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Relationship between kidney findings and systemic vascular damage in elderly hypertensive patients without overt cardiovascular disease

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Few studies have investigated the influence of age on the relationships between systemic vascular damage, kidney dysfunction, and intrarenal hemodynamic changes in patients with hypertension without overt cardiovascular disease. The authors enrolled 126 elderly patients with hypertension (aged ≥65 years) and 350 nonelderly patients with hypertension (aged <65 years). Carotid intima-media thickness, renal resistive index, and aortic pulse wave velocity were performed in all patients. Elderly patients with hypertension had lower estimated glomerular filtration rates and higher albuminuria, renal resistive index, carotid intima-media thickness, and aortic pulse wave velocity compared with nonelderly patients with hypertension ($P < .001$). Carotid intima-media thickness independently correlated with renal resistive index and estimated glomerular filtration rate in nonelderly patients with hypertension, whereas it was significantly related to renal resistive index only in elderly patients with hypertension. Aortic pulse wave velocity was independently associated with albuminuria in nonelderly patients with hypertension, whereas it did not independently correlate with any indexes of renal damage in elderly patients with hypertension. Age is an important modifier of the relationships between renal function and renal hemodynamics with subclinical vascular involvement in elderly persons without cardiovascular disease.

1 | INTRODUCTION

Age is a well-known risk factor and a strong predictor of cardiovascular events in the general population.

Several studies have shown that aging leads to enhanced risk at least in part through progressive and gradual development of morphofunctional vascular changes,[1–3] and this particularly occurs when hypertension, a very common finding in elderly persons,[4,5] coexists.[6] Greater carotid atherosclerotic damage, an expression of systemic vascular impairment, has been found in older individuals than in younger persons in different clinical settings.[7] Moreover, a progressive increase in aortic stiffness, a well-known prognostic marker of subclinical vascular damage in the general population as well as in patients with hypertension,[8–10] has been widely demonstrated with aging, likely as a result of arterial remodeling and alteration of viscoelastic properties of the vessel wall.[2,11-13]

On the other hand, renal impairment related to aging has also been suggested to explain the increased cardiovascular risk in elderly patients with hypertension.[14] Several studies showed the close association between age and the decline of renal function.[15–17] Similarly, intrarenal hemodynamic alterations, assessed by ultrasonographic intraparenchymal renal resistive index (RRI) and related to systemic

vascular changes,[18,19] were correlated with increasing age in previous studies.[20–22] However, the prognostic contribution to risk stratification of an increased RRI remains to be demonstrated in elderly patients.[23]

Morphofunctional vascular impairment and kidney damage have been strongly associated but they have different dynamics of progression over time,[2,3,15,21] and it is not known how age could modify this relationship.

The aim of this study was therefore to evaluate, in a group of patients with hypertension without overt cardiovascular disease, the influence of age on the association between indexes of renal damage (glomerular filtration rate, albuminuria, and RRI) and markers of subclinical vascular damage such as carotid intima-media thickness (cIMT) and aortic pulse wave velocity (aPWV), the latter being an expression of arterial stiffness.

2 | MATERIALS AND METHODS

2.1 | Patients

This cross-sectional study includes a total of 476 outpatients with hypertension aged between 30 and 90 years. This population was selected from white patients with essential hypertension consecutively attending our nephrology and hypertension unit. All patients had been referred to our institution by their general practitioners for specialist advice. In agreement with more recent European Society of Hypertension guidelines, hypertension was defined as a blood pressure ≥140/90 mm Hg or treatment with antihypertensive drugs.[24]

The exclusion criteria were:

- Severe obesity, defined as a body mass index ≥40 kg/m^2.
- Renovascular, malignant, or endocrine hypertension as described elsewhere.[25-27]
- Stenosis of renal arteries as assessed with Doppler ultrasound criteria.[28]
- Rapid deterioration of renal function, defined as an increased serum creatinine >1.5 times baseline.[29]
- Estimated glomerular filtration rate (eGFR) <15 mL/min per 1.73 m^2 or renal replacement therapy (in patients with transplant or dialysis).
- Previous carotid percutaneous angioplasty or endarterectomy.
- Heart failure (New York Heart Association class III or IV)
- Permanent atrial fibrillation or heart rate >100 beats per minute or <50 beats per minute.[28]
- Moderate to severe aortic/mitral valve disease as reported elsewhere: echocardiographic mitral valve area ≤1.5 cm^2 (mitral valve stenosis); aortic jet velocity ≥3.0 m/s (aortic valve stenosis); central jet ≥4 cm^2 or ≥20% of left atrium area or regurgitant volume ≥30 mL/beat (mitral valve regurgitation); width of central jet ≥25% of left ventricular outflow tract or regurgitant volume ≥30 mL/beat (aortic valve regurgitation)[30]
- Previous or current coronary or cerebrovascular events.
- Major noncardiovascular diseases (liver cirrhosis, chronic obstructive lung disease, and anamnestic presence of neoplasms).

