Arterial Remodeling Associates with CKD Progression

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ABSTRACT

In CKD, large arteries remodel and become increasingly stiff. The greater pulsatile pressure reaching the glomerulus as a result of increased aortic stiffness could induce renal damage, suggesting that the stiffening and remodeling of large arteries could affect the progression of CKD. We measured carotid-femoral pulse wave velocity, aortic pressure and carotid remodeling and stiffness parameters in 180 patients with CKD (mean measured GFR, 32 ml/min per 1.73 m^2) and followed them prospectively for a mean of 3.1 years. During follow-up, carotid stiffness significantly increased ($+0.28 \pm 0.05$ m/s; $P < 0.0001$) but aortic stiffness did not. Carotid intima-media thickness decreased significantly during follow-up and the internal diameter of the carotid increased, producing increased circumferential wall stress ($+2.08 \pm 0.43$ kPa/yr; $P < 0.0001$). In a linear mixed model, circumferential wall stress significantly associated with faster GFR decline after adjustment for risk factors of cardiovascular disease and progression of CKD. In a multivariable Cox model, carotid circumferential wall stress and pulse pressure independently associated with higher risk for ESRD. None of the arterial stiffness parameters associated with progression of CKD. In conclusion, maladaptive remodeling of the carotid artery and increased pulse pressure independently associate with faster decline of renal function and progression to ESRD.

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Chronic kidney disease (CKD) is a significant public health concern.[1] CKD is associated with a dramatically increased risk of cardiovascular disease.[2,3] Damage to large arteries in CKD patients has been described in the last years and is mainly characterized by an outward remodeling of the carotid artery without wall thickening, leading to an increased circumferential wall stress, and by an increased aortic and carotid stiffness.[4–7] Large artery damage could be predictive for CKD progression through several mechanisms. It has been postulated that increased aortic stiffness could lead to increased pulsatile pressure reaching the glomerulus.[8] In addition, pulsatile pressure could induce damage to the glomerulus through altered myogenic tone.[9,10] In hypertensive patients, with normal or slight alteration of GFR, indirect markers of arterial stiffness such as brachial pulse pressure are independently

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associated with GFR decline.[11,12] In moderate CKD, the relation between aortic stiffness and GFR decline is still debated.[6,13] The association between arterial remodeling and arterial stiffness and CKD progression remains to be established.

We therefore studied 180 patients from the NephroTest prospective cohort with mild to moderate CKD to evaluate the association between arterial stiffness and arterial remodeling parameters and CKD progression using gold standard methods including the measurement of carotid-femoral pulse wave velocity, carotid geometric, and functional parameters with high-resolution echotracking system and renal function with ^{51}Cr-EDTA clearance.

RESULTS

Clinical Characteristics of the Patients

The baseline characteristics of the 180 patients are detailed in Table 1. Mean age of participants at entry was 59.6 years and measured GFR (mGFR) was 32 ml/min per 1.73 m^2. Most of the patients had hypertension (91%), and 68% had dyslipidemia. During the 3.5 years of follow-up, from the 180 patients included in the study, 41 patients underwent dialysis, 10 patients died, and 3 patients were lost to follow-up (Figure 1). The baseline characteristics of arterial parameters were similar to those previously published[4] and confirmed the outward remodeling of the carotid artery (increased diameter and circumferential wall stress) and the moderate increase in aortic and carotid stiffness (11.5 ± 3.1 and 7.4 ± 2.5 m/s, respectively; Table 2).

Longitudinal Follow-Up of Arterial Parameters in CKD Patients

During follow-up, progression of CKD was characterized by a decreased mGFR (adjusted slope, −1.6 ± 0.3 ml/min per 1.73 m^2 per year; $P < 0.0001$). Brachial and carotid BP remained stable over time except a moderate decrease in carotid diastolic BP over time (adjusted slope, −0.8 ± 0.3 mmHg/yr; $P = 0.01$; Table 3).

