Association of echocardiographic abnormalities with mortality in men with non-dialysis-dependent chronic kidney disease

Jason Payne1, Smriti Sharma1, Dexter De Leon1, Jun L. Lu2, Fregenet Alemu3, Rasheed A. Balogun4, Sandra M. Malakauskas3,4, Kamyar Kalantar-Zadeh5,6 and Csaba P. Kovesdy3,4

1Department of Medicine, Carilion Clinic, Roanoke, VA, USA, 2Salem Research Institute, Salem, VA, USA, 3Division of Nephrology, Salem Veterans Affairs Medical Center, Salem, VA, USA, 4Division of Nephrology, University of Virginia, Charlottesville, VA, USA, 5Harold Simmons Center for Chronic Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance CA, USA and 6Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Correspondence and offprint requests to: Csaba P. Kovesdy; E-mail: csaba.kovesdy@va.gov

Abstract

Background. The interrelationship of left ventricular hypertrophy (LVH) with ejection fraction (EF) and their impact on mortality in non-dialysis-dependent chronic kidney disease (NDD-CKD) is unclear.

Methods. We examined the associations of EF and LVH with all-cause mortality in a historic cohort of 650 male US veterans with moderate-to-advanced NDD-CKD. EF and LVH were examined both separately and after categorizing patients according to their concomitant EF and presence/absence of LVH. Associations with mortality were examined in Cox models with adjustments for demographics, blood pressure, comorbidities, smoking status, medication use and biochemical characteristics.

Results. EF <30 and 30–50% were associated with higher all-cause mortality compared to EF >50% even after multivariable adjustments [multivariable adjusted hazard ratio, 95% confidence interval (CI): 2.83 (1.86–4.30) and 1.38 (1.06–1.78), P < 0.001 for linear trend]. LVH in itself was not associated with mortality [multivariable adjusted hazard ratio, 95% CI: 0.83 (0.66–1.05), P = 0.12], but the presence of LVH combined with an EF <50% was associated with the highest mortality [multivariable adjusted hazard ratios, 95% CI in patients with EF >50% + LVH, EF ≤50%–LVH and EF ≤50% + LVH, compared to EF >50%–LVH: 0.84 (0.63–1.13), 1.36 (1.00–1.83) and 1.62 (1.07–2.46)].

Conclusions. Low EF is associated with higher mortality in patients with NDD-CKD. In the presence of a low EF, LVH is also associated with higher mortality. Clinical trials are needed to determine if interventions targeting patients with low EF and LVH can lower mortality in NDD-CKD.

Keywords: chronic kidney disease; echocardiography; ejection fraction; left ventricular hypertrophy; mortality