Endocrine hypertension and renovascular hypertension were ruled out by clinical examination, by duplex-Doppler assessment of intrarenal and extraparenchymal renal arteries, and by laboratory determination of serum electrolytes, plasma renin activity, and plasma aldosterone concentration; when appropriate, plasma catecholamine level was determined and renoscintigraphy was performed.

Written informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the local review board.

2.2 | Clinical and laboratory evaluation

Clinical history and physical examination were performed in all patients. Participants who reported smoking cigarettes regularly during the past year were considered current smokers. Body weight and height were measured by a nurse. Clinic blood pressure was recorded by a doctor with an electronic oscillometric validated device (Microlife Watch BP Office).[31] It was assessed as the mean of three consecutive measurements obtained, at 2-minute intervals, after 5 minutes of rest in the sitting position, following the recommendations of the 2013 European Society of Hypertension/European Society of Cardiology guidelines.[24]

Routine biochemical parameter determination was performed with standard techniques using an autoanalyzer (Boehringer Mannheim for Hitachi system 911). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[32] A 24-hour urine sample was collected on nonworking days, and albumin excretion rate was assayed by a solid-phase enzyme immunoassay (Microalbumin-ELISA, DRG Diagnostics). The adequacy and completeness of the collection were assessed by measuring urinary creatinine excretion. Creatinine excretion <10 mg/kg per day for women and <15 mg/kg per day for men was considered as undercollection, and a urinary creatinine outuput >25 mg/kg per day in women and >30 mg/kg per day in men was considered as overcollection. None of our patients had urinary creatinine values outside these ranges. Chronic kidney disease was defined as eGFR <60 mL/min per 1.73 m^2 or albumin excretion rate ≥30 mg/24 h for at least 3 months.

Moreover, aortic stiffness was determined by measuring aPWV, and B-mode and Doppler ultrasonographic examinations of both carotid and renal vasculature were performed in all patients to assess cIMT and RRI.

2.3 | Aortic pulse wave velocity

Arterial stiffness was assessed using the operator-independent, noninvasive Arteriograph system (Tensiomed Kft.), which was previously validated.[31] aPWV measurements were performed in patients in the supine position with an upper-arm BP cuff when the pressure exceeded systolic BP by 35 to 40 mm Hg, with a completely occluded brachial artery. As previously described, aPWV was calculated with the formula: aPWV = (distance Jug/Sy[m])/(RT/2[s]), where distance Jug/Sy(m) is the distance between the jugulum (sternal notch) and the pubic symphysis, and RT is the sum of the forward and the backward transit time.[31] An aPWV value ≥10 m/s was chosen to identify

patients with prognostic validated alterations of aortic elastic properties, as previously described.[24,31]

2.4 | Renal ultrasonography

The intrarenal color duplex ultrasonography was performed with a GE Logiq P5-PRO instrument (GE Healthcare) by a 4-MHz transducer operating at 2.5 MHz for Doppler analysis. Doppler signal was obtained from the interlobar arteries by placing the sample volume at the level of the corticomedullary junction. Peak systolic velocity and telediastolic velocity were measured with a Doppler angle <60°, and RRI was calculated by the formula: RRI = (peak systolic velocity − telediastolic velocity)/peak systolic velocity. The values were computed as the average of six measurements (three from each kidney). A cutoff of 0.7 for RRI was chosen to identify patients with an increased prevalence of hypertensive target organ damage and a faster progression of renal diseases, as described elsewhere.[31]

2.5 | Carotid ultrasonography

The carotid ultrasonographic investigation was performed with a GE Logiq P5-PRO instrument by a 10-MHz linear-array transducer for the measurements, operating at 5 MHz for Doppler analysis.

cIMT was defined as the distance between the vascular lumen-intima interface and the media-adventitia transition, and we used the overall average cIMT value of six measurements obtained for each side. We considered plaques those focal structures encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding cIMT value, or demonstrating a cIMT >1.5 mm.[33] In correspondence of a carotid plaque, cIMT measurement was not obtained and was shifted proximally on the plaque-free site. The executing technique and the cutoff values (cIMT >0.90 mm) were previously described.[34] Systemic vascular damage (SVD) was defined as the presence of at least one of either cIMT >0.9 mm or carotid plaques or aPWV ≥10 m/s.

