Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Heart transplantation in insulin-treated diabetic patients with diabetes-related complications

Yoshifumi Ikeda,* Gero Tenderich, Armin Zittermann, Kazutomo Minami and Reiner Koerfer

Department of Cardio-Thoracic Surgery, Heart Center North-Rhine Westfalia, Ruhr University of Bochum, Bad Oeynhausen, Germany

Keywords
diabetes mellitus, diabetes-related complications, heart transplantation, immunosuppressive therapy.

Correspondence
Yoshifumi Ikeda MD, Department of Cardio-Thoracic Surgery, Heart Center North-Rhine Westfalia, Ruhr University of Bochum, Bad Oeynhausen, Germany.
*Present address: Department of Cardiology, Saitama Medical University, Saitama, Japan.
Tel.: +81 49 276 1317; fax: +81 49 276 1317; e-mail: yooikeda@aol.com

Received: 10 December 2006
Revision requested: 2 January 2007
Accepted: 26 February 2007

doi:10.1111/j.1432-2277.2007.00478.x

Summary

Heart transplantation is the most effective therapy for end-stage heart failure in patients with diabetes mellitus (DM). However, diabetes-related complications (DRCs) are a relative contraindication for heart transplantation. Nevertheless, the increasing prevalence of both DM and congestive heart failure makes it necessary to perform heart transplantation even in those patients with advanced DM. We performed a retrospective analysis on long-term survival in 47 patients with insulin-treated DM and DRCs (group 1). Survival rate and causes of death were compared with data of a group of heart transplant recipients without DM ($n = 1061$, group 2). Mean follow-up time of all heart transplant recipients was 68.2 months (range: 0–204 months). Overall mortality during follow-up was 42.9%. Long-term survival did not differ significantly between study groups, but tended to be shorter in group 1 than in group 2 ($P = 0.07$). In group 1, steroid-free immunosuppressive therapy was associated with a higher percentage of long-term survivors compared with no steroid-free immunosuppression. Our data demonstrate that long-term survival is acceptable in heart transplant recipients with preoperatively diagnosed DM and DRCs. Consequently, advanced DM should no longer be a relative contraindication for heart transplantation.

Introduction

Diabetes mellitus (DM) is an important independent risk factor for coronary heart disease and also for mortality in patients with congestive heart failure [1–4]. It has also been suggested that DM increases mortality risk in heart transplant recipients by intensifying peripheral vascular disease and accelerating coronary artery disease (CAD). This is one reason why DM has long been regarded as relative contraindication for heart transplantation. Another reason was that corticosteroids are routinely prescribed as immunosuppressive agents in most heart centers. However, immunosuppressive therapy with corticosteroids may be diabetogenic and may increase the already high incidence of infections and hypertension in the group of DM patients [5–7]. Therefore, heart transplantation has often been considered undesirable in insulin-treated DM patients. It has also been speculated that DM patients with diabetes-related complications (DRCs) such as diabetic neuropathy, retinopathy and nephropathy have a high risk for complications. Consequently, it was assumed that prognosis after heart transplantation is poor for insulin-treated DM patients with or without DRCs.

Meanwhile, immunosuppressive therapy with low doses of corticosteroids or even the withdrawal of steroids is routinely performed [8,9]. This trend has led to a liberalization of the old criteria for heart transplantation and has extended the number of heart transplant recipients with DM.

Independent of the gradual increase in heart transplantation in patients with DM, there is an ongoing discussion concerning the outcome of these patients. Systemic studies

Correction made after online publication 18th April 2007: Title change from Heart transplantation in insulin-treated diabetic mellitus patients with diabetes-related complications to Heart transplantation in insulin-treated diabetic patients with diabetes-related complications

are scant. Moreover, there are no reports on the clinical outcome of insulin-treated DM patients with DRCs.

Therefore, we performed a retrospective data analysis at our heart center to compare the outcomes in heart transplant recipients with insulin-treated DM with DRCs and without DM.

