Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 45, No. 7, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.11.061

Effect of Kidney Transplantation on Left Ventricular Systolic Dysfunction and Congestive Heart Failure in Patients With End-Stage Renal Disease

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OBJECTIVES We examined the impact of kidney transplantation on left ventricular ejection fraction (LVEF) in end-stage renal disease (ESRD) patients with congestive heart failure (CHF).

BACKGROUND The ESRD patients with decreased LVEF and a poor New York Heart Association (NYHA) functional class are not usually referred for transplant evaluations, as they are considered to be at increased risk of cardiac and surgical complications.

METHODS Between June 1998 and November 2002, 103 recipients with LVEF ≤40% and CHF underwent kidney transplantation. The LVEF was re-assessed by radionuclide ventriculography gated-blood pool (MUGA) scan at six and 12 months and at the last follow-up during the post-transplant period.

RESULTS Mean pre-transplant LVEF% increased from 31.6 ± 6.7 (95% confidence interval [CI] 30.3 to 32.9) to 52.2 ± 12.0 (95% CI 49.9 to 54.6, $p = 0.002$) at 12 months after transplantation. There was no perioperative death. After transplantation, 69.9% of patients achieved LVEF ≥50% (normal LVEF). A longer duration of dialysis (in months) before transplantation decreased the likelihood of normalization of LVEF in the post-transplant period (odds ratio 0.82, 95% CI 0.74 to 0.91; $p < 0.001$). The NYHA functional class improved significantly in those with normalization of LVEF ($p = 0.003$). After transplantation, LVEF >50% was the only significant factor associated with a lower hazard for death or hospitalizations for CHF (relative risk 0.90, 95% CI 0.86 to 0.95; $p < 0.0001$).

CONCLUSIONS Kidney transplantation in ESRD patients with advanced systolic heart failure results in an increase in LVEF, improves functional status of CHF, and increases survival. To abrogate the adverse effects of prolonged dialysis on myocardial function, ESRD patients should be counseled for kidney transplantation as soon as the diagnosis of systolic heart failure is established. (J Am Coll Cardiol 2005;45:1051–60) © 2005 by the American College of Cardiology Foundation

Observational studies indicate that congestive heart failure (CHF) is 12 to 36 times more prevalent in dialysis patients as compared with the general population (1–5). The probability of survival in a dialysis patient is decreased by almost 50% after the diagnosis of CHF is established, based on clinical symptoms (3). The analysis of the U.S. Renal Dialysis Morbidity and Mortality Study (DMMS) Wave 2 revealed that mortality at three years after hospitalization for CHF is almost similar to that after acute myocardial infarction (83% vs. 80%), respectively (6,7). Thus, CHF is the most common cardiovascular risk factor for death in dialysis patients.

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The optimal management of CHF due to left ventricular (LV) dysfunction (systolic heart failure) in patients with end-stage renal disease (ESRD) remains controversial. It is not known whether the recommendations for the treatment of systolic heart failure in the general population are equally effective and safe in ESRD patients with systolic heart failure (8).

At present, ESRD patients with systolic heart failure are considered to be at high risk for surgery. Due to a lack of evidence determining if kidney transplantation can be performed without increased perioperative morbidity and mortality, there is reluctance on the part of nephrologists and cardiologists to refer ESRD patients with systolic heart failure for transplant evaluation. When dialysis patients with CHF due to reduced left ventricular ejection fraction (LVEF) present for kidney transplantation evaluation, it is unclear whether such patients should be

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Manuscript received August 25, 2004; revised manuscript received November 23, 2004, accepted November 29, 2004.

JACC Vol. 45, No. 7, 2005
April 5, 2005:1051–60

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CABG = coronary artery bypass graft
CHF = congestive heart failure
ESRD = end-stage renal disease
LVEF = left ventricular ejection fraction
MUGA = radionuclide ventriculography gated-blood pool scan
NYHA = New York Heart Association
PTCA = percutaneous transluminal coronary angioplasty
PTH-I = intact parathyroid hormone
URR = urea reduction ratio

accepted and wait-listed for transplantation. Furthermore, the effects of correction of azotemia/uremia on LV systolic function, New York Heart Association (NYHA) functional class status and patient survival are poorly understood.

Left ventricular systolic dysfunction, per se, is an independent cardiovascular risk factor for poor prognosis, even in patients with normal renal function (9–11), in the elderly population (12) and in patients with asymptomatic LV systolic dysfunction (13). It is likely that decreased LVEF may portend a similar adverse prognosis in ESRD patients, despite transplantation.

We studied ESRD patients with LVEF ≤40% and CHF to determine the impact of renal transplantation on LVEF, symptoms of CHF, and risk factors for changes in LVEF in the post-transplant period.

METHODS

Patient population. Between June 1998 to November 2002, 138 patients with ESRD and reduced LV systolic function (LVEF ≤40%) with CHF underwent either kidney or kidney/pancreas transplantation at the University of Maryland Medical Center. The median number of hospitalizations for CHF, based on the hospital discharge summaries at the time of transplant evaluation, was at least two (range two to eight) per year for the management of recurrent heart failure. Thirty-five patients were excluded from the final analysis: patients with a combination of kidney and pancreas transplants (n = 8), kidney retransplantation (n = 3), valvular heart disease and valve surgery (n = 4), obstructive sleep apnea syndrome (n = 4), amyloidosis (n = 2), lack of immediate graft function (n = 7), and early graft loss within the first three months of transplantation due to either technical reasons or primary nonfunction (n = 4). Three patients were lost to follow-up. Patients with a functioning graft for three months or more after transplantation were included in this analysis (n = 103). All patients were treated with a standard triple immunosuppression protocol consisting of tacrolimus (FK506) or cyclosporine A (CsA) in combination with mycophenolate mofetil and maintenance-dose prednisone therapy.

