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Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease

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Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular morbidity and mortality. Arterial stiffness and remodeling have been well documented in patients with end-stage renal disease, but little is known about arterial phenotype in CKD patients with moderate reduction in glomerular filtration rate (GFR). In total, 95 patients (58 ± 15 years, mean ± s.d.) with CKD and GFR measured by renal clearance of ^{51}Cr-ethylenediaminetetraacetate were compared to 121 hypertensive patients without CKD (59 ± 11 years), and 57 normotensive subjects (56 ± 6 years). Common carotid artery diameter, intima–media thickness (IMT), distensibility, and Young's elastic modulus were noninvasively determined with a high-definition echotracking system. Patients with CKD had a significantly larger carotid internal diameter than in hypertensives and normotensives (6.32 ± 1.05, 5.84 ± 0.74, and 5.50 ± 0.64 m × 10^{-3}, respectively; $P < 0.001$), resulting in 25% and 11% increases in circumferential wall stress, respectively, since no significant difference in IMT was observed. Carotid distensibility and elastic modulus did not significantly differ between CKD and hypertensives; normotensives had significantly higher distensibility and lower elastic modulus than CKD and hypertensive patients. Carotid-femoral pulse wave velocity was significantly higher in CKD patients than in hypertensives and normotensives. In multivariate analyses either involving the entire population or restricted to CKD patients, GFR was independently and strongly related to carotid diameter and elastic modulus. Arterial enlargement and increased arterial stiffness occur in parallel with the decline in renal function in patients with mild-to-moderate CKD.

Kidney International (2006) **69,** 350–357. doi:10.1038/sj.ki.5000047

KEYWORDS: carotid arteries; ultrasonography; pathology; mechanical stresses; kidney disease; hypertension; glomerular filtration rate

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Received 29 June 2005; revised 9 August 2005; accepted 12 August 2005

Chronic kidney disease (CKD) is a worldwide public health problem. Epidemiological studies have shown a rising prevalence and incidence of CKD in all Western countries.[1] Evolution towards end-stage renal disease exposes patients to a well-known increased risk of cardiovascular morbidity and mortality.[2] CKD has also been recently individualized as an independent risk factor for cardiovascular disease, proportionally with the decline in glomerular filtration rate (GFR), indirectly estimated either from the Modification of Diet in Renal Disease (MDRD) or Cockcroft formula.[2–4]

Subclinical markers of arterial disease include aortic stiffness and carotid intima–media thickness (IMT). Aortic stiffness has shown an independent predictive value for total and cardiovascular mortality, coronary heart disease, and fatal stroke, in essential hypertensive patients,[5–7] end-stage renal disease,[8,9] and diabetic patients.[10] The predictive values of aortic and carotid stiffness for cardiovascular events were the strongest in patients with end-stage renal disease (ESRD).[8,9] Carotid IMT has shown an independent predictive value for coronary heart disease and stroke in a general population,[11,12] and for cardiovascular mortality in ESRD patients.[13]

Although arterial phenotype has been well documented in ESRD,[14–16] available data about arterial wall properties in patients with mild-to-moderate CKD, not yet on dialysis therapy,[17–19] are hampered by indirect estimation of GFR.

Pathogenic mechanisms of arterial disease in CKD include various mechanisms such as endothelial dysfunction,[20] leading to vasoconstriction and arterial growth, oxidant stress,[21,22] dysfunction of nitric oxide metabolism,[23] inflammation,[24] glycoxidation,[25] and vascular calcification.[26] As these mechanisms are also involved in the progression of kidney disease,[22,27] we hypothesized that the reduction in GFR would be related to the extent of arterial stiffness and thickness.

We took advantage of the high precision and repeatability of the measurements of GFR by ^{51}Cr-ethylenediaminetetraacetate (EDTA) and arterial parameters by echotracking techniques to (1) characterize the functional and structural properties of large arteries in patients with CKD, by comparison with patients with normal renal function having

either hypertension or not, and (2) put in evidence the relationship between GFR reduction and the extent of arterial damage. The present study is the cross-sectional analysis of patients with CKD entering a 3-year longitudinal follow up of renal function together with large artery properties, the REN-ART (RENal dysfunction and large ARTeries properties: a longitudinal study).

