Kidney and Heart

Relationship of Left Ventricular Hypertrophy and Diastolic Function With Cardiovascular and Renal Outcomes in African Americans With Hypertensive Chronic Kidney Disease

Gail E. Peterson, Tine de Backer, Gabriel Contreras, Xuelei Wang, Cynthia Kendrick, Tom Greene, Lawrence J. Appel, Otelio S. Randall, Janice Lea, Miroslaw Smogorzewski, Tudor Vagaonescu, Robert A. Phillips; for the African American Study of Kidney Disease Investigators

See Editorial Commentary, pp 455–456

Abstract—African Americans with hypertension are at high risk for adverse outcomes from cardiovascular and renal disease. Patients with stage 3 or greater chronic kidney disease have a high prevalence of left ventricular (LV) hypertrophy and diastolic dysfunction. Our goal was to study prospectively the relationships of LV mass and diastolic function with subsequent cardiovascular and renal outcomes in the African American Study of Kidney Disease and Hypertension cohort study. Of 691 patients enrolled in the cohort, 578 had interpretable echocardiograms and complete relevant clinical data. Exposures were LV hypertrophy and diastolic parameters. Outcomes were cardiovascular events requiring hospitalization or causing death; a renal composite outcome of doubling of serum creatinine or end-stage renal disease (censoring death); and heart failure. We found strong independent relationships between LV hypertrophy and subsequent cardiovascular (hazard ratio, 1.16; 95% confidence interval, 1.05–1.27) events, but not renal outcomes. After adjustment for LV mass and clinical variables, lower systolic tissue Doppler velocities and diastolic parameters reflecting a less compliant LV (shorter deceleration time and abnormal E/A ratio) were significantly (P<0.05) associated with future heart failure events. This is the first study to show a strong relationship among LV hypertrophy, diastolic parameters, and adverse cardiac outcomes in African Americans with hypertension and chronic kidney disease. These echocardiographic risk factors may help identify high-risk patients with chronic kidney disease for aggressive therapeutic intervention. (Hypertension. 2013;62:518-525.)

Key Words: African Americans | diastolic heart failure | echocardiography | hypertension | hypertrophy

In studies that have predominantly evaluated white populations of European descent, left ventricular hypertrophy (LVH) has been associated with more coronary heart disease and higher cardiovascular morbidity and mortality.1-4 African Americans bear a large burden of cardiovascular morbidity and mortality in the United States; those with hypertension have a greater risk for the development of chronic kidney disease (CKD),5,6 yet they are underrepresented in most epidemiological studies. Many investigators have identified a higher prevalence of LVH in African Americans compared with whites,7-9 and African Americans with established CKD are at even greater risk for adverse events.10 The LVH associated with CKD may be responsible for the increased incidence of cardiovascular disease (CVD) and mortality seen in patients with CKD.10 In addition, animal studies suggest that renal insufficiency induces cardiac fibrosis and diastolic dysfunction.11 Diastolic dysfunction is common among patients with hypertension and LVH and is an adverse prognostic marker.12-14 However, no study has specifically evaluated the association of LVH and diastolic abnormalities with outcomes in African Americans with hypertension and CKD.

We have previously reported a high incidence of baseline LVH in the African American Study of Kidney Disease and Hypertension (AASK) cohort.15 We sought to determine how strongly LVH is associated with CVD and renal outcomes in this population, and whether echocardiographic parameters of diastolic dysfunction add independent prognostic value in a model containing LV mass (LVM) and clinical variables.

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From the Division of Cardiology, UT Southwestern Medical Center, Dallas, TX (G.E.P.); Heart Center and Clinical Pharmacology, University Hospital Ghent, Ghent, Belgium (T.d.B.); Department of Medicine, University of Miami Miller School of Medicine, Miami, FL (G.C.); Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, OH (X.W., C.K.); Division of Epidemiology, University of Utah, St. Lake City, UT (T.G.); Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD (L.J.A.); Department of Medicine, Howard University, Washington, DC (O.S.R.); Emory Center for Hypertension and Renal Disease Research, Emory University, Atlanta, GA (J.L.); Division of Nephrology, University of Southern California Keck School of Medicine, Los Angeles, CA (M.S.); UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ (T.V.); and Cardiovascular Medicine, UMass Memorial Medical Center and Medical School, Worcester, MA (R.A.P.).
Correspondence to Gail E. Peterson, Division of Cardiology, UT Southwestern, 5909 Harry Hines Blvd, Dallas, TX 75235-9047. E-mail Gail.Peterson@UTSouthwestern.edu
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Methods