Data collection and management. This is an observational cohort study. All data related to the dialysis period were collected at the time of transplant evaluation. Episodes of CHF in the pretransplant period were retrieved from the hospital discharge summaries, as reported in several observational studies in a dialysis population (4,7,14). Clinical data in the post-transplant period were prospectively collected by four investigators (R.K.W., G.S.W., L.B., and R.H.), coded, and entered into a computer data base. An independent physician Data and Safety Monitoring Board periodically assessed data safety throughout the study. During the post-transplant follow-up period, the clinical management of the patient was the responsibility of the treating physicians: a team consisting of a transplant surgeon, nephrologist, and consulting cardiologist, none of whom had knowledge of the study objectives. The data analysis was performed with permission from the Institutional Committee on Human Research.

Cardiac evaluation (pretransplant and post-transplant period). In accordance with our standard pretransplant evaluation protocol, all potential recipients ≥50 years old, as well as patients of any age with a history of diabetes mellitus (type 1 or 2) or ischemic heart disease, were evaluated for inducible myocardial ischemia by either dobutamine echocardiography or myocardial perfusion scans (single-photon emission computed tomography study). Based on these results, coronary artery interventional procedures were performed, if clinically indicated, before transplant listing. Similarly, patients of any age with a history of CHF, with or without diabetes mellitus, were also evaluated for inducible myocardial ischemia. Either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG) was performed if clinically indicated. In addition, patients with CHF were also evaluated by radionuclide ventriculography gated-blood pool scans (MUGA scan) before transplant listing. The MUGA scans in patients on hemodialysis were performed the day after their regular dialysis to avoid the impact of variable volume status on LV function during the interdialytic period.

After transplantation, LVEF was reassessed by MUGA scan at six and 12 months and at the last follow-up during the post-transplant period. Three physicians who were blinded to the study objectives independently analyzed the hospital records, discharge summaries, and/or death certificates to define the cause for hospitalization or death. It was determined whether the patient was hospitalized for CHF based on the Framingham criteria (15) and if the cause of death was due to cardiovascular events.

Pretransplant and post-transplant clinical and biochemical parameters. Body mass index (kg/m^2), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP: [DBP + 1/3 (SBP − DBP)]) (mm Hg) were measured after each dialysis session and during the post-transplant follow-up visits. Pretransplant biochem-

ical measurements such as hematocrit, albumin, calcium, phosphate, calcium × phosphate, intact-parathyroid hormone (PTH-I), and urea reduction ratios (URR [%]) (a measure of the dose of dialysis therapy) were obtained from the dialysis records. During the post-transplant period, the hematocrit, a comprehensive metabolic panel, and 12-h trough levels of either cyclosporine A or tacrolimus were obtained every month until the last follow-up or up to the time of death. The PTH-I levels were performed every three to six months in the post-transplant period. All hemodynamic and biochemical values are reported as an average of values obtained six consecutive months before the date of transplant surgery and are similarly reported (except URR) in the post-transplant follow-up period.

Primary objectives. Our primary goal was to assess the impact of a functioning kidney transplant on LVEF. Epidemiologic studies have often defined LVEF ≥50% as normal LV systolic function. Based on this "a priori definition," patients in the post-transplant period were categorized into three groups:

Group 1 consisted of patients in whom LVEF increased to ≥50%.

Group 2 included patients in whom LVEF increased to >40% but <50%.

Group 3 consisted of patients in whom LVEF persisted at <40%.

In addition, our goal was to identify predictors of normalization of LVEF.

Secondary objectives. We assessed perioperative mortality and changes in the functional status (baseline to post-transplant) of patients by using the NYHA functional classification (class I to IV). The baseline NYHA functional class was assessed at the time of evaluation for transplant listing. Other secondary objectives included death (all-cause mortality), death due to cardiovascular causes, and cardiovascular events such as hospitalizations for symptomatic CHF during the post-transplant period.

Statistical analysis. Baseline data between the groups were compared using the chi-square test for discrete variables. One-way analysis of variance (ANOVA) was used for continuous variables. All subgroup comparisons were made by the Tukey method of multiple comparisons. The Wilcoxon signed-rank test was used to compare pre- and post-transplant variables between the groups. For the patients who died before the last follow-up date, the most recently determined values for LVEF and other post-transplant characteristics were used in the analysis.

A preliminary analysis was performed with 26 covariates that were used in two independent models of logistic regression analysis for the comparison of risk factors in the pretransplant period (dialysis related) and post-transplant period for normalization of LVEF. The covariates in the pretransplant period included race (African-American), gender (male), and the presence (yes/no) of diabetes mellitus, coronary artery disease, PTCA, or CABG. Other covariates included age (years), MAP (mm Hg), pretransplant LVEF (%), time on dialysis (months), URR (%), hematocrit (%), calcium (mg/dl), phosphate (mg/dl), albumin (g/dl), calcium × phosphate, and PTH-I (pmol/dl). The covariates in the post-transplant period included all the selected pretransplant covariates except age, race, time on dialysis, and URR, with addition of the use (yes/no) of calcineurin inhibitors, beta-blockers (any type), and angiotensin-converting enzyme (ACE) inhibitors (any type). However, a limited number of events made it impossible to include all desired covariates. Thus, those that were deemed clinically important and statistically significant were included in the final and reduced model(s) of multivariate analysis.

The functional status of CHF based on the NYHA functional class before and after transplantation was analyzed by Kendall's tau cross-tabulation for ordinal variables. The Kaplan-Meier analysis with the log-rank test was used to calculate the unadjusted survival.

The combined risk of death (all-cause mortality) or hospitalization for symptomatic CHF was evaluated with the use of a time-to-first-event analysis by a Cox proportional hazards model, using post-transplant LVEF as a continuous variable. The covariates used in the Cox model (test) included all the selected pre- and post-transplant variables that were used in the test model of logistic regression analysis. Due to a limited number of events, only those covariates that were used in the final and reduced model(s) of regression analysis were also used in the final Cox model.