Aortic stiffness did not change significantly during follow-up. Carotid stiffness significantly increased during follow-up (adjusted slope, +0.28 ± 0.05 m/s per year; $P < 0.0001$). Young's elastic modulus significantly increased over time (adjusted slope, 59.9 ± 9.9 kPa/yr; $P < 0.0001$; Table 3).

Carotid intima-media thickness decreased significantly during follow-up (adjusted slope, −22 ± 4 μm/yr; $P < 0.0001$), associated with an increase in carotid internal diameter (adjusted slope, 83 ± 15 μm/yr; $P < 0.0001$) and a lower increase in carotid external diameter (adjusted slope, 39 ± 14 μm/yr; $P = 0.006$). In accordance with these finding, wall to lumen ratio and wall cross-sectional area decreased significantly over time (adjusted slope, −1.1 ± 0.2/yr; $P < 0.0001$ and −0.39 ± 0.09 mm^2/yr; $P < 0.0001$, respectively). Carotid circumferential wall stress increased significantly over time (adjusted slope, 2.08 ± 0.43 kPa/yr; $P < 0.0001$; Table 3).

Table 1. Clinical, biological, and arterial characteristics of the 180 patients

Parameters	Mean	(SD)
Age (years)	59.6	(14.2)
Gender (F/M)	47/133	
Body mass index (kg/m^2)	25.7	(4.7)
Hypertension, *n* (%)	164 (91%)	
Tabacco, current *n* (%)	29 (16%)	
Dyslipidemia, *n* (%)	122 (68%)	
Diabetes, *n* (%)	25 (14%)	
Previous CV event, *n* (%)	51 (29%)	
ACEi, *n* (%)	103 (57%)	
ARB, *n* (%)	110 (61%)	
Dual blockade, *n* (%)	61 (34%)	
ACEi or ARB, *n* (%)	152 (74%)	
Calcium channel blockers, *n* (%)	96 (53%)	
β blockers, *n* (%)	70 (39%)	
Diuretics, *n* (%)	70 (39%)	
Nb anti-hypertensive drugs	2.5	(1.3)
Statins, *n* (%)	104 (58%)	
Erythropietin, *n* (%)	17 (9%)	
Alfacalcidol, *n* (%)	44 (25%)	
Calcium supplementation, *n* (%)	31 (17%)	
Mean follow-up (years)	3.1	(0.3)
Slope mGFR, (ml/min per 1.73 m^2 per year)	−1.7	(3.7)
Dialysis during follow-up, *n* (%)	41 (27%)	
Death, *n* (%)	10 (6%)	
Brachial BP		
systolic BP (mmHg)	134	(22)
mean BP (mmHg)	94	(13)
diastolic BP (mmHg)	74	(10)
Heart rate (bpm)	65	(11)
Biological parameters		
measured GFR (ml/min per 1.73 m^2)	32	(16)
creatinine (μmol/L)	224	(113)
UACR (mg/mmol)	19.8	(70)[a]
HbA1C (%)	5.6	(1.08)
total cholesterol (mmol/L)	4.8	(1.13)
HDL cholesterol (mmol/L)	1.15	(0.4)
LDL cholesterol (mmol/L)	2.9	(1.02)
triglycerides (mmol/L)	1.5	(0.84)

ACEi, angiotensinogen converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CV, cardiovascular; UACR, urinary albumin creatinine ratio.
[a]Median (interquartile range).

Outcome and Prognostic Impact of Arterial Remodeling and Stiffening on CKD Progression

In mixed model regression analysis, increased circumferential wall stress was significantly associated with faster decrease in mGFR, independent of urinary albumin creatinine ratio, age, gender, carotid pulse pressure, previous cardiovascular events, body mass index, smoking status, dyslipidemia, and diabetes (Table 4). No independent association

