The prognostic value of left ventricular mechanical dyssynchrony using gated myocardial perfusion imaging in patients with end-stage renal disease

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Background. **Prior studies show that left ventricular mechanical dyssynchrony (LVD), measured by gated SPECT myocardial perfusion imaging (MPI), identifies patients with end-stage renal disease (ESRD) at higher risk for all-cause mortality but these were in small number of patients. We sought to assess the interaction between LVD and LV perfusion pattern in risk-stratification of a large sample size of patients with ESRD.**

Methods. **From the renal transplantation database maintained at the University of Alabama at Birmingham, we identified consecutive patients with ESRD who had gated SPECT MPI between 2003 and 2007. MPIs were reprocessed to derive LV ejection fraction (EF), perfusion defect size, and LVD [phase bandwidth (BW) and phase standard deviation (SD)]. The primary end-point was all-cause mortality, which was prospectively collected and verified against the social security death index database.**

Results. **There were 828 patients aged 52.6 ± 0.36 years (45% were women and 60% had diabetes mellitus). The LVEF was 54.8 ± 0.4% and the perfusion pattern was abnormal in 334 patients (41%). During a follow-up period of 61 ± 0.9 months, 230 patients (28%) received renal transplants and 290 patients (35%) died. The phase BW (73.1 ± 2.6° vs 66.3 ± 1.8°, $P = .02$) and SD (25.2 ± 0.8° vs 23.4 ± 0.5°, $P = .06$) were greater in patients who died than those who survived indicating greater dyssynchrony. Patients with phase BW >56° or SD ≥21° (median values) had worse 5-year survival (64% vs 72%, and 66% vs 71%, log-rank $P = .005$ and $P = .07$, respectively). After adjusting for demographics, co-morbidities, LVEF, and perfusion pattern, phase BW was associated with worse outcome (hazard ratio 1.289 95% CI 1.010-1.644, $P = .04$).**

Conclusions. **LVD by phase analysis of gated SPECT MPI provides prognostic value in ESRD beyond myocardial perfusion and EF. (J Nucl Cardiol 2014;21:739–46.)**

Key Words: LV dyssynchrony • Phase analysis • End-stage renal disease • Myocardial perfusion imaging • Left ventricular ejection fraction

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INTRODUCTION

Cardiovascular complications are the leading cause of mortality in patients with chronic kidney disease.[1,2] The prognosis is worst in patients with end-stage renal disease (ESRD).[1,2] In this population, sudden cardiac death constitutes 62% of cardiovascular mortality and 25% of all-cause mortality.[3] The risk remains high even in patients with normal left ventricular (LV) ejection fraction (EF) and no evidence of ischemia or scar. LV mechanical dyssynchrony (LVD) by phase analysis of gated single photon emission tomography (SPECT) myocardial perfusion imaging (MPI) has been associated with increased risk of death and implantable cardioverter defibrillator (ICD) shock in patients with LV dysfunction.[4] Studies have shown that patients with ESRD are more likely to have LVD by phase analysis than a control group of patients with normal renal function.[5,6] The mechanism for LVD in these patients is not very clear but it has been attributed to the presence of myocardial interstitial fibrosis, volume overload, and pulmonary venous hypertension.[6] A recent study using echocardiography to assess LVD showed that some indices of LVD are preload dependent and can be improved with hemodialysis.[7] In a pilot study, we demonstrated that LVD can be used as a predictor of all-cause mortality in patients with ESRD.[8] Interestingly, in this population electrical dyssynchrony (prolonged QRS on 12-lead electrocardiogram) was not associated with poor outcome.[9] In the current study, we examined the association between LVD, and all-cause mortality in a larger sample size of patients with ESRD and sought to determine whether this association is dependent on perfusion pattern on MPI.

