# Structural and Functional Echocardiographic Changes Following Kidney Transplantation: The Role of Allograft Function

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**ABSTRACT:** **Background:** Kidney transplantation is associated with early improvement in cardiac function and structure; however, data on cardiac adaptation and its relation to kidney allograft function remain sparse.

**Objectives:** To investigate the relationship between post-transplant kidney function and echocardiographic measures in patients with normal/preserved pre-transplant cardiac structure and function.

**Methods:** The study included 113 patients who underwent kidney transplantation at a single tertiary medical center from 2000 to 2012. The patients were evaluated by echocardiography before and after transplantation, and the relation between allograft function and echocardiographic changes was evaluated. Echocardiography was performed at a median of 510 days after transplantation.

**Results:** The post-transplantation estimated glomerular filtration rate (eGFR) was directly correlated with left ventricular (LV) systolic function and inversely correlated with LV dimensions, LV wall thickness, left atrial diameter, and estimated systolic pulmonary arterial pressure. In patients with significant allograft dysfunction (eGFR ≤ 45 ml/min), LV hypertrophy worsened, with no improvement in LV dimensions. In contrast, in patients with preserved kidney function, there was a significant reduction in both LV diameter and arterial pulmonary systolic pressure.

**Conclusions:** The results show that in kidney transplant recipients, allograft function significantly affects cardiac structure and function. Periodic echocardiographic follow-up is advisable, especially in patients with kidney graft dysfunction.

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**KEY WORDS:** allograft function, cardiac structural and functional changes, kidney graft dysfunction, kidney transplantation

Cardiac structural and functional changes are common in patients with chronic kidney disease, including left ventricular (LV) hypertrophy (LVH), LV dilatation, and diastolic and systolic dysfunction [1,2]. The changes reflect the complex interaction between heart and kidney function, along with the adverse impact of such common risk factors as hypertension and diabetes on both organs [3]. The reversibility of these risk factors following kidney transplantation, at least in part, is indicated by reports of an early improvement in functional capacity and LV systolic function, and regression of hypertrophy in renal transplant recipients [4-6]. Most studies, however, have assessed only selected patients with significant pre-transplantation LV dysfunction or hypertrophy [4,5,7].

Data on the natural history of these cardiac alterations in kidney transplant recipients with preserved pre-transplantation cardiac structure and function remain inconclusive. Yet this population, which comprises the vast majority of patients with end-stage renal disease who have undergone kidney transplantation, may acquire clinically significant cardiac disease over time [8] but none have addressed the development of congestive heart failure (CHF). In addition, the magnitude and characteristics of the cardiac structure and function alterations in relation to allograft dysfunction, which affects up to 70% of kidney transplant recipients, have not been fully explained [9,10] transplanted during the years 1990, 1994, 1998, and 2002 in 34 centers in Spain with allograft survival of at least 1 year, were included in the study. GFR was estimated using the four-variable equation of the Modification of Diet in Renal Diseases (MDRD). Thus, the aims of the present study were twofold: to investigate intermediate-term post-transplantation cardiac structural and functional changes, and to evaluate the relationship of these changes with regard to graft function in a cohort of kidney transplant recipients without significant cardiac dysfunction.

## PATIENTS AND METHODS

A retrospective cohort study design was implemented. Data were collected on all consecutive patients who underwent kidney transplantation from January 2000 to December 2012 at Rabin Medical Center, a tertiary university-affiliated hospital, for whom detailed and specified pre- and post-transplantation echocardiographic data were available.

### DATA EXTRACTION

Data for the study were extracted electronically from two separate databases at the Rabin Medical Center:

- Registry from the department of transplantation. All baseline and operative characteristics of both transplant recipients and donors are prospectively recorded. Data include post-transplantation outcomes, including re-hospitalization-related parameters, return to dialysis, and re-transplantation
- Echocardiography database, which includes examination dates and detailed echocardiographic measurements

Of note, patients with echocardiographic measurements within 14 days after transplantation were excluded to minimize bias against more severe patients who needed an immediate estimation of their cardiac function.

The following data were collected:

- Age and gender
- ICD-9 diagnostic codes of chronic diseases including diabetes, hypertension, and ischemic heart disease
- Duration of dialysis prior to transplantation
- Serial serum creatinine levels on post-transplantation days 1, 7, 30, 90, 180, and 360, and annually thereafter
- Post-transplantation immunosuppressive and blood pressure-lowering medications
- Diagnosis of newly developed hypertension
- Blood pressure values

Survival status was obtained from the Rabin Medical Center registry, which is updated monthly from the registry of the Israel Ministry of the Interior.

