Heart transplantation in patients with previous cardiac operations

Excellent clinical results

A significant proportion of potential transplant recipients have undergone previous cardiac procedures and may be subject to an increased risk because of technical and other factors inherent in a reoperation. Between December 1985 and June 1991, 155 orthotopic heart transplantations were carried out in 146 patients. Eighty-five transplantations (54.8 %) were carried out as the initial cardiac operation (group I); 61 operations (45.2 %) were performed in patients who had previous nontransplant cardiac operations (group II). Preoperative variables including hemodynamic indexes, renal function, and status on the waiting list were similar between these groups; however, group II patients tended to be older than group I patients (51.9 ± 10.7 versus 47.7 ± 11.6 years, respectively; $p < 0.05$) and were more likely to have ischemic heart disease (80.3% versus 34.1%) than were those in group I. Significantly longer cardiopulmonary bypass time (127.6 ± 44.7 minutes versus 108.2 ± 18.8 minutes, $p < 0.01$) and duration of operation (448.1 ± 120.9 minutes versus 353.2 ± 85.1 minutes, $p < 0.01$) was found in group II. Operative mortality in group I was 4.7% and in group II was 6.6% ($p > 0.9$). Group I actuarial survival at 1 year and 5 years was $87.1\% \pm 3.6\%$ and $72.9\% \pm 6.2\%$, respectively. Group II actuarial survival was $85.3\% \pm 4.5\%$ and $76.0\% \pm 6.6\%$, respectively, for the same time periods. In spite of the greater technical challenge implied by previous cardiac operations, no significant survival differences occurred between these groups ($p > 0.9$). However, patients undergoing a second cardiac transplantation ($n = 9$) were identified as a high-risk subset with operative mortality of 22.8% and 1-year survival of only $33.3\% \pm 15.7\%$ ($p < 0.0003$). Cardiac transplantation in patients who have undergone previous nontransplant cardiac operations can be carried out without compromising immediate or long-term outcome. (J THORAC CARDIOVASC SURG 1994;107:203-9)

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Cardiac transplantation has evolved into a treatment modality of last resort for patients who are increasingly older and are at a higher risk. In particular, patients who have undergone previous cardiac operations are frequently considered for cardiac transplantation. The technical difficulties of reoperation have been emphasized in several nontransplant reports.^{1,2} In our experience, a significant proportion of potential transplant recipients have undergone previous cardiac procedures and may be sub-

Fig. 1. Significantly longer bypass times and total length of operation in patients who underwent transplantation after previous cardiac operation.

Table I. Diagnoses

Disease	Group I (n = 85)	Group II (n = 61)	Total (n = 146)
Ischemic	29	49	78
Idiopathic	38	2	40
Viral	12	1	13
Valvular	0	6	6
Congenital	0	3	3
Toxic	2	0	2
Amyloid	1	0	1
Other	3	0	3

ject to an increased risk because of factors inherent in a reoperation. In an effort to optimize the use of scarce donor resources, the effect of previous cardiac operations has been evaluated through a retrospective review of 155 cardiac transplantations.

Patients and methods

Between December 1985 and June 1991, 155 orthotopic heart transplant procedures were carried out in 146 patients. Transplantation was the initial cardiac procedure in 85 patients (54.8%; group I); 61 operations (45.2%) were performed in patients who had previous nontransplant cardiac operations (group II). In group II, the cause of cardiac failure was ischemic cardiomyopathy in 49 patients (80.3%) and valvular cardiomyopathy in six patients. In contrast, idiopathic cardiomyopathy (38 of 85 patients, 44.7%) was the most common cause in group I (Table I).

Of group II patients ($n = 61$), 31 had previously undergone one coronary bypass procedure, 11 had undergone two previous coronary bypass procedures, and three had undergone three

bypass procedures. Valve replacement had previously been performed in 12 patients, and aneurysm/automatic implantable cardioverter defibrillator operation had been performed in four patients. Nine patients in this series underwent two cardiac transplantations; these procedures are not included in the group II cohort.

