Valvular Heart Disease

Prognosis of Carcinoid Heart Disease
Analysis of 200 Cases Over Two Decades

Jacob E. Møller, MD, PhD; Patricia A. Pellikka, MD; Alain M. Bernheim, MD; Hartzell V. Schaff, MD; Joseph Rubin, MD; Heidi M. Connolly, MD

Background—The long-term prognosis of patients who develop carcinoid heart disease and the effect of cardiac surgery on outcome are not well established.

Methods and Results—In this retrospective study, we identified 200 patients with carcinoid syndrome referred for echocardiography in whom the diagnosis of carcinoid heart disease was confirmed. Patients were divided into 3 groups of similar size according to the date from first diagnosis of carcinoid heart disease. Group A comprised patients diagnosed from 1981 through June 1989; group B, diagnosed July 1989 through May 1995; and group C, June 1995 through 2000. The end point was all-cause mortality. Median survival was significantly lower in group A (1.5 years, 95% CI 1.1 to 1.9 years) compared with groups B (3.2, 95% CI 1.3 to 5.1 years) and C (4.4, 95% CI 2.4 to 7.1 years; \(P=0.009\)). In a multivariate model adjusted for treatment and clinical characteristics, the risk of death in groups B (hazard ratio 0.67, 95% CI 0.46 to 0.99, \(P=0.04\)) and C (hazard ratio 0.61, 95% CI 0.39 to 0.92, \(P=0.006\)) was significantly reduced relative to group A. Cardiac surgery was performed in 87 patients. When cardiac surgery was included as a time-dependent covariate in a multivariate analysis, it was associated with a risk reduction of 0.48 (95% CI 0.31 to 0.73, \(P<0.001\)), whereas the time period of diagnosis was no longer significant.

Conclusions—The prognosis of patients with recognized carcinoid heart disease has improved over the past 2 decades at our institution. This change in survival may be related to valve replacement surgery. (Circulation. 2005;112:3320-3327.)

Key Words: carcinoid • echocardiography • prognosis • surgery • valves

Carcinoid tumors are uncommon malignancies that arise from enterochromaffin cells typically located in the gastrointestinal tract or lungs.1 At the time of diagnosis, 20% to 30% of patients have disseminated disease and present with carcinoid syndrome, characterized by cutaneous vaso¬motor flushing, secretory diarrhea, and bronchospasm.1,2 The syndrome is caused by tumor release of serotonin and other vasoactive substances. In 50% to 60% of these patients with carcinoid syndrome, cardiac lesions of some degree may be found. Classically, fibrous plaque—like endocardial thickening causes retraction and fixation of the right-sided heart valves, often leading to severe right heart failure.3-6

Data on survival of patients with carcinoid heart disease have been somewhat conflicting; median survival rates of patients in reported series vary from less than 1 year to more than 4 years.6,8-9 Furthermore, most of these data include patients diagnosed and treated between 1980 and 1990. Since 1990, somatostatin analogues, hepatic artery dearterialization, and more recently, heart valve replacement have been used widely. The importance of this for the outcome of patients with carcinoid heart disease is incompletely understood. The purpose of the present study is to describe the prognosis of patients with metastatic carcinoid disease and echocardiographic evidence of carcinoid heart disease seen at Mayo Clinic during the past 2 decades.

Methods

Patient Selection

The study was approved by the Institutional Review Board. From 1981 to 2000, 270 patients with metastatic carcinoid and carcinoid syndrome were referred for echocardiographic evaluation at Mayo Clinic, Rochester, Minn. Diagnosis of metastatic carcinoid disease was based on review of outside records, pathology specimens, thoracoabdominal computed tomography, and increased levels of 5-hydroxyindole acetic acid (5-HIAA) in a 24-hour urine sample. Echocardiograms were clinically indicated owing to symptoms or physical findings of valvular heart disease or preoperative assessment before partial hepatectomy. In 200 patients, the diagnosis of carcinoid heart disease was confirmed by echocardiography; these patients were included in the study. The cohort was divided into 3 groups of equal size according to the date of first diagnosis of carcinoid heart disease. Group A comprised patients in whom the diagnosis of carcinoid heart disease was made from 1981 through June 1989 (n=66); group B included patients in whom the initial diagnosis was made from July 1989 through May 1995 (n=67); and group C included patients in whom the initial diagnosis was made from June 1995 through May 2000 (n=67).