RESULTS

The characteristics of the populations are presented in Table 1. CKD, hypertensive, and normotensive subjects were comparable for age and sex ratio. In addition, hypertensives and CKD patients had no significant difference in brachial systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and PP. CKD patients had more often diabetes and hypercholesterolemia than hypertensive patients. According to the recommendations in use, CKD patients were more intensively treated with antihypertensive drugs (mostly blockers of the renin–angiotensin–aldosterone system) and statins. Blood cholesterol was subsequently significantly lower in CKD patients.

Arterial geometry

In CKD patients, carotid internal diameter, normalized to body surface area (BSA), was 9 and 12% higher than in hypertensive and normotensive subjects, respectively (analysis of variance (ANOVA), $P<0.001$) (Table 2). Carotid IMT was not significantly different between hypertensive, CKD, and normotensive subjects. In CKD patients, carotid wall cross-sectional area (WCSA) was 3 and 16% higher than in hypertensive and normotensive subjects, respectively (ANOVA, $P<0.001$). According to a higher carotid diameter and a similar IMT, wall-to-lumen ratio was significantly lower in CKD than in hypertensives ($P<0.05$). In CKD patients, carotid circumferential wall stress was 11 and 25% higher than in hypertensive and normotensive subjects, respectively (ANOVA, $P<0.001$).

In multivariate analysis involving the entire population (Table 3), carotid PP, age, and GFR (MDRD) were all independently related to carotid internal diameter, and GFR explained 9% of the variance. In CKD patients, a significant, negative, and independent relationship between GFR (^{51}Cr-EDTA) and carotid internal diameter was found (Table 4 and Figure 1): the lower the GFR, the higher the diameter.

Table 1 | Characteristics of studied populations

Parameters	Chronic kidney disease (CKD)	Hypertensives (HT)	Normotensives (NT)	*P*-value			
				ANOVA	CKD vs HT	CKD vs NT	HT vs NT
N	95	121	57				
Age (years)	58.4±14.9	58.8±10.6	56.3±6.1	0.38	NS	NS	NS
Sex ratio (% men)	74	59	59	0.07	NS	NS	NS
BSA (m^2)	1.8±0.2	1.8±0.2	1.8±0.2	0.22	NS	NS	NS
BMI (kg/m^2)	25.6±4.5	25.5±3.2	23.5±2.8	<0.001	NS	<0.05	<0.05
Smoking (%)	13	9	17.5	0.15	NS	NS	NS
Hypertension (%)	89	100	0	<0.001	<0.05	<0.05	<0.05
Diabetes (%)	11	5	0	<0.001	<0.05	<0.05	<0.05
Hypercholesterolemia (%)	71	28	23	<0.001	<0.05	<0.05	<0.05
GFR MDRD ($ml/min/1.73\,m^2$)	31±14	86±24	92.2±21.2	<0.001	<0.05	<0.05	NS
GFR ^{51}Cr-EDTA ($ml/min/1.73\,m^2$)	36±16	—	—	<0.001	<0.05	—	—
Glycemia (mmol/l)	5.5±1.2	5.6±0.2	5.0±0.7	0.05	NS	<0.05	<0.05
Cholesterolemia (mmol/l)	4.6±0.9	5.5±1.0	5.6±1.0	<0.001	<0.05	<0.05	NS
Triglyceridemia (mmol/l)	1.5±0.9	1.5±2.3	1.21±0.8	0.54	NS	NS	NS
Cholesterol HDL (mmol/l)	1.1±0.3	1.4±0.5	1.4±0.3	<0.001	<0.05	<0.05	NS
Cholesterol LDL (mmol/l)	2.9±0.9	3.9±1.2	2.63±0.8	<0.001	<0.05	NS	<0.05
Antihypertensive therapy (%)	94	87	0				
No. of antihypertensive drugs	2.49±1.24	1.68±1.23	—	<0.001	<0.05	—	—
Patients with RAS blockers (%)	84	69	—	<0.001	<0.05	—	—
Patients with statins (%)	60	15	—	<0.001	<0.05	<0.05	NS
Patients with calcium-channel blockers (%)	48	34	—	<0.001	<0.05	—	—
Brachial blood pressure							
Systolic BP (mmHg)	134±20	134±19	117±12	<0.001	NS	<0.05	<0.05
Mean BP (mmHg)	94±11	96±12	86±8	<0.001	NS	<0.05	<0.05
Diastolic BP (mmHg)	74±9	77±10	71±7	<0.001	NS	<0.05	<0.05
Pulse pressure (mmHg)	60±17	57±14	46±9	<0.001	NS	<0.05	<0.05
Heart rate (bpm)	64±10	65±10	66±9	0.5	NS	NS	NS
Carotid blood pressure							
Systolic BP (mmHg)	124±20	128±22	109±14	<0.001	NS	<0.05	<0.05
Diastolic BP (mmHg)	73±12	77±11	71±8	<0.001	<0.05	NS	<0.05
Pulse pressure (mmHg)	50±16	50±17	46±9	<0.001	NS	<0.05	<0.05

ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; BSA, body surface area; GFR, glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; RAS renin–angiotensin system.

Table 2 | Carotid artery and aortic parameters in patients with chronic kidney disease and in control subjects

Parameters	Chronic kidney disease (CKD)	Hypertensives (HT)	Normotensives (NT)	*P*-value ANOVA	CKD vs HT[1]	CKD vs NT[1]	HT vs NT[1]
Carotid artery							
Internal diastolic diameter ($m \times 10^{-3}$)	6.32 ± 1.05	5.84 ± 0.74	5.50 ± 0.64	< 0.001	< 0.05	< 0.05	NS
Internal diastolic diameter ($m \times 10^{-3}/1.73\ m^2$)	6.03 ± 0.95	5.52 ± 0.68	5.38 ± 0.69	< 0.001	< 0.05	< 0.05	NS
Intima-media thickness ($m \times 10^{-6}$)	727 ± 157	756 ± 137	714 ± 96	NS	NS	NS	NS
Wall cross-sectional area ($m^2 \times 10^{-6}$)	16.2 ± 4.9	15.7 ± 3.7	13.9 ± 2.7	< 0.001	NS	< 0.05	< 0.05
Thickness/radius ratio (*h*/*r*)	0.23 ± 0.05	0.26 ± 0.06	0.26 ± 0.05	< 0.001	< 0.05	< 0.05	NS
Circumferential wall stress (kPa)	56.3 ± 15.2	50.8 ± 13.1	45.1 ± 10.6	< 0.001	< 0.05	< 0.05	< 0.05
CS distensibility ($kPa^{-1} \times 10^{-3}$)	24.0 ± 14.1	21.2 ± 10.3	29.4 ± 13.2	< 0.001	NS	< 0.05	< 0.05
CS compliance ($m^2\,kPa^{-1} \times 10^{-7}$)	7.0 ± 3.0	5.6 ± 2.7	7.0 ± 0.3	< 0.001	< 0.05	NS	< 0.05
Young's Elastic modulus ($kPa \times 10^3$)	0.517 ± 0.325	0.497 ± 0.283	0.330 ± 0.147	< 0.001	NS	< 0.05	< 0.05
Carotid pulse pressure (mmHg)	50 ± 16	50 ± 17	46 ± 9	< 0.001	NS	< 0.05	< 0.05
Augmentation index (%)	32 ± 13	35 ± 14	35 ± 13	NS	NS	NS	NS
Aorta							
Carotid-femoral pulse wave velocity (m/s)	11.3 ± 2.7	10.6 ± 2.02	9.5 ± 1.07	< 0.001	< 0.05	< 0.05	< 0.05

[1]GLM-ANOVA completed by Bonferonni *post-hoc* tests.

Table 3 | Multivariate relationships of aortic and carotid parameters in the three groups of patients considered as a whole

