Heart transplantation in diabetic recipients: A decade review of 161 patients at Columbia Presbyterian

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Objective: Diabetes is considered by some transplant centers to be a relative contraindication for cardiac transplantation because of concerns regarding decreased survival, as well as increased incidence of infection and transplant coronary artery disease. We evaluated our experience with diabetic recipients over the last 10 years.

Methods: From January 1992 through June 2002, 881 patients underwent cardiac transplantation at New York Presbyterian Hospital. Of these, 161 (18.3%) were diabetic patients. Diabetic recipients were compared with a control group of 161 nondiabetic recipients matched for age, sex, cause of heart failure, United Network for Organ Sharing status, and immunosuppression era. Outcome measures included posttransplantation survival, incidence of infection, rejection, and transplant coronary artery disease.

Results: There was no statistically significant difference in survival between diabetic and nondiabetic recipients, with actuarial survival at 1, 5, and 10 years of 89.3%, 66.9%, and 45.6%, respectively, for diabetic patients and 87.4%, 78.8%, and 59.1%, respectively, for nondiabetic patients ($P = .168$). There was no significant difference in freedom from infection, rejection, or transplant coronary artery disease between the groups. By using Cox proportional hazard models, development of infection, rejection, and transplant coronary artery disease were independent predictors of decreased survival ($P < .001$, $P = .004$, and $P = .004$, respectively).

Conclusions: These results demonstrate similar short-term and long-term survivals, as well as similar risks for infection and transplant coronary artery disease, in diabetic and nondiabetic patients undergoing cardiac transplantation. The trend toward worse survival in the diabetic cohort, however, raises the possibility that if a greater number of diabetic patients were evaluated, a significant difference in survival might be observed, suggesting the need for a multicenter analysis to validate these outcomes.

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Diabetes mellitus (DM) affects 16 million Americans and 150 million persons worldwide and is the seventh leading cause of death.[1,2] There are 800,000 new cases of diabetes diagnosed each year in the United States, with an incidence of 13% and 12%, respectively, in male and female subjects older than 65 years of age. By the year 2025, the International Diabetes Foundation predicts that there will be as many as 300 million diabetic patients worldwide.[3-5]

Diabetic patients have a 4-fold increase in the incidence of ischemic heart disease, with myocardial infarction being the leading cause of death in this population.[6-9] Although many centers recommend aggressive surgical intervention for diabetic patients with coronary artery disease, DM is considered by some transplant

centers to be a relative contraindication for cardiac transplantation because of concerns regarding decreased survival, as well as increased infection, rejection, and transplant coronary artery disease (TCAD).[10,11] Furthermore, there is concern that hyperglycemia will be exacerbated and more difficult to control because of steroid treatment.[12,13]

There are several series in the literature that have examined this issue. However, the total number of diabetic patients studied in these series is relatively small, and follow-up is limited.[14-19] These studies only analyzed short-term and midterm survival to a maximum of 5 years after transplantation. Our previously reported experience of 76 diabetic patients, transplanted from January 1995 through December 1999, demonstrated similar survival, infection, rejection, and incidence of TCAD for diabetic and nondiabetic patients, but this study was limited to early and midterm (5-year) follow-up.[20] The long-term outcome of diabetic recipients remains unknown. Our current series of 161 diabetic patients transplanted from January 1992 through June 2002 addresses this issue by analyzing long-term survival, development of infection, rejection, and incidence of TCAD. It represents the largest single-center experience with long-term (10-year) follow-up and complements our previously reported series of 76 patients with 5-year follow-up.

Patients and Methods

We evaluated our experience with diabetic recipients over the last 10 years. From January 1992 through June 2002, 881 patients underwent cardiac transplantation at New York Presbyterian Hospital–Columbia Medical Center. Of these patients, 18.3% (n = 161) had diabetes, of whom 46.0% (n = 74) had type 1 DM, and 54.0% (n = 87) had type 2 DM. All patients in the diabetic group had DM for at least 3 months before cardiac transplantation.

Diabetic recipients were compared with a control group of 161 nondiabetic recipients and matched for age, sex, cause of heart failure, United Network for Organ Sharing status, and immunosuppression era by using strict propensity matching. Outcome measures included posttransplantation survival and the incidence of infection, rejection, and TCAD.

