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Determination of renal function in long-term heart transplant patients by measurement of urinary retinol-binding protein levels

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Abstract

Significant improvements have been noted in heart transplantation with the advent of cyclosporine. However, cyclosporine use is associated with significant side effects, such as chronic renal failure. We were interested in evaluating the incidence of long-term renal dysfunction in heart transplant recipients. Fifty-three heart transplant recipients were enrolled in the study. Forty-three patients completed the entire evaluation and follow-up. Glomerular (serum creatinine, creatinine clearance measured, and creatinine clearance calculated) and tubular functions (urinary retinol-binding protein, uRBP) were reanalyzed after 18 months. At the enrollment time, the prevalence of renal failure ranged from 37.7 to 54% according to criteria used to define it (serum creatinine ≥1.5 mg/dL and creatinine clearance <60 mL/min). Mean serum creatinine was 1.61 ± 1.31 mg/dL (range 0.7 to 9.8 mg/dL) and calculated and measured creatinine clearances were 67.7 ± 25.9 and 61.18 ± 25.04 mL min^{-1} (1.73 m^2)$^{-1}$, respectively. Sixteen of the 43 patients who completed the follow-up (37.2%) had tubular dysfunction detected by increased levels of uRBP (median 1.06, 0.412-6.396 mg/dL). Eleven of the 16 patients (68.7%) with elevated uRBP had poorer renal function after 18 months of follow-up, compared with only eight of the 27 patients (29.6%) with normal uRBP (RR = 3.47, P = 0.0095). Interestingly, cyclosporine trough levels were not different between patients with or without tubular and glomerular dysfunction. Renal function impairment is common after heart transplantation. Tubular dysfunction, assessed by uRBP, correlates with a worsening of glomerular filtration and can be a useful tool for early detection of renal dysfunction.

Key words
- Renal function
- Urinary retinol-binding protein
- Heart transplant
- Graft survival
- Chronic renal failure

Introduction

Heart transplantation is considered to be the best therapeutic option for patients with end-stage heart failure. In the cyclosporine era, there was a significant improvement in the survival rate of solid organ transplantation, including the heart (1). The main barrier to graft success, acute rejection, was overcome by the use of cyclosporine. One-year graft survival is now considered to be about 91% in patients after hospital discharge

(2). However, cyclosporine usage has been associated with several side effects, mainly hypertension, hyperlipidemia, hyperuricemia, gingival hyperplasia, hypertrichosis, neurotoxicity, glucose intolerance, and renal toxicity (3-5).

Cyclosporine causes two forms of nephrotoxicity: functional or acute nephrotoxicity and structural or chronic nephrotoxicity. Functional nephrotoxicity is related to the dose of cyclosporine, may be reversible with drug withdrawal, is associated with alterations in renal hemodynamics and glomerular filtration rate that begin soon after initiation of cyclosporine treatment and is largely mediated by an imbalance of vasoconstrictors and vasodilators. The renal vasculature is primarily affected in cyclosporine-related functional nephrotoxicity. Structural or chronic nephrotoxicity may not be reversible and often is progressive, involving both the renal arterioles and tubules, and may be mechanistically distinct from functional nephrotoxicity (6).

Cyclosporine usage in heart transplant patients has been linked to nephrotoxicity that ranges from mild renal function impairment to severe renal failure, needing substitutive renal replacement therapy (7-9).

Several studies have evaluated the prevalence of chronic renal failure among heart transplant patients. Its prevalence ranged from 3 to 10%, probably due to differences in the transplant follow-up time, to the criteria used to define renal impairment, to the cyclosporine dose used in the maintenance phase of transplantation, and to the inter-population variability (2,7,10-19). Recently, it has been demonstrated in a large group of patients that heart transplantation is associated with a 10.9% 5-year cumulative incidence of chronic renal failure (20).

We have demonstrated that heart transplant patients with tubular dysfunction had a worsening of renal function, mainly due to cyclosporine nephrotoxicity. Tubular dysfunction was evaluated by measurements of urinary retinol-binding protein (uRBP), a low-molecular weight protein that is totally filtered by the glomeruli and is almost completely reabsorbed by proximal tubules, therefore making it a good marker of tubular function (21,22).