The study was approved by the institutional ethics committee of Rabin Medical Center; protocol number 0320-14-RMC; approval number 255105.

### DEFINITION OF COVARIATES

Patient age was defined as age, in years, at transplantation. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Post-transplantation eGFR was calculated using the serum creatinine level at the time of echocardiography. Patients were stratified into two groups according to eGFR: eGFR ≤ 45 ml/min/1.73 m$^2$ and eGFR > 45 ml/min/1.73 m$^2$. This cutoff level has been found to be a predictor of adverse cardiovascular outcome in kidney transplant recipients [11].

LV systolic function was assessed as a continuous variable using fractional shortening (FS). Diastolic dysfunction was classified as none (grade 0), relaxation abnormality (grade 1), pseudo-normal filling (grade 2), restrictive LV filling with reversibility at peak Valsalva maneuver (grade 3), and restrictive pattern without reversibility (grade 4). The severity of valvular disease was categorized as no disease (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3). The estimated pulmonary arterial systolic pressure (EPASP) was derived from the peak tricuspid regurgitant velocity on Doppler echocardiography, presuming a right arterial pressure of 5 mmHg unless specific values were indicated. LVH was defined as posterior wall and/or interventricular wall thickness of 11 > mm.

### STATISTICAL ANALYSIS

Statistical analysis was performed with SAS software, version 9.4 for Windows (SAS Inc. Cary, NC, USA). Continuous variables and differences are expressed as mean ± standard deviation, categorical variables as percentages, and both types as median [interquartile range (IQR)] when indicated. Comparisons between the two groups were performed by Student's *t*-test for continuous variables and Fisher's exact test for categorical values. Paired *t*-test was used to compare post- to pre-transplantation measures within groups. Pearson correlation was used to assess linear associations between continuous measures. Overall survival was analyzed using the Kaplan–Meier method with log-rank test. All tests of significance were two-tailed. $P < 0.05$ was considered significant.

## RESULTS

### PATIENT CHARACTERISTICS

During the study period, 113 patients with end-stage renal disease who had specified echocardiographic details, underwent kidney transplantations, and met the study's inclusion criteria were recruited for the study. Of these, 37 had eGFR ≤45 ml/min/1.73 m$^2$ (group 1) and 76 with eGFR > 45 ml/min/1.73 m$^2$ (group 2). There was no between-group difference in clinical parameters before transplantation [Table 1]. Hypertension was

**Table 1.** Pre-transplantation patient characteristics

| Characteristics | All patients (n=113) | eGFR ≤ 45 ml/min/1.73 m$^2$ (n=37) | eGFR > 45 ml/min/1.73 m$^2$ (n=76) | *P* value |
|---|---|---|---|---|
| Age (years), mean ± SD | 52 ± 12 | 52 ± 13 | 53 ± 12 | 0.55 |
| Males, % | 79 | 78 | 80 | 0.81 |
| Hypertension, % | 86 | 81 | 89 | 0.34 |
| Diabetes mellitus, % | 40 | 40 | 39 | 1 |
| Ischemic heart disease, % | 37 | 40 | 36 | 0.82 |
| Living donor, % | 45 | 38 | 48 | 0.051 |
| Prior transplantation, % | 17 | 11 | 20 | 0.24 |
| **Primary kidney disease, %** | | | | |
| Diabetes mellitus | 28 | 32 | 24 | 0.39 |
| Hypertension | 6 | 3 | 8 | 0.36 |
| AD-PCKD | 11 | 12 | 11 | 0.86 |
| Glomerulonephritis | 26 | 24 | 27 | 0.69 |
| Others | 30 | 29 | 30 | 0.93 |
| Time on dialysis (months), mean ± SD | 45 ± 35 | 46 ± 32 | 45 ± 42 | 0.84 |

AD-PCKD = autosomal dominant polycystic kidney disease, eGFR = estimated glomerular filtration rate

the most prevalent co-morbidity, followed by diabetes mellitus and ischemic heart disease. Diabetic nephropathy was the most frequent primary kidney disease, followed by glomerulonephritis and autosomal dominant kidney disease. There was no significant difference between the groups regarding time on dialysis before transplantation, although patients with eGFR > 45 ml/min/1.73 m$^2$ (group 2) more frequently underwent living-donor transplantation. After transplantation, mean eGFR values were three times higher in group 1 than group 2 (25.7 ± 14.9 vs. 74.7 ± 19, $P < 0.0001$). Blood pressure values and rates of hypertension were similar in the two groups, but hypertensive drug treatment varied. There was no between-group difference in the administration of immunosuppressive agents added to steroids and mycophenolate. Among patients with eGFR > 45 ml/min/1.73 m$^2$ (group 2), creatinine levels remained stable throughout the follow-up period, whereas wide fluctuations were noted in patients with eGFR ≤ 45 ml/mi/1.73 m$^2$ (group 1) after the first 2 years.