Definition of Infection

Posttransplantation infection was defined by the presence of a positive culture in the blood, respiratory tract, sternum, throat, urine, stool, or viral-cytomegalovirus in the setting of clinical symptomatology consistent with infection (fever, abnormal white blood cell count, or both) and was evaluated in both groups.

Diagnosis and Treatment of Rejection

The degree of rejection was categorized as per the International Society for Heart Lung Transplantation (ISHLT) Registry biopsy grading system, with endomyocardial biopsy specimens consistent with ISHLT Grade 1B or higher considered positive for rejection.[21] Biopsies were performed weekly for the first 4 weeks and then every 2 weeks for the next month, monthly for 4 months, every 2 months for the next 6 months, every 3 months for the next 6 months, and then every 6 to 12 months. Routine treatment of ISHLT grade 3A or greater rejection consisted of an increase in oral prednisone to 100 mg/d for 3 days, followed by a taper for 1 week to the baseline dose. If rejection persisted on the basis of a repeat endomyocardial biopsy or if rejection was accompanied by altered hemodynamics, intravenous methylprednisolone (1 g daily for 3 days) was used. Intravenous OKT3 (anti-CD3 monoclonal antibody; 5 mg/d) was used in 2 conditions: grade 3A/3B or 4 rejection that persisted despite the use of a second intravenous steroid pulse or rejection with severely compromised hemodynamics. Four weeks after completion of the OKT3 course, antibodies against murine OKT3 were measured. Patients with titers of anti-OKT3 antibodies greater than 1:100 and persistent cellular rejection in the setting of compromised hemodynamics were treated with antithymocyte globulin (ATGAM). Hemodynamically stable patients with either persistent grade 3A/3B or 4 rejection despite multiple courses of steroids, OKT3, and ATGAM or recurrence of grade 3A/3B rejection within 2 weeks of having completed therapy with OKT3 or ATGAM were candidates for photopheresis therapy.

Detection of TCAD

All patients underwent annual coronary angiography to evaluate for TCAD. The diagnosis was based on the following: (1) discrete lesions resulting in 50% or greater obstruction of the proximal or middle portion of the major graft vessels or (2) diffuse and concentric narrowing of the whole vessels, including their branches. Reports of "luminal irregularities" were considered positive for TCAD, whereas reports of "mild tapering of coronary artery" were considered negative. If a patient had TCAD, the frequency of angiography was increased to biannually. Patients were not given routine vasodilators before coronary injections. All angiograms were reviewed by a cardiologist and compared with the previous year's films to detect the presence of luminal irregularities, discrete stenoses, loss of third-order branches, or pruning of vessels.

Donor Acceptance Criteria

Donors and recipients were matched for ABO blood type compatibility and size (generally within 20% of body weight). Prospective HLA matching was not used; however, recipients with high levels of panel-reactive anti-HLA antibodies (>20%) underwent a prospective cross-match. Male donors less than 40 years of age and female donors less than 45 years of age met the criteria as suitable donors if there was no evidence of preexisting heart disease or impaired myocardial dysfunction by means of echocardiography. Older individuals also met the criteria as suitable donors provided that coronary atherosclerotic lesions could be excluded, ideally by means of cardiac catheterization. Individuals with serologies positive for HIV, hepatitis B (hepatitis B sAg), hepatitis C, or nonprimary brain cancer were excluded from being donors.

Graft Procurement

Donor hearts were harvested from beating-heart, brain-dead individuals. Graft procurement and preservation were performed with cold University of Wisconsin solution (Viaspan; DuPont Pharmaceuticals, Wilmington, Del) and topical hypothermia. Before 1996, orthotopic cardiac transplantation was performed by using the biatrial technique described by Lower and Shumway.[22,23] Since

TABLE 1. Inclusion and exclusion criteria for cardiac transplantation in diabetic patients with end-organ damage

End-organ damage	Excluded (severe)	Included (mild to moderate)
Diabetic retinopathy	Blind or history of ophthalmic surgery	Retinopathy present but not legally blind and no prior history of ophthalmic surgery
Diabetic nephropathy	Serum creatinine level >2.5 mg/dL or urinary protein level >1 g/d	Serum creatinine level of 2.0-2.5 mg/dL or urinary protein level of 300 mg/d −1 g/d
Peripheral vasculopathy	History of toe or lower extremity amputation	ABI <1.0 in either lower extremity without a prior lower extremity amputation
Autonomic dysfunction	Symptomatic orthostasis	Peripheral neuropathy or gastroparesis

ABI, Ankle-brachial index.

