

Renal dysfunction after orthotopic heart transplantation: incidence, natural history, and risk factors

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Abstract

Background. Renal dysfunction is a common complication after orthotopic heart transplantation (HT). The importance of factors other than exposure to immunosuppressive drugs is unclear. The purpose of this study was to determine the incidence and natural history of renal dysfunction following heart transplantation, and to evaluate a number of variables as risk factors for this condition.

Methods. We examined the creatinine levels at 1, 6, 12, 24, and 60 months in 262 consecutive heart transplant patients who survived at least 1 year. The potential risk factors included pre- and posttransplantation diabetes mellitus, arterial hypertension, and drugs used to control arterial hypertension.

Results. 17.2% of patients showed mild renal dysfunction (creatinine 1.5-2.5 mg/dL) and 1.9% moderate dysfunction (creatinine >2.5 mg/dL) at 1 month; 29.8% showed mild and 1.1% moderate dysfunction at 6 months; 33.2% showed mild and 1.9% moderate dysfunction at 1 year; 40% showed mild, 0.9% moderate and 0.4% severe dysfunction (requiring dialysis or renal transplantation) at 2 years; and 43.6% showed mild, 1.7% moderate and 0.9% severe dysfunction at 5 years. None of the conditions analyzed as possible risk factors showed a significant association with renal dysfunction except the use of diuretics.

Conclusion. The incidence of renal dysfunction after orthotopic heart transplantation was 33.6% within the first year after transplant and 44% within the first five years, although more than 95% of cases were mild. The incidence increased with time after transplantation. Renal dysfunction seems likely to be multifactorial in origin, but no individual risk factors were identified.

Renal Dysfunction is a common complication of heart transplantation (HT). In a small number of cases it leads to requirements for dialysis or kidney transplantation. According to past estimates, 3% to 7% of patients who survive the first month after HT develop terminal kidney failure between 5 and 10 years later.^{1, 2 and 3} Posttransplant renal dysfunction is considered to be chiefly due to the well-documented nephrotoxicity of calcineurin inhibitors,^{3, 4, 5 and 6} although pretransplant function is also relevant.⁷ A number of other possible risk factors have also recently been suggested, including dyslipidemia,⁸ posttransplant arterial hypertension⁸ and pre- and posttransplant diabetes mellitus.⁹ The real influence of these variables is unknown. It seems likely that the incidence of posttransplant renal dysfunction may have changed since the introduction of less aggressive immunosuppressive protocols using lower doses of cyclosporine or tacrolimus and the use of other immunosuppressants, such as mycophenolate mofetil or rapamycin. The objective of this study was to determine the incidence and natural history of renal dysfunction following heart transplantation, and to evaluate pre- and posttransplantation diabetes mellitus, arterial hypertension and the major classes of antihypertensive drugs as risk factors.

Patients and methods

Patients

Among the 363 patients who underwent orthotopic heart transplantation in the Juan Canalejo Hospital of A Coruña between April 1991 and May 2001, we studied the 262 including 221 men and 41 women of mean age 54 ± 11.38 years, who had not undergone an accompanying transplantation operation, had survived for at least 1 year after HT and were followed at our hospital.

Between 1991 and 1998, the immunosuppressive protocol for HT patients consisted of induction with OKT3 and maintenance with cyclosporine, azathioprine and prednisone. Trough levels of cyclosporine in whole blood, as measured by the FPIA-TDX method, were maintained at 300 to 350 ng/mL for the first month, 250 to 350 ng/mL for the second and third months, 150 to 250 ng/mL between the third and 24th

month, and ca, 150 ng/mL thereafter. For patients who underwent HT after April 1998 this protocol was replaced by a combination of cyclosporine, mycophenolate mofetil, and prednisone, with whole blood cyclosporine trough levels maintained at 250 to 350 ng/mL in the first month, 200 to 300 ng/mL in the second and third months, 100 to 200 ng/mL between the third and 24th month, and around 100 ng/mL thereafter. Of the 135 patients who had initially received cyclosporine and azathioprine, 82 were at some time switched to cyclosporine and mycophenolate mofetil, because of rejection or impaired kidney function. Since 1997, cyclosporine has been replaced by tacrolimus when the side effects of cyclosporine have been persistent, and when the patient experienced rejection refractory to combined treatment with cyclosporine, mycophenolate mofetil and prednisone, as indicated by an ISHLT rating of 3A or worse on at least two endomyocardial biopsies performed 10 days after successive intravenous steroid treatment;¹⁰ tacrolimus levels in whole blood were kept between 5 and 20 ng/mL. As the result of these changes in immunosuppressive strategy, by the end of the period for which they supplied data for this study, 59.9% of the patients were taking cyclosporine, mycophenolate mofetil, and prednisone; 24.1% tacrolimus, mycophenolate mofetil, and prednisone; 13.5% cyclosporine, azathioprine, and prednisone; and 2.5% tacrolimus, azathioprine, and prednisone.