2.6 | Statistical analysis

The study was planned to have a sample size of at least 120 patients in the elderly group. These figures were calculated on the basis of a previous pilot investigation on the same topic by our group.[35] We hypothesized that we would find correlation coefficients relating eGFR with both cIMT and aPWV of at least 0.250. Thus, it was estimated that the study would have a power of >80% to detect the expected results (with $\alpha < 0.05$).

Statistical analysis was initially performed in the whole study population, and it was subsequently performed in two groups: patients 65 years and older (elderly patients with hypertension [EH], n = 126) and patients younger than 65 years (nonelderly patients with hypertension [NEH], n = 350).

Continuous variables were given as mean ± SD. Albuminuria and triglycerides (expressed as median and interquartile range because of their skewed distribution) were log-transformed to better satisfy distributional assumptions before parametric tests were used. Categorical variables were expressed as percentage values.

Student *t* test for independent samples was used to compare continuous variables between the two groups, whereas proportional differences between groups were assessed by the $\chi 2$ test, with Yates correction (or Fisher exact test when appropriate). The effects of age and SVD on eGFR were assessed by a two-way analysis of variance, initially without any adjustments and then with adjustment for potential confounders. Interaction between age (as dichotomous variable) and SVD was formally tested by assessing the significance of the multiplicative two-way interaction term "age × SVD" along with the main effects of SVD. The univariate and multivariate relationships were tested by simple and multiple linear regression analyses. The strength of the associations between the variables was expressed respectively by the Pearson correlation coefficients (*r*) and the standardized (β) multiple regression coefficients. All of the above-mentioned analyses were initially performed in the entire study population, and subsequently in both EH and NEH groups.

The stepwise multiple regression models were performed considering age as the outcome variable, and including into the models as potential explanatory parameters: sex (0 = women, 1 = men), smoking habit (0 = nonsmokers, 1 = smokers), body mass index, aPWV, cIMT, eGFR, (log)albuminuria, RRI, serum uric acid, glycemia (or diabetes mellitus as dichotomous variable), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, (log)triglycerides, clinic mean blood pressure, and clinic pulse pressure. To better assess the role of RRI as a marker of renal impairment, a similar multivariate model was built in the overall study population including among covariates the same variables as the previous model, except for eGFR and albuminuria.

Further stepwise multivariate models were built on the overall study population and in the NEH group considering alternatively cIMT or aPWV as the outcome variable, and including, as confounders, age and those variables regarded as regressors in the previous multivariate model. In the EH group, given the low number of patients enrolled, we included as covariates only parameters associated with cIMT or aPWV at univariate analyses: age, sex, smoking status, eGFR, RRI, albuminuria, low-density lipoprotein cholesterol (only for aPWV), high-density lipoprotein cholesterol (only for cIMT), uric acid (only for cIMT), clinic pulse pressure and therapy with statins, and β-blockers (only for cIMT, or alternatively angiotensin-converting enzyme inhibitors or calcium antagonists).

In all multiple regression analyses, a backward stepwise procedure was used, with α=0.15 as the cutoff for entry or removal of variables. Collinearity was assessed by calculating the variance inflation factor (VIF): variables with VIF ≥2 were excluded from the models.

The null hypothesis was rejected at a two-tailed *P* value ≤.05.

The statistical analyses were performed using the IBM SPSS Statistics software package, version 22 for Macintosh.

3 | RESULTS

The main clinic and demographic characteristics of the entire study population and of the two groups (EH and NEH) are summarized in Table 1.

