Effect of Neurologic Complications on Outcome After Heart Transplant

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Objective: To study neurologic complications after heart transplant.

Design: Retrospective cohort study.

Setting: Cardiac transplant program at Mayo Clinic, Rochester, Minnesota.

Patients: We retrospectively studied 313 patients who underwent heart transplant at Mayo Clinic Rochester from January 1, 1988, through October 31, 2006.

Main Outcome Measures: Neurologic symptoms, neurologic complications, score on the Glasgow Outcome Scale, and mortality.

Results: Causes of end-stage heart failure were idiopathic dilated myopathy (34%), ischemic heart failure (29%), congenital disorders (12%), amyloidosis (11%), and miscellaneous (15%). Perioperative neurologic complications occurred in 23% of patients and included delirium or encephalopathy (9%), cerebrovascular complications (5%), and diseases of the peripheral nerves and muscles (4%); however, only perioperative cerebrovascular complications were associated with 1-year mortality (hazard ratio, 4.17; 95% confidence interval, 1.04-16.76; \( P = .04 \)). Most of these cerebrovascular complications occurred after the second postoperative day and were related to mechanical support of the circulation. Over 18 years, the risk for neurologic complications was 81%: sleeping disorders, 32%; polyneuropathy, 26%; and cerebrovascular diseases, 14%. Cause of death was neurologic in 12 of 95 patients (13%), and the most common were cerebrovascular disease (n=6) and central nervous system infectious diseases (n=3). Adjusting for baseline predictors, central nervous system infection (hazard ratio, 4.29; 95% confidence interval, 1.69-10.91; \( P = .002 \)), depression (hazard ratio, 1.81; 95% confidence interval, 1.06-3.09; \( P = .03 \)), and seizures (hazard ratio, 3.44; 95% confidence interval, 1.33-8.85; \( P = .01 \)) were predictive for mortality.

Conclusions: Perioperative neurologic complications are frequent in heart transplant recipients, but most are transient and inconsequential. However, perioperative stroke is the most important neurologic complication affecting survival in the first year after heart transplant. Infectious diseases of the central nervous system are associated with fatal outcome.

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METHODS

We retrospectively studied patients who underwent heart transplant in the Mayo Clinic cardiac transplant program from January 1, 1988, through October 31, 2006. The following sources of information were used: Mayo Clinic Transplant Database, Diagnostic Index Database, paper and electronic medical records, records of the Mayo Clinic clinical laboratories, and results of cranial imaging. Data were extracted on patients' history, baseline characteristics, perioperative period (between heart transplant and discharge), histopathological stenosis of coronary arteries of explanted hearts (grades I-IV), and occurrence of neurologic events. The entire spectrum of potentially neurologic complications was scored, including pain, depression, and anxiety. Patient characteristics were recorded according to the judgment of the treating physician.

Immunosuppressive programs were recorded at 2 and 6 months and 2 and 6 years after transplant. Functional outcome was graded according to the Glasgow Outcome Scale at discharge 1 year after transplant. A score of 1 on this scale indicates death; a score of 2, a vegetative state (the patient is unable to inter-
act with the environment); a score of 3, severe disability (the patient is unable to live independently but can follow commands); a score of 4, moderate disability (the patient is capable of living independently but unable to return to work or school); and a score of 5, mild or no disability (the patient is able to return to work or school). A favorable outcome was defined as a score of 5, and an unfavorable outcome was defined as a score of 1 to 4; this scale does not define whether deficits that might prevent a child from returning to school or an adult to work were on a neurologic basis.

This study was approved by the institutional review board of the Mayo Clinic. Two patients who underwent transplant and gave no authorization concerning medical record research studies were excluded.

Data were summarized using means and standard deviations for numeric variables or medians with interquartile ranges (IQRs) as appropriate, and counts and percentages were used for categorical variables. Parametric (t test or analysis of variance) and nonparametric (Mann-Whitney U test or Kruskall-Wallis H test) tests as appropriate were used to identify differences between groups in continuous outcomes, and χ² tests were used to compare categorical outcomes. The associations between baseline variables, neurologic complications, and mortality were assessed using Cox regression. Predictors changing after baseline were included in the Cox model as time-dependent predictors, eg, neurologic complications, when predicting mortality. The Kaplan-Meier method adapted to account for the competing risk of death was used to describe cumulative incidences for neurologic complications, and the standard Kaplan-Meier method was used for describing mortality incidences. Tests were performed at the 5% level and confidence limits constructed at the 95% level.

