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Chronic renal dysfunction in maintenance heart transplant patients: the ICEBERG study

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Abstract

Chronic renal dysfunction (CRD) is a major complication after heart transplantation. We sought to describe the renal function over time, to assess the risk factors associated with CRD development, and to evaluate the clinical attitudes on diagnosis and treatment of CRD. A retrospective, cross-sectional, multicenter study was conducted in 13 outpatient clinics in Spain. A total of 244 heart recipients who survived more than 2 years after transplantation were included. Post-transplantation follow-up was 7.7 years (range: 2-22 years). CRD was diagnosed in 32.4% of patients at a mean of 3.3 years after transplantation. Serum creatinine increased 0.1 ± 0.2 mg/dL per year in CRD group compared with 0.0 ± 0.2 mg/dL per year in non-CRD group (P = .003) and glomerular filtration rate decreased −1.5 ± 4.3 mL/min/1.73 m^2 per year in CRD group versus −0.1 ± 4.8 mL/min/1.73 m^2 per year in non-CRD group (P = .027). After CRD diagnosis, major changes in immunosuppression based on calcineurin inhibitors reduction were instituted in 46.8% of patients. Multivariate model identified recipient age (P < .0001), female sex (P = .0398), and time since transplant (P < .0001) as predictors of CRD. In conclusion, the prevalence of CRD in long-term heart recipient survivors was quite high. CRD was associated with nonmodifiable factors (age, gender, and time since transplant).

At present, chronic renal dysfunction (CRD) constitutes a major cause of morbidity and mortality after heart transplantation. Overall, the incidence of CRD after transplantation of a nonrenal organ is associated with a greater than fourfold increase in mortality [1]. Thus, early detection of CRD is decisive to delay the progression of chronic kidney disease and improve the long-term outcomes.

Although post-transplant CRD has a multifactorial etiology [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], it is considered that calcineurin inhibitors (CNI)-related nephrotoxicity plays a key role [14], [15]. Estimates of the prevalence of CRD following solid organ transplants vary as a result of differences in the definitions used. For instance, the prevalence of Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines [16] stage 3 or worse CRD (glomerular filtration rate [GFR] less than 60 mL/min/1.73 m^2) among heart transplant patients was 61% 7 years after transplantation [12]. When defined as a GFR less than 30 mL/min/1.73 m^2 (stage 4 or worse), the 5-year risk of CRD was 11% for heart transplants [1].

The present study analyzed retrospectively the renal function in cardiac transplant recipients in 13 centers of Spain and aimed to describe the changes over time of serum creatinine and GFR levels and the clinical factors associated with the development of CRD. Additionally, we attempted to define the clinical attitudes with respect to diagnosis and therapy of CRD in real life over the study period.

Patients and Methods

The ICEBERG study was a retrospective, cross-sectional, multicenter study conducted in 13 cardiac transplantation outpatient clinics in Spain. All patients were aged 18 years or older and had a functioning cardiac allograft for at least 2 years before inclusion. Recipients of a multiorgan transplant and patients on renal replacement therapy were excluded. The study was conducted according to 2000 Declaration of Helsinki, with approval of the protocol by an Institutional Ethics Committee. All patients signed the informed consent prior to their participation.

A systematic, nonrandom sequential sampling was performed in each center during a 1-week period by the treating cardiologists participating in the study, yielding 244 patients fulfilling inclusion and exclusion criteria. Information was gathered between May and June 2007 by means of patient interviews and review of medical records. Relevant information included patient demographics and medical history, cardiac failure etiology, transplantation date, donor age and gender, recipient viral serologies, and immunosuppressive regimen used at hospital discharge after transplantation. Detailed post-transplant information was also obtained, including information on post-transplant medical history (graft rejection, graft vascular disease, diabetes mellitus, hypertension, and malignancy), diagnosis of CRD, proteinuria determinations, and information on antiproteinuric treatment (ie, angiotensin converting enzyme [ACE]) inhibitors/angiotensin receptor [AR] blockers), serum levels of creatinine, and changes in the immunosuppressive treatment. Post-transplant data were gathered at the study visit and at 5 previous different points: nadir visit (corresponding to the visit with the lowest creatinine value within the first year post-transplant), 1 year after transplantation, and three next visits (from third to fifth visit), which were distributed equally in the period between the first year visit and the study visit. Creatinine and GFR slopes from nadir (mg/dL per year and mL/min/1.73 m^2 per year, respectively) were calculated for each patient by the linear least squares method. Finally, the investigators were requested to establish the presence of CRD according to their own clinical assessment with knowledge of serum creatinine and GFR levels, and the results were tested for the presence of a meaningful degree of renal failure, defined as GFR $\leq$ 45 mL/min/1.73 m^2 (grade 3B of the K/DOQI guidelines [16]). GFR was estimated using the abbreviated or four-variable Modification of Diet in Renal Disease equation [17], [18].

