ORIGINAL RESEARCH

Aortic Stiffness and Pulsatile Pressures as Potential Mediators of Chronic Kidney Disease Induced Impaired Diastolic Function

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Purpose: We assessed whether aortic stiffness and pulsatile pressures can mediate chronic kidney disease (CKD)-associated impaired diastolic function.

Participants and Methods: In 276 black Africans including 46 CKD (19 non-dialysis; 27 dialysis) and 230 control subjects, pulse wave velocity (PWV) estimated aortic stiffness and pulsatile pressures (forward and backward wave pressure, central systolic blood pressure (CSBP) and pulse pressure (CPP)) were determined by applanation tonometry; e' as an index of left ventricular active relaxation and E/e' as a measure of left ventricular filling pressure or passive relaxation were evaluated by echocardiography.

Results: In age, sex, traditional cardiovascular risk factor and mean arterial pressure (MAP) adjusted regression models, CKD was inversely associated with e' (p = 0.03) and directly with E/e' (p < 0.01). The CKD-e' relationship was attenuated and no longer significant (p = 0.31) upon additional adjustment for aortic PWV but not pulsatile pressures (p = 0.03–0.05). In product of coefficient mediation analysis, PWV accounted for 47.6% of the CKD-e' association. CSBP (22.9%) and CPP (18.6%) but not PWV (11.3%) accounted for a significant and relevant proportion of the CKD-E/e' relationship. However, CKD remained strongly associated with E/e' independent of aortic function measures (p < 0.01). Treatable covariates that were or tended to be consistently associated with diastolic function included MAP (p < 0.01) and diabetes (p = 0.02–0.07) for the CKD-e' and CKD-E/e' relations, respectively.

Conclusion: Aortic stiffness rather than pulsatile pressures mediates CKD-related impaired left ventricular active relaxation. By contrast, aortic pulsatile pressures (and not stiffness) contribute to CKD-related left ventricular filling pressures but do not fully account for the respective association.

Keywords: chronic kidney disease, diastolic function, arteriosclerosis, aortic stiffness, pulsatile pressures

Introduction

Uraemic cardiomyopathy[1] and marked premature arteriosclerosis[2] are the most characteristic cardiovascular abnormalities that are experienced by patients with chronic kidney disease (CKD). The core feature of uraemic cardiomyopathy comprises impaired diastolic function, which results in inadequate left ventricular filling and ultimately often heart failure with preserved ejection fraction (HFpEF).[1–5] Uremic cardiomyopathy also enhances the risk of ventricular arrhythmias and sudden cardiac death.[6] Impaired diastolic function in CKD is engendered by (1) decreased active reuptake of calcium from the cytoplasm into the endoplasmic reticulum that leads to impaired active relaxation and (2) myocardial fibrosis that causes decreased passive relaxation and increased left ventricular filling pressures.[1] Uraemic cardiomyopathy is also associated with pronounced compensatory left ventricular hypertrophy.[1]

The haemodynamic factors that are implicated in impaired diastolic function among CKD patients are increased preload and afterload.[1,2] Increased preload is mostly due to volume overload and anaemia, whereas premature arteriosclerosis augments afterload in CKD.[1,2]

Premature arteriosclerosis increases aortic stiffness that enhances the forward and subsequent backward or reflected wave pressure.[2] These changes account for increased central systolic blood pressure and pulse pressure.[2] Aortic stiffness and pulsatile pressures thereby impact cardiac function, a phenomenon that is mostly referred to as ventricular-vascular coupling.[7] However, aortic stiffness can also contribute to ventricular-vascular coupling in a mechanical way.[7–9] Indeed, during early diastole, particularly proximal aortic stiffness impairs the rapid upward movement of the left ventricle around stationary blood in the left atrium that normally contributes markedly to left ventricular filling, this when the left ventricle fails to compensate for aortic stiffening.

The relative contributions of aortic stiffness and pulsatile pressures to CKD induced impaired active and passive left ventricular relaxation are currently unknown. In this study, we performed pulse wave analysis and echocardiography in black African CKD patients and matched healthy controls.[10–12] We determined early diastolic mitral annulus displacement velocity (e') and inflow velocity (E) by tissue and pulsed Doppler, respectively. E' was used as a measure of active relaxation, and we calculated E/e' as an index of left ventricular filling pressure or passive relaxation. We hypothesized that in traditional cardiovascular risk factor and mean arterial pressure adjusted analysis, both aortic stiffness and pulsatile pressures can mediate the relationship of CKD with impaired diastolic function.

Participants and Methods
Study Participants
This study was conducted in line with the principles of the Helsinki declaration. The Committee for Research on Human Subjects of the University of Witwatersrand approved the protocols for investigation of non-CKD and CKD participants (M02-04-72 and renewed as M07-04-69, M12-04-108 and M17-04-01 in non-CKD subjects and M15-08-43 in CKD patients). Participants gave informed, written consent. Our study design was previously reported.[10–13] Briefly, 46 consecutive black CKD participants including 19 non-dialysis and 27 dialysis patients were enrolled at the Milpark Hospital in Johannesburg, South Africa. Patients with active infection or/and cancer were excluded. Non-dialysis patients had a Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate (eGFR)[14] of $<60\text{mL/min}/1.73\text{m}^2$ at enrolment; their mean (SD) eGFR was 26 (18) mL/min/1.73m^2. Dialysis was performed thrice weekly for 4 hour sessions; measurements were made on the day prior to dialysis in the respective patients. Non-CKD controls comprised 230 age-, sex- and race-matched participants of a population study on cardiovascular disease risk in Johannesburg, which includes randomly recruited families of black African descent with siblings older than 16 years; their mean (SD) eGFR was 96 (18) mL/min/1.73m^2. None of the study participants had atrial fibrillation at the time of the investigation. Data were missing in fewer than 3% of any of the recorded characteristics among study participants.