Parameters	In/Out	R^2 increment %	Beta coeff.	Lower CI	Upper CI	*P*
Dependent variable: carotid diameter (BSA adjusted)						
MBP	IN	3	0.01	0.002	0.017	0.001
Age	IN	10	0.018	0.011	0.024	0.0001
Glomerular filtration rate (MDRD)	IN	9	−0.006	−0.008	−0.004	0.0001
Heart rate	OUT	—	—	—	—	—
Carotid pulse pressure	OUT	—	—	—	—	—
R^2=0.25						
Sqrt(MSE)=0.57						
Dependent variable: carotid circumferential wall stress						
Carotid pulse pressure	IN	4	0.16	0.07	0.25	0.0001
Age	IN	6	−0.27	−0.4	−0.14	0.0001
Glomerular filtration rate (MDRD)	IN	4	−0.08	−0.125	−0.04	0.0001
Heart rate	OUT	—	—	—	—	—
R^2=0.12						
Sqrt(MSE)=10.9						
Dependent variabe: carotid Young's elastic modulus						
Mean BP	IN	25	8.4	6.8	9.9	0.0001
Age	IN	13	6.2	4.7	7.8	0.0001
Glomerular filtration rate (MDRD)	IN	2	−0.9	−1.45	−0.35	0.001
Heart rate	OUT	—	—	—	—	—
R^2=0.44						
Sqrt(MSE)=135.5						
Dependent variable: Carotid-femoral pulse wave velocity						
Sex	IN	1	−0.31	−0.62	−0.001	0.05
Mean BP	IN	17	0.06	0.05	0.08	0.0001
Heart rate	IN	2	0.03	0.01	0.04	0.0001
Age	IN	26	0.8	0.07	0.09	0.0001
Glomerular filtration rate (MDRD)	IN	2	−0.007	−0.012	−0.003	0.001
R^2=0.52						
Sqrt(MSE)=1.135						

MBP, mean blood pressure; CI, consicence interval, BP, blood pressure.

In multivariate analysis involving the entire population (Table 3), MBP, age, and GFR (MDRD) were all independently related to circumferential wall stress, and GFR explained 4% of the variance. In CKD patients, a significant, negative, and independent relationship between GFR (^{51}Cr-EDTA) and circumferential wall stress was found, GFR explaining 7% of the variance (Table 4 and Figure 1).

Table 4 | Multivariate relationships of aortic and carotid parameters in patients with chronic kidney disease

Parameters	In/Out	R^2 increment %	Beta coeff.	Lower CI	Upper CI	P
Dependent variable: CCA diameter (BSA adjusted)						
Age	IN	16	0.02	0.012	0.029	0.0001
Heart rate	IN	5	−0.02	−0.03	−0.0004	0.03
Calcium antagonist use	IN	3	0.29	0.03	0.56	0.03
Glomerular filtration rate (^{51}Cr-EDTA)	IN	3	−0.009	−0.02	−0.001	0.03
R^2=0.44						
Sqrt(MSE)=0.54						
Dependent variable: Circumferential wall stress						
Calcium-channel blockers	IN	6	7.8	2.1	13.4	0.01
Cholesterol HDL	IN	4	−12.7	−21.6	−3.9	0.03
Glomerular filtration rate (^{51}Cr-EDTA)	IN	7	−0.23	0.39	−0.07	0.008
R^2=0.21						
Sqrt(MSE)=13.9						
Dependent variabe: E_{inc}						
Mean blood pressure	IN	19	10.1	6.7	13.5	0.0001
Age	IN	18	6.7	4	9.3	0.0001
Glomerular filtration rate (^{51}Cr-EDTA)	IN	3	−2.5	−4.7	−0.2	0.03
Diuretic use	OUT	—	—	—	—	—
R^2=0.58						
Sqrt(MSE)=160						
Dependent variable: CF-PWV						
MBP	IN	15	0.09	0.06	0.12	0.0001
Age	IN	33	0.09	0.07	0.12	0.0001
Glomerular filtration rate (^{51}Cr-EDTA)	OUT	—	—	—	—	—
R^2=0.63						
Sqrt(MSE)=1.39						

CCA, common carotid artery; BSA, body surface area; ^{57}Cr-EDTA, ^{51}Cr-ethylenediaminetetraacetate; MBP, mean blood pressure; CF-PWV, carotid femoral pulse wave velocity.

Elastic properties of the common carotid artery and aorta

Carotid distensibility was significantly lower in CKD than in normotensive subjects (CKD vs normotensives, −18%, $P<0.001$), but did not differ between CKD and hypertensives. Carotid Young's elastic modulus (E_{inc}) did not differ between CKD and hypertensive patients, but was significantly higher in CKD than in normotensive subjects (+57%, $P<0.001$). Carotid compliance was significantly higher in CKD patients than in hypertensive patients (CKD vs hypertensive patients, +25%, $P<0.001$) according to an increase in internal diameter. In multivariate analysis involving the entire population (Table 3), MBP, age, and GFR (MDRD) were all independently related to carotid elastic modulus, with age explaining 13% of the variance and GFR 2%. In CKD patients, a significant, negative, and independent relationship between GFR (^{51}Cr-EDTA) and carotid elastic modulus was confirmed (Table 4 and Figure 1), with GFR explaining 3% of the variance. On the contrary, carotid elastic modulus was the only significant determinant of GFR (^{51}Cr-EDTA), explaining 12% of variance.