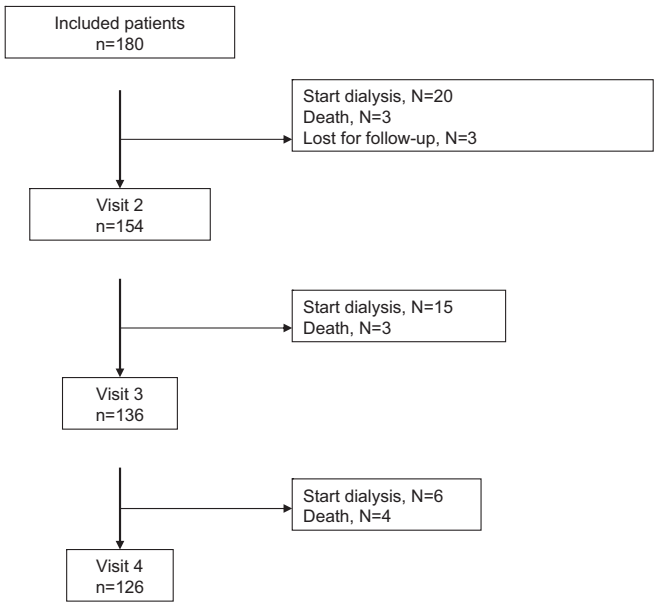

Figure 1. Study flowchart.

Table 2. Arterial parameters of the 180 patients at inclusion

Parameters	Mean	(SD)
Common carotid artery		
carotid systolic BP (mmHg)	125	(25)
carotid diastolic BP (mmHg)	74	(10)
carotid pulse pressure (mmHg)	52	(21)
augmentation index (%)	32	(13)
internal diameter ($m \times 10^{-3}$)	6.30	(1.0)
intima-media thickness ($m \times 10^{-6}$)	760	(156)
wall cross-sectional area ($m^2 \times 10^{-6}$)	17.1	(5.2)
wall to lumen ratio	24.5	(5.3)
circumferential wall stress (kPa)	48.0	(13.3)
carotid stiffness (m/s)	7.4	(2.5)
Young's elastic modulus (kPa)	540	(438)
Aorta		
carotid femoral pulse wave velocity (m/s)	11.5	(3.1)

was found between carotid stiffness, carotid-femoral pulse wave velocity, Young's elastic modulus, and CKD progression.

Outcome and Prognostic Impact of Arterial Remodeling and Stiffening on ESRD

During follow-up, 41 patients started dialysis; no patient was transplanted before starting dialysis.

In multivariate Cox analysis, carotid circumferential wall stress, carotid pulse pressure, and mGFR slope remained independent determinants of ESRD (hazard ratio: 1.40 [1.08 to 1.83], $P = 0.01$; 1.24 [1.03 to 1.49], $P = 0.02$; and 0.77 [0.68 to 0.86], $P < 10^{-6}$, respectively; Table 5). No independent association was found between carotid stiffness, carotid-femoral pulse wave velocity, Young's elastic modulus, and ESRD.

To show the association between circumferential wall stress and renal survival, we separated the population in two groups according to the median of carotid circumferential wall stress (Figure 2). Crude hazard ratio of ESRD significantly increased with increasing circumferential wall stress (hazard ratio, 2.48, [1.63 to 3.78]).

DISCUSSION

This longitudinal study is the first designed to evaluate the association between arterial remodeling and stiffness parameters and the decline of renal function in patients with CKD stages 2 to 5. All outcome data were prespecified. We showed that common carotid artery phenotype in CKD stages 2 to 5 evolves over time with internal diameter enlargement and intima-media thickness reduction, resulting in an increase in circumferential wall stress. The major result of this study is that increased carotid circumferential wall stress is independently associated with CKD progression, independently of classical factors of CKD progression including urinary albumin to creatinine ratio. We confirmed the independent association between arterial remodeling and CKD progression with a hard clinical endpoint, *i.e.,* the necessity to start dialysis.

