

# The effect of renal transplantation on left ventricular function, electrocardiography, and mechanical synchrony by gated myocardial perfusion imaging

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**Background.** Depressed left ventricular ejection fraction (LVEF), LV mechanical dyssynchrony (LVMD), and prolonged QTc interval predict poor outcomes in end-stage renal disease (ESRD). Renal transplantation improves mortality in ESRD patients but the effects of transplantation on these indices remain undefined.

**Methods.** We identified patients with myocardial perfusion imaging (MPI) before and after renal transplantation. A control group consisted of ESRD patients who underwent 2 MPIs but did not receive a transplant. Changes in LVEF, LVMD indices [phase standard deviation (SD) and bandwidth (BW)] by MPI, and electrocardiogram (ECG) indices were determined.

**Results.** The study population consisted of 32 ESRD patients (53% male,  $50 \pm 11$  years, 59% African American, 65% diabetic). The second MPI was performed 31 months (13–59 months) after renal transplantation. LVEF ( $72 \pm 10\%$  vs.  $67 \pm 10\%$ ,  $P < 0.001$ ) but not SD ( $22 \pm 15^\circ$  vs.  $22 \pm 11^\circ$ ,  $P = 0.9$ ) or BW ( $58 \pm 35^\circ$  vs.  $57 \pm 29^\circ$ ,  $P = 0.9$ ) improved after transplantation. There were no changes in these indices in the control group. QTc ( $425 \pm 30$  ms vs.  $447 \pm 32$  ms,  $P = <0.001$ ) but not QRS ( $90 \pm 21$  ms vs.  $90 \pm 21$  ms,  $P = 0.9$ ) improved significantly after renal transplantation.

**Conclusions.** LVEF and QTc improved after renal transplantation but LVMD indices and QRS did not change, which suggests that LVMD and electrical dyssynchrony may be irreversible in ESRD. (J Nucl Cardiol 2019;26:1962–70.)

**Key Words:** Physiology of myocardial/coronary perfusion • Physiology of LV/RV function • Myocardial biology

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### Abbreviations

BW	Bandwidth
ECG	12-lead electrocardiography
EF	Ejection fraction
ESRD	End-stage renal disease
LV	Left ventricle or left ventricular
MD	Mechanical dyssynchrony
MPI	Myocardial perfusion imaging
SD	Standard deviation

**See related editorial, pp. 1971–1973**

## INTRODUCTION

Chronic kidney disease is strongly associated with cardiovascular morbidity and mortality.<sup>1</sup> The association is particularly pronounced in patients with end-stage renal disease (ESRD) where sudden cardiac death attributes to 25% of all-cause mortality.<sup>2</sup> This has led to increasing interest in identifying prognostic indicators in this high-risk patient population. Our group has shown that a depressed left ventricular ejection fraction (LVEF), an abnormal perfusion pattern on gated-SPECT myocardial perfusion imaging (MPI), and QT prolongation on 12-lead electrocardiography (ECG) are independent predictors of mortality in the ESRD population.<sup>3,4</sup> We recently reported that LV mechanical dyssynchrony (LVMD) by phase analysis of MPI is associated with increased all-cause mortality in ESRD and provides incremental prognostic value beyond myocardial perfusion and LVEF.<sup>5,6</sup>

Renal transplantation is preferred over long-term dialysis for the treatment of patients with ESRD since it is associated with prolonged survival and better quality of life.<sup>7</sup> Multiple groups have demonstrated that renal transplantation can lead to improvement in LVEF.<sup>8–14</sup> However, the effect of renal transplantation on other prognostic indicators such as LVMD or ECG parameters has not been studied. In the current study, we tested the hypothesis that renal transplantation is associated with improvement in LVEF, LVMD, QRS, and QT intervals.