**Table 2.** Post-transplantation echocardiography measurements

| Indices | All patients (n=113) | eGFR ≤ 45 ml/min/ 1.73 m$^2$ (n=37) | eGFR > 45 ml/min/ 1.73 m$^2$ (n=76) | *P* value |
|---|---|---|---|---|
| Time from transplantation to echocardiography (days), median (IQR1, IQR3) | 510 (174, 1135) | 466 (162, 831) | 535 (183, 1273) | 0.50 |
| LA diameter (mm), mean ± SD | 40.8 ± 7.2 | 43.2 ± 6.4 | 39.5 ± 7.4 | 0.02 |
| LA area (cm$^2$), mean ± SD | 22.1 ± 5.1 | 24.8 ± 5.9 | 21.0 ± 4.3 | 0.002 |
| IVS (mm), mean ± SD | 12.2 ± 2.1 | 12.5 ± 2.3 | 12.0 ± 1.9 | 0.24 |
| LVPW (mm), mean ± SD | 11.4 ± 2.2 | 11.8 ± 2.4 | 11.2 ± 2.1 | 0.18 |
| LVEDD (mm), mean ± SD | 47.8 ± 5.9 | 49.6 ± 6.3 | 46.9 ± 5.5 | 0.02 |
| LVESD (mm), mean ± SD | 30.4 ± 6.1 | 32.9 ± 7.8 | 29.2 ± 4.8 | 0.01 |
| FS% | 36.7 ± 7.4 | 34.5 ± 8.4 | 37.8 ± 6.8 | 0.03 |
| EPASP (mmHg), mean ± SD | 33.3 ± 8.7 | 37.1 ± 10.2 | 31.6 ± 7.3 | 0.01 |
| Diastolic dysfunction grade, median (IQR1, 3) | 1 (1, 1) | 1 (1, 1.5) | 1 (1, 1) | 0.11 |
| AR grade, median (IQR1, 3) | 0 (0, 2) | 0 (0, 2) | 0 (0, 2) | 0.53 |
| MR grade, median (IQR1, 3) | 1 (0,2) | 2 (1,2) | 1 (0,2) | 0.03 |

AR = aortic regurgitation, eGFR = estimated glomerular filtration rate, EPASP = estimated pulmonary arterial systolic hypertension, FS = fractional shortening, IVS = interventricular septum, IQR = 1st and 3rd interquartile range, LA = left atrium, LVEDD = left ventricular diastolic diameter, LVESD = left ventricular systolic diameter, LVPW = left ventricular posterior wall, MR = mitral regurgitation

**Table 3.** Temporal changes in echocardiographic indices

| | eGFR ≤ 45 ml/min/1.73 m$^2$ (n=37) | | | eGFR > 45 ml/min/1.73 m$^2$ (n=76) | | |
|---|---|---|---|---|---|---|
| Measurement | Pre-transplant | Post-transplant | *P* value | Pre-transplant | Post-transplant | *P* value |
| LA diameter, mm | 39.5 ± 6.2 | 43.2 ± 6.4 | 0.02 | 39.3 ± 8.5 | 39.5 ± 7.4 | 0.89 |
| LA area, cm$^2$ | 21.9 ± 4.8 | 24.8 ± 5.9 | 0.02 | 22.1 ± 4.9 | 21.0 ± 4.3 | 0.22 |
| IVS, mm | 11.0 ± 1.7 | 12.5 ± 2.3 | 0.001 | 11.7 ± 2.1 | 12.0 ± 1.9 | 0.32 |
| LVPW, mm | 10.5 ± 2.3 | 11.8 ± 2.4 | 0.08 | 11.1 ± 1.7 | 11.2 ± 2.1 | 0.61 |
| LVEDD, mm | 50.6 ± 6.1 | 49.6 ± 6.3 | 0.55 | 49.7 ± 6.8 | 46.9 ± 5.5 | 0.009 |
| LVESD, mm | 32.3 ± 7.0 | 32.9 ± 7.8 | 0.46 | 31.5 ± 7.4 | 29.2 ± 4.8 | 0.03 |
| FS% | 35.6 ± 7.4 | 34.5 ± 8.4 | 0.60 | 35.8 ± 10.0 | 37.8 ± 6.8 | 0.19 |
| EPASP, mmHg | 30.6 ± 6.8 | 37.1 ± 10.2 | 0.17 | 34.0 ± 9.7 | 31.6 ± 7.3 | 0.07 |