Categorical and continuous variables were summarized as percentages and mean ± standard deviation, respectively. Chi-square tests were used to compare frequencies between subgroups for qualitative variables. Continuous variables were compared by Student *t* test. The relationship between quantitative variables was assessed by Pearson correlation. To determine the factors associated with the change in GFR over time, a linear mixed-effect model with repeated measures was fitted [19]. The variables included in the model were gender, age, CNI therapy, post-transplant diabetes mellitus, post-transplant hypertension, renoprotective treatment, and time since transplantation (all of them recognized as risk factors in previous reports). All factors were included as fixed effects. A random patient intercept and identity scale covariance matrix were used. The rate of change in GFR over time was analyzed by the factor by time interaction of those variables included in the model. Significance was established at a P value $\leq .05$. Data were analyzed using SPSS 12.0 statistical package (SPSS Inc, Chicago, Ill, United States).

Results

Patient Characteristics

Table 1 shows the demographic and clinical characteristics of the study patients. The vast majority of patients were men and Caucasian, with a mean age of 58.9 ± 12.0 years at the time of study visit. Ischemic and idiopathic cardiomyopathies were the most frequent causes leading to cardiac transplantation. Seventy-three per cent of the recipients were positive for cytomegalovirus serology. Antibody induction therapy was used in 70% of patients. The most frequently used immunosuppressants were cyclosporine (81.6%) and azathioprine (57.8%). Acute rejection of International Society for Heart and Lung Transplantation grade ≥ IIIA had been diagnosed in 46% of patients, and the mean number of rejection episodes was 2.5 ± 2.5. Twenty percent of patients developed a malignancy, and 15.8% were diagnosed with graft vascular disease. Serious infections occurred in one third of the patients. Diabetes mellitus was present in 25% of patients. Hypertension was detected in 47.5% of patients. The mean time between transplantation and study visit was 7.7 ± 4.0 years (range: 2-22 years). Visit 3 was carried out at a mean of 2.9 ± 1.8 years post-transplant, visit 4 at a mean of 4.6 ± 2.5 years post-transplant, and visit 5 at 6.3 ± 3.3 years post-transplant.

Table 1. Demographics and Clinical Characteristics of Heart Recipients With or Without Diagnosis of Chronic Renal Dysfunction (79 and 165 Patients, Respectively)

