Decreased Arterial Elasticity in Children With Nondialysis Chronic Kidney Disease Is Related to Blood Pressure and Not to Glomerular Filtration Rate

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Abstract—We compared large artery mechanical properties in children with nondialysis stages of chronic kidney disease with those in children with normal renal function, examining the potential effect of blood pressure (BP) components and level of renal dysfunction. Common carotid artery mechanical properties, carotid-femoral pulse wave velocity, and carotid and peripheral BP were measured in children (n=226) with nondialysis chronic kidney disease (n=188; 11.9±3.7 years; 26%, 25%, 30%, 16%, and 3% in stages 1, 2, 3, 4 and 5, respectively) and healthy controls (n=38; 11.5±3.3 years). In children with nondialysis chronic kidney disease when compared with healthy controls, at similar levels of peripheral and carotid BP, carotid artery diastolic diameter and wall thickness were similar. In those with suboptimal BP (≥75th percentile), indices of arterial elasticity indicated greater stiffness than in healthy normotensive controls (distensibility: 92±31 versus 114±33 $kPa^{-1}\times10^{-3}$, P=0.03; compliance: 2.1±0.7 versus 2.6±0.7 m^2 $kPa^{-1}\times10^{-6}$, P=0.02; Young elastic modulus: 0.151±0.068 versus 0.109±0.049 $kPa\times10^3$, P=0.02; and wall stress: 83.6±23.5 versus 68.7±14.9 kPa, P=0.02). In all children, mechanical properties were independently related to carotid and peripheral BP components but not to estimated glomerular filtration rate. In children with nondialysis chronic kidney disease, changes in elastic properties of the carotid artery are primarily related to BP and not to glomerular renal function. **(*Hypertension*. 2015;66:809-815. DOI: 10.1161/HYPERTENSIONAHA.115.05516.)** ● **Online Data Supplement**

Key Words: blood pressure ■ cardiovascular diseases ■ renal insufficiency, chronic ■ vascular diseases ■ vascular stiffness

In adults with chronic kidney disease (CKD), including those with onset of CKD in childhood, adverse cardiovascular outcomes are closely related to arterial stiffening.[1–3] Arterial stiffening is related to the severity of CKD, being the greatest in those with dialysis-dependent CKD, and is thought to be driven, at least in part, by metabolic changes associated with CKD.[4–6] To what degree such change occurs early in childhood is unknown but could contribute to the greatly increased cardiovascular mortality and morbidity in young adults with childhood onset CKD.[7,8]

Previous studies in children about structural and functional properties of large arteries have included cohorts of nondialysis CKD, dialysis dependent, and children after kidney transplantation. Pulse wave velocity (PWV) of the carotid-femoral pathway (ie, mainly the aorta) and measures of carotid mechanics have been examined, but the latter have been limited by the lack of concurrent measures of carotid blood pressure (BP; required to determine the functional elasticity of the carotid artery).[9–13] Furthermore, although the potential effect of age and BP has been adjusted for, when comparing differences between children with and without CKD, this comparison has not been performed between age- and BP-matched groups. The objectives of this study were to compare large artery mechanical properties including carotid-femoral PWV (PWVcf) and carotid mechanics derived from carotid BPs in children with nondialysis CKD and healthy children in an analysis incorporating a case–control design with appropriate matching for age and BP and to examine the effect of BP on these measures.

Methods

The study was performed at the Evelina London Children's Hospital, United Kingdom, with the approval of the Local Research Ethics Committee. Potential participants were attending CKD outpatient clinics and were identified after review of their health records at the authors' tertiary pediatric nephrology center serving the South East of England.[14] All participants included in this study report were enrolled sequentially and included if they had acceptable quality of BP and vascular assessments. Written informed consent was obtained from parents and children if appropriate. A total of 226 children including 188 children with CKD were recruited and 38 healthy children from

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the local population. Inclusion criteria were age 2 to 18 years and nondialysis CKD irrespective of the presence or absence of hypertension. We excluded children with arrhythmias and those with clinical evidence of heart failure. Hypertension was defined as systolic BP (SBP) or diastolic BP (DBP) above the 95th percentile for age and height or if the patient was on antihypertensive therapy using the Fourth Report Criteria.[15] Renal function was estimated using the modified Schwartz formula,[14,16,17] and CKD stage was classified as described previously.[18] Eighteen healthy children did not have any blood tests, and in them, the average estimated glomerular filtration rate (eGFR) for healthy children was imputed. Clinical markers of mineral bone disease including serum calcium, phosphate, calcium–phosphate product, intact parathyroid hormone, and 25-hydroxy vitamin D3 concentrations (in a subsample of n=91) were measured.