Methods

From the clinical records of the patients, the following data were retrospectively obtained: creatinine levels at 1, 6, 12, 24, and 60 months after HT; donor age and sex, cause of the cardiopathy leading to HT; number and severity of rejection episodes; years since HT; presence or absence of pre-HT diabetes mellitus; presence or absence of post-HT diabetes mellitus and post-HT arterial hypertension. Renal dysfunction was considered mild if the creatinine level was 1.5 to 2.5 mg/dL, moderate if creatinine level was >2.5 mg/dL, and severe if dialysis or kidney transplant were required. Patients were deemed diabetic if they were taking oral antidiabetics or insulin to control glycemia, and to be hypertensive if their systolic or diastolic blood pressures were ≥ 160 and 95 mm Hg, respectively, on any post-HT follow-up examination. All hypertensive patients were treated with diltiazem, amlodipine, a diuretic, an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist, or with some combination of these drugs.

Statistical analysis

Continuous variables are reported as mean values \pm standard deviations, and hypotheses were tested using Student's *t*-test. Qualitative variables are reported as percentages, and hypotheses were tested using the chi-squared test.

Results

In 45.4% of cases HT was performed because of ischemic cardiomyopathy. Following HT, 63.4% of patients suffered at least one rejection episode with an ISHLT rating of at least 3A. Before HT, 233 patients (89%) displayed normal kidney function. Follow-up time was 1813 ± 960 days (shortest, 371 days; longest, 4058 days).

Creatinine data were available for 262 patients at 1 and 6 months post-HT, and for 259, 225, and 117 respectively, at 1, 2, and 5 years post-HT. Between 1 and 60 months post-HT the proportion of patients with mild dysfunction rose from 17.2% to 43.6%, while the proportion with moderate dysfunction remained almost invariant at 1% to 2%; and the only case of severe dysfunction began between 1 and 2 years after HT (Table 1).

Table 1.

	1 month	6 months	1 year	2 years	5 years
No dysfunction	212 (80.9%)	181 (69.1%)	168 (64.9%)	132 (58.7%)	63 (53.8%)
Renal dysfunction	50 (19.1%)	81 (30.9%)	91 (35.1%)	93 (41.3%)	54 (46.2%)
Mild	45 (17.2%)	78 (29.8%)	86 (33.2%)	90 (40.0%)	51 (43.6%)
Moderate	5 (1.9%)	3 (1.1%)	5 (1.9%)	2 (0.9%)	2 (1.7%)
Severe	0	0	0	1 (0.4%)	1 (0.9%)
Total	262 (100%)	262 (100%)	259 (100%)	225 (100%)	117 (100%)

There were no significant differences in the incidence of renal dysfunction 1 year post-HT between patients with and without pre-HT diabetes mellitus, post-HT diabetes mellitus or post-HT arterial hypertension; or between patients who were and were not taking diltiazem, amlodipine, an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist; but there was a significant difference in an increased incidence between those who were versus were not taking a diuretic ($P = .002$).

Discussion

The total incidence of renal dysfunction after HT at our center is 35.1% after 1 year and 46.2% after 5 years. These figures contrast with the report of Greenberg et al² that 94% of a group of patients, including some with pre-HT renal dysfunction, some of whom were given high cyclosporine doses, displayed creatinine levels higher than 1.7 mg/dL at 3 years after HT, findings may be in agreement with Esposito et al⁸ more recent observation that among patients with normal pre- and peri-HT kidney function the incidence was 20.2% at 3 years post-HT. The incidence of terminal renal dysfunction among our patients was zero during the first year and only 0.9% after 5 years (one other patient developed terminal renal dysfunction after 9 years), whereas figures of 4.5% to 7.0% between 5 and 10 years after HT have been observed in other series.^{2, 3, 11 and 12} We believe that the relatively low incidence of mild and severe renal dysfunction in our series, which included patients with pre-HT dysfunction, reflects the trend towards the use of lower doses of calcineurin inhibitors and the addition of mycophenolate mofetil.

Although it has been suggested that pre- and/or post-HT diabetes mellitus might favor the development of renal dysfunction, neither this study nor others^{8 and 9} support this suggestion. We did not find any relationship between renal dysfunction and post-HT arterial hypertension. These conditions apparently had no influence on the development of renal dysfunction possibly due to HT patients constituting a highly motivated, closely monitored group who continue their therapeutic regimens more strictly than diabetic or hypertensive patients in general.

The only class of antihypertensive drug associated with renal dysfunction in this study was diuretics. However, this would seem to reflect their use to treat the dysfunction itself, rather than an increase in the risk of dysfunction due to their use to treat arterial hypertension.

Conclusions

In our center, the incidence of renal dysfunction after HT increases from 19.1% at 1 month to 35.1% at 1 year and 46.2% at 5 years. Almost all cases were mild. Moderate renal dysfunction affected just 1% to 2% of patients. Dialysis/kidney transplant was required in just one case within 5 years of HT (5-year incidence 0.9%). Although the toxicity of calcineurin inhibitors and pre-HT kidney function seem likely to be major determinants of post-HT renal dysfunction, its etiology appears to be multifactorial. However, this study failed to identify other individual risk factors.

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