



Kidney Function and Aortic Stiffness, Pulsatility, and Endothelial Function in African Americans: The Jackson Heart Study

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Rationale & Objective: The relation of vascular stiffness, endothelial function, and kidney function is incompletely elucidated in African Americans. Our hypothesis was that increased vascular stiffness and endothelial dysfunction are associated with low estimated glomerular filtration rate (eGFR) and albuminuria in African Americans.

Study Design: Cross-sectional cohort analysis of data from the Jackson Heart Study.

Settings & Patients: 2,244 Jackson Heart Study participants (2012-2017 after Exam 3) who had undergone noninvasive hemodynamic assessment using arterial tonometry.

Predictors: Baseline carotid-femoral pulse wave velocity, pulsatile hemodynamics forward wave amplitude, and hyperemic brachial artery flow were measured. Reduced eGFR was defined as eGFR between 15 and 60 mL/min/1.73 m².

Outcomes: Prevalent albuminuria, urinary albumin-creatinine ratio.

Analytical Approach: 2-sample *t* test for continuous variables and χ^2 test for categorical variables in

addition to logistic and linear regression models to assess the risk for chronic kidney disease with each proposed hemodynamic variable.

Results: Among 2,244 participants, mean age was 66 ± 11 years and 64% were women. Reduced eGFR was present in 233 (10.4%), and elevated urinary albumin-creatinine ratio, in 232 (10.4%). In multivariable-adjusted analyses, higher carotid-femoral pulse wave velocity was associated with the presence of reduced eGFR (OR, 1.37 [95% CI, 1.08-1.75] per SD; *P* = 0.01) and with prevalent albuminuria (OR, 1.66 [95% CI, 1.32-2.11]; *P* < 0.001). Higher forward wave amplitude was significantly associated with prevalent albuminuria (OR, 1.37 [95% CI, 1.14-1.65]; *P* = 0.001).

Limitations: Cross-sectional analyses cannot inform causality.

Conclusions: Higher arterial stiffness and pulsatility are associated with higher odds of reduced eGFR in African Americans. Future studies should focus on whether improving arterial stiffness contributes to kidney protection in African Americans.

Visual Abstract included

Complete author and article information provided before references.

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Chronic kidney disease (CKD) is defined by a long-term reduction in glomerular filtration rate (GFR) or the presence of kidney damage and is an important cause of death in the United States.¹ Latest data estimates in the United States put the number of citizens with CKD at 37 million (15% of the adult population).^{2,3} The prevalence of CKD, including CKD stage 3a, defined by an estimated GFR (eGFR) of 45 to 60 mL/min per 1.73 m² and which accounts for most individuals with CKD in United States, is lower in African Americans.^{2,4,5} However, African Americans are more likely to progress to kidney failure when compared with non-Hispanic White counterparts.^{6,7} Recent publications from the Jackson Heart Study (JHS) suggest higher risk for eGFR deterioration in African American participants with masked hypertension⁸ or with high uric acid levels,^{9,10} as well as among African American women with metabolic syndrome.¹¹

CKD progression can be identified through both worsening eGFR and the presence and severity of urinary albumin excretion. Urinary albumin levels are associated with risk for eGFR decline across all stages of CKD, and

albuminuria may not only be a manifestation of CKD but may also contribute to GFR loss.¹² In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study that evaluated individuals at high risk for stroke, among participants with baseline eGFRs ≤ 60 mL/min per 1.73 m², those with prevalent albuminuria had the fastest progression to kidney failure and the highest mortality, regardless of racial group.¹³ Several population-based studies show that African Americans with CKD are more likely to die than non-Hispanic Whites with CKD.^{14,15} These trends reverse among individuals receiving maintenance dialysis.¹⁶

Increased aortic stiffness as assessed by carotid-femoral pulse wave velocity (PWV) is often present in patients with CKD and is considered a strong risk factor for cardiovascular mortality and morbidity.¹⁷ Increased aortic stiffness leads to the transmission of pulsatile power to the distal microcirculation, resulting in increased risk for damage to the microcirculation in end-organs.¹⁸⁻²⁰ Most organs sustain microvascular damage secondary to changes in vascular impedance; although such changes are systemic

PLAIN-LANGUAGE SUMMARY

In an entirely African American cohort of Jackson Heart Study participants, we examined the association between endothelial function as assessed by vascular function parameters and kidney function as assessed by estimated glomerular filtration rate, albuminuria, and urinary albumin-creatinine ratio (UACR). We found that in this cohort of African Americans, increased vascular stiffness and loss of pulsatility of the vascular bed is associated with kidney disease, which is exemplified by the presence of albuminuria and the UACR. This study helps define the vascular function parameters that affect kidney function by identifying vascular parameters that can lead to worsening kidney function. This knowledge will help clinicians identify and intervene on modifiable risk factors that affect vascular function in individuals at risk for or with early-stage kidney disease.

in nature, organs with low impedance sustain early microvascular damage compared with ones with high impedance microcirculation.²¹ There have been very few studies that have evaluated end-organ damage and adverse effects of transmission of excess pulsatile energy into the kidney vasculature in African Americans.