All data are reported as mean ± SD. We used SPSS statistical software (SPSS version 9.0; SPSS Chicago, Illinois) for statistical analysis.

RESULTS

Changes in LVEF in pre- and post-transplant period (Table 1). Overall, the mean pretransplant LVEF% improved from 31.6 ± 6.7 (95% confidence interval [CI] 30.3 to 32.9) to 47.2 ± 10.7 (95% CI 50.8 to 54.1, $p < 0.001$) at 6.6 ± 1.1 months after transplantation. This improvement persisted, with a further increase in LVEF% to 52.2 ± 12.0 (95% CI 49.9 to 54.6, $p = 0.002$) at 12.5 ± 2.1 months after transplantation.

The majority of patients (72 [69.9%] of 103) had "normalized" LVEF in the post-transplant period (Group 1). Sixteen patients (15.5%) had an increase in LVEF to >40% but remained <50% (Group 2). In 15 patients (14.5%), LVEF <40% persisted (Group 3) (Table 1). More than 86% of patients had an increase in LVEF by >5%. A 5% increase in LVEF on a MUGA study is generally considered a true improvement (16).

Perioperative course. At the time of admission to the hospital for surgery, volume status was carefully controlled by intensive hemofiltration. Patients who were not on beta-blockers were carefully started on beta-blockers. In the

Table 1. Description of the Left Ventricular Ejection Fraction (LVEF%) at Different Time Periods: At the Time of Transplant Evaluation, While on the Waiting List to be Transplanted, and During the Follow-Up After Kidney Transplantation

		Groups Based on Post-Transplant LVEF%			p Value		
	All Patients (N = 103)	LVEF ≥50% Group 1 (n = 72)	LVEF ≥40% to <50% Group 2 (n = 16)	LVEF <40% Group 3 (n = 15)	Group 1 vs. 2	Group 2 vs. 3	Group 3 vs. 1
Pretransplant evaluation							
LVEF% (initial transplant evaluation)							
Mean ± SD	31.6 ± 6.7	31.7 ± 6.7	31.6 ± 7.6	31.2 ± 6.1	1.00	0.98	0.98
(95% CI)	(30.3–32.9)	(30.1–33.3)	(27.5–35.6)	(27.7–34.6)			
LVEF% (repeat evaluation before transplant surgery)*							
Mean ± SD	29.3 ± 6.2	29.0 ± 6.0	30.5 ± 8.0	29.6 ± 5.3	0.87	0.97	0.98
(95% CI)	(28.1–30.6)	(27.6–30.5)	(26.2–34.8)	(26.6–32.5)			
Post-transplant evaluation							
Post-transplant LVEF% (at six months)							
Mean ± SD	47.2 ± 10.7	52.5 ± 6.9	39.2 ± 6.1	30.6 ± 6.5	<0.0001	0.002	<0.0001
(95% CI)	(45.1–49.3)	(50.8–54.1)	(35.9–42.5)	(26.9–34.2)			
Post-transplant LVEF% (at 12 months)†							
Mean ± SD	52.2 ± 12.0	58.8 ± 6.8	42.1 ± 2.4	31.6 ± 4.9	<0.001	0.001	<0.001
(95% CI)	(49.9–54.6)	(57.2–60.4)	(40.8–43.4)	(28.9–34.4)			

The groups are based on the LVEF % obtained during the post-transplant period. *Repeat LVEF% (second pretransplant measurement) while on the waiting list for more than 12 months was obtained in 61 patients. †Repeat LVEF% (second post-transplant measurement) was obtained in 101 patients.
CI = confidence interval; LVEF = left ventricular ejection fraction.

postoperative period, 44 of 103 patients were monitored in the intensive care unit after surgery. Twenty-nine patients required right heart catheterization in the perioperative period. Patients with delayed graft function (33 of 103) required daily dialysis and hemofiltration for a median period of two weeks in the post-transplant period (data not shown).

Patient characteristics. The baseline clinical characteristics of the patients are described in Table 2. The mean age of patients was 55.0 ± 10.2 years; 58% were African-Americans; and 70% were men. Most patients had more than one comorbid condition at the time of transplantation. Among the patients with coronary artery disease, 54% and 37% had either PTCA or CABG, respectively, before transplantation. The remaining 9% had diffuse multivessel disease and were treated with medical therapy. The patients with coronary artery disease were without inducible ischemia at the time of measurement of LVEF before transplantation.

Pretransplant LVEF was measured at the time of the initial transplant evaluation and repeated in those who remained on the waiting list for more than 12 months. There was a trend toward a further decrease in LVEF% between the initial and repeat evaluations (31.6 ± 6.7 vs. 29.3 ± 6.2, $p < 0.05$), respectively, while on dialysis. At the time of transplantation, 11 (10%) of 103 patients had LVEF <20%, 50 (49%) of 103 had LEVF between >20% and <30%, and another 42 (41%) of 103 had LVEF ≥30% to 40%. In the pretransplant period, more than one-half (57%) of the patients were in NYHA functional class IV, 40.5% in class III, and 2.5% in class II (Table 2). While on dialysis, nearly 58% of the cohort were on beta-blockers (any type) and 64% were receiving the combination of both beta-blockers and ACE inhibitors (data not shown).

An inverse association between the duration of dialysis therapy before transplantation and normalization of LVEF in the post-transplant period was observed. Patients with post-transplant LVEF ≥50%, compared with those with LVEF >40% but <50% (Group 1 vs. 2: 14.7 ± 10.6 vs. 40.4 ± 14.7; $p < 0.001$) and compared with those in whom LVEF in the post-transplant follow-up period remained ≤40% (Group 1 vs. 3: 14.7 ± 10.6 vs. 45.1 ± 19.9; $p < 0.001$), had a significantly shorter duration of dialysis treatment (in months) before transplantation. In contrast, the duration of dialysis therapy before transplantation was similar in patients in whom LVEF persisted <50% in the post-transplant period; LVEF ≥40% but <50% versus LVEF ≤40% (Group 2 vs. 3: 40.4 ± 14.7 vs. 45.1 ± 19.9; $p = 0.32$) (Table 2). Other comorbidities, including the presence of diabetes mellitus and coronary artery disease with or without intervention for underlying coronary artery disease, were not significantly different between the groups. Even the measure of dialysis adequacy (URR%), type of dialysis therapy, and type of hemodialysis access (arteriovenous graft or fistula or permanent catheter) were similar between the groups.

