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Importance of anemia in the chronic Cardiorenal syndrome: Effects on renal function after heart transplantation

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Alexandre Braga Libório[1ABCDEF], Russian Soares Uchoa[2ABC], Alessa Peixoto Aragão[2ABC], João David de Sousa Neto[3ABC], Juan Miguel Cosquillo Valdivia[2ABC], Filipe de Alencar Matos[2AB], Ricardo Everton Dias Mont'Alverne[2AB], Francisco Ivan Benício de Sá Filho[2ABC], Juan Alberto Cosquillo Mejia[4CDE]

[1] Public Health Post-graduate Program, Universidade de Fortaleza (Unifor), Fortaleza, Ceará, Brazil
[2] Universidade de Fortaleza (Unifor), Fortaleza, Ceará, Brazil
[3] Cardiac Transplantation Service, Hospital Messejana, Fortaleza, Ceará, Brazil
[4] Coordinator of the Program of Heart Transplant, Hospital Messejana, Fortaleza, Ceará, Brazil

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Summary

Background: Cardiorenal syndrome has been recently divided into 5 categories, according to acute or chronic evolution and primary organ dysfunction. Anemia can also accompany this disorder, leading to a more complex situation. This study aims to analyze the renal outcomes of patients, specifically patients with chronic Cardiorenal syndrome, with or without anemia, long-term after heart transplantation.

Material/Methods: This was a retrospective cohort study on chronic Cardiorenal syndrome patients submitted to heart transplantation. Patients were divided according to presence of anemia and renal dysfunction before heart transplantation.

Results: A total of 108 patients (92 males) with the mean age of 45±12 years were included. The etiologies of the heart failure were hypertensive dilated myocardiopathy (66%), ischemic (14%) and Chagasic (12%). Before the heart transplantation, 51 patients had an eGFR less than 60 mL/min. From these, 24 had concomitant anemia. One year after the transplantation, patients with previous isolated renal dysfunction ameliorates eGFR (45±11 *vs.* 65±26 mL/min, p<0.001), while those patients with previous renal dysfunction and anemia presented no improvement (eGFR 44±14 *vs.* 47±13 mL/min, p=0.619) 1 year after heart transplantation. Moreover, higher hemoglobin was an independent predictor of eGFR improvement after heart transplantation when associated with previous renal dysfunction (OR 1.8; CI 1.2–3.6, p<0.01 for each hemoglobin increment of 1 g/dL).

Conclusions: Patients with isolated Cardiorenal syndrome presented partial renal function recovery after heart transplantation, while the presence of cardiorenal anemia was a marker of renal function non-recovery 1 year after heart transplantation.

key words: **chronic kidney disease • heart transplantation • Cardiorenal syndrome**

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Author's address: Alexandre Braga Libório, Public Health Post-graduate Program, Universidade de Fortaleza (Unifor), Fortaleza, Ceará, Brazil, e-mail: alexandreliborio@yahoo.com.br

Background

Cardiorenal syndrome (CRS) has been recently defined as the concomitant presence of heart and kidney failure [1]. Acute or chronic heart failure can lead to kidney dysfunction. The concept of acute or chronic CRS is determined by whether the heart failure is acute or chronic, respectively. Similarly, primary kidney failure (acute or chronic) can lead to or worsen heart failure – acute/chronic reno-cardiac syndrome. Recently, a consensus conference of the Acute Dialysis Quality Initiative (ADQI) has defined 5 types of Cardiorenal syndromes (Table 1) [2].

The interaction between the kidneys and the heart is important in controlling extracellular volume and blood pressure; however, it is more than a simple pressure/perfusion interaction. Recent investigations support the role of central venous congestion, neurohormonal elaboration, anemia, oxidative stress and sympathetic activity as other potential contributors to this complex syndrome [3,4].

In the presence of anemia, the syndrome is more specifically classified as cardiorenal anemia syndrome (CRA) [5]. Hemoglobin levels in these patients are generally correlated with renal function and are associated with serum erythropoietin deficit [6]. Low hemoglobin levels are associated with faster progression of heart failure [7]. In relation to the progression of kidney disease, it is controversial whether anemia has a detrimental effectt [8]. Some studies suggest that higher hemoglobin levels are associated with a slower progression of kidney disease and that erythropoietin treatment can attenuate this progression [9]. However, some researchers argue that anemia correction might actually worsen kidney disease [10]. Another controversial point is whether erythropoietin itself (rather than hemoglobin level) is associated with kidney disease progression [8].

It is unknown if renal dysfunction is reversible after heart transplantation (HT) in patients with type 2 CRS. Moreover, to our best knowledge, there is no data analyzing the importance of adding anemia to type 2 CRS in relation to kidney dysfunction after HT. This study's objective is to analyze renal outcomes differences in patients with type 2 CRS, with or without anemia, long-term after HT.