Introduction

The mortality rate in chronic kidney disease (CKD) patients is very high, including patients with end-stage renal disease (ESRD) on hemodialysis (HD) [1–3] and patients with non-dialysis-dependent (NDD)-CKD [3, 4]. Cardiovascular mortality accounts for most of these deaths, emphasizing the importance of investigating and treating identifiable cardiovascular abnormalities in CKD and ESRD. Echocardiography has been a useful tool, as it provides information on both functional and anatomical characteristics such as left ventricular hypertrophy (LVH) and ejection fraction (EF). LVH is very common in patients with ESRD; it has been found to be present in 46–74% of patients at the time of initiation of dialysis therapy [5–7], compared to 51% in patients with coronary artery disease (CAD) and 12–20% in patients with hypertension [8, 9]. This high prevalence of LVH in ESRD can be explained by the confluence of various factors in this patient population, including afterload-dependent (arterial resistance and renin–angiotensin activation), preload-dependent (volume overload, anaemia and arterio-venous fistulas) and non-preload- or afterload-dependent factors (hyperparathyroidism, hyperphosphatemia, hyperhomocysteinemia, cytokine aberrations, hyperaldosteronism and vitamin D deficiency) [6, 7, 10–13]. Additionally, LVH has also been recognized as a compensatory mechanism in patients with left ventricular (LV) dilatation and with high afterload. The presence of LVH has been associated with increased mortality in some studies of ESRD patients [14–16] but another study examining the predictive ability of LVH in the context of LV function suggested the presence of an interaction between these two characteristics, and patients with both LVH and decreased LV function had the highest mortality [17]. The same study established low LV function as a significant predictor of increased cardiovascular mortality independent of LVH or other classic or novel cardiovascular risk factors in ESRD [17], and the importance of LV function was further emphasized by the
finding that longitudinal changes in this parameter were also shown to be significant predictors of cardiovascular morbidity and mortality [18]. The complex relationship between LVH and LV function was also highlighted by an earlier study in ESRD patients with normal systolic function showing that despite both high LV mass and high LV volume being independent predictors of late mortality, prognosis was unaffected when both lesions were noted [19], possibly because the prognostic effects of LVH may be dependent on concomitant EF. Similarly, detailed descriptions of the characteristics and consequences of LVH and LV function in patients with NDD-CKD have not been previously performed, in spite of the larger numbers of patients with this condition and their high mortality [20]. Since the development of LVH in patients with normal and with decreased EF may be related to fundamentally different pathophysiological processes, it is important to consider both characteristics when examining outcomes associated with them [21].

We conducted a study to assess the association of echocardiographic abnormalities (LVH and reduced EF) with mortality in a large historical cohort of male US veterans with NDD-CKD from a single medical center.

Materials and methods

Study population and data collection

We reviewed the medical records of all patients who were referred for NDD-CKD evaluation at Salem Veterans Affairs Medical Center (VAMC) between 1 January 1990 and 30 June 2005 [22, 23]. Of 1012 total patients, 661 (65%) underwent echocardiography for clinical indications. Patients with available echocardiography were similar in age, race and gender to patients without echocardiographic studies, but they were significantly more likely to have cardiovascular disease and diabetes mellitus (data not shown). Seven female patients and four patients whose race was other than white or black were excluded. The final study population consisted of 650 patients.

Clinical characteristics recorded at the time of the patients’ undergoing echocardiography were extracted retrospectively, including demographic and anthropometric characteristics, comorbid conditions and laboratory results. Medication use including that of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB), aspirin and beta blockers was assessed at baseline and also over the entire follow-up period. Glomerular filtration rate (GFR) was estimated using the abbreviated equation developed for the Modification of Diet in Renal Disease Study (MDRD) [24] and categorized according to the staging system introduced by the Kidney/Dialysis Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines for CKD: Evaluation, Classification, and Stratification [25]. All the biochemical measurements were performed in a single laboratory at the Salem VAMC. Echocardiography reports were reviewed for the level of EF and for the presence/absence of LVH. If only a qualitative assessment was available for EF in the report, then ‘normal EF’ was categorized as >50%, ‘mild’ or ‘moderate decrease in EF’ as 30–50% and ‘severe decrease in EF’ as <30%. For analyses that considered EF as a continuous variable arbitrary EF values of 55, 45, 35 and 25% were assigned to correspond with the above qualitative categories.

Statistical analyses

Data points were missing for comorbidity index (1.2% missing), body mass index (21.7% missing), smoking status (5.4% missing), blood pressure (15.7% missing), serum albumin (0.8% missing), phosphorus (0.6% missing), blood cholesterol (2% missing), haemoglobin (1% missing), white blood cell count (WBC, 0.5% missing), percent lymphocytes in WBC (0.8% missing) and 24-h urine protein (2.8% missing). Missing data points were not imputed in primary multivariable analyses. Imputations were performed for sensitivity analyses by using linear regression with all the other patient characteristics as independent variables for continuous variables and by creating dummy categories corresponding for the missing data points for categorical variables.