## METHODS

### Study Population

The study population was derived from the renal transplantation database maintained at the University of Alabama at Birmingham (UAB). The database has been described in full previously.<sup>3</sup> Briefly, all patients who are evaluated for possible renal transplantation at our institution are entered in the database at the time of evaluation and baseline clinical characteristics are collected at initial evaluation and outcomes prospectively monitored and entered in real-time into the database. For this study, we selected consecutive renal

transplant recipients who had MPI as part of the renal transplant evaluation between June 2003 and August 2006 and then underwent a 2nd MPI after renal transplantation for clinical indications as part of their care at our medical facility (Renal Transplant Group). We excluded patients with abnormal perfusion on either set of images ( $n = 15$ ) since myocardial ischemia has been shown in some studies to alter LVMD indices and would be a confounding variable in analysis.<sup>15–17</sup> Patients with a left bundle branch block, ventricular pacing or atrial fibrillation at time of MPI, and those with images that made phase analysis not technically feasible were excluded. Patients with renal failure requiring dialysis at time of second MPI were also excluded. In order to evaluate whether the changes are related to renal transplantation we matched the patients 1:1 for age (within 3 years) and gender to a Control Group which consisted of consecutive patients evaluated for renal transplantation during the same time interval and had two MPIs, at least 3 years apart, with normal perfusion on both sets of images but not separated by renal transplantation. Resting ECGs performed on the day of MPI were collected and parameters of interest (PR, QRS, QT, and QTc) were entered in the database. All-cause mortality was verified against the U.S. Social Security Death Master File on November 9th, 2013.

### Myocardial Perfusion Imaging

All gated-SPECT stress images were retrieved and reprocessed with Emory Cardiac Toolbox (Emory University/Syntermed, Inc, Atlanta GA) as previously described using 8 interval frames.<sup>18</sup> Briefly the short-axis dataset provided a full count distribution of myocardial density and was processed through Fourier analysis to develop a phase distribution which correlates with myocardial activation over the R-R interval. Phase analysis software generated quantitative variables from this phase distribution including its standard deviation (SD) and bandwidth (BW), which is the degrees which encompass 95% of the distribution curve. LV volumes and EF were measured based on the method described by Germano et al.<sup>19</sup>

### Statistical Analysis

Continuous data were expressed as mean  $\pm$  standard deviation of the mean and compared using the paired or unpaired student *t*-test as appropriate. Categorical data were displayed as frequencies and percentages, and comparisons were made using Chi-square test. All statistical tests were two sided and a *P*-value  $< 0.05$  was determined to be significant. All statistical analyses were performed using the Statistical Package for Social Sciences, version 17, for Windows (SPSS, Chicago, Illinois).

## RESULTS

The baseline characteristics of the Renal Transplant Group and the Control Group are shown in Table 1. There were no significant differences between the groups at time of evaluation in age, gender, prevalence

**Table 1.** Baseline characteristics

Baseline characteristics	Renal transplant group (n = 32)	Control group (n = 32)	P-Value
Age (years)	50 ± 11	52 ± 11	0.60
Male gender	17 (53%)	20 (62%)	0.45
African American	19 (59%)	28 (88%)	0.01
Diabetes	21 (65%)	17 (53%)	0.30
Hypertension	30 (93%)	23 (72%)	0.02
Tobacco use	5 (16%)	5 (16%)	> 0.90
Coronary artery disease	6 (19%)	5 (16%)	0.74
Prior myocardial infarction	3 (9%)	0 (0%)	0.08
Paroxysmal atrial fibrillation or flutter	4 (13%)	0 (0%)	0.04
Peripheral vascular disease	0 (0%)	2 (6%)	0.16
Prior cerebrovascular event	1 (3%)	0 (0%)	0.57
Dialysis dependence	24 (75%)	28 (80%)	0.16
Deceased donor transplantation	17 (53%)	N/A	
Presumed cause of renal disease			
Hypertension	14 (44%)	23 (72%)	0.03
Diabetes	19 (59%)	19 (59%)	> 0.90
Glomerulonephritis	3 (9%)	0 (0%)	0.16
Interstitial nephritis	1 (3%)	0 (0%)	0.32
Amyloidosis	1 (3%)	0 (0%)	0.32
Sarcoidosis	1 (3%)	0 (0%)	0.32

