Original Article

Renal insufficiency after heart transplantation: a case-control study

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Abstract

Background. In Rotterdam 304 heart transplants have been performed since 1984. End-stage renal failure, necessitating renal replacement therapy, has developed in 24 patients (8%) after an interval of 25–121 months (median 79 months). After starting renal replacement therapy one-year survival was only 60%. Overall survival after heart transplantation, however, was favourable: 5 and 10 year survival rates of 79% and 50% respectively.

Methods. A case-control study was performed to identify possible risk factors in cases who went on to develop end-stage renal failure compared to controls.

Results. We found that renal failure was not limited to elderly patients with ischaemic heart disease, but also occurred in young patients having dilated cardiomyopathy. A significant rise in the serum creatinine was found in cases compared to controls as early as 3 months after transplantation. Cyclosporin dose and trough levels were not different between cases and controls. Neither were there differences in the use of calcium-antagonists or other antihypertensive drugs, allopurinol or diuretics. Rejection incidence was also similar between the two groups.

Conclusions. Renal failure after heart transplantation is a long term complication of cyclosporin use that is not limited to elderly patients with ischaemic heart disease. Cyclosporin dose and trough levels in the cases were not different from patients maintaining stable good renal function, indicating that cyclosporin nephrotoxicity is the result of an individually determined susceptibility to cyclosporin. Suggestions for future strategies to prevent renal failure are given.

Key words: nephrotoxicity cyclosporin heart transplantation side effects

Introduction

The results of cardiac transplantation have improved considerably over the last two decades. Especially the introduction of cyclosporin as an immunosuppressive agent has made cardiac transplantation a viable option in end-stage heart failure. Patient survival rates of 50% at 10 years are now achieved and in general the quality of life during these years is excellent. An inevitable consequence of improved survival is that an increasing number of patients is faced with the long-term complications of transplantation [1]. The three most important complications are: development of coronary artery disease, an increased risk of malignancy and progressive renal dysfunction as a result of cyclosporin [2]. In contrast to acute cyclosporin nephrotoxicity which is usually reversible, chronic cyclosporin nephrotoxicity is accompanied by pronounced anatomical changes, such as interstitial fibrosis, tubular atrophy and arteriolar hyalinosis [3,4], and is not reversible [5,6]. The pathogenesis of chronic cyclosporin nephrotoxicity is unclear [7]. What is clear is that 2 years after heart transplantation renal function is moderately impaired (serum creatinine $>150\,\mu mol/l$) in half of the patients, and that severe renal impairment (serum creatinine $>250\,\mu mol/l$) occurs in more than 10% of these patients after 4 years [8]. Most heart transplant centers have a number of patients that have developed end-stage renal failure (ESRF) and who are on dialysis [9]. In Rotterdam a total number of 305 heart transplants have been performed since 1984. Twenty-four (8%) patients have progressed towards ESRF, requiring renal replacement therapy. This high incidence of renal failure urged us to see whether patients at risk for ESRF could be identified at an early stage.

Patients and methods

Patients

From 1984 to February 1997 in Rotterdam a total of 305 heart transplants were performed in 304 patients. Patients were only selected for cardiac transplantation when renal function was reasonably preserved (creatinine clearance $>30\,ml/min$). Of the 304 heart recipients 24 have reached ESRF. These patients will be referred to as 'cases'. A control group ('controls') was selected according to the following criteria: (i) date of transplant close to that of the case, (ii) survival after transplantation at least 3 years, and (iii) serum

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creatinine at follow-up of <150 μmol/l. All cases and controls in this study were transplanted between January 1985 and May 1992. The clinical characteristics of cases and controls are shown in Table 1. Follow-up of all patients was performed at our out-patient clinic. In all patients progressing to ESRF duplex ultrasound was performed in order to exclude other causes of renal failure. In two patients in which duplex scanning indicated suspicion of renal artery stenosis a renal angiogram was performed, in both instances failing to demonstrate abnormalities. A renal biopsy was performed in only three patients, showing marked cyclosporin-related changes in each case.