	Patients with CRD, *n* (%)	Patients without CRD, *n* (%)	Total, *n* (%)
Age (y), mean ± SD*	63.2 ± 10.4	56.8 ± 12.1	58.9 ± 12.0
Gender (male)	68 (86.1)	129 (78.2)	197 (80.7)
Race (Caucasian)	78 (98.7)	163 (98.8)	241 (98.8)
Reason for transplantation			
Ischemic cardiomyopathy	43 (54.4)	55 (33.3)	98 (40.2)
Dilated cardiomyopathy	21 (26.6)	73 (44.2)	94 (38.5)
Other	64 (81.0)	128 (77.6)	52 (21.3)
Cytomegalovirus serology (positive)	59 (74.7)	119 (72.1)	178 (72.9)
Induction therapy*	58 (73.4)	113 (68.5)	171 (70.0)
Anti-CD25	21 (25.6)	36 (21.8)	57 (23.4)
OKT3	18 (22.8)	66 (40.0)	84 (34.4)
Thymoglobulin	19 (24.0)	11 (6.7)	30 (12.3)
Immunosuppressant therapy (at discharge)			
Cyclosporine	65 (82.3)	134 (81.2)	199 (81.6)
Tacrolimus	15 (19.0)	28 (17.0)	43 (17.7)
Mycophenolate mofetil	31 (39.2)	66 (40.0)	97 (39.8)
Azathioprine	44 (55.7)	97 (58.8)	141 (57.8)
Mycophenolic sodium	0 (0.0)	1 (0.6)	1 (0.4)
Everolimus	0 (0.0)	2 (2.5)	2 (0.8)
Sirolimus	1 (1.3)	4 (2.4)	5 (2.1)
Prednisone	76 (96.2)	155 (93.9)	231 (94.7)
Concomitant therapies			
Alpha-blockers	13 (6.4)	15 (4.0)	28 (11.4)
Beta-blockers	13 (6.4)	11 (3.0)	24 (9.8)
Calcium channel blockers	30 (14.8)	66 (17.7)	96 (39.3)
ACE inhibitors/AR blockers	42 (53.2)	79 (47.9)	121 (49.5)
Diuretics	36 (28.4)	47 (28.4)	83 (34.0)
Statins	63 (31.0)	137 (36.8)	200 (81.9)
None	6 (3.0)	17 (4.6)	23 (9.4)
Acute rejection (ISHLT grade ≥ IIIA)	38 (48.1)	74 (44.8)	112 (45.9)
Graft vascular disease	10 (12.7)	26 (15.8)	36 (14.8)
Malignancy	21 (26.6)	26 (15.8)	47 (19.2)
Diabetes mellitus post-transplant*	23 (29.1)	38 (23.0)	61 (25.0)
Hypertension post-transplant	44 (55.7)	72 (43.6)	116 (47.5)
Serious infection	29 (36.7)	52 (31.5)	81 (31.1)
Opportunistic infection	17 (21.5)	27 (16.4)	44 (18.0)
Time since transplantation (y), mean ± SD	7.7 ± 4.1	7.7 ± 3.9	7.7 ± 4.0

ACE, angiotensin converting enzyme; AR, angiotensin receptor; ISHLT, International Society for Heart and Lung Transplantation; CRD, chronic renal dysfunction; SD, standard deviation.

∗ Differences between groups were statistically significant according to: age ($P < .0001$), induction therapy ($P = .0003$), and diabetes mellitus post-transplant ($P = .0203$).

Renal Function Evaluation

For the whole group, the evolution of renal function is summarized in Fig 1. GFR mirrored serum creatinine levels and both showed deterioration in renal function within the first year after transplantation from near normal values. At this point, approximately one fifth of patients had at least grade 3B renal failure. After the first year, renal function only showed a mild decrease, although by 8 years after transplantation, nearly one third of patients had moderate to severe renal failure (GFR < 45 mL/min/1.73 m^2).

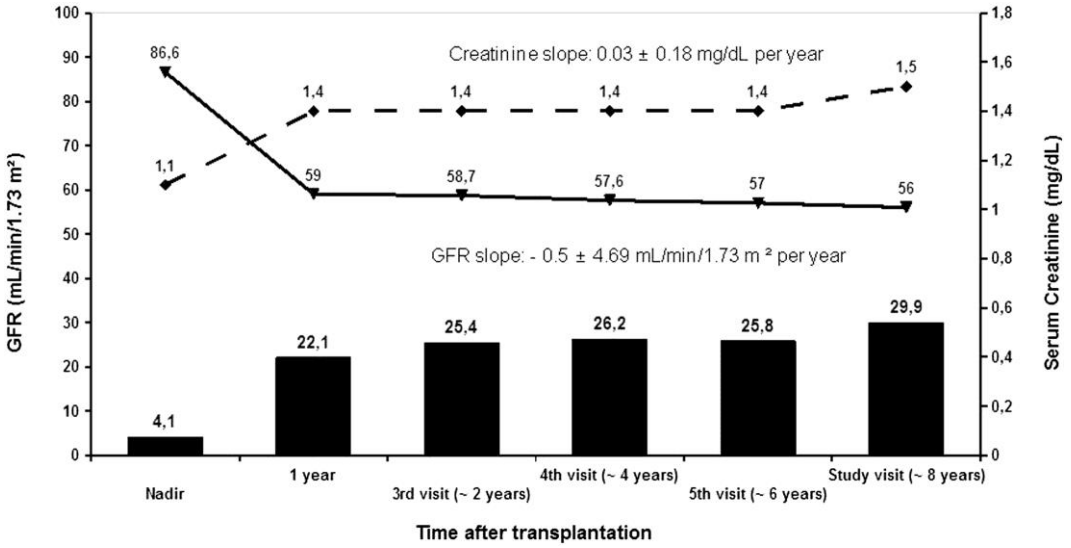

Fig 1. Evolution of renal function according to serum creatinine levels and glomerular filtration rate (GFR) in 242 chronic heart transplant recipients. Solid columns represents the percentage of patients with GFR < 45 mL/min/1.73 m^2.