of diabetes mellitus, coronary artery disease, or tobacco use. Patients in the Renal Transplant Group were more likely to be of Caucasian race and to have hypertension than those in the Control Group. The etiology of renal disease had a similar distribution in the two groups except for a higher prevalence of hypertensive renal disease in the control group. Most patients in both groups were dialysis-dependent at time of evaluation for a median of 10 months (interquartile range 5-34 months,  $n = 19$ ). Medication use at both time points was overall similar between groups (Table 2) with the exception that more patients in the Renal Transplant Group were on insulin treatment compared to Control Group (40% vs. 16%,  $P = 0.03$ ). MPI and ECG indices for both groups at baseline are shown in Tables 3 and 4 respectively. There were no differences in these indices between groups.

Patients in the Renal Transplant Group underwent transplantation at a median of 7 months (interquartile range 5-27 months) after the first MPI. The second MPI was performed at a median of 31 months (13-59 months) after renal transplantation for a total separation between MPIs of 58 months (interquartile range

35-77 months) in the Renal Transplant Group and 61 months (interquartile range 45-66 months) in the Control Group ( $P = 0.5$ ). During this period, one patient in each group developed diabetes (3% vs. 3%,  $P > 0.99$ ) while 1 patient in the Renal Transplant Group developed hypertension (3% vs. 0%,  $P = 0.33$ ). Three myocardial infarctions occurred in the interim in the Renal Transplant Group compared to one in the Control Group (3 vs. 1,  $P = 0.33$ ). One patient from each group had a percutaneous coronary intervention and coronary artery bypass graft ( $P > 0.99$  for both). During a follow-up of 29 months (interquartile range 17-32 months), after the second MPI, 9% of the patients in the Renal Transplant Group died compared to 44% in the Control Group ( $P = 0.006$ ).

In the Renal Transplant Group, LVEF ( $72 \pm 10\%$  vs.  $67 \pm 10\%$ ,  $P < 0.001$ ) improved after transplantation but there was no significant change in LV end-diastolic volume ( $144 \pm 51$  mL vs.  $139 \pm 66$  mL,  $P = 0.6$ ) or LV end-systolic volume ( $45 \pm 29$  mL vs.  $51 \pm 33$  mL,  $P = 0.2$ ) (Figure 1). There was no improvement in the phase analysis indices, SD ( $23 \pm 15$  vs.  $22 \pm 11^\circ$ ,  $P = 0.9$ ) or BW ( $58 \pm 35^\circ$  vs.

**Table 2.** Medications between renal transplant group and control

Medications	Renal transplant Group		Control group	
	MPI 1 (pre-transplant) (%)	MPI 2 (post-transplant) (%)	MPI 1 (%)	MPI 2 (%)
Oral hypoglycemics	9 (28)	7 (22)	7 (22)	7 (22)
Insulin	13 (40)*	20 (62) <sup>a</sup>	3 (16)	6 (19)
BB	26 (81)	26 (81)	19 (59)	22 (68)
ACE-i/ARB	17 (53)	17 (53)	18 (56)	17 (53)
CCB	15 (47)	17 (53)	14 (44)	14 (44)
Clonidine	10 (31)	11 (34)	12 (38)	12 (38)
Aldosterone Antagonist	1 (3)	1 (3)	0 (0)	0 (0)
Thiazide diuretics	1 (3)	3 (9)	2 (6)	2 (6)
Nitrates	3 (9)	3 (9)	5 (15)	5 (15)
Hydralazine	3 (9)	3 (9)	5 (15)	5 (15)
Clopidogrel	0 (0)	1 (3)	1 (3)	1 (3)
Aspirin	6 (19)	19 (59)	12 (38)	12 (38)
Statin	13 (40)	23 (71) <sup>b</sup>	13 (41)	13 (41)
Warfarin	3 (9)	5 (16)	2 (6)	2 (6)
Cyclosporine		2 (6)		
Mycophenolate		31 (96)		
Mofetil				
Azathioprine		1 (3)		
Tacrolimus		27 (84)		

