Pulmonary Hypertension Is Associated With a Higher Risk of Heart Failure Hospitalization and Mortality in Patients With Chronic Kidney Disease

The Jackson Heart Study

Senthil Selvaraj, MD, MA; Sanjiv J. Shah, MD; Mark J. Ommerborn, MPH; Cheryl R. Clark, MD, ScD; Michael E. Hall, MD, MS; Robert J. Mentz, MD; Saadia Qazi, DO, MPH; Jeremy M. Robbins, MD; Thomas N. Skelton, MD; Jiaying Chen, MS; J. Michael Gaziano, MD, MPH; Luc Djoussé, MD, DSc

Background—African Americans develop chronic kidney disease and pulmonary hypertension (PH) at disproportionately high rates. Little is known whether PH heightens the risk of heart failure (HF) admission or mortality among chronic kidney disease patients, including patients with non–end-stage renal disease.

Methods and Results—We analyzed African Americans participants with chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2 or urine albumin/creatinine >30 mg/g) and available echocardiogram-derived pulmonary artery systolic pressure (PASP) from the Jackson Heart Study (N=408). We used Cox models to assess whether PH (PASP>35 mm Hg) was associated with higher rates of HF hospitalization and mortality. In a secondary, cross-sectional analysis, we examined the relationship between cystatin C (a marker of renal function) and PASP and potential mediators, including BNP (B-type natriuretic peptide) and endothelin-1. In our cohort, the mean age was 63±13 years, 70% were female, 78% had hypertension, and 22% had PH. Eighty-five percent of the participants had an estimated glomerular filtration rate >30 mL/min per 1.73 m^2. During follow-up, 13% were hospitalized for HF and 27% died. After adjusting for potential confounders, including BNP, PH was found to be associated with HF hospitalization (hazard ratio, 2.37; 95% confidence interval, 1.15–4.86) and the combined outcome of HF hospitalization or mortality (hazard ratio, 1.84; confidence interval, 1.09–3.10). Log cystatin C was directly associated with PASP (adjusted β =2.5 [95% confidence interval, 0.8–4.1] per standard deviation change in cystatin C). Mediation analysis showed that BNP and endothelin-1 explained 56% and 40%, respectively, of the indirect effects between cystatin C and PASP.

Conclusions—Among African Americans with chronic kidney disease, PH, which is likely pulmonary venous hypertension, was associated with a higher risk of HF admission and mortality. **(*Circ Heart Fail*. 2017;10:e003940. DOI: 10.1161/CIRCHEARTFAILURE.116.003940.)**

Key Words: African American ■ chronic kidney disease ■ echocardiography ■ heart failure ■ pulmonary hypertension

Chronic kidney disease (CKD) affects >10% of all United States adults and is associated with high morbidity and mortality.[1] The role of pulmonary hypertension (PH) as a potential contributor to adverse events in CKD remains unclear. Furthermore, African Americans develop both CKD and PH independently at disproportionate rates compared with other ethnicities.[2,3] However, data evaluating the relationship between CKD and PH, particularly in African American populations, are limited. The associations between CKD, PH, and adverse cardiovascular events have been explored mostly in patients with end-stage renal disease or postrenal transplant, and limited data are available in earlier stages of CKD.[4,5]

See Clinical Perspective

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From the Department of Medicine, VA Boston Healthcare System, MA (S.S., S.Q.); Division of Aging, Department of Medicine (S.S., S.Q., J.C., J.M.G., L.D.) and Center for Community Health and Health Equity and Department of Medicine (M.J.O., C.R.C.), Brigham and Women's Hospital, Boston, MA; Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL (S.J.S.); Division of Cardiology, Department of Medicine, University of Mississippi Medical Center, Jackson (M.E.H., T.N.S.); Duke Clinical Research Institute, Durham, NC (R.J.M.); Division of Cardiology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA (J.M.R.); and Massachusetts Veterans Epidemiology and Research Information Center (MAVERIC), VA Boston Healthcare System (J.M.G., L.D.).

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Correspondence to Senthil Selvaraj, MD, MA, Division of Aging, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont St, Boston, MA 02120. E-mail sselvaraj@partners.org

These studies in end-stage renal disease and posttransplantation are small, show significant variability in the definition of PH, or were performed after surgical fistula procedures for hemodialysis.[6–8] Understanding the link between earlier stages of renal disease and PH may allow for timely targeted therapy and prevention of disease progression. Furthermore, whether CKD patients with PH are at higher risk of heart failure (HF) hospitalization or mortality merits further attention given limited published data.[4,5]

We sought to assess the association of CKD with estimated pulmonary artery systolic pressure (PASP) and subsequent morbidity and mortality in African Americans. We hypothesized that in patients with baseline CKD, PH would be associated with higher HF hospitalization and mortality rates. We also hypothesized that measures of glomerular filtration rate (GFR) would be inversely associated with PASP.