Baseline Characteristics Including Traditional Cardiovascular Risk Factors
We recorded demographic characteristics, traditional cardiovascular risk factors and cardiovascular events as previously reported[10–13] and detailed in the Supplementary Data Methods. Mean or distending arterial blood pressure for the peripheral waveform was determined electronically by the SphygmoCor device (see below) and using the formula

$$MP = \frac{\sum_{i=T_0}^{T_F} P_i}{n}$$

where T_0=start of the waveform; T_F=end of waveform; P_i=pressure points and n=number of pressure points.

Arterial Function
Central haemodynamic assessments were determined from central arterial pressure recordings obtained from pulse wave analysis by applanation tonometry and SphygmoCor software as previously described[10–13] and detailed in the Supplementary Data Methods. We recorded aortic pulse wave velocity (PWV) as an index of arterial stiffness, forward

wave pressure (Pf), reflected wave pressure (Pb), central systolic blood pressure (CSBP) and central pulse pressure (CPP).

Echocardiography

Echocardiography was performed as recommended by the American Society of Echocardiography convention.[15] We employed a Philips XC50 POC Compact CompactXtreme ultrasound system (Philips Medical System (Philips Medical Systems (Pty) Ltd, USA) in CKD patients (performed by C. Robinson) and an Acuson SC2000 Diagnostic ultrasound system (Siemens Medical Solutions, USA, Inc.) in healthy control subjects (performed by A.J. Woodiwiss and C.D. Liebhaber). Measurement details were reported previously.[10–13] Intra-observer echocardiographic measurement variability is low in our setting with Pearson's correlation coefficients and variances (mean % difference (SD)) for left ventricular end-diastolic diameter, septal wall thickness, posterior wall thickness, E and e' of 0.92, 0.72, 0.76, 0.88 and 0.93 (p < 0.0001 for all), and −0.41 (4.16), 0.45 (7.74), 1.74 (6.08), 0.16 (9.95) and −1.46 (8.58), respectively.[16] Participants were examined in the partial left decubitus position. Left ventricular dimensions were determined by 2-dimensional directed M-mode echocardiography. Left ventricular mass (LVM) was determined using a standard formula.[17] Left ventricular hypertrophy (LVH) was identified when the left ventricular mass index was >95 g/m^2 in women and >115g/m^2 in men. Left ventricular end diastolic and systolic volumes were determined using the Teichholz method.[18] Left ventricular ejection fraction (EF) was calculated as [(left ventricular end diastolic volume − left ventricular end systolic volume)/left ventricular end diastolic volume] × 100. Left ventricular diastolic function was assessed by measuring the pulsed Doppler determined early mitral valve blood inflow velocity (E) and the tissue Doppler determined early mitral valve annulus upward displacement velocity (e'). Results were expressed as e', which is a marker of active relaxation, and the E/e' ratio, which is an index of left ventricular diastolic filling pressure that is mediated by passive relaxation or left ventricular stiffening.

Data Analysis

Results are expressed as mean (SD), median (interquartile range) of number (percentages) as appropriate. Non-normally distributed characteristics were logarithmically transformed upon entering them in multivariate regression models.

The recorded characteristics were compared between controls and CKD patients and between dialysis and non-dialysis patients in age and sex adjusted linear and logistic regression models with additional adjustments for anti-hypertensive and lipid lowering therapy for blood pressure and lipid variables, respectively.

Among all study participants, the association of CKD with e' and E/e' were first assessed in age and sex adjusted linear regression models. We subsequently adjusted additionally for established confounders in the present context (height, heart rate and mean arterial pressure)[10–13] as well as those traditional cardiovascular risk factors that differed between control and CKD participants (waist–hip ratio, HDL-cholesterol concentrations, diabetes prevalence and current smoking status) (base model). Thereafter, we adjusted additionally for aortic stiffness (PWV), central pulsatile pressures (Pf, Pb, CSBP, CPP), LVEVD and LVM in separate models. For the latter models, associations of the respective factors with e' and E/e' were also illustrated by giving partial correlation coefficients and their 95% confidence intervals. Partial correlation coefficients comprise a measure of the strength and direction of a linear relationship between two continuous variables whilst controlling for the effect of one or more other variables (covariates or control variables).

Age, sex, established confounder and traditional cardiovascular risk factor adjusted product of coefficient mediation analysis that accounts for hierarchical causal structures,[17–22] was then performed to determine the contribution of aortic stiffness, central pulsatile pressures, LVEVD and LVM to CKD-e' and CKD-E/e' relations. In this analysis, the fraction to which the respective factors contributed to the total effect on e' and E/e' was calculated by dividing the regression coefficient (estimate) for the factor-e' and factor-E/e' relationships by the regression coefficient for the total effect on e' and E/e'.

Data analysis was performed on IBM SPSS statistical program (version 27.0 IBM, USA). Significance was set at p < 0.05.

Results

Baseline Characteristics Including Cardiovascular Risk Factors in Controls and CKD Patients

Recorded characteristics of CKD patients that formed part of this study were reported previously.[12] In Table 1, baseline characteristics including traditional cardiovascular risk factors are compared between control and CKD participants and among non-dialysis and dialysis patients. Age and sex did not differ significantly in control compared to CKD participants.

CKD patients had a similar body mass index but larger waist circumference and waist–hip ratio compared to control subjects. Hypertension, dyslipidemia and diabetes prevalence were each larger in CKD patients than in controls. Antihypertensive drugs were used in all CKD patients with hypertension (n = 45 (97.8%)) and 60 (26.1%) controls; lipid lowering agents were employed by 21 (45.7%) CKD patients and none of the controls. Systolic blood pressure and peripheral pulse pressure were larger, whereas HDL-cholesterol concentrations were smaller in CKD compared to control participants. CKD patients smoked less frequently than did control subjects. Heart rate was larger in CKD patients compared to controls. The Framingham score was 2.9 fold larger in CKD compared to control participants.