1996, almost all transplants have been performed by using the bicaval anastomosis technique.[24]

Immunosuppressive Regimen

There was no difference in the immunosuppression protocol for diabetic and nondiabetic recipients. Until January 1996, all patients received cyclosporine (INN: ciclosporin), steroids, and azathioprine. Dosing of cyclosporine consisted of a preoperative oral dose of 3 to 6 mg/kg, followed by an intravenous dose of 1 to 2 mg/kg every 24 hours until oral intake was tolerated. Daily oral doses of 3 to 6 mg/kg were adjusted to maintain a serum level of 300 to 350 mg/mL. After 6 to 12 months, cyclosporine doses were reduced to maintain a serum level between 100 and 150 ng/mL. Azathioprine was also administered preoperatively as an oral dose of 4 mg/kg, followed by daily doses of 2 mg/kg, with adjustments in dosing made on the basis of the patients' white blood cell count, platelet count, and hepatic function.

Since January 1996, mycophenolate mofetil, starting at a dose of 1000 mg twice daily, replaced azathioprine as part of cyclosporine-based therapy. Intravenous methylprednisolone (500 mg) was administered during the operation and postoperatively, with 125 mg given every 8 hours for 3 doses. Prednisone was then instituted at a daily dose of 1 mg/kg and gradually tapered over 4 months to 0.1 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}. Intravenous murine monoclonal antibody OKT3 (5 mg/d) took the place of cyclosporine for the first 4 days after transplantation for patients with severe renal dysfunction. Beginning in 1998, induction therapy with daclizumab was added to our standard immunosuppression regimen in selected patients.

Exclusion Criteria

Diabetic recipients with severe end-organ damage were not considered candidates for cardiac transplantation. This included patients with evidence of retinopathy who were either legally blind or had undergone previous ocular surgery, nephropathy with serum creatinine levels of greater than 2.5 mg/dL or urinary protein levels of greater than 1 g/d, symptomatic orthostasis, or significant peripheral vascular disease requiring a prior amputation (Table 1).

Diabetic patients with mild or moderate organ dysfunction, however, did undergo transplantation. This included patients with retinopathy not requiring an operation, nephropathy with serum creatinine levels of 2 to 2.5 mg/dL or 24-hour urinary protein levels of 300 mg/d to 1 g/d, peripheral neuropathy, gastroparesis, and peripheral vascular disease with an ankle-brachial index of less than 1.0 but no prior history of amputation (Table 1).

Other exclusion criteria for cardiac transplantation not specific to diabetic patients included the presence of factors that adversely affect long-term survival (eg, cancer), increase perioperative morbidity and mortality (eg, recent pulmonary embolus or active infection), or affect a patient's ability to care for himself or herself (eg, untreated major psychiatric illness or recent substance abuse). Pretransplantation severe pulmonary hypertension, defined as greater than 6 Woods units, was also considered to be a relative contraindication to transplantation.

Statistical Analysis

Data are presented as frequency distributions and percentages. Values of continuous variables were expressed as means $\pm$ SD. Continuous variables of diabetic patients and control subjects were compared by using Student unpaired t tests, whereas categoric variables were compared by means of χ^2 tests. Kaplan-Meier analysis was used to calculate survival. Actuarial survival at 1, 3, 5, and 10 years after transplantation was calculated by constructing life tables. Significant predictors of survival were identified by using multivariate Cox proportional hazard models. All data were analyzed with SPSS 11.5 software (SPSS Inc, Chicago, Ill).