Pre- and post-transplant hemodynamic and biochemical parameters. The hemodynamic and biochemical parameters in the pre- and post-transplant periods are shown in Table 3. In the post- compared with pretransplant period, the mean SBP, DBP, and MAP were significantly higher in those with post-transplant LVEF >50%, as compared with those with post-transplant LVEF <50% (Groups 2 and 3). In the latter groups, these parameters remained unchanged

Table 2. Demographic Characteristics and Dialysis-Related Factors in All Patients and Different Groups Based on the Post-Transplant Left Ventricular Ejection Fraction (LVEF%)

		Groups Based on Post-Transplant LVEF%			p Values		
Characteristics	All Patients (N = 103)	LVEF ≥50% Group 1 (n = 72)	LVEF >40% to 50% Group 2 (n = 16)	LVEF <40% Group 3 (n = 15)	Group 1 vs. 2	Group 2 vs. 3	Group 3 vs. 1
Age (yrs)	55.0 ± 10.2	55.4 ± 10.5	54.8 ± 11.2	53.4 ± 7.7	0.83	0.69	0.48
Race					0.13	0.37	0.68
African American	59 (58%)	38 (54%)	12 (75%)	9 (60%)			
Caucasian	42 (40%)	32 (43%)	4 (25%)	6 (40%)			
Others	2 (2%)	2 (3%)					
Male gender	72 (70%)	50 (69%)	12 (75%)	10 (67%)	0.66	0.60	0.83
BMI (kg/m^2)	27.1 ± 4.8	27.0 ± 5.2	27.3 ± 4.2	27.3 ± 3.7	0.82	0.97	0.86
Hypertension	99 (96%)	71 (98%)	15 (96%)	13 (89%)	0.77	0.84	0.45
Diabetes mellitus	54 (52%)	37 (51%)	11 (68%)	6 (40%)	0.20	0.10	0.42
Coronary artery disease*	52 (51%)	34 (47%)	9 (56%)	9 (60%)	0.51	0.83	0.36
Of those treated with CABG	19 (37%)	11 (32%)	5 (55%)	3 (33%)	0.13	0.47	0.65
Of those treated with PTCA	28 (54%)	19 (55%)	4 (44%)	5 (55%)	0.90	0.60	0.58
Multivessel disease (insignificant lesion)	5 (9%)	4 (11%)		1 (11%)			
Type of dialysis†					0.59	0.20	0.38
Hemodialysis	81 (79%)	57 (79%)	13 (81%)	11 (73%)			
Peritoneal dialysis	16 (16%)	10 (14%)	2 (13%)	4 (26%)			
Hemodialysis access‡					0.33	0.30	0.14
AVG	35 (34%)	19 (26%)	8 (50%)	8 (53%)			
AVF	35 (34%)	27 (37%)	5 (31%)	5 (20%)			
Catheters	14 (14%)	11 (15%)	2 (13%)	1 (7%)			
Time on dialysis (months)§	23.4 ± 18.4	14.7 ± 10.6	40.4 ± 14.7	45.1 ± 19.9	<0.0001	0.32	<0.0001
Urea reduction ratio (%)‖	68 ± 9.9	67 ± 11.2	67 ± 6.6	70 ± 7.8	0.82	0.39	0.40
NYHA functional class					0.29	0.61	0.52
I	0	0	0	0			
II	5 (5%)	5 (7%)	0	0			
III	42 (41%)	31 (43%)	5 (31%)	6 (40%)			
IV	56 (54%)	36 (50%)	11 (69%)	9 (60%)			
LVEF (pretransplant)					0.96	0.31	0.31
<20%	11 (10%)	9 (82%)	2 (18%)				
20% to <30%	50 (49%)	34 (68%)	7 (14%)	9 (18%)			
30% to 40%	42 (41%)	29 (69%)	7 (16%)	6 (15%)			

*These results are based on the pretransplant evaluation for coronary artery disease at the time of initial transplant evaluation. Patients with coronary artery disease had coronary interventions performed before surgery for transplantation. The numbers and percentages across the row are based on the number of patients in the coronary artery disease category. All these patients were without inducible ischemia at the time of measurement of left ventricular ejection function at baseline (LVEF before transplantation). †Six patients had a preemptive transplant; five patients were in Group 1 and other patient was in Group 2. ‡Some patients could have more than one type of hemodialysis access if AVG or AVF did not function. §Time on dialysis was the only factor that was significantly different among the patients with and without normalization of left ventricular function in the post-transplant period. Time on dialysis was calculated in 97 patients: 81 patients on hemodialysis and 16 patients on peritoneal dialysis. ‖The URR ratio was calculated in 79 patients on hemodialysis and was missing from two patients. The chi-square test was used for the comparison of all categorical variables. Continuous variables and across-group comparisons were made with analysis of variance and Tukey's method of multiple comparisons, respectively. Data are presented as the mean value ± SD or number (%) of patients.

AVF = arteriovenous fistula; AVG = arteriovenous graft; BMI = body mass index; CABG = coronary artery bypass grafting; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty.

compared with baseline. Serum phosphate and calcium × phosphate values were significantly lower in the post-transplant period, but this change did not differ between those who did or did not achieve LVEF ≥50% in the post-transplant period. In all patients, there was a significant increase in hematocrit and serum albumin in the post-transplant period (pre- vs. post-transplant: 33.0 ± 4.4 vs. 35.7 ± 4.1, p = 0.03) and (3.4 ± 0.5 vs. 3.6 ± 0.4, p = 0.02), respectively. However, this change in hematocrit and albumin was similar in those who did or did not have an improvement of LVEF in the post-transplant period. Other biochemical parameters, such as the PTH-I level, were lower in the post-transplant period, but this decrease in PTH-I in the post-transplant period was similar in all three groups.