Preoperative variables of these groups were compared, and no significant differences in renal dysfunction (preoperative creatinine > 2 mg/dl), sex distribution, hepatic dysfunction (preoperative total bilirubin > 2 mg/dl), need for intravenous or mechanical inotropic support, ejection fraction, calculated pulmonary vascular resistance, or cardiac index were found (Table II). However, group II patients tended to be older (51.9 ± 10.7 years versus 47.7 ± 11.6 years, $p < 0.05$) and were more likely to have ischemic heart disease (80.3% versus 34.1%, $p < 0.05$) than those in group I. Use of anticoagulants (warfarin sodium [Coumadin], intravenous heparin, or aspirin) before the operation was also similar between groups. Of the patients in group I ($n = 85$), 25 received preoperative systemic anticoagulation treatment with heparin, and 15 required warfarin therapy. In group II ($n = 61$), 20 received heparin, and 10 were treated with warfarin before the operation.

Operative technique was standardized in this series. Conventional bypass was established with bicaval cannulation via the right atrium and arterial return to the ascending aorta. Moderate systemic hypothermia (26°C) was used in all patients. Attention to hemostasis was aided by routine use of the Cell Saver device (Haemonetics Corp., Braintree, Mass.); all patients in group II also received a prime of fresh frozen plasma in the bypass circuit.

A routine immunosuppression protocol of cyclosporine-based triple therapy was used throughout this study. Doses of cyclosporine were 8 mg/kg per day, and doses of azathioprine were 2 mg/kg per day. Frequent adjustments were made as graft status, renal function, drug levels, and hematologic parameters dictated. Eight patients in the entire series were treated with

Fig. 2. Survival of all patients who underwent transplantation in this series. Operative mortality was $5.5\% \pm 1.9\%$ for all patients.

Table II. Patient profiles (primary transplant only)

Preoperative variable	Group I	Group II	p Value
Age (excludes pediatric patients)	47.7 ± 11.6	51.9 ± 10.7	0.03
UNOS status 1 listing	30/85 (35.3%)	23/61 (37.7%)	
Ejection fraction (%)	20.1 ± 12.1	21.2 ± 10.0	0.56
Cardiac index	$2.21 \pm .625$	$2.29 \pm .75$	0.51
Pulmonary resistance (Wood units)	2.60 ± 1.50	2.14 ± 1.0	0.26
Preoperative creatinine (gm/dl)	1.16 ± 0.37	1.25 ± 0.45	0.19

UNOS, United Network of Organ Sharing.

perioperative monoclonal antibody induction therapy (five from group I and three from group II). Serial endomyocardial biopsies were used to evaluate graft rejection. Specimens were scored according to the histopathologic grading system of the International Society of Heart and Lung Transplantation.³ Rejection episodes of Grade II (moderate) and greater are termed significant in this report.

Statistical analyses for group comparison were carried out with Pearson χ^2 analysis with and without constancy correlation. Life table and actuarial survival data were calculated with the Lee-Desu statistic for comparison of survival experience.

Results

Overall, longer total operation times ($p < 0.001$) and increased duration of cardiopulmonary bypass ($p < 0.001$) were found in group II patients (Fig. 1). Cold

ischemia times for the two groups were not significantly different, with a mean of 158.2 ± 85.1 minutes for group I and 170.5 ± 49.7 minutes for group II ($p = 0.121$). Sternal reexploration for hemorrhage was necessary in only one instance in this series. Sternal wound infections necessitating operative correction occurred in four patients overall, two from each group. Three wound hernias were found, all from group II. A summary of post-operative complications is found in Table III. Significant transfusion requirements (platelets or greater than 2 U of packed red blood cells) were noted in 44.0% of group I and 51.7% of group II ($p = 0.36$). Within group I, four patients required platelets, 20 received 2 or more U of packed red blood cells, and six required both. Of those in

Fig. 3. Survival by subgroup. No significant early or late survival advantage occurred between these groups ($p > 0.9$).