METHODS

Patient Selection

The study population was derived from the renal transplantation database at the University of Alabama at Birmingham. The database was previously described in details.[10] In brief, ESRD patients referred to our institution for possible renal transplantation are prospectively enrolled in the database. Informed consent is obtained at the time of enrollment to use individual data for clinical, quality-improvement, and research purposes. The study was approved by the institutional review board at the University of Alabama at Birmingham.

Between June 2003 and August 2007, 1687 ESRD patients were screened for renal transplant. Of these, 986 patients underwent stress-gated SPECT MPI. Exclusion criteria included left bundle branch block, ventricular pacing, inability to perform phase analysis (due to improper image archiving or gating), and renal transplantation prior to MPI (N = 158). Thus, the study population for this analysis consisted of 828 patients (Figure 1).

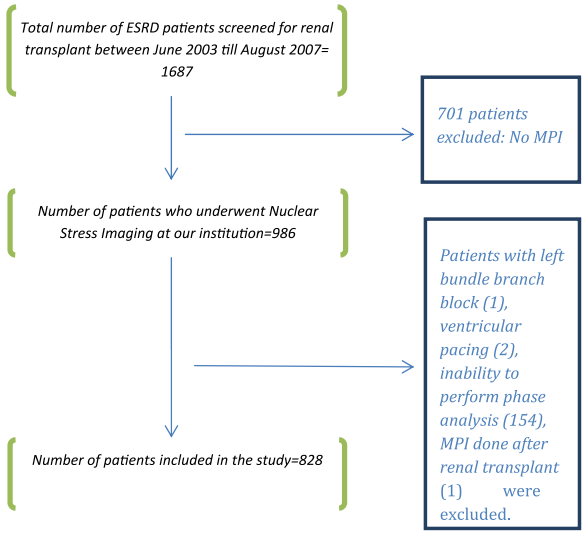

Figure 1. Flow chart depicting inclusion and exclusion criteria.

Patients' demographics, co-morbidities, electrocardiographic indices, and basic laboratory tests were collected at the time of evaluation and subsequently retrieved for analysis.

SPECT Imaging and Phase Analysis

Gated Tc-99m Sestamibi SPECT MPI was performed using stress/rest or stress only 1-day protocol according to the American Society of Nuclear Cardiology guidelines and as previously described.[11-13] Stress modalities included either exercise treadmill or vasodilator pharmacologic testing using adenosine infusion as previously described.[11,14] Image interpretation was done without attenuation or scatter correction. All images were processed by a single investigator who was blinded to the clinical characteristics of the patients and their outcome. The LVEF, end-diastolic volume (EDV), and end-systolic volume (ESV) were measured based on the method described by Germano et al[15] LV mass was calculated by multiplying LV wall volume (mL) by the specific gravity of myocardial tissue (1.053 g/mL). The presence of a perfusion defects (reversible, fixed, or a combination) was quantitated as % of LV myocardium using a validated program (Corridor 4DM, Ann Arbor, MI, USA). A cut-off value of 5% was considered abnormal. The perfusion defect size (PDS) was expressed as total PDS (scar and ischemia), fixed PDS (scar only), and reversible PDS (ischemia only). Although ''scar'' and fixed PDS are not interchangeable (the latter can have hibernating and thus viable myocardium), we will use this terminology interchangeably here for the sake of simplicity.

LVD was performed using phase analysis of gated SPECT MPI as previously described in detail.[6,8,16,17] In brief, a three dimensional count distribution was extracted from each of the LV short-axis datasets and submitted to a Fourier analysis,

generating a phase distribution (0°-360°) spanning the entire R-R interval and displayed on a polar map and a histogram (Figure 2). Two indices were extracted, phase bandwidth (BW), which marked the range of degrees of the cardiac cycle during which 95% of the myocardium-initiated contraction and phase standard deviation (SD), which represented the SD of the phase distribution. Since our laboratory uses a strategy of ''stress-only imaging'' in patients with normal perfusion,[14] we analyzed LVD on the stress scan. We have previously shown that the presence of perfusion defects, including reversible defects, does not impact LVD indices since the ''stress scans'' are actually acquired at rest.[18]