TABLE 1 Demographic and clinic data of overall study population and of two groups of NEH and EH

	Overall study population (N = 476)	NEH (n = 350)	EH (n = 126)	*P* value
Age, y	54 ± 16	48 ± 12	72 ± 6	<.001
Men, %	55.3	57.7	48.4	NS
Smokers, %	29.8	28.3	34.1	NS
Diabetes mellitus, %	26.1	19.7	43.7	<.001
BMI, kg/m^2	28.2 ± 10.5	28.2 ± 4.49	28.2 ± 4.6	NS
Serum glucose, mg/dL	110.7 ± 35.8	112.3 ± 38	106.4 ± 33.7	NS
Serum uric acid, mg/dL	6.32 ± 1.60	6.32 ± 1.82	6.31 ± 1.60	NS
Serum total cholesterol, mg/dL	191 ± 44	193 ± 42	186 ± 46	NS
HDL-C, mg/dL	49 ± 15	49 ± 15	49 ± 17	NS
LDL-C, mg/dL	120 ± 38	123 ± 36	113 ± 39	.009
Triglycerides, mg/dL	115 (80-155)	117 (78-158)	114 (84-147)	NS
Serum creatinine, mg/dL	1.18 ± 0.85	1.06 ± 0.71	1.53 ± 1.10	<.001
eGFR, mL/min per 1.73 m^2	80.5 ± 28.7	86.6 ± 24.8	63.5 ± 28.4	<.001
Albuminuria, mg/24-h	28.2 (13.8-112.3)	24.5 (12.4-61.8)	67.6 (25.2-295.7)	<.001
Serum sodium, mEq/L	139 ± 5	139 ± 3	138 ± 8	NS
Serum potassium, mEq/L	4.49 ± 2.97	4.52 ± 3.50	4.40 ± 0.53	NS
Clinic systolic BP, mm Hg	136 ± 16	136 ± 16	138 ± 16	NS
Clinic diastolic BP, mm Hg	81 ± 11	83 ± 11	76 ± 10	<.001
Clinic pulse pressure, mm Hg	55 ± 14	53 ± 13	61 ± 14	<.001
Clinic mean BP, mm Hg	98 ± 11	99 ± 11	97 ± 11	.045
Clinic heart rate, beats/min	71 ± 10	73 ± 10	66 ± 11	<.001
RRI	0.63 ± 0.07	0.62 ± 0.06	0.67 ± 0.05	<.001
cIMT, mm	0.92 ± 0.22	0.88 ± 0.22	1.02 ± 0.19	<.001
aPWV, m/s	11.32 ± 2.34	10.90 ± 2.32	12.50 ± 1.96	<.001

Abbreviations: aPWV, aortic pulse wave velocity; BMI, body mass index; cIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; EH, elderly patients with hypertension; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NEH, nonelderly patients with hypertension; NS, not significant ($P \geq .05$); RRI, renal resistive index.

The percentages of patients treated with cardiovascular drugs are presented in Table S1. Patients treated with angiotensin-converting enzyme inhibitors and calcium antagonists had higher values of RRI and cIMT, and those treated with β-blockers had greater RRI, when compared with patients not treated with these drugs (all $P < .05$). No difference was detected between patients treated or not treated with other cardiovascular drugs concerning the effect on vascular and kidney damage.

EH had higher values of cIMT and PWV compared with NEH (all $P < .001$). Similarly, significantly lower eGFR and higher albuminuria and RRI were observed in the EH group compared with the NEH group (all $P < .001$) (Table 1). analysis of covariance (<0.001). Moreover, the percentages of kidney damage (defined as eGFR <60 mL/min per 1.73 m^2, albuminuria ≥30 mg/24 h, RRI ≥0.70) and vascular damage (defined as cIMT >0.90 mm and aPWV ≥10 m/s) were significantly greater in EH compared with NEH (all $P < .001$) (Figure A and B).

In the whole population, findings from two-way analysis of variance showed a significant effect of age ($F = 89.3$; $P < .001$) and SVD ($F = 21.9$; $P < .001$) on eGFR. The analysis of the interaction term "age × SVD" revealed a significant effect of age on the association between SVD and eGFR, both before ($F = 44.7$; $P < .001$) and after adjustment for systolic blood pressure, diastolic blood pressure, body mass index, and diabetes mellitus ($F = 32.9$; $P < .001$).

Main univariate correlations in the overall study population and in the groups of NEH and EH are reported in Table 2. Age significantly correlated with eGFR, albuminuria, RRI, cIMT, and aPWV in the entire study population (all $P < .001$), and similar results were obtained in the two subgroups divided by age. In the EH group, as well as in the NEH group, cIMT was strongly associated with eGFR and RRI ($P < .01$) but not with albuminuria. In contrast, aPWV significantly correlated with all indexes of renal damage (eGFR and albuminuria: $P < .001$; RRI: $P < .01$) in the NEH group, whereas it showed significant association only with eGFR in the EH group ($P < .001$). Complete lists of the univariate correlations in the NEH and EH groups are shown in Tables S2 and S3.