Interpretation of the Data

We showed that arterial remodeling evolutes overtime with an enlargement and a thinning of the carotid artery, leading to an increased carotid circumferential wall stress. This kind of arterial remodeling evolution is unusual in this high cardiovascular risk population. The pathophysiology of increased carotid circumferential wall stress is not obvious. In response to increased BP, in particular, the pulsatile component, degenerative changes, and fractures of the extracellular matrix component occur in the arterial wall, leading to arterial enlargement.[14] The response to dilation is a thickening of the arterial wall, generally considered as adaptive, aiming at normalizing circumferential wall stress. We have previously shown in hypertensive patients that local pulse pressure was associated with increased diameter and intima-media thickness; however, circumferential wall stress was not fully normalized.[15] In this study, we showed that this response does not occur in CKD patients and instead we observed a thinning of the carotid artery wall, leading to an increase in circumferential wall stress that may be considered as an inappropriate response. We showed that this phenotype worsens during longitudinal follow-up. The rate of decrease in intima-media thickness is fast (-22 μm/yr), matching the fastest reported increase in intima-media thickness in patients with atherosclerosis, but in the opposite way.[16] A significant proportion of the studied patients have diabetes where inappropriate remodeling of the carotid artery was already observed.[17] In our study, increased circumferential wall stress is independent of the diabetic status of the patients, and diabetes is not independently associated with the decline of mGFR (data not shown). An inappropriate remodeling of the carotid artery of CKD patients

Table 3. Clinical and arterial parameters changes during follow-up of the 180 studied patients

Changes	Age- and Gender-Adjusted Slopes ± SE (unit per year)	*P*
Parameters		
age (years)	—	—
body mass index (kg/m²)	0.13 ± 0.04	0.002
brachial systolic BP (mmHg)	−0.4 ± 0.5	0.45
brachial diastolic BP (mmHg)	−0.7 ± 0.3	0.02
brachial mean BP (mmHg)	−0.5 ± 0.3	0.14
brachial pulse pressure (mmHg)	0.4 ± 0.3	0.22
heart rate (beats/min)	0.5 ± 0.3	0.06
Large arteries		
carotid-femoral pulse wave velocity (m/s)	−0.01 ± 0.04	0.89
augmentation index (%)	−0.8 ± 0.4	0.045
carotid systolic BP (mmHg)	−0.5 ± 0.7	0.50
carotid diastolic BP (mmHg)	−0.8 ± 0.3	0.01
carotid pulse pressure (mmHg)	0.47 ± 0.52	0.37
carotid intima-media thickness (μm)	−22 ± 4	<0.0001
carotid wall cross-sectional area (mm²)	−0.39 ± 0.09	<0.0001
carotid external diastolic diameter (mm)	0.039 ± 0.014	0.006
carotid internal diastolic diameter (mm)	0.083 ± 0.015	<0.0001
carotid wall to lumen ratio (%)	−1.1 ± 0.2	<0.0001
carotid stiffness (m/s)	0.28 ± 0.05	<0.0001
carotid Young's elastic modulus (kPa)	59.9 ± 9.9	<0.0001
carotid circumferential wall stress (kPa)	2.08 ± 0.43	<0.0001
Kidney		
creatinine (μmol/L)	13 ± 3	<0.0001
measured GFR (ml/min per 1.73 m²)	−1.6 ± 0.3	<0.0001
urinary albumin/creatinine ratio (mg/mmol)	0.30 ± 0.05	<0.0001

Table 4. Relation between circumferential wall stress and measured GFR change after adjustment on cardiovascular and chronic kidney disease progression risk factors

Parameters (unit/year)	Slope	SE	*P*[a]
Dependent variable			
measures GFR (ml/min per 1.73 m²)	−1.34	0.25	<0.0001
Independent parameters			
age (years at baseline)	−0.15	0.09	0.07
gender (male/female)	−6.09	2.29	0.0084
previous CV events (yes/no)	−7.35	2.41	0.0026
circumferential wall stress (kPa)	−0.28	0.08	0.0013
log UACR	−8.14	1.18	<0.0001
carotid pulse pressure (mmHg)	−0.00	0.06	NS

UACR, urinary albumin creatinine ratio; NS, not significant.
[a]Linear mixed-model regression over time, adjusted on body mass index, smoking status, diabetes, and dyslipidemia.