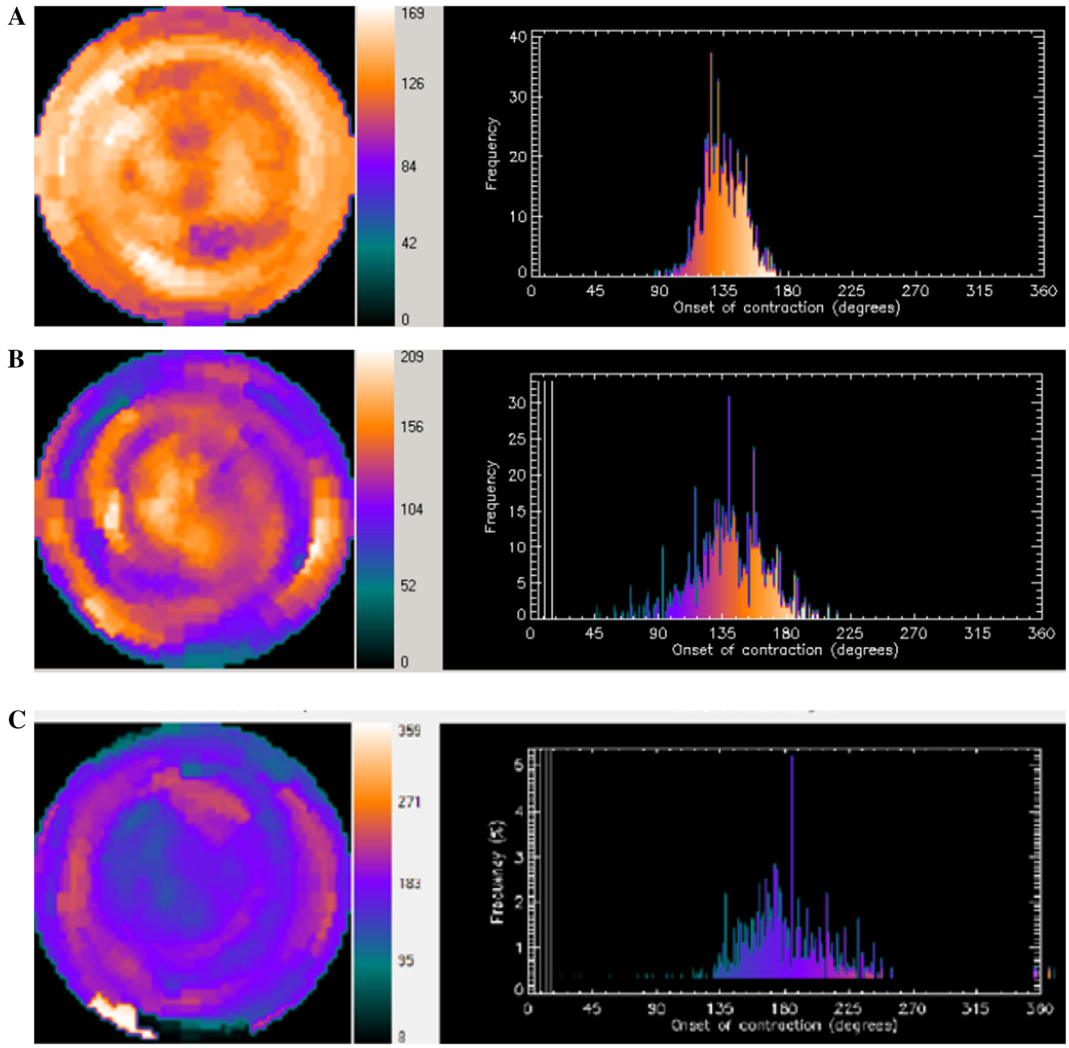

Figure 2. Representative phase *histograms*. The *x*-axis represents one cardiac cycle (R-R interval) in degrees (0-360); the *y*-axis represents the percentage of the myocardium contracting at a particular phase of the cardiac cycle. The *color maps* and the phase *histograms* have 256 levels, ranging from *black* (minimum) to *white* (maximum). (**A**) A phase histogram of a 66-year-old woman with end-stage renal disease secondary to diabetes mellitus and hypertension who was started on hemodialysis in March 2006. She underwent myocardial perfusion imaging in August, 2006 depicting a narrow BW (45°) and SD (14°) and went on to receive a deceased-donor kidney transplant on October 7, 2010. Patient was alive on January 10, 2012. (**B**) A phase *histogram* of a 71-year-old male with end-stage renal disease secondary to hypertension who was started peritoneal dialysis in February 2005 and underwent myocardial perfusion imaging in August 2006 showing LV ejection fraction of 37%, significant perfusion defect (38%), wide BW (85°) and SD (26°) indicating significant LVD. Patient died in 2008 before he received renal transplant. (**C**) A phase *histogram* of 61-year-old male with end-stage renal disease secondary to diabetes mellitus and hypertension, started on hemodialysis in January 2006. Patient underwent myocardial perfusion imaging in August 2006 showing normal LV ejection fraction (53%) and no perfusion defect. He had wide BW (92°) and SD (25°) indicating significant LVD. Patient died in 2010 before he received renal transplant.

Outcome Data

The primary end-point was all-cause mortality. Data on mortality were prospectively collected in the database and verified against the social security death index database. The data were censored on January 10, 2012.

Statistical Methods

Continuous data were expressed as mean ± standard error of the mean or median (Q1, Q3), and compared using the unpaired Student's *t* test or Wilcoxon rank test as appropriate. Categorical data were displayed as frequencies and percentages, and comparisons were made using Chi-square tests or Fisher exact tests as appropriate. For survival