Methods

Study Population

JHS (Jackson Heart Study) is a prospective, population-based cohort study of 5306 self-identified African American participants recruited from 2000 to 2004 in Jackson, Mississippi. The methodology of the study has been previously reported.[9] In brief, participants answered predefined questionnaires and underwent comprehensive echocardiography during the first examination period from 2000 to 2004. Participants have been followed for 2 subsequent examinations, with the last follow-up occurring in 2012. All JHS participants gave written informed consent, and the JHS was approved by the University of Mississippi Medical Center review board. The current analysis was also approved by the Partners Healthcare institutional review board. For the present analysis, study participants with CKD as defined below and with measurable PASP were included.

Clinical Characteristics

Demographic, clinical, physical examination and laboratory data were collected during the initial JHS visit. At baseline, information on age, sex, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, comorbidities, and cardiovascular medications was collected. Diabetes mellitus was defined by a history of diabetes mellitus, use of diabetes mellitus medications, or a fasting blood glucose ≥126 mg/dL. Presence of systemic hypertension was defined by a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Atrial fibrillation was based on direct clinical examination, while myocardial infarction, chronic lung disease (including asthma or chronic obstructive pulmonary disease), alcohol use, and smoking were obtained by self-report. History of HF was considered present if the participant answered in the affirmative to the following question: "Has a doctor ever said you had HF or congestive HF?".

Laboratory markers include serum creatinine, blood urea nitrogen, BNP (B-type natriuretic peptide), plasma endothelin-1, low-density lipoprotein, cystatin C, 25-hydroxy vitamin D3, spot urine albumin, spot urine creatinine, as well as 24-hour collection of albumin and creatinine.

CKD was defined using the Kidney Disease Improving Global Outcomes criteria, which included either a reduced estimated GFR (eGFR) ≤60 mL/min per 1.73 m^2 or presence of albuminuria (urine albumin to creatinine ratio ≥30 mg/g). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Albuminuria measurements were derived from either 24-hour collection or spot collection; previous analysis in the JHS has shown high correlation between the 2 tests in participants who underwent collection of both tests.[10] Pulmonary function testing includes forced expiratory volume in 1 second and forced vital capacity.

Echocardiography

Echocardiography (including 2-dimensional, M-mode, and Doppler imaging) was acquired on all study participants by certified ultrasonographers and interpreted by cardiologists at the University of Mississippi Medical Center.[11,12] Windows from the parasternal, apical, and subcostal views were recorded. The reading cardiologist was blinded to the clinical characteristics of the study participants. PASP was calculated by adding 5 mm Hg (assumed right atrial pressure) to the tricuspid regurgitant jet peak. Assessment and categorization of left ventricular (LV) ejection fraction, LV hypertrophy, valvular disease, and other measurements can be found elsewhere.[13] Diastolic function was assessed using early diastolic (*E*) and late/atrial diastolic (*A*) transmitral velocities, *E*/*A* ratio, and isovolumic relaxation time.

Outcome Variables

The primary outcome of the study is a composite of HF hospitalization and all-cause mortality. Secondary outcomes include HF hospitalization, as well as all-cause mortality. Follow-up telephone interviews were conducted to obtain incident information on hospitalizations. All HF hospitalizations were adjudicated starting on January 1, 2005, using history, physical examination, laboratory analysis, and medication use data by a trained abstractor. HF hospitalizations defined as either probable or definite were included. Data on the HF outcome are missing in 106 participants who self-reported HF hospitalization or had an uncertain HF hospitalization status before incidence assessment start time point. Hence, analytic sample for HF hospitalization was 302. Death was determined by family member interviews, physician short questionnaires, and coroner records.[14]

Statistical Analysis

Clinical, laboratory, and echocardiographic data are stratified by the presence or absence of PH. Continuous data are presented as mean±standard deviation. Categorical variables are presented as a count and percentage. Skewed data are presented as median and 25th–75th percentile and log-transformed for regression analyses. We compared groups using *t* tests for continuous variables (or nonparametric equivalent) and Chi-squared (or Fisher) tests for categorical variables.