There is an impending consensus that renal failure is associated with higher mortality in heart transplant patients, demonstrating the impact of this event on patient outcomes (7,20). Indeed, it was observed that heart transplanted patients with renal failure had a 1.5 times higher mortality rate than chronic renal failure patients in the first year of hemodialysis therapy (18,23). However, the criterium used to define end-stage renal failure in heart transplant recipients is variable, with some investigators using serum creatinine values and others estimating renal function by measuring serum and urinary levels of creatinine in 24-h voided urine. Tubular dysfunction is rarely assessed, although considered to be a relevant factor for renal function prognosis. In the present study, we analyzed the incidence of glomerular and tubular dysfunctions in heart transplant patients and correlated it with renal outcomes.

Material and Methods

Subjects

The study was conducted at the Nephrology and Cardiology Divisions of Universidade Federal de São Paulo and was approved by the Ethics Committee for Human Study of the institution. All patients read, accepted and signed an informed consent term before being enrolled. Among the 56 patients followed at our clinic, 53 agreed to participate in this study and were enrolled. Of the 53 patients, 43 (76.7%) participated in the entire evaluation and follow-up from December 1999 to December 2001 (18 months). The median post-transplantation time was 66.9 months (range 6-167 months).

The demographic data of the patients are shown in Table 1.

Renal function evaluation

Serum creatinine levels (mg/dL), 24-h creatinine clearance (measured) corrected for total body surface (mL min^{-1} (1.73 m^2)$^{-1}$) and Cockcroft Gault creatinine clearance (estimated; glomerular evaluation) (24), 24-h proteinuria and uRBP levels (tubular evaluation) were determined at enrollment and at the end of the follow-up (18 months). Serum and urinary creatinines were measured using semi-automatized Hitachi methodology (colorimetric assay based on the modified Jaffe method). uRBP was determined by a monoclonal antibody immunoenzymometric assay and the upper normal limit was considered to be 0.400 mg/L and the lower sensitivity was 0.001 mg/L according to Pereira et al. (21,22,25) who observed that uRBP concentrations in 95 normal adults ranged from 0.004 to 0.385 mg/L, defining normal uRBP <0.400. All assays were done at the same time excluding interassay variation. The intra-assay variation was <6.6%.

Urine samples were collected and frozen until RBP determination. No conservative or special precautions were considered to be necessary since RBP is stable in urine. Briefly, 96-well plates (Nunc A/S, Roskilde, Denmark) were coated with 100 µL of a solution containing monoclonal antibody, 10 mg/L, in coating buffer. After overnight incubation at 4ºC, the wells were washed three times and 100 µL of the samples was added. After incubation for 2 h at 37ºC, the wells were washed and the biotinylated antibody was added. After 1 h of incubation, streptavidin-peroxidase and the color reagent (Amersham Pharmacia Biotech, Little Chalfont, Buckinghamshire, UK) were added in sequence. Absorbance rates were read at 490 nm in a plate reader (Model EL 311; Bio-Tek Instruments Inc., Winooski, VT, USA). Concentrations in the samples were calculated by comparison with the standard curve, prepared by using nonlinear regression, usually as a third-degree polynomial.

Renal failure was defined when patients had serum creatinine levels above 1.5 mg/dL or creatinine clearance below 60 mL min^{-1} (1.73 m^2)$^{-1}$ (measured or estimated creatinine clearance). According to the K/DOQI study (26) and, more recently, to the KDIGO study (27), chronic kidney disease is defined as kidney damage or a glomerular filtration rate of <60 mL min^{-1} (1.73 m^2)$^{-1}$ for 3 months or more, irrespective of cause. Worsening of renal function was defined as a change of 20% or higher in the basal level of serum creatinine during follow-up.

Patients with good glomerular function (creatinine levels under 1.5 mg/dL) and altered tubular function (uRBP >0.400 mg/L) were presumed to be at a higher risk of developing renal failure (21,22).

Renal dysfunction prevalence data were analyzed in the 53 patients who agreed to participate. Of these, 43 completed the entire follow-up period for the analysis of the worsening of tubular and renal function.

Table 1. Demographic and clinical characteristics of the patients studied (N = 53).

Age (years)	49.2 ± 12.5
Male sex	86.6%
Post-transplantation time (months)	66.9 ± 35.3
End-stage heart disease	
Dilated	71.7%
Ischemic	22.6%
Others	5.7%
Systemic arterial hypertension	88.7%
High serum cholesterol levels	60.4%
Immunosuppressive drugs dose (mg kg^{-1} day^{-1})	
Cyclosporine	3.2 ± 0.6
Azathioprine	1.6 ± 0.5
Prednisone	0.13 ± 0.06
Cyclosporine trough levels (ng/mL)	196 ± 90.6
Cholesterol levels (mg/dL)	
Total	194.2 ± 52.3
HDL	43.2 ± 20.5
LDL	117.4 ± 38.8
Triglycerides levels (mg/dL)	151 ± 70.8
Uric acid (mg/dL)	7.3 ± 2.2
Proteinuria in isolated sample (g/L)	0.3 ± 0.5

Data are reported as means ± SD unless otherwise stated.