RESULTS

From January 1988 through June 2006, 315 patients underwent heart transplant in the Mayo Clinic cardiac transplant program; 313 of them were included in this study (median [IQR] age, 52 [38-59] years), 24 children (median [IQR] age, 9 [4-14] years) and 289 adults (median [IQR] age, 53 [44-59] years). The most common causes of heart failure were idiopathic dilated myocardopathy and ischemic heart failure, causing heart failure in 198 of 315 patients (63%). A considerable number of patients had amyloidosis (11%). Donor information was present for 296 patients (median [IQR] age, 29 [20-43] years).

Baseline characteristics varied with cause of heart failure. Cardiovascular risk factors were more likely to be present in patients with ischemic cardiomyopathy. These patients as compared with other heart transplant recipients were older (median age, 57 vs 43 years, respectively; P < .001), had higher body mass index (calculated as the weight in kilograms divided by the height in meters squared) at baseline (26.0 vs 23.8, respectively; P < .001), and were more likely to have a history of hypertension (61 of 92 patients [66%] vs 24 of 221 patients [11%], respectively; P < .001), diabetes mellitus (16 of 92 patients [17%] vs 13 of 221 patients [6%], respectively; P = .002), dyslipidemia (73 of 92 patients [79%] vs 71 of 221 patients [32%], respectively; P < .001), and smoking (60 of 92 patients [65%] vs 44 of 221 patients [20%], respectively; P < .001). The cardiovascular status of patients with ischemic heart failure as compared with other heart transplant recipients was reflected in higher median levels of serum creatinine (1.29 vs 1.20 mg/dL, respectively [to convert milligrams per deciliter to micromoles per liter, multiply by 88.4]); P < .001) and higher median grades of histopathological stenosis of the explanted heart (grade 4 vs grade 1, respectively; P < .001).

The proportions in groups of causes changed over the periods from January 1, 1988, to December 31, 1993, January 1, 1994, to December 31, 1999, and January 1, 2000, to June 30, 2006 (P = .001) (Table 1). The proportion of transplant recipients with ischemic cardiomyopathy decreased over time, whereas the proportion of patients in the miscellaneous group increased. This miscellaneous group included patients with cardiomyopathy after radiation therapy or chemotherapy, valvular disease, and failed heart transplant. Multiple-organ transplant was performed in 25 of 313 patients (8%) (heart, liver, and kidney in 14 patients; heart and liver in 9 patients; and heart and kidney in 2 patients) and was particularly common in patients with amyloidosis (10 of 33 patients [30%]).

Perioperative neurologic complications occurred in 61 of 313 patients (19%); perioperative neurologic diseases are listed in Table 2. There was a difference in com-

### Table 1. Cause of Heart Failure, Survival, and Perioperative Neurologic Complications

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<tr>
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</thead>
<tbody>
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<td>Cause</td>
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</tr>
<tr>
<td>Idiopathic</td>
<td>106 (34)</td>
<td>18 (29)</td>
<td>32 (27)</td>
<td>40 (31)</td>
<td>16.99 (2.61)</td>
<td>11.87-22.11</td>
<td>23 (22)</td>
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<tr>
<td>Ischemic</td>
<td>92 (29)</td>
<td>31 (50)</td>
<td>40 (34)</td>
<td>35 (27)</td>
<td>11.72 (0.83)</td>
<td>10.10-13.34</td>
<td>20 (22)</td>
</tr>
<tr>
<td>Congenital</td>
<td>36 (12)</td>
<td>6 (10)</td>
<td>18 (15)</td>
<td>14 (11)</td>
<td>14.37 (1.98)</td>
<td>10.48-18.25</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>33 (11)</td>
<td>3 (5)</td>
<td>18 (15)</td>
<td>12 (9)</td>
<td>7.53 (1.51)</td>
<td>4.57-10.48</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>46 (15)</td>
<td>6 (10)</td>
<td>9 (8)</td>
<td>31 (24)</td>
<td>11.72 (2.49)</td>
<td>6.83-16.60</td>
<td>17 (37)</td>
</tr>
<tr>
<td>Children</td>
<td>24 (8)</td>
<td>3 (5)</td>
<td>11 (10)</td>
<td>10 (8)</td>
<td>10.46 (3.05)</td>
<td>4.84-16.43</td>
<td>7 (29)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Miscellaneous causes included hypertrophic cardiomyopathy (n = 9), radiation cardiomyopathy (n = 9), valvular disease (n = 9), restrictive cardiomyopathy (n = 5), intractable ventricular tachycardia (n = 2), failed heart transplant (n = 2), postpartum cardiomyopathy (n = 2), cardiomyopathy after chemotherapy (n = 3), cardiomyopathy after radiotherapy or chemotherapy (n = 1), aortic valve disease (n = 1), and postmyocardial infarction (n = 1).
had both computed tomography and magnetic resonance imaging was done in 11 patients, and 5 patients had magnetic resonance imaging performed. Results of neuroimaging were no abnormalities (n=6), posterior cerebral reversible leuken cephalopathy (n=3), remote cerebral infarction (n=3), cerebral ischemic small-vessel disease (n=2), cerebral infarction (n=1), cerebral hemorrhage (n=1), meningioma (n=1), and sinusitis (n=1).