analysis, Event-free survival curves were constructed using the product-limit method (Kaplan-Meier) and differences among survival curves were estimated by the log-rank test. Survival analysis treated the time of MPI as ''time 0.'' For graphical illustration, the median value of BW and SD was used. Cox proportional hazard analysis was used to estimate the unadjusted and adjusted (multivariate) risks of LVD on overall mortality. The model was adjusted for baseline demographics (age and gender), co-morbidities (diabetes mellitus and hypertension), and MPI variables (abnormal perfusion and LVEF). LVD indices (BW and SD) were entered in the model one at a time (due to co-linearity) and analyzed as dichotomous (using the median value as cut-off). The proportionality assumption was met for the Cox model and time-dependent covariates were not used. A best-fit model was then built using backward elimination (Likelihood Ratio) starting from the variables included in the original multivariate model. Estimated risks were reported as hazard ratios (HR) with correspondent 95% confidence intervals (CI). A ratio of 10-20 events per degree of freedom of the model was maintained. All statistical tests were two sided. A P value <.05 was set a priori and considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences, version 17, for Windows (SPSS, Chicago, IL, USA).

RESULTS

The study population included 828 ESRD patients. The baseline characteristics of the population are summarized in Table 1 and the MPI results in Table 2. During a mean follow-up period of 61 ± 0.9 months, 230 (28%) patients underwent renal transplantation. There were 290 (35%) deaths reported in the whole group including patients who received transplant.

Perfusion Pattern and EF

The mean LVEF was significantly lower in the patients who died compared to those who survived (52.2 ± 0.7 vs 56.2 ± 0.5, P = <.001) (Table 2). There was no difference in the proportion of patients with abnormal perfusion pattern between the patients who died vs those who survived (43% vs 39%, P = .4). Similarly, the total, fixed, and reversible PDSs were not statistically significant between those who survived and those who died (Table 2).