ACE-i/ARB angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BB beta-blocker, CCB calcium channel blocker

<sup>a</sup>*P* < 0.05 compared with control group

<sup>b</sup>*P* < 0.05 compared with pre-transplant group

**Table 3.** Baseline SPECT characteristics between renal transplant group and control

	Renal transplant group (n = 32)	Control group (n = 32)	P-Value
LVEF	67 ± 10%	64 ± 9%	0.34
LVEDV	139 ± 66 mL	145 ± 51 mL	0.71
LVESV	51 ± 33 mL	56 ± 30 mL	0.55
SD	22 ± 11°	21 ± 13°	0.92
BW	57 ± 29°	55 ± 25°	0.74

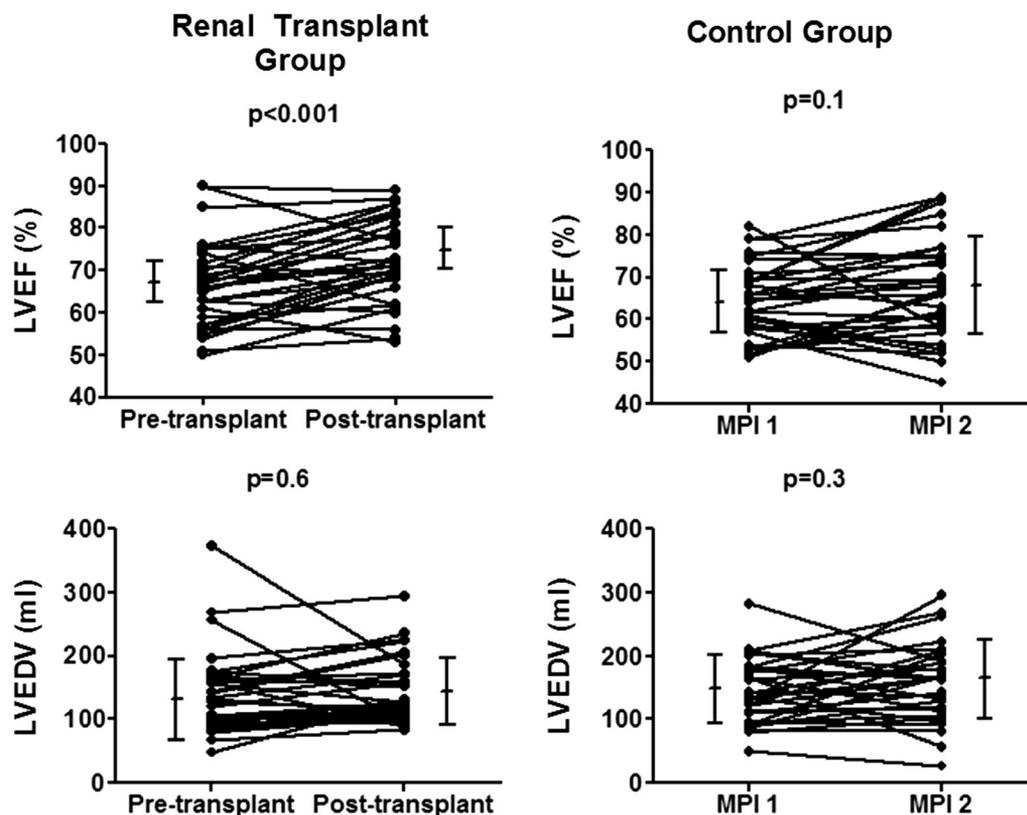
LVEF left ventricular ejection fraction, LVEDV left ventricular end diastolic volume, LVESV left ventricular end systolic volume, SD standard deviation, BW band width