In CKD patients, aortic stiffness, assessed by carotid-femoral pulse wave velocity (CF-PWV), was 7 and 19% higher than in hypertensive and normotensive subjects, respectively (ANOVA, $P<0.001$) (Table 2). In multivariate analysis involving the entire population (Table 3), sex, MBP, HR, age, and GFR (MDRD) were all independently related to aortic stiffness, with age explaining 26% of the variance and GFR 2%. We did not find significant and independent relationship between GFR (^{51}Cr-EDTA) and CF-PWV in the population of CKD patients (Table 4).

DISCUSSION

The present study is the first one to report relationships between GFR, measured with the gold standard ^{51}Cr-EDTA technique, and arterial parameters, in mild-to-moderate CKD patients. The three major findings are the following. Compared to hypertensive patients without CKD, patients with CKD had an outward remodeling of the carotid artery, with enlargement of lumen diameter predominating over carotid wall thickening and stiffening. Estimated GFR (MDRD) was independently related to arterial diameter, circumferential wall stress, and aortic and carotid stiffness in the whole population. Compared to age and blood pressure (BP), GFR had a similar independent influence on arterial enlargement, but a weaker influence on arterial stiffness. In addition, and most importantly, GFR measured with ^{51}Cr-EDTA renal clearance is a strong and independent determinant of arterial dilatation and stiffening within CKD patients. Carotid stiffness was the only determinant of GFR (^{51}Cr-EDTA), accounting for 12% of variance.

Interpretation of findings

Compared to hypertensive patients without CKD, the remodeling of the carotid artery in CKD patients involves

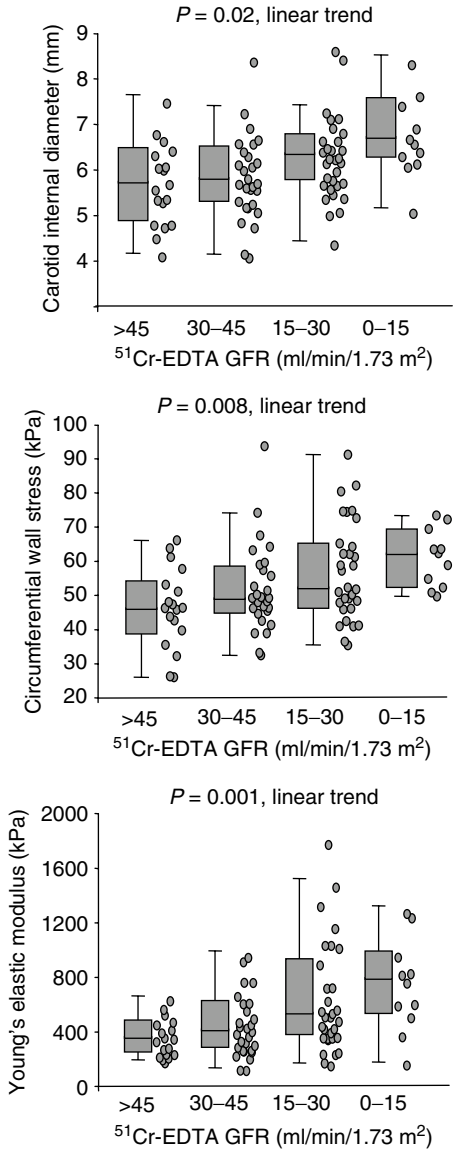

Figure 1 | Box plots of CCA internal diameter, circumferential wall stress, and Young's elastic modulus for patients with CKD, and ^{51}Cr-EDTA GFR as the classification variable. Boxes represent interquartile range (IQR, i.e. 50% of the distribution); the horizontal bar is the median; upper whisker represents the 75th percentile + 1.5 IQR; lower whisker 25th percentile−1.5 IQR.

mainly an enlargement of lumen diameter predominating over carotid wall thickening, in parallel with stiffening. Although arterial dilatation has been shown in patients with ESRD,[16] to our knowledge, this is the first report in patients with mild-to-moderate CKD, not yet on dialysis therapy.