has also been shown by Hermans *et al.*[5] in the Hoorn study. The authors described an independent association between circumferential wall stress and proteinuria but no association with estimated GFR.[5] That study differs from the present one with respect to the design, particularly the cross-sectional approach and the stage of CKD of included patients, mostly stage 2 and early stage 3.[5]

The defect of arterial wall thickening could be caused by different mechanisms, involving either an excessive extracellular matrix turnover,[18–20] a lack of vascular smooth muscle cell proliferation, or apoptosis.[21] Renin-angiotensin system (RAS) blockers, often prescribed to CKD patients, could play a role in the defect of thickening because of their anti-proliferative properties.[22,23] In our study, the higher the use of angiotensin II receptor blockers, the higher the risk for ESRD (data not shown). However, in this observational study, the most likely hypothesis is indication bias (*i.e.,* angiotensin II receptor blocker given to the patients more susceptible to aggravation), which is impossible to disentangle from the potential effect of RAS blockers on CKD progression. Further interventional studies are necessary to explore the effect of antihypertensive treatment on arterial remodeling in CKD patients.

Interestingly, aortic stiffness remains stable over time, whereas carotid stiffness increases moderately, but neither were associated with CKD progression. Aortic stiffness has a well-established predictive value for all-cause mortality in ESRD.[24] Ford *et al.*[25] recently showed that aortic stiffness has an independent predictive value for CKD progression. The discrepancy between this study and our data could be caused by the methodology used to measure GFR and consequently CKD progression. Ford *et al.*[25] used the Modification of Diet in Renal Disease formula to estimate GFR, whereas, in this study, GFR was precisely measured by ^{51}Cr-EDTA urinary clearance. Association studies do not provide a clearer view. Indeed, aortic stiffness has been found to be correlated with reduced GFR in some cross-sectional studies,[4,6,7,26] but not all.[13] In the latter study, the authors failed to show that pulse wave velocity predicts incident CKD in longitudinal analysis, which is in accordance with our findings. Others indirect markers of arterial stiffness such as brachial pulse pressure have an independent predictive value for GFR decline in hypertensive patients.[12] In this study, carotid-femoral pulse wave velocity remained stable during follow-up, which can be because of the intensive treatment associating RAS blockers, diuretics, and statins, thus explaining the lack of association between aortic stiffness and CKD progression.

Only central pulse pressure was associated with ESRD in this population. Central pulse pressure is only partially dependent on aortic stiffness because it also depends on wave reflection and left ventricular function. In contrast with

Table 5. Multivariate Cox regression analyses of the determinants of ESRD

Parameters	Hazard Ratio	Lower 95% Confidence Interval	Upper 95% Confidence Interval	*P*
Sex (male/female)	4.22	1.86	9.58	0.0006
Log UACR	2.31	1.23	4.33	0.008
Slope GFR (ml/min per 1.73 m^2 per year)	0.77	0.68	0.86	$<10^{-6}$
Circumferential wall stress (/10 kPa)	1.40	1.08	1.83	0.01
Carotid pulse pressure (/10 mmHg)	1.24	1.03	1.49	0.02

Adjusted for age, previous cardiovascular events, body mass index, smoking status, diabetes, dyslipidemia, and variables nonsignificantly associated. UACR, urinary albumin creatinine ratio.