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from June 1995 through 2000 (n=67). Demographic data, management of carcinoid syndrome, and New York Heart Association (NYHA) functional class were obtained by review of medical charts. NYHA class was recorded at time of first diagnosis of carcinoid heart disease and immediately before cardiac surgery. Among the patients included in the study, 2 had been taking a serotonin reuptake inhibitor, and 1 patient had been taking ergot alkaloid. None of the patients had taken fenfluramine, phentermine, or pergolide.

**Echocardiography**

2D and Doppler echocardiography was performed with standard techniques and equipment. All studies were performed by experienced sonographers and reviewed by staff cardiologists with advanced training in echocardiography.

The diagnosis of carcinoid heart disease was based on presence of characteristic thickening, reduced mobility and/or retraction of tricuspid and pulmonary valves leading to dysfunction of the involved valves, or the presence of myocardial metastases. Right ventricular size, systolic function, and right atrial size were assessed visually and graded semiquantitatively on the basis of 2D images obtained in 3 planes. Tricuspid valve regurgitation was also assessed semiquantitatively on the basis of visual interpretation of size of regurgitant jet with color-flow and Doppler recordings of transtricuspid inflow and hepatic vein flow. Pulmonary valve regurgitation was graded semiquantitatively on the basis of the width and size of regurgitant jet determined by color Doppler and from Doppler recordings of right ventricular outflow. From continuous-wave Doppler recordings across the tricuspid valve, the peak tricuspid regurgitant velocity and mean inflow gradient were measured. From recordings of right ventricular outflow, the peak antegrade velocity across the pulmonary valve was measured.

**Biochemical Tests**

All patients had multiple 24-hour urine samples quantitatively analyzed for 5-HIAA. For this study, the highest value before or at the time of diagnosis of carcinoid heart disease and the value immediately before cardiac surgery were recorded.

**Follow-Up**

Vital status was assessed from chart review and through the Social Security Agency Death Index (April 2004). The primary end point was death due to all causes.

**Statistical Analyses**

Continuous data are represented by medians with 25th and 75th percentiles unless otherwise specified. Rank sum tests were used for comparisons of continuous variables with the Mann-Whitney test for comparison of 2 independent groups and the Kruskal-Wallis test for comparison of 3 independent groups. Categorical variables were compared with the χ² test.

Survival was calculated by the product-limit method and was plotted according to the Kaplan-Meier method. Comparisons of death rates between subgroups were tested with the log-rank test. Observation time was calculated from first diagnosis of carcinoid heart disease to death or censoring (April 2004). To assess changes in mortality during the 3 time periods, multivariate Cox proportional hazards analysis was performed. First, an analysis with group A as the reference group (hazard ratio =1.0) relative to the 2 other groups with adjustment for clinical characteristics and treatment at diagnosis of carcinoid heart disease was performed (model 1). Then, cardiac surgery was included in this model (model 2). Because the assumptions of proportional hazard were not valid for cardiac surgery (P=0.01), cardiac surgery was entered as a time-dependent covariate. A probability value of less than 0.05 was considered significant.

SPSS version 10.0 (SPSS Inc) was used for calculations.

**Results**

Clinical characteristics, 5-HIAA level, and management of carcinoid syndrome at diagnosis of carcinoid heart disease are shown in Table 1. Carcinoid heart disease was diagnosed 1.5 years (0.3 to 4.6 years) after diagnosis of carcinoid disease in group A. This was not different in the other groups (group B 1.1 years [0.2 to 3.8 years]; group C 1.4 years [0.3 to 5.9 years]; P=0.63). There were no significant differences in age, gender, or primary tumor site between groups (Table 1). Patients with a diagnosis of carcinoid heart disease during the most recent period were characterized by lower peak 5-HIAA and greater use of treatment with somatostatin and hepatic artery embolization than among patients from the other 2 time periods (Table 1).

Echocardiography (Table 2) demonstrated characteristic carcinoid involvement of right-sided valves (Figure 1) in 199 patients. Among 87 surgically treated patients, pathology specimens confirmed the presence of carcinoid plaque, with gross thickening in all resected valves. Involvement of the tricuspid valve alone was reported in 33 patients (16%). Myocardial metastasis without valvular involvement was seen in 1 patient. There were no differences in severity of tricuspid valve disease at first echocardiography between groups. Pulmonary valve disease was more frequent in group C (Table 2). Although most patients had symptoms of heart failure at diagnosis, moderate or severe tricuspid valve regurgitation was present in 23 patients (11%) with no fatigue or dyspnea on exertion (NYHA class I).