Study Population
The AASK cohort study, an extension of the AASK trial, is a prospective, observational study of African Americans with nondiabetic hypertensive kidney disease. Details of the inclusion and exclusion criteria for patients enrolled in the AASK trial are described elsewhere. All surviving participants in the AASK trial who had not reached end-stage renal disease were invited to enroll in the cohort study. The study was approved by the institutional review committee at each participating site. All of the subjects gave informed consent. Patients enrolled in the AASK cohort study had excellent blood pressure (BP) control during the trial; average BP of cohort participants during the trial was 128/78 mm Hg in the lower BP group (mean arterial pressure, <92 mm Hg) and 141/85 mm Hg in the usual BP group (mean arterial pressure, 102–107 mm Hg). On the basis of trial results, patients in the cohort phase were treated with an angiotensin-converting enzyme inhibitor unless there was a contraindication. At the direction of the study’s Data Safety Monitoring Board, the BP goal in the cohort was <130/80 mm Hg.

Echocardiography
Patients enrolled in the cohort had an echocardiogram performed at their baseline visit, and at 24- and 48-month follow-up visits. Two-dimensional, M-mode, and Doppler echocardiography examinations were performed at each of the 21 enrolling centers using commercially available equipment. To ensure data quality, echocardiograms were obtained by trained technologists using a standardized protocol and read centrally at the AASK Cardiovascular Core Laboratory. At the core laboratory, echocardiographic tracings were coded, digitized, and interpreted without source identification using the DigiView Digital/Video System(s), Model DV-DVRS-100 (Digisonics, Inc), and measurements were performed according to the American Society of Echocardiography guidelines. Details of echocardiographic acquisition and correlation statistics have been previously reported. LVM was calculated using an anatomically validated formula and normalized to allometric height. LVH was defined according to sex-specific criterion as LVM index >49.2 g/m² in men and >46.7 g/m² in women. We divided mitral E/A ratios into 3 clinically relevant categories on the basis of prior studies: impaired LV relaxation with E/A ≤0.75, normal with E/A >0.75 and <1.5, or restrictive filling with E/A ≥1.5.

Ambulatory BP Measurements
Ambulatory BP monitoring was performed during a 24-hour period, using the SpaceLabs 90217 Ultralite or SpaceLabs 90207 devices as previously reported. Urinary albumin excretion was determined by measuring 24-hour urine albumin (Ucr) of >0.22 was used to define albuminuria. Albuminuria was estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using an equation developed from baseline data in the AASK trial.

Outcomes
The following prespecified outcomes were assessed:

1. Main CVD composite outcome defined as CVD death or the first CVD hospitalization (censoring, end-stage renal disease).
2. Main renal composite of doubling serum creatinine or end-stage renal disease (censoring death).
3. Heart failure (HF) outcome alone defined as the first hospitalization or death for an episode of HF.

The definitions of each individual event included in the main CVD composite outcome are described elsewhere and events were adjudicated by the Cardiovascular Outcome Committee.

Statistical Analysis
Baseline characteristics, including both clinical and echocardiographic characteristics at entry into the cohort, were summarized as means±SD for continuous variables, and as frequencies and percentages for categorical variables and were compared between those with and without LVH at baseline using a 2-sample t test or χ² test, as appropriate.

Event rates for CVD composite outcome, HF, and the renal composite outcome, expressed as the number of events per 100 patient-years, were calculated as the ratio of the number of patients reaching the event divided by the total patient-years of follow-up before an event or until censoring. Follow-up time for the CVD composite and HF was censored at occurrence of end-stage renal disease or noncardiovascular death, and follow-up time for the renal composite was censored at all-cause death. Cox proportional hazards regression models were used to assess the association between LV myocardial infarction (MI) and each of these 3 event outcomes, with adjustment of age, sex, and eGFR (model 1). Model 2 included further adjustment for prior CVD, tobacco use, diabetes mellitus, non–high-density lipoprotein-cholesterol, albuminuria, nighttime systolic blood pressure, and LV fractional shortening along with its interaction with time. Sensitivity analysis was performed to assess the effect of baseline left ventricular mass index (LVM) on outcomes with and without prespecified diastolic function parameters of E/e′ and left atrial (LA) area. The assumption of proportional hazards in the Cox regression models was checked using Schoenfeld residuals for all included covariates. The assumption of linearity in the Cox regression models was checked using restricted cubic smoothing splines. Because of the presence of nonlinear relationships, segmented linear spline terms were used to provide separate estimates of the hazard ratios (HRs) of baseline eGFR below and above 40 mL/min per 1.73 m² for renal composite event. Significant violations of the proportional hazards assumption were found for baseline eGFR and LV fractional shortening with the renal composite outcome. Therefore, linear interaction terms between eGFR and LV fractional shortening with follow-up time were added to the corresponding models. No significant violation was observed in covariates for CVD composite outcome and HF outcome. Pearson correlation analysis was used to determine the relationship among LVM, LA area, and diastolic parameters. Cox regression models were used to assess the association between each of the diastolic parameters and CVD composite outcome and HF outcome. Factors included in models 1 and 2 are similar to the previous analyses but with adjustment of LVM. The assumption of proportional hazards and linearity was also checked for all included covariates. Because of the presence of nonproportional hazards, linear interaction terms between sex and LVM with follow-up time were added to the corresponding models. Because of the relatively small number of HF events, adjustments were made for a more limited suite of factors, which excluded non–high-density lipoprotein-cholesterol, albuminuria, and diabetes mellitus in model 2 for all the analyses. All statistical analyses were conducted with SAS, version 9.2.