Results

Demographics

Recipient data. Table 2 lists the clinical characteristics of diabetic and nondiabetic patients. There were no significant differences in age, sex, race, cause of heart failure, or United Network for Organ Sharing status between the groups. The diabetic cohort weighed significantly more than the control subjects ($P = .009$) and had a greater body mass index ($P = .005$). Within the diabetic cohort, 92 (57.1%) patients demonstrated 1 or more of the clinical manifestations of mild-to-moderate end-organ damage compared with 82 (50.9%) nondiabetic patients ($P = .152$). The most common manifestations of severe end-organ damage that formulated the basis for exclusion were severe renal disease

TABLE 2. Clinical characteristics of diabetic and nondiabetic patients

Variable	Diabetic patients	Nondiabetic patients	*P* value†
Recipient data			
Age (y)	55.4 ± 10.7*	54.6 ± 10.5	.480
Sex			
Male	132 (82.0%)	132 (82.0%)	1.0
Female	29 (18.0%)	29 (18.0%)	1.0
Race			
White	118 (73.3%)	129 (80.1%)	.147
African American	19 (11.8%)	16 (9.9%)	.591
Other	24 (14.9%)	16 (9.9%)	.176
Cause of heart failure			
CAD	86 (53.4%)	86 (53.4%)	1.0
ICM	65 (40.4%)	65 (40.4%)	1.0
Other	10 (6.2%)	10 (6.2%)	1.0
UNOS status			
1	135 (83.9%)	135 (83.9%)	1.0
2	26 (16.1%)	26 (16.1%)	
Weight (kg)	78.3 ± 10.7	73.4 ± 11.8	.009
BMI (kg/m$^{2)}$	26.0 ± 4.4	24.4 ± 5.2	.005
Bridged to transplantation with LVAD	30 (18.6%)	36 (22.4%)	.278
End-organ damage	92 (57.1%)	82 (50.9%)	.152
Retinopathy	49 (30.4%)	41 (25.5%)	.224
Nephropathy	36 (22.4%)	30 (18.6%)	.362
Peripheral vasculopathy	34 (21.1%)	29 (18.0%)	.305
Autonomic dysfunction	14 (8.7%)	8 (5.0%)	.183
Donor data			
Age (y)	32.5 ± 12.6	33.8 ± 13.0	.364
DIT (min)	163.0 ± 57.6	169.6 ± 61.4	.416
MFM	107 (66.5%)	111 (68.9%)	.548

CAD, Coronary artery disease; *ICM,* idiopathic cardiomyopathy; *UNOS,* United Network for Organ Sharing; *BMI,* body mass index; *LVAD,* left ventricular assist device; *DIT,* donor ischemic time; *MFM,* male-female mismatch.
*Mean ± SD.
†*P* values were obtained from paired *t* tests and χ^2 tests.

and vasculopathy with prior amputation, although an accurate numeric account was unavailable.

Donor data. There was no statistically significant difference in donor ischemic time (163.0 ± 57.6 minutes for diabetic patients vs 169.6 ± 61.4 minutes for nondiabetic patients) or donor age (32.5 ± 12.6 for diabetic patients vs 33.8 ± 13.0 years for nondiabetic patients) between the groups.

Survival

Overall survival for diabetic and nondiabetic patients is depicted in Figure 1. There was no significant difference in survival, although there was a trend toward worse survival in the diabetic cohort ($P = .168$). Median survival was 7.8 years for diabetic patients and 9.7 years for nondiabetic patients. Actuarial survival at 1, 5, and 10 years was 89.3%, 66.9%, and 45.6%, respectively, for diabetic patients compared with 87.4%, 78.8%, and 59.1%, respectively, for nondiabetic patients. When analyzing only those diabetic and nondiabetic patients with coronary artery disease as their cause of heart failure (excluding idiopathic cardiomyopathy), survival between the 2 groups was still similar ($P = .190$).

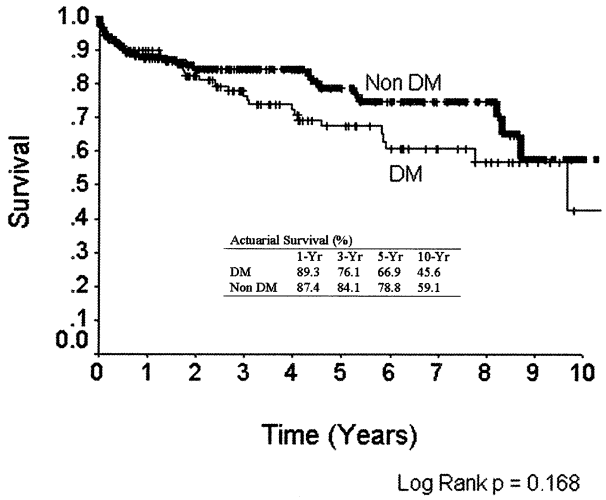

Figure 1. Long-term survival for diabetic and nondiabetic patients undergoing cardiac transplantation from January 1992 through June 2002. *DM,* Diabetes mellitus.