Biochemical analyses were also performed in our study population in Roche/Hitachi 912, including determination of total cholesterol and fractions, triglycerides, glycemia, and uric acid levels. Cholesterol and HDL were determined by an enzymatic colorimetric assay using cholesterol esterase and cholesterol oxidase, triglycerides were determined by the enzymatic colorimetric assay Trinder endpoint reaction, and uric acid was determined by an enzymatic colorimetric assay using uricase and peroxidase.

Statistical analysis

Data are reported as means ± SD unless otherwise stated. Parametric and non-parametric tests, the chi-square and exact Fisher tests were used to compare the groups. The differences were considered statistically significant when $P < 0.05$. The statistical analysis was performed with the SPSS 10.0 for Windows software.

Results

Demographic data

Of the 56 patients followed at our outpatient clinic, 53 (94.6%) agreed to participate in this study, being submitted to all clinical and laboratory evaluations. However, only 43 (76.7%) completed entire 18-month evaluation. The median post-transplantation time was 66.9 months (range 6-167). Our enrolled population was predominantly male (86.6%), Caucasian (75.5%) and 49.2 ± 12.5 years old. The etiologies of terminal heart failure were mainly dilated (71.7%) and ischemic cardiomyopathies (22.6%). Chagas' disease was present in 39.5% of the patients with dilated cardiomyopathy. The demographic profile is detailed in Table 1.

Most of the patients (83%) were on double-based immunosuppressive therapy, cyclosporine/steroid or cyclosporine/azathioprine. All patients but one were treated with cyclosporine-based immunosuppression (the exception used Tacrolimus for two years after a recurrent acute rejection). The mean cyclosporine trough level was 196 ± 90.6 ng/mL (Table 1). The incidence of hypertension and dyslipidemia along with the daily immunosuppressive drugs are also presented in Table 1.

Renal dysfunction prevalence

Glomerular filtration rate was evaluated by three methods: routine serum creatinine measurements, creatinine clearance calculated after 24-h voided urine collection, and by the Cockcroft-Gault formula. Considering the entire population, the mean serum creatinine level was 1.30 mg/dL (0.6-3.8). Calculated and measured creatinine clearances were 67.7 ± 25.9 mL/min and 61.18 ± 25.04 mL min^{-1} $(1.73\ m^2)^{-1}$, respectively. The prevalence of renal failure varied, as did the criteria used by us to define it. When considering the serum creatinine levels (cut-off of 1.5 mg/dL) commonly used in clinical evaluations, we observed that 20 patients (37.7%) had levels above 1.5 mg/dL. Considering a measured creatinine clearance below 60 mL min^{-1} $(1.73\ m^2)^{-1}$, the prevalence was higher (54%). Further refinement using estimated creatinine clearance below 60 mL/min showed that this prevalence was 38%. Interestingly, after the beginning of the present study, one patient needed renal replacement therapy with dialysis (2.3%) and another was successfully renal grafted (2.3%).

When we divided the groups by the level of estimated creatinine clearance, we observed that they were similar concerning age of recipient, time of transplantation, immunosuppressive drug dosage, cyclosporine trough levels, and 24-h proteinuria (data not shown).

Considering all patients who completed the entire follow-up (43 patients), their initial and final serum creatinine levels were

1.405 ± 0.517 and 1.633 ± 0.539 mg/dL, respectively.

Tubular dysfunction prevalence

We investigated the incidence of tubular dysfunction by measuring a low-molecular weight tubular protein, RBP, in urine. Only patients who participated through the entire follow-up were included (43 patients). Previously, we demonstrated that urinary levels of RBP correlate with tubular dysfunction and later with graft survival (20,21). uRBP was higher in patients with creatinine clearance below 60 mL min^{-1} (1.73 m^2)$^{-1}$ (0.608 ± 1.12 *vs* 0.173 ± 0.153 mg/L, P = 0.037). Sixteen patients (37.2%) presented higher levels of uRBP (1.06, 0.412-6.396 mg/L) and 27 (62.8%) patients had normal levels (0.128, 0.009-0.395 mg/L, P < 0.01). High uRBP levels at the beginning of the study were significantly correlated with the 18-month serum creatinine levels (R = 0.562, P < 0.001; Figure 1), but not with cyclosporine trough levels (R = -0.01, P > 0.05). Indeed, patients with high and normal uRBP had similar cyclosporine trough levels (213.9 ± 180.2 and 177.8 ± 101.7 ng/mL, respectively; P = 0.509; Table 2).