Table 1. Definition and classification of the Cardiorenal syndrome (adapted from reference).

Cardiorenal syndrome general definition: Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other
Acute Cardiorenal syndrome (Type 1): Acute worsening of cardiac function leading to renal dysfunction
Chronic Cardiorenal syndrome (Type 2): Chronic abnormalities in cardiac function leading to renal dysfunction
Acute Renocardiac syndrome (Type 3): Acute worsening of renal function causing cardiac dysfunction
Chronic Renocardiac syndrome (Type 4): Chronic abnormalities in renal function leading to cardiac disease
Secondary CRS (Type 5): Systemic conditions causing simultaneous dysfunction of the heart and kidney

Material and Methods

Study design

This study was conducted at a tertiary referral center specializing in heart disease (Hospital Doctor Carlos Alberto Studart Gomes, Fortaleza, Ceará, Brazil). It is a retrospective cohort study on patients submitted to HT from 2003 to 2010. We did not include patients submitted to dual heart and kidney transplantation, with acute heart failure or with end-stage renal disease undertaking maintenance dialysis. The study protocol was approved by the Institutional Ethics Committee.

Data collection

The clinical investigation included a review of clinical and laboratory data 1 month before HT, where patients were classified as normal renal function, CRS or CRA (see definitions below). After HT, patients were revaluated 1 year after HT. Laboratory data included the assessment of serum urea, creatinine, transaminases (AST, ALT), direct and indirect bilirubin, lactate dehydrogenase (LDH), blood count and platelets. Additional investigation included the ejection fraction measured by echocardiography and serum trough level of cyclosporine. The estimated Glomerular Filtration Rate (eGFR) was calculated using the simplified MDRD equation.

Definitions

Anemia was defined as Hb level less than 12 g/L in males or 11 g/L in females. Isolated CRS was considered when heart failure was associated with an eGFR less than 60 mL/min/1.73 m^2 and no anemia. Cardiorenal anemia was considered when heart failure was associated with an eGFR less than 60 mL/min/1.73 m^2 with concomitant anemia.

Treatment protocol

Maintenance immunosuppressive therapy was an association of mycophenolate mofetil, cyclosporine and steroids. Mean cyclosporine trough level was the mean of serum cyclosporine level at 1, 6 and 12 months after HT.

Statistical analysis

Statistical analysis was performed using the SPSS 19.0 program. Descriptive statistics were expressed as mean ±SD. The primary analysis compared patients according to group allocation. All variables were tested for normal distribution using the Kolmogorov-Smirnov test. We applied the analysis of variance (ANOVA) test with Tukey's post-hoc test, utilized for numerical values, and the chi-squared test for trends in assessing categorical data. When comparing continuous variables according to time point, the paired t-test was used. A multiple logistic regression model was built,

Table 2. Clinical and laboratory data before heart transplantation.

	Control (n=32)
Age (years)	45±12
Gender (M/F)	92/16
Ejection fraction pre-HT (%)	26±8
Hb pre-HT (g/dL)	11.3±0.8
Hypertension diagnosis	71/108
Previous diabetes mellitus (%)	16/108
ACE inhibitor/ ARB therapy (%)	77/108
Beta-blocker therapy (%)	56/108
Diuretic therapy (%)	87/108
Digoxin therapy (%)	80/108
eGFR pre-HT (mL/min)	68±14

Hb – hemoglobin; HT – heart transplantation; ACE – angiotensin-conversing inhibitor.

and association measures were calculated (adjusted odds ratio), with confidence interval of 95%. Stepwise backward elimination multivariate analysis was performed to investigate the independent risk factors associated with an eGFR increment greater than 5 mL/min in patients with previous CKD, which included factors presenting a significance level <20% according to the univariate analysis. P values <0.05 were considered statistically significant.

Results

Patient characteristics

From 2003 to 2010, a total of 108 patients (92 males) with a minimum follow-up of 12 months after HT were included. The mean age at time of HT was age 45±12 years and the main heart failure etiologies was hypertensive dilated myocardiopathy (66%), ischemic (14%) and Chagasic (12%). The great majority (88%) had a New York Heart Association (NYHA) functional class 4, with a mean ejection fraction of 26±8%. Before HT, 77 (71%) patients were on an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; 56 (52%) were receiving selective beta-blocker therapy; 85 (79%) were using aldosterone-receptor inhibitor, and 87 (81%) were receiving diuretic therapy. Other clinical and laboratory data is presented in Table 2.