There was no significant difference in survival between patients with type 1 (46.0%, n = 74) and type 2 (54.0%, n = 87) diabetes ($P = .437$). Additionally, there was no significant difference in short-term or long-term survival when comparing diabetic patients with and without evidence of mild-to-moderate end-organ damage at the time of transplantation ($P = .242$).

Infection

There was no significant difference between diabetic and nondiabetic patients in the incidence of infection. Freedom from infection at 1, 3, and 5 years was 86.0%, 42.4%, and 23.9% for diabetic patients and 87.3%, 46.6%, and 31.0% for nondiabetic patients ($P = .632$, Figure 2). Although not statistically significant, diabetic patients were more prone to becoming bacteremic in the setting of infection, with bacteremia developing in 39.5% of diabetic infections compared with 32.3% of nondiabetic infections ($P = .074$).

The majority of both diabetic (66.3%) and nondiabetic (58.1%) patients were hospitalized for treatment of their infection episodes ($P = .447$) for a mean number of 18.5 ± 15.1 and 11.2 ± 11.8 days, respectively ($P = .155$). Patients admitted to the hospital for infection did not have a decreased survival compared with those patients with infection not admitted to the hospital.

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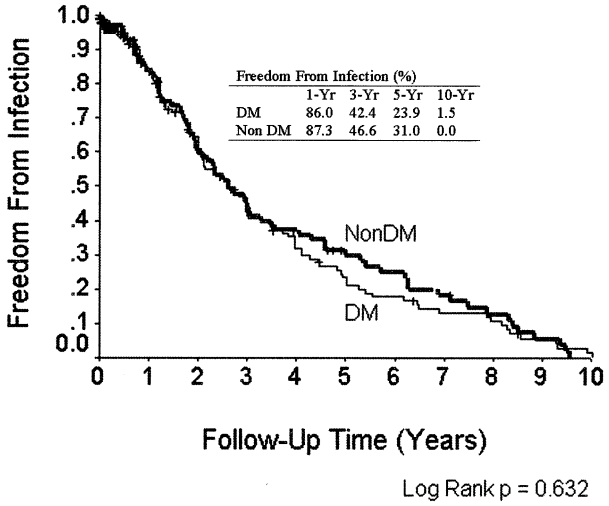

Figure 2. Freedom from infection for diabetic and nondiabetic patients after cardiac transplantation. There was no significant difference between the groups in freedom from infection at 1, 3, 5, and 10 years. *DM,* Diabetes mellitus.

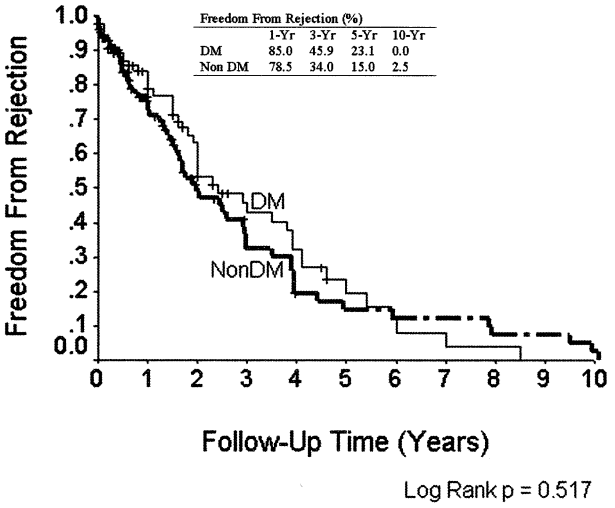

Figure 3. Freedom from rejection for diabetic and nondiabetic patients after cardiac transplantation. There was no significant difference between the groups in freedom from rejection at 1, 3, 5, and 10 years. *DM,* Diabetes mellitus.