Eleven of the 16 patients (68.7%) with tubular dysfunction had poorer renal function by the end of follow-up compared with 8 of 27 (29.6%) patients with normal uRBP. Indeed, uRBP above 0.400 mg/L had a relative risk of 3.47 of poorer renal function over one year (95% CI = 1.2919-9.3320, P = 0.0095). The initial and final serum creatinine levels of patients with adequate glomerular and tubular function were 1.053 ± 0.184 and 1.321 ± 0.278 mg/dL, respectively. Considering patients with tubular dysfunction, their initial and final serum creati-

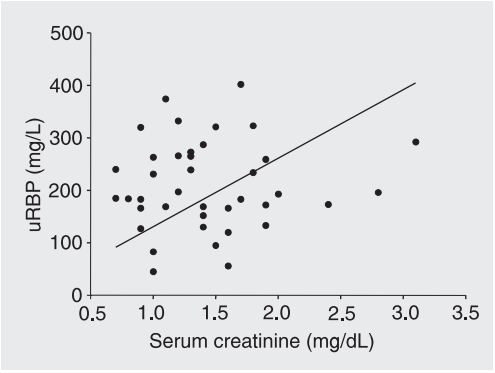

Figure 1. Pearson's correlation between urinary retinol-binding protein (uRBP) levels and serum creatinine after 18 months (R = 0.562, P < 0.001).

Table 2. Comparative analysis of characteristics of the patients studied according to estimated creatinine clearance (CrCl) and urinary retinol-binding protein (uRBP).

Variables	Estimated CrCl		uRBP	
	<60 mL/min	≥60 mL/min	≤0.400 mg/L	>0.401 mg/L
Age (years)	52.94 ± 10.09	46.58 ± 11.07	48.9 ± 11.1	49.5 ± 11.3
Transplantation time (months)	75.1 ± 34.4	61.38 ± 32.7	63.1 ± 36	75.2 ± 26.8
Immunosuppressive dose (mg kg^{-1} day^{-1})				
Prednisone	0.089 ± 0.03	0.12 ± 0.05	0.08 ± 0.05	0.15 ± 0.04
Azathioprine	1.51 ± 0.52	1.73 ± 0.48	1.63 ± 0.49	1.86 ± 1.26
Cyclosporine	2.90 ± 0.6	3.2 ± 0.6	3.07 ± 0.58	3.09 ± 0.67
Cyclosporine trough levels (ng/mL)	204.2 ± 80.6	209.7 ± 90.9	177.8 ± 101.7	213.9 ± 180.2
Total cholesterol (mg/dL)	196.2 ± 47.8	194.9 ± 57.3	189.6 ± 38.6	197.9 ± 53.7
Triglyceride levels (mg/dL)	160.4 ± 53.1	135.2 ± 74.6	146 ± 70.3	161.7 ± 62.4
Serum creatinine (mg/dL)	1.7 ± 0.63	1.2 ± 0.30*	1.33 ± 0.45	1.85 ± 067*
Calculated CrCl (mL/min)	51.5 ± 23.2	65.5 ± 20.0	51.7 ± 22.8	39.1 ± 12.6
Estimated CrCl (mL/min)	51.17 ± 12.61	81.31 ± 20*	71.9 ± 21.1	50.1 ± 14*
24-h proteinuria (g/L)	0.55 ± 0.99	0.051 ± 0.11*	0.03 ± 0.09	0.775 ± 1.09*
uRBP (mg/L)	1.166 ± 1.665	0.283 ± 0.301*	0.166 ± 0.12	1.50 ± 1.63*

*P < 0.05 compared to group with lower CrCl or uRBP value (*t*-test).

nine was 1.200 ± 0.245 and 1.450 ± 0.214 mg/dL, respectively.