Table III. Postoperative complications

	Group I	Group II
Sternal infection	2	2
Wound hernia		3
Pericardial effusion	2	
Pneumothorax	1	1
Cerebral vascular accident		2
Reoperation for bleeding	1	
Intraaortic balloon embolectomy		1
Wire erosion		1
Splenic injury		1
Phrenic palsy	1	
Purulent pericarditis		1

group II, eight patients required platelets, 21 received 2 or more units of packed red blood cells, and 12 received both. No association was found between perioperative transfusion requirements and preoperative use of warfarin, heparin, and aspirin, alone or in combination ($p = 0.51$).

Renal dysfunction (creatinine > 2 mg/dl) developed after the operation in 40.2% of group I patients; in group II, the prevalence of renal failure was 52.8% ($p = 0.111$). Hepatic dysfunction (bilirubin > 2 mg/dl) occurred at a

Table IV. Causes of death

	Group I	Group II	Total
Rejection	5	5	10
Infection	2	6	8
Right ventricular failure	2	1	3
Graft coronary disease	0	2	2
Malignant disease	2	0	2
Other	2	4	

lesser rate with a group I prevalence of 24.3% and a group II prevalence of 29.1% ($p = 0.063$). These trends toward increased morbidity are reflected in longer postoperative length of stay (16.2 ± 7.0 days in group II and 13.7 ± 9.3 days in group I [$p = 0.051$]) and stay in the intensive care unit in group II (10.0 ± 8.1 days versus 7.4 ± 6.1 days [$p = 0.041$]). Early rejection episodes (30-day follow-up) necessitated inpatient treatment in 71.3% of group I and in 66.7% of group II ($p = 0.699$).

Actuarial survival data indicate no significant survival advantage between groups I and II. Survival at 30 days, 1 year and 5 years was $95.3\% \pm 2.3\%$, $87.1\% \pm 3.6\%$, and $72.9\% \pm 6.2\%$, respectively, for group I and $93.4\% \pm 3.2\%$, $85.3\% \pm 4.5\%$, and $76.0\% \pm 6.6\%$,

Fig. 4. Patients undergoing a second cardiac transplantation are identified as a high-risk subgroup. Urgent transplantation in the setting of primary graft failure gave poor results (see text).

respectively, for group II ($p > 0.9$). For the entire series, 30-day survival was $94.5\% \pm 1.9\%$, 1-year survival was $86.3\% \pm 2.8\%$, and 5-year survival $73.9\% \pm 4.7\%$ (Fig. 2). However, patients undergoing a second cardiac transplant procedure ($n = 9$) are a subset with high risk, an operative mortality of 22.8%, and a 1-year survival of $33.3\% \pm 15.7\%$ ($p < 0.0003$). The causes of death are summarized in Table IV. Although the prevalence of death resulting from rejection are similar, trends toward infection and graft coronary disease are increased in group II.

Discussion

Steadily improving results in orthotopic heart transplantation have encouraged the application of this treatment modality to patients who are at increasingly high risk. However, despite intensive efforts to increase donor availability, only 3033 orthotopic heart transplantations were performed worldwide in 1990; this number has not increased significantly over the past 4 years.⁴ Optimal use of the finite donor pool is imperative and requires critical evaluation of potentially high-risk patient groups. Presently, the bulk of recipients are 45 to 64 years of age and comprise 63.2% of all patients who underwent transplan-

tation in 1990.⁵ This important demographic group involves a significant proportion of individuals who have previously undergone sternotomy for cardiac operations.

