Effects of Conversion from Cyclosporine to Tacrolimus on Left Ventricular Structure in Cardiac Allograft Recipients

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Twelve heart transplant recipients selected for conversion from cyclosporine to tacrolimus because of adverse effects of cyclosporine therapy underwent echocardiography at baseline and 6 months after conversion. Left ventricular mass decreased by 24% and left ventricular geometry returned toward normal at 6 months after conversion, without significant changes in blood pressure. J Heart Lung Transplant 2005;24:1969–72. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

Left ventricular hypertrophy (LVH) occurs frequently after orthotopic heart transplantation.[1] The causes of LVH after transplantation are unclear but could be multifactorial to include hypertension, immune injury, and the intrinsic effect of immunosuppressant drugs.[1,2] Cyclosporine therapy, the mainstay of immunosuppression in cardiac transplantation, is often complicated by the development of hypertension, LVH, hirsutism, dyslipidemia, and gingival hyperplasia.[3] An alternative regimen using tacrolimus, a more potent immunosuppressant than cyclosporine, is being used to avoid these side effects.[4] However, whether conversion to tacrolimus from cyclosporine prevents LVH or alters LV structure in the adult cardiac allograft has not been examined.

METHODS

Study Population

Twelve cardiac allograft recipients who received transplants at the Medical University of South Carolina were studied in a prospective fashion from November 2001 to July 2002, with follow-up completed in January 2003. Patients were selected for conversion from cyclosporine to tacrolimus based on the presence of 1 or more of the following reasons: cyclosporine-induced hypertension (systolic blood pressure of more than 135 mm Hg and diastolic blood pressure of more than 85 mm Hg despite aggressive anti-hypertensive therapy), refractory hyperlipidemia (total cholesterol greater than 200 mg/dl and low-density lipoprotein greater than 100 mg/dl despite lipid lowering agents), hirsutism, or gingival hyperplasia. In addition to cyclosporine, our standard immunosuppressant regimen included 5 mg/day prednisone in every patient plus either mycophenolate mofetil (9 patients) or azathioprine (3 patients). The institutional review board approved the protocol, and patients gave written informed consent before enrollment.

Protocol

Echocardiographic and blood pressure measurements were performed by using standard techniques at baseline on cyclosporine therapy before conversion and after 6 months of tacrolimus therapy. At both time points, patients underwent the standard post-transplant follow-up, including endomyocardial biopsy, to determine rejection status. Echocardiographic measurements and calculation of volumes were made using the American Society of Echocardiography criteria. LVH was defined by mean LV mass values greater than 150 g.[1]

Statistical Analysis

The Student's *t*-test for paired observations was used to compare the difference between values at baseline and at 6 months. Results are reported as mean ± SEM; $p < 0.05$ was considered statistically significant. The relative risk was calculated with the Woolf procedure and was reported with 95% confidence interval.

RESULTS

Clinical Data

At baseline, 12 patients (10 men and 2 women), mean age 57 ± 3.7 years, were converted from cyclosporine to tacrolimus. At the time of conversion, the average time from transplant was 2.5 ± 1.0 years (range, 0.75–4.5 years). The reasons for conversion were refractory hypertension in 7 patients, dyslipidemia in 3

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patients, and gingival hyperplasia in 2 patients. Before conversion, all patients were being treated for hypertension, most patients were taking 3 or more anti-hypertensive agents.

After conversion to tacrolimus, blood pressure management did not significantly change in terms of dosage, number, or classes of anti-hypertensive agents used. Moreover, the difference in mean blood pressure readings at baseline on cyclosporine vs at 6 months after conversion to tacrolimus was not statistically significant (Table 1). No patients had clinical or histologic evidence of rejection either at the time of conversion or at 6 months after conversion.

Echocardiographic Data

Before conversion from cyclosporine to tacrolimus, all 12 patients had evidence of concentric remodeling or LVH (Table 1.) Six months after conversion to tacrolimus, the mean LV mass showed a 24% reduction, with LV mass decreasing in all 12 patients (Figure 1A). LV wall thickness was reduced 17%, and the ratio of LV end-diastolic volume to LV mass increased by 30%. The observed change in LV mass and geometry seemed to be independent of blood pressure at baseline and at 6 months (Figure 1B), and occurred irrespective of the primary indication for conversion to tacrolimus. The calculated risk ratio of a patient having LVH when treated with cyclosporine compared with tacrolimus was 2.8 (6.3–1.2).

DISCUSSION

This study demonstrates that conversion from cyclosporine to tacrolimus in adult heart transplant recipients (1) resulted in reverse remodeling of the cardiac allograft, characterized by a 24% reduction in LV mass and normalization of LV geometry; and (2) these structural changes seemed to occur independent of changes in hemodynamic variables such as blood pressure. Hypertension occurs in more than 90% of cyclosporine-treated heart transplant recipients and may be due to effects of cyclosporine and possibly the loss of native cardiac innervation in orthotopic heart transplantation.[5] There is not always a strong correlation between the presence of hypertension and the development or regression of LV hypertrophy in cardiac transplant patients, suggesting that while hypertension may contribute to the development of cardiac allograft hypertrophy, this process is multifactorial and may also be attributed to immune mechanisms.[2]

In the current study, unlike previous multicenter trials, conversion from cyclosporine to tacrolimus did not result in a significant decrease in blood pressure despite a consistent decrease in LV mass being observed for all enrolled patients. This was because the indication for conversion to tacrolimus was not based solely on the presence of resistant hypertension, the number of patients studied was smaller, and the average blood pressure for our patients was lower than previous multicenter studies.[3] Although mean blood pressures appear lower in the tacrolimus group, a direct correlation between blood pressure change and LV mass regression is not evident (Figure 1B).