In this study, we hypothesize that increased aortic stiffness and aortic pulsatility are significantly associated with kidney disease in African Americans. We further hypothesize that the association of aortic hemodynamics is stronger among participants with prevalent albuminuria than with reduced eGFRs, and that older age affects the relationship between aortic dynamics and CKD. Because increased vascular stiffness and albuminuria are correlated and share common risk factors, we hypothesize that taken together, increased vascular stiffness and albuminuria represent a continuum in the African American population; that is, individuals with less severe vascular stiffness may express only one of these markers, whereas individuals with more severe stiffness may express both. Systematic screening of this continuous spectrum of expression of these markers is lacking in adults despite its value in predicting vascular mortality and morbidity.²²

METHODS

The JHS is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I), and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I, and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities.

The design and details of the JHS have been described.^{23,24} Those included in the current study are participants who attended Exam 3 of the JHS between 2008 and 2013 and who also had vascular function measures performed as part of an ancillary study between 2012 and 2017 (N = 2884). Participants were excluded for the following indications in hierarchical order: missing risk factors or covariates (n = 359), missing albuminuria and eGFR data (n = 151), missing brachial flow data (n = 118), and dialysis ever or eGFR < 15 mL/min per 1.73 m² (n = 12). Written informed consent was obtained from all study participants, and the JHS research protocol was approved by the Institutional Review Board of the University of Mississippi Medical Center.

Measurement of Kidney Function

Details on the measurements for CKD and their relation to interview and medical data in the JHS have been published previously.²⁵ Kidney function was determined based on eGFR, calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation.²⁶

In the current investigation, CKD stage 3-4 was defined as eGFR < 60 to >15 mL/min per 1.73 m² or by the presence of albuminuria (urinary albumin-creatinine ratio [UACR] > 25 mg/g in men and >35 mg/g in women on spot or 24-hour urine collection).²⁷⁻²⁹ We also assessed the association of aortic stiffness with the KDIGO (Kidney Disease: Improving Global Outcomes)-defined eGFR stages, adjusting for the same covariates and confounders as in primary analyses.³⁰

Image Acquisition and Flow Velocity Analyses

Brachial artery flow analyses were performed as described previously.³¹ Flows were measured at baseline and following 5 minutes of ischemia produced by inflating a cuff, which was positioned on the forearm just distal to the antecubital fold, to 200 or ≈50 mm Hg above systolic pressure.³² Doppler flows were assessed with a Siemens Acuson S2000 ultrasound system mounted with 4Vc and 9L4 transducers using a carrier frequency of 4.0 MHz and an insonation angle of ≈60°. Ultrasound data were digitized during the primary acquisition and transferred to the core laboratory (Cardiovascular Engineering, Inc, Norwood, MA) for analyses that were performed masked to clinical data. Flows were analyzed from the digitized Doppler audio data by using a semi-automated signal-averaging technique as described previously.³³ During the examination for brachial flows, after cuff deflation, sonographers monitored and recorded flow (for up to 15 seconds after cuff release) until flow peaked. During secondary analysis, timing of peak flow was visually confirmed from a raw spectral analysis of individual beats; only 3 to 5 beats—representing the peak flow response—were marked for inclusion in the signal-averaged spectrum. Flow spectra were signal-averaged with the electrocardiogram as a fiducial point and corrected for actual insonation angle.³⁴

Measures of Aortic Stiffness and Pulsatility

Aortic stiffness and pulsatility were assessed as described previously.³¹ We measured central pulse pressure, forward wave amplitude (FWA), characteristic impedance, and carotid-femoral PWV to assess distinct but related measures of aortic stiffness. Central pulse pressure, FWA, and characteristic impedance were examined as measures of pressure pulsatility and are related to aortic wall stiffness and lumen area. Carotid-femoral PWV is related directly to aortic wall stiffness. In addition, using high-resolution ultrasound and Doppler flow, we assessed brachial flow velocity at baseline and during reactive hyperemia after 5 minutes of forearm cuff occlusion. Baseline brachial flow velocity depends on forearm microvascular density, tone, and structure, and hyperemic flow velocity reflects the near-maximal microvessel dilation of the forearm produced by ischemia-induced vasodilator generation, including nitric oxide.

Statistical Analyses

We calculated descriptive statistics to summarize characteristics of the study sample. The mean (standard deviation) or median (25th and 75th percentiles) were computed for continuous variables, and proportions, for categorical variables. We then compared characteristics of eligible participants versus those excluded for failing to meet the inclusion criteria. We used 2-sample t test for continuous variables and χ^2 test for categorical variables. Statistics were partitioned across 8 not mutually exclusive subpopulations, first by the 2 analysis types (aortic stiffness and brachial microvascular function measures), then by the 4 discrete disease states (normal kidney function, CKD by eGFR, albuminuria present, and albuminuria absent).