Results

Study Participants
Of 691 patients enrolled in the cohort study, 645 patients had an interpretable baseline echocardiogram. We used a constant cohort analysis, including only patients with complete relevant clinical data, for a final study sample of 578 patients. Follow-up clinical outcomes were assessed during a 60-month period. Demographic and clinical data are displayed in Table 1. Compared with those with normal LVM, patients with LVH were younger, had higher 24-hour day and night BP, higher pulse pressures, greater history of CVD, higher uric acid and prevalence of albuminuria, and lower hematocrit.
Echocardiographic Data

Echocardiographic characteristics are shown in Table 2. Mean LVMI was 61 g/m².² Compared with patients with normal LVM, those with LVH had greater LV dimensions, wall thicknesses, relative wall thickness, and LA area. Subjects with LVH had lower early (e′) and late (a′) diastolic peak myocardial velocities, lower systolic myocardial velocity (s′), higher early mitral inflow velocity (E), and higher E/e′ ratio. Patients with E/A in the normal range comprised the majority (n=339 and n=59.8%); 198 patients had E/A <0.75 (34.9%) and 30 patients had E/A >1.5 (5.3%). There was no difference in the pattern of E/A ratio between those with and without LVH. Overall LV fractional shortening was normal and similar in both groups.

LVH and Outcomes

During the follow-up period, 87 patients had a CVD event, 44 had HF requiring hospitalization, and 133 reached the renal end point. Figure 1 is a descriptive graph showing event rates per 100 patient-years for each outcome, stratified by presence of LVH. All events occurred more frequently in patients with LVH. The average LVMI was 70.6±24 g/m².⁷ in patients with CVD events compared with 59.2±21 g/m².⁷ in those without, 75.6±24 g/m².⁷ versus 59.7±21.2 g/m².⁷ for patients with and without HF events, and 66.2±26.4 g/m².⁷ versus 59.8±20.6 g/m².⁷ for patients with and without renal events.

Association Between LVM and Outcomes

When adjusted for clinical factors (gender, sex, baseline eGFR), greater LVMI was significantly associated with higher risk of CVD outcomes (HR, 1.23; 95% confidence interval [CI], 1.14–1.34), first occurrence of HF (HR, 1.31; 95% CI, 1.18–1.45), and renal events (HR, 1.09; 95% CI, 1.02–1.16; Figure 2, model 1). After further adjustment for clinical variables and systolic function (model 2), LVMI remained significantly associated with CVD events (HR, 1.16; 95% CI, 1.05–1.27; P=0.002) and HF (HR, 1.23; 95% CI, 1.10–1.39; P<0.001), but was no longer associated with renal outcomes (HR, 1.03; 95% CI, 0.96–1.11). After further adjustment for diastolic parameters of LA size and E/e′, there remained a significant relationship between LVMI and CVD and HF events.
outcomes (HR, 1.22; 95% CI, 1.07–1.39 and 1.22; 95% CI, 1.03–1.45), respectively.

### Association Between Diastolic Parameters and Outcomes

In Cox regression analysis relating each of the diastolic parameters to outcomes, after adjusting for age, sex, and eGFR, there was a significant association between increased LA area and CVD outcomes (Figure 3, model 1). However, after additional adjustment for clinical variables (model 2), a significant relationship remained among deceleration time (DT; HR, 0.95; 95% CI, 0.9–1.0; \( P=0.03 \)), \( s' \) (HR, 0.85; 95% CI, 0.74–0.98; \( P=0.03 \)), and HF, and there was a trend for association between higher E/e' and HF (\( P=0.07 \)).