**Management of Carcinoid Syndrome and Carcinoid Heart Disease**

Somatostatin analogues were used infrequently in patients diagnosed in the first period, whereas the majority of patients in the remaining time periods were treated with somatostatin analogues (Table 1). Hepatic artery ligation was used more frequently in the early groups, whereas hepatic artery embolization was preferred in the most recent group (Table 1). Cytotoxic chemotherapy was used more often in group A than in groups B and C (Table 1).

Cardiac surgery with replacement of dysfunctional valves was performed 5 months (1 to 19 months) after first diagnosis of carcinoid heart disease in 87 patients (Table 3). Patients who underwent surgery had more advanced valvular dysfunction than medically treated patients. The percentage of patients who underwent surgery increased over the 3 time periods (Table 4). In group A, 12 patients (18%) underwent surgery. This increased to 32 patients (48%) in group B and 43 patients (64%) in group C (P<0.001). Although most patients were severely symptomatic, 1 patient in group A, 3 in group B, and 11 in group C were only mildly symptomatic (NYHA class II) at time of surgery (P=0.03). All of those patients had severe tricuspid and pulmonary valve dysfunction and right ventricular volume overload.

**Outcome**

In the entire population, 149 patients died during follow-up, and the median survival was 2.6 years (95% CI 1.6 to 3.2 years) from first diagnosis of carcinoid heart disease and 5.9 years (95% CI 5.0 to 6.8 years) from first diagnosis of metastatic carcinoid disease. Median survival was significantly lower in group A (1.5 years, 95% CI 1.1 to 1.9 year; 62 deaths) than in groups B (3.2 years, 95% CI 1.3 to 5.0 years;
In a multivariate model adjusted for treatment and clinical characteristics (model 1), the risk of death in groups B (hazard ratio 0.67, 95% CI 0.46 to 0.99, \( P = 0.04 \)) and C (hazard ratio 0.61, 95% CI 0.39 to 0.92, \( P = 0.006 \)) was significantly reduced relative to group A (Table 5). In this model, age, NYHA class III or IV, moderate or severe right ventricular dilation, and excessive excretion of 5-HIAA were predictors of death. Figure 3 shows Kaplan-Meier survival estimates in patients divided according to NYHA class and right ventricular size stratified for cardiac surgery.

Among the 87 patients in whom valve replacement was performed, median survival from first diagnosis of carcinoid heart disease was 4.8 years (3.8 to 5.7 years). Early postoperative mortality after surgical intervention (death within 30 days of surgery) among all patients was 16% (95% CI 8% to 24%). Postoperative mortality was 25% in group A (3 patients), 22% (7 patients) in group B, and 9% (4 patients) in group C (\( P = 0.22 \)). In patients who died within the first 30 postoperative days, 5-HIAA immediately before surgery was higher than in patients who survived the early postoperative period (median 250 [161–270] mg/24 h versus 147 [78–241] mg/24 h, \( P = 0.03 \)). However, preoperative NYHA class, age, preoperative management (use of somatostatin, hepatic dearterializations), and frequency of performance of a pulmonary valve procedure were not different among those who died or survived the early postoperative period (all \( P > 0.20 \)). Among patients in NYHA class II who underwent surgery, no early postoperative deaths were seen, and median survival was 5.2 (5.3 to 6.7) years. Pulmonary valve replacement was done in 23 patients, with a median survival of 2.8 (1.6 to 4.8) years in group B and 6.0 (2.9 to 11.0) years in group C. In a multivariate analysis that included cardiac surgery as a time-dependent covariate, performance of cardiac surgery was found to be associated with a significantly improved outcome (hazard ratio 0.44, 95% CI 0.29 to 0.61, \( P = 0.001 \); Table 5). When cardiac surgery was included in the model, the time period of diagnosis of carcinoid heart disease became insignificant (Table 5).

**Discussion**

The present study demonstrates that the prognosis of patients with metastatic carcinoid disease and carcinoid heart disease has improved substantially over the past 2 decades despite the lethal nature of the disease. Although the definitive cause for the improvement in survival cannot be determined from this retrospective study, the data suggest that valvular surgery for carcinoid heart disease may have contributed.
The cardiovascular effects of carcinoid disease include structural damage to the heart and hemodynamic derangement. The structural lesions are characterized by plaquelike fibrous endocardial thickening that classically involves the right side of the heart. Because of retraction and fixation of the valves, tricuspid regurgitation is a nearly universal finding. Involvement of the pulmonary valve is also common, the valves, tricuspid regurgitation is a nearly universal finding, aggressive intervention to attenuate serotonin release.