Peripheral and Carotid BP

Peripheral SBP (pSBP) and peripheral DPB were measured 3× in succession at the brachial artery by a trained observer after children had been seated for at least 5 minutes using a calibrated aneroid sphygmomanometer with an appropriate sized arm cuff according to British Hypertension Society guidelines. Carotid SBP (cSBP) was obtained from radial artery tonometry using a transfer function and from carotid distension waveforms (with no transfer function). Radial pressure waveforms were obtained from the right wrist by applanation tonometry using a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX) and processed by the SphygmoCor device (Atcor Medical, West Ryde, Australia). Radial waveforms were calibrated from brachial measures of pSBP and peripheral DPB, from which mean arterial pressure (MAP) was calculated by integrating the radial waveform. Transformed radial waveforms (ie, estimated aortic waveforms) were calibrated from these values of MAP and DBP to give a radial tononometric estimate of cSBP calibrated from noninvasive measures of pSBP and peripheral DPB. Operators checked waveform quality, and radial waveforms were only accepted if in-built quality control measures were achieved. Aortic augmentation index was derived from the synthesized aortic waveform. cSBP was also derived from carotid waveforms (obtained by echo-tracking as described below) calibrated from MAP and DBP. Amplification of SBP (pSBP–cSBP) was calculated using the values of cSBP derived from carotid waveforms.

Carotid Dimensions and Biomechanics

The right common carotid artery was imaged using the ART.LAB system.[19–21] A linear transducer (range, 4 to 13 MHz) was used to image a 4-cm segment of artery ≈1 to 5 cm proximal to the flow divider. Mean carotid intimal medial thickness (IMT) was obtained from automated analysis of the posterior wall over this segment of the artery. Radiofrequency wall tracking was used to obtain distension waveforms averaged for 6 cardiac cycles. Diastolic internal lumen diameter (D_d), systolic lumen diameter (D_s), and carotid distension ($\Delta D=D_s-D_d$) were derived from each distension waveforms (each obtained for 6 cardiac cycles) and averaged for 3 such waveforms. The following measurements/indices of geometry and elasticity as described by Laurent et al[22] were then derived from these measures of lumen diameter, distension, and IMT:

Carotid-wall thickness/radius ratio (CWTR):

$$\mathrm{CWTR}=2\times\mathrm{IMT}/\left(\mathrm{D_d}+\mathrm{IMT}\right).$$

Wall cross-sectional area (WCSA):

$$\mathrm{WCSA}=\pi\left[\left(D_d+\mathrm{IMT}\right)^2-D_d^{\,2}\right]/4.$$

Cross-sectional compliance coefficient (CC), the absolute change in lumen area during systole for a given pressure change: $\mathrm{CC}=\Delta A/\mathrm{PP}$, where ΔA is the change in cross-sectional area ($\Delta A=\pi\Delta D_d^{\,2}/4$) and PP the local pulse pressure.

Cross-sectional distensibility coefficient (DC), the relative change in lumen area during systole for a given pressure change: $\mathrm{DC}=(\Delta A/A)/\mathrm{PP}$, where A is lumen area in diastole ($A=\pi D_d^{\,2}/4$).

Circumferential wall stress (CWS) calculated using the Lame equation[23,24]: $\mathrm{CWS}=\mathrm{MAP}\times D_m/2\times\mathrm{IMT}_m$, where D_m and IMT_m are the mean values of internal diameter and wall thickness during the cardiac cycle.

Young incremental elastic modulus (E_{inc}), elasticity that is independent of the vessel geometry: $E_{inc}=[3(1+\mathrm{A/WCSA})]/\mathrm{DC}$.

Carotid-Femoral PWV

PWVcf was measured in the supine position using the Vicorder volumetric system (Skidmore Medical, Bristol, United Kingdom). Simultaneous arterial pulse waveforms were recorded using pulse volume recording measurements from standard vascular cuffs placed over the right carotid artery and the right femoral artery. All measurements were performed consecutively 3× in succession, and the average of 3 measurements was taken. The waveforms acquired at 2 sites simultaneously gave a transit time, and PWVcf was calculated from the distance between the suprasternal notch and the top of the thigh cuff divided by transit time (PWVcf=distance/transit time).