We investigated the association of PH with HF hospitalization and mortality using cumulative incidence curves and Cox proportional hazard models. We estimated cumulative incidence curves as (1- the Kaplan–Meier estimator). For Cox regression, we constructed sequential models: after the crude model, model 1 adjusted for age, sex, diabetes mellitus, eGFR, and LV ejection fraction. Model 2 included all variables used in model 1 with addition of BNP. Candidate covariates were chosen based on clinical relevance (prespecified based on face validity) or association with HF or mortality (either in prior studies or in our study).[15,16] We used the partial likelihood ratio test within nested models to support that we did not miss important confounding variables for covariate selection. Person-time of follow-up was computed from baseline to the first occurrence of the primary outcome, loss to follow-up, end of study period, or death. In sensitivity analysis, we excluded patients with prevalent HF or use of hemodialysis. Because incident end-stage renal disease is not documented in a consistent fashion in the JHS, there was no explicit exclusion of these patients in the present analysis. We explored interactions by sex and higher eGFR value (defined as >30 mL/min per 1.73 m^2). A P value <0.05 was significant for further exploration.

For cross-sectional analysis, we performed multivariable-adjusted regression models to assess whether cystatin C was associated with PASP. We used cystatin C as the surrogate marker of GFR given that it is more strongly correlated to true GFR than creatinine and possesses superior test characteristics.[17] Using a model that established risk factors for PH in the JHS, we adjusted for age, sex, body mass index, hypertension, diabetes mellitus, coronary heart disease, severe mitral/aortic valvular heart disease, chronic lung disease, spirometry profile (normal, obstructive, and restrictive), and an LV ejection fraction <50% (pulse pressure was initially omitted because it was later

Table 1. Characteristics of the Chronic Kidney Disease Cohort According to Presence of Pulmonary Hypertension

Characteristic	All Participants (N=408)	Pulmonary Hypertension (N=88)	No Pulmonary Hypertension (N=320)	*P* Value
Age, y	63±13	69±10	61±13	<0.001
Female, n (%)	284 (70)	69 (78)	215 (67)	0.043
Comorbidities, n (%)				
Hypertension	317 (78)	77 (87)	240 (75)	0.013
Diabetes mellitus	153 (39)	34 (41)	119 (39)	0.75
Coronary heart disease	75 (18)	19 (22)	56 (18)	0.38
Atrial fibrillation	7 (2)	4 (5)	3 (1)	0.042
Chronic lung disease	17 (6)	3 (5)	14 (6)	0.99
Heart failure	35 (9)	8 (9)	27 (8)	0.85
Dialysis	14 (3)	4 (5)	10 (3)	0.51
Alcohol history, n (%)				0.003
Never drinker	133 (33)	42 (48)	91 (28)	
Former drinker	142 (34)	24 (27)	118 (37)	
Current drinker	133 (33)	22 (25)	111 (35)	
Smoking history, n (%)				0.55
Never smoker	275 (68)	63 (72)	212 (67)	
Former smoker	86 (21)	15 (17)	71 (22)	
Current smoker	44 (11)	10 (11)	34 (11)	
Medications, n (%)				
Antihypertensive medication	210 (51)	50 (57)	160 (50)	0.26
ACE inhibitor	84 (21)	21 (24)	63 (20)	0.39
Angiotensin receptor blocker	39 (10)	8 (9)	31 (10)	0.87
β-Blocker	81 (20)	19 (22)	62 (19)	0.64
Diuretic	202 (50)	47 (53)	155 (48)	0.47
Physical examination				
Systolic blood pressure, mm Hg	132±19	137±21	131±19	0.006
Diastolic blood pressure, mm Hg	75±10	72±9	75±10	0.005
Heart rate, beats per minute	68±11	67±12	68±11	0.59
Body mass index, kg/m^2	31.8±7.2	32.8±7.2	31.5±6.7	0.22
Laboratory data				
eGFR, mL/min per 1.73 m^2	68±32	60±30	70±32	0.012
eGFR classification, n (%)				0.23
eGFR>60 mL/min per 1.73 m^2	180 (44)	32 (36)	148 (46)	
45<eGFR≤60 mL/min per 1.73 m^2	120 (30)	27 (31)	93 (29)	
30<eGFR≤45 mL/min per 1.73 m^2	45 (11)	12 (14)	33 (10)	
15<eGFR≤ mL/min per 1.73 m^2	21 (5)	8 (9)	13 (4)	
eGFR≤15 mL/min per 1.73 m^2	42 (10)	9 (10)	33 (10)	
Urine albumin–creatinine ratio, mg/g*	48 (18–108)	61 (17–218)	45 (18–94)	0.14
Cystatin C, mg/L*	0.93 (0.74–1.21)	1.04 (0.83–1.41)	0.90 (0.72–1.62)	0.003
25-hydroxy vitamin D, ng/mL	13±6	13±5	13±6	0.49
Low-density lipoprotein, mg/dL	128±41	129±44	128±40	0.81