The association between age and eGFR, as well as the association between age with cIMT and aPWV, remained statistically significant even after adjustment for various confounding factors at stepwise multiple linear regression analysis performed in the whole population (all $P < .001$) (Table S4). When a further multivariate model was performed without eGFR and albuminuria among the covariates, age significantly correlated with RRI ($\beta = 0.098$; $P = .018$).

Further multivariate models were also built in the entire study population considering alternatively cIMT or aPWV as an outcome variable, and similar statistical analyses were performed in the NEH and EH groups. The cIMT independently correlated with RRI and eGFR in the NEH group, whereas it was significantly related only to RRI in the EH group (Table 3). On the contrary, the aPWV was independently associated with albuminuria in the NEH group, whereas it did not independently correlate with any indexes of renal damage in the EH group (Table 4).

4 | DISCUSSION

Our findings suggest that age might represent an important modifier of the relationships between renal dysfunction and hemodynamics (eGFR, albuminuria, and RRI) with markers of systemic vascular involvement (cIMT and aPWV) in patients with essential hypertension with no cardiovascular events. These results also seem to imply that the search for vascular organ damage in older patients with chronic kidney disease might be less important than in younger patients.

Previous studies have shown a strong association between age and subclinical atherosclerotic damage,[7,36] and many authors observed increased arterial stiffness with aging[2,10] caused by impaired collagen/elastin ratio of the vessel wall and subsequent reduced vascular elasticity.[2] Similarly, the association between age and eGFR (or albuminuria) was previously demonstrated,[15,16] and our results are in line with these evidences. Tedesco and colleagues[37] also observed that RRI significantly increased with age in 566 patients with hypertension with preserved kidney function, and other authors reached similar conclusions in different clinical subsets.[20–22]

In our study, SVD independently correlated with eGFR, albuminuria, and RRI in the entire study population, regardless of age. A close association between renal impairment with vascular damage has been observed in previous studies.[38–40] In MESA (Multi-Ethnic Study of Atherosclerosis), cIMT was highly correlated with eGFR,[41] and similar results were also reported in patients with proteinuria without severely reduced eGFR.[42]