Statistics

Subject characteristics are expressed as mean±SD for continuous variables, with 2-group comparisons via Student unpaired t test and ≥3 groups via an ANOVA test or χ^2 test for categorical values. Given the age-related change in BP throughout childhood, peripheral BP measurements were presented both as mm Hg and as SD scores (the number of SDs above or below a population mean assigned a value of 0) using published reference values.[15] To assess the effect of BP, those with CKD were subdivided into subjects with SBP or DBP ≥75th percentile and those with SBP or DBP <75th percentile. Multiple regression analysis was used to examine the relationship between measures of arterial stiffness, BP, GFR, and other confounders including age, sex, body mass index (BMI), heart rate, antihypertensive treatment (yes/no), and biochemical markers of metabolic bone disease. Because arterial stiffness may lead to a rise in pulse pressure (PP) and SBP, the primary analysis was performed using MAP. To examine which components of BP were most closely associated with the measures of stiffness, an additional analysis was performed in which the MAP, cSBP, and carotid PP (cPP) were included in a regression analysis. To investigate differences associated with renal dysfunction, we performed a case–control subanalysis with 2:1, age (to within 1 year) and sex matching (2 CKD subjects for each control), with similar peripheral and carotid BP levels. All analyses were performed using SPSS 21.0 (SPSS Inc, Chicago, IL), and a P value of <0.05 was considered statistically significant.

Results

All children with CKD were nondialysis dependent, and none had previously received a kidney transplant. There were 49 (26.1%), 47 (25%), 56 (29.8%), 31 (16.5%), and 5 (2.7%) in CKD stages 1 to 5, respectively.

The primary cause of CKD was congenital anomalies of the kidney and urinary tract (hypo/dysplasia, obstructive uropathy, and vesicoureteric reflux±reflux nephropathy) in 92 (48.9%), glomerular diseases in 43 (22.9%), renovascular disease in 13 (6.9%), metabolic renal disease in 14 (7.4%), tubulointerstitial disease in 2 (1.1%), cystic diseases (autosomal recessive polycystic kidney disease and nephronophthisis) in 7 (3.7%), and unknown cause in 17 (9.0%) of the cohort. Subject characteristics are described in Table 1. Those with CKD were comparable with control children for age and ethnicity. There were more boys when compared with girls with CKD, reflecting the usual sex distribution of CKD in children. Those with CKD were significantly shorter (P=0.002) but had comparable BMI SDS (P=0.46) and body surface area (P=0.38) when compared with controls. There were no significant differences in characteristics other than BP between those with BP ≥75th percentile versus BP <75th percentile CKD subgroups (Table 1). A higher proportion of children with stages 3 to 5 of CKD were on antihypertensive

Table 1. Characteristics of Children According to the Presence of CKD and BP ≥75th Percentile

	CKD			Controls	ANOVA		
Measures	All (A)	BP <75th (B)	BP ≥75th (C)	D	B–D	CKD BP <75th vs Control	CKD BP ≥75th vs Control
n (%)	188 (83.2)	144 (63.7)	44 (19.5)	38 (16.8)	…	…	…
Age, y	11.9±3.7	11.8±3.5	12.2±4.2	11.5±3.3	0.70	0.65	0.43
Male sex, n (%)	129 (57.1)	90 (62.5)	26 (59)	13 (34.2)	0.002	0.002	0.025
Ethnicity, n (%)					0.64	0.46	0.28
White	172 (76.1)	108 (75)	36 (81.8)	28 (73.7)			
Asian	24 (10.6)	14 (9.7)	6 (13.6)	4 (10.5)			
Black	20 (8.9)	14 (9.7)	2 (4.6)	4 (10.5)			
Other	10 (4.4)	8 (5.6)	0	2 (5.3)			
Height, m	1.47±0.22	1.47±0.21	1.46±0.23	1.49±0.21	0.77	0.57	0.49
Weight, kg	45.6±19.9	44.4±18.8	49.4±23.0	49.2±23.4	0.22	0.18	0.97
Height SDS	−0.29±1.31	−0.23±1.36	−0.47±1.16	0.44±1.26	0.005	0.007	0.001
Weight SDS	0.28±1.35	0.21±1.32	0.52±1.46	0.85±1.49	0.03	0.01	0.31
BMI SDS	0.58±1.33	0.46±1.33	0.97±1.27	0.76±1.41	0.07	0.23	0.48
BSA, m^2	1.35±0.38	1.33±0.36	1.39±0.43	1.41±0.42	0.44	0.28	0.90
eGFR, (mL/min per 1.73 m^2)	64±33.8	63.9±34.8	64.3±30.4	104.5±9.0	<0.001	<0.001	<0.001
Antihypertensive drugs, n (%)	63 (27.8)	47 (33.5)	16 (80)	0	<0.001	<0.001	<0.001
Serum calcium, mmol/L	2.33±0.10	2.34±0.10	2.31±0.10	2.30±0.07	0.18	0.20	0.81
Serum phosphate, mmol/L	1.38±0.20	1.38±0.20	1.35±0.18	1.38±0.18	0.73	0.95	0.66
Serum Ca–P product, $mmol^2/L^2$	3.19±0.52	3.21±0.54	3.13±0.45	3.18±0.42	0.72	0.84	0.74
Serum iPTH, ng/L*	50 (31–76)	49 (32–76)	52 (29–72)	25 (21–30)	0.10	0.03	0.13
25 (OH) vitamin D3, μg/L*†	53 (41–67)	55 (43–67)	48 (34–70)	65 (49–226)	<0.001	<0.001	0.01

BMI indicates body mass index; BP, blood pressure; BSA, body surface area; Ca–P, calcium–phosphate product; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; and SDS, SD score.