Logistic and linear regression models were used to assess the risk for CKD or albuminuria associated with each proposed hemodynamic variable and to assess the association of hemodynamic variables with UACR, respectively. We implemented both age- and sex- and multivariable-adjusted models for each analysis. Our independent variables of interest were in 2 broad domains: aortic stiffness (forward pressure wave, carotid-femoral PWV, mean arterial pressure [MAP], characteristic impedance, and central pulse pressure) and brachial microvascular function (baseline and hyperemic flow). Besides age and sex, the other clinical comorbid conditions and interventions at the time of the vascular function laboratory visit and therefore accounted for multivariable analyses included body mass index, triglyceride levels, heart rate, MAP, fasting plasma glucose level, and fasting total and high-density lipoprotein cholesterol levels, as well as diabetes mellitus status and the use of antihypertensive or antihyperlipidemic medications.

We also examined effect modification of sex and diabetes status in each fully adjusted model by including an additional interaction term in the model. We then conducted stratified analysis if the interaction is significantly

associated with the dependent variable. Slopes to assess and identify the extent of each effect evaluated these stratified analyses numerically and visually.

In secondary analyses, we tested for the presence of a direct association between each vascular measure and CKD stages based on eGFR, dividing CKD stage 3 into 3a and 3b. This sensitivity analysis tested proposed incremental changes masked in the reduction of data caused by CKD by eGFR categorization. We then used multinomial logistic regression to assess the association with vascular measures and endothelial function with eGFR stages.

Carotid-femoral PWV was negatively inverse transformed ($-1,000/\text{carotid-femoral fPWV}$) before analysis, whereas UACR and all continuous non-normal covariates were log transformed and then standardized (mean = 0 and variance = 1). All analyses were performed using SAS (SAS Corporation), version 9.4, and 2-sided $P < 0.05$ and <0.10 were used to denote statistical significance test of hypotheses and presence of interaction, respectively.

RESULTS

After exclusions, the final maximum study sample consisted of 2,244 participants (mean \pm SD age, 66 ± 11 years; 64% women), and 10.4% had CKD by eGFR ($n = 233$) and 10.4% ($n = 232$) had prevalent albuminuria (see [Table S1](#) for characteristics of included vs excluded participants). The lowest sample size of 1,796 (average age, 65 ± 11 years; 64% women; and 10.6% with CKD and albuminuria) was observed in analysis involving carotid-femoral PWV. Clinical and vascular characteristics of participants are presented in [Tables 1](#) and [2](#), respectively. Participants with CKD stage 3-4 tended to be slightly older, had a higher prevalence of diabetes and higher triglyceride levels, and were more likely to use antihypertensive and antihyperlipidemic medications. All other clinical characteristics between included and excluded groups were similar. [Table 2](#) shows vascular function characteristics listed by the presence or absence of CKD stage 3-4 and the presence or absence of albuminuria. Among 2,244 participants, 233 had CKD stage 3-4, whereas 232 participants had albuminuria.

[Table 3](#) shows age- and sex-adjusted associations of vascular stiffness and endothelial function measures with CKD stage 3-4, albuminuria status, and UACR. Higher negative inverse carotid-femoral PWV and FWA were significantly associated with the presence of CKD stage 3-4. In the same age- and sex-adjusted model, all variables of vascular stiffness and pulsatility measures were significantly associated with albuminuria and UACR ($P < 0.001$). Hyperemic brachial flow as a measure of microvascular structure and function was significantly related to UACR. However, baseline brachial flow was not associated with CKD stage 3-4, albuminuria, or UACR.

[Table 4](#) shows the multivariable-adjusted associations of vascular function measures with the presence of CKD stage 3-4, presence of albuminuria, and UACR. Higher