Differences in baseline characteristics between patients and controls were overall consistent irrespective of CKD status. Cardiovascular disease was recorded in 17.4% of CKD patients. Baseline characteristics did not differ significantly in non-dialysis compared to dialysis patients with the exception of diabetes prevalence that was 1.5 larger in non-dialysis participants. However, the sample size of the 2 CKD subgroups was too small to reliably identify potentially clinically relevant differences amongst non-dialysis and dialysis patients through statistical analysis.

Aortic Function and Echocardiographic Characteristics in Controls and CKD Patients

Aortic function indices and echocardiographic findings are shown in Table 2. PWV, Pf, Pb, CSBP and CPP were each larger in CKD patients compared to control subjects.

E' was smaller, and E and the E/e' ratio were larger in CKD compared to control participants. LVEDV, LVM and left ventricular hypertrophy prevalence were each larger in CKD patients than control subjects. EF did not differ among CKD patients and control subjects.

Differences in arterial function indices and echocardiographic findings between patients and controls were overall consistent irrespective of CKD status. Although aortic and diastolic function measures and LVEDV and LVM did not differ significantly among non-dialysis and dialysis patients, some of the numerical differences noted are likely to be clinically relevant.

Associations of CKD with E' and E/e'

In age and sex adjusted analysis among all study participants, CKD was associated with e' (partial R = −0.216, p < 0.01) and E/e' (partial R = 0.392, p < 0.01).

Table 3 and Figure 1 give the associations of CKD with e' in multivariable regression models before and after adjustment for PWV, pulsatile pressures (Pf, PB, CSBP and CPP), LVED or LVM. In the base model in which age, sex, other established confounders and traditional cardiovascular risk factors that differed between CKD patients and control subjects were adjusted for, CKD remained associated with e' (SB (SEM)=−0.121 (0.055), p = 0.03). Upon additional adjustment for pulsatile pressures, LVEDV and LVM, CKD remained (p < 0.05) or tended to remain (p = 0.05) associated with e'. However, upon additional adjustment for PWV, CKD was no longer associated with e' (SB (SEM)=−0.064), p = 0.31). Among the covariates in the respective models, age and mean arterial pressure were consistently or tended to be consistently associated (p < 0.01 to 0.05) with e'.

Table 4 and Figure 2 show the associations of CKD with E/e' in multivariable regression models before and after adjustment for PWV, pulsatile pressures, LVEDV or LVM. In the base model, CKD remained strongly associated with E/e' (SB (SEM)=0.351 (0.060), p < 0.01). Upon additional adjustment for LVEDV or LVM, CKD remained equally strongly associated with E/e' (p < 0.01). Upon additional adjustment for PWV and central pressures, particularly CSBP and CPP, the CKD-E/e' relationship was attenuated but remained strongly significant (p < 0.01). Among the covariates in

Table 1 Baseline Characteristics Including Traditional Cardiovascular Risk Factors in Control Subjects and Chronic Kidney Disease Patients

Characteristics	Controls (n=230)	Chronic Kidney Disease Patients			P value			
		All (n=46)	Non-Dialysis (n=19)	Dialysis (n=27)	C vs CKD	C vs Non-Dialysis	C vs Dialysis	Dialysis vs Non-Dialysis
Demographics								
Age (years)	50.1 (16.01)	54.3 (14.6)	55.7 (14.2)	53.3 (15)	0.10	0.14	0.33	0.58
Sex (female)	96 (41.7)	18 (39.1)	6 (31.6)	12 (44.4)	0.74	0.39	0.79	0.38
Anthropometry								
Body mass index (kg/m2)	26.9 (4.9)	26.6 (5.3)	26.5 (5.2)	26.7 (5.5)	0.61	0.76	0.66	0.94
Waist (cm)	89.7 (13.7)	96.5 (13.1)	97.1 (10.4)	96.1 (14.9)	<0.01	0.04	0.04	0.83
Waist-hip ratio	0.87 (0.11)	0.98 (0.11)	0.97 (0.14)	0.99 (0.09)	<0.01	<0.01	<0.01	0.40
Height (m)	1.64 (0.09)	1.68 (0.10)	1.70 (0.08)	1.66 (0.11)	<0.01	<0.01	0.06	0.24
Major traditional risk factors								
Hypertension	120 (52)	45 (97.8)	19 (100)	26 (96.3)	<0.01	-	<0.01	-
Systolic blood pressure (mmHg)	129 (20)	148 (24)	145 (25)	150 (24)	<0.01	0.08	<0.01	0.37
Diastolic blood pressure (mmHg)	83 (76–92)	84 (73–91)	80 (69–88)	85 (73–98)	0.91	0.04	0.91	0.07
Peripheral pulse pressure (mmHg)	40 (34–50)	64 (50–78)	62 (50–78)	65(48–80)	<0.01	<0.01	<0.01	1.00
Mean blood pressure (mmHg)	99 (91–108)	104 (97.3–114.3)	99 (95–109)	107 (98–115)	0.25	0.43	0.25	0.10
Dyslipidemia	50 (21.7)	30 (65.2)	12 (63.2)	18 (66.7)	<0.01	<0.01	<0.01	0.84
Cholesterol (mmol/l)	4.7 (0.9)	4.3 (1.2)	4.2 (1.2)	4.3 (1.2)	0.29	0.32	0.54	0.74
LDL cholesterol (mmol/l)	2.7 (0.7)	2.3 (0.9)	2.2 (0.7)	2.4 (1.0)	0.08	0.12	0.26	0.58
HDL cholesterol (mmol/l)	1.36 (1.20–1.50)	1.06 (0.82–1.45)	1.00 (0.80–1.30)	1.10 (0.90–1.60)	<0.01	<0.01	0.12	0.18
Non-HDL cholesterol (mmol/l)	3.3 (0.9)	3.1 (1.1)	3.2 (1.3)	3.1 (1.1)	0.47	0.52	0.64	0.92
Chol-HDL chol ratio	3.5 (3.0–3.9)	3.8 (2.7–5.2)	3.7 (3.1–5.4)	3.8 (2.6–5.0)	0.12	0.13	0.36	0.33
Triglycerides (mmol/l)	1.2 (0.9–1.6)	1.3 (0.9–1.8)	1.4 (1.1–1.9)	1.4 (0.8–1.8)	0.40	0.24	0.84	0.15
Diabetes	30 (13.0)	21 (45.7)	13 (68.4)	8 (29.6)	<0.01	<0.01	0.04	<0.01
Smoking	55 (23.9)	2 (4.4)	2 (10.5)	0 (0.0)	<0.01	0.10	-	-
Heart rate (beats/minute)	64 (11)	79 (14)	76 (15)	81 (13)	<0.01	<0.01	<0.01	0.27
Framingham score (%)	5.9 (2.2–19.3)	16.9 (8.4–31.85)	20.6 (14.7–42.7)	14.2 (6.0–25.5)	<0.01	<0.01	<0.01	0.20
Cardiovascular disease	-	8 (17.4)	4 (21.1)	4 (14.8)	-	-	-	0.47