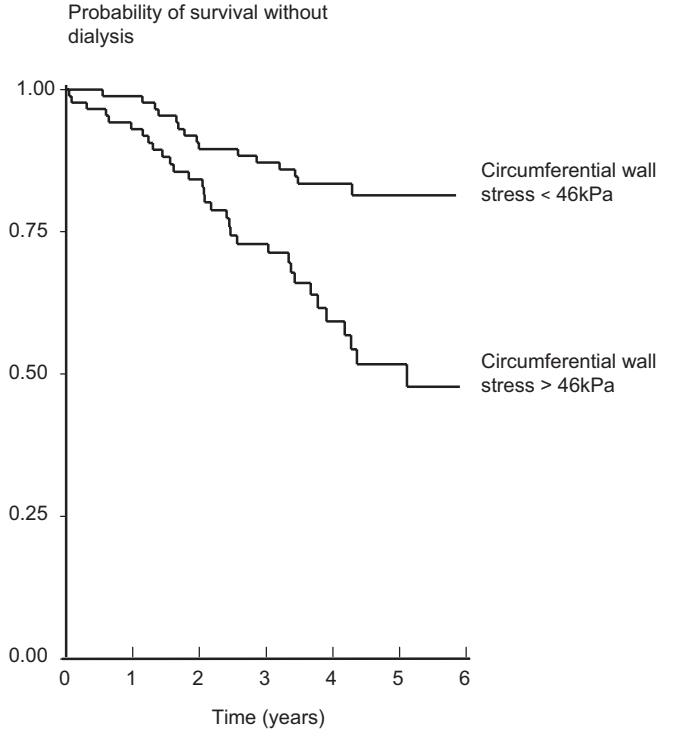

Figure 2. Higher values of circumferential wall stress associate with increased risk of ESRD. Comparisons between survival curves were significant (log rank test, $P = 0.0003$).

heart, skin, and brain, where microcirculation is protected by high resistance of precapillary arterioles, glomerular capillaries are positioned between afferent and efferent arterioles. Resistance in efferent arterioles is higher than in afferent arterioles to maintain hydrostatic pressure. Consequently, the pressure drop across the afferent arteriole is low, and pulsatile pressure reaching the glomerulus is relatively high. In a normal situation, two mechanisms are involved to counteract excessive pulse pressure and to maintain GFR: the myogenic tone in the afferent arteriole and the tubuloglomerular feedback regulating the vasoconstriction of the efferent arteriole.[27] Bidani *et al.*[9] already showed that myogenic tone is altered by chronically increased in pulsatile pressure, thus leading to higher dissipation of pulsatile energy in the microcirculation and subsequent glomerular damage.[27]

Mean GFR progression rate was rather low in this cohort (−1.6 ml/min per 1.73 m^2 per year), which is about 60% higher than the rate of 1 ml/min per 1.73 m^2 per year described in early studies for normal aging.[28] More recent studies conducted in potential kidney donors, however, tended to revise this rate downward: −0.49 ml/min per 1.73 m^2 per year in the study from the Mayo clinic,[29] and −0.37 and −0.75 ml/min per 1.73 m^2 per year up to the age of 45 and thereafter, respectively, in the pooled Mayo and CCF clinics analysis.[30] Compared with these more recent data, the slope we observed would therefore be 2.2 to 3.5 steeper than expected with normal aging. Nevertheless, the high proportion of nephroangiosclerosis (40%) and tubulo-interstitial nephritis (23%) may also explain the slow progression of the studied population, together with the low rate (28%) of heavy albuminuria and the broad use of renin-angiotensin system blockade (74%) at baseline. The low proportion of diabetic nephropathy is likely to reflect a combination of low prevalence of the disease in the Paris area (18% of the prevalent ESRD population has diabetic nephropathy compared with 23% nationally[31]) and the later referral to nephrologists, commonly at stage 5, of patients with diabetes compared with other CKD patients, as well as recruitment bias from university hospitals. Although patient selection may have biased progression rate estimate toward a lower value, this should not alter the studied associations. It is worth noting that, in a recent meta-analysis of 13 CKD patient cohorts, ESRD incidence rate in the NephroTest cohort was very similar to that of other cohorts, including patients at similar mean baseline estimated GFR, such as the Ramipril Efficiency in Nephropathy Study, the Reduction of Endpoints in Non-insulin dependent diabetes with Angiotensin II Antagonist Losartan study, or the African American Study of Kidney Disease and Hypertension.