AR = aortic regurgitation, eGFR = estimated glomerular filtration rate, EPASP = estimated pulmonary arterial systolic hypertension, FS = fractional shortening, IVS = interventricular septum, LA = left atrium, LVEDD = left ventricular diastolic diameter, LVESD = left ventricular systolic diameter, LVPW = left ventricular posterior wall, MR = mitral regurgitation

### BASELINE ECHOCARDIOGRAPHIC MEASURES

Echocardiography was performed at a median of 230 days (IQR1 128, IQR3 428) before transplantation, with no difference between the groups. Patients had normal or preserved systolic function, no (or grade 1) diastolic dysfunction, no significant valvular disease, mild concentric hypertrophy, and mild left atrial dilatation. No significant differences were noted between any of these parameters in the groups.

### POST-TRANSPLANTATION CARDIAC CHANGES

The median time from transplantation to echocardiography was 510 days (IQR1 174, IQR3 1135), with no significant difference between the groups [Table 2]. Patients in group 1 were characterized by significantly larger LV dimensions, larger left atrium (LA) area, lower FS%, and higher EPSAP than patients in group 2. Mild concentric LVH was noted in both groups, with similar wall thickness. There was a clear distinction in the trends and magnitude of the changes in echocardiographic measures before and after transplantation between the groups [Table 3]. Patients with eGFR ≤ 45 ml/min (group 1) showed a worsening of LVH and diastolic function, increase in the severity of mitral and aortic regurgitation, enlargement of the LA area, and no change in LV dimensions and function. By contrast, patients with eGFR > 45 ml/min (group 2) showed a significant reduction in LV dimensions, a trend toward reduction of EPASP, and no change in LVH or severity of valvular disease.

### RELATIONSHIP OF ALLOGRAFT FUNCTION TO ECHOCARDIOGRAPHIC MEASURES

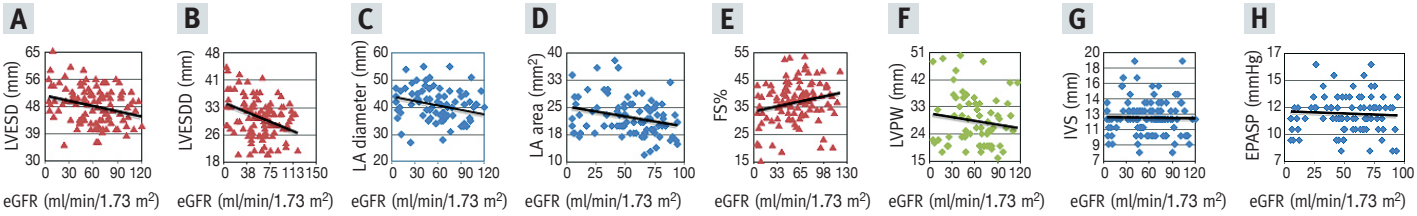
Post-transplantation renal function was significantly correlated with both cardiac structural and functional echocardiographic measures [Figure 1]. A significant direct correlation was found between eGFR and FS%, and a significant inverse correlation was found between eGFR and both LV and LA dimensions. There was no correlation between post-transplantation eGFR and EPASP and LV wall thickness.

## DISCUSSION

We examined the relationship of post-transplantation allograft function to alterations in echocardiographic cardiac measures.

**Figure 1.** Echocardiography measurements after transplantation as a function of eGFR

We found a significant reciprocal correlation between renal function and echocardiographic measures: **[A]** left ventricular diastolic diameter, **[B]** left ventricular systolic dimensions, **[C]** left atrial diameter, and **[D]** left atrial area. There was a significant reciprocal correlation between renal and LV function **[E]**. There was no correlation between renal function and EPASP **[F]**, IVS **[G]**, and LVPW **[H]**




eGFR = estimated glomerular filtration rate, EPASP = estimated pulmonary arterial systolic hypertension, FS = fractional shortening, IVS = interventricular septum, LA = left atrium, LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end systolic diameter, LVPW = left ventricular posterior wall

We noted two main findings:

- Post-transplantation cardiac alterations are significantly correlated with allograft function
- Post-transplantation eGFR ≤45 ml/min/1.73 m$^2$ is associated with a worsening of LVH, diastolic dysfunction, and valvular lesion severity, whereas eGFR >45 ml/min/1.73 m$^2$ is associated with improvements in LV and LA dimensions, LV function, and ESPAP

Several studies have examined the impact of kidney transplantation on structural cardiac measures [4,6,7,12]. A restorative effect of kidney transplantation on LV function was observed in patients with significant pre-transplantation LV systolic dysfunction, with an improvement in ejection fraction from a baseline of 30–40% to an average of approximately 50% [13,14]. In addition, a small study of 13 patients with preserved LV function and dimensions before transplantation reported an improvement in these measures at 4 months after renal transplantation [5].