Notes: Data are expressed as mean (SD), median (interquartile range) or n (percentage) as appropriate. Intergroup comparisons were made in age and sex adjusted linear and logistic regression models with additional adjustments for antihypertensive agent and lipid lowering drugs for blood pressure and lipid variables, respectively.
Abbreviations: C, controls; CKD, chronic kidney disease; LDL, low density lipoprotein; chol, cholesterol.

Table 2 Arterial Function Indices and Echocardiographic Characteristics in Controls and Chronic Kidney Disease Patients

| Characteristics	Controls (n=230)	Chronic Kidney Disease Patients			P value			
		All (n=46)	Non-Dialysis (n=19)	Dialysis (n=27)	C vs CKD	C vs Non-Dialysis	C vs Dialysis	Dialysis vs Non-Dialysis
Arterial function								
PWV (cm/sec)	5.4 (4.6–6.8)	11.6 (9.0–14.8)	12.9 (9.1–14.9)	11.2 (8.7–14.0)	<0.01	<0.01	<0.01	0.88
Pf (mmHg)	22.0 (18.0–26.0)	32 (27–43)	31 (25–35)	37 (28–45)	<0.01	<0.01	<0.01	0.21
Pb (mmHg)	16.0 (12.0–20.0)	25.0 (14.0–29.0)	24.0 (14.0–29.0)	25.0 (14.0–28.5)	<0.01	<0.01	<0.01	0.94
CSBP (mmHg)	121 (20)	136 (22)	132 (21)	139 (22)	<0.01	0.08	<0.01	0.21
CPP (mmHg)	32 (25–40)	51 (34–61)	48 (35–58)	52 (31–62)	<0.01	0.08	<0.01	0.94
Echocardiography								
E' (cm/sec)	10.5 (3.2)	8.2 (2.6)	8.4 (2.4)	8.1 (3.9)	<0.01	0.02	<0.01	0.60
E/e'	6.2 (4.9–7.7)	10.1 (7.5–15.6)	9.9 (6.8–15.6)	10.3 (7.5–15.9)	<0.01	<0.01	<0.01	0.66
E (cm/sec)	68.2 (57.4–87.6)	84.8 (60.1–111.0)	86.1 (52.5–108.0)	79.1 (66.0–114.0)	<0.01	0.02	0.02	0.97
LVEDV (mL)	104 (85–127)	120 (91–171)	111 (83–156)	136 (92–186)	<0.01	<0.01	<0.01	0.12
LVM (g)	119 (49)	191 (93)	187 (79)	193 (104)	<0.01	<0.01	<0.01	0.58
LVH	18 (7.8)	21 (45.7)	6 (31.6)	15 (51.6)	<0.01	<0.01	<0.01	0.06
Ejection fraction (%)	67.3 (9.1)	65.0 (13.7)	65.7 (15.7)	66.1 (12.3)	0.36	0.53	0.47	0.99

Notes: Data are expressed as mean (SD), median (interquartile range) or n (percentage) as appropriate. Intergroup comparisons were made in age and sex adjusted linear and logistic regression models.
Abbreviations: C, controls; CKD, chronic kidney disease; PWV, pulse wave velocity; Pf, forward wave pressure; Pb, backward wave pressure; CSBP, central systolic blood pressure; CPP, central pulse pressure; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; LVH, left ventricular hypertrophy.

Table 3 Associations of CKD with e' in Base Model and Multivariate Regression Models