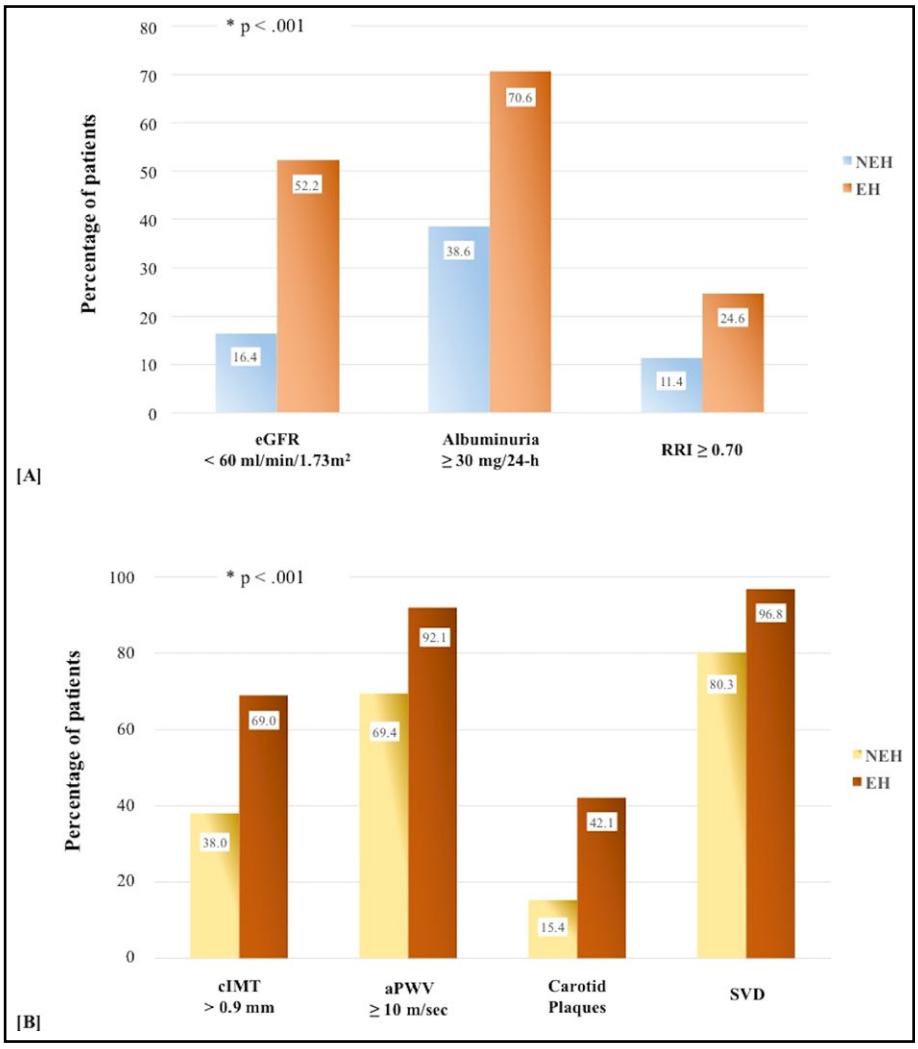

FIGURE Percentage of patients with renal (A) and vascular (B) damage in the two groups of nonelderly patients with hypertension (NEH) and elderly patients with hypertension (EH)

TABLE 2 Main univariate correlations in the overall study population (A) and in the two groups of NEH (B) and EH (C)

	eGFR	Albuminuria	RRI	cIMT	aPWV
	r	*r*	*r*	*r*	*r*
(A)	Overall study population (N = 476)				
Age	−.608***	.282***	.334***	.456***	.393***
eGFR	/	−.545***	−.313***	−.344***	−.309***
Albuminuria	−.545***	/	.236***	.163***	.292***
RRI	−.313***	.236***	/	.327***	.255***
cIMT	−.344***	.163***	.327***	/	.364***
aPWV	−.309***	.292***	.255***	.364***	/
(B)	NEH (n = 350)				
Age	−.479***	.179***	.147**	.417***	.307***
eGFR	/	−.482***	−.153**	−.256***	.213***
Albuminuria	−.482***	/	.167**	.088^{NS}	.274***
RRI	−.153**	.167**	/	.267***	.199***
cIMT	−.256***	.088^{NS}	.267***	/	.352***
aPWV	.213***	.274***	.199***	.352***	/
(C)	EH (n = 126)				
Age	−.272**	.051^{NS}	.089^{NS}	.271**	.029^{NS}
eGFR	/	−.549***	−.262**	−.254**	−.262**
Albuminuria	−.549***	/	.161^{NS}	.152^{NS}	.112^{NS}
RRI	−.262**	.161^{NS}	/	.231**	.050^{NS}
cIMT	−.254**	.152^{NS}	.231**	/	.138^{NS}
aPWV	−.272**	.051^{NS}	.089^{NS}	.271**	.029^{NS}

Abbreviations: aPWV, pulse wave velocity; BMI, body mass index; cIMT, carotid intima-media thickness; EH, elderly patients with hypertension; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NEH, nonelderly patients with hypertension; NS, not significant ($P > .05$); RRI, renal resistive index.

*$P < .05$.

**$P \leq .01$.

***$P \leq .001$.

However, when we divided the population based on age, cIMT independently correlated with eGFR and RRI in the NEH group, whereas only the relationship with RRI held significance in the EH group. aPWV was significantly associated with albuminuria in the NEH group, and its association with RRI was near to borderline statistical significance ($P = .056$) in these patients. In contrast, none of the indexes of renal damage independently related with aPWV in the EH group.

No study is underway to clarify why the relationship between vascular changes and kidney damage could be modified by age; however, some hypotheses can be proposed.

An earlier onset of vascular damage than kidney impairment, as well as a different progression over time of vascular and renal injury, might in part justify the results. In our population, SVD was present in 80.3% of NEH, whereas an eGFR <60 mL/min per 1.73 m^2 was observed in only 16.4% of NEH and in a larger percentage of EH (52.2%) (Figure A).