Table 1. Clinical Characteristics of Study Participants

Characteristics	eGFR		Albuminuria	
	≥60 mL/min/1.73m ² (n = 2,011)	15-60 mL/min/1.73m ² (n = 233)	Absent (n = 2,012)	Present (n = 232)
Age at tonometry visit, y	65 ± 10	74 ± 9	66 ± 11	69 ± 11
Female sex	1,287 (64%)	149 (64%)	1,327 (66%)	123 (53%)
Height, cm	168 ± 9	167 ± 8	168 ± 9	170 ± 9
Weight, kg	89 ± 19	87 ± 17	88 ± 18	91 ± 20
Body mass index, kg/m ²	31.1 ± 6.1	31.1 ± 6.0	31.0 ± 6.0	31.8 ± 6.5
Pressure, mm Hg				
Brachial systolic	136 ± 18	144 ± 22	136 ± 18	146 ± 20
Brachial diastolic	72 ± 10	70 ± 11	72 ± 10	73 ± 11
Cholesterol, mg/dL				
Fasting total	198 ± 39	201 ± 47	198 ± 39	203 ± 48
Fasting HDL cholesterol	59 ± 16	58 ± 17	59 ± 16	57 ± 17
Ratio of total to HDL cholesterol	3.56 ± 1.06	3.72 ± 1.22	3.55 ± 1.06	3.75 ± 1.13
LDL cholesterol	120 ± 35	122 ± 44	120 ± 35	124 ± 42
Fasting triglycerides, mg/dL	84 [62, 113]	95 [75, 128]	84 [63, 113]	96 [71, 133]
Fasting glucose, mg/dL	105 ± 32	107 ± 32	103 ± 30	119 ± 43
Concomitant disease and risk factors				
Diabetes mellitus	563 (28%)	91 (39%)	543 (27%)	111 (48%)
Antihypertensive medications	402 (20%)	75 (32%)	382 (19%)	88 (38%)
Antihyperlipidemic medications	1,428 (71%)	214 (92%)	1,449 (72%)	204 (88%)

Note: Values expressed as mean ± standard deviation, number (percent), or median [interquartile range; 25th, 75th percentile]. Albuminuria is defined by urinary albumin-creatinine ratio > 25 mg/g in men and >35 mg/g in women on spot or 24-hour urine collection.

Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

carotid-femoral PWV was significantly associated with greater odds of CKD stage 3-4, whereas greater carotid-femoral PWV, higher forward pressure wave amplitude, higher central pulse pressure, higher MAP, and increased characteristic impedance were all associated with albuminuria and increased UACR in adjusted analyses. Similar to the unadjusted analyses evaluating measures of microvascular integrity, higher hyperemic flow but not baseline brachial flow was significantly associated with lower odds of albuminuria and lower UACR. We further assessed the relation of vascular function measures to CKD stages and found no differences in the association between vascular function measures and CKD stage (Table S2).

In models assessing UACR, there was a significant interaction between diabetes status and carotid-femoral PWV. Among participants with diabetes, higher carotid-femoral PWV was associated with significantly greater UACR than among those without diabetes (Fig 1 [$P_{\text{interaction}} < 0.001$]). Test for interaction of sex with FWA and central pulse pressure showed that sex modified the effect of FWA and central pulse pressure on UACR levels (Figs 2 and 3).

DISCUSSION

In our moderate-sized cross-sectional analysis in a middle-aged to elderly African American community-based cohort, we found that higher mean aortic stiffness was significantly associated with higher odds of prevalent CKD stage 3-4. In the multivariable-adjusted model, we

observed that most stiffness pulsatility measures were significantly associated with the presence of albuminuria and higher UACR. Furthermore, we observed a significant interaction on the relation between vascular stiffness and UACR by diabetes status, such that within this high-risk group, the association between albuminuria and vascular stiffness is most notable. These findings highlight the importance of pulsatile hemodynamics to kidney disease in African Americans.

In the Framingham Heart Study, a predominantly non-Hispanic White cohort, investigators found that multiple clinical risk factors were positively associated with baseline flow velocities and vascular stiffness measures and were inversely related to hyperemic brachial flow velocities. However, unlike the current study, carotid-femoral PWV was not significantly associated with reduced eGFR after multivariable adjustment.³⁵ In our study, the relation of vascular hemodynamics to albuminuria and UACR was similar to findings in Framingham, although in contrast to the Framingham findings, we observed significant positive relations of MAP and characteristic impedance with albuminuria and UACR.³⁵ This lack of relation of vascular function parameters to CKD, yet the presence of statistically significant relations of UACR and urinary albuminuria with vascular function measures in our African American cohort, might indicate differences in the relation of vascular parameters to measures of kidney disease based on ancestry. Albuminuria and UACR represent preclinical phases in the pathogenesis of CKD.³⁶ Thus, these findings

Table 2. Vascular Function Characteristics of Study Participants

Characteristics	eGFR		Albuminuria	
	≥60 mL/min/1.73 m ² (n = 2,011)	15-60 mL/min/1.73 m ² (n = 233)	Absent (n = 2,012)	Present (n = 232)
Heart rate-tonometry, $\frac{\text{beats}}{\text{min}}$	65 ± 10	74 ± 10	65 ± 10	66 ± 10
Pulse wave velocity, $\frac{\text{m}}{\text{s}}$				
Carotid-femoral	10.9 ± 4.1	14.0 ± 5.2	10.9 ± 4.1	13.7 ± 5.2
Carotid-brachial	9.4 ± 2.1	9.8 ± 2.4	9.3 ± 2.1	10.1 ± 2.2
Forward wave amplitude, mm Hg	53 ± 15	63 ± 20	53 ± 16	62 ± 16
Central pulse pressure, mm Hg	65 ± 20	77 ± 24	65 ± 20	74 ± 21
Mean arterial pressure, mm Hg	99 ± 12	101 ± 13	99 ± 12	102 ± 13
Characteristic impedance, $\frac{\text{dyne} \cdot \text{s}}{\text{cm}^5}$	266 ± 110	316 ± 113	266 ± 110	308 ± 121
Brachial flow velocity, $\frac{\text{cm}}{\text{s}}$				
Baseline	5.5 ± 3.2	4.8 ± 2.9	5.4 ± 3.2	5.1 ± 3.3
Hyperemic	47.8 ± 18.6	39.7 ± 16.6	47.5 ± 18.5	41.6 ± 18.1