Characteristic	Base Model		Base Model + PWV		Base Model + Pf		Base Model + Pb		Base Model + CSBP		Base Model + CPP		Base Model + LVEDV		Base Model + LVM	
	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value
Age	−0.437 (0.056)	<0.01	−0.389 (0.063)	<0.01	−0.439 (0.056)	<0.01	−0.440 (0.056)	<0.01	−0.439 (0.061)	<0.01	−0.434 (0.064)	<0.01	−0.446 (0.056)	<0.01	−0.434 (0.057)	<0.01
Sex	0.011 (0.070)	0.87	0.013 (0.070)	0.86	0.009 (0.071)	0.90	0.014 (0.071)	0.85	0.011 (0.071)	0.88	0.012 (0.071)	0.87	0.015 (0.070)	0.83	0.009 (0.071)	0.89
Height	0.082 (006)	0.21	0.090 (0.066)	0.17	0.082 (0.066)	0.21	0.084 (0.066)	0.20	0.082 (0.066)	0.21	0.082 (0.066)	0.21	0.042 (0.068)	0.53	0.084 (0.066)	0.20
Waist-hip ratio	−0.088 (0.054)	0.10	−0.082 (0.054)	0.13	−0.103 (0.056)	0.07	−0.100 (0.056)	0.08	−0.088 (0.054)	0.10	−0.088 (0.054)	0.10	−0.085 (0.054)	0.12	−0.088 (0.054)	0.10
HDL-cholesterol	0.007 (0.052)	0.90	0.013 (0.052)	0.81	0.007 (0.053)	0.90	0.009 (0.053)	0.86	0.006 (0.052)	0.90	0.007 (0.053)	0.89	0.021 (0.053)	0.69	0.007 (0.052)	0.87
Diabetes	−0.076 (0.054)	0.17	−0.060 (0.055)	0.27	−0.059 (0.055)	0.28	−0.064 (0.055)	0.25	−0.076 (0.055)	0.12	−0.076 (0.055)	0.17	−0.077 (0.054)	0.161	−0.076 (0.055)	0.16
Smoking	−0.036 (0.054)	0.51	−0.027 (0.054)	0.62	−0.035 (0.054)	0.52	−0.036 (0.054)	0.51	−0.036 (0.054)	0.51	−0.035 (0.054)	0.52	−0.027 (0.054)	0.62	−0.036 (0.054)	0.51
Heart rate	−0.005 (0.053)	0.92	−0.006 (0.054)	0.92	−0.007 (0.054)	0.89	−0.008 (0.054)	0.89	−0.004 (0.057)	0.94	−0.007 (0.056)	0.90	−0.006 (0.054)	0.91	−0.005 (0.054)	0.93
MAP	−0.251 (0.049)	<0.01	−0.223 (0.052)	<0.01	−0.259 (0.050)	<0.01	−0.255 (0.050)	<0.01	−0.260 (0.131)	0.05	−0.248 (0.056)	<0.01	−0.269 (0.050)	<0.01	−0.250 (0.049)	<0.01
PWV			−0.128 (0.071)	0.07												
Pf					0.073 (0.052)	0.17										
Pb							0.031 (0.050)	0.53								
CSBP									0.011 (0.142)	0.94						
CPP											−0.007 (0.071)	0.93				
LVEDV													0.115 (0.053)	0.03		
LVM															−0.013 (0.050)	0.79
CKD	−0.121 (0.055)	0.03	−0.064 (0.062)	0.31	−0.133 (0.056)	0.03	−0.112 (0.057)	0.05	−0.123 (0.062)	0.04	−0.119 (0.061)	0.05	−0.127 (0.055)	0.02	−0.120 (0.055)	0.03

Abbreviations: CKD, chronic kidney disease; PWV, pulse wave velocity; Pf, forward wave pressure; Pb, backward wave pressure; CSBP, central systolic blood pressure; CPP, central pulse pressure; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; SB, standard regression coefficient; SEM, standard error of the mean; MAP, mean arterial pressure.
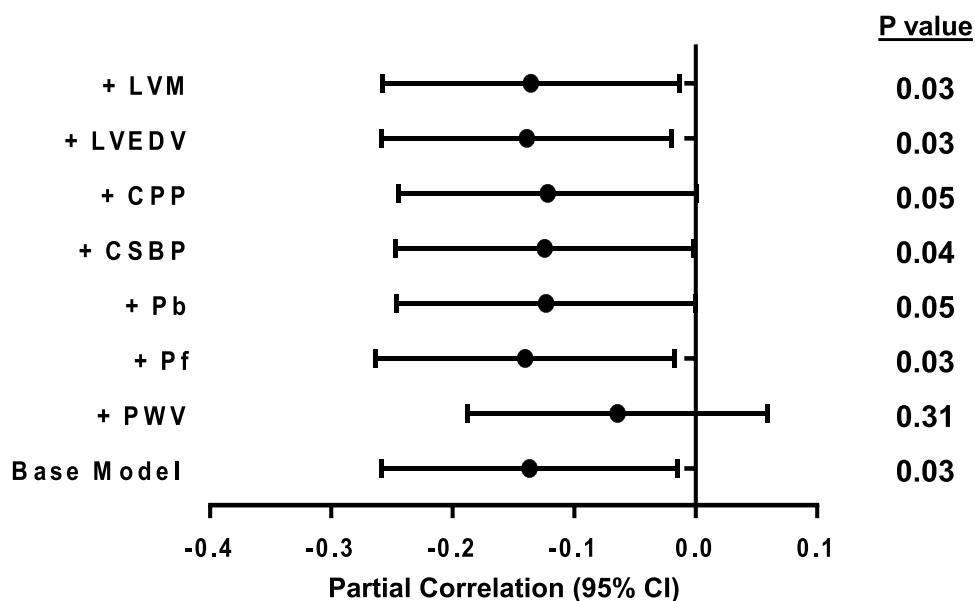
Figure 1 Partial correlations (95% CI) for the associations of chronic kidney disease with e' in the base model (adjusted for age, sex, height, waist–hip ratio, HDL-cholesterol concentration, diabetes, smoking, heart rate and mean arterial pressure; see Table 3) and after additional adjustment for PWV, Pf, Pb, CSBP, CPP, LVEDV and LVM.
Abbreviations: CKD, chronic kidney disease; PWV, pulse wave velocity; Pf, forward wave pressure; Pb, backward wave pressure; CSBP, central systolic blood pressure; CPP, central pulse pressure; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; SB, standard regression coefficient; SEM, standard error of the mean; MAP, mean arterial pressure.

the respective models, height and diabetes were consistently or tended to be consistently associated ($p < 0.01$ to 0.07) with E/e'.

Potential Mediators of the Confounder Adjusted Associations of CKD with e' and E/e'

Table 5 gives the potential mediating effects of PWV, pulsatile pressures, LVEDV and LVM in the confounder adjusted association of CKD with e'. In this regard, PWV mediated 47.6% of the CKD-e' relationship. By contrast, Pf and LVEDV strengthened the CKD-e' association by 26.3% and 14.3%, respectively.