(*Continued*)

Table 1. Continued

Characteristic	All Participants (N=408)	Pulmonary Hypertension (N=88)	No Pulmonary Hypertension (N=320)	*P* Value
Plasma endothelin-1, pg/mL*	1.4 (1.1–1.8)	1.7 (1.1–2.3)	1.4 (1.1–1.8)	0.007
B-type natriuretic peptide, pg/mL*	16 (6–42)	39 (11–83)	13 (5–28)	<0.001
Spirometry				
FEV1/FVC	0.79±0.09	0.78±0.08	0.80±0.10	0.07
Echocardiographic parameter				
Pulmonary artery systolic pressure, mm Hg	30±8	42±7	27±5	<0.001
Tricuspid regurgitation				<0.001
None	8 (2)	0 (0)	8 (3)	
Mild	315 (77)	51 (59)	264 (83)	
Moderate	63 (15)	24 (28)	39 (12)	
Severe	21 (5)	12 (14)	9 (3)	
LV end-diastolic diameter, mm	50±5	51±6	50±5	0.20
LV end-systolic diameter, mm	31±6	30±6	31±6	0.78
LV mass index, g/m^2	41.9±13.1	48.6±16.4	40.0±11.5	0.001
LV hypertrophy, n (%)	49 (20)	22 (41)	27 (14)	<0.001
Left atrial diameter, cm	37±5	39±6	36±5	0.002
LV ejection fraction, %	61±9	61±12	62±8	0.94
E/A ratio	1.00±0.38	1.07±0.50	0.99±0.34	0.14
Isovolumic relaxation time, ms	98±24	94±24	99±24	0.07

ACE indicates angiotensin-converting enzyme inhibitor; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 s; FVC; forced vital capacity; and LV, left ventricular.

*Data presented as median (25th–75th percentile).

entered as a mediating factor).[15] Beta-coefficients are reported per standard deviation increase in the parameter.

To examine the extent to which the relationship between PASP and renal function is explained by potential intermediate factors, we estimated the β-coefficient after addition of 4 covariates. Based on putative mechanisms, potential mediators included pulse pressure (marker of arterial stiffness), 25-hydroxy vitamin D level (associated with vascular hyperproliferation), BNP (marker of volume overload), and plasma endothelin-1 level (marker of endothelial dysfunction).[4,18,19] We calculated the proportion explained by the intermediate factors as follows: $100\% \times (\beta\text{-coefficient}_{model} - \beta\text{-coefficient}_{model+intermediate\ factor}) / (\beta\text{-coefficient}_{model})$.[20]

We performed multiple imputation analyses for missing model covariates using the Markov chain Monte Carlo method in PROC MI and PROC MIANALYZE in SAS. We imputed all missing data using 10 sets of values using nonmissing predictors and ultimately pooled using Rubin's combination rules. A 2-sided *P* value <0.05 was considered statistically significant. Statistical analyses were performed using SAS v.9.4.

Results

Characteristics of Study Participants

Out of the 728 participants with CKD, 408 had available PASP data and were included in the study population (Table 1). Nearly a quarter of the study participants had PH at baseline (88/408, 22%). The mean age was 63±13 years and 70% were female, 78% had hypertension, and 38% had diabetes mellitus. Only 9% had prevalent HF, while 3% were dialysis-dependent. Mean systolic blood pressure was 132±19/mm Hg, and the mean body mass index was 31.8±7.2 kg/m^2. Median BNP was 16 (25th–75th percentile, 6–42) pg/mL, and most participants

Table 2. HR (95% CI) for Heart Failure Hospitalization or Death by Pulmonary Hypertension Status in the Jackson Heart Study

Outcome	Events, N (%)	Crude		Model 1*		Model 2†	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Heart failure hospitalization or death‡							
No pulmonary hypertension	52 (21)	1.0 (ref)	…	1.0 (ref)	…	1.0 (ref)	…
Pulmonary hypertension present	28 (47)	2.19 (1.36–3.53)	0.001	2.18 (1.20–3.70)	0.003	1.84 (1.09–3.10)	0.02

CI indicates confidence interval; and HR, hazard ratio.

*Model 1 adjusted for age, sex, diabetes mellitus, estimated glomerular filtration rate, and ejection fraction.

†Model 2 adjusted for B-type natriuretic peptide in addition to covariates in model 1.