The factors associated with the change rate in GFR over time are summarized in Table 2. The most relevant effect related to a best renal function was the male gender as compared to female gender (P = .0398). The factors related with a worse evolution in renal function were age at transplantation (−0.7 mL/min/1.73 m^2 for each additional year, P < .0001), and time since transplantation (P < .0001). On the contrary, there were no differences related to the presence of diabetes mellitus post-transplant (P = .1653), hypertension post-transplant (P = .1779), CNI therapy (P = .1021), or renoprotective treatment (P = .1740).

Table 2. Linear Mixed-Effects Model for Response of Renal Function

Factor	F	*P* value
Intercept	120.13	<.0001
Recipient gender (male vs female)	5.85	.0398
Age	−0.67	<.0001
CNI therapy (yes vs no)	1.64	.1021
Diabetes mellitus post-transplant (yes vs no)	−3.57	.1653
Hypertension post-transplant (yes vs no)	−3.03	.1779
Renoprotective treatment (no vs yes)	−1.59	.1740
Time since transplantation		
1-y visit vs nadir	−27.29	<.0001
3rd visit (~ 2 y) vs nadir	−28.56	<.0001
4th visit (~ 4 y) vs nadir	−29.59	<.0001
5th visit (~ 6 y) vs nadir	−29.57	<.0001
Study visit (~ 8 y) vs nadir	−30.28	<.0001

CNI, calcineurin inhibitor.

CRD was clinically diagnosed by treating physicians in 79 out of 244 patients (32.4%). The mean time until physicians considered the diagnosis of CRD was 39.5 ± 42.8 months after transplantation. Patients with the diagnosis of CRD showed steeper creatinine (0.1 ± 0.2 mg/dL per year) and GFR slopes (−1.5 ± 4.3 mL/min/1.73 m^2 per year) as compared to those patients without CRD (0.0 ± 0.2 mg/dL per year, $P = .0003$; and −0.1 ± 4.8 mL/min/1.73 m^2 per year, $P = .027$, respectively; Fig 2). A steady increase in serum creatinine levels was observed in patients with CRD from the time of transplantation, whereas they remained relatively stable over time in those patients without CRD. In turn, changes in GFR showed similar evolution in both groups. We observed a steep decline within 1 year after transplantation and a stable course thereafter, although patients with CRD tended to have a higher decline in GFR as compared to those patients without CRD over this later period. Nadir creatinine serum levels were not different between CRD and non-CRD patients. Creatinine curves commenced to separate between groups beyond the first year after transplantation (Fig 2A). In contrast to creatinine levels, differences for GFR between CRD and non-CRD patients could be observed from the nadir point (Fig 2B). Figure 3 summarizes the proportion of patients having a GFR ≤ 45 mL/min/1.73 m^2 according to the clinical diagnosis of CRD. At the study visit, more than two thirds of patients had at least grade 3B renal failure. Noteworthy, 10% of patients without CRD according to physician's criteria had moderate to severe decline in GFR. Differences between CRD and non-CRD patients were significant for age at the study visit ($P < .0001$), antibody induction at the time of transplantation ($P = .0003$), and post-transplant diabetes ($P = .02$; Table 1).