Immunosuppression

Since 1984 several immunosuppressive regimens have been used in our heart transplant unit. Trials have been performed using induction treatment with OKT3, rATG and BT563 (a monoclonal anti Interleukin-2 Receptor antibody). All patients received cyclosporin (Sandimmune) treatment in the early postoperative period as well as for maintenance treatment. Cyclosporin administration in the first weeks after transplantation was initiated at 10 mg/kg/day, aiming at trough levels between 200 and 250 ng/ml (polyclonal assay; note: see Laboratory measurements). From the third postoperative month onwards doses were slowly tapered, aiming at blood levels between 100 and 150 ng/ml (polyclonal assay). Maintenance treatment further consisted of prednisone (after the first month in a dose of 10 mg/day). Rejection surveillance was performed by endomyocardial biopsy. The grading of biopsies was initially done according to the conventional criteria of Billingham [10] and later using the guidelines of the International Society of Heart Transplantation [11].

Laboratory measurements

Before 1988 a polyclonal antibody assay (Cyclotrac-SP) was used for the determination of cyclosporin trough levels. From 1988 until 1993 cyclosporin trough levels were measured using a monoclonal antibody assay (RIA) directed against the native compound in plasma. From 1993 a whole blood assay (Cyclotrac Incstar) has been in use. For this study almost all relevant cyclosporin trough levels were measured before 1993. Target cyclosporin trough levels, determined with the polyclonal vs the monoclonal cyclosporin assay, were considerably different: at 3 months 150 vs 250 ng/ml and at 12–24 months 50 vs 150 ng/ml respectively.

Serum creatinine was measured using a modified Jaffé reaction [12]. Total cholesterol levels were available from all patients at 1 year post-transplantation.

Table 1. Baseline characteristics

	Cases	Controls
Median age at tx (range)	48 (15–59)	46 (13–57)
Underlying disease		
Ischaemic heart disease	13	11
Dilated cardiomyopathy	8	11
Other	3	2
Body weight at tx (kg)	70 (51–92)	70 (40–85)
Gender (M/F)	23/1	22/2

Statistical methods

The data for this manuscript were retrospectively obtained by means of patient chart review. As most data did not follow a normal distribution they are presented as median and range unless stated otherwise. For the comparison of serum creatinine, cyclosporin doses and trough levels between cases and controls, we used the Student's t-test (unpaired, two-tailed). The SPSS statistical package was used. P-values below 0.05 were considered significant. Survival curves for patients reaching ESRD were made using Kaplan-Meier techniques.

Results

As shown in Table 1 cases and controls were not different with respect to age, gender, underlying heart disease or body weight. There were also no differences in renal function (serum creatinine) before transplantation (see Table 2). Calculated creatinine clearances, using the Cockroft-Gault formula, were not different either (cases vs controls: mean 64 vs 62; median 65 vs 61; data not shown). However, serum creatinine was significantly higher in the cases, as early as 3 months after transplantation. Cyclosporin dose and trough levels at 3, 12 and 24 months after transplantation were similar (Table 3). There were also no differences between cases and controls in the use of calcium antagonists (18/24 vs 15/24 in cases and controls respectively) or other anti-hypertensive drugs (mean number of drugs 1.2 vs 0.9 respectively), in the use of allopurinol (4/24 vs 4/24 respectively) or in the use of

Table 2. Serum creatinine in heart transplant recipients before and 3 and 12 months after transplantation

Serum creatinine	Cases		Controls	
	Median	Range	Median	Range
Before transplantation	114	69–152	105	63–116
t=3 months	133*	102–207	116	56–199
t=12 months	184**	140–459	126	83–176

*$P<0.05$; **$P<0.05$ two-tailed unpaired t-test, cases compared to controls.