‡Because of missing data on heart failure hospitalization (N=106), the total N for this analysis is 302 (242 in the no PH group and 60 in the PH group). Please see Methods section for more details.

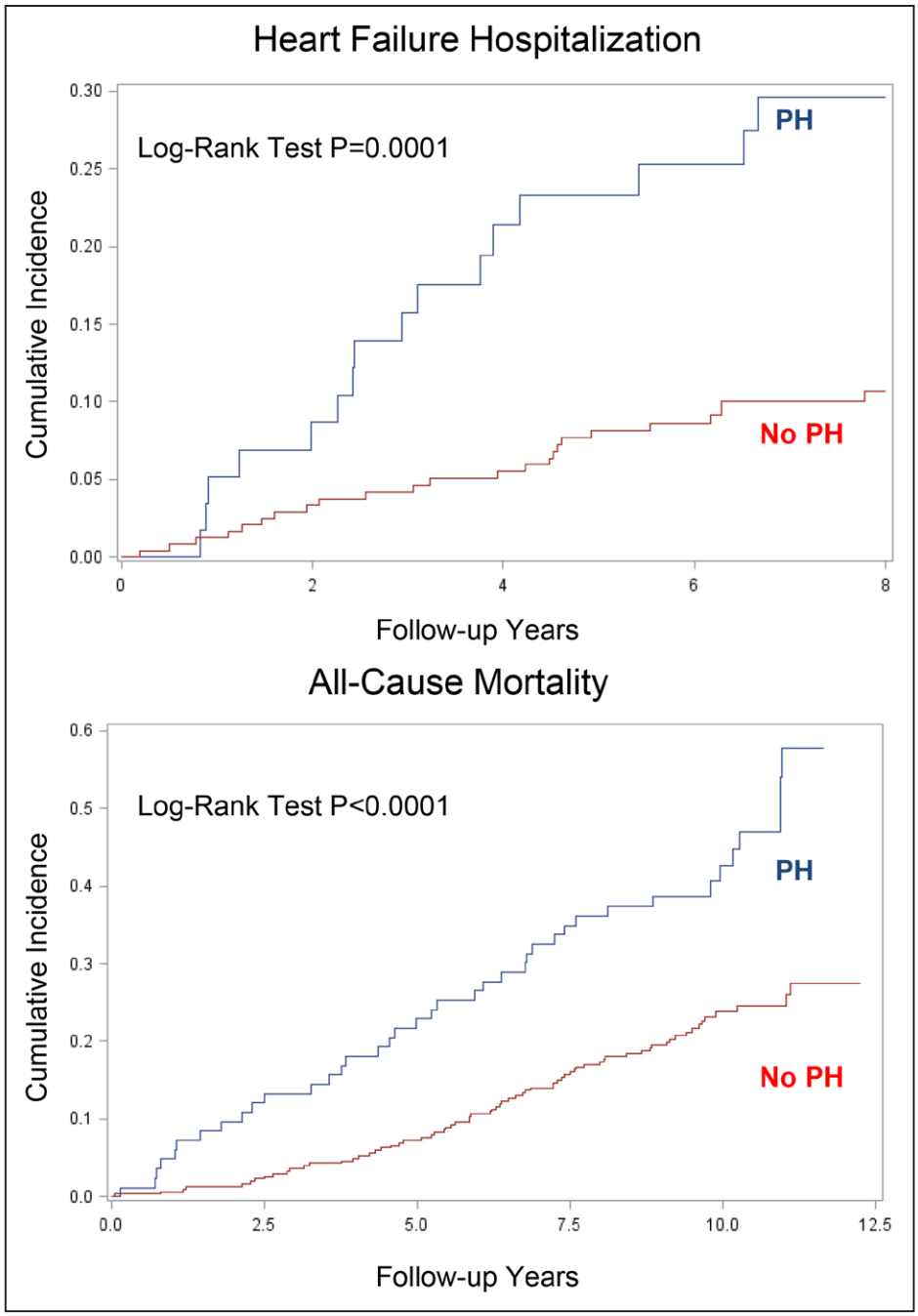

Figure. Cumulative incidence of heart failure hospitalization and all-cause mortality stratified by the presence of pulmonary hypertension (PH) in patients with chronic kidney disease. PH is associated with greater risk for heart failure hospitalization and all-cause mortality in participants with preexisting chronic kidney disease. *P* values are shown for the log-rank test.

had an eGFR >30 mL/min per 1.73 m^2 (85%). Individuals with PH were older, more often female, more often had hypertension and atrial fibrillation, had higher systolic blood pressure and lower diastolic blood pressure, and had lower eGFR, higher urine albumin to creatinine ratio, and higher BNP.