57 ± 29°, *P* = 0.9) (Figure 2). QT (381 ± 44 ms vs. 414 ± 38 ms, *P* < 0.001) and QTc (425 ± 30 ms vs. 447 ± 32 ms, *P* < 0.001) interval improved after renal transplantation but not PR (155 ± 31 ms vs. 160 ± 18 ms, *P* = 0.2) or QRS (90 ± 21 ms vs. 90 ± 22 ms, *P* = 0.8) interval (Figure 3, Table 4). There was no difference in heart rate at time of MPI before and after renal transplantation (92 ± 17 bpm vs.

96 ± 21 bpm, *P* = 0.3). In the Control Group, there were no significant changes in LVEF (67 ± 12% vs. 64 ± 9%, *P* = 0.1), LV end-diastolic volume (157 ± 60 mL vs. 145 ± 51 mL, *P* = 0.3), or LV end-systolic volume (57 ± 35 mL vs. 56 ± 30 mL, *P* = 0.8). There was no improvement in SD (21 ± 11° vs. 21 ± 13°, *P* = 0.7) or BW (60 ± 30°, 55 ± 25°, *P* = 0.4). There was no difference in heart rate between

**Table 4.** Electrocardiography between renal transplant group and control

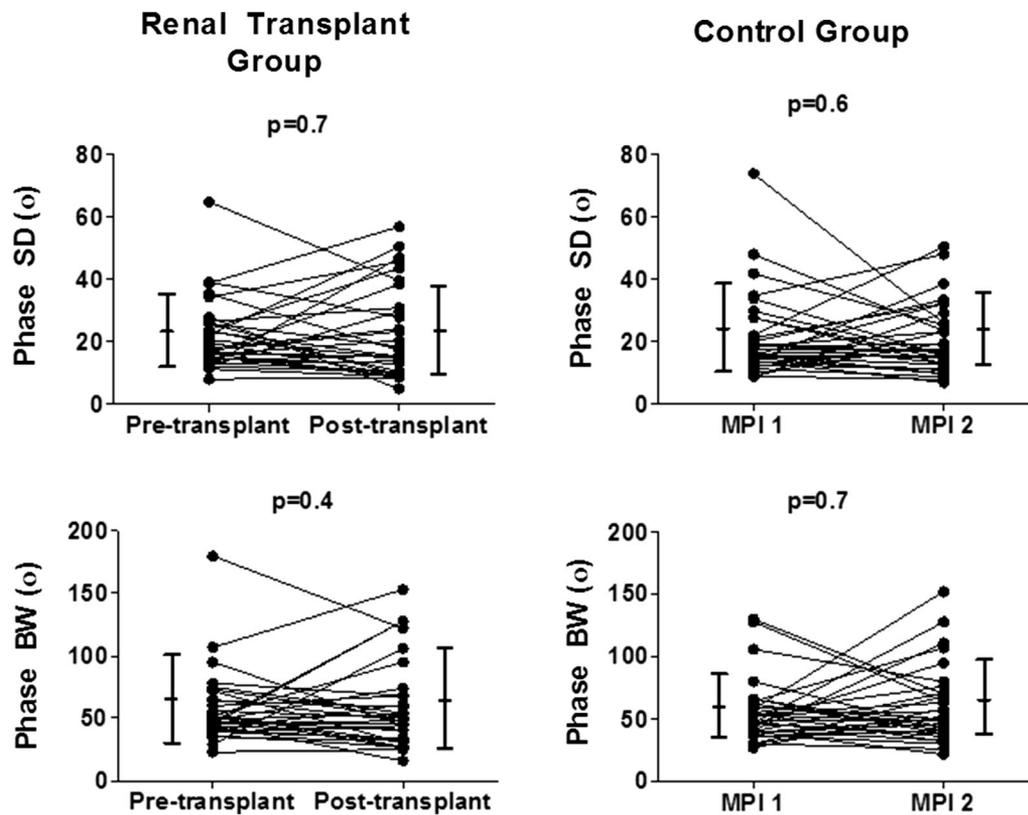
	Renal transplant group			Control group		
	ECG 1 (N = 32)	ECG 2 (N = 32)	P-value	ECG 1 (N = 32)	ECG 2 (N = 23)	P-value
PR interval	160 ± 18 ms	155 ± 31 ms	0.2	171 ± 28 ms	169 ± 29 ms	0.8
QRS interval	90 ± 22 ms	90 ± 21 ms	0.8	90 ± 11 ms	90 ± 29 ms	0.9
QT interval	414 ± 38 ms	381 ± 44 ms	< 0.001	393 ± 27 ms	398 ± 32 ms	0.6
QTc interval	447 ± 32 ms	425 ± 30 ms	< 0.001	435 ± 29 ms	451 ± 32 ms	0.052