The lack of a relationship between cIMT and eGFR (or albuminuria) in EH might have another explanation. Unlike in NEH, the severity of atherosclerosis in EH is expressed by the presence and extent of carotid plaques rather than by the intima-media thickness, even as a result of the limitations in the cIMT evaluation: a cIMT >1.5 mm is conventionally defined as atherosclerotic plaque,[33] and this represents a speculative threshold that cIMT value cannot exceed. Consistent with this interpretation, EH had a higher prevalence of carotid plaques (42.1%) compared with NEH (15.4%; $P < .001$) (Figure B).

Moreover, the influence of multiple extrarenal and extravascular factors in determining eGFR and albuminuria is lower in middle-aged patients compared with elderly patients,[43] and this might present a bias for evaluation of renal function in the latter group. In several studies, the calculation of glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration equation showed a greater margin of error in the elderly.[43–45]

In our study, only RRI was independently associated with cIMT in elderly patients with hypertension. It seems to relate to vascular damage better than eGFR or albuminuria, and this would further confirm that RRI not only detects derangement of intrarenal circulation but may also be considered as a sensor of systemic vascular changes,

TABLE 3 Independent multivariate correlates of cIMT in the overall study population (A) and in NEH (B) and EH (C)

	Standardized regression coefficients	
Outcome variable: cIMT	β	*P* value
(A) Model (R^2 = 0.30)		
Age	0.370	<.001
Serum uric acid	0.210	<.001
RRI	0.165	<.001
Statins	−0.104	.009
(B) Model (R^2 = 0.18)		
RRI	0.188	<.001
eGFR	−0.200	.001
Serum uric acid	0.169	.001
Serum glucose	0.117	.021
(C) Model (R^2 = 0.20)		
Serum uric acid	0.335	<.001
RRI	0.177	.039

See text for further explanation about the multivariate models. Abbreviations: cIMT, carotid intima-media thickness; EH, elderly patients with hypertension; NEH, nonelderly patients with hypertension; RRI, renal resistive index.

TABLE 4 Independent multivariate correlates of aPWV in the overall study population (A) and in NEH (B) and EH (C)

	Standardized regression coefficients	
Outcome variable: aPWV	β	*P* value
(A) Model (R^2 = 0.25)		
Constant	/	<.001
Age	0.258	<.001
Albuminuria	0.177	<.001
Sex	−0.135	.001
Smoking habit	0.118	.005
Pulse pressure	0.103	.018
(B) Model (R^2 = 0.20)		
Constant	/	.004
Albuminuria	0.212	<.001
Pulse pressure	0.173	.001
Sex	−0.158	.001
Serum glucose	0.109	.030
Heart rate	−0.104	.035
(C) Model (R^2 = 0.14)		
Constant	/	<.001
Sex	−0.314	.001
LDL-C	−0.242	.007
Smoking habit	0.197	.031

See text for further explanation of the multivariate models. Abbreviations: aPWV, aortic pulse wave velocity; EH, elderly patients with hypertension; LDL-C, low-density lipoprotein cholesterol; NEH, nonelderly patients with hypertension.

independently of level of renal function.[13,31] We previously demonstrated in 463 patients with hypertension that RRI, cIMT, and aPWV were strongly associated, even if the relationship of RRI with aPWV was lost after adjustment for clinic pulse pressure. However, the influence of age on these relationships was not evaluated.[13]

On the other hand, it is possible that in elderly patients, RRI could reflect the worsening of renal damage more accurately, or more precociously, compared with traditional indexes of kidney function, perhaps because it is less influenced by factors that affect eGFR or albuminuria.

The above-mentioned hypotheses are not mutually exclusive, and all together might explain the role of age on the complex link between SVD and renal damage. It is noteworthy that in our study a significant effect of diabetes mellitus (or serum glucose) on systemic vascular changes was documented only in NEH. The lack of this association in the overall population and in EH may be caused by the prevailing impact of variables, such as albuminuria or RRI, that are strongly related to diabetes mellitus and that may be considered expressions of vascular complications of diabetes mellitus.

5 | CONCLUSIONS

The conclusions of this study need to be interpreted in the context of its limitations. First, the cross-sectional design of the study does not allow us to establish a causality relationship and does not permit us to compare variations of vascular and renal parameters over time. Second, the use of eGFR based on a single assay of serum creatinine reduces the accuracy on the assessment of "true" renal function. Moreover, the limited number of patients with low glomerular filtration rate cannot allow us to exclude that the relationship between SVD and renal damage might also exist in EH with a greater impairment of renal function. Therefore, further studies are needed to better clarify the results of our investigation.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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