Methodological Issues

This study has several strengths. First, this is the first longitudinal study designed to evaluate the association between arterial remodeling and stiffness parameters and CKD progression. Second, large arteries were studied with gold standard techniques, echotracking, aplanation tonometry, and pulse wave velocity. The progression of CKD was precisely established with direct GFR measurement with ^{51}Cr-EDTA urinary clearance. Third, patients were evaluated at each yearly visit for kidney function, arterial remodeling, and stiffness parameters. Last, follow-up was exhaustive. This design allowed us to precisely describe arterial remodeling evolution and CKD progression over time.

This study also has limitations. First, we included patients with CKD stage 3 or less and a significant part of the studied population did not complete all measurements be-

cause progression of CKD lead to left the study earlier and start dialysis. The second limitation concerns the methods. Given the large number of inter-related parameters tested, findings for circumferential wall stress may be sample dependent and should be replicated in other cohorts. However, at baseline, carotid circumferential wall stress did not correlate significantly with carotid or aortic stiffness. Its correlation with Young's elastic modulus was significant ($r = 0.31$, $P = 0.0002$), because intima-media thickness entered the calculation of both parameters.

Perspectives

One could hypothesize that maladaptive remodeling of large arteries could impact the transmission of pulse pressure with a stronger intensity further down the microcirculation. Excessive pulsatility could induce damage to the microcirculation such as capillary rarefaction and increased small arteries stiffness; these damages could be greater in patients with increased circumferential wall stress value. Thus, identifying the pathophysiology of maladaptive remodeling in CKD patients is of importance. Considering the hypotrophic properties of RAS blockade agents, a U-shape response curve could be hypothesized with a beneficial effect on survival and GFR progression rate at moderate dosage and deleterious effects on arterial remodeling and CKD progression at higher dose. This hypothesis needs to be tested in an interventional trial.

Conclusion

This longitudinal study showed for the first time a strong and independent relationship between arterial remodeling, CKD progression, and occurrence of ESRD. Whether the assessment of carotid remodeling may help for caring for CKD patients remains to be determined.

CONCISE METHODS

Design and Patients

From November 2004 to December 2006, 180 patients with CKD stages 3 to 5, not yet on dialysis, were included in this study on the basis of reduced estimated GFR (Modification of Diet in Renal Disease equation, GFR <60 ml/min per 1.73 m^2). Briefly, the studied population is a subset of the NEPHROTEST prospective cohort, which includes all adult CKD patients who underwent a yearly extensive check-up in two departments of physiology and nephrology in the Paris area, as described previously.[32,33] Enrolled patients were 18 years of age or older and had not been on dialysis or received a kidney transplant. Pregnant women were excluded. Diabetic nephropathy was identified in 11 patients, tubulointerstitial nephropathy in 43 patients, nephroangiosclerosis in 73 patients, polycystic kidney disease in 5 patients, primitive glomerulonephritis in 22 patients and undetermined nephropathy in 26 patients. The patients underwent a yearly annual work-up including medical interview, clinical examination, blood samples, measurement of GFR directly through ^{51}Cr-EDTA urinary clearance, and evaluation of arterial parameters. The protocol was approved by the St Germain en Laye hospital ethics committee, and all patients gave written informed consent.

Arterial Parameters

All patients were studied in a quiet room with controlled temperature of 22 ± 1°C as described previously.[15,34] BP was monitored every 3 minutes with an oscillometric method (Colins, BP 8800; Colin Corporation Ayashi, Komaki, Japan).

End-diastolic internal diameter, stroke change in diameter, and intima-media thickness were measured on the right common carotid artery with a high precision echotracking device (Wall Track System; Esaote, Maastricht, The Netherlands), as described previously and validated.[15,34] Right radial artery and common carotid artery pressure waveforms were recorded noninvasively by aplanation tonometry (Sphygmocor; Atcor Medical, Sydney, Australia), as described previously and validated.[35–37] Tonometry takes advantage of the transfer function from radial to aortic BP and absolute calibration using brachial cuff measurements of systolic BP and diastolic BP to calculate aortic pressure waveform. Tonometry was also performed at carotid level, and local carotid artery pulse pressure was used for further calculations.