Rejection

There was no significant difference between diabetic and nondiabetic patients in the incidence of rejection. The overall number of rejection episodes per patient was 0.60 ± 0.79 in diabetic patients versus 0.69 ± 0.78 in nondiabetic patients ($P = .304$). Freedom from rejection at 1, 3, and 5 years was 85.0%, 45.9%, and 23.1% for diabetic patients versus 78.5%, 34.0%, and 15.0% for nondiabetic patients ($P = .517$, Figure 3). The frequency and duration of hospitalization for rejection episodes was similar for both groups: 34.2% of diabetic patients for 7.8 ± 7.2 days compared with 25.8% of nondiabetic patients for 9.2 ± 5.8 days ($P = .129$ and $P = .944$).

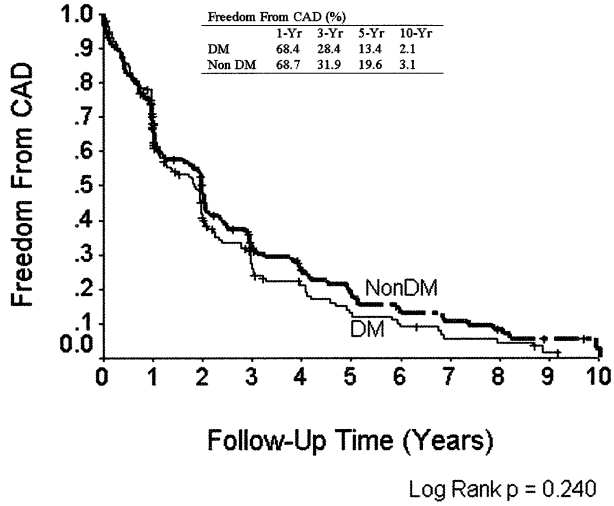

Figure 4. Freedom from TCAD for diabetic and nondiabetic patients after cardiac transplantation. There was no significant difference between the groups in freedom from TCAD at 1, 3, 5, and years. *DM,* Diabetes mellitus.

TCAD

There was no significant difference between the groups in freedom from TCAD at 1, 3, and 5 years: 68.4%, 28.4%, and 13.4% for diabetic patients compared with 68.7%, 31.9%, and 19.6% for nondiabetic patients ($P = .240$, Figure 4).

Predictors of Survival

Univariate analysis. By using univariate analysis, the presence of diabetes was not an independent predictor of adverse outcome ($P = .171$). Sex (with male patients demonstrating improved survival over that of female patients, $P < .001$), male-female mismatching ($P = .022$), infection ($P = .001$), rejection ($P = .002$), and TCAD ($P = .002$) were significant independent predictors of decreased postoperative long-term survival (Table 3).

Multivariate analysis. By means of multivariate analysis with Cox proportional hazard models, recipient sex ($P < .001$), infection ($P < .001$), rejection ($P = .004$), and TCAD ($P = .004$) were significant risk factors for decreased long-term survival (Table 4). When isolating each individual infection type for its effect on survival, only sepsis was found to significantly decrease survival.

Discussion

Many transplant centers consider DM to be a relative contraindication for cardiac transplantation, even though there

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TABLE 3. Factors affecting survival: Univariate analysis

Variable	*P* value*
Recipient characteristics	
Age	.711
Sex	<.001
Race	
White	.139
African American	.081
Other	.845
Cause of heart failure	
CAD	.633
ICM	.802
Other	.640
Height	.089
Weight	.071
Obesity	.123
BMI	.565
Pretransplantation LVAD	.614
DM	.171
Preoperative creatinine level	.753
DIT	.346
MFM	.022
Donor characteristics	
Age	.971
Sex	.467
Height	.583
Weight	.425
Postoperative events	
Infection	.001
Rejection	.002
TCAD	.002

CAD, Coronary artery disease; *ICM,* idiopathic cardiomyopathy; *BMI,* body mass index; *LVAD,* left ventricular assist device; *DM,* diabetes mellitus; *DIT,* donor ischemic time; *MFM,* male-female mismatch; *TCAD,* transplant coronary artery disease.