Patients and methods

Between March 1989 and December 2004, 1396 heart transplantations were performed at the heart center NRW, Bad Oeynhausen, Germany. Forty-seven patients met the criteria of insulin-treated DM with DRCs such as retinopathy, nephropathy, and neuropathy (designated group 1). However, severe DRCs such as macro-angiopathy, limb amputation, and hemodialysis are the exclusion criteria for cardiac transplantation at our heart center. One thousand and sixty-one patients without DM served as control group (designated group 2). Sixty not insulin-treated DM patients and 85 insulin-treated DM patients without DRCs were excluded from data analysis. These patients were, however, included in a survival analysis, where all DM patients were compared with the control group. Twenty-eight patients with re-transplantation and 115 patients with an age below 18 years were definitively excluded from data analysis.

All heart transplant recipients received 1 g of methylprednisone intra-operatively. This dose was continued for the next 2 days. Since May 1993, 250 mg steroids have been administered preoperatively. Maintenance immunosuppressive therapy was initially performed with 5–10 mg/kg cyclosporine (CsA) and 2.5 mg/kg azathioprine (AZA) on day 0. Thereafter, immunosuppressive agents were adjusted according to whole blood trough levels (CsA) or white blood cell counts (AZA). The cyclosporine target range for our patients is 140–190 ng/ml within the first six postoperative months, 110–140 ng/ml within the following 6 months, and 60–80 ng/ml thereafter.

According to the International Society for Heart and Lung Transplantation (ISHLT) classification, a grade 2 rejection was treated with steroid pulse therapy. One gram per day was administered over three consecutive days. In case of severe rejection (grade 3 or 4 rejection) or clinical signs of left ventricular dysfunction (cardiac index <1.6 l/min/m^2; low output syndrome), a rescue therapy was performed with mono/polyclonal antibodies.

We used the medical records of the patients to assess patient characteristics, survival rates and causes of death.

Statistical evaluation was performed with SPSS, version 11 (SPSS Inc. Chicago, IL, USA). Categorical variables were reported by using the number (n) and percent of observations. Continuous variables were expressed as mean values with SD. Comparisons between groups of patients were made by using the t-test and the chi-square test if appropriate. Survival rates were calculated with the Kaplan–Meier product limit estimator. The log-rank test was used to test for differences in survival rates between groups. P-values <0.05 were considered statistically significant.

Results

Follow-up time of the entire group was 68.2 ± 57.6 months, ranging from 0 month to 204 months. Patients' characteristics of groups 1 and 2 at the time of heart transplantation are shown in Table 1. The two groups differed significantly according to age, weight, body mass index, pulmonary artery pressure, and serum creatinine levels. Moreover, the percentage of CAD was higher in the DM patients with DRCs before heart transplantation compared with the control group.

In group 1, 6 out of the 47 patients suffered from type-I diabetes and 41 from type-II diabetes. All patients required daily insulin therapy. Insulin requirement ranged from 10 to 77 U. Hba1c values ranged from 5.6 to 14.2. Amongst the 19 patients who suffered from single DRC prior to heart transplantation, 12 patients had nephropathy, five patients suffered from retinopathy and two patients from neuropathy. The other 10 patients suffered from multiple DRCs. Out of these 10 patients, there were five patients with nephropathy and neuropathy and five patients with nephropathy and retinopathy. Two patients were diagnosed as having nephropathy, retinopathy and neuropathy before heart transplantation. During follow-up, three patients developed macro-angiopathy and four patients needed hemodialysis.

Figure 1 shows the cumulative survival curves for groups 1 and 2, respectively. The survival curve of group 1 was slightly lower than that of group 2, but there were no significant differences ($P = 0.07$). The survival rate of the first year after heart transplantation group 1 and group 2 was 70% and 79% ($P = 0.16$) (Table 2). Five year and 10-year survival rates were 60% and 45%, respectively, for group 1, and 68% and 53%, respectively, for group 2. Results did not differ significantly ($P = 0.20$ at 5 years, $P = 0.15$ at 10 years). We also compared the survival curves of all patients who were diagnosed as having DM before heart transplantation ($n = 192$) and the control group. This survival curves did not differ when the data of all DM patients with heart transplantation were plotted against the data of group 2 (Fig. 2). One-, 5-, and 10-year survival rates did not differ between controls and all DM patients (Table 3).