**Figure 1.** Effect of Renal Transplantation on LVEF and LVEDV. Pre- and post-renal transplantation values for left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume (LVEDV) are shown on the left. Corresponding values for the control group that did not undergo renal transplantation are shown on the right. *MPI* myocardial perfusion imaging.

the two MPIs ( $90 \pm 14$  bpm vs.  $97 \pm 22$  bpm,  $P = 0.1$ ). There was no improvement in PR ( $169 \pm 29$  ms vs.  $171 \pm 28$  ms,  $P = 0.8$ ), QRS ( $90 \pm 29$  ms vs.  $90 \pm 11$  ms,  $P = 0.9$ ), QT ( $398 \pm 32$  ms vs.  $393 \pm 27$  ms,  $P = 0.6$ ), or QTc ( $451 \pm 32$  ms vs.  $435 \pm 29$  ms,  $P = 0.052$ ) interval in Control Group (Figure 3, Table 4).

## DISCUSSION

The main finding of our study is that renal transplantation improves LV systolic function (LVEF) and electrical repolarization (QT interval) but does not significantly alter electrical (QRS) or mechanical synchrony (phase SD and BW). To our knowledge, this is

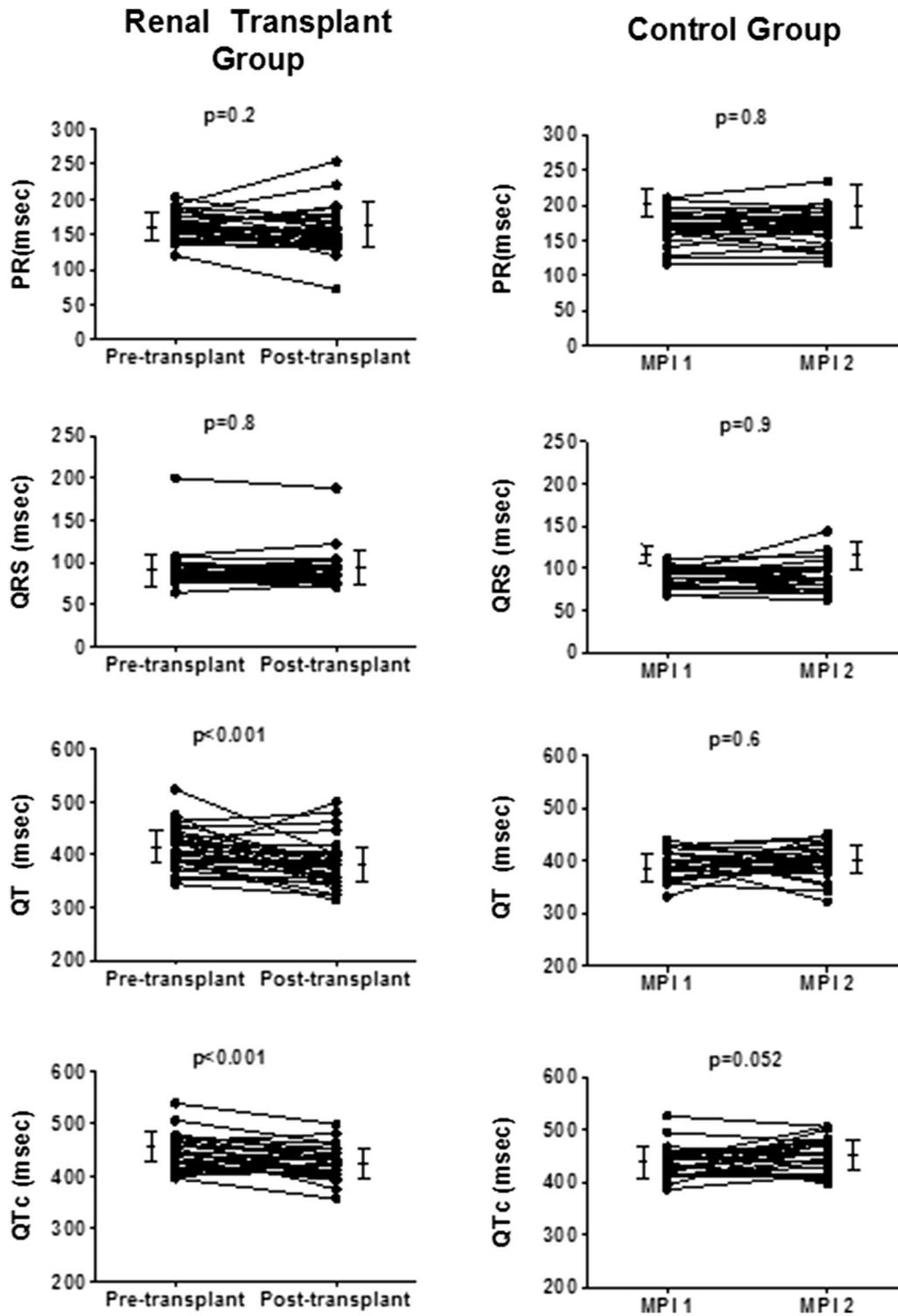


**Figure 2.** Effect of Renal Transplantation on Phase Analysis Indices. Pre- and post-renal transplantation values for phase standard deviation (SD) and band width (BW) are shown on the left. Corresponding values for the control group that did not undergo renal transplantation are shown on the right. *MPI* myocardial perfusion imaging.

the first study that evaluates the changes in these parameters in relation to renal transplantation.

Renal transplantation improves mortality for ESRD patients compared to intermittent hemodialysis, but its effects on cardiovascular function are not well established.<sup>7</sup> Prior studies have documented improvements in LVEF as well as other echocardiographic parameters including fractional systolic shortening, E/A ratio, and LV torsion after renal transplantation.<sup>8–14</sup> Our study reinforces this literature noting a significant improvement in LVEF as measured by gated-SPECT MPI after renal transplantation. Notably, LVEF did not improve in a control group of ESRD patients on the transplant waiting list that did not undergo transplantation. It has been postulated that the increase in LV systolic function may be related to improved volume management with physiologic diuresis after transplantation.<sup>12</sup> The improvement in LVEF in our patients in the absence of any significant change in LV volume is more consistent with the hypothesis that transplantation leads to clearance of toxins, which have been associated with the development of uremic cardiomyopathy.<sup>20</sup>