Table 3. Cyclosporin (CsA) dose and trough level in cases vs controls. No significant differences were found

	Cases		Controls	
	Median	Range	Median	Range
CsA dose (mg/kg)				
t=3 months	7.5	3.6–12.0	7.3	3.9–11.1
t=12 months	6.1	2.8–10.0	5.8	3.5–16.0
t=24 months	5.8	2.9–8.9	4.9	3.4–9.5
CsA trough level (ng/ml)				
t=3 months	120	60–230	120	70–250
t=12 months	84	50–184	90	50–200
t=24 months	60	30–130	75	40–160

diuretics (2/24 *vs* 3/24 patients). Cholesterol levels were not different between the two groups (respectively mean 7.2 *vs* 7.4 mmol/l). Treatment with non-steroidal anti-inflammatory drugs and nephrotoxic antibiotics was avoided if possible in all heart recipients and was not different between the two groups. The number of acute rejection episodes within the first year was also similar in both groups.

The median interval between heart transplantation and the occurrence of ESRF was 79 months (range: 25–121 months). Renal replacement therapy consisted of peritoneal dialysis (CAPD) in 11 patients and hemodialysis (CIHD) in 13 patients. Five patients underwent kidney transplantation. A survival curve for the total heart transplant population in Rotterdam (Figure 1) shows a 5 and 10 year survival of 79% and 50% respectively. Figure 2 shows the survival curve for the patients from the moment they started dialysis treatment.

Discussion

This case-control study was performed in a center with a relatively high incidence of end-stage renal failure (8%) in heart transplant recipients. That renal replacement therapy in these patients is associated with major morbidity is beyond doubt. The prognosis for these
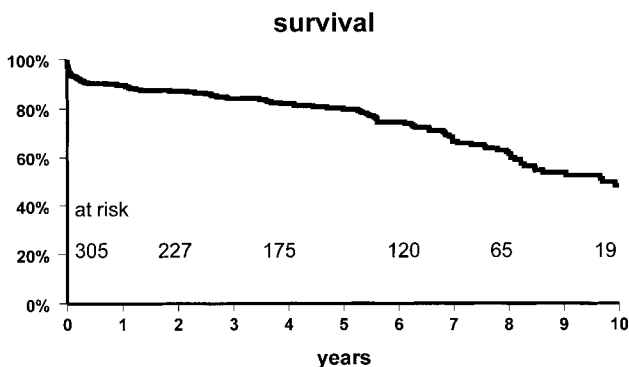
survival

Fig. 1. Survival after heart transplantation (*n* = 305) in Rotterdam.
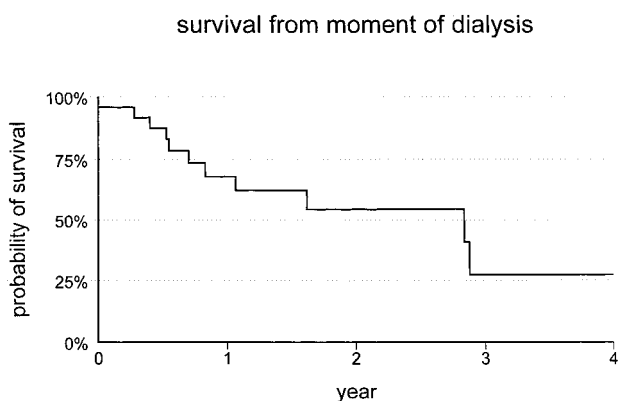
survival from moment of dialysis

Fig. 2. Survival of heart transplant recipients after reaching end-stage renal failure and starting renal replacement therapy (*n* = 24).

patients that develop renal failure is bleak, as shown in Figure 2. One year after starting dialysis treatment 40% of patients are dead. Stanford reported an ESRF incidence of 14/416 (3.4%) in heart transplant recipients surviving at least 6 months after transplantation and with a median follow-up of 52 months [13]. Bryan Myers reported on a cumulative incidence of 10% by actuarial analysis [14]. The Papworth group found a similar incidence of 17/495 (3.4%) in their heart transplant group (patients surviving at least 3 months) [2]. A recent paper from the Columbia Presbyterian Medical Center in New York reported an incidence of ESRF of 6.5% (19/293) in all cardiac recipients surviving at least 3 years [15]. They also found an increased risk of death compared to the other cardiac allograft recipients, with a 1-year survival after starting haemodialysis of 75%.