Table 6 shows the potential mediating effects of PWV, pulsatile pressures, LVEDV and LVM in the confounder adjusted association of CKD with E/e'. CSBP and CPP mediated the CKD-E/e' relationship by 22.9% and 18.6%, respectively. None of the other characteristics made a relevant contribution to the association of CKD with E/e'.

We previously reported that determinants of diastolic function may differ in dialysis and non-dialysis CKD patients.[9] In this regard, in the present study, the associations of PWV with e' and CSBP with E/e' did not differ by CKD status (interaction $p = 0.1$ and interaction $p = 0.7$, respectively, in multivariate models).

Discussion

To our knowledge, this is the first study that assessed the potential mediating effects of aortic stiffness and pulsatile pressures to CKD induced impaired left ventricular active relaxation as indexed by e' and filling pressure or passive relaxation as estimated by E/e'. Our main findings are 2-fold. Firstly, we found that CKD was inversely associated with e' independent of non-modifiable and modifiable traditional cardiovascular risk factors including mean arterial pressure; this relationship was markedly attenuated and no longer significant after additional adjustment for aortic stiffness but not pulsatile pressures; accordingly, in product of coefficient mediation analysis, PWV accounted for 47.6% of the CKD-e' relationship. Secondly, CKD was directly associated with E/e' independent of traditional cardiovascular risk factors; however, CSBP (22.9%) and CPP (18.6) but not arterial stiffness (11.3%) accounted for a significant and relevant proportion of the CKD-E/e' relationship, and CKD remained strongly associated with E/e' independent of any of the aortic function measures; this indicates that non-traditional or renal cardiovascular risk factors are likely to mediate, at least in part, CKD induced impaired left ventricular passive relaxation.[1,2] Such risk factors include anaemia, compromised bone

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Table 4 Associations of CKD with E/e' in Base Model and Multivariate Regression Models

Characteristic	Base Model		Base Model + PWV		Base Model + Pf		Base Model + Pb		Base Model + CSBP		Base Model + CPP		Base Model + LVEDV		Base Model + LVM	
	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value	SB (SEM)	p value
Age	0.120 (0.061)	0.05	0.089 (0.070)	0.21	0.119 (0.063)	0.06	0.118 (0.063)	0.06	0.047 (0.067)	0.48	0.040 (0.070)	0.57	0.128 (0.063)	0.04	0.109 (0.062)	0.08
Sex	0.043 (0.077)	0.57	0.041 (0.078)	0.60	0.056 (0.079)	0.48	0.059 (0.079)	0.46	0.020 (0.077)	0.80	0.019 (0.077)	0.81	0.042 (0.078)	0.59	0.049 (0.078)	0.25
Height	−0.190 (0.072)	<0.01	−0.194 (0.073)	<0.01	−0.189 (0.074)	0.01	−0.188 (0.074)	0.01	−0.191 (0.071)	<0.01	−0.203 (0.072)	<0.01	−0.151 (0.075)	0.05	−0.198 (0.073)	<0.01
Waist-hip ratio	0.021 (0.059)	0.73	0.013 (0.060)	0.82	0.055 (0.062)	0.38	0.056 (0.062)	0.37	0.022 (0.059)	0.71	0.020 (0.059)	0.74	0.015 (0.060)	0.81	0.020 (0.059)	0.73
HDL-cholesterol	0.072 (0.057)	0.21	0.068 (0.058)	0.24	0.065 (0.056)	0.27	0.065 (0.059)	0.27	0.061 (0.057)	0.28	0.056 (0.057)	0.30	0.055 (0.059)	0.35	0.072 (0.057)	0.21
Diabetes	0.137 (0.060)	0.02	0.123 (0.061)	0.04	0.112 (0.061)	0.07	0.110 (0.061)	0.07	0.133 (0.059)	0.02	0.133 (0.059)	0.02	0.134 (0.061)	0.03	0.138 (0.060)	0.02
Smoking	−0.043 (0.059)	0.47	−0.050 (0.060)	0.41	−0.039 (0.061)	0.52	−0.039 (0.061)	0.52	−0.054 (0.059)	0.36	−0.055 (0.059)	0.35	−0.052 (0.060)	0.39	−0.043 (0.059)	0.47
Heart rate	−0.119 (0.059)	0.04	−0.126 (0.060)	0.03	−0.109 (0.060)	0.07	−0.109 (0.060)	0.07	−0.063 (0.062)	0.31	−0.074 (0.061)	0.23	−0.121 (0.060)	0.04	−0.122 (0.059)	0.04
MAP	0.213 (0.054)	<0.01	0.192 (0.057)	<0.01	0.212 (0.056)	<0.01	0.213 (0.056)	<0.01	−0.137 (0.143)	0.34	0.148 (0.061)	0.01	0.234 (0.056)	<0.01	0.211 (0.054)	<0.01
PWV			0.094 (0.079)	0.24												
Pf					0.030 (0.058)	0.60										
Pb							0.023 (0.056)	0.68								
CSBP									0.409 (0.154)	<0.01						
CPP											0.181 (0.077)	0.02				
LVEDV													−0.112 (0.059)	0.06		
LVM															0.046 (0.055)	0.40
CKD	0.351 (0.060)	<0.01	0.306 (0.069)	<0.01	0.303 (0.066)	<0.01	0.309 (0.064)	<0.01	0.271 (0.067)	<0.01	0.286 (0.066)	<0.01	0.358 (0.062)	<0.01	0.348 (0.061)	<0.01