Outcomes analysis

The start time for survival analysis was the date when the echocardiogram was performed. Patients were considered lost to follow-up if no contact was documented with them for >6 months, and they were censored at the date of the last documented contact. The outcome measure of interest was all-cause mortality (ascertained from VA electronic records). The associations of EF, LVH and the combination of EF and LVH with all-cause mortality were evaluated in Cox models with adjustment for potential confounders. Selection of variables to be included in the final multivariable models was done a priori by determining probable confounders [26] based on differences in baseline characteristics between patients with different EF levels and presence/absence of LVH and based on theoretical considerations. Models were thus constructed to assess unadjusted (Model 0), age, race, comorbidity (CAD, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, malignancies and Charlson comorbidity index), medication use and smoking-adjusted (Model 1) and Model 1 + estimated GFR, albumin, cholesterol, calcium, phosphorus, haemoglobin, WBC count, percent of lymphocytes in WBC count and 24 h urine protein-adjusted (Model 2) associations. Since blood pressure could be a confounder but could also be in the path of the outcomes associated with EF and/or LVH, we constructed additional models to include further adjustments for baseline systolic and diastolic blood pressures (Model 3). EF was examined both as a continuous variable and after categorizing it according to prespecified cutoffs (<30, 30–50 and >50%). The concomitant effects of EF and LVH were examined in patients who were categorized according to their EF level and the concomitant presence or absence of LVH: EF <50% and no LVH (referent category), EF >50% and LVH, EF <50% and no LVH and EF >50% and LVH. Prespecified subgroup analyses were performed in patients categorized by their age, race, systolic and diastolic blood pressure, presence/absence of CAD and estimated GFR. Sensitivity analyses were performed by imputing missing values of independent variables and by adjusting for future medication use analogous to intent to treat analyses. The proportionality assumption was tested by using Schoenfeld residuals. P-values of <0.05 were considered significant. Statistical analyses were performed using STATA statistical software version 11 (STATA Corporation, College Station, TX). The study protocol was approved by the Research and Development Committee at the Salem VAMC.

Results

The mean (± SD) age of the cohort was 68 ± 10 years, 23% of patients were black and the mean estimated GFR was 37 ± 21 mL/min/1.73m². Most patients had CKD Stages 3 (46%) and 4 (26%) with fewer patients categorized as CKD Stages 1 (2%), 2 (11%) and 5 (14%). A total of 455 patients died [mortality rate: 154/1000 patient-years, 95% confidence interval (CI): 140–169] over a median follow-up of 3.7 years. Thirty-two patients (5%) were lost to follow-up; their characteristics were not significantly different (data not shown).

Baseline characteristics in patients divided by categories of EF and by the presence/absence of LVH are shown in Table 1 and Table 2. Patients with lower EF had lower systolic blood pressure, cholesterol and proteinuria, higher Charlson index, were more likely to have CAD and to use ACEI/ARB and were less likely to have LVH to be active smokers and to have malignancies. Patients with LVH were more likely to be black and less likely to be active smokers and to have CAD had a lower EF and estimated GFR and had higher serum phosphorus and proteinuria.

Figure 1 shows Kaplan–Meier survival curves in patients with different levels of baseline EF, indicating significantly higher mortality in patients with lower EF. In unadjusted Cox models, a 10% lower EF was associated with a hazard ratio (95% CI) of mortality of 1.26 (1.16–1.37), P < 0.001,
which remained consistent after adjustments for confounders: 1.19 (1.09–1.30), P < 0.001 (Model 1), 1.24 (1.14–1.35), P < 0.001 (Model 2) and 1.25 (1.15–1.36), P < 0.001 (Model 3). Compared to EF >50%, an EF of 30–50 and <30% were associated with higher mortality even after sequential adjustments for various potential confounders (Table 3). Figure 2 shows Kaplan–Meier survival curves in patients with and without LVH on echocardiography, indicating similar mortality in the two groups. LVH was not associated with mortality in any of the multivariable adjusted models, except in Model 2, in which it was associated with significantly lower mortality (Table 3). Table 4 shows hazard ratios (95% CI) of all-cause mortality in patients grouped according to their EF level and the concomitant presence or absence of LVH. Patients with EF >50% had similar hazard ratios for mortality irrespective of the presence or absence of LVH. Patients with EF ≤50% had significantly higher hazard ratios of mortality compared to patients with EF >50% irrespective of the presence or absence of LVH. The presence of LVH combined with an EF <50% was associated with the highest hazard ratio of mortality after adjustment for blood pressure levels in Model 3 (Table 4).