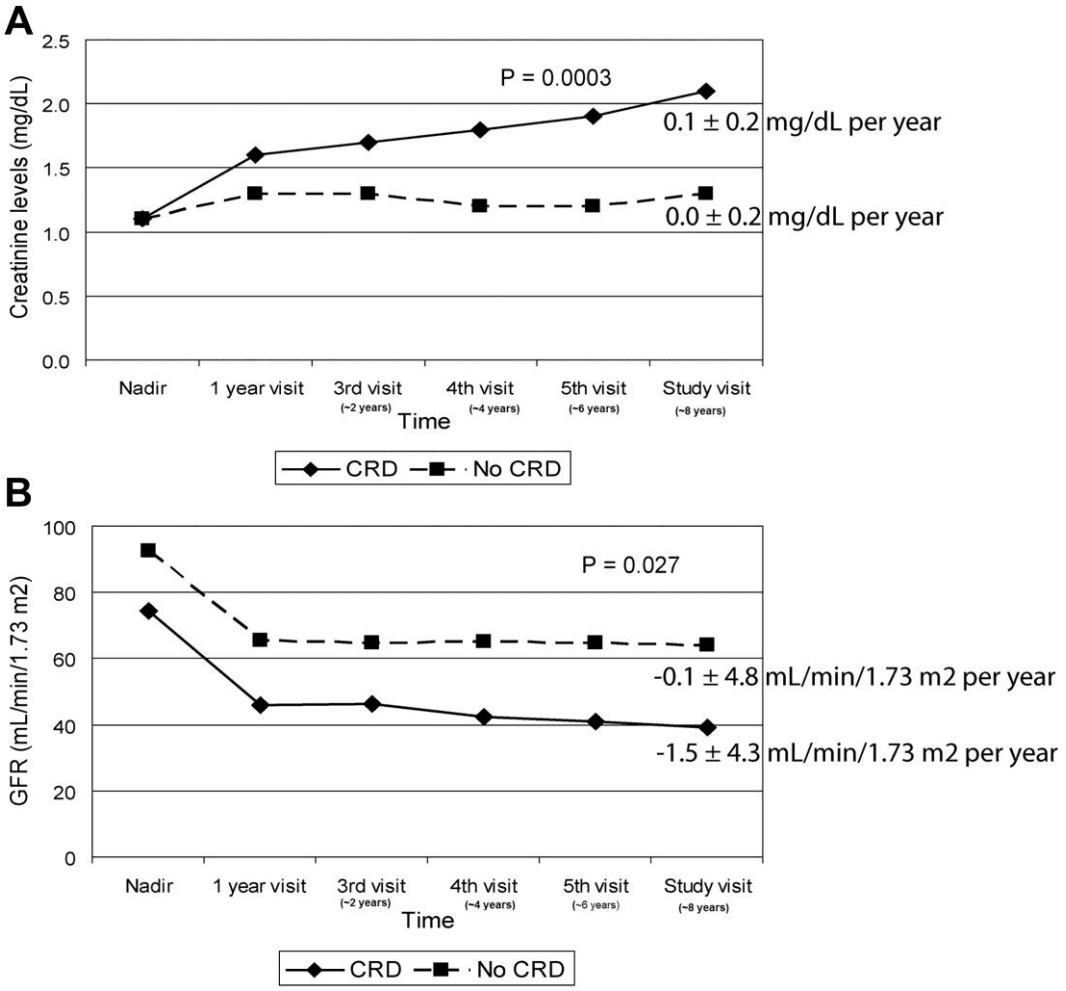

Fig 2. Evolution of serum creatinine levels **(A)** and glomerular filtration rate (GFR) **(B)** in 242 chronic heart recipients with chronic renal dysfunction (CRD; solid line, rhombus marks) and with no renal dysfunction (dashed line; square marks). Creatinine and GFR slopes from nadir are shown on the right. Time since transplant (years) for third visit, fourth visit, fifth visit, and study visit corresponds roughly to 2, 4, 6, and 8 years, respectively.