Post-transplant follow-up. The mean duration of follow-up was 36.8 ± 12.3 months and was similar in all three groups. Sixty-five percent of patients were recipients of deceased donor kidney allografts, and the type of kidney graft (whether from a living or deceased donor) did not differ between the groups. The type of immunosuppression treatment and number of patients on combinations of beta-blockers and ACE inhibitors in the post-transplant period were similar in those with or without normalization of LV function. However, a significantly higher number of patients with a post-transplant LVEF <50% (groups 2 and

Table 3. Comparison of Hemodynamic and Biochemical Parameters in the Pre- and Post-Transplant Periods in All Patients and Different Groups Based on the Left Ventricular Ejection Fraction in the Post-Transplant Period

Characteristics	All Patients (N = 103)			Post-Transplant LVEF ≥50% Group 1 (n = 72)			Post-Transplant LVEF >40% to <50% Group 2 (n = 16)			Post-Transplant LVEF <40% Group 3 (n = 15)		
	Pre-Tx*	Post-Tx	p Value	Pre-Tx*	Post-Tx	p Value	Pre-Tx*	Post-Tx	p Value	Pre-Tx*	Post-Tx	p Value
SBP (mm Hg)	127.3 ± 20.8	142.0 ± 17.7	<0.001	127.4 ± 19.5	146.3 ± 16.0	<0.001	131.6 ± 21.6	134.4 ± 21.6	0.06	120.6 ± 21.4	132.5 ± 17.2	0.49
DBP (mm Hg)	79.4 ± 13.9	84.4 ± 11.2	0.002	78.3 ± 15.0	85.9 ± 11.0	<0.001	80.0 ± 10.2	82.6 ± 11.1	0.46	83.9 ± 11.0	78.9 ± 11.3	0.06
MAP (mm Hg)	95.4 ± 14.5	103.6 ± 11.8	<0.001	94.7 ± 15.1	106.1 ± 11.0	<0.001	93.5 ± 12.7	99.2 ± 11.2	0.09	100.7 ± 13.0	96.4 ± 12.3	0.09
Hct (%)	33.0 ± 4.4	37.7 ± 4.1	0.03	33.4 ± 4.7	34.5 ± 4.2	0.16	32.0 ± 3.6	33.9 ± 3.7	0.33	32.2 ± 3.1	34.2 ± 4.3	0.46
Albumin (g/dl)	3.4 ± 0.5	3.6 ± 0.4	0.02	3.5 ± 0.4	3.6 ± 0.3	0.24	3.3 ± 0.6	3.6 ± 0.4	0.08	3.4 ± 0.6	3.6 ± 0.4	0.19
Calcium (mg/dl)	8.9 ± 0.9	8.8 ± 0.8	0.08	9.0 ± 0.8	8.5 ± 0.8	0.06	9.1 ± 0.6	8.3 ± 0.9	0.02	8.2 ± 1.0	8.9 ± 0.7	0.02
Phosphate (mg/dl)	4.7 ± 1.6	2.8 ± 0.5	<0.001	4.5 ± 1.5	2.7 ± 0.5	<0.001	5.7 ± 2.1	3.0 ± 0.5	<0.001	4.9 ± 1.2	3.0 ± 0.6	<0.001
Calcium × phosphate	42.6 ± 14.5	25.3 ± 5.7	<0.001	40.9 ± 13.7	24.7 ± 5.7	<0.0001	51.5 ± 17.4	26.4 ± 5.9	<0.0001	41.2 ± 12.5	26.9 ± 5.2	<0.001
PTH-I (pm/ml)	250 ± 122	247 ± 95	0.42	260 ± 133	255 ± 97	0.70	242 ± 82	218 ± 75	<0.05	214 ± 101	239 ± 104	0.35
LVEF (%)†	31.6 ± 6.7	52.2 ± 12.6	<0.001	31.6 ± 7.6	58.8 ± 6.8	<0.001	31.6 ± 7.6	42.1 ± 2.4	<0.001	31.2 ± 6.1	31.6 ± 4.9	0.21

*Pretransplant blood pressure (systolic and diastolic) was measured in the sitting position at the end of each dialysis session. †Left ventricular ejection fraction (LVEF) represents the values obtained at the time of initial transplant evaluation (103 patients). All values (mean ± SD) are the average of six consecutive values obtained in the pre- and post-transplant periods. Pre- and post-transplant variables were compared by Wilcoxon signed rank test. To convert phosphate mg/dl to mmol/l, multiply by 10; calcium from mg/dl to mmol/l, multiply by 0.25; albumin from g/dl to g/l, multiply by 10; PTH-I from pg/dl to ng/l, multiply by 10.
DBP = diastolic blood pressure; HCT = hematocrit; MAP = mean arterial pressure; PTH-I = intact parathyroid hormone; SBP = systolic blood pressure; Tx = transplant.

3) required treatment with hydralazine, diuretics, and digoxin in the post-transplant period (Table 4).

Functional status by NYHA functional class before and after transplantation. The clinical status of patients assessed by NYHA functional classification improved significantly in the post-transplant period (Table 4). Before transplantation, there was no patient with NYHA class I functional status. At the last follow-up, 73% of all patients who survived were in NYHA functional class I. Before transplantation, 57.5% of patients were in NYHA functional class IV. After transplantation, none of the patients with LVEF ≥50%, but 24% patients with LVEF <50% had class IV symptoms. Paired comparisons of the pre- and post-transplant NYHA functional classes demonstrated significant improvement in the functional status in the post-transplant period (Kendall's tau-b value = 0.25; p = 0.003).

