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Retinal vascular caliber associated with cardiac and renal target organ damage in never-treated hypertensive patients

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Abstract

Objective: The aim of this study was to assess the relationship between retinal vascular caliber and target organ damage in HT patients.

Methods: Data were collected on cardiac, renal, vascular, and retinal variables in 88 consecutive never-treated HT subjects. Retinal vascular calibers were