The mean pulmonary artery pressure was 30±8 (minimum to maximum, 11–66) mm Hg. The average LV dimensions fell within normal limits (LV end-systolic diameter, 31±6 mm; LV end-diastolic diameter, 50±5 mm; LV mass index, 41.9±13.1 kg/m^2), though one fifth had evidence of LV hypertrophy. The ejection fraction was 61±9%. Individuals with PH had more significant tricuspid regurgitation, higher LV mass index, and larger left atrial diameter, but no difference was observed in LV dimensions, ejection fraction, *E*/*A* ratio, and isovolumic relaxation time. Few participants had any evidence of right atrial or right ventricular enlargement (4 and 1 participants, respectively).

Association of PH With HF Hospitalization and Mortality

The mean follow-up was 6.71±2.18 years for HF hospitalization and 8.35±3.26 years for death. Twenty-seven percent

Table 3. HR (95% CI) for Heart Failure Hospitalization and Death by Pulmonary Hypertension Status in the Jackson Heart Study

Outcome	Events, N (%)	Crude		Model 1*		Model 2†	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Heart failure hospitalization‡							
No pulmonary hypertension	24 (10)	1.0 (ref)	…	1.0 (ref)	…	1.0 (ref)	…
Pulmonary hypertension present	16 (27)	3.19 (1.70–6.02)	<0.001	2.90 (1.45–5.81)	0.003	2.37 (1.15–4.86)	0.0189
Death							
No pulmonary hypertension	70 (22)	1.0 (ref)	…	1.0 (ref)	…	1.0 (ref)	…
Pulmonary hypertension present	39 (44)	2.39 (1.62–3.54)	<0.001	1.83 (1.21–2.76)	0.004	1.37 (0.89–2.13)	0.16

CI indicates confidence interval; and HR, hazard ratio.

*Model 1 adjusted for age, sex, diabetes mellitus, estimated glomerular filtration rate, and ejection fraction.

†Model 2 adjusted for B-type natriuretic peptide in addition to covariates in model 1.

‡Because of missing data on heart failure hospitalization (N=106), the total N for this analysis is 302 (242 in the no PH group and 60 in the PH group). Please see Methods section for more details.

and 10% of the participants with and without PH were hospitalized for HF, while 44% and 22% died during follow-up, respectively. After adjusting for covariates in model 1, PH was still associated with the composite outcome (hazard ratio, 2.18; 95% confidence interval, 1.20–3.70; Table 2). Additional adjustment for BNP in model 2 did not eliminate the association. Exclusion of participants with prevalent HF or hemodialysis yielded similar results. For secondary outcomes, PH was associated with higher cumulative incidence for HF hospitalization and mortality (*P*<0.001; Figure). Table 3 shows that PH was associated with higher risk for HF hospitalization (hazard ratio, 2.90; 95% confidence interval, 1.45–5.81) and mortality (hazard ratio, 1.83; 95% confidence interval, 1.21–2.76) after adjustment for variables in model 1. Additional adjustment for BNP in model 2 did not alter the statistical significance for HF hospitalization (*P*=0.019), though it did for all-cause mortality (*P*=0.16). Table I in the Data Supplement shows no interaction by sex or eGFR (*P*>0.05 for all outcomes).

Association of Cystatin C With PASP on Mediation Analysis

After adjusting for age, sex, body mass index, hypertension, diabetes mellitus, coronary heart disease, severe valvular heart disease, chronic lung disease, spirometry profile, and reduced ejection fraction, log cystatin C was associated with PASP (β-coefficient per standard deviation change, 2.5; 95% confidence interval, 0.8–4.1), as shown in Table 4. Mediation analysis was performed to evaluate the contribution of several potential intermediate factors. Log BNP and plasma endothelin-1 levels explained 56% and 40%, respectively, of the indirect effects of the relationship between cystatin C and higher PASP; together, they explained 88% of the indirect effects.

Discussion

In an analysis of 408 African American participants from the JHS with long-term follow-up, we found that PH was common in an unselected cohort of CKD patients (22%) and was associated with a significantly higher risk for HF hospitalization and all-cause mortality. These associations persisted after adjusting for several covariates, including BNP (with the exception of all-cause mortality). In addition, cystatin C, a surrogate marker of GFR, was significantly associated with PASP on multivariable analysis. These data show that echocardiographic PH identifies a high-risk cohort of CKD patients beyond that predicted by BNP and may offer insight into the relationship between CKD and adverse cardiovascular events.