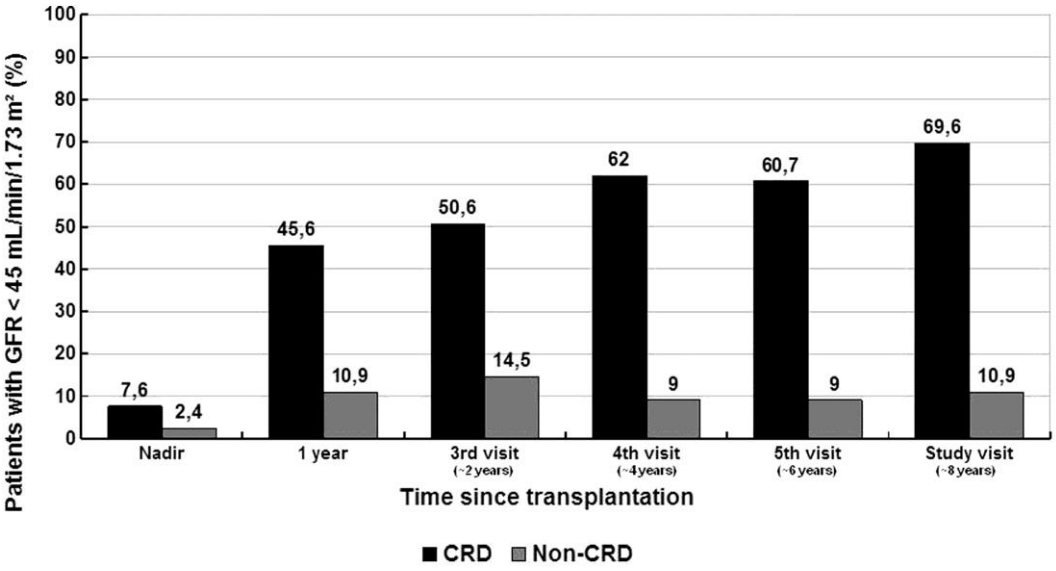

Fig 3. Percentage of patients with glomerular filtration rate <45 mL/min/1.73 m^2 in patients with and without clinical diagnosis of chronic renal dysfunction (CRD).

Therapy Changes After Clinical Diagnosis of CRD

In 83.5% of the cases, the treating physicians considered calcineurin nephrotoxicity as the main cause of CRD. Changes in immunosuppressive therapy were carried in 37 of 79 patients (46.8%). All changes were based on the reduction of CNI. Major changes included also modifications of mycophenolic acid (MPA) therapy or introduction of proliferation signal inhibitors, which were carried out in 16 patients. Patients with major changes showed significantly higher creatinine slope compared with those with isolated CNI reduction (P = .028; Table 3).

Table 3. Changes in Immunosuppressive Therapy After the Diagnosis of Chronic Renal Dysfunction in 79 Heart Recipients

Change	*n* (%)	Creatinine slope (mg/dL per year), mean (95% CI)
CNI reduction and no other changes	21 (26.5)	0.03 (−0.05–0.11)
CNI reduction/withdrawal + MPA (MMF/MPS) modification	8 (10.2)	0.21 (0.09–0.34)
CNI reduction/withdrawal + PSI introduction	8 (10.2)	0.19 (0.07–0.32)
No changes	42 (53.1)	0.06 (0.0–0.12)

CI, confidence interval; CNI, calcineurin inhibitor; MPA, mycophenolic acid; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; PSI, proliferation signal inhibitor.

Assessment of proteinuria was carried out only in 4 patients. After CRD diagnosis, ACE inhibitor/AR blocker therapy was introduced in 13 patients (16.5%). However, there were no differences between CRD group (53.1%) and non-CRD group (47.8%; $P = .49$) for the use of these drugs at the end of follow-up.

Discussion

Although significant improvements have been made in the survival rate in heart transplantation, cardiac recipients are still subjected to serious complications, particularly renal failure. As renal function deteriorates since time from transplantation [10], [12], we first sought to assess the temporal course of renal function worsening over time. Overall, we observed a steep decline in renal function within the first year after transplantation, followed by a slow rate of deterioration over the next years. The initial worsening of renal function could be related with the high CNI serum levels maintained in this period [20] but also to the high prevalence of potential nephrotoxic conditions, such as infections and allograft rejections. As previously reported [3], [21], renal dysfunction at 1 year after transplantation is a powerful and independent predictor of CRD and long-term all-cause mortality in heart transplantation. The prevalence of K/DOQI 3B renal dysfunction or worse (GFR < 45 mL/min/1.73 m^2) reached 22% at 1 year and 30% by 8 years after transplantation. These results are in between those recently reported by Crespo-Leiro et al [22] in a study of 1065 patients. They found that at 6.2 to 9.5 years after transplantation, 24% of patients had moderate renal dysfunction as defined by serum creatinine levels between 1.6 and 2.5 mg/dL, whereas using GFR-based criteria (30-60 mL/min/1.73 m^2), the prevalence of renal dysfunction was 55%. Interestingly, the estimation of change over time in renal function determined by creatinine and GFR slopes displayed a similar evolution over time, which means that worsening of renal function was not due only to the aging population but to a real deterioration of renal function.