Like with other Doppler parameters, abnormal E/A ratios were significantly associated with CVD and HF outcomes (Figure 4, model 1). When additional clinical exposures, LVMI, and LV systolic function were added into the model (model 2), E/A ≤0.75 remained significantly associated with the outcome of HF (HR, 2.05; 95% CI, 1.03–4.06; \( P=0.04 \)). There was a trend toward association between high E/A and HF as well (\( P=0.06 \)).

Pearson correlation coefficient analysis showed LVMI was most strongly correlated with LA area (\( r=0.48; \ P<0.001 \)). A correlation was also demonstrated between LVMI and E/e' (\( r=0.30; \ P<0.001 \)), \( e' \) (\( r=-0.18; \ P<0.001 \)), \( s' \) (\( r=-0.16; \ P<0.001 \)), and E (\( r=-0.13; \ P=0.001 \)). No correlation was found between LVMI and fractional shortening, DT, or E/A ratio.

### Discussion

This is the first study that prospectively and systemically evaluated the relationship between LVH, diastolic function, and adverse outcomes in African Americans with hypertensive CKD. We previously reported that a high proportion of subjects (69%) had LVH at enrollment in the AASK cohort.\(^{15} \) In this report, we now demonstrate that echocardiographically defined LVH is a strong predictor of HF and other CVD events independent of clinical variables, including nighttime systolic blood pressure, albuminuria, and LV systolic and diastolic function.

Prior studies have shown LVH is associated with adverse outcomes across diverse populations\(^{1–3,27} \) and these events occur to a greater degree in African Americans with
ECG-defined LVH compared with whites and Latinos. The prognostic significance of echocardiographically defined LVH in African Americans has not been extensively studied, although compared with whites, LVH in African Americans without CKD is associated with higher CV mortality. The mechanisms behind progression from LVH to adverse outcomes have been recently reviewed and are still being elucidated. LVH is associated with increased arrhythmogenic substrate and abnormalities of intramyocardial coronary vasculature, including medial hypertrophy and perivascular fibrosis. Progressive changes in the extracellular matrix of patients with LVH result in fibrosis, increased stiffness, and diastolic dysfunction ultimately leading to HF. Variability in LVM in response to pressure overload is likely because of multiple variables, including genetic factors, comorbid conditions, and differences in the duration, severity and rate of increase of pressure and volume load.

Our patient population differs from prior populations studied, as the majority had echocardiographically defined LVH and all had established CKD, putting them at higher risk for adverse outcomes. In our cohort, LVH was associated with CVD outcomes but was not independently associated with renal events. This may be because of confounding between LVM and albuminuria, a powerful correlate of increased renal progression, or because both were dependent on BP. Prior studies have shown LVM correlates with the severity of GFR impairment in patients with CKD, but none have demonstrated that the severity of LVH is associated with renal outcomes.

There was a high correlation between LVMI and most diastolic parameters, which may account for the fact that Doppler parameters were not independently associated with cardiovascular events as a whole. However, certain measures of diastolic function (DT and E/A ratio) were associated with...
subsequent HF. Shortened DT is a marker of increased LV stiffness, and generally reflects higher LA pressure. DT has been associated with CVD events in patients with LV systolic dysfunction and after MI, but has not been shown to have prognostic value in asymptomatic patients with preserved LV systolic function before now. Our study differs from prior ones that excluded patients with clinical CVD, and unlike the LIFE study, our population was younger. Our finding that shortened DT is associated with future HF hospitalizations may help identify at-risk patients with hypertensive CKD.

We also found an association between HF and E/A ≤0.75 and a trend of association with mitral E/A ≥1.5. Others have reported restrictive filling (E/A ≥1.5) is a powerful predictor of HF in patients with CAD and an independent predictor of cardiac death in older adults after adjustment for clinical risk factors, LVH, and LV ejection fraction. Although E/A ≥1.5 was associated with a trend for association with HF in our patients, this did not reach significance, likely because of small numbers in this group (n=30). Our finding that low E/A ratio is associated with adverse outcomes differs from 1 study enrolling patients with untreated hypertension and normal renal function (a population in which certain diastolic filling patterns may be less important than BP reduction), but was similar to other studies.