Several studies[7,8,18] have shown a relationship between CKD and PH in late-stage renal disease, but few studies have examined this relationship in earlier-stage CKD,[4] which is much more common. Only a small percentage of patients in our study were dialysis-dependent, and the vast majority of participants had an eGFR>45 mL/min per 1.73 m^2. Thus, the association between PH and adverse events found in this

Table 4. Association of Cystatin C With Pulmonary Artery Systolic Pressure on Mediation Analysis in the Jackson Heart Study

Dependent Variable	Multivariable Adjustment*		Proportion of PASP Explained by Mediator
	β-Coefficient (95% CI)	*P* Value	
Log cystatin C, mg/L	2.5 (0.8–4.1)	0.0029	…
Log cystatin C+log BNP, pg/dL	1.1 (–0.6 to 2.8)	0.22	56%
Log cystatin C+pulse pressure, mm Hg	2.3 (0.7–4.0)	0.0047	8%
Log cystatin C+25-hydroxy vitamin D level, ng/mL	2.5 (0.8–4.1)	0.0035	0%
Log cystatin C+log endothelin-1 level, pg/mL	1.5 (–0.3 to 3.2)	0.10	40%
Log cystatin C+log BNP+log endothelin-1 level	0.3 (–1.5 to 2.1)	0.74	88%
Log cystatin C+all intermediary factors	0.2 (–1.53 to 1.97)	0.81	92%

BNP indicates B-type natriuretic peptide; CI, confidence interval; and PASP, pulmonary artery systolic pressure.

*All models adjusted for age, sex, body mass index, hypertension, diabetes mellitus, chronic lung disease, spirometry profile, coronary heart disease, severe mitral/aortic valvular heart disease, and reduced ejection fraction.

cohort demonstrates the adverse association with PH, despite largely mild renal insufficiency. Notably, pulmonary pressures in our PH participants were only mildly elevated in most patients with PH (average PASP, 42 mm Hg), which demonstrates that even such pressures are valuable in identifying a high-risk phenotype. In 2 recent analyses of CKD patients, echocardiographic PH was present in a similar percentage of patients and also predicted adverse events, including HF.[5,21] These studies, however, were limited by a potential referral bias,[5] failed to adjust for BNP to show the additional benefits of PASP,[5,21] and lacked additional laboratory data to understand the relationship between renal function and PASP.[5]

Elevated PASP in CKD patients may indicate a preclinical HF with preserved ejection fraction state. Interestingly, the median BNP in our cohort was 16 pg/mL (25th–75th percentile, 6–42), while those with echocardiographic PH had a median BNP of 39 pg/mL (25th–75th percentile, 11–83). Thus, the majority of patients in our study had a BNP<40 pg/mL even with echocardiographic PH, and there was significant overlap in BNP values. This underscores 2 important points. First, the range of normal BNP is truly narrow. For instance, while some practitioners consider values <100 pg/mL to rule out HF, this cutoff only applies to acutely decompensated patients.[22] In a study of elderly patients with stable HF, the average BNP level for those with diastolic HF was 56 pg/mL, while control patients had an average BNP of 3 pg/mL.[23] Indeed, in another study of stable HF with preserved ejection fraction patients, BNP levels were <100 pg/mL in nearly 30% of patients.[24] Thus, BNP levels even >40 pg/mL (or likely less) should at least raise concern for the progression to clinical signs and symptoms of HF. Second, because the range of BNP values in our study is narrow with significant overlap between those with and without echocardiographic PH, we have demonstrated that PASP is a useful adjunct to risk stratification for HF hospitalization and mortality in CKD patients.

The pathophysiological correlates of CKD with PH are numerous and complex. CKD is associated with volume overload, endothelial dysfunction, vascular calcification, and arterial stiffening.[8,18] These processes are most apparent in late-stage renal disease. We attempted to understand the contribution of these components on mediation analysis, which suggested a role for both BNP (a measure of volume overload) and endothelin-1 (a measure of endothelial dysfunction) on elevated pulmonary pressures. Endothelin-1 is a potent vasopressor and is disproportionately elevated in African Americans.[25] Endothelin levels are associated with pulmonary vascular remodeling and are increased in both systemic and pulmonary circulations in PH.[26]