Similar associations were detected in subgroup analyses. The results also did not change significantly in sensitivity analyses using imputed values for missing covariates and by adjusting for future medication usage (data not shown).

### Discussion

We describe an independent association of lower EF with higher mortality in patients with moderate and advanced NDD-CKD. Importantly, in patients with higher EF, the presence of LVH had no impact on mortality (and was even associated with a trend towards a protective effect in adjusted models), but in those with lower EF, the presence of LVH was associated with higher mortality. LVH has been shown to predict mortality independent of clinical risk factors in the general population and in hypertensive patients [15], and systolic dysfunction and LV dilation have also been associated with increased cardiovascular risk and mortality in the general population and patients with ESRD [19]. Furthermore, in an earlier prospective cohort of 254 ESRD patients, Zoccali et al. [17] described low LV function (measured with three different methods) as a significant predictor of cardiovascular mortality independent of the presence of LVH and described a significant interaction between LVH and low LV function in that patients who had both of these characteristics experienced the highest mortality. The importance of low LV function as both a predictor of poor outcomes and also as a potential therapeutic target was further emphasized by a subsequent study based on the same prospective cohort showing that a decrease in LV function on repeated
evaluation was associated with poor cardiovascular outcomes, but an improvement was associated with significantly improved outcomes [18]. Our results corroborate some of these findings and extend them to patients with NDD-CKD, suggesting that low EF is a significant predictor of outcomes in them, and that the complex interaction between LVH and LV function extends to this much larger group of patients. LVH is both a target organ response to hemodynamic as well as non-hemodynamic stimuli and a risk factor responsible for cardiac events. Clinical factors responsible for generation of LVH are not physiologically homogenous and this may underlie the differences in outcomes associated with LVH in different settings including reduced versus normal EF. CKD patients have many factors associated with the generation of LVH [6, 7, 10–13], and it is possible that LVH in this setting may be a distinct lesion and may have distinct cardiac sequelae from LVH generated in the context of other disease states. It has previously been shown that the generation of LVH due to pressure versus volume overload has a distinct underlying signaling mechanism and different patterns and mechanisms of growth [21]. LVH is a compensatory mechanism, but it is not perfectly regulated via a typical feedback loop. As a result, while the initially developing LVH may be compensatory, adverse remodeling often develops whereby the ventricle becomes more dilated and ultimately diastolic and systolic dysfunction ensue. Patients with preserved EF and LVH may represent those who have a more balanced and hence purely adaptive stage of LVH, which could explain their lack of association with mortality.

Another possible explanation for the discordant association of LVH with mortality is an imbalance in LV functional and anatomical characteristics. LV dysfunction may manifest as systolic dysfunction (fractional shortening
<25%), LVH (LV mass >131 g/m²) or LV dilation (LV volume >90 mL/m²) [27, 28]. Each of these abnormalities may occur independently or in combination. Thus, a patient may have LV dilation with normal or reduced fractional shortening or LVH with normal or reduced fractional shortening. An earlier prospective study in ESRD patients on maintenance hemodialysis who all had normal EF, a high LV mass was associated with adverse prognosis only in those with normal cavity volume but not in those with LV dilation [15]. Volume overload and LV dilation is common in CKD patients. Even though we did not have LV cavity volume measurements available for our analyses, it is possible that a high prevalence of LV dilation in our patients with normal EF may explain our results. As LV dilation results in greater wall tension, LVH would decrease wall tension, oxygen utilization, improve perfusion gradient and reduce subendocardial ischemia, based on the law of Laplace [29].