There was a trend toward more graft vascular disease-related deaths in group 1 compared with group 2 (Table 4). Within the first postoperative year, infection-related causes of death tended to be higher in group 1 than

Table 1. Clinical characteristics of heart transplant recipients with insulin-treated DM and diabetes-related complications (group 1) or controls without DM (group 2).

	Group 1 ($n = 47$)	Group 2 ($n = 1061$)	*P*-value
Male recipients	91% ($n = 43$)	86% ($n = 909$)	NS
Age at Htx (years)	59.7 ± 7.31	53.7 ± 11.59	0.001
Height	174.9 ± 7.38	174.5 ± 7.96	NS
Weight (kg)	76.8 ± 10.96	71.2 ± 10.96	0.001
Body mass index (kg/m^2)	25.1 ± 2.85	23.3 ± 3.02	<0.0001
Pulmonary vascular resistance (dyne·s·cm^{-5})	238.5 ± 126.42	214.7 ± 124.66	NS
Pulmonary arterial pressure (mmHg)	36.3 ± 9.52	31.8 ± 11.02	0.009
Serum creatinine (mg/dl)	1.5 ± 0.52	1.3 ± 0.51	0.005
Bilirubin (mg/dl)	1.1 ± 0.50	1.3 ± 1.09	NS
Triglycerides (mg/dl)	148.3 ± 84.26	130.1 ± 86.33	NS
Total cholesterol (mg/dl)	178.3 ± 52.61	187.1 ± 61.13	NS
Hba1c (%)	8.1 ± 1.90	NA	
Insulin requirement (U/day)	32.1 ± 16.86	NA	
Ischemic time (min)	197.4 ± 38.81	193.7 ± 41.56	NS
VAD bridging to Htx (%)	4% ($n = 2$)	8% ($n = 80$)	NS
Diagnosis			
Coronary artery disease	68% ($n = 32$)	40% ($n = 422$)	
Dilated cardiomyopathy	32% ($n = 15$)	46% ($n = 493$)	
Valvular disease	0% ($n = 0$)	4% ($n = 38$)	
Other	0% ($n = 0$)	10% ($n = 108$)	
Type I DM	13% ($n = 6$)	NA	
Type II DM	87% ($n = 41$)	NA	

Data are given as mean ± SD for all continuous variables. NS, not significant; NA, not assessed or not applicable; VAD, ventricular assist device; DM, diabetes mellitus.

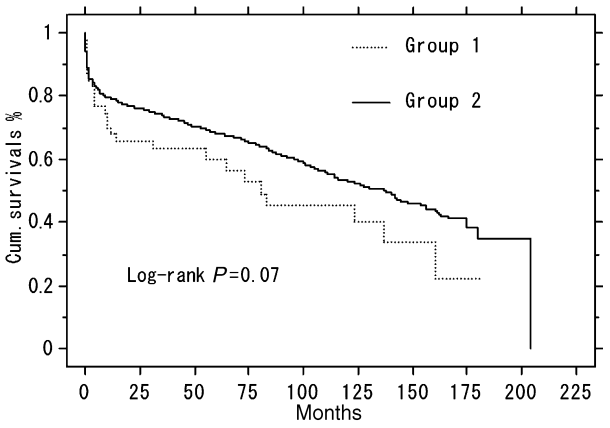

Figure 1 Kaplan–Meier survival curves for heart transplant recipients with insulin-treated diabetes mellitus (DM) and diabetes-related complications (group 1) vs. controls without DM (group 2).

Table 2. Kaplan–Meier survival estimates for heart transplant recipients with insulin-treated diabetes mellitus (DM) and diabetes-related complications (group 1) and for patients without DM (group 2).

	Group 1		Group 2		
	Number at risk	Survival rate %	Number at risk	Survival rate %	*P*-value
0 year	47	100	1061	100	
1 year	32	70	798	79	0.16
5 years	18	60	524	68	0.20
10 years	9	45	256	53	0.15
15 years	1	22	11	39	0.07

in group 2 (Table 5). In the patients with insulin-treated DM and DRCs, steroid-free immunosuppressive resulted in a higher percentage of long-term survivors (>3 years) compared with those patients who did not receive steroid-free immunosuppression (73.9% vs. 20.8%; Table 6).