*Median (interquartile range).

†Measured in subset of sample.

treatment (83% [25/30], 72% [13/18], and 80% [4/5]) compared with children in stages 1 to 2 of CKD (26% [10/39] and 31% [11/36]), respectively. The CKD subgroups were also comparable for markers of mineral bone disease including serum calcium, phosphorus, calcium–phosphate product, and intact parathyroid hormone. Vitamin D3 concentrations were significantly lower in children with CKD when compared with controls.

Peripheral and Carotid BP and Pulse Wave Analyses

Children with CKD and BP <75th percentile had similar peripheral and carotid BP to normotensive control children, whereas those with BP ≥75th percentile had significantly higher pSBP, cSBP, and diastolic BP but not pulse pressure (Table 2). Carotid augmentation index was also significantly higher in the children with CKD and BP ≥75th percentile compared with normotensive controls but similar in children with and without CKD in whom BP was similar.

Carotid Biomechanical Properties

Carotid lumen and wall dimensions were similar in all groups. By contrast, circumferential wall stress and functional measures of arterial stiffness differed between children with CKD and BP ≥75th percentile compared with normotensive controls but not between children with and without CKD in whom BP was similar. Thus, circumferential wall stress and Young elastic modulus were significantly greater, and cross-sectional distensibility and compliance coefficient were significantly lower in children with CKD and BP ≥75th percentile than those in controls (Table 3, each $P<0.05$). Thus, the anatomy of the carotid artery was maintained, and functional elastic properties of the wall were impaired only in children with CKD in whom BP was greater than in those without CKD. There was no significant difference between subgroups by CKD stage for any carotid biomechanical property evaluated.

Carotid-Femoral PWV

PWVcf was similar in all 3 groups: 5.34±0.82, 5.24±0.83, and 5.50±1.11 m/s in healthy normotensive control children, those with CKD and BP <75th percentile, and those with CKD and BP ≥75th percentile, respectively.

Relationship of Indices of Carotid Stiffness With BP, eGFR, and Other Characteristics

In all children with CKD, indices of elasticity except circumferential wall stress were independently related to age. Compliance was additionally related to MAP and circumferential wall stress to BMI (Table 4). However, none of the indices of elasticity were independently related to GFR (Table 4). There were no significant differences in arterial measures between boys and

Table 2. Peripheral and Carotid Blood Pressure

	CKD			Controls	ANOVA		
Measures	All (A)	BP <75th (B)	BP ≥75th (C)	D	B–D	CKD BP <75th vs Control	CKD BP ≥75th Vs Control
Peripheral (brachial) blood pressure and heart rate							
pSBP	104±15	100±11	117±19	103±11	<0.001	0.11	<0.001
pDBP	57±13	53±10	71±14	56±10	<0.001	0.11	<0.001
MAP	73±12	69±9	86±12	72±9	0.001	0.053	<0.001
Pulse pressure	46±15	47±12	45±23	47±12	0.90	0.91	0.75
SBP SDS	−0.21±1.22	−0.61±0.87	1.06±1.33	−0.31±0.74	<0.001	0.057	<0.001
DBP SDS	−0.41±1.18	−0.80±0.86	0.85±1.21	−0.56±0.86	<0.001	0.13	<0.001
Heart rate, bpm	76±13	76±13	78±14	76±12	0.68	0.85	0.59
Carotid blood pressure, amplification, and augmentation							
$cSBP_{CWT}$	89±14	85±10	102±17	88±11	<0.001	0.13	<0.001
$cSBP_{RT}$	89±13	85±8	104±14	87±8	<0.001	0.20	<0.001
cPP	32±13	32±11	31±20	32±9	0.91	0.83	0.84
Amplification*	16±6	15±4	19±9	15±4	0.01	0.52	0.03
AIx, %†	5±13	4±13	9±13	0.4±11	0.04	0.12	0.01

AIx indicates augmentation index; BP, blood pressure; CKD, chronic kidney disease; cPP, carotid pulse pressure; $cSBP_{CWT}$, carotid SBP measured using carotid-wall tracking; $cSBP_{RT}$, radial tononometric estimate of cSBP; MAP, mean arterial pressure; pDBP, peripheral diastolic BP; pSBP, peripheral systolic BP; and SDS, SD score.

*Amplification, pSBP−$cSBP_{CWT}$ calculated as the difference between peripheral and carotid systolic BP.