Our study had a number of limitations. Because our study was a retrospective study, causality cannot be implied. The study examined patients over an extended period of time during which secular trends in applied treatments and in echocardiographic methods could have changed and thus could have affected our findings. This was a single center study done in an entirely male cohort; hence, the results may not apply to the entire population with CKD. Additionally, only 65% of the available patients underwent echocardiography, most likely as a result of selection bias, as echocardiograms in clinical practice are most often performed after clinical events or symptoms. The excluded patients indeed had a lower prevalence of diabetes mellitus and cardiovascular disease, it is hence likely that many or most of them would have had no or mild echocardiographic abnormalities, and hence their inclusion in the study is unlikely to have altered the results significantly. Echocardiography was used to define LVH, which has been shown to overestimate LVH in the dialysis population [30]. However, this was a retrospective study and echocardiography is the most practical way of evaluating cardiac function and LV geometry. Additionally with the increasing awareness of gadolinium-induced nephrogenic systemic fibrosis, magnetic resonance imaging is less often used in patients with CKD, and hence, it is likely that echocardiography will remain the preferred clinical tool for routine noninvasive evaluation of cardiac function and structure. We had limited information derived from the echocardiographic studies obtained for clinical purposes. EF was not always quantified and hence we made assumptions about its level based on qualitative wording from the interpreter (normal, mild, moderate and severe); however, such interpretation is fairly standard in Cardiology practice. The lack of data on LV volume and geometry limits our ability to explore pathophysiological mechanisms that explain our findings. More detailed echocardiographic parameters allow for the differentiation of eccentric and concentric LVH and for the calculation of other parameters describing LV function, such as midwall fractional shortening. Due to lack of pertinent data, we could not extend our analyses to examine these additional parameters, but a study in ESRD patients suggested that the predictive ability of EF was similar to that of midwall fractional shortening [17]. Our lack of data on LV mass also prevented us from refining our analyses by indexing LV mass for either body surface area or for height[3], the latter method having been shown to make LV mass a more powerful predictor of cardiovascular outcomes in ESRD patients [31]. We attempted to correct for several potential confounders, but residual confounding by unmeasured factors cannot be excluded. We speculate that the associations of echocardiographic abnormalities with all-cause mortality is due to higher rates of cardiovascular deaths in the affected patients, but we did not have data on causes of death to test this hypothesis.

Low EF is a robust and independent predictor of increased mortality in patients with NDD-CKD. LVH is
also associated with adverse prognostic in those with reduced EF but has no association with mortality in those with normal EF. Further studies in this area are needed to replicate our findings and to better describe echocardiographic characteristics, including assessment of LV volume and LV mass indexed to body size. Clinical trials are needed to test the hypothesis that interventions targeting patients with low EF can lead to improved outcomes in the NDD-CKD population.

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Transparency declaration. None of the authors have declared any competing financial interests.

Conflict of interest statement. None declared.

References


Table 4. Hazard ratios (95% CIs) of all-cause mortality in patients categorized according to their EF and the concomitant presence or absence of LVH

<table>
<thead>
<tr>
<th>EF &gt;50%, No LVH (referent) N = 196</th>
<th>EF &gt;50%, LVH N = 209</th>
<th>EF ≤50%, No LVH N = 176</th>
<th>EF ≤50%, LVH N = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 0 1</td>
<td>0.92 (0.73–1.17)</td>
<td>1.38 (1.08–1.75)</td>
<td>1.33 (0.96–1.83)</td>
</tr>
<tr>
<td>Model 1 1</td>
<td>0.92 (0.71–1.19)</td>
<td>1.25 (0.96–1.62)</td>
<td>1.25 (0.88–1.79)</td>
</tr>
<tr>
<td>Model 2 1</td>
<td>0.80 (0.61–1.04)</td>
<td>1.22 (0.92–1.60)</td>
<td>1.31 (0.91–1.90)</td>
</tr>
<tr>
<td>Model 3 1</td>
<td>0.84 (0.63–1.13)</td>
<td>1.36 (1.00–1.83)</td>
<td>1.62 (1.07–2.46)</td>
</tr>
</tbody>
</table>