The present study is the first to assess temporal changes of mortality rates in patients with carcinoid heart disease. We demonstrate an improvement in median survival from 1.3 years in the 1980s to more than 4 years in the late 1990s. The marked changes in the therapeutic management of carcinoid disease during the study period may account for the improvement in survival. The introduction of somatostatin analogues in 1986 revolutionized the management of carcinoid syndrome. The somatostatin analogues act by binding to somatostatin receptors, inhibiting secretion of tumor byproducts, and alleviating symptoms in the majority of patients. Despite somatostatic benefit, radiological tumor regression is rare, and an effective in relieving symptoms by decreasing blood supply to the right atrial; RV, right ventricular.

Data are median (25th and 75th percentiles) or n (%).

*P=0.006 vs patients diagnosed 1981–1988; all other between-group differences were not statistically significant.

†For difference between all groups by nonparametric Kruskal-Wallis test.

The development of cardiac carcinoid plaques has been related to the exposure of the right heart to serotonin and other tumor byproducts released from hepatic metastases. This has been based on higher concentrations of 5-HIAA in patients with carcinoid heart disease than in carcinoid patients with no cardiac involvement and on in vitro studies demonstrating the presence of serotonin receptors in subendocardial cells, with receptor stimulation leading to cell proliferation. However, the development of carcinoid heart disease remains incompletely understood, because development and progression of cardiac lesions may occur despite aggressive intervention to attenuate serotonin release.

Owing to the rarity of the disease, few studies have investigated the prognosis of patients with carcinoid heart disease. In 19 patients with confirmed carcinoid heart disease and a large number of patients with carcinoid disease but no cardiac involvement, Robiolio et al reported that survival appeared to be similar. More recently, Westberg and associates demonstrated that the severity of tricuspid valve regurgitation was an important predictor of outcome in 52 patients referred for echocardiography owing to suspicion of carcinoid heart disease. In the present study, only patients with carcinoid heart disease were evaluated. Among these patients with advanced metastatic carcinoid disease, prognosis was poor, with a median survival of only 2.6 years after diagnosis of cardiac involvement. Advanced NYHA class and right ventricular size were identified as important predictors of outcome. This suggests that the severity and hemodynamic consequence of carcinoid heart disease contributes to the high mortality.

The present study is the first to assess temporal changes of mortality rates in patients with carcinoid heart disease. We demonstrate an improvement in median survival from 1.3 years in the 1980s to more than 4 years in the late 1990s. The marked changes in the therapeutic management of carcinoid disease during the study period may account for the improvement in survival. The introduction of somatostatin analogues in 1986 revolutionized the management of carcinoid syndrome. The somatostatin analogues act by binding to somatostatin receptors, inhibiting secretion of tumor byproducts, and alleviating symptoms in the majority of patients. Despite somatostatic benefit, radiological tumor regression is rare, and an improved survival with somatostatin treatment has not been demonstrated. In addition, hepatic artery dearterialization is effective in relieving symptoms by decreasing blood supply to the right atrial; RV, right ventricular.

Data are median (25th and 75th percentiles) or n (%).

*P=0.006 vs patients diagnosed 1981–1988; all other between-group differences were not statistically significant.

†For difference between all groups by nonparametric Kruskal-Wallis test.
metastases. Similar to treatment with somatostatin analogues, the effect of liver dearterialization has mainly been symptomatic, and data demonstrating a significant impact on survival are lacking. In accordance with this, the present study suggests that the improved median survival was largely unrelated to somatostatin treatment and hepatic dearterialization. Given the disappointing results of cytotoxic chemotherapy in malignant carcinoid syndrome, the difference in the use of chemotherapy between groups is unlikely to have affected the results.