Combined end point of death or hospitalizations for CHF in post-transplant period. There was no perioperative death. There were a total of 25 deaths during the mean follow-up of 36.8 ± 12.3 months, with an eight-fold increase in the rate of death in patients with persistence of LVEF <50% in the post-transplant period. Death due to all-cause mortality was 8% in Group 1 as compared to 62% and 60% in those with post-transplant LVEF <50% (Groups 2 and 3, respectively). In contrast, all-cause mortality in patients with LVEF <50% in the post-transplant period was similar (Group 2 vs. 3, p = 0.88). Unadjusted survival by the log-rank test was significant (p < 0.0001) (Fig. 1).

The combined end point of death or hospitalization for CHF was analyzed to avoid the conflict of the competing risks of patients who died and could not be hospitalized. Increased LVEF in the post-transplant period was significantly associated with a lower hazard for these events (relative risk 0.90, 95% CI 0.86 to 0.95; p < 0.0001).

Analysis of patients with pretransplant LVEF ≤30% and subgroups of patients. Because the pretransplant LVEF varied between 10% and 40%, we analyzed whether patients with severe LV dysfunction during the dialysis period had a different outcome in the post-transplant period. The majority of patients (9 [82%] of 11) with pretransplant LVEF ≤20% had an increase in LVEF to >50%, and in the remaining 2 (18%) of 11 patients, LVEF improved to >40% but remained <50%. In addition, 49% of patients had pretransplant LVEF <30%, and 68% of these patients had normalized LVEF in the post-transplant period (Table 2). Subgroup analysis of patients with different comorbidities showed a significant and consistent increase in LVEF in the post-transplant period (Fig. 2).

Pre- and post-transplant covariates for the normalization of LVEF in the post-transplant period (Table 5). Based on the logistic regression analysis for selected pre- and post-transplant covariates, including those variables that were significant in the univariate analysis, time on dialysis (duration of dialysis in months) before transplantation was the only significant factor that had an impact on normal-

Table 4. Post-Transplant Characteristics in All Patients as Well as in Different Groups Based on Left Ventricular Ejection Fraction in the Post-Transplant Period

Descriptives	All Patients (N = 103)	Groups Based on Post-Transplant LVEF%			p Values		
		LVEF ≥50% Group 1 (n = 72)	LVEF >40% to <50% Group 2 (n = 16)	LVEF <40% Group 3 (n = 15)	Group 1 vs. 2	Group 2 vs. 3	Group 3 vs. 1
Follow-up* (months)	36.8 ± 12.3	37.7 ± 12.8	36.4 ± 11.8	36.9 ± 10.9	0.16	0.98	0.17
Serum creatinine (mg/dl)							
At six months	2.1 ± 0.7	2.0 ± 0.6	2.2 ± 0.8	2.3 ± 0.6	0.60	0.56	0.21
At 12 months	2.3 ± 0.9	2.1 ± 0.6	2.3 ± 0.8	3.1 ± 1.6	0.43	0.03	<0.001
NYHA functional class					<0.001	0.48	<0.001
I	53 (51%)	48 (67%)	4 (25%)	1 (7%)			
II	31 (31%)	22 (30%)	5 (31%)	4 (26%)			
III	12 (11%)	2 (3%)	4 (25%)	6 (40%)			
IV	7 (7%)		3 (19%)	4 (27%)			
CHF therapy†							
Beta-blockers	92 (89%)	63 (87%)	15 (93%)	14 (93%)	0.47	0.96	0.51
ACE-I	61 (59%)	36 (50%)	13 (81%)	12 (80%)	0.02	0.93	0.03
ARB	8 (8%)	6 (8%)	1 (6%)	1 (7%)	0.78	0.96	0.82
Hydralazine	44 (42%)	20 (28%)	13 (81%)	11 (74%)	0.00	0.59	<0.001
Digoxin	21 (20%)	7 (10%)	8 (50%)	6 (40%)	0.00	0.57	0.003
Diuretics	68 (66%)	43 (60%)	12 (75%)	13 (86%)	0.25	0.41	0.04
Hospitalization for CHF (first episode)	46 (44%)	19 (26%)	12 (75%)	15 (100%)	<0.0001	0.03	<0.0001
Time to CHF in months (first episode)	4.0 ± 3.1	3.9 ± 2.6	4.9 ± 4.2	3.4 ± 2.8	0.85	0.68	0.94
Hospitalization for CHF (more than one episode)	22 (21%)	6 (9%)	6 (37%)	10 (66%)	0.002	0.10	<0.0001
Time to CHF in months (more than one episode)	9.4 ± 5.0	9.2 ± 2.5	9.6 ± 8.1	9.4 ± 4.2	0.99	0.99	0.94
Deaths‡	25 (24%)	6 (8%)	10 (62%)	9 (60%)	<0.0001	0.88	<0.0001
CV causes§	10	3	3	4			
Sepsis	4	1	2	1			
Unknown	11	2	5	4			

*After censoring for death. †Therapy for CHF was chosen by the consulting cardiologist and the nephrologist who were blinded to the study objectives. ‡Death due to all-cause mortality. §Cardiovascular causes included acute myocardial infarction, CHF, sudden death, and strokes. All variables were compared by the chi-square test. To convert creatinine from mg/dl to mmol/l, multiply by 88.4. Data are presented as the mean value ± SD or number (%) of patients.

ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor type I blockers; CHF = congestive heart failure; CV = cardiovascular; LVEF% = percent left ventricular ejection fraction; MMF = mycophenolate mofetil; NYHA = New York Heart Association.

ization of LVEF in post-transplant period (odds ratio 0.82, 95% CI 0.74 to 0.91; $p < 0.001$). A longer duration of dialysis before transplantation was associated with a decreased likelihood of achieving LVEF ≥50% in the post-transplant period.