aAssociations were examined in unadjusted Cox models (Model 0) and with adjustments for age, race, CAD, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, malignancies, Charlson index, baseline medication use and smoking (Model 1), for Model 1 variables + estimated GFR, albumin, cholesterol, calcium, phosphorus, haemoglobin, WBC count, percent of lymphocytes in WBC count and 24 h urine-adjusted (Model 2) and for Model 2 variables + systolic and diastolic blood pressure.
Predictors of heart rate variability and its prognostic significance in chronic kidney disease

Preeti Chandra1,2, Robin L. Sands2, Brenda W. Gillespie2, Nathan W. Levin3, Peter Kotanko3, Margaret Kiser4, Fredric Finkelstein5, Alan Hinderliter6, Rodica Pop-Busui1, Sanjay Rajagopalan7 and Rajiv Saran1,2

1Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA, 2University of Michigan-Kidney Epidemiology and Cost Center, Ann Arbor, MI, USA, 3Renal Research Institute, New York, NY, USA, 4Department of Internal Medicine, University of North Carolina, Chapel Hill, NC, USA, 5Hospital of St Raphael Yale University, New Haven, CT, USA, 6Department of Internal Medicine, University of North Carolina, Chapel Hill, NC, USA and 7Department of Cardiovascular Medicine, Ohio State University, Columbus, OH, USA

Correspondence and offprint requests to: Rajiv Saran; E-mail: rsaran@umich.edu

Abstract

Background. Heart rate variability (HRV), a noninvasive measure of autonomic dysfunction and a risk factor for cardiovascular disease (CVD), has not been systematically studied in nondialysis chronic kidney disease (CKD).

Methods. HRV was assessed using 24-h Holter monitoring in 305 subjects from the Renal Research Institute-CKD Study, a four-center prospective cohort of CKD (Stages 3–5). Multiple linear regression was used to assess predictors of HRV (both time and frequency domain) and Cox regression used to predict outcomes of CVD, composite of CVD/death and end-stage renal disease (ESRD).

Results. A total of 47 CVD, 67 ESRD and 24 death events occurred over a median follow-up of 2.7 years. Lower HRV was significantly associated with older age, female gender, diabetes, higher heart rate, C-reactive protein and phosphorus, lower serum albumin and Stage 5 CKD. Lower HRV (mostly frequency domain) was significantly associated with higher risk of CVD and the composite end point of CVD or death. Significantly, lower HRV (frequency domain) was associated with higher risk of progression to ESRD, although this effect was relatively weaker.

Conclusions. This study draws attention to the importance of HRV as a relatively under recognized predictor of adverse cardiovascular and renal outcomes in patients with nondialysis CKD. Whether interventions that improve HRV will improve these outcomes in this high-risk population deserves further study.

Keywords: autonomic nervous system; cardiovascular disease risk factors; cardiovascular outcomes; cohort study; end-stage renal disease

Introduction

Increased cardiovascular (CV) morbidity and mortality is well documented in chronic kidney disease (CKD) [1]. Sudden cardiac death accounts for about a third of total mortality among dialysis patients, that could in part, be due to autonomic nervous system (ANS) dysfunction [2] and increased sympathetic activity, in particular [3]. Increased sympathetic activity is also noted in patients with CKD [4] and likely contributes to the higher risk of cardiovascular disease (CVD) and also renal damage.

Heart rate variability (HRV) is a noninvasive measure of autonomic function that reflects beat-to-beat variability in heart rate. It is best assessed by continuous electrocardiography over a 24-h period, although shorter recordings have also been utilized. It is quantified by ‘time domain’ or...