* = 12) (ms)	99 ± 25	114 ± 31	0.1	–
Echocardiography[b]				
LVED (*n* = 8) (mm)	41 ± 6.9	45 ± 4.8	0.08	–
LVES (*n* = 3) (mm)	20 ± 2.1	32 ± 4.4	0.09	–
LVFS (*n* = 3) (%)	39 ± 7.9	26 ± 7.5	0.06	–
La (*n* = 6) (mm)	37 ± 5.5	39 ± 5.6	0.4	–
Peak velocity TV (*n* = 6) (m/s)	1.3 ± 0.43	1.1 ± 0.15	0.5	–
Peak velocity PV (*n* = 6) (m/s)	2.2 ± 0.37	1.4 ± 0.52	0.04	

5-HIAA: 5-hydroxyindolacetic acid; LVED: left ventricular end-diastolic volume; LVES: left ventricular end-systolic volume; LVFS: left ventricular fractional shortening; La: left atrium; TV: tricuspid valve; PV: pulmonic valve.
[a]Data are presented as median (range).
[b]Data are presented as mean ± standard deviation.

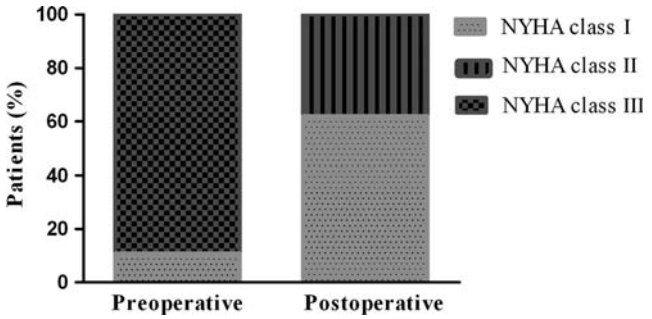

Figure 2: NYHA functional class preoperatively and at 1 year after surgery for carcinoid heart disease.

Long-term follow-up after the operation

Nine patients were still alive at the time of data analysis after a mean follow-up of 6.3 ± 6.1 years (Table 5 and Fig. 1). Although not significant, the mean preoperative 5-hydroxyindolacetic acid (5-HIAA) was lower in the patients who were still alive compared with patients who died (800 and 1204 μmol/24 h, respectively). All patients were in sinus rhythm. All patients reported improvement in functional capacity after valve surgery, and the median NYHA class at last follow-up was I. Echocardiography showed improvement of right ventricular dilatation in 80% of patients. We could not identify any prognostic factor for survival.

DISCUSSION

The development of carcinoid heart disease results in reduced survival and significant morbidity [4, 7, 11, 13, 16, 18, 20]. The perioperative mortality increases as advanced clinical heart failure develops [1, 4, 7, 10, 21, 22]. Progressive heart failure is thereby the most important cause of death, instead of the carcinoid syndrome itself [7, 9, 14, 20]. In this study, we show low perioperative mortality after cardiac surgery for carcinoid heart disease and a significant improvement in functional capacity after valve replacement. We found a survival rate of 71 and 43% at 1 year and 5 years, respectively, with one patient still alive 16 years after surgery. A clear improvement in clinical condition and an improvement of right ventricular dilatation towards a normal right ventricular size were found. To determine whether a patient with carcinoid heart syndrome will benefit from cardiac surgery remains an individual decision and depends on the clinical condition, but as soon as right heart failure symptoms are emerging, the negative sequence of events need to be interrupted by decisive surgical intervention. Although most of our patients were severely ill, in NYHA class III and with symptoms of right heart failure, our results show a 90% early postoperative survival.

Most of our patients underwent implantation of one or two mechanical valve prosthesis (*n* = 16) and only three patients received bioprosthetic valves. A mechanical valve is reported to be favourable compared with bioprosthetic valve replacement because of possible damage by the carcinoid process with premature degeneration, but this is still not certain [1, 4, 8–10, 14, 16, 23].

We did not register any complications regarding both types of valve prosthesis. The follow-up period after implantation of bioprosthetic valves may be too short to reveal valve degeneration. Until the end of the follow-up, no thromboembolic events were encountered in the 17 patients with one or two right-sided mechanical St. Jude prosthesis after valve surgery in 76.2 patient years. This finding may be important for other patient groups who need valve surgery at the right side of the heart, such as patients with tetralogy of Fallot or pulmonary regurgitation.

The serotonin level is higher among patients with carcinoid heart disease compared with patients without cardiac involvement and a peak level of 5-HIAA has also been found as a significant predictor of progressive carcinoid heart disease [4, 8, 9, 11, 13, 15, 24, 25]. In our study, no preoperative risk factor could be detected, especially the weight of the patient, urinary 5-HIAA

Table 5: Results before valve replacement and at last follow-up of patients still alive[a]

Variable	Before valve replacement	After a mean follow-up of 6.3 years
NYHA class	3 ± 0.33 (2–3)	1 ± 0.50 (1–2)
5-HIAA (μmol/24 h)	800 ± 358 (250–1455)	786 ± 489 (27–1511)
Creatinine (μmol/l)	97 ± 18 (73–125)	82 ± 24 (45–133)
ECG		
QRS duration (ms)	102 ± 25 (80–160)	117 ± 28 (83–175)
QRS morphology (%)		
Normal	56	44
RBBB	11	56
IVCD, Ra overload	11	–
Ra overload	22	–
Heart rate (beats/minute)	74 ± 13.8 (56–96)	76 ± 10.4 (57–86)
Echocardiography (%)		
Right atrium and ventricular dilatation	78	22
Right atrium dilatation	11	11
Right ventricular dilatation	11	–
Absence of dilatation	–	67
LVED (mm)	38 ± 6.82 (28–48)	42 ± 6.84 (32–52)
LVES (mm)	26 ± 5.82 (18–35)	30 ± 4.07 (24–36)
LVFS (%)	31 ± 4.89 (22–36)	29 ± 11.3 (14–44)
Left atrium (mm)	30 ± 5.52 (24–41)	33 ± 7.37 (20–44)
Peak velocity TV (m/s)	1.0 ± 0.44 (0.7–1.5)	1.2 ± 0.30 (07–1.6)
Peak velocity PV (m/s)	2.0 ± 0.68 (1.0–2.7)	2.2 ± 0.80 (1.3–3.4)
RVF (%)		
Normal	25	44
Mildly impaired	50	44
Moderately impaired	25	–
Severely impaired	–	12

NYHA: New York Heart Association; 5-HIAA: 5-hydroxyindolacetic acid; RBBB: right bundle branch block; IVCD: intraventricular conduction delay; Ra: right atrium; LVED: left ventricular end-diastolic volume; LVES: left ventricular end-systolic volume; LVFS: left ventricular fractional shortening; La: left atrium; Tapse: tricuspid annulus excursion; TV: tricuspid valve; PV: pulmonic valve; RVF: right ventricular function.
[a]Data are presented as mean ± standard deviation (range) unless stated otherwise.

secretion, ECG or echo parameters were not helpful. Although the mean preoperative 5-HIAA was higher among patients who deceased after surgery compared with patients who were still alive (1204 and 800 μmol/24 h, respectively), no significant association could be found. Tumour progression and the carcinoid syndrome itself were the main causes of mortality during follow-up.

In conclusion, our results indicate that although carcinoid syndrome is a progressive disease, valve surgery is possible with low early postoperative mortality, with survival benefit and with functional improvement on the long-term.

Conflict of interest: none declared.

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