**P* value from Cox regression univariate analysis.

TABLE 4. Factors affecting survival by Cox proportional hazard models

Variable	OR	95% CI	*P* value	SE
Sex	2.372	2.225-2.613	<.001	0.255
Infection	2.501	1.540-4.061	<.001	0.247
Rejection	1.496	1.308-1.798	.004	0.243
TCAD	1.346	1.168-1.712	.004	0.369

OR, Odds ratio; *CI,* confidence interval; *TCAD,* transplant coronary artery disease.

have been several previous reports on heart transplantation in diabetic patients that have demonstrated similar short-term and midterm survival for diabetic and nondiabetic recipients. This might be because these studies analyzed a relatively small cohort of diabetic patients (n = 9-76) and did not evaluate long-term outcome.[14-19] In our previously reported series of 76 diabetic patients who underwent cardiac transplantation, we demonstrated similar survival, infection, rejection, and incidence of TCAD for diabetic and nondiabetic patients.[20] However, follow-up time was limited to 5 years. Our current series of 161 diabetic patients transplanted from June 1992 through January 2002 provides long-term (10-year) follow-up on survival, infection, rejection, and incidence of TCAD. The increased number of patients in this study has also enabled us to perform a more extensive statistical analysis, including a Cox regression multivariate analysis on various factors to identify predictors of survival, as well as to outline inclusion and exclusion criteria for diabetic patients presenting with manifestations of end-organ damage at the time of transplantation.

Our results demonstrate similar perioperative, short-term, and long-term survival for diabetic and nondiabetic patients undergoing cardiac transplantation. Furthermore, the presence of end-organ damage at the time of transplantation did not significantly affect survival within the diabetic cohort.

Some series have demonstrated a higher incidence of infection in diabetic patients undergoing cardiac transplantation compared with the incidence in nondiabetic patients.[14] This might be due to their baseline immunocompromised state and poor circulation.[14] More specifically, the impairment in antibody response to bacterial antigens and delay in migration of granulocytes in diabetic patients might predispose to development of infection.[14] In our series, however, we were unable to corroborate these results. We found no significant difference between the groups in the incidence of posttransplantation infection.

However, the increased incidence of associated mortality from sepsis in diabetic patients raises the following questions: Should we be more aggressive in our choice of antibiotic regimens when treating diabetic patients with infection? Should dosages of immunosuppressants be decreased for diabetic patients with infection? A more aggressive antibiotic approach along with a diminution in immunosuppression might limit the magnitude and spread of infection, allowing diabetic patients to gain local control, which might decrease the incidence of sepsis and infection-related death. These questions should be addressed in a randomized clinical trial, perhaps a multicenter one that focuses on altering doses of baseline immunosuppressants and antibiotics in the setting of infection for diabetic patients after transplantation.

Some series have demonstrated a lower incidence of rejection in diabetic patients undergoing cardiac transplantation compared with that in nondiabetic patients.[25,26] This might be due to an associated decrease in cell-mediated immune function in diabetic patients.[25,26] Because cardiac allograft rejection is primarily orchestrated by T cell–mediated immune processes, diabetic patients with decreased cell-mediated activity and responsiveness might exhibit a lower incidence of rejection. In our series, however, we did

not find a significant difference in the incidence of rejection between the groups.

Diabetic and nondiabetic patients demonstrated a similar incidence of TCAD. This is consistent with other reports in the literature that have also demonstrated similar incidences of TCAD in diabetic and nondiabetic patients.[15-20] The latter suggests that TCAD might be more a function of rejection related to antecedent episodes of acute rejection.

The limitations of this study include those related to a retrospectively performed analysis. Data were obtained by means of chart review, which has inherent limitations, such as access and accuracy of the data. Additionally, although we demonstrated no statistically significant difference in survival between diabetic and nondiabetic patients, a trend toward worse survival in the diabetic cohort raises the possibility that if a larger cohort of diabetic patients was studied in a multi-institutional analysis, a statistically significant difference in survival might be observed.

In conclusion, our results demonstrate that cardiac transplantation can be performed safely in diabetic patients, with similar short-term and long-term survival, infection, rejection, and incidence of TCAD compared with those seen in nondiabetic patients, although there are limitations in our study, as described above. Our results do not support modifying immunosuppression protocols in diabetic patients undergoing cardiac transplantation. Future studies include assessing long-term renal function and the requirement for dialysis in diabetic patients who have undergone heart transplantation. We support liberalization of the transplant criteria and proceeding with transplantation in carefully selected diabetic patients.