Note: Values expressed as mean ± standard deviation. Albuminuria is defined by urinary albumin-creatinine ratio > 25 mg/g in men and >35 mg/g in women on spot or 24-hour urine collection.

Abbreviation: eGFR, estimated glomerular filtration rate.

may help identify African American participants who are at higher risk for progressing to CKD.

Carotid-femoral PWV is a well-established marker of aortic stiffness and has been studied extensively as a risk factor for cardiovascular disease and mortality in CKD and related conditions.³⁷ Increased aortic stiffness increases pressure, flow pulsatility, and transmission of excessive pulsatility into the peripheral vasculature.^{18,38}

The kidney vasculature is highly vulnerable to pressure and flow pulsatility changes due to low resistance

circulation with high kidney blood flow.^{38,39} At least 2 potential mechanisms have been suggested as mediators of the harmful effect of higher carotid-femoral PWV on kidney function. First, increased pulsatility may lead to constriction of small resistance vessels in the kidney and thus reduce the GFR and induce oxidative stress on glomeruli.^{40,41} Second, increased transmission of this pulsatility may lead to structural kidney damage at the level of small vessels, particularly in the renal cortex, where pressure and flow pulsatility are high.^{18,42,43} Both these

Table 3. Age- and Sex-Adjusted Associations of Vascular Function Measures With CKD, Albuminuria Status, and Urinary Albumin-Creatinine Ratio

Predictor	CKD Stage 3-4		Albuminuria ^a		Urinary Albumin-Creatinine Ratio ^b	
	OR (95% CI)	P	OR (95% CI)	P	% Change ^c (95% CI)	P
Hemodynamic parameters ^d						
Carotid-femoral pulse wave velocity	1.48 (1.19 to 1.84)	<0.001	2.07 (1.68 to 2.57)	<0.001	25 (17 to 32)	<0.001
Forward pressure wave amplitude	1.30 (1.10 to 1.53)	0.002	1.65 (1.38 to 1.97)	<0.001	23 (15 to 32)	<0.001
Central pulse pressure	1.28 (1.08 to 1.51)	0.004	1.46 (1.24 to 1.70)	<0.001	19 (12 to 26)	<0.001
Mean arterial pressure	1.19 (1.01 to 1.39)	0.03	1.43 (1.23 to 1.66)	<0.001	15 (9 to 22)	<0.001
Characteristic impedance	1.14 (0.97 to 1.33)	0.11	1.36 (1.17 to 1.58)	<0.001	14 (7 to 21)	<0.001
Brachial vascular reactivity parameters ^e						
Flow						
Baseline	0.96 (0.82 to 1.12)	0.60	0.94 (0.81 to 1.09)	0.43	1 (-3 to 6)	0.66
Hyperemic	0.94 (0.79 to 1.12)	0.51	0.79 (0.67 to 0.94)	0.006	-10 (-15 to -6)	<0.001

Note: Age standardized. Model parameters: measure adjusted for sex and age at tonometry visit.

Abbreviations: CKD, chronic kidney disease; OR, odds ratio.

^aLogistic regression.

^bLog transformed, linear regression.

^cPercent changes indicate change in carotid-femoral pulse wave velocity per incremental increase in log-transformed urinary albumin/creatinine ratio.

^dn = 1,702.

^en = 2,244.

Table 4. Multivariable-Adjusted Associations of Vascular Function Measures With CKD, Albuminuria Status, and Urinary Albumin-Creatinine Ratio