Wall cross-sectional area was calculated as $\pi(Re^2 - Ri^2)$, where Re and Ri are values of diastolic external and internal radii, respectively. Wall to lumen ratio was calculated in diastole as $2\,h_d/D_d$, where h_d and D_d are the values of wall thickness and internal diameter during end diastole, respectively. Circumferential wall stress ($\sigma\theta$, kPa) was calculated according to Lamé-s equation as $\sigma\theta = (DBP.D_d)/2h_d$, where DBP is mean BP, and D_d and h_d are the diastolic values of internal diameter and wall thickness during the cardiac cycle, respectively.[15,38] This was preferred to calculation at mean blood pressure because intima-media thickness and diameter are measured in diastole.

Carotid distensibility was determined from systolic-diastolic variations in arterial cross-sectional area (ΔA) and local pulse pressure (ΔP) as described previously,[34] assuming the lumen to be circular. Cross-sectional distensibility coefficient (DC) was calculated as $DC = \Delta A/A\Delta P$. Carotid stiffness was calculated as $(DC)^{-1/2}$. Incremental Young's elastic modulus was calculated as [3(1 + A/wall cross-sectional area)]/DC, where A is the diastolic lumen area.[34,38] Distensibility and stiffness express the elastic properties of the artery as a hollow structure, and elastic modulus expresses the elastic properties of the arterial wall material.

Aortic stiffness was measured through the carotid to femoral pulse wave velocity between the two sites by the foot-to-foot velocity method (Complior; ALAM Medical, Pantin, France), as described previously and validated.[39,40] Briefly, pulse wave velocity was calculated from measurements of pulse transit time and the distance traveled by the pulse between two recording sites: pulse wave velocity = distance (m)/transit time (seconds). It expresses the elastic properties of the descending and abdominal aorta and the iliofemoral segments.

Biologic Parameters

We collected blood and urine samples to determine the levels of serum plasma creatinine with an isotope dilution mass spectrometry-standardized modified kinetic Jaffe colorimetric

method, hemoglobin, triglyceride, HDL and LDL cholesterol, urinary albumin, and creatinine at baseline. Serum plasma creatinine, urinary albumin, and creatinine were determined at each visit.

Outcome

We studied both GFR decline and ESRD incidence. GFR was determined by the renal clearance of ^{51}Cr-EDTA, as described previously.[4,41] Briefly, 1.8 to 3.5 MBq of ^{51}Cr-EDTA (GE Healthcare, Velizy, France) was injected intravenously as a single bolus. After allowing 1 hour for distribution of the tracer in the extracellular fluid, average renal ^{51}Cr-EDTA clearance was determined on five to six consecutive 30-minute clearance periods. Progression of CKD was estimated by the slope of GFR decline calculated using simple regression for each patient using the two, three, or four visits depending on patient outcome, except when mixed models were used for analysis. For patients starting dialysis, GFR was estimated as 5 ml/min per 1.73 m^2 at the first dialysis date.

ESRD was defined by the necessity to start dialysis or kidney transplantation. Censoring dates were either the date of the first dialysis or end of follow-up.

Statistical Analysis

The arterial parameters of interest, carotid-femoral pulse wave velocity, carotid stiffness, Young's elastic modulus, and circumferential wall stress were entered in mixed model regression analyses with random-effects statement on the slope and intercept of each subject. These four arterial parameters were also entered in a Cox model for multivariate analysis of the determinants of ESRD. Survival curves were estimated by the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. The assumption of normality of continuous covariates was verified before analysis, and data were log-transformed when necessary.

To study the evolution of clinical and arterial parameters during longitudinal follow-up, changes overtime of each parameter were estimated by a linear mixed model regression with random-effects statement on the slope and intercept of each subject. Changes over time were systematically adjusted for age at baseline and gender.

Data are expressed as mean $\pm$ SD. Statistical analysis were performed with SAS Analytics Statistics 9.1 software (SAS Institute, Cary, NC) and NCSS 2007 software (Gerry Hintze, Kaysville, UT).

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