Phase Analysis

There was no difference in QRS duration between patients that died vs those that survived (Table 1). We found a weak but statistically significant correlation between QRS duration and phase BW (R^2 0.009, P = .009) and no correlation between QRS duration and phase SD (R^2 0.01, P = .07). The phase BW (73.1 ± 2.6° vs 66.3 ± 1.8°, P = .02) and SD (25.2 ± 0.8° vs 23.4 ± 0.5°, P = .06) were larger in patients who died than those who survived (Table 2). Kaplan-Meier analysis revealed a stepwise increase in mortality with increasing BW in tertiles (Figure 3). Patients with phase BW above the median (>56°) had worse 5-year survival (64% vs 72%, log-rank P = .005) than those with lower BW (Figure 4). Similarly, patients with phase SD above the median (≥21°) had worse 5-year survival but this association was of borderline statistical significance (66% vs 71%, log-rank, P = .07).

After adjusting for demographics, co-morbidities, abnormal perfusion and LVEF, BW >56° was associated with worse outcome (adjusted HR 1.342 CI 1.063-1.695, P = .01, Table 3). Since renal transplantation may alter the association between LVD and mortality, we repeated the analysis censoring at the time of renal transplant. BW >56° continued to be associated with worse survival, albeit with borderline statistical significance (adjusted HR 1.274 CI 1.002-1.619, P = .048).

In order to explore the interaction between LVD and perfusion pattern with survival, we stratified the patients by perfusion pattern. A wide histogram BW (>56°) was associated with worse survival in patients with abnormal perfusion (log-rank P = .004) but not in those with normal perfusion (log-rank P = .2) (Figure 5). In the subset of patients with abnormal perfusion, phase BW >56° was significantly associated with higher mortality even after controlling for the size of the perfusion defect (HR 1.72 95% CI 1.18-2.52, P = .005). We also explored whether this association is dependent on abnormal LVEF. After excluding patients with severely depressed LVEF (≤35%, n = 54, 7% of cohort), a wide BW continued to be associated with increased mortality (HR 1.33 95% CI 1.05-1.70, P = .02).

DISCUSSION

To the best of our knowledge, this is the largest study that examined the prognostic value of LVD in patients with ESRD using three independent indices

Table 1. Baseline characteristics of the patients

	All patients (828)	Survived (538)	Died (290)	*P* value
Age	52.6 ± 0.36	51.8 ± 0.45	54.2 ± 0.62	.001
Male	459 (55%)	287 (53%)	172 (59%)	.1
Diabetes (n = 824)	493 (60%)	294 (55%)	199 (69%)	<.001
Hypertension (n = 825)	778 (94%)	508 (95%)	270 (94%)	.6
Cerebrovascular disease	27 (3%)	14 (3%)	13 (5%)	.3
Renal transplantation	230 (28%)	214 (40%)	16 (6%)	<.001
Serum creatinine (mg/dL, n = 817)	7.9 ± 0.12	7.9 ± 0.16	8.0 ± 0.17	.2
QRS (ms, n = 769)	81 ± 0.5	80 ± 0.6	82 ± 0.9	.3

BW, Bandwidth; *CVD*, cerebrovascular disease

Table 2. Quantitative phase analysis results of gated SPECT MPI

	All patients (829)	Survived (539)	Died (290)	*P* value
LVEF (%)	54.8 ± 0.4	56.2 ± 0.5	52.2 ± 0.7	<.001
LVEF ≤35%	54 (7%)	28 (5%)	26 (9%)	.04
ESV (mL)	58 ± 1	55 ± 2	64 ± 2	.002
EDV (mL)	120 ± 2	117 ± 2	124 ± 3	.04
LVM (g)	167 ± 1	166 ± 2	169 ± 2	.3
Abnormal MPI (TPD >5%)	334 (41%)	211 (39%)	123 (43%)	.4
Total PDS (%)	8.3 ± 0.4	8.0 ± 0.5	8.9 ± 0.7	.2
Fixed PDS (%)	4.8 ± 0.3	4.7 ± 0.4	4.8 ± 0.5	.3
Reversible PDS (%)	3.6 ± 0.3	3.4 ± 0.3	3.8 ± 0.4	.4
BW (°)	68.7 ± 1.5	66.3 ± 1.8	73.1 ± 2.6	.02
BW >56°	398 (48%)	239 (44%)	159 (55%)	.004
SD (°)	24.0 ± 0.5	23.4 ± 0.6	25.2 ± 0.8	.06
SD ≥21°	406 (51%)	251 (48%)	155 (55%)	.06
Peak phase (°)	134.8 ± 0.8	134.4 ± 1.0	135.6 ± 1.3	.5