Several arguments suggest that arterial dilatation is probably due to the inability of elastic fibers to sustain physiological pulsatile stress, by analogy with aging.[28,29] The progressive disorganization of elastic fibers with aging (thinning and fragmentation) is generally considered as a sign of mechanical failure and fatigue of biomaterial. In addition, qualitative alterations of elastin fibers (calcification, glycoxidation, and lipid peroxidation)[30] and quantitative alterations (decrease in elastin content)[31] have been shown in experimental CKD models. The observed negative relationship between GFR and carotid lumen diameter is consistent with an accelerated aging of the arterial wall in CKD patients.[32] Many other factors that could potentially explain carotid dilatation had no independent influence, and GFR remained significant in multivariate analysis either in the entire population or in CKD patients only. After age, BP, and GFR, calcium channel blockers, known to dilate carotid artery in hypertensive patients,[33] were independently associated with carotid dilatation in CKD patients (Table 4). Volume overload may have influenced also the arterial diameter; however, no significant correlation was found between extracellular volume (measured by the volume of distribution of ^{51}Cr-EDTA) and arterial diameter within the population of CKD patients (data not shown). Hematocrit and hemoglobin were both correlated with internal diameter, but were not independently correlated after inclusion of GFR in the model, further indicating that dilatation and increased stress were not related to chronic increase in flow due to hypervolemia or anemia.

It is assumed that thickening is an adaptative response of the arterial wall to increased BP or dilatation, to normalize circumferential wall stress. In CKD, increased lumen diameter was not compensated by wall thickening, leading to increased circumferential wall stress. This suggests a defect in mechanotransduction, that is, the control of smooth muscle cell growth and migration, and production of extracellular matrix in response to diameter enlargement. The link between reduced renal function and this process is reinforced by the gradual increase in circumferential wall stress with a decrease in GFR (^{51}Cr-EDTA) in CKD patients (Figure 1), with GFR explaining 7% of the variance of circumferential wall stress (Table 4).

Aortic stiffness was significantly higher in CKD than in hypertensives, despite similar age and BP in both groups. Since BP levels, including central pulse pressure, are comparable in CKD and hypertensive patients, this exaggerated response probably involves a mechanism different from the passive loading of arterial wall stiff components by increased BP. An increase in aortic stiffness in hemodialysis patients has been consistently demonstrated by various investigators[3,9,14,16,34–37] and partially attributed to an increase in the calcium content of the arterial wall.[38,39] Arterial calcification has also been demonstrated in patients with moderate chronic renal failure.[40] Calcium, iron metabolisms, and microinflammation had no independent effect on arterial stiffening or dilatation. Other mechanisms could be involved, including qualitative changes in arterial wall during CKD (advanced glycation end products, lipid peroxidation, and elastin fragmentation)[30] and/or quantitative changes (increased amount of wall material, hyperplasia of smooth muscle cell, increased collagen content, and reduced amount of elastic fibers).[31] Carotid stiffness was not higher in CKD than in hypertensives. This suggests an exaggerated sensitivity

of the aorta to stiffening in CKD; however, the fact that GFR reduction was strongly associated with carotid stiffness in CKD shows that renal function *per se* has adverse influence on arterial stiffness. Increased stiffness in CKD patients was not accompanied by increased pulse pressure. This could be explained by the more intensive treatments with renin–angiotensin–aldosterone antagonists and statin therapy, correcting BP with more marginal effect on stiffness, as already observed in ESRD patients.[41]

Our results, showing that GFR was significantly and independently associated with carotid and aortic stiffness, are consistent with those of previous studies in CKD patients without ESRD,[17–19] which used an indirect estimation of GFR known to have a residual influence of age and body size. The present study demonstrates a gradual alteration of arterial function with reduced GFR, independent of age and other confounders. Moreover, we provide quantitative information through the percentage of explained variance (Tables 3 and 4). Multivariate analyses, either in the entire population or in CKD patients only, showed that GFR explained 2–3% of the variance of carotid elastic modulus or aortic PWV. When assessed in the reversed way, carotid stiffness was the only significant determinant of GFR (^{51}Cr-EDTA), explaining 12% of its variance. GFR had thus a weaker independent influence on arterial stiffness than age and BP (which explained 15–33% of the variance of carotid elastic modulus or aortic PWV), but arterial stiffness was strongly associated with altered renal function. The interplay of GFR with arterial stiffness in CKD was undetected in previous studies.[17–19]