References

1. Larkin M. Diabetes on the rise worldwide and webwide. *Lancet*. 2001;357(9258):815.
2. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1999;100(10):1134-46.
3. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287(19):2570-81.
4. Mitka M. Rethinking treatment for patients with diabetes and cardiovascular disease. *JAMA*. 2002;287(19):2488-91.
5. Howard BV, Rodriguez BL, Bennett PH, Harris MI, Hamman R, Kuller LH, et al. Prevention conference VI: diabetes and cardiovascular disease: writing group I: epidemiology. *Circulation*. 2002;105(18): e132-7.
6. Hannan EL, Racz MJ, McCallister BD, Ryan TJ, Arani DT, Isom W, et al. A comparison of three-year survival after coronary artery bypass surgery and percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol*. 1999;33(1):63-72.
7. Goraya TY, Leibson CL, Palumbo PJ, Weston SA, Killian JM, Pfeifer EA, et al. Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. *J Am Coll Cardiol*. 2002;40(5):946-53.
8. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557-62.
9. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women. NHANES I epidemiologic follow-up study. *Arch Intern Med*. 2001; 161:996-1002.
10. Szabo Z, Hakanson E, Svedjeholm R. Early postoperative outcome and medium-term survival in 540 diabetic and 2239 nondiabetic patients undergoing coronary artery bypass grafting. *Ann Thorac Surg*. 2002;74(3):712-9.
11. Steinman TI, Becker BN, Frost AE, Olthoff KM, Smart FW, Suki WN, et al. Guidelines for the referral and management of patients eligible for solid organ transplantation. *Transplantation*. 2001;71:1189-204.
12. Griepp RB. A decade of human heart transplantation. *Transplant Proc*. 1979;11:285-92.
13. Lower RR, Szentpetery S, Quinn J, Thomas FT. Selection of patients for cardiac transplantation. *Transplant Proc*. 1979;11:293-5.
14. Rhenman MJ, Rhenman B, Icenogle T, Christensen R, Copeland J. Diabetes and heart transplantation. *J Heart Transplant*. 1988;7:356-8.
15. Badellino MM, Cavarocchi NC, Narins B, Jessup M, Alpern JB, McClurken JB, et al. Cardiac transplantation in diabetic patients. *Transplant Proc*. 1990;22:2384-8.
16. Landowski JS, Kormos RL, Uretsky BF, Griffith BF, Armitage JM, Hardesty RL. Heart transplantation in diabetic recipients. *Transplantation*. 1990;49:303-5.
17. Faglia E, Favales F, Mazzola E, Pizzi G, De Maria R, Mangiavacchi M, et al. Heart transplant in mildly diabetic patients. *Diabetes*. 1990; 39:740-2.
18. Munoz E, Lonquist JL, Radovancevic B, Baldwin RT, Ford S, Duncan M, et al. Long-term results in diabetic patients undergoing heart transplantation. *J Heart Lung Transplant*. 1992;11(5):943-9.
19. Aleksic I, Czer LSC, Freimark D, Dalichau H, Takkenberg JJM, Blanche C, et al. Heart transplantation in patients with diabetic end-organ damage before transplantation. *Thorac Cardiovasc Surg*. 1996; 44:282-8.
20. Lang CC, Beniaminovitz A, Edwards N, Mancini DM. Morbidity and mortality in diabetic patients following cardiac transplantation. *J Heart Lung Transplant*. 2003;22(3):244-9.
21. Winters GL, Marboe CC, Billingham ME. The International Society for Heart and Lung Transplantation grading system for heart transplant biopsy specimens: clarification and commentary. *J Heart Lung Transplant*. 1998;17(8):754-60.
22. Lower RR, Stofer RC, Shumway NE. Homovital transplantation of the heart. *J Thorac Cardiovasc Surg*. 1961;41:196-204.
23. Shumway NE, Lower R, Stofer RC. Transplantation of the heart. *Adv Surg*. 1966;2:265-84.
24. Sievers HH, Leyh R, Jahnke A, Petry A, Kraatz EG, Herrmann G, et al. Bicaval versus atrial anastomoses in cardiac transplantation. *J Thorac Cardiovasc Surg*. 1994;108:780-4.
25. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care*. 2003;26(2):510-3.
26. Spatz M, Eibl N, Hink S, Wolf HM, Fischer GF, Mayr WR, et al. Impaired primary immune response in type-1 diabetes: results from a controlled vaccination study. *Clin Immunol*. 2002;103:249-59.