Predictor	CKD Stage 3-4		Albuminuria ^a		Urinary Albumin-Creatinine Ratio ^b	
	OR (95% CI)	P	OR (95% CI)	P	% Change (95% CI)	P
Hemodynamic parameters^c						
Carotid-femoral pulse wave velocity	1.37 (1.08 to 1.75)	0.01	1.66 (1.32 to 2.11)	<0.001	13 (6 to 21)	<0.001
Forward pressure wave amplitude	1.16 (0.96 to 1.40)	0.13	1.37 (1.14 to 1.65)	0.001	15 (8 to 23)	<0.001
Central pulse pressure	1.11 (0.90 to 1.37)	0.33	1.28 (1.05 to 1.57)	0.02	13 (5 to 21)	0.001
Mean arterial pressure	1.18 (1.01 to 1.39)	0.04	1.38 (1.19 to 1.61)	<0.001	13 (7 to 19)	<0.001
Characteristic impedance	1.06 (0.89 to 1.26)	0.50	1.19 (1.00 to 1.40)	0.04	6 (1 to 13)	0.03
Brachial vascular reactivity parameters^d						
Flow						
Baseline	0.97 (0.82 to 1.14)	0.71	0.88 (0.75 to 1.03)	0.11	-1 (-6 to 3)	0.52
Hyperemic	1.00 (0.83 to 1.20)	0.99	0.81 (0.68 to 0.95)	0.01	-10 (-14 to -5)	<0.001

Note: Age, triglyceride level, total cholesterol level, high-density lipoprotein cholesterol level, heart rate, and mean arterial pressure standardized. Model parameters: measure adjusted for sex, age at tonometry visit, triglyceride level, antihypertensive medications, total cholesterol level, high-density lipoprotein cholesterol level, diabetes mellitus status, antihyperlipidemic medications, antihypertensive medications, heart rate, and mean arterial pressure.

Abbreviations: CKD, chronic kidney disease; OR, odds ratio.

^aLogistic regression.

^bLog transformed, linear regression.

^cn = 1,702.

^dn = 2,244.

postulated mechanisms would be expected to reduce the arterial volume in the cortex and increase kidney vascular resistance.⁴³

Previous studies suggest that healthy young African Americans have impaired vasodilator function compared with non-Hispanic White Americans, as indicated by reduced flow-mediated dilation and lower vasodilation during mental stress and hand-grip exercise.⁴⁴ African American men have been shown to have higher arterial

stiffness and augmentation indexes than non-Hispanic White men. Women have greater age-associated increases in arterial stiffness and augmentation index than men. Young African American and non-Hispanic White Americans exhibited different responses in central stiffness and central blood pressure after acute maximal exercise.⁴⁵ There is inadequate understanding of mechanisms involved in elevated systemic vascular resistance in African Americans, particularly in early stages of hypertension. Reduced vasodilatory effects of β -adrenergic receptors and enhanced sensitivity of α -adrenergic receptors might be contributing factors.^{46,47} Faulty endothelial function may contribute to increased systemic vascular resistance in African Americans, which in turn leads to arterial stiffness and early onset of end-organ damage.⁴⁸ As hypertensive changes progress, vascular hypertrophy evidenced by thickening of the intima media layer of the vessel wall may contribute to these changes, which may occur even during initial stages of hypertension.⁴⁹

In general, the prevalence of early CKD is lower among African Americans compared with non-Hispanic Whites. However, minorities not only tend to have earlier onset of CKD but also progress more quickly from earlier CKD stages to kidney failure.⁵⁰ Consequently, an aggressive and comprehensive approach to slow this progression by using therapies to control blood pressure and prevent albuminuria is necessary.⁵⁰

We observed that participants with higher carotid-femoral PWV and brachial pulse pressure exhibited attenuated forearm brachial flow velocity during hyperemia (in

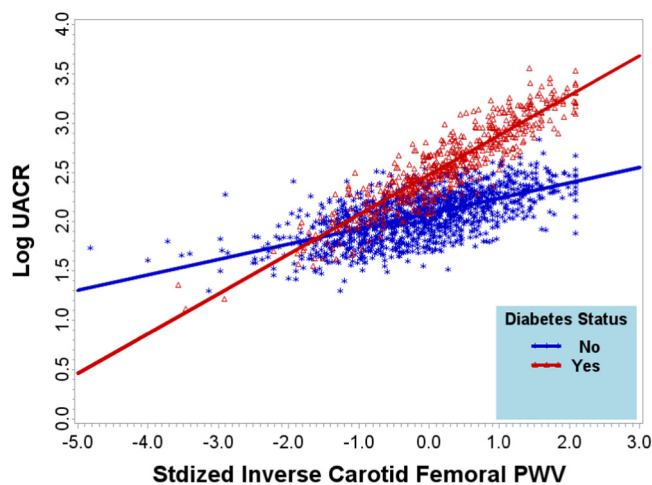


Figure 1. Effect modification by diabetes on relation between carotid-femoral pulse wave velocity (PWV) and urinary albumin-creatinine ratio (UACR).