†AIx (%) performed using radial tonometry based on pulse wave analyses.

girls; the relative effect (sequential R^2 coefficient) of age, sex, CKD or control group, and MAP on arterial measures is shown in Tables S1 and S2 in the online-only Data Supplement). All measures of elasticity were related to cPP (Table S3).

In the case–control analysis, there was a significant difference in GFR between the CKD and control group (54.3±17.7 versus 103.5±8.5 mL/min per 1.73 m^2; P<0.001). Despite this marked difference in GFR, measures of arterial stiffness were similar in age- and sex-matched control children with similar BP (Table 5).

Discussion

To our knowledge, this is the first study to provide a comprehensive characterization of arterial biomechanics in children with CKD. Our main findings are novel and 2-fold: (1) when children with nondialysis CKD are compared with healthy

Table 3. Arterial Biomechanical Properties

	CKD			Controls	ANOVA		
Measures	All (A)	BP <75th (B)	BP ≥75th (C)	D	B–D	CKD BP <75th vs Control	CKD BP ≥75th vs Control
Carotid-femoral aortic stiffness (n=226)							
Carotid-femoral PWV, m/s	5.3±0.9 (n=188)	5.2±0.8 (n=144)	5.5±1.1 (n=44)	5.3±0.8 (n=38)	0.23	0.48	0.48
Anatomic measures							
Internal diastolic diameter, $m\times10^{-3}$	5.43±0.53 (n=90)	5.42±0.48 (n=70)	5.50±0.67 (n=20)	5.47±0.55 (n=30)	0.78	0.59	0.90
Internal diastolic diameter, $m\times10^{-3}$ per 1.73 m^2	2.36±0.57 (n=90)	2.38±0.53 (n=70)	2.28±0.71 (n=20)	2.44±0.66 (n=30)	0.64	0.62	0.41
Intima-media thickness, $m\times10^{-6}$	437±65 (n=102)	435±61 (n=79)	441±80 (n=23)	430±61 (n=32)	0.83	0.67	0.58
Wall CS area, $m^2\times10^{-6}$	8.1±1.6 (n=90)	8.0±1.6 (n=70)	8.2±1.6 (n=20)	8.1±1.8 (n=28)	0.87	0.88	0.75
Thickness/radius ratio	0.14±0.02 (n=90)	0.14±0.02 (n=70)	0.14±0.03 (n=20)	0.14±0.02 (n=30)	0.65	0.37	0.46
Functional elasticity measures							
Circumferential wall stress, kPa	67.7±17.7 (n=89)	63.3±12.8 (n=70)	83.6±23.5 (n=19)	68.7±14.9 (n=30)	<0.001	0.07	0.009
CS distensibility, $kPa^{-1}\times10^{-3}$	104±38 (n=88)	107±39 (n=69)	92±31 (n=19)	114±33 (n=30)	0.13	0.39	0.03
CS compliances coefficient, $m^2\ kPa^{-1}\times10^{-6}$	2.3±0.7 (n=88)	2.4±0.7 (n=69)	2.1±0.7 (n=19)	2.6±0.7 (n=30)	0.06	0.13	0.02
Young elastic modulus, $kPa\times10^3$	0.132±0.059 (n=88)	0.127±0.055 (n=69)	0.151±0.068 (n=19)	0.109±0.049 (n=29)	0.04	0.14	0.02

BP indicates blood pressure; CKD, chronic kidney disease; CS, cross-section; and PWV, pulse wave velocity.

Table 4. Multiple Linear Regression Analysis of Correlates of Functional Elasticity With Brachial Mean Arterial Pressure in Children With Nondialysis Chronic Kidney Disease

Variable	Coefficient	95% CI	*P* Value	Model-Adjusted R^2
Circumferential wall stress, kPa				0.088
BMI, kg/m^2	0.817	0.153, 1.482	0.017	
CS distensibility, kPa$^{-1}\times10^{-3}$				0.124
Age, y	−4.722	−7.661 to −1.784	0.002	
CS compliance coefficient, m^2 kPa$^{-1}\times10^{-6}$				0.112
MAP, mm Hg	0.016	0.000 to 0.031	0.046	
Age, y	−0.094	−0.154 to −0.033	0.003	
Young elastic modulus, kPa$\times10^3$				0.088
Age, y	0.006	0.002 to 0.011	0.009	

Confounders in all models included MAP (not included in circumferential wall stress), glomerular filtration rate in mL/min per 1.73 m^2, age, sex, BMI, heart rate, antihypertensive treatment (yes/no), and markers of mineral bone disease. BMI indicates body mass index; CI, confidence interval; CS, cross-section; and MAP, mean arterial pressure.

children with normal renal function, at similar levels of peripheral and carotid BP, anatomic and functional elastic properties of the large arteries, such as lumen diameter, wall thickness, PWVcf, and elastic modulus, remain comparable; but (2) when children with CKD and suboptimal BP control (≥75th percentile) are compared with normotensive controls, there are significant differences in functional elastic properties of the carotid artery. Furthermore, we found neither independent relationship between any biomechanical property and GFR when age, sex, and BP (both peripheral and carotid) were adjusted for nor a difference between biomechanical properties in children with or without CKD using an age and sex case–control analysis in children with similar BP. This suggests that BP rather than renal disease per se is the main determinant of functional arterial elasticity in children with predialysis CKD.