Discussion

In the present study, we could demonstrate that long-term survival in heart transplant recipients with DM and DRCs did not differ significantly in comparison with patients without DM. Moreover, long-term survival was similar between study groups, if all DM patients were compared with all non-DM patients. Results confirm previous study results of our group demonstrating that 10-year survival is similar in insulin-treated DM patients compared with non-DM patients [10]. The similar survival rates of the total group of diabetics and the nondiabetics are remarkable. Results are comparable with the data of a recently published large US study [11]. Although the level of statistical significance was not achieved in that earlier study, outcome in diabetics was slightly better than in nondiabetics. One can assume that diabetics have a better compliance than nondiabetics

Journal compilation © 2007 European Society for Organ Transplantation **20** (2007) 528–533

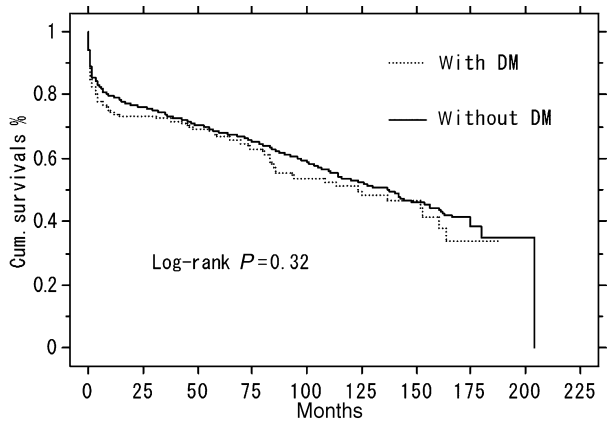

Figure 2 Kaplan–Meier survival curves for heart transplant recipients with diabetes mellitus (DM) vs. controls without DM.

Table 3. Kaplan–Meier survival estimates for all heart transplant recipients with DM and for control patients without DM.

	with DM		without DM		
	Number at risk	Survival rate %	Number at risk	Survival rate %	*P*-value
0 year	192	100	1061	100	
1 year	133	74	798	79	0.11
5 years	92	67	524	68	0.54
10 years	36	51	256	53	0.37
15 years	2	34	11	39	0.31

DM, diabetes mellitus.

Table 4. Causes of death in patients with diabetes mellitus and diabetes-related complications (group 1) and controls (group 2).

Causes of death	Group 1 ($n = 25$)	Group 2 ($n = 453$)	*P*-value
Infection	28% ($n = 7$)	17% ($n = 75$)	0.164
Rejection	12% ($n = 3$)	19% ($n = 86$)	0.597
Acute rejection	12% ($n = 3$)	6% ($n = 28$)	0.215
Malignancy	8% ($n = 2$)	13% ($n = 60$)	0.758
MOF	8% ($n = 2$)	6% ($n = 27$)	0.658
ACI	0% ($n = 0$)	5% ($n = 23$)	0.624
GVD	12% ($n = 3$)	4% ($n = 17$)	0.080
CVA	4% ($n = 1$)	4% ($n = 20$)	1.00
Primary failure	0% ($n = 0$)	3% ($n = 12$)	1.00
Technical	0% ($n = 0$)	1% ($n = 5$)	1.00
Other	12% ($n = 3$)	8% ($n = 34$)	0.446
Unknown	4% ($n = 1$)	15% ($n = 66$)	0.231

MOF, multiple organ failure; ACI, acute circulatory insufficiency. ACI includes circulatory insufficiency, acute right heart failure, and acute hemorrhage; GVD, graft vascular disease; CVA, cerebrovascular accident.

because of their experience in disease management. This might have a positive effect on disease outcome in those diabetics who do not have diabetes-related complications.

Table 5. Causes of death within 1 year in patients with diabetes mellitus and diabetes-related complications (group 1) and controls (group 2).