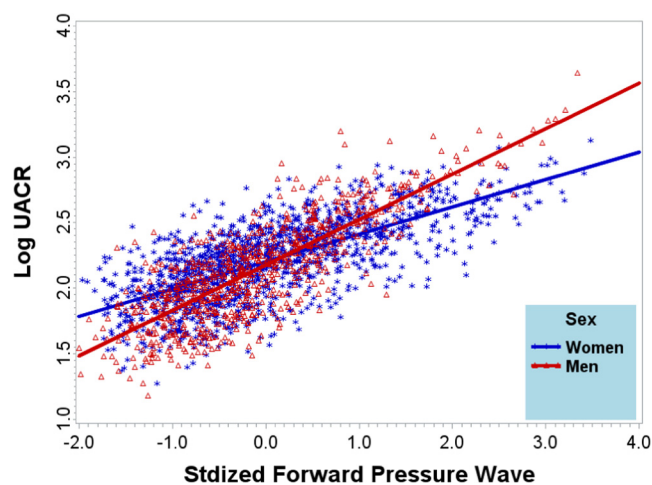


Figure 2. Effect modification by sex on relation between forward wave amplitude and urinary albumin-creatinine ratio (UACR). Interaction $P < 0.001$. Model: measure adjusted for sex, age at tonometry visit, age squared, triglyceride level, antihypertensive medications, total cholesterol level, high-density lipoprotein cholesterol level, antihyperlipidemic medications, heart rate, and mean arterial pressure. Age, carotid femoral pulse wave velocity, triglyceride level, total cholesterol level, high-density lipoprotein cholesterol level, and mean pressure standardized.

models adjusted for potentially common cardiovascular disease risk factors).⁵¹ This finding suggests that abnormal aortic stiffness and elevated arterial pressure pulsatility are associated with structural and functional abnormalities in peripheral small vessels. Thus, our data in this middle-aged

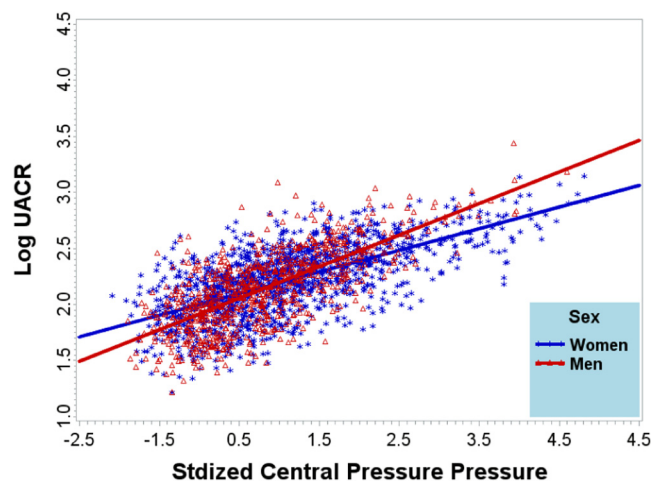


Figure 3. Effect modification by sex on relation between central pulse pressure and urinary albumin-creatinine ratio (UACR). Interaction $P < 0.001$. Model: measure adjusted for sex, age at tonometry visit, age squared, triglyceride level, antihypertensive medications, total cholesterol level, high-density lipoprotein cholesterol level, antihyperlipidemic medications, heart rate, and mean arterial pressure. Age, carotid femoral pulse wave velocity, triglyceride level, total cholesterol level, high-density lipoprotein cholesterol level, and mean pressure standardized.

to elderly African American sample further contribute to the growing body of evidence linking elevated vascular stiffness, microvascular dysfunction, and kidney disease. Beyond midlife, the aortic impedance increases disproportionately to the peripheral muscular arteries, leading to impedance matching between the aorta and first-generation arteries and a reduction in wave reflection.⁵² This reduction in wave reflection eliminates the protective mechanism that normally buffers the peripheral microcirculation against excessive pressure and pulsatility.^{43,52} For example, previous studies have shown that microvascular dysfunction may contribute to the progression of structural and functional damage to the brain and kidneys.⁵³ In addition, we recently showed that changes in microvascular functions are associated with adverse cardiovascular events.^{51,54} Thus, disparities in the extent and progression of microvascular dysfunction may contribute to racial/ethnic differences in target-organ diseases with microvascular causes. However, longitudinal studies that assess relative risks between African American and other racial/ethnic groups are warranted.

However, certain authors also propose that presence of a significant arterial stiffness gradient (aortic PWV is less than peripheral PWV), partial pulse wave reflections occur distant from microcirculation and return at low PWV to the aorta in diastole, maintaining aortic to peripheral amplification. It is also proposed that such partial reflections may limit the transmission of pulsatile pressure energy to the periphery and thus may actually be protective to the kidney microvasculature. The same authors also propose that in the disappearance or inversion of stiffness gradient (aortic PWV > peripheral PWV), pulse pressure is not sufficiently dampened and thus is significantly transmitted toward the renal microcirculation, contributing to its damage. Along with this, the aortic to peripheral pressure amplification is attenuated, increasing cardiovascular risk significantly.⁵⁵ However, though many pathophysiologic models are proposed, the exact mechanism of the microvascular damage is still not fully elucidated.