Mechanical synchrony plays an important role in cardiac hemodynamics. Left ventricular contractility is characterized in terms of pressure-volume relationships with the assumption that all myocytes contract simultaneously; an assumption that has been shown to be invalid in multiple pathologic states.<sup>21</sup> Phase analysis evaluates myocardial activation throughout the R-R cycle and displays this as a phase distribution curve. Two variables (phase SD and BW) can be used to characterize this curve and are considered markers of mechanical synchrony.<sup>22</sup> We have previously shown that patients with ESRD have LVMD (increased SD, BW) compared to controls without renal disease.<sup>5</sup> The phases SD and BW in the current cohort have elevated phases SD and BW consistent with the presence of LVMD (Figure 2). We have also shown that LVMD in ESRD patients is independently associated with worse outcomes independent of myocardial perfusion and LVEF.<sup>6</sup> We hypothesized here that renal transplantation would result in an improvement in LVMD indices. Figure 2 shows that some patients with elevated phase SD and BW pre-transplantation had lower values post-



**Figure 3.** Effect of Renal Transplantation on Electrocardiography. Pre- and post-renal transplantation values for electrocardiography indices (PR, QRS, QT and QTc) are shown on the left. Corresponding values for the control group that did not undergo renal transplantation are shown on the right. *MPI* myocardial perfusion imaging.

transplant while others with low indices pre-transplant had higher values post-transplant. Interestingly, the same can be seen in the control group that did not undergo transplantation. Overall, our results indicate that renal transplantation was not associated with an improvement in LVMD. Thus, in our patients the LVMD indices continued to be elevated to a similar extent after transplantation despite improvement in renal function. ESRD patients have been shown to have myocardial fibrosis by late gadolinium enhancement on cardiac magnetic resonance,<sup>23</sup> which may be the underlying cause of LVMD. The effects of renal transplantation on myocardial fibrosis have not, to our knowledge, been evaluated and may be irreversible.

QT prolongation is an independent predictor of mortality in the ESRD population and is considered a risk factor for sudden cardiac death.<sup>4</sup> Yildiz et al noted improvement in QT dispersion, which evaluates variance in QT interval, after renal transplantation in 24 hemodialysis-dependent patients and correlated this improvement with ionized calcium and regression in LV mass.<sup>24</sup> Monfared et al. have shown a reduction in QTc in 34 subjects at 2 weeks after renal transplantation.<sup>25</sup> Our results extend these reports by showing an improvement in QT and QTc that is preserved at a median of 31 months (interquartile range 12–59 months) after transplantation, and importantly, include a control group of ESRD patients that did not undergo transplantation.

There are several limitations to our report. This is a retrospective cohort study at a single tertiary referral center with a limited number of patients. This increases selection and referral bias and decreases the generalizability of our findings. The generalizability of our findings may also be limited since our cohort overrepresented transplant recipients from living donors (47%) compared to national levels (< 1/3).<sup>26</sup> In exploratory analysis, our findings were unchanged in the subset of patients who were recipients of kidneys from deceased donors. The study may be underpowered to detect a significant difference between the two groups in some variables and therefore larger prospective studies may be needed to confirm these findings. While a prior report indicated that indices of mechanical synchrony by phase analysis are highly repeatable, serial images in that report were separated by 30 minutes rather than by several years.<sup>27</sup> It is therefore possible that the variability in measurement of these indices precluded the detection of true change in mechanical synchrony. Also, the mean LVEF at baseline was normal although improvement was statistically significant. Changes in hemodynamics between the studies may have affected the results but this data was not available for analysis. This study does not control for left ventricular

hypertrophy, which is highly prevalent in this patient population and varying wall thickness could alter volumetric assessment. Lastly, we did not evaluate the outcome of these patients due to the small sample size of the cohort.

## NEW KNOWLEDGE GAINED

Renal transplantation improves LVEF and QT interval but has no effect on LVMD indices and QRS duration. This divergence in response to renal transplantation suggests that LV electrical and mechanical dyssynchrony, unlike LV systolic dysfunction and prolonged repolarization, may be irreversible in ESRD.

## Disclosure

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