Follow-up was complete for 306 of 313 patients (98%); 9 patients were lost to follow-up after 1 (n=4), 2 (n=1), 5 (n=1), and 6 (n=3) years after transplant. During the studied period, 95 of 313 patients (30%) died and the median (IQR) clinical follow-up was 5.5 (2.2-9.9) years. Stepwise Cox regression identified 4 baseline predictors of mortality: creatinine level (hazard ratio [HR], 2.14; 95% confidence interval [CI], 1.55-2.95; P < .001), amyloidal cause (HR, 3.00; 95% CI, 1.69-5.34; P < .001), history of hypertension (HR, 2.19; 95% CI, 1.39-3.47; P < .001), and female sex (HR, 2.22; 95% CI, 1.34-3.68; P = .002). Functional outcome was graded on the Glasgow Outcome Scale 1 year after transplant; 23 patients (8%) had a score of 1 (death), 35 (12%) had a score of 4 (moderate disability), and 237 (80%) had a score of 5 (no disability).

Perioperative neurologic complications were associated with unfavorable functional outcome 1 year after transplant in univariate analysis (19 of 61 patients with unfavorable outcome [31%] vs 39 of 232 patients with favorable outcome [17%]; 1 year after transplant; P = .02). In multivariate analysis, perioperative cerebrovascular complications were associated with 1-year mortality (HR, 4.17; 95% CI, 1.04-16.76; P = .04). Perioperative delirium or encephalopathy, diseases of peripheral nerves and muscles, and seizures were not related to 1-year mortality (P > .79).

Perioperative cerebrovascular complications occurred in 15 patients, with a median (IQR) age of 50 (41-59) years (Table 3). Clinical manifestations were focal neurologic abnormalities (n=11), failure to awaken (n=2), and seizures (n=2), and they occurred after the second postoperative day in 10 of 15 patients (67%). Additional risk factors such as mechanical support of the circulation, cardiac tamponade or arrest, or atrial fibrillation were present in 11 of 15 patients (73%). Death or persisting neurologic sequelae occurred in 5 of 15 patients (33%).

The most frequently prescribed immunosuppressive treatments were corticosteroids (100%), cyclosporine (98%), and azathioprine (89%). High proportions of patients developed complications considered directly related to immunosuppressive treatment, such as decrease of renal function (defined as iothalamate clearances < 50 mL/min on scintigraphic analysis; 224 of 313 patients [71%]) or de novo diabetes (71 of 313 patients [23%]). The use of tacrolimus and sirolimus increased over time, and 17% and 37% of patients, respectively, were switched from cyclosporine-based therapy to these newer classes of immunosuppressive drugs.

One or more neurologic events developed after the perioperative period (initial transplant admission) in 226 of 313 patients (72%) (Table 4). The cumulative risk 15 years after transplant was 81% (Table 4). The most frequent neurologic events 15 years after transplant were depression (35%), pain or pain syndromes (37%), sleeping disorders (32%), polyneuropathy (26%), and cerebral ischemic small-vessel disease (26%).

### Table 2. Perioperative Neurologic Complications

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%)</th>
<th>(N = 313)</th>
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<tbody>
<tr>
<td>Cerebrovascular complications</td>
<td>15 (5)</td>
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<tr>
<td>Cerebral infarction</td>
<td>7 (2)</td>
<td></td>
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<tr>
<td>Cerebral hemorrhage</td>
<td>2 (1&lt;)</td>
<td></td>
</tr>
<tr>
<td>Postanoxic encephalopathy</td>
<td>1 (1&lt;)</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>7 (2)</td>
<td></td>
</tr>
<tr>
<td>Peripheral nerve or muscle disorders</td>
<td>11 (4)</td>
<td></td>
</tr>
<tr>
<td>Brachial plexopathy</td>
<td>4 (1)</td>
<td></td>
</tr>
<tr>
<td>Mononeuropathy of the peroneal nerve</td>
<td>3 (1)</td>
<td></td>
</tr>
<tr>
<td>Critical illness encephalopathy or myopathy</td>
<td>3 (1)</td>
<td></td>
</tr>
<tr>
<td>Vocal cord paralysis</td>
<td>4 (1)</td>
<td></td>
</tr>
<tr>
<td>Delirium or encephalopathy</td>
<td>27 (9)</td>
<td></td>
</tr>
<tr>
<td>Posterior reversible leukoencephalopathy</td>
<td>3 (1)</td>
<td></td>
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</tbody>
</table>

Abbreviation: TIA, transient ischemic attack.