Table 3. Clinical Characteristics of Patients With Carcinoid Heart Disease Treated Medically and Surgically

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medically Treated (n=113)</th>
<th>Surgically Treated (n=87)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60 (49–69)</td>
<td>57 (50–64)</td>
<td>0.07</td>
</tr>
<tr>
<td>Female gender</td>
<td>55 (45)</td>
<td>33 (38)</td>
<td>0.31</td>
</tr>
<tr>
<td>Ur-5-HIAA, mg/24 h</td>
<td>257 (173–395)</td>
<td>267 (188–391)</td>
<td>0.83</td>
</tr>
<tr>
<td>Medical management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatostatin analogue</td>
<td>74 (66)</td>
<td>81 (93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatic artery embolization</td>
<td>23 (20)</td>
<td>32 (37)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hepatic artery ligation</td>
<td>36 (32)</td>
<td>13 (15)</td>
<td>0.006</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>42 (37)</td>
<td>30 (35)</td>
<td>0.70</td>
</tr>
<tr>
<td>Echocardiographic appearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or severe increase in RV size</td>
<td>61 (54)</td>
<td>66 (76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Moderate or severe increase in RA size</td>
<td>66 (58)</td>
<td>69 (79)</td>
<td>0.002</td>
</tr>
<tr>
<td>Moderate or severe tricuspid valve regurgitation</td>
<td>90 (80)</td>
<td>78 (90)</td>
<td>0.06</td>
</tr>
<tr>
<td>Moderate or severe pulmonary valve regurgitation</td>
<td>36 (35)</td>
<td>55 (63)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Ur-5-HIAA indicates urinary 5-HIAA excretion; RV, right ventricular; and RA, right atrial. Data are median (25th and 75th percentiles) or n (%).
An important change in the management of patients with advanced cardiac involvement was the introduction of cardiac surgery with replacement of dysfunctional valves. Previous studies from our institution have suggested that cardiac intervention with replacement of the tricuspid valve (and in selected patients, replacement of the pulmonary valve) improves functional status and attenuates right ventricular remodeling,22 2 important predictors of adverse outcome in the present study. In 1995, Connolly et al7 reported that despite high perioperative mortality, a trend toward improved long-term outcome was achieved in patients managed surgically. A high perioperative mortality has also been reported by Robiolio et al,23 especially in carcinoid patients over the age of 60 years. The present study demonstrates that the perioperative mortality rate has been reduced from \( \frac{1}{2} \times 10^2 \) to \( \frac{1}{10} \). The criteria for referral to cardiac surgery were based on symptomatic right ventricular failure due to carcinoid heart disease, or before major hepatic resection of metastases. However, the smooth postoperative course led to a more liberal referral for valve replacement in the most recent period. Hence, whereas surgery in the early periods was performed only in severely symptomatic patients, an increasing number of mildly symptomatic patients were offered surgery in the most recent period. The referral to surgery in these patients was based on severe valvular dysfunction and right ventricular volume overload. Although the numbers were small, this was apparently done without excess mortality, and long-term survival after surgery was favorable. In addition, symptomatic improvement was noted in the majority. Finally, the multivariate analyses demonstrate that when cardiac surgery was included in the model, time of diagnosis was no longer significant. In light of these results, it appears likely that in selected patients, the observed improvement in median survival could be related to surgical management of carcinoid heart disease.

We were not able to identify definite predictors of early adverse postoperative outcome based on preoperative characteristics. However, preoperative 5-HIAA was higher in patients with perioperative mortality, warranting caution in patients with inadequate control of systemic disease.

**Study Limitations**

The present data must be interpreted in light of the retrospective, nonrandomized design. The observed improvement in prognosis could simply be related to an increasing use of echocardiography and referral bias. Echocardiograms may have been obtained earlier in less symptomatic patients in the more recent cohorts. Although the patients in the most recent cohort were severely symptomatic with advanced cardiac lesions, it is possible that owing to referral bias, these patients had carcinoid disease that responded well to palliative treatment, which made the patients more suitable for cardiac surgery and possibly yielded a more favorable outcome. Although we sought to reduce this bias through the multivariate analyses, the optimal approach would have been a prospective randomized trial, but given the rarity of the disease, this would not be feasible. From the data, it appears that pulmonary valvular