Cause of death	Group 1 ($n = 14$)	Group 2 ($n = 217$)	*P*-value
Infection	43% ($n = 6$)	26% ($n = 56$)	0.087
Rejection	14% ($n = 2$)	18% ($n = 39$)	1.00
Acute rejection	21% ($n = 3$)	13% ($n = 28$)	0.404
Malignancy	0% ($n = 0$)	1% ($n = 2$)	1.00
MOF	14% ($n = 2$)	10% ($n = 21$)	0.632
ACI	0% ($n = 0$)	6% ($n = 14$)	1.00
GVD	0% ($n = 0$)	1% ($n = 2$)	1.00
CVA	0% ($n = 0$)	3% ($n = 7$)	1.00
Primary failure	0% ($n = 0$)	6% ($n = 12$)	1.00
Technical	0% ($n = 0$)	2% ($n = 5$)	1.00
Other	7% ($n = 1$)	6% ($n = 14$)	0.556
Unknown	0% ($n = 0$)	8% ($n = 17$)	0.607

MOF, multiple organ failure; ACI, acute circulatory insufficiency; GVD, graft vascular disease; CVA, cerebrovascular accident.

Until the middle of the 1990s, only results on mid-term survival were available in heart transplant recipients with DM. Although some of these studies have shown that DM patients had a higher incidence of infections and a stronger progressing of graft vascular disease, 1- to 4-year survival did not differ significantly compared with non-DM patients [12,13]. In 1996, Aleksic *et al.* [14] reported that heart transplant recipients with advanced DM had a similar 1-year survival rate compared with non-DM patients, despite of slightly higher CMV infections in the group with DM. Others also found no differences in morbidity and mortality between groups with no DM, moderate DM, and advanced DM [15]. In contrast, some groups reported that long-term survival is significantly shorter in DM patients than in non-DM patients [16,17]. Older age, the higher percentage of ischemic heart disease, and the higher serum creatinine levels of the DM patients compared with the non-DM patients were made responsible for these results [16]. The trend toward a shorter survival rate in our insulin-treated DM patients with DRCs compared with non-DM patients may support these earlier data. Note that our patients had several of the aforementioned risk factors for long-term survival such as old age, high serum creatinine levels, and a high percentage of patients with ischemic heart disease (Table 1). The tendency for more graft vascular disease-related deaths in the patients with DM and DRCs compared with the patients without DM is in line with the generally high prevalence of cardiovascular disease in DM patients. Elevated concentrations of triglycerides and LDL-cholesterol, and lower HDL-cholesterol levels have been associated with the development or progression of graft vascular disease [18,19].

Interestingly, steroid-free immunosuppressive therapy resulted in a higher number of long-term survivors com-

Table 6. Immunosuppression in patients with diabetes mellitus and diabetes-related complications.

Maintenance therapy	*n*	Long-term survivors* (*n*)	Deaths (*n*)	Cause of death
Steroid-free immunosuppression				
Monotherapy	14	9	5	Infection 1 malignancy 2 other 1 unknown 1
Double drug therapy	9	8	1	Infection 1
No steroid-free immunosuppression				
Double drug therapy	10	3	7	Infection 2 Rejection 2 Other 2 GVD1
Triple drug therapy	14	2	12	Infection 3 rejection 4 MOF 2 GVD 2 CVA 1
Total	47	22	25	

*More than 3 years.

pared with no steroid-free therapy in our patients with insulin-treated DM and DRCs. Data support earlier assumptions that corticosteroids may increase the already high incidence of infection and hypertension in the group of DM patients [5–7]. Indeed, only 26% of the insulin-treated DM patients with DRCs and steroid-free immunosuppressive therapy but 79% of the DM patients with DRCs and no steroid-free immunosuppressive therapy died during follow-up. Data indicate that steroid-free immunosuppressive therapy may result in fewer infection-related and other causes of death in insulin-treated DM patients with DRCs. Our data are in line with earlier reports that DM patients are more prone to infections than non-DM heart transplant recipients [13,20].

It was known for a long time that low-dose corticosteroid medication or withdrawal of corticosteroids does not adversely affect outcome of heart transplant recipients [9,21–23]. Therefore, such a strategy is now widely accepted as routine immunosuppressive medication and may be especially successful in patients with advanced DM.

In conclusion, our retrospective study demonstrates that heart transplant recipients with preoperatively diagnosed DM and DRCs have an acceptable long-term survival rate. Consequently, advanced DM should no longer be a relative contraindication for heart transplantation. Corticosteroid-free immunosuppressive therapy may further improve long-term survival of this group of patients.