Strengths of the study include detailed echocardiographic analysis, long duration of follow-up, and adjudication of events. Additionally, our results show the utility of measuring PASP beyond BNP. There are some limitations. PH was defined by echocardiography, though the gold standard is right heart catheterization.[27] Right heart catheterization is also useful in distinguishing pulmonary arterial hypertension and pulmonary venous hypertension. However, echocardiography is noninvasive, less costly, and more widely available. Thus, it is more conducive to larger epidemiological studies of PH. Tissue Doppler measurements as well as left atrial volume index were not available in JHS, which would be helpful to better evaluate LV diastolic function in this population as a cause of the elevated pulmonary pressures. However, given the larger left atrial dimensions and LV mass index (without much right ventricular or right atrial remodeling), it is likely that the majority of patients had pulmonary venous hypertension. Another limitation is the lack of serial echocardiograms to assess changes in cardiac structure and function over time in relation to renal disease. Additionally, ejection fraction was not collected at the time of HF hospitalization. Finally, an assumed right atrial pressure was used for all patients given lack of inferior vena cava measurements.

In summary, we found that PH is associated with elevated risk for HF hospitalization and all-cause mortality in African Americans with CKD. The relationships, with the exception of all-cause mortality, remained significant after adjustment for BNP. In addition, cystatin C was directly associated with higher PASP. Based on the clinical and echocardiographic phenotype of these participants, PH is likely because of increased venous pressures. Whether screening echocardiography may be useful in patients with CKD to identify high-risk groups in need of further testing and therapies and to reduce morbidity and mortality should be further evaluated.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Chronic kidney disease (CKD) is common among adults in the United States and is associated with high morbidity and mortality. Whether pulmonary hypertension (PH) may contribute to adverse events in CKD remains unclear. Data evaluating the relationship between CKD and PH, particularly in African American populations, are limited. Understanding the link between earlier stages of renal disease and PH may allow for timely targeted therapy and prevention of disease progression. We studied 408 participants with CKD from the Jackson Heart Study, a prospective, population-based cohort study of African American participants recruited from 2000 to 2004 in Jackson, Mississippi. We found that PH was common (22%) and was associated with a significantly higher risk for heart failure hospitalization and all-cause mortality. These associations persisted after adjusting for a number of covariates, including B-type natriuretic peptide, with the exception of all-cause mortality. In mediation analysis, we showed that cystatin C, a marker of renal function, was significantly associated with pulmonary artery systolic pressure. Upon further analysis, B-type natriuretic peptide and endothelin-1 levels explained a significant proportion of this relationship, indicating that volume overload and endothelial dysfunction are likely important in the pathophysiology. These data show that echocardiographic PH identifies a high-risk cohort of CKD patients beyond that predicted by B-type natriuretic peptide and may offer insight into the relationship between CKD and adverse cardiovascular events.

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Heart Failure

Pulmonary Hypertension Is Associated With a Higher Risk of Heart Failure Hospitalization and Mortality in Patients With Chronic Kidney Disease: The Jackson Heart Study

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Supplemental Material

Table S1. Interaction Analysis P-values

Outcome	Interaction term	P-value for the interaction term
Heart failure hospitalization	Pulmonary hypertension × sex	0.54
	Pulmonary hypertension × later stage renal disease*	0.18
Death	Pulmonary hypertension × sex	0.72
	Pulmonary hypertension × later stage renal disease*	0.25
Heart failure hospitalization or death	Pulmonary hypertension × sex	0.29
	Pulmonary hypertension × later stage renal disease*	0.13

In addition to the specified interaction term, the models above were adjusted for age, sex, diabetes mellitus, estimated glomerular filtration rate, ejection fraction, and b-type natriuretic peptide.

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Chronic kidney disease (CKD) is common among adults in the United States and is associated with high morbidity and mortality. Whether pulmonary hypertension (PH) may contribute to adverse events in CKD remains unclear. Data evaluating the relationship between CKD and PH, particularly in African American populations, are limited. Understanding the link between earlier stages of renal disease and PH may allow for timely targeted therapy and prevention of disease progression. We studied 408 participants with CKD from the Jackson Heart Study, a prospective, population-based cohort study of African American participants recruited from 2000-2004 in Jackson, MS. We found that PH was common (22%) and was associated with a significantly higher risk for HF hospitalization and all-cause mortality. These associations persisted after adjusting for a number of covariates, including BNP (with the exception of all-cause mortality). In mediation analysis, we showed that cystatin C, a marker of renal function, was significantly associated with pulmonary artery systolic pressure. Upon further analysis, BNP and endothelin-1 levels explained a significant proportion of this relationship, indicating that volume overload and endothelial dysfunction are likely important in the pathophysiology. These data show that echocardiographic PH identifies a high-risk cohort of CKD patients beyond that predicted by BNP, and may offer insight into the relationship between CKD and adverse cardiovascular events.