Abbreviations: CKD, chronic kidney disease; PWV, pulse wave velocity; Pf, forward wave pressure; Pb, backward wave pressure; CSBP, central systolic blood pressure; CPP, central pulse pressure; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; SB, standard regression coefficient; SEM, standard error of the mean; MAP, mean arterial pressure.
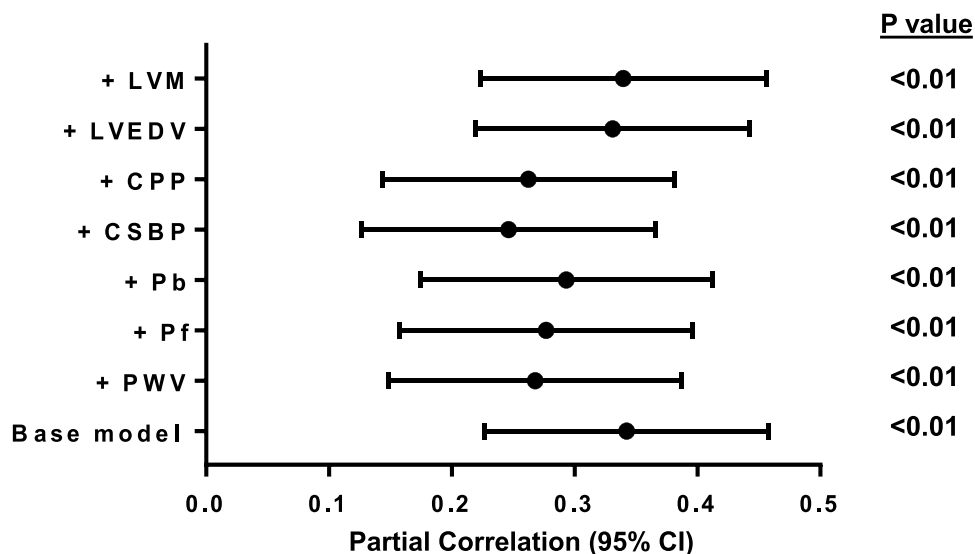
Figure 2 Partial correlations (95% CI) for the associations of chronic kidney disease with E/e' in the base model (adjusted for age, sex, height, waist–hip ratio, HDL-cholesterol concentration, diabetes, smoking, heart rate and mean arterial pressure; see Table 4) and after additional adjustment for PWV, Pf, Pb, CSBP, CPP, LVEDV and LVM.
Abbreviations: CKD, chronic kidney disease; PWV, pulse wave velocity; Pf, forward wave pressure; Pb, backward wave pressure; CSBP, central systolic blood pressure; CPP, central pulse pressure; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; SB, standard regression coefficient; SEM, standard error of the mean; MAP, mean arterial pressure.

mineral metabolism, inflammation and oxidative stress in CKD induced left ventricular fibrosis and stiffness with consequent impaired diastolic function.[1,2]

During systole, contraction of the left ventricle results in longitudinal downward stretching of the ascending aorta towards its apex.[7,8] This translates into energy storage in the aorta that causes its elastic recoil during early diastole. The aorta thereby pulls left ventricle around the blood in the left atrium, which contributes to left ventricular filling. It follows that when the left ventricle fails to compensate for aortic stiffening, reduced aortic recoil can impair its early diastolic filling.[7] Our findings of a potential mediating effect of arterial stiffness and not central pulsatile pressures on the CKD-e' relationship are in line with this recently proposed hypothesis.[7] More specifically, previously reported data in non-CKD persons[7–9] together with our current results suggest that impaired left ventricular active relaxation is mediated by mechanical rather than hemodynamic effects of increased aortic stiffness on ventricular-vascular coupling in CKD. Notably, although not significant, Pf was directly related to e' and accounted for 26.3% of the CKD-e' relationship in product of coefficient mediation analysis. Since this concurred with a significant direct association between cardiac preload as indexed by LVEDV,[10,11] with e', increased Pf was likely flow mediated and a consequence rather than a cause of left ventricular relaxation.

Although blood pressure lowering with angiotensin-renin-aldosterone system inhibitors can reduce operating arterial stiffness,[23,24] the structural changes that underlie aortic stiffness are considered to be largely untreatable at present.[23] In this regard, mean arterial pressure comprised the one covariate and treatable cardiovascular risk factor that was consistently associated with e' in multivariate regression models (Table 3). The potential impact of adequate blood pressure control on the development of impaired left ventricular active relaxation in the present context merits further longitudinal study.

In sharp contrast to our findings on e', we found that the relationship of CKD with E/e' was mediated, at least in part, by CSBP and CPP and not PWV. Whereas this result may further argue towards blood pressure control, perhaps more importantly, the CKD-E/e' association in the present study remained consistently strong after adjusting for aortic function measures in addition to traditional cardiovascular risk factors. This finding indirectly substantiates the potential importance of non-traditional or renal cardiovascular risk factors.

Diabetes is strongly associated with increased arterial stiffness among CKD patients[25] as well as an established risk factor for not only CKD[26] but also HFpEF[27] in the population at large. Our finding that diabetes was the one treatable

Table 5 Potential Mediators of the Confounder Adjusted Association[a] of CKD with e'

Potential Mediator	Direct and Indirect Potential Effects on e'		
	Estimate	**95% Confidence Interval**	**% Contribution**
Direct effect	−0.618	−1.756 to −0.520	52.4
PWV effect	−0.561	−1.170 to 0.027	47.6
Total effect	−1.179	−2.156 to −0.211	100
Direct effect	−1.300	−2.380 to −0.221	126.3
Pf effect	0.272	−0.095 to 0.664	−26.3
Total effect	−1.028	−2.040 to −0.017	100
Direct effect	−1.171	−2.217 to −0.126	105.8
Pb effect	0.070	−0.150 to 0.339	−5.8
Total effect	−1.101	−2.123 to −0.081	100
Direct effect	−1.255	−2.359 to −0.151	103.1
CSBP effect	0.038	−0.420 to 0.531	−3.1
Total effect	−1.217	−2.205 to −0.228	100
Direct effect	−1.209	−2.294 to −0.124	99.4
CPP effect	−0.007	−0.432 to 0.463	0.6
Total effect	−1.216	−2.205 to −0.228	100
Direct effect	−1.215	−2.259 to −0.172	114.3
LVEDV effect	0.152	0.034 to 0.451	−14.3
Total effect	−1.063	−2.106 to −0.021	100
Direct effect	−1.129	−2.148 to −0.110	99.3
LVM effect	−0.008	−0.367 to 0.067	0.7
Total effect	−1.137	−2.152 to −0.122	100