References

1. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB. Mortality among diabetics in a national sample. *Am J Epidemiol* 1988; **128**: 389.
2. Shindler DM, Kostis JB, Yusuf S, *et al.* Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol* 1996; **77**: 1017.
3. 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.
4. Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. *J Am Coll Cardiol* 2001; **38**: 421.
5. Griepp RB. A decade of human heart transplantation. *Transplant Proc* 1979; **11**: 285.
6. Lower RR, Szentpetery S, Quinn J, Thomas FT. Selection of patients for cardiac transplantation. *Transplant Proc* 1979; **11**: 293.
7. Badellino MM, Cavarocchi NC, Narins B, *et al.* Cardiac transplantation in diabetic patients. *Transplant Proc* 1990; **22**: 2384.
8. Livi U, Bortolotti U, Faggian G, Chiominto B, Mazzucco A, Gallucci V. Safety of cyclosporine monotherapy after heart transplantation. *Transplant Proc* 1990; **22**: 1441.
9. Livi U, Luciani GB, Boffa GM, *et al.* Clinical results of steroid-free induction immunosuppression after heart transplantation. *Ann Thorac Surg* 1993; **55**: 1160.
10. Tenderich G, Schulte-Eistrup S, Petzoldt R, Koerfer R. Cardiac transplantation in patients with insulin treated diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2000; **108**: 249.
11. Russo MJ, Chen JM, Hong KN, *et al.* Survival after heart transplantation is not diminished among recipients with uncomplicated diabetes mellitus: an analysis of the United States Network of Organ Sharing Database. *Circulation* 2006; **114**: 2280.
12. Rhenman MJ, Rhenman B, Icenogle T, Christensen R, Copeland J. Diabetes and heart transplantation. *J Heart Transplant* 1988; **7**: 356.
13. Munoz E, Lonquist JL, Radovancevic B, *et al.* Long-term results in diabetic patients undergoing heart transplantation. *J Heart Lung Transplant* 1992; **11**: 943.
14. Aleksic I, Czer LS, Freimark D, *et al.* Heart transplantation in patients with diabetic end-organ damage before transplantation. *Thorac Cardiovasc Surg* 1996; **44**: 282.
15. Lang CC, Beniaminovitz A, Edwards N, Mancini DM. Morbidity and mortality in diabetic patients following cardiac transplantation. *J Heart Lung Transplant* 2003; **22**: 244.

16. Czerny M, Sahin V, Fasching P, *et al.* The impact of diabetes mellitus at the time of heart transplantation on long-term survival. *Diabetologia* 2002; **45**: 1498.
17. Klingenberg R, Gleissner C, Koch A, *et al.* Impact of pre-operative diabetes mellitus upon early and late survival after heart transplantation: a possible era effect. *J Heart Lung Transplant* 2005; **24**: 1239.
18. Kapadia SR, Nissen SE, Ziada KM. Impact of lipid abnormalities in development and progression of transplant coronary disease: a serial intravascular ultrasound study. *J Am Coll Cardiol* 2001; **38**: 206.
19. Valantine H, Rickenbacker P, Kemna M. Metabolic abnormalities characteristic of dysmetabolic syndrome predict the development of transplant coronary artery disease: a prospective study. *Circulation* 2001; **103**: 2144.
20. Marelli D, Laks H, Patel B, *et al.* Heart transplantation in patients with diabetes mellitus in the current era. *J Heart Lung Transplant* 2003; **22**: 1091.
21. Yacoub M, Alvizatos P, Khagani A, Mitchell A. The use of cyclocporine, azathioprine and antithymocyte globuline with or without low dose steroids for immunosuppression of cardiac transplant patients. *Tranplant Proc* 1985; **17**: 221.
22. Oaks TE, Wannenberg T, Close SA, Tuttle LE, Kon ND. Steroid-free maintenance immunosuppression after heart transplantation. *Ann Thorac Surg* 2001; **72**: 102.
23. Felkel TO, Smith AL, Reichenspurner HC, *et al.* Survival and incidence of acute rejection in heart transplant recipients undergoing successful withdrawal from steroid therapy. *J Heart Lung Transplant* 2002; **21**: 530.