DISCUSSION

This study demonstrates that kidney transplantation can be performed safely in ESRD patients with decreased LVEF, advanced heart failure, and without inducible ischemia. Kidney transplantation resulted in an increase in LVEF in more than 86% of patients and was associated with an improvement in NYHA functional status in more than two-thirds of patients. Even a majority of patients with pretransplant LVEF ≤20% had normalized LVEF in the post-transplant period. The duration of dialysis therapy before kidney transplantation was the only significant factor that predicted the normalization of LVEF (defined as LVEF ≥50%).

The optimal management of systolic heart failure in the dialysis population remains poorly understood. As compared with the robust evidence-based therapeutic strategies for the treatment of systolic heart failure in the general population (8), only one published study to date demonstrated that the use of carvedilol was associated with an improved outcome of systolic heart failure in dialysis-dependent patients (17). Unfortunately, even a mild degree of renal failure was an exclusion criterion in almost all randomized studies in the general population with CHF. Nonetheless, more than 50% of our patients were being treated with beta-blockers and ACE inhibitors while on dialysis therapy.

There are a few reports of an improvement of LV systolic function, defined either as an improvement in LV fraction shortening (n = 12) (18) or as an improvement in LVEF; there is a report of four patients (19) and another report of two patients (20) after kidney transplantation. These studies, however, did not assess other outcomes. Other studies have demonstrated changes in LV morphology but without assessment of LVEF (18,21). The present study systematically examined a large sample of ESRD patients with systolic heart failure, defined by the strict criteria of LVEF

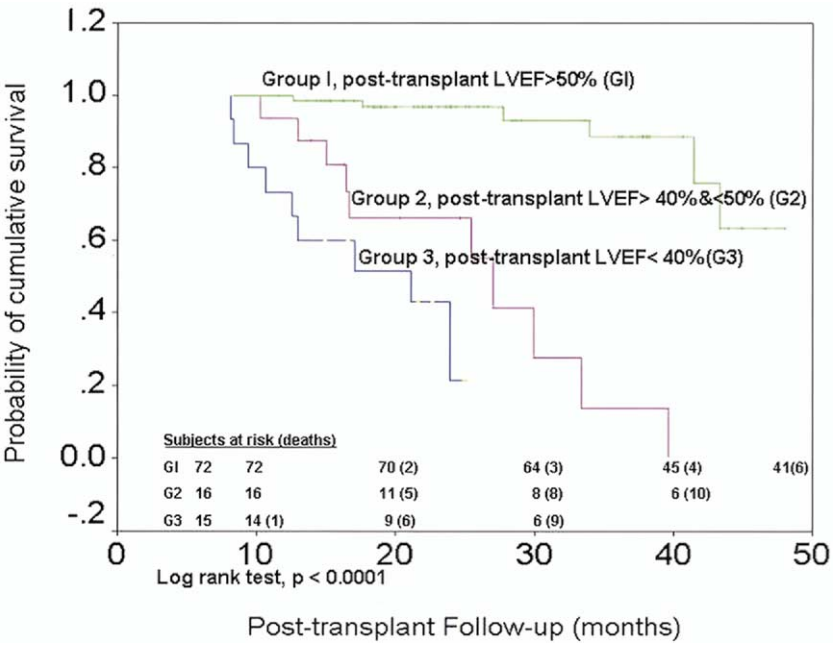

Figure 1. Kaplan-Meier analysis of survival plots for death in the post-transplant period (after first six months after transplantation). Persistence of left ventricular ejection fraction (LVEF) <50% in the post-transplant period was associated with an eight-fold increase in the rate of death. The number (%) of deaths in patients with post-transplant LVEF >50%: 6 (8%) of 72; in patients with post-transplant LVEF >40% but <50%: 10 (62%) of 16; and in patients with post-transplant LVEF <40%: 9 (60%) of 15. $p < 0.0001$ by the log-rank test.

≤40% at the time of transplantation, and reevaluated their LVEF, functional status, and morbidity and mortality in the post-transplant period.

Why did LV systolic function improve in more than 86% of our patients? End-stage renal disease is a complex metabolic syndrome, and the uremic milieu may affect myocardial contractility and function (22). Kidney transplantation is associated with a significant improvement in azotemia. In contrast, prolonged exposure to uremic toxins has been demonstrated to affect myocardial contractility. Although the exact nature of such toxins remains yet to be determined, several potentially negative inotropic and chronotropic factors have been demonstrated in uremic plasma (23,24), and prolonged exposure to these uremic toxins can result in myocyte fibrosis and death (25,26). A prolonged duration of dialysis therapy results in an extended exposure of myocytes to these uremic toxins. That may be why an increased duration of dialysis therapy decreased the likelihood of improvement in LVEF in the post-transplant period. Similarly, Eknoyan et al. (27) demonstrated that a longer duration of dialysis and reduced clearance of middle

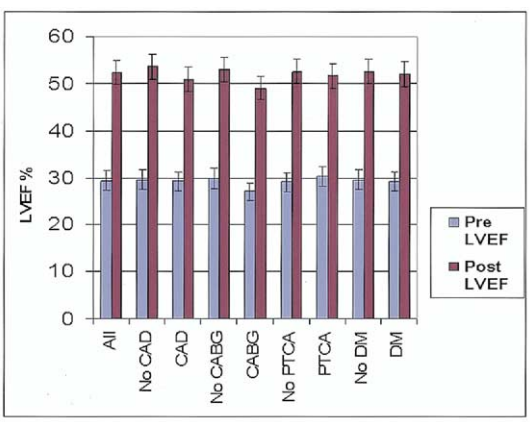

Figure 2. Pretransplant (while on dialysis) and post-transplant left ventricular ejection fraction (LVEF) in different subgroups of patients. All = all patients; CAD = pretransplant coronary artery disease; CABG = pretransplant coronary artery bypass grafting; DM = pretransplant diabetes mellitus (type 1 or 2); PTCA = pretransplant percutaneous transluminal coronary angioplasty. **Error bars** = standard deviations.