In a comparable series, Lammermeier and associates⁶ noted no differences in survival but a trend in increased morbidity for patients who underwent heart transplantation after having undergone previous cardiac operations. In particular, postoperative hemorrhage necessitating reexploration was more likely in the reoperation group. In addition, association of bleeding with antiplatelet medication was strongly suggested. In the present series, a trend toward increased blood component therapy is noted in group II but does not achieve statistical significance. It is certainly our impression, however, that group II patients undergoing aspirin or warfarin therapy have presented an increased challenge with hemostasis. In view of this, all reoperative procedures performed in a setting of preoperative anticoagulation included a pump prime of fresh frozen plasma. The operative strategy also includes a willingness to devote extended time periods, if necessary, to obtain secure hemostasis before closing. In part, the longer total operation times found in group II may be a result of this strategy. Multivariate analysis failed to identify preoperative use of aspirin, heparin, or warfarin

as a risk factor for perioperative hemorrhage. Our policy has been to allow the use of medically indicated anticoagulants for patients on the recipient waiting list. Marked ventricular dysfunction or arrhythmias that imply a high risk of thrombotic complications warranted heparin or warfarin therapy. Aspirin was indicated primarily for patients with coronary artery disease. Despite this, only a single patient in the entire series required reexploration for postoperative bleeding. A slightly increased prevalence of significant hemorrhage (4% to 5%) in nontransplant cardiac reoperative procedures has been reported.^{1,2} In this series, evaluation of platelet and packed red blood cell transfusion requirements along with hemorrhagic morbidity revealed no significant increased risk in reoperative transplant procedures.

The increased technical difficulty encountered in reoperative cases, however, has been reflected in the markedly longer cardiopulmonary bypass times and the increased duration of the total operative procedure. To some degree, this also is a result of our policy to allow extra time for the recipient dissection in those patients with previous sternotomy. Recipient procedures in this group of patients are timed somewhat early to avoid a rushed dissection under hazardous conditions; this timing also tends to minimize donor organ ischemia time. The longer pump time, in particular, may contribute to the trend (not statistically significant) toward development of renal failure in group II (52.8% versus 40.2% for group I). Also related to this is the slightly longer postoperative stay in the intensive care unit noted in group II patients.

These trends toward increased morbidity in group II were not associated with early or late mortality in this series. No distinguishable differences in survival are noted between groups I and II. Overall series mortality data compare well with current collected statistics.^{4,7} Causes of death reflect an increased prevalence of infection-related mortality in group II patients. Advanced age may have some influence on this factor, as suggested by others.⁶

Review of our experience, however, did identify the nine patients who underwent a second heart transplantation as a high-risk group for poor early and late survival. Graft coronary disease was the operative indication in five patients, and rejection was the cause of graft loss in the remaining four patients. No instances of primary graft failure have been identified. Operative results were predictably poor, with retransplantations carried out in the setting of acute primary graft failure caused by rejection. Disappointingly, only two of these nine patients survived, one from the rejection subgroup and graft coronary disease subgroup. Small numbers prevent broad generaliza-

tions regarding survival advantage on the basis of retransplantation indication. Dein and colleagues⁸ have found that patients who undergo retransplantation for graft coronary disease have survival rates similar to those with a primary transplant. On the basis of their experience, we authors recommended retransplantation in the setting of acute rejection as a high-risk salvage procedure only. Recent reports^{9,10} have been guardedly more optimistic, with early retransplantation (within 6 months) and uncontrolled rejection in the first transplanted heart remaining significant risk factors. Review of the International Society for Heart and Lung Transplantation registry¹⁰ remains sobering, however, with an overall 1-year survival of only 48% in patients who undergo retransplantation. Our experience and these reported experiences lead us to believe that a decision to offer retransplantation should be made selectively on a case by case basis.

The technical difficulties inherently present in the performance of reoperative cardiac operation have been emphasized by unacceptably high mortality for heart transplantation candidates undergoing reoperative nontransplant cardiac procedures.^{11,12} In our series of patients undergoing transplant procedures, reoperative procedures were associated with longer operation times and duration of bypass. However, this did not infer increased risk of early or late mortality, prevalence of significant perioperative hemorrhage, or need for transfusion of blood products. Patients undergoing a second cardiac transplantation were identified as a high-risk group and should be considered for operation on an individual basis.

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