### Figure

Temporal trends of perioperative neurologic complications.
brovascular disorders (14%). Depression was the sole event in 11 patients. The diagnosis of depression was related to presence of pain (HR, 3.17; 95% CI, 1.94-5.20; \( P \leq .001 \)). Sleeping disorders were related to baseline body mass index (HR, 1.08; 95% CI 1.04-1.13; \( P \leq .001 \)), with a mean (IQR) body mass index of 26.8 (24.1-30.4) for the patients with sleeping disorders vs 24.5 (21.8-27.2) for the patients without sleeping disorders. Polyneuropathy was more likely to occur in the 33 patients with amyloidosis (HR, 7.78; 95% CI, 4.30-14.01; \( P \leq .001 \)), with 55% of the patients with amyloidosis and 13% of the patients without amyloidosis incurring polyneuropathy.

Cerebrovascular events occurred in 29 of 313 patients (9%), with a cumulative incidence of 6%, 11%, and 14% at 5, 10, and 15 years, respectively. Infarction occurred in 19 patients, transient ischemic attack in 8 patients, and hemorrhage in 5 patients. The crude incidence of stroke was calculated to be 14 per 1000 person-years. Cerebrovascular events were more likely to occur in patients with heart failure of miscellaneous cause (HR, 3.60; 95% CI, 1.57-8.28; \( P \leq .002 \)) and tended to happen more often in patients with a history of stroke or transient ischemic attack at baseline (HR, 2.37; 95% CI, 0.96-5.85; \( P \leq .06 \)). Four of 5 patients (80%) with cerebral hemorrhage were included in the group with heart failure of miscellaneous cause (\( P \leq .001 \)).

To evaluate the association between neurologic complications and mortality, we included history of neurologic complications in the Cox model as time-dependent predictors, together with the baseline predictors described earlier (serum creatinine level, amyloidic cause, history of hypertension, and female sex). Considered individually, central nervous system (CNS) infection (HR, 4.29; 95% CI, 1.69-10.91; \( P \leq .002 \)), sei-
This study shows that heart transplant recipients are at high risk for neurologic complications (cumulative risk, 81% at 15 years). The most common major complication was stroke, and although the frequency of CNS infectious diseases was low, they were often fatal. Previous studies have reported substantially lower rates of neurologic complications in heart transplant recipients (7%-70%).

Stroke was the major perioperative neurologic complication and was related to 1-year mortality. The prevalence of stroke in heart transplant recipients is higher compared with that in patients undergoing coronary artery bypass grafting or other transplant populations, such as liver and bone marrow transplant recipients. Prevalently lower than with liver transplant. Encephalopathy was transient in all of the patients, and neuroimaging showed structural lesions in only 2 of 27 patients. Three patients had drug-induced posterior reversible leukoencephalopathy. The prevalence of encephalopathy increased over time, and this was related to increasing numbers of heart failure of miscellaneous cause. Although the retrospective design precludes firm conclusions, this group can be regarded as a high-risk group with more acute and complicated disease and therefore at higher risk for perioperative encephalopathy.

Sleeping disorders were present in many patients. Sleep apnea syndrome has been described in 25% to 40% of patients with chronic heart failure and may persist after heart transplant. A prospective study using polysomnography, sleep survey questionnaires, and health survey questionnaires showed sleeping disorders in 36% of heart transplant recipients. High rates of sleeping disorders also occur in kidney transplant recipients and have been related to male sex, obesity, use of hypnotic drugs, and comorbidity.

Our study has 2 limitations. First, outcome events were recorded according to the judgment of the treating physician. Therefore, it is unclear to what extent these data represent a true evaluation of their number and nature. Second, an unknown proportion of neurologic events may have nothing to do with the cardiac transplant. Neurologic complications in the cardiac transplant population can be regarded as a complex interaction between pretransplant risk factors, a complicated surgical procedure, and several postneurosurgical factors (ie, immunosuppressive regimens).

In conclusion, perioperative neurologic complications are frequent in heart transplant recipients, but most are inconsequential. Perioperative stroke is the most important neurologic complication affecting survival in the first year after heart transplant. Central nervous system infections are the strongest independent predictors of mortality in the longer term, although stroke remains highly prevalent.

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Author Contributions: Drs van de Beek and Kremers had access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: van de Beek, Kremers, Daly, and Wijdicks. Acquisition of data: van de Beek, McGregor, and Wijdicks. Analysis and interpretation of data: van de Beek, Kremers, Daly, Edwards, Clavell, and Wijdicks. Draft-
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REFERENCES