Discussion

Cyclosporine was vital for the success of heart transplantation, being responsible for improving patient survival rate in the 1980-90's. However, cyclosporine, as a calcineurin inhibitor, has important side effects, namely acute and chronic toxicity. Acute toxicity is commonly seen in kidney recipients in the first weeks post-transplantation as an impairment in renal function associated with hypertension, proximal tubular dysfunction and normal histology in a graft biopsy. During its chronic usage, cyclosporine is related to interstitial fibrosis and tubular atrophy, a feature commonly described as chronic nephrotoxicity. The clinical importance of cyclosporine nephrotoxicity in the heart transplantation setting is the cumulative incidence of renal failure and its impact on patient survival. Senechal et al. (28) have shown that end-stage renal failure was associated with an increased risk of mortality in heart recipients and that hypertriglyceridemia correlates with cardiac mortality (relative risk of 3.89).

Several studies demonstrated a high incidence of end-stage renal failure. Rubel et al. (29) demonstrated a 20% incidence of end-stage renal failure in a group of 320 heart transplant recipients. Through actuarial analyses, they showed that glomerular filtration rate decreased by 24% during the first year and, after 10 years of follow-up, 20% of the patients had developed end-stage renal failure. The cyclosporine trough levels in the first 6 months and the presence of diabetes correlated with renal failure. Hetzer et al. (16) demonstrated that 58 of 77 (75.32%) heart transplant patients with 11-13 years of post-transplantation time had some degree of renal dysfunction, with a mean serum creatinine of 2.09 ± 1.5 mg/dL. Moreover, 7 patients (9.09%) were on dialysis treatment.

One issue that needs to be raised is that the definition and the measurement of glomerular filtration rate in heart transplant patients have not been established. Here, we report a 30-54% prevalence of renal dysfunction in heart transplant recipients, similar to that reported by others (2,7,10-20). When we considered creatinine clearance (<60 mL min^{-1} (1.73 m^2)$^{-1}$), we could observe that serum creatinine (>1.5 mg/dL) underestimated the real incidence, indicating that its routine interpretation should be made with caution. Although serum creatinine is currently used in the clinical management of transplant patients, there is evidence suggesting that it does not reflect glomerular filtration rate. Many investigators are undertaking clinical trials to validate other biomarkers such as cystatin C as a better renal function index (30). Others suggest that estimated creatinine clearance using Cockcroft-Gault's formula could provide more information since it correlates with calculated creatinine clearance. Although most studies imply a role for calcineurin inhibitors in the pathogenesis of renal failure, a direct correlation between them based on their trough levels or on their daily concentration has not been totally established. By univariate analysis, we could not implicate a role for cyclosporine, cholesterol or triglyceride levels in renal failure. Patients with renal dysfunction estimated by the Cockcroft-Gault formula had only uRBP levels different from those with normal rates. It is possible that an association of direct renal effects through induction of renal hypoxia and an indirect action, such as hypertension and dyslipidemia, could actually determine renal dysfunction that ultimately progresses to end-stage renal failure.

Chronic renal failure can increase the mortality rate in heart transplant patients. New protocols advocate calcineurin inhibitor withdrawal or the addition of mycophenolate mofetil and rapamicyn to the treatment of recipients with renal function impairment.

Groetzner et al. (31,32) conducted a prospective study in which heart transplant recipients with impaired renal function, possibly due to calcineurin inhibitor-related toxicity, were converted to mycophenolate mofetil and rapamicyn therapy. After the conversion, renal function improved significantly and, more importantly, with no serious side effects.

Additionally, we also evaluated tubular dysfunction in these heart transplant patients. Although glomerular involvement is associated with renal failure, tubule-interstitial dysfunction is in fact better correlated with kidney outcomes. Usually, evaluation of tubule-interstitial dysfunction is neglected in transplant recipients; however, its impact on graft survival in kidney transplant patients has long been described. LeBidois et al. (33) demonstrated that tubular and interstitial lesions were present in renal biopsies of pediatric heart transplant patients on cyclosporine-based immunosuppressive therapy.

The measurement of uRBP is a useful noninvasive method for the diagnosis of tubular dysfunction. RBP is a low-molecular weight protein that is totally filtered and almost completely reabsorbed by the proximal tubules. There is no known condition associated with its high serum protein levels and the protein is very stable in the entire range of urinary pH (25). Our group has demonstrated the importance of uRBP in predicting renal graft failure in heart and kidney transplanted recipients (21,22,34).

We have recently addressed the question of whether tubular dysfunction has a negative impact on renal function and graft survival. Thirty-six heart transplant recipients were studied and RBP was measured in urine. Patients with higher levels of uRBP had impaired renal function with a relative risk of 3.87 ($P = 0.003$) to double serum creatinine level over a 5-year of follow-up. In renal transplantation, uRBP levels were associated with chronic allograft nephropathy and with decreased long-term graft survival (34). Therefore, we were interested in investigating the prevalence of glomerular and tubular dysfunction in a larger group of patients in correlation with their renal outcomes.