Table 5. Logistic Regression Models for Pre- and Post-Transplant Predictors for Normalization of Left Ventricular Ejection Fraction (LVEF ≥50%) in the Post-Transplant Period (Reference Group: Group With LVEF ≥50% in the Post-Transplant Period)

	OR	95% CI	p Value
Pretransplant covariates			
Age (yrs)	0.98	0.88–1.09	0.75
Race (African-American)	0.60	0.05–6.11	0.83
Gender (male)	0.31	0.02–3.6	0.95
Time on dialysis (months)	0.82	0.74–0.91	0.001
Diabetes mellitus (yes/no)	2.11	0.22–19.5	0.50
Coronary artery disease (yes/no)	1.2	0.11–14.3	0.33
URR (%)	0.94	0.74–1.08	0.45
Post-transplant covariates			
MAP (mm Hg)	1.16	0.99–1.36	0.05
Hematocrit (%)	1.99	0.72–1.36	0.95
Albumin (mg/dl)	2.7	0.19–37.7	0.45
Post-PTH-I (pg/dl)	1.00	0.99–1.02	0.18
Beta-blockers (yes/no)	2.8	0.20–40.5	0.43
ACE-I (yes/no)	0.22	0.03–1.58	0.13

ACE-I = angiotensin-converting enzyme inhibitors; CI = confidence interval; MAP = mean arterial pressure; OR = odds ratio; PTH-I = parathyroid hormone intact; URR = urea reduction ratio.

molecules (a component of the uremic toxin) were associated with an increased risk of death from cardiac causes.

We suggest that dialysis-dependent patients with reduced LVEF should be thoroughly evaluated for underlying ischemia. These patients should be treated aggressively for volume control while on dialysis, including optimization of beta-blocker, ACE inhibitor, or angiotensin receptor blocker therapy. If the patient continues to remain symptomatic with a progressive decrease in LVEF, these patients should be counseled regarding the overall benefits of transplantation and, in particular, other benefits, such as improvement of LV systolic function, improvement in symptoms of CHF, and decreased likelihood of death. Such patients should be encouraged to seek a living donor in order to obviate the wait-time for deceased donor kidney transplantation. Further studies are needed to determine whether there is a critical period on dialysis beyond which there is an irreversible damage to myocytes and lack of potential improvement in LV systolic function.

It may be argued that the improvement in LVEF in the post-transplant period was due to the new steady state of the patient's volume status secondary to the normalization or near normalization of kidney function after transplantation. However, either intensive hemodialysis (22) or nocturnal hemodialysis (28) in a select group of patients resulted in an improvement (without normalization) of LVEF. This improvement in CHF was independent of changes in volume status, hematocrit, and MAP. This suggests that volume alone does not account for changes in ejection fraction in patients with ESRD. Furthermore, our patient cohort had a tendency toward increased body mass index and increased SBP, DBP, and MAP in the post-transplant period, as would be expected with the use of corticosteroids and calcineurin inhibitors after transplantation (29). These factors usually increase afterload and impair systolic function (30) and can negatively affect the process of cardiac remodeling (31,32). Therefore, one might actually expect worsening of systolic function after transplantation.

Ischemic heart disease is an important cause of reduced LVEF (33,34) and usually progresses with time in patients with ESRD. Among our patients with established coronary artery disease, 60% had an increase in their LVEF to ≥50% in the post-transplant period. Hence, dialysis patients with underlying established coronary artery disease but without inducible ischemia may have some degree of myocardial dysfunction attributable to azotemia, which appears to be reversible after kidney transplantation.

Spontaneous fluctuations in LVEF have been described (16). We purposefully included only patients with LVEF ≤40% and used LVEF ≥50% as an indicator of normal LV function to minimize the possibility of variability in the repeat measurements of LVEF as a cause of our findings. Furthermore, repeated measurements of LVEF by the MUGA technique showed a trend toward a progressive decrease in LVEF in those patients who had repeat measurements while on the waiting list for transplantation. This observation is consistent with Foley et al. (35), who showed a progressive decrease in fractional shortening with an increased duration of dialysis. Other strengths of this study are the inclusion of patients with pretransplant LVEF ≤20% and a higher than expected number of patients with underlying comorbidities, such as diabetes mellitus and coronary artery disease, as compared with the USRD 2001 cohort (5).

Study limitations. The major limitation of this study could be that it is an observational cohort study. Given that LVEF improved in almost 86% of our patients, it may be argued that the worst cases of congestive heart failure were not referred for kidney transplantation. However, nearly half of the patient cohort had LVEF <30% before transplantation. In addition, the question arises as to whether we selected only healthy patients. This is unlikely because of the inclusion of patients with pretransplant LVEF ≤20% and a higher than expected number of patients with diabetes mellitus and coronary artery disease. The findings of this study may not be applicable to all ESRD patients with LV systolic dysfunction, as our patient population was relatively young as compared with the USRD cohort of dialysis patients (5). Therefore, these findings should be applied with caution in the older ESRD patients with systolic heart failure.

Conclusions. This study demonstrates that kidney transplantation is associated with a substantial improvement in LVEF in ESRD patients with systolic heart failure (systolic heart failure of uremia). Even patients with severely compromised cardiac function (pretransplant LVEF <20%) were able to successfully undergo the procedure and derived a significant benefit after kidney transplantation. We suggest that kidney transplantation should be considered the treatment of choice for ESRD patients with systolic heart failure, because a longer duration of dialysis in these patients may result in progressive and ultimately irreversible myocardial dysfunction. Therefore, patients with ESRD and systolic heart failure should be encouraged to undergo kidney transplantation as soon as the diagnosis of systolic heart failure is established, preferably from a living donor, to obviate the current wait-time for deceased donor kidney transplantation.

Acknowledgements

We are indebted to William L. Henrich, MD, for his continuous support and mentorship, and Eva K. Ritzl, MD, for her invaluable help with the preparation of the manuscript, and our special thanks to Ms. Geetha Stachowiak for her skillful administrative help.

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