Notes: [a]Adjusted for age, sex, height, waist to hip ratio, HDL cholesterol, diabetes, smoking status, heart rate and mean arterial pressure.
Abbreviations: CKD, chronic kidney disease; PWV, pulse wave velocity; Pf, forward wave pressure; Pb, backward wave pressure; CSBP, central systolic blood pressure; CPP, central pulse pressure; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; SB, standard regression coefficient; SEM, standard error of the mean; MAP, mean arterial pressure.

covariate that related or tended to relate (p = 0.02 to p = 0.07) to E/e' in multivariate regression models (Table 4) is in line with these reported findings.

A small body height reportedly associates with increased risk of cardiovascular disease including heart failure.[28,29] This relationship was previously attributed to arterial stiffness, enhanced wave reflection and pulse pressure in relation to short stature.[29] In this regard, Montero et al[29] recently documented an inverse association between height and left ventricular end-diastolic pressure in patients with HFpEF. However, arterial function was not evaluated in the Montero study. It is therefore of interest that in our multivariate models in Table 4, body height was associated with increased E/e' independent of PWV, Pb, CPP and CSBP (p < 0.01 to p = 0.01) as well as LVEDV and LVM (p < 0.01 to p = 0.05). In this regard, genetic factors, nutritional and social deprivation during early life may also contribute to the observed relationship between short stature and increased cardiovascular disease risk.[28,30] However, in the present investigation, body height was larger in CKD compared to healthy control participants. This may be because CKD patients and healthy controls were enrolled in a private healthcare setting (a marker of sociodemographic advantage in Africa)[30] and the community at large, respectively. Taken together, the potential mechanisms underlying the association of small body height with diastolic function and the assessment and therapeutic implications thereof require further elucidation in future studies.

As this study was cross-sectional in design, the direction of causality could not be inferred. All study participants were black Africans. Whether our findings apply to potential CKD induced impaired diastolic function among other populations requires further investigation. Also, whether our findings apply to peritoneal dialysis patients awaits further study. Additionally, whether the timing of measurement during the interdialytic period influences findings in relation to the impact of aortic function on diastolic function in CKD merits future research. As applies to previously reported

Table 6 Potential Mediators of the Confounder Adjusted Association[a] of CKD with E/e'

Potential Mediator	Direct and Indirect Potential Effects on E/e'		
	Estimate	95% Confidence Interval	% Contribution
Direct effect	0.180	0.100 to 0.261	88.7
PWV potential effect	0.023	−0.016 to 0.063	11.3
Total effect	0.203	0.132 to 0.274	100.0
Direct effect	0.179	0.102 to 0.256	96.2
Pf potential effect	0.007	−0.021 to 0.035	3.8
Total effect	0.186	0.114 to 0.258	100
Direct effect	0.183	0.108 to 0.256	98.2
Pb potential effect	0.003	−0.015 to 0.021	1.8
Total effect	0.186	0.114 to 0.258	100
Direct effect	0.160	0.082 to 0.237	77.1
CSBP potential effect	0.047	0.004 to 0.094	22.9
Total effect	0.207	0.137 to 0.277	100
Direct effect	0.169	0.092 to 0.245	81.4
CPP potential effect	0.038	0.004 to 0.073	18.6
Total effect	0.207	0.137 to 0.277	100.0
Direct effect	0.213	0.141 to 0.285	104.5
LVEDV potential effect	−0.009	−0.031 to 0.009	−4.5
Total effect	0.204	0.132 to 0.276	100
Direct effect	0.205	0.135 to 0.275	99.0
LVM potential effect	0.002	−0.005 to 0.039	1.0
Total effect	0.207	0.137 to 0.277	100

Notes: [a]Adjusted for age, sex, height, waist to hip ratio, HDL cholesterol, diabetes, smoking status, heart rate and mean arterial pressure.
Abbreviations: CKD, chronic kidney disease; PWV, pulse wave velocity; Pf, forward wave pressure; Pb, backward wave pressure; CSBP, central systolic blood pressure; CPP, central pulse pressure; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; SB, standard regression coefficient; SEM, standard error of the mean; MAP, mean arterial pressure.

studies by us,[10,11,13] our aim was to determine relationships of recorded characteristics with e' and E/e', which necessitates including low as well as high values. In this regard, since we did not determine atrial volume index and tricuspid regurgitation velocity, we could not apply suggested algorithms for the identification of diastolic dysfunction as recently reported by Nagueh et al.[31] Our study was designed prior to Nagueh report.[31] However, since 45.7% of CKD participants in the present investigation had left ventricular hypertrophy, it is likely that a considerable proportion of them had diastolic dysfunction. We did not measure vitamin D concentrations, which are known to be reduced in CKD and are associated with arterial stiffness in heart failure[32] and several other disorders.[33] Strengths of the present study are the identification of relationships in comprehensively adjusted regression models and the application of product of coefficient mediation analysis that accounts for hierarchical causal structures.[19–21]

Conclusion

This study demonstrates that aortic stiffness rather than pulsatile pressures mediates CKD related impaired left ventricular active relaxation. By contrast, aortic pulsatile pressures (and not stiffness) contribute to CKD related left ventricular filling pressures but do not fully explain the respective association.

Ethics Statement

This study was conducted in line with the principles of the Helsinki declaration. The Committee for Research on Human Subjects of the University of Witwatersrand approved the protocols for investigation of non-CKD and CKD participants (M02-04-72 and renewed as M07-04-69, M12-04-108 and M17-04-01 in non-CKD subjects and M15-08-43 in CKD patients). Participants gave informed, written consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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