Methodological features and limitations of the study

The present study has several strengths. First, because age, BP, and gender are important determinants of arterial stiffness and thickness, we compared CKD patients to hypertensive and normotensive patients of similar age and sex ratio, and to hypertensive patients of similar BP. Second, this study is the first to combine two gold standard methods: an echotracking apparatus for measuring arterial parameters in the entire population, as published previously,[28,42,43,29] and ^{51}Cr-EDTA technique for measuring GFR in CKD patients. Indeed, the indirect estimate of renal function through creatinine measurement affords limited information because it is affected by factors other than creatinine filtration, such as muscular mass and extrarenal elimination. Formulae including anthropometric parameters, such as the Cockcroft and Gault or the MDRD formula,[44] allow GFR estimation but they still lack precision.[45] Moreover, the inclusion of age in the calculation of estimated GFR hampers the interpretation of GFR's influence on parameters themselves strongly dependent on age (such as CF-PWV). Renal clearance of EDTA has been shown to be identical to renal clearance of inulin[46] and is currently one of the gold standard methods for the measurement of GFR. As the administration of radioisotopes could not be performed in healthy subjects, even in hypertensives with normal creatinine levels, we used the MDRD formula to relate GFR to arterial parameters in the entire population.

The present study has some limitations. First, kidney disease underlying reduced GFR was of miscellaneous origin, as described below. In multivariate analysis, we checked that the origin of CKD was not retained as an independent determinant of arterial parameters. Second, these patients were cared about according to the Kidney Disease Outcomes Quality Initiative (K-DOQI) and Agence Nationale pour l'Accréditation des Etablissements de Santé (ANAES) recommendations, and received multiple-drug therapy aiming at reducing their cardiovascular risk factors. This high level of treatment made it difficult to find a population matched for all the characteristics of the CKD patients. Thus, we chose to match CKD patients with hypertensive patients without CKD for BP and treatment, and to normotensive control subjects. This matching process may explain the absence of difference for IMT between groups.

Conclusions and perspectives

This cross-sectional study shows that arterial enlargement, increased arterial stiffness, and increased circumferential wall stress occur in parallel with the decline of GFR in patients with mild-to-moderate CKD. It would be interesting to correlate baseline arterial damage (notably aortic stiffness and carotid diameter/circumferential stress) with accelerated degradation of renal function. This question will be addressed in the ongoing 3-year longitudinal follow up of a larger cohort during the REN-ART study.

MATERIALS AND METHODS

A total of 273 patients and subjects were included in the present study. On the basis of reduced estimated GFR (GFR estimated with MDRD formula as $\leqslant 60$ ml/min/1.73 m^2), a group of 95 CKD patients referred to the nephrology vascular medicine unit of Georges Pompidou Hospital was recruited. The underlying diseases were glomerulopathy (21%), chronic interstitial nephritis (22%), hypertensive nephropathy (28%), and unknown (28%). In all, 95 patients had measurements of GFR directly through ^{51}Cr-EDTA clearance and arterial parameters, as described below. Besides GFR determination, cardiovascular risk factors were evaluated and biological parameters measured, according to the recommendations of the American and European clinical practice guidelines – K-DOQI (http://www.kidney.org/professionals/kdoqi/guidelines.cfm) and ANAES (http://www.anaes.fr/), respectively.

Control groups were composed of 121 patients with essential hypertension and no reduction in GFR, consulting at the hypertension clinic of our institution, and 89 normal subjects recruited among staff members and families. They beneficiated from arterial measurements, standardized questionnaires for cardiovascular risk factors, and standard biology, including plasma creatinine.

The protocol was approved by the local ethics committee, and all patients gave written informed consent.