Abnormal tissue Doppler parameters have been associated with adverse outcomes, particularly in patients with systolic dysfunction. Similar to other studies, we found a significant association between lower s’ and adverse outcomes (in our case HF) even after adjusting for clinical risks, systolic function, and LVM. Tissue Doppler has also been used to calculate the E/e’ ratio to estimate LV filling pressures, and recently From et al. found increased E/e’ was associated with risk of new onset HF in patients with diabetes mellitus and subclinical diastolic dysfunction. Although our study confirms these findings, we found, similar to others, that the association was attenuated after adjusting for clinical variables, LVM and LV systolic function to the point that E/e’ was no longer predictive of outcomes. Our patient population had higher LVM than those in the study of From et al., suggesting that LVM may in fact be a more prominent factor in the risk for new onset HF.

The present study has several strengths. This is the largest cohort of African Americans with CKD with systematically collected and analyzed echocardiographic and ambulatory BP measurements. All echocardiographic data were collected by staff trained with a common protocol, and all measurements made at a common core laboratory. All CVD events were reviewed and classified by a Cardiovascular Outcomes Committee. The design, size, and length of the study allowed for parallel evaluation of CVD and renal events. There are also limitations. Diastolic parameters were significantly associated with HF, but the margin of difference in outcomes was small; further studies with larger numbers of patients may help determine the clinical significance of this finding. We did not assess for dietary sodium intake. Because of its effects on ECG-determined LVH in hypertensive individuals, some authors have suggested taking into account the dietary sodium may improve cardiac risk assessment. Fractional shortening is a well-recognized means of assessing LV systolic function, but using it as the sole means is a potential limitation of the study.

We measured only lateral and not septal tissue Doppler; however, recent studies suggest that in the setting of normal LV ejection fraction lateral tissue Doppler signals have the best correlations with LV filling pressures and invasive indices of LV stiffness. Because only CVD events that required hospitalization were collected, it is likely that more CVD events occurred of a less significant nature that were not captured. Finally, the extent to which these results can be generalized to non-African American participants with CKD of various pathogeneses is not clear.

In summary, this is the first study that has prospectively and systematically evaluated the relationship among LVH, diastolic function, and adverse CVD and renal outcomes in African Americans with hypertensive CKD. Even after adjusting for multiple clinical factors and diastolic dysfunction, LVH is a strong independent predictor for adverse outcomes in this population. After adjusting for clinical factors and LVM, diastolic function parameters, including shorter DT, lower E/A and lower s’ are associated with the development of HF. Echocardiographic risk factors may help identify high-risk patients with CKD for aggressive therapeutic intervention.

**Perspectives**

Because of the heavy burden of CVD events and renal function decline in patients with hypertensive CKD, it is important to identify readily available parameters that can identify those at risk. To study the value of echocardiography in predicting cardiovascular and renal events, we obtained baseline echocardiography in 691 African Americans with hypertensive CKD and followed them during a 5-year period, during which the BP treatment goal was <130/80 mm Hg. We demonstrated that even after accounting for multiple risk factors, exposures, and diastolic function, LVM remained significantly associated with cardiovascular outcomes. Similarly, readily obtained measures of diastolic function also were predictive of HF events even after correction for risk factors, exposures, and LVM. Our study helps to clarify the role of echocardiography in identifying those patients with hypertensive CKD who are at risk for adverse outcomes. Future studies may determine whether modification of these echocardiographic parameters (eg, LVM reduction) could reduce the risk of adverse outcomes in this group.

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**Disclosures**

None.

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**Novelty and Significance**

**What Is New?**

- This is the first study to evaluate prospectively and systemically the relationship between left ventricular (LV) hypertrophy, diastolic dysfunction, and adverse outcomes in African Americans with hypertensive chronic kidney disease.
- There is a strong independent relationship between LV hypertrophy and subsequent cardiovascular events (hazard ratio, 1.16; 95% confidence interval, 1.05–1.27) but not renal events.
- Lower systolic tissue Doppler velocities and diastolic parameters reflecting a less compliant LV (short deceleration time and abnormal E/A ratios) are associated with future heart failure events (P<0.05) even after adjustment for LV mass and clinical variables.

**What Is Relevant?**

- LV mass and diastolic function are related to adverse cardiac outcomes in African Americans with hypertension and chronic kidney disease. These echocardiographic parameters may help identify patients with high-risk chronic kidney disease for aggressive therapeutic intervention.

**Summary**

In a population of African Americans with hypertension secondary to chronic kidney disease, readily available echocardiographic measures of LV mass and diastolic function independently predict future cardiovascular events and may be used to risk stratify this patient population.
Relationship of Left Ventricular Hypertrophy and Diastolic Function With Cardiovascular and Renal Outcomes in African Americans With Hypertensive Chronic Kidney Disease

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