These findings contrast to those of previous studies that have reported structural and functional changes including increased arterial wall thickness, increased arterial wall cross-sectional area, and stiffness[9–13] in children with CKD compared with healthy controls. Children with predialysis stages of CKD in these studies had abnormal mechanical arterial measures that were associated with increased BP, dyslipidemia, and markers of mineral bone metabolism,[9–11] with stronger associations in subjects on dialysis.[9–13] Metabolic derangements associated with mineral bone disease in CKD are well known to contribute to arterial calcification and could explain the changes seen in children with advanced CKD.[25] Mitsnefes et al[11] have reported that, in a group of children with CKD, including children on dialysis, carotid IMT and arterial stiffness are associated with disturbances of calcium–phosphate product metabolism and hyperparathyroidism. In this study, children with predialysis CKD had increased carotid IMT and measures of arterial stiffness compared with control children, but this may have been explained by BP that was higher in children with predialysis CKD compared with controls. Thus, their results are consistent with those of this study.

However, Briet et al[6] compared biomechanical properties of the carotid artery (similar to those measured in this study) in adults with CKD with those in patients with hypertension (but without CKD) and healthy controls. Their main finding was that, compared with controls with similar levels of BP, patients with CKD had an outward remodeling of the carotid artery with enlargement of the lumen diameter predominating over carotid-wall thickening and stiffening. This may be a response to increased wall stress, which together with carotid diameter was independently related to age, BP, and GFR. This study, by contrast, reveals no evidence of any form of remodeling in children with predialysis CKD. We did observe higher wall stress in the CKD group with higher BP compared with normotensive controls (explicable by the difference in BP alone), but even in this group, there was no evidence of remodeling. This may reflect a relatively short duration of hypertension in children with CKD. Were hypertension sustained, this

Table 5. Case–Control Analysis of Age- and Sex-Matched CKD Children With Healthy Controls, With Similar Peripheral and Carotid BP Levels

Measures	Controls	CKD	*P* Value
n, %	29	58	…
Age, y	11.8±3.4	11.7±3.4	0.944
Male sex, n (%)	13 (44.8)	33 (56.9)	0.287
eGFR, mL/min per 1.73 m^2	103.5±8.5	54.3±17.7	<0.001
Height SDS	0.46±1.15	−0.08±1.29	0.084
BMI SDS	0.56±1.44	0.71±0.99	0.622
pSBP	103±11	102±11	0.957
pDBP	56±10	55±11	0.838
MAP	71±8	71±10	0.863
Pulse pressure	47±13	47±9	0.891
SBP SDS	−0.39±0.75	−0.36±0.91	0.88
Antihypertensive drugs, n (%)	0	18 (31)	<0.001
Heart rate, bpm	76±13	74±13	0.61
$cSBP_{CWT}$	88±11	87±11	0.803
Carotid-femoral PWV, m/s	5.4±0.9	5.5±0.9	0.695
Internal diastolic diameter, m$\times10^{-3}$	5.52±0.57	5.39±0.45	0.32
Internal diastolic diameter, m$\times10^{-3}$ per 1.73 m^2	2.47±0.70	2.45±0.60	0.912
Intima-media thickness, m$\times10^{-6}$	434±62	443±53	0.542
Wall CS area, m$^2\times10^{-6}$	8.3±1.9	8.1±1.3	0.749
Thickness/radius ratio	0.135±0.014	0.142±0.016	0.112
Circumferential wall stress, kPa	68.1±13.4	63.9±11.1	0.193
CS distensibility, kPa$^{-1}\times10^{-3}$	113±35	105±36	0.405
CS compliance coefficient, m^2 kPa$^{-1}\times10^{-6}$	2.7±0.8	2.4±0.6	0.092
Young elastic modulus, kPa$\times10^3$	0.109±0.053	0.124±0.041	0.233

BP indicates blood pressure; BMI, body mass index; CKD, chronic kidney disease; CS, cross-section; $cSBP_{CWT}$, carotid systolic BP measured using carotid-wall tracking; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; pDBP, peripheral diastolic BP; pSBP, peripheral SBP; PWV, pulse wave velocity; and SDS, SD score.