GFR measurements

In the entire population, the simplified MDRD equation (GFR (ml/min/1.73 m^2) $= 186 \times$ (serum Cr (mg/dl))$^{-1.154} \times$ (age)$^{-0.203} \times$ (0.742 if female) $\times$ (1.212 if black))[44] was used to estimate GFR. In

patients with CKD, renal clearance of ^{51}Cr-EDTA was determined as described previously.[45] Briefly, 3.5 MBq of ^{51}Cr-EDTA (Amersham Health, SA, Pantin, France) was injected intravenously as a single bolus. After allowing 1 h for distribution of the tracer in the extracellular fluid, average renal ^{51}Cr-EDTA clearance was determined on five consecutive 30-min clearance periods. In our hands, the coefficients of variation of renal clearance of ^{51}Cr-EDTA and plasma clearance of ^{51}Cr-EDTA were $5.3 \pm 3.7\%$.

Arterial parameters

All patients and subjects were studied in a quiet room with a controlled temperature of $22 \pm 1^{\circ}$C as described previously.[28,42] BP was monitored with an oscillometric method (Dinamap model 845, Critikon). Aortic stiffness was estimated by CF-PWV measured along the descending thoraco-abdominal aorta by the foot-to-foot velocity method (Complior, Artech Medical, Pantin, France), as published previously and validated.[47]

End-diastolic internal diameter, stroke change in diameter, and IMT were measured on the right common carotid artery (CCA) with a high-precision echotracking device (Wall Track System),[48] as described previously and validated.[28,42,43,29] End-diastolic internal diameter was normalized to BSA in order to take into account anthropometric variation.

Circumferential wall stress was calculated using the Lamé equation,[43] with $\sigma\theta$ (kPa) = (MBP D_m)/2IMT$_m$ (where MD_m and IMT$_m$ are the mean values of internal diameter and wall thickness during the cardiac cycle).

Right CCA pressure waveform was recorded noninvasively by aplanation tonometry, using the Sphygmocor device (AtCor Medical, Sydney, Australia), as described previously and validated,[29] and local carotid artery pulse pressure was used for further calculations.

Carotid distensibility was determined from the systolic–diastolic variations in arterial cross-sectional area (ΔA) and local pulse pressure (ΔP) as described previously,[42] assuming the lumen to be circular. Cross-sectional distensibility coefficient (DC) was calculated as $DC = \Delta A/A\,\Delta P$. Cross-sectional compliance coefficient (CC) was calculated as $CC = \Delta A/\Delta P$. Incremental Young's elastic modulus (E_{inc}) was calculated as described previously:[42] $E_{inc} = [3(1 + A/WCSA)]/DC$, where WCSA is the mean WCSA.

Statistical analysis

Statistics were performed using NCSS 2004 software (Gerry Hintze, Kaysville, UT, USA). Data are expressed as mean $\pm$ s.d. Between-group comparisons for quantitative variables were performed using GLM-ANOVA, completed by Bonferonni *post hoc* tests, corrected for multiple comparisons. χ^2 test was used for discrete variables. Multivariate robust regressions with stepwise selection of variables were performed to determine the relationship between arterial parameters and GFR, as described previously.[28,29]

In order to sort out the contribution of the numerous redundant variables recorded (for instance, body mass index (BMI) and weight expressing different aspects of obesity, or C-reactive protein (CRP) and fibrinogen expressing different aspects of inflammation), we performed clustered selection of variables, each cluster corresponding to a given pathophysiological domain. Clusters were constituted as follows: morphometric (sex, height, weight, BMI, BSA), blood pressure (MBP, Pulse pressure, augmentation index), lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides), blood (hematocrit, hemoglobin, white blood cells), inflammation (fibrinogen, CRP), mineral metabolism (calcium, phosphorus, parathyroid hormone (PTH)), and treatment (calcium channel blockers, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), diuretics). Within each cluster, variables were included in a competitive manner in multivariate models. If covariance was too high within clusters, the variable having the highest univariate signification level was retained. In the second step, variables retained in separate clusters were included in the first multivariate model. Then, age was introduced in the second model, and finally GFR was introduced in the third model (presented in Tables 3 and 4).

ACKNOWLEDGMENTS

This study was funded by the French Ministry of Health, Délégation à la Recherche Clinique, Assistance Publique-Hôpitaux de Paris, Programme hospitalier de Recherche Clinique, Grant AOM 03023 P030439.

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