Type 2 Cardiorenal syndrome

Before HT, 51 (47%) patients had an eGFR of less than 60 mL/min during a minimum 3 months follow-up, characterizing presence of chronic kidney disease (CKD) and, consequently, being diagnosed as type 2 CRS. The mean eGFR of these patients was 44±12 mL/min, less than patients with no CKD (91±17 mL/min, p<0.001). Compared with renal function before HT, patients with CKD had an improvement in eGFR (mean eGFR: 44±12 *vs.* 57±9 mL/min, p<0.01). However, patients with no previous CKD had a significant reduction in eGFR when comparing pre- and 1-year post-HT eGFR (91±17 *vs.* 73±14 mL/min, p=0.002). A complete comparison between patients with or without CKD before HT is showed in Table 3.

Anemia and type 2 Cardiorenal syndrome

To further explore the role of previous Cardiorenal syndrome/anemia in the progression of renal function after HT, patients with CKD before HT were divided into 2 further groups according to presence of anemia before HT – the isolated CRS group and the CRA group. From 51 patients with CKD before HT, 27 had normal Hb (isolated CRS) and 24 had anemia (CRA Group) (Table 4).

The patients had comparable eGFR before HT. One year after HT, the CRA group had persistently lower hemoglobin levels than the CRS group. Interestingly, patients with only CRS had a significant improvement in renal function 1 year after HT (eGFR: 45±11 *vs.* 65±26 mL/min, p<0.001 for paired t-test), while patients with CRA had stable eGFR after HT (44±14 *vs.* 47±13 mL/min, p=0.619 for paired t-test). Figure 1 displays evolution of renal function before and 1 year after HT in patients with CRS and CRA.

At multivariate analysis, after adjusting for sex, age, cyclosporine level, basal eGFR, acute kidney injury during HT, diabetes mellitus and hypertension, hemoglobin level was an associated factor for an eGFR improvement greater than 5 mL/min after HT (OR 1.8; CI 1.2–3.6, p<0.01 for each hemoglobin increment of 1 g/dL).

Discussion

The present study describes renal function evolution in a retrospective cohort of patients submitted to HT after 1-year follow up. Our data demonstrate the importance of anemia in prognosis when evaluating patients with CKD before HT. While patients with isolated CRS had a partial renal function recovery after HT, patients with CRA had no significant change in eGFR.

Renal dysfunction is highly prevalent in patients with advanced heart failure [11]. Roughly half of patients with systolic heart failure have a GFR less than 60 mL/min [12]. The mechanisms underlying renal dysfunction in heart failure are mainly hemodynamic. Guglin et al. [4] recently suggested that venous congestion is more important than low output and poor renal perfusion in determining renal failure. Regardless, the 2 proposed hemodynamic mechanisms are potentially fully reversed after HT.

Our data disclosed 3 different renal function evolutions, according to whether patients had no CKD, CRS or CRA. In the first group, there was a decline in eGFR. This is in agreement with previous studies demonstrating a high prevalence of renal dysfunction after HT [13,14]. Patients with previous CRS presented an improvement in GFR after HT, indicating a reversible renal lesion was presented, mainly due to hemodynamic factors. The third group (CRS) had no significant alteration after HT. Although some studies have demonstrated that previous CKD is associated with later and progressive CKD in patients following HT [15] and this renal lesion is worsened by cyclosporine nephrotoxicity [16], other studies failed to demonstrate this association [13].

Table 3. Clinical and Laboratory data between groups according renal function before heart transplantation.

	No previous CKD (n=57)	CRS (n=51)	p
Age (years)	4113	51±9	0.01
Gender (M/F)	56/9	42/9	0.4
Ejection fraction pre-HT (%)	27±7	25±10	0.2
Hb pre-HT (g/dL)	12.8±0.9	11.9±1.3	0.02
Hypertension diagnosis	41/57	41/51	0.94
Previous diabetes mellitus	7/57	9/51	0.92
ACE inhibitor/ ARB therapy	43/57	39/51	0.98
Beta-blocker therapy	36/57	30/51	0.94
Diuretic therapy (%)	55/57	46/51	0.99
Digoxin therapy (%)	38/57	22/51	0.59
eGFR pre-HT (mL/min)	91±17	44±12	<0.001
Mean cold ischemia (min)	124±32	12935	0.79
Mean extracorporeal circulation time (minutes)	152±47	152±48	0.82
AKIN post-HT (%)	43	39	0.8
Mean serum CSA (pg/mL)	232±61	242±62	0.4
Ejection fraction year post-HT (%)	65±6	67±11	0.9
Hb one year post-HT (g/dL)	12.8±1.1	12.2±1.3	0.08
eGFR year post-HT (mL/min)	73±14	58±9	0.01

CRS – Cardiorenal syndrome; CRA – cardiorenal anemia; Hb – hemoglobin; HT – heart transplantation; CSA – cyclosporine.