persistent increase in circumferential wall stress might result in arterial remodeling as described by Briet et al[6]

Other studies have demonstrated childhood BP to predict increased arterial stiffness in adulthood.[26–28] In the Young Finn study, reduced carotid arterial compliance and increased Young elastic modulus were predicted by increased SBP and skinfold thickness/BMI during childhood.[28] Findings with respect to PWVcf have been more variable with an association of adult PWVcf with childhood BP reported in the Bogalausa[26] but not in the Atherosclerosis Risk in Young Adults (ARYA) study.[27] It is possible that Young elastic modulus is a more sensitive index of susceptibility to the influence of BP than is PWV (which is proportional to the square root of *E*), and this would be consistent with findings of this study where we observed increased Young elastic modulus in the carotid but not increased PWVcf in children with CKD and higher BP compared with controls. It is also possible that, as a more muscular artery, the carotid artery is more susceptible to BP-induced remodeling than the aorta (the major contributor to PWVcf).

In healthy children, both BP and BMI track throughout childhood and subsequently as young adults.[29,30] In children with CKD, BP control deteriorates with worsening renal function,[31,32] and both BP and BMI increase after transplantation from pretransplantation levels.[33–36] We would suggest, therefore, that persistently, high BP and BMI in children with predialysis CKD are likely to lead to increased functional stiffness of the carotid artery. BP reduction may be an effective means to protect against arterial stiffening or remodeling in children with CKD and hypertension that persists into adulthood. In this study, we found no association of arterial properties with metabolic derangements. However, phosphate was well controlled in the children in this study. In children with more advanced CKD, particularly those on dialysis, it is likely that metabolic derangements contribute to arterial stiffening, and in this case, BP reduction may be of more limited value.

The main limitation of our study is its cross-sectional nature that limits conclusions on causality. Nearly a third of children with CKD were receiving antihypertensive therapy (usually as monotherapy in the form of angiotensin-converting enzyme inhibitors). It is possible that angiotensin-converting enzyme inhibitors may affect arterial properties, although subgroup analyses did not suggest a specific effect of treatment. We acknowledge though that it remains difficult to discount the inherent confounding in this cohort particularly from treatments causally associated with CKD. However, our results are applicable to the children with CKD representative of those in the general population with CKD (in whom a similarly high proportion is on antihypertensive treatment).

Perspectives

This study provides data that changes in functional elastic properties of the carotid artery are some of the earliest identifiable biomechanical properties in children with nondialysis CKD. We observed no changes in carotid lumen and wall dimensions, findings that are in contrast to those of previous studies. These changes seem to be related primarily to BP and not GFR or markers of mineral bone disease. Because of the smaller number of subjects with more advanced stages of CKD, these findings need further testing in a larger cohort with advanced CKD. BP reduction may be an effective means to protect against arterial stiffening and needs to be evaluated using a controlled clinical trial.

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Disclosures

P.J. Chowienczyk and King's College London have an interest in Centron Diagnostics, a King's College London spin-out company developing technology for measurement of central blood pressure (not used in this study). The other authors report no conflicts.

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Novelty and Significance

What Is New?

- This study provides a comprehensive characterization of arterial biomechanics in children with chronic kidney disease using state of the art techniques.
- This study observed that the changes in elastic properties of the carotid artery were related to increased blood pressure and not decreased estimated glomerular filtration rate.

What Is Relevant?

- Children with chronic kidney disease with suboptimal blood pressure control (≥75th percentile) when compared with normotensive healthy controls have significant differences in their functional elastic arterial properties.
- Changes in the functional elastic properties of the carotid artery are some of the earliest identifiable biomechanical properties in children with nondialysis chronic kidney disease.

Summary

In children with nondialysis chronic kidney disease, changes in elastic properties of the carotid artery are related primarily to blood pressure and not to glomerular filtration rate. Blood pressure reduction may be an effective means to protect against arterial stiffening and needs to be evaluated using a controlled clinical trial.

Decreased Arterial Elasticity in Children With Nondialysis Chronic Kidney Disease Is Related to Blood Pressure and Not to Glomerular Filtration Rate

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DECREASED ARTERIAL ELASTICITY IN CHILDREN WITH NON-DIALYSIS CHRONIC KIDNEY DISEASE RELATES TO BLOOD PRESSURE AND NOT TO GFR

SHORT TITLE: ARTERIAL ELASTICITY IN CHILDREN WITH CKD

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Table S1: Comparison of arterial measures by gender in healthy children and those with CKD.