Initially, we observed a prevalence of 37.2% (16/43 patients) of tubular dysfunction in the 43 patients who completed the entire evaluation. Of note, 11/16 patients (68.7%) with high uRBP levels presented a deterioration of glomerular renal function over the follow-up time compared to 8/27 (29.6%) of patients with normal uRBP levels. High uRBP levels were then associated with a relative risk of 3.47 of progressing renal function ($P = 0.0095$). Although, the cyclosporine trough levels were slightly higher in patients with elevated uRBP levels, they did not differ significantly for those with or without tubular dysfunction. Total exposure time and individual susceptibility could be related to the side effects of cyclosporine.

We showed that serum creatinine levels significantly correlate with uRBP levels. In the present study group, 8 patients presented normal glomerular filtration, but altered tubular function, indicating the beginning of renal damage. This condition establishes a gap between the diagnosis of tubular renal damage and the decrease in glomerular filtration rate. This gap can be defined as an "opportunity gap" that could allow initiation of a preventive therapy in an attempt to halt progression of the lesion. Changes in immunosuppressive drugs such as reducing the cyclosporine dose can be this preventive therapy.

A combination of cyclosporine-induced hemodynamic changes and direct toxic effects of cyclosporine on tubular epithelial cells may lead to the structural lesions characteristic of chronic cyclosporine nephrotoxicity. Cyclosporine may advance these lesions by promoting two interrelated pathophysiological processes. Sustained renal ischemia and enhanced apoptosis, and angio-

tensin II may play important roles in both of these processes. Proximal tubular cell injury has been proposed to play a prominent role in tubulointerstitial disease through the release of various substances affecting vasoconstriction, the influx of inflammatory cells into the interstitium, fibroblast proliferation, and matrix synthesis. Injury to the proximal tubular cells induced either by sustained ischemia secondary to enhanced cyclosporine-related vasoconstriction or by direct toxic effects of cyclosporine may cause the release of endothelin-1 and other substances. This injury stimulates a local inflammatory response which includes macrophage infiltration and osteopontin expression. Osteopontin is a macrophage chemoattractant and/or adhesion protein that facilitates the localization of macrophages to the site of injury. Both macrophages and tubular cells may then release TGF-ß1, which promotes fibrosis by both increasing the expression and decreasing the degradation of extracellular matrix protein. Cyclosporine has also been shown to activate apoptosis genes and to increase apoptosis in tubular and interstitial cells. Cyclosporine-induced apoptosis correlates with tubular atrophy and tubulointerstitial fibrosis (6). Since renal impairment due to cyclosporine nephrotoxicity is a common feature in heart transplant recipients, patients were not subjected to a kidney biopsy because their clinical and laboratory data were compatible for this diagnosis.

Considering all of these correlations between cyclosporine and renal tubular lesion, by lowering the cyclosporine dose we can expect diminished toxicity to tubular cells and consequently a decrease in uRBP levels.

Some investigators advocate genetic susceptibility to the nephrotoxic effect of cyclosporine. Two recent studies (35,36) on heart-transplanted patients suggest that the polymorphism of a TGF-ß1 gene can be involved in the susceptibility to the nephrotoxic effects of cyclosporine. TGF-ß1 is a pro-fibrotic cytokine. It was demonstrated by several investigators (37-39) that cyclosporine promotes hyperexpression of this cytokine both *in vitro* and *in vivo*.

In a 7-year follow-up of heart transplant recipients, Baan et al. (36) demonstrated that 23 of a total of 89 patients (26%) who were Leu/Pro heterozygotes or Pro/Pro homozygotes presented renal insufficiency in contrast to only 3 of a total of 42 patients (7%) who were Leu/Leu homozygotes. It is still in discussion in the literature which genotype in the codon 10 of TGF-ß1 is related to the largest susceptibility to cyclosporine nephrotoxicity.

We presented data demonstrating a high prevalence of renal dysfunction among heart transplant recipients. We assessed tubular dysfunction and demonstrated that it correlates with a worsening of renal function over time. Many times tubular dysfunction is detected while glomerular filtration is adequate. This may provide an opportunity to intervene with changes in the immunosuppressive drugs used in an attempt to avoid progression of the renal damage.

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