Our results extend these observations to characteristic real-world kidney transplant recipients with preserved LV function and structure. They suggest, for the first time (to the best of our knowledge), that further improvement in systolic LV function can be anticipated after kidney transplantation in patients in whom eGFR is not reduced. It is noteworthy that the improvement in LV systolic function was parallel to a reduction in LV dimensions, suggesting a potential physiological alteration in both volume overload and non-hemodynamic factors [15,16]. Among patients with reduced eGFR, we noted no improvement in LV dimensions, a worsening of LV hypertrophy and diastolic function, and an increase in LA dimensions. These alterations, in concert, suggest possible deleterious effects of increased afterload, continuous volume overload, and persistent overactivity of the renin-angiotensin-aldosterone and sympathetic nervous systems, all strongly related to the degree of chronic kidney disease [17,18]. Thus, kidney transplant recipients with eGFR > 45 ml/min/1.73 m$^2$ may experience improvement in cardiac structure and function, whereas a significant proportion of patients with reduced eGFR may not have similar positive changes and, indeed, will probably have adverse cardiac alterations.

The observed correlation between post-transplantation eGFR and alterations in echocardiographic measures may have important clinical implications. First, patients with GFR ≤ 45 ml/min/1.73 m$^2$ may experience subclinical changes including a worsening in LVH and diastolic function and an increase in LA dimensions. The importance of identifying structural cardiac changes in patients at risk but without overt symptoms (i.e., stage B heart failure) is underscored in the heart failure guidelines of the European Society of Cardiology and the American Heart Association [19,20]. Both organizations advise initiating cardiac-specific medical treatment, including inhibitors/blockers of the renin-angiotensin-aldosterone system and beta-blockers, as disease-modified interventions. Kidney transplant recipients should undergo regular scheduled echocardiographic follow-up regardless of the pre-transplantation cardiac measures. Furthermore, patients with normal pre-transplantation cardiac measures may experience mild subclinical alterations, with values within the normal range. To evaluate these subtle changes, which may well progress over time, a comparative analysis with pre-transplantation echocardiography measures is imperative.

In the present study, we observed no significant overall change in LV wall thickness, although patients with eGFR ≤ 45 ml/min/1.73 m$^2$ experienced a worsening of hypertrophy. Several other studies have evaluated the regression of hypertrophy in kidney transplant recipients, with inconsistent results [21-23]. The disparities among the studies may reflect differences in myocardial composition, such as cardiac fibrosis, which can interfere with reverse remodeling. Using echocardiography and magnetic resonance T1 mapping, a group of researchers recently found that cardiac fibrosis affects patients on hemodialysis [24]. In addition, the process of LVH regression is probably slow and time-dependent, as shown in a longitudinal study of 767 patients in whom regression was found to increase from only 7.5% at 1 year to 35% at 5 years [25].

This study has several limitations. First, in order to conduct a fully detailed comparison of echocardiographic indices, we used only patients with all pre- and post-measurements. Second, although we found significant correlations of eGFR with cardiac measures, they were only modest to moderate, indicating a potential impact of other factors. At the same time, the significance of our findings is supported by the correlation of eGFR with several different cardiac measures rather than just a single one. Previous studies reported a correlation with other parameters such as post-transplantation hemoglobin levels and pre-transplantation echocardiographic measures. Therefore, a large dedicated study is needed to better assess the associations among multiple factors and post-transplantation cardiac alterations. Finally, there were no scheduled echocardiography studies. Hence, we cannot rule out the possibility that at least some of the studies were performed on clinical grounds. This finding, however, is a common denominator of other published studies assessing echocardiographic measures in kidney transplant recipients [14,22,24].

## CONCLUSIONS

Alterations in cardiac structure and function are common in kidney transplant recipients with preserved pre-transplantation cardiac measures. Kidney allograft function significantly affects these adaptations. Scheduled, comparative echocardiographic follow-up is advised, especially for patients with significant allograft dysfunction.

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**"The true secret to genius is in creativity, not in technical mechanics"**

Al Seckel (born 1958), American authority on illusions, author of books on visual and other types of sensory illusions, and how they related to perception