### TABLE 4. Characteristics of Patients With Cardiac Surgery According to Period of Diagnosis

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57 (47–63)</td>
<td>55 (47–66)</td>
<td>53 (45–63)</td>
<td>58 (50–65)</td>
<td>0.49</td>
</tr>
<tr>
<td>NYHA class III or IV†</td>
<td>72 (83)</td>
<td>11 (92)</td>
<td>30 (94)</td>
<td>31 (72)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ur-5-HIAA, mg/24 h</td>
<td>164 (88–266)</td>
<td>155 (113–253)</td>
<td>205 (89–271)</td>
<td>164 (71–234)</td>
<td>0.71</td>
</tr>
<tr>
<td>Tricuspid valve replacement</td>
<td>87 (100)</td>
<td>12 (100)</td>
<td>32 (100)</td>
<td>43 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pulmonary valve replacement</td>
<td>23 (26)</td>
<td>1 (8)</td>
<td>8 (25)</td>
<td>14 (33)</td>
<td>0.26</td>
</tr>
<tr>
<td>Pulmonary valvectomy and enlarge</td>
<td>51 (59)</td>
<td>9 (81)</td>
<td>25 (76)</td>
<td>18 (43)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mitral valve replacement or repair</td>
<td>8 (9)</td>
<td>3 (25)</td>
<td>1 (3)</td>
<td>4 (9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>10 (11)</td>
<td>1 (8)</td>
<td>3 (9)</td>
<td>6 (14)</td>
<td>0.83</td>
</tr>
<tr>
<td>PFO closure</td>
<td>17 (20)</td>
<td>3 (27)</td>
<td>7 (23)</td>
<td>7 (17)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Ur-5-HIAA indicates urinary 5-HIAA excretion; PFO, patent foramen ovale.
Data are median (25th and 75th percentiles) or n (%).
*For difference between all groups by nonparametric Kruskal-Wallis test or \( \chi^2 \) test.
†Class at time of surgery.

**Figure 2.** Outcome of 200 patients with carcinoid heart disease according to year of diagnosis. Group A denotes patients with a first diagnosis of carcinoid heart disease between 1981 and June 1989; group B, patients with a diagnosis between July 1989 and May 1995; and group C, patients diagnosed between June 1995 and 2000. \( P=0.04 \), group A vs group B; \( P=0.008 \), group A vs group C; \( P=0.90 \), group B vs group C.
involvement was more advanced in the most recent group. Because echocardiographic visualization of the pulmonary valve can be challenging, improvements in echocardiographic equipment with better temporal and spatial resolution may have resulted in improved recognition of pulmonary valve involvement.

Conclusions
The present study demonstrates that the prognosis for metastatic carcinoid syndrome and carcinoid heart disease has improved over the past 2 decades. The study also documents that the perioperative mortality has decreased and that long-term outcome after valve surgery is favorable. Although no definitive cause for the improvement in overall survival can be determined from this retrospective study, the data suggest that the introduction of surgical intervention for carcinoid heart disease may be a contributor.

Acknowledgments
Dr Møller was supported by a grant from the Danish Heart Foundation. Dr Bernheim was supported by a grant from the Swiss National Science Foundation.

**TABLE 5. Predictors of 10-Year All-Cause Mortality by Multivariate Cox Proportional Hazards Analysis According to Period of Diagnosis of Carcinoid Heart Disease**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 (n=200)</th>
<th>Model 2 (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>First diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1981–1989</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1989–1995</td>
<td>0.67</td>
<td>0.46–0.99</td>
</tr>
<tr>
<td>1995–2000</td>
<td>0.61</td>
<td>0.39–0.92</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.02</td>
<td>1.01–1.04</td>
</tr>
<tr>
<td>Gender</td>
<td>0.88</td>
<td>0.61–1.27</td>
</tr>
<tr>
<td>Ur-5-HIAA, per 100 mg/24 h</td>
<td>1.11</td>
<td>1.01–1.21</td>
</tr>
<tr>
<td>NYHA class III–IV*</td>
<td>2.04</td>
<td>1.35–3.09</td>
</tr>
<tr>
<td>Moderate or severe RV dilation</td>
<td>1.88</td>
<td>1.20–2.70</td>
</tr>
<tr>
<td>Moderate or severe TR</td>
<td>1.27</td>
<td>0.75–2.15</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>0.77</td>
<td>0.50–1.19</td>
</tr>
<tr>
<td>Hepatic dearterialization</td>
<td>0.85</td>
<td>0.60–1.20</td>
</tr>
<tr>
<td>Cytotoxic chemotherapy</td>
<td>1.23</td>
<td>0.85–1.80</td>
</tr>
<tr>
<td>Cardiac surgery†</td>
<td>0.48</td>
<td>0.31–0.73</td>
</tr>
</tbody>
</table>

HR indicates hazard rate; Ur-5-HIAA, urinary 5-HIAA excretion; RV, right ventricular; and TR, tricuspid regurgitation.

*Class at time of diagnosis of carcinoid heart disease.
†Cardiac surgery was included in the analysis as a time-dependent covariate.

**Figure 3.** Effects of right ventricular (RV) dilation (left) and NYHA class (right) on survival among 200 patients with carcinoid heart disease stratified for cardiac surgery.
References


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