We found that the rate of change over time in GFR was independently associated with nonmodifiable factors such as age at transplant, female sex, and time since transplantation. Increasing age as a risk factor for developing renal dysfunction has been described in numerous previous studies [1], [3], [5], [6], [7], [9], [10], [12], [13]. Female sex and time since transplant were well-known risk factors for development of CRD in patients with heart transplantation, as well [1], [7], [9], [10], [12]. Comorbidities such as hypertension and diabetes were not related to the rate of change in renal function, in disagreement with previous studies [1], [4], [6], [9], [19], although there was a tendency to be associated with worsening of renal function. Remarkably, neither withdrawal of CNI therapy nor the use of renoprotective therapy (mainly ACE inhibitors) were associated with a better evolution in renal function. In fact, the creatinine slope was higher in those patients with CNI reduction or avoidance. These findings suggest that these therapy measures were carried out in patients with the most unfavorable evolution of renal function after transplantation and later, when the renal damage was irreversible [19].

This study also intended to assess the clinical attitudes with respect to the diagnosis and therapy of CRD. We found that the clinical diagnosis of renal failure was considered in quite advanced stages of renal dysfunction. In fact, in every point of the follow-up, most of the patients diagnosed with CRD by the treating physicians had GFR < 45 mL/min/1.73 m^2. This has important practical implications, as the efficacy of renal-sparing strategies is probably limited to early stages of renal damage [23]. In turn, 10% of patients with no CRD at the physician's criteria had moderate to severe renal failure as assessed by GFR. This probably reflects that the clinical diagnosis of CRD in the period in which the study was performed was based on serum creatinine levels, which tends to underestimate the degree of renal failure [22]. It is also remarkable that in the present series, proteinuria, an early marker of renal damage, was only evaluated in 1.6% of patients.

More than 80% of cases of CRD were considered to be mainly attributable to CNI-related nephrotoxicity by the investigators. Accordingly, in nearly 50% of cases, a strategy based on minimization or withdrawal of CNI therapy was attempted. This relatively low rate of modification of CNI therapy may be due to several reasons: absence of well-proven alternatives within the period in which many patients were diagnosed of CRD, and concerns about the benefit-risk ratio of therapy changes in this particular clinical context. We found the highest creatinine slopes for the patients in whom changes in CNI therapy were accompanied by introduction of MPA therapy [24], [25] or substitution for proliferation signal inhibitors [26]. This suggests that major changes in immunosuppression were used mainly in the cases with more advanced renal damage, a clinical situation where the usefulness of those changes could likely be more limited [27].

The ACE inhibitors are useful in limiting chronic damage of kidney allografts [28], a situation in which CNI therapy plays an important role. In our series, the introduction rate of ACE inhibitor/AR blocker therapy after the diagnosis of CRD was relatively low (16.5% of patients). This finding could be attributable to three reasons: (1) physicians' concerns about a likely deterioration of an already damaged kidney; (2) a relatively high rate of previous use of ACE inhibitor/AR blocker therapy (nearly 50% of patients); and (3) the lack of proteinuria determinations.

The present study has several limitations. The inherent limitations of the retrospective, cross-sectional design studies regarding the possibility of data inaccuracy, lack of information (such as pretransplant renal function or CNI target levels), and patient selection bias. Another constraint worth mentioning is that the information for this study was gathered in 2007, which means that the number of patients treated with the immunosuppressant azathioprine is much higher than in the currently used strategy, which has been now largely optimized with the introduction of MPA. On the other hand, since deceased patients and patients requiring renal replacement therapy were excluded, our study sample represents the best of the clinical scenarios for chronic heart transplantation. Moreover, the sequential recruitment and the large number of participating centers suggest that our sample is representative of heart transplant population in Spain.

In conclusion, CRD was a relatively prevalent and progressive condition in long-term heart recipient survivors. CRD was associated with nonmodifiable factors such as recipient age, gender, or time after transplantation. Thus, further efforts should be made to detect CRD early, in order to implement preventive measures at earlier stages.

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