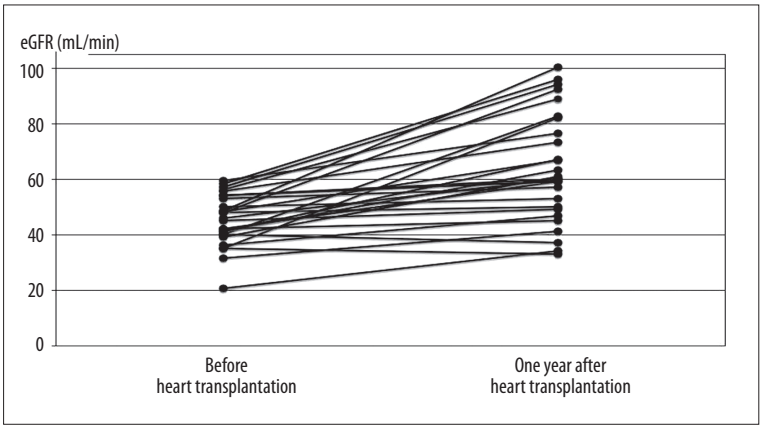

Figure 1. Estimated Glomerular Filtration Rate (mL/min/1.73 m^2) before and one year after heart transplantation in patients with previous chronic kidney disease and no anemia (isolated Cardiorenal syndrome).

In the setting of renal dysfunction, erythropoietin deficiency plays a major role in anemia pathophysiology. Interstitial cells, located near the renal proximal tubule, produce erythropoietin [17]. Under hypoxia conditions its production is augmented several times. In CKD, this response is attenuated and anemia supervenes. In our study we identified 51 patients with pre-HT eGFR less than 60 mL/min, and of these 47% had concomitant anemia.

Regardless of comparable renal function pre-HT, patients in the CRS group had an improvement in renal function in the first year after HT, while patients with only CRS before HT maintained eGFR. Moreover, higher hemoglobin pre-HT was independently associated with renal function improvement after HT.

Cyclosporine is considered to be the main cause of renal dysfunction post-HT [18]. After HT, there is a loss of renal function within 3–6 months, which is both CsA dose-dependent and progressive [19]. Identification of risk factors in the development of CsA nephrotoxicity has proven to be difficult and somewhat controversial. Although some groups

Table 4. Clinical and Laboratory data between CKD patients.

	CRS (n=27)	CRA (n=24)	p
Age (years)	4911	53±8	0.33
Gender (M/F)	22/5	20/4	0.41
Ejection fraction pre-HT (%)	25±9	26±11	0.86
Hb pre-HT (g/dL)	13.4±1.3	10.2±0.7	0.004
Hypertension diagnosis	22/27	19/24	0.94
Previous diabetes mellitus (%)	5/27	4/24	0.92
ACE inhibitor/ ARB therapy (%)	21/27	18/24	0.98
Beta-blocker therapy (%)	16/27	14/24	0.94
Diuretic therapy (%)	25/27	21/24	0.99
Digoxin therapy (%)	12/27	10/24	0.59
eGFR pre-HT (mL/min)	45±11	44±14	0.82
Mean cold ischemia (min)	136±34	125±38	0.49
Mean extracorporeal circulation time (minutes)	152±51	151±41	0.82
AKIN post-HT (%)	41	37	0.63
Mean serum CSA (pg/mL)	265±72	233±55	0.59
Ejection fraction year post-HT (%)	66±11	67±11	0.9
Hb one year post-HT (g/dL)	13.4±1.3	10.8±1.2	0.002
eGFR year post-HT (mL/min)	65±26	47±13	0.003

CRS – Cardiorenal syndrome; CRA – cardiorenal anemia; Hb – hemoglobin; HT – heart transplantation; CSA – cyclosporine.

have reported no correlation between preoperative renal function and post-transplant risk of chronic kidney disease, others have found that an impaired preoperative eGFR increased the risk of renal failure [13,14]. In our data, isolated CRS patients had increased eGFR, even with comparable serum cyclosporine trough levels, compared to patients with no previous CKD.

Pallet et al. [20] demonstrated that erythropoietin administration has antiapoptotic properties and protects epithelial tubular cells against cyclosporine nephrotoxicity. Also, erythropoietin appears to stimulate angiogenesis in a model of chronic cyclosporine nephrotoxicity [21]. One possible explanation for our findings is that those patients with underlying CKD before HT, but with no anemia, had a better renal function after HT due to erythropoietin-mediated protection against cyclosporine-induced nephrotoxicity; however, this remains speculative.

This study has several important limitations besides the small number of patients – it is a retrospective study and we have no data about the serum erythropoietin levels of the patients.

Conclusions

In conclusion, we identified that CRA has a different evolution than CRS after HT in relation to renal function and, moreover, hemoglobin level is independently associated with increased renal function after HT in patients with previous CKD.

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