Why we have such a large number of patients with ESRF compared to these centres is not clear. A potential explanation could be a difference in the pre-transplantation selection criteria. In our centre only patients with a creatinine clearance above 30 ml/min are accepted for heart transplantation. Whether the renal function limit in the other centres is more strict than ours is not known. If so, this could explain their lower incidence of ESRF. What militates against this possibility is the fact that we could not find a difference in pre-transplant creatinine clearance between cases and controls and that even some patients with a pre-transplant creatinine clearance above 70 ml/min developed renal failure. The results of this study do not support the strategy of applying even more stringent renal function criteria in the selection of transplant candidates in our centre.

Another possible explanation for the relatively high number of patients with ESRF is that we have treated our patients with a higher dose of cyclosporin than the other centres have. Comparison of cyclosporin treatments is complicated by the fact that over time several assays have been used for trough level measurement and that transplant centres may have used different assays. We have used maintenance treatment with cyclosporin and prednisone only. Many centres have treated their patients with triple drug regimens (cyclosporin, prednisone, azathioprine), enabling them to reduce the cyclosporin dosage. Our data, however, show that cases and controls did not differ in respect to either cyclosporin dosage or cyclosporin trough levels. This suggests that cyclosporin nephrotoxicity is not simply a matter of dose–effect relationship, but more a result of individual susceptibility to the nephrotoxic effects of cyclosporin. This is also the experience of others [16,17]. Some studies however do relate renal deterioration to higher cyclosporin doses and trough levels [18,19]. As only trough levels were measured one can not exclude the possibility that the trough cyclosporin levels did not correlate well with the total cyclosporin area under the curve (AUC) or whatever other measurement to calculate the total drug burden. It is possible that cyclosporin AUC's or cyclosporin peak concentrations in the patients developing renal

failure were higher, especially because during the study period all patients were still on the Sandimmune formulation.

Another interesting possibility is the hypothesis that patients developing severe cyclosporin nephrotoxicity have a cytokine genotype, that makes them susceptible to the adverse effects of cyclosporin [20]. TGF-β gene polymorphism may well be one of these cytokines, explaining why some cyclosporin treated patients do develop nephrotoxicity, whereas others do not [21].

Remarkable is the observation that renal failure is not limited to patients with ischemic heart disease or to the older patient group. This is in contrast to the findings of Sehgal et al., who found that heart recipients with moderate renal failure were older than patients with low serum creatinines [22]. In our centre the patients with ESRF form a representation of the overall heart transplant patient population.

The favourable 5 and 10 year survival rates of 79% and 50% in our heart transplant programme, indicate that although we do have a high incidence of renal failure the overall prognosis after heart transplantation in Rotterdam is good. It may well be that the occurrence of renal failure we observe in our centre is caused by the relatively agressive cyclosporin treatment in the first year(s) after transplantation. The morbidity associated with this high dose cyclosporin treatment could be offset by an associated beneficial effect in early survival in these patients. Apart from length of survival, a high quality of life after heart transplantation remains a major goal. To achieve this strategies to lower the incidence of renal failure certainly have to be developed. Potential solutions include treatment with modified cyclosporin doses in patients with early mild renal function impairment [23]. Myers et al. compared low versus high dose cyclosporin treatment and found only marginal differences [24]. Waser et al. also found that late cyclosporin reduction did not improve renal function and even observed an associated increased risk of cellular rejection in these patients [25]. Combining cyclosporin with other drugs, such as mycophenolate mofetil, rapamycin or azathioprine, may prove to be useful. After an initial decline in renal function a more or less stable situation is usually reached [26], which makes it hard to predict which patient is going to progress towards ESRF. Because many patients develop at least mild renal function disturbances, a modified treatment regimen will probably be indicated in a large proportion of patients. Other strategies to preserve renal function include the use of urodilatin [27], calcium antagonists [28–30] and prostaglandin analogues [31] in the post-operative period. Hopefully the accumulating data on the interaction between cyclosporin and endothelium will result in a therapeutic or preventive solution for the problem of nephrotoxicity in transplant recipients.

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