Measures	Controls			CKD		
	Male	Female	P value	Male	Female	P value
Age (years)	12.4± 3.2	11.1± 3.4	0.248	11.8± 3.8	12.2± 3.4	0.463
eGFR (ml/min/1.73m^2)*	101.6± 4.9	106.0± 10.2	0.154	61.5± 31.2	68.2± 37.4	0.187
MAP (mmHg)†	74± 10	70± 8	0.257	72± 12	73± 12	0.639
cSBP$_{CWT}$ (mmHg)‡	92± 11	86± 10	0.154	88± 14	89± 13	0.800
Circumferential wall stress (kPa)	73.4±12.7	66.6±15.6	0.257	66.0±17.5	69.7±17.8	0.319
Cross-sectional Distensibility (kPa^{-1} x 10^{-3})	110±35	116±34	0.692	105±41	103±35	0.855
CS Compliance coefficient (m^2 kPa^{-1} x 10^{-6})	2.8±0.8	2.6±0.7	0.579	2.4±0.8	2.3±0.6	0.438
Young's Elastic Modulus (kPa x 10^3)	0.120±0.030	0.104±0.056	0.438	0.133±0.067	0.130±0.048	0.807

*eGFR, glomerular filtration rate; †MAP, mean arterial pressure; ‡cSBP$_{CWT}$, carotid SBP measured using carotid-wall tracking

Table S2: Multivariate analyses with sequential R^2 changes for arterial measures showing the relative influence of age and mean arterial pressure following adjustment for gender and CKD* or control group.

Arterial parameter	Variable	β	P Value	R^2	Adjusted R^2
Circumferential wall stress (kPa)	Age	1.717	<0.001	0.112	0.105
	Age	1.736	<0.001	0.116	0.101
	Sex	-2.193	0.459		
	Age	1.768	<0.001	0.119	0.096
	Sex	-1.791	0.555		
	CKD/ control group	2.19	0.533		
Cross-sectional Distensibility (kPa^{-1} x 10^{-3})	Age	-4.569	<0.001	.167	.160
	Age	-4.565	<0.001	.167	.153
	Sex	-.467	.941		
	Age	-4.474	<0.001	.173	.151
	Sex	.691	.914		
	CKD/ control group	6.372	.391		
	Age	-4.860	<0.001	.178	.149
	Sex	.889	.890		
	CKD/ control group	6.345	.394		
	MAP†	.248	.416		
CS Compliance coefficient (m^2 kPa^{-1} x 10^{-6})	Age	-.046	.025	.042	.034
	Age	-.046	.024	.046	.029
	Sex	.083	.532		
	Age	-.042	.039	.075	.051
	Sex	.137	.310		
	CKD/ control group	.296	.059		
	Age	-.069	.002	.135	.105
	Sex	.151	.250		
	CKD/ control	.294	.054		

	group				
	MAP	.017	.006		
Young's Elastic Modulus (kPa x 10^3)	Age	.007	<0.001	.168	.161
	Age	.007	<0.001	.172	.157
	Sex	.007	.470		
	Age	.007	<0.001	.184	.163
	Sex	.005	.650		
	CKD/ control group	-.015	.194		
	Age	.008	<0.001	.197	.168
	Sex	.004	.689		
	CKD/ control group	-.015	.198		
	MAP	-.001	.188		

*CKD, chronic kidney disease; †MAP, mean arterial pressure

Table S3: Results of multivariable regression analyses of relevant functional elastic carotid artery parameters with brachial mean arterial pressure, carotid systolic BP and carotid pulse pressure. A separate model was constructed for each blood pressure component and adjusted with the same confounders throughout (as shown in Table 4 in the manuscript). Coefficients for the different components of peripheral and carotid pressure are shown from each of the models (coefficients for confounders not shown).

Variable	Coefficient	SE	P	model adjusted R^2
Circumferential wall stress (kPa)				
Mean arterial pressure (mmHg)	-	-	-	-
Carotid systolic BP (mmHg)	0.821	0.131	<0.001	0.379
Carotid pulse pressure (mmHg)	-0.359	0.248	0.152	0.097
Cross-sectional Distensibility (kPa^{-1} x 10^{-3})				
Mean arterial pressure (mmHg)	0.518	0.441	0.245	0.096
Carotid systolic BP (mmHg)	-0.198	0.443	0.657	0.078
Carotid pulse pressure (mmHg)	-	-	-	-
CS Compliance coefficient (m^2 kPa^{-1} x 10^{-6})				
Mean arterial pressure (mmHg)	0.016	0.008	0.046	0.112
Carotid systolic BP (mmHg)	0.001	0.009	0.885	0.010
Carotid pulse pressure (mmHg)	-	-	-	-
Young's Elastic Modulus (kPa x 10^3)				
Mean arterial pressure (mmHg)	-0.001	0.001	0.084	0.078
Carotid systolic BP (mmHg)	0.0001	0.001	0.811	0.030
Carotid pulse pressure (mmHg)	0.005	0.001	<0.001	0.470