It is interesting to note in our study that individuals with elevated UACRs had abnormal vascular function, even in the presence of normal eGFRs. Accordingly, assessing albuminuria in high-risk individuals may identify those who will benefit from interventions to prevent kidney function decline, thus potentially reducing the morbidity and mortality associated with CKD in African Americans.⁵⁶

Findings in the current investigation show a strong link between vascular stiffness, pulsatility, and kidney disease. Abnormal vascular function parameters predate clinical syndromes such as CKD, stroke, and coronary artery disease and recent studies demonstrate that arterial stiffening is an early sign of cardiovascular dysfunction in CKD, often detectable before changes in diastolic function and ejection fraction.⁵⁷ Identification and quantification of aortic stiffness in this early pathophysiologic phase may help identify these changes in microcirculation and act as an attractive imaging biomarker given the expense associated with

invasive approaches to measure aortic stiffness such as cardiac catheterization, which also carries some risk associated with the procedure. Evaluation of vascular function parameters, which predate clinical disease syndromes, may have implications for prevention, treatment, and interventional studies.⁵⁸ This is important given the previous studies clearly demonstrating that microvascular dysfunction mediates relations between aortic stiffness and cardiovascular events.^{51,54}

Current measures of elevated risk for progression to more advanced stages of CKD include elevated UACR. However, progressive GFR decline is still seen in a substantial number of patients despite current clinical measures to address this risk. Thus, developing and considering clinical and pharmacologic measures to substantially reduce such progression to CKD is a rising new area of vascular research.⁵⁶

It is evident that vascular resistance influences the development and progression of CKD among African Americans, though the origin of this pattern remains unclear. Although our results are similar to that of the Framingham Heart Study, which was done in a largely non-Hispanic White population, it is important to note that in the JHS African American cohort, certain vascular parameters such as MAP and vascular impedance were also associated with UACR and albuminuria, and that the vascular function parameter carotid-femoral PWV is clearly associated with CKD in African Americans.

Given that these are cross-sectional data, we cannot compare and contrast temporal associations between changes in micro- and macrovascular functional parameters with the development and progression of CKD. Although it appears that microvascular changes might predate macrovascular functional abnormalities, we cannot determine a causative relation between vascular stiffness measures and kidney disease in this cross-sectional analysis. There is an interval of 2.8 years between the vascular measures and kidney function measures; the impact of this time lag was not found to be significant after time-gap-adjusted analysis. There was a higher prevalence of hypertension and of treated hypertension in the JHS than in Framingham. We adjusted for hypertensive medications. Given the significantly higher percentage of African Americans with CKD compared with the general population,^{33,59} this study presents a unique evaluation of preclinical factors associated with eGFR and albuminuria in African Americans.

In our middle-aged and older African American cohort, greater arterial stiffness was associated with higher levels of albuminuria. The association between FWA and central pulse pressure with UACR is modulated by sex, whereas that between carotid-femoral PWV and CKD stage 3-4 is modulated by diabetes status. Therefore, findings suggest that increased stiffness and pulsatility may result in small-vessel damage and subsequent kidney disease. In particular, male sex and diabetes seem to play a critical role in the relation linking vascular stiffness and pulsatility to

kidney disease in this population. Our study should further stimulate future studies to investigate interactions between preclinical determinants that lead to more advanced CKD stages. Further studies are also warranted to assess whether improving arterial stiffness could contribute to kidney protection in African Americans.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Clinical characteristics of excluded and included participants

Table S2: Multivariable-adjusted associations of vascular function measures with estimated glomerular filtration rate (eGFR): sensitivity analysis

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Are vascular function parameters related to kidney disease in African Americans?



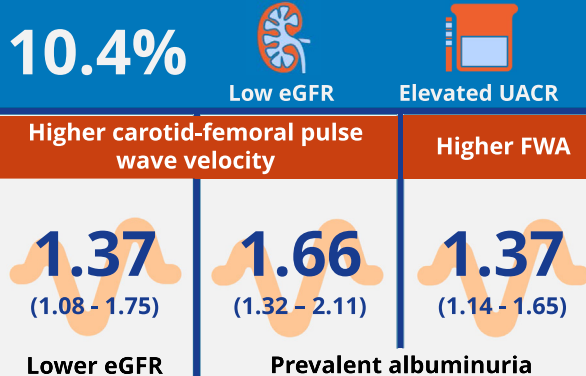
Methods and cohort

- Cross-sectional cohort
- 2244 individuals from the Jackson Heart Study
- Vascular function measures
- 2012-2017

Predictors

- Baseline carotid-femoral pulse wave velocity
- Forward wave amplitude
- Hyperemic brachial artery
- eGFR >15 and <60 mL/min/1.73m²
- UACR >25 mg/g in men >35 mg/g in women

Findings



JHS, Jackson Heart Study; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; FWA, forward wave amplitude.

Conclusion: Higher arterial stiffness and pulsatility are associated with higher odds of low eGFR in African Americans.

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