Appropriate control of blood pressure in heart transplant recipients usually results in a 10% reduction in LV mass after 1 year of anti-hypertensive therapy[6]; whereas in our study, conversion to tacrolimus resulted in a 24%

Table 1. Clinical, Hemodynamic, Functional and Structural Parameters

Parameters	Baseline	Six Months	*p* Values
Systolic blood pressure (mm Hg)	136 ± 6	123 ± 5	$p = 0.137$
Diastolic blood pressure (mm Hg)	85 ± 3	78 ± 4	$p = 0.190$
Mean Arterial Pressure (mm Hg)	102 ± 3	93 ± 5	$p = 0.141$
Heart rate (bpm)	85 ± 4	87 ± 3	$p = 0.141$
Body surface area (m^2)	2.1 ± 0.1	2.1 ± 0.1	$p = 0.190$
Cyclosporine (ng/ml)	178 ± 14		
Tacrolimus (ng/ml)		10 ± 1	
LV end-diastolic volume (ml)	94 ± 23	94 ± 28	$p = 0.920$
LV end-systolic Volume (ml)	22 ± 7	18 ± 7	$p = 0.030$
Ejection fraction (%)	67 ± 2	72 ± 3	$p = 0.178$
End-diastolic wall thickness (cm)	1.2 ± 0.05	0.99 ± 0.04	$p < 0.001$
LV mass (g)	256 ± 16	195 ± 13	$p = 0.002$
Dimension/wall thickness	3.82 ± 0.23	4.71 ± 0.27	$p = 0.004$
Volume/mass (ml/g)	0.38 ± 0.03	0.49 ± 0.05	$p = 0.006$
E/A ratio	2.1 ± 0.3	1.8 ± 0.2	$p = 0.232$
Deceleration time (m/sec)	161 ± 12	171 ± 13	$p = 0.554$
IVRT (m/sec)	69 ± 4	69 ± 3	$p = 0.511$

Values reported as mean ± SEM. E/A ratio, early diastolic velocity/late filling velocity; IVRT, is volumetric relaxation time; LV, left ventricular; Volume/mass, left ventricular end diastolic volume/left ventricular mass.

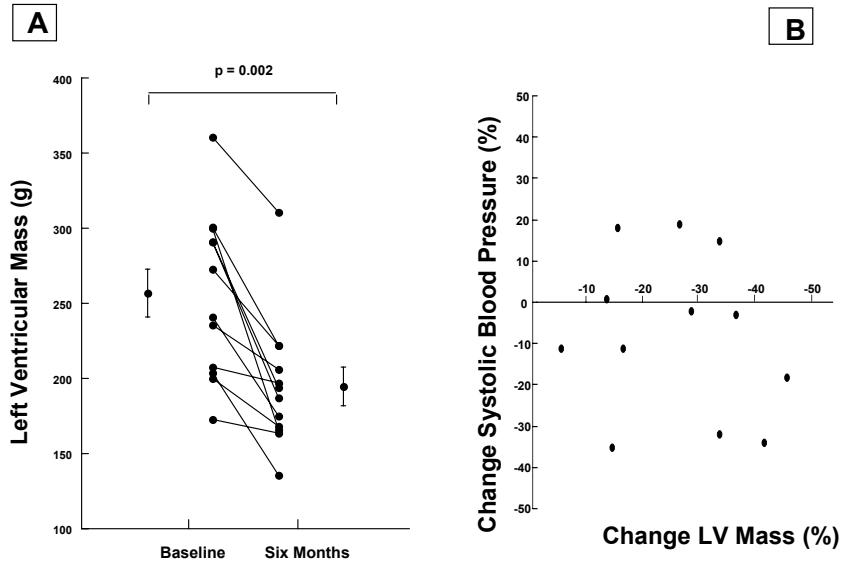

Figure 1. (A) Changes in left ventricular (LV) mass before (baseline) and after (6 months) conversion from cyclosporine to tacrolimus. (B) Relationship between the percent change in LV mass and the percent change in systolic blood pressure that occurred after conversion from cyclosporine to tacrolimus.

regression of LV mass at just 6 months. The extent of this change is suggestive of other contributory mechanisms than hypertension.

Treatment with immunosuppressive agents may modify the activation of growth regulatory cytokines like tumor necrosis factor-α and transforming growth factor-β[7] and the consequent development of LVH, but whether cyclosporine and tacrolimus differ in their effect on cytokine activation is not known. Initial reports suggested that tacrolimus may cause an increase in LV mass and even the development of hypertrophic cardiomyopathy.[8] These studies were limited by the small number of patients studied, the concomitant use of high doses of steroids, high serum levels of tacrolimus, the presence of significant hypertension, and involved patients who had undergone transplantation of organs other than the heart. When tacrolimus was examined in larger cohorts, either alone or in comparison with cyclosporine, tacrolimus was shown to either cause no increase in LV mass or an increase in LV mass equivalent to that seen with cyclosporine.[9]

Limitations

The data from the current study suggest, but do not prove, that the structural changes observed after conversion from cyclosporine to tacrolimus may have been related to differences in the effects that these immunosuppressive agents have on factors other then hemodynamics, such as the differences in the extent or pathway by which they alter growth regulatory mechanisms. The apparent lack of a relationship between the blood pressure and LV mass regression should be interpreted with caution because of the small number of patients studied.

CONCLUSION

This study demonstrates that (1) conversion from cyclosporine to tacrolimus in adult heart transplant recipients resulted in reverse remodeling of the cardiac allograft, characterized by a 24% reduction in LV mass and normalization of LV geometry, and (2) that these structural changes seemed to occur independent of change in hemodynamic variables such as blood pressure.

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