BW, Bandwidth; *LVEF*, left ventricular ejection fraction; *ESV*, end-systolic volume; *EDV*, end-diastolic volume; *LVM*, left ventricular mass; *PDS*, perfusion defect size; *MPI*, myocardial perfusion imaging

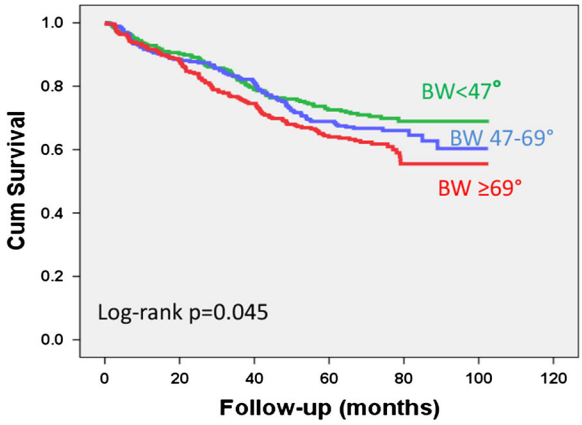

Figure 3. Kaplan-Meier survival curves of patients with ESRD stratified by tertiles of phase BW.

derived by gated MPI (perfusion, function, and dyssynchrony). The main findings of the study are: (1) LVD was associated with survival in patients with ESRD, particularly in those with abnormal perfusion; and (2) LVD added prognostic value beyond myocardial perfusion and LVEF.

Patients with ESRD are at significantly increased risk for cardiovascular mortality.[1,2] This is partially explained by the overabundance of cardiac risk factors such as hypertension, LV hypertrophy, diabetes mellitus, peripheral vascular disease, and advanced atherosclerosis. Prior studies from our group showed that in patients with ESRD, LVEF and perfusion pattern by MPI and QTc but not electrical dyssynchrony (prolonged QRS) are independent predictors of outcome.[9,10,19] Recently, LVD by phase analysis of gated SPECT MPI has emerged as an

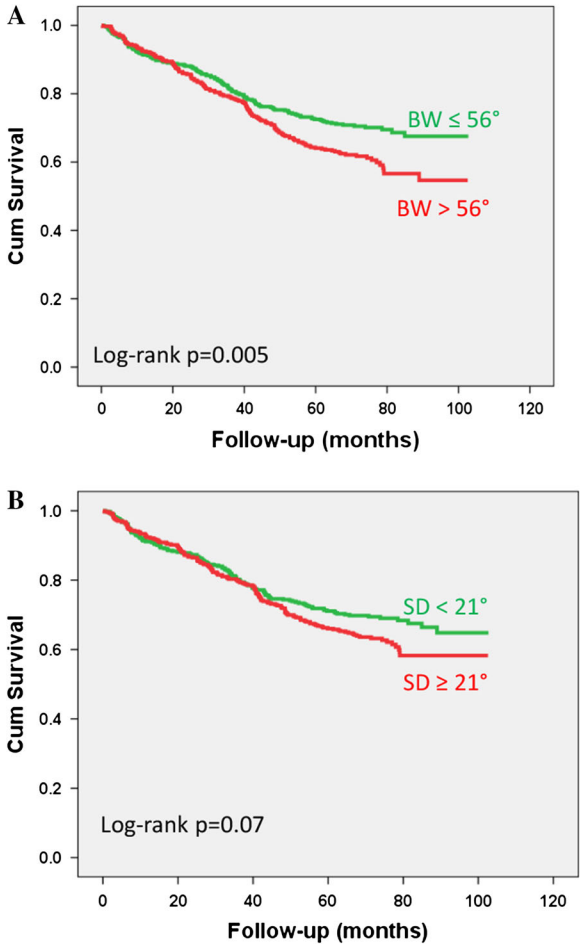

Figure 4. Kaplan-Meier survival curves of patients with ESRD stratified by medians of phase BW (**A**) and SD (**B**).

important prognostic tool.[4,20] In an independent cohort of patients with ischemic cardiomyopathy, LVD was also shown to be an independent predictor of all-cause mortality and helped identify patients with a differential survival benefit from coronary revascularization.[21]

Since patients with ESRD are known to have an elevated risk of cardiovascular mortality, especially sudden cardiac death, and have been shown to have LVD (compared to control group),[5,6] the association between LVD and risk in this population is plausible although the biological link remains not well explained. We have previously reported an association of LVD with mortality in a pilot study of 144 patients with ESRD who underwent both MPI and coronary angiography within 6 months of each other.[8] In this study, LVD was associated with increased 2-year mortality.[8] In the current study, we report on a larger cohort that is not restricted to patients who had coronary angiography and with longer follow-up. Our current results show that LVD provided prognostic data independent of traditional MPI findings including abnormal perfusion and depressed LVEF.

The pathophysiologic link between ESRD and LVD remains elusive. It is possible that this association is related, at least partially, to chronic pressure and volume overload patterns, right ventricular dilation and septal flattening, myocardial interstitial fibrosis, and others. Of note, we excluded patients with left bundle branch block, and ventricular pacing. While the cause of death is not available in our study, sudden cardiac death is known to be the most common cause of death in ESRD, far more common than in patients with normal renal function.[1] LVD has been associated with myocardial scar and fibrosis which are known substrates for ventricular arrhythmias.[22] Therefore, an interesting subject for future studies would be to examine the relationship between ESRD, myocardial fibrosis, LVD and sudden cardiac death. A major limitation for performing such a study is that gadolinium administration, for the assessment of myocardial fibrosis by magnetic resonance imaging, is relatively contraindicated in ESRD due to its association with nephrogenic systemic fibrosis.[23] It is interesting that in our study LVD was associated with

Table 3. Univariate and multivariate analysis

Variable	Unadjusted HR	*P* value	Adjusted HR	*P* value	Final adjusted HR	*P* value
Age (years)	1.018 (1.006-1.030)	.003	1.018 (1.006-1.030)	.003	1.018 (1.006-1.029)	.003
Male	1.190 (0.941-1.504)	.1	1.140 (0.897-1.450)	.3		
Diabetes	1.653 (1.288-2.123)	<.001	1.678 (1.301-2.165)	<.001	1.656 (1.289-2.129)	<.001
Hypertension	0.913 (0.567-1.472)	.7	0.772 (0.475-1.254)	.3		
Abnormal perfusion (>5%)	1.075 (0.851-1.358)	.5	0.926 (0.727-1.178)	.5		
LVEF <35%	1.549 (1.035-2.318)	.03	1.399 (0.916-2.135)	.1		
BW >56°	1.382 (1.096-1.742)	.006	1.289 (1.010-1.644)	.04	1.342 (1.063-1.695)	.01

BW, Bandwidth; *LVEF*, left ventricular ejection fraction

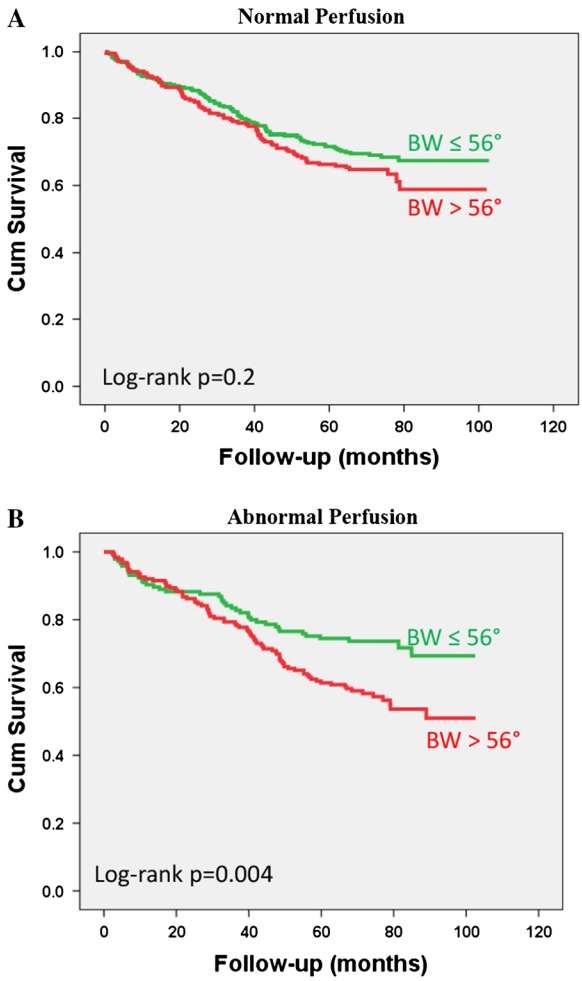

Figure 5. Kaplan-Meier survival curves of patients with ESRD stratified by median of phase BW in those with normal (**A**) and abnormal (**B**) myocardial perfusion.

death only in patients with abnormal perfusion on MPI. Nevertheless, in these patients LVD was independently associated with poor outcome even after controlling for PDS on MPI. It remains unknown whether LVD could be reversed post-renal transplant. These issues are worth exploring in future studies.

Strengths and Limitations

To the best of our knowledge, this is the largest study that assessed the prognostic value of LVD in patients with ESRD. However, we acknowledge several limitations. This is a retrospective study that used a prospectively populated database from a single tertiary referral center with likely selection and referral bias. We encountered technical difficulties that prevented us from analyzing a sizable portion of the population (16%) that potentially could have altered or strengthened the findings of our study. All-cause mortality rather than cardiovascular death or sudden cardiac death was used as primary end-point. While it would have been preferable to use sudden cardiac death as an end-point, this data were not available to us. We were not able to account for the effect of coronary revascularization on the association between LVD and outcomes. Since coronary revascularization presumably occurred more often in patients with abnormal rather than normal perfusion, we do not believe that this led to the differential association between LVD and poor outcomes in patients with abnormal perfusion. Although LVD is likely influenced by volume status and fluid shifts during hemodialysis, we do not have precise data on the timing of MPI in relation to hemodialysis. Nevertheless, most MPIs at our institution are performed midweek to reduce the influence of volume overload and uremia. The database lacked several key variables such as cardiac medications, important co-morbidities such as COPD, atrial fibrillation, and right ventricular function. We were unable to account for the presence of heart failure or cardiac resynchronization therapy. However, we excluded patients with LBBB from our analysis since the mortality benefit attributed to cardiac resynchronization therapy has been largely limited to patients with LBBB.[24]

NEW KNOWLEDGE GAINED

In patients with ESRD undergoing gated SPECT MPI as part of their renal transplant evaluation, LVMD indices (particularly phase BW) are independently associated with all-cause mortality and provide prognostic data beyond traditional MPI variables especially in patients with abnormal myocardial perfusion pattern.

Disclosures

Dr Iskandrian is a scientific advisor for Rapidscan, Pharma and has received research grants from the Astellas Pharma USA. Dr Hage has received research grants from the Astellas Pharma USA. Dr Hage is a scientific advisor for Astellas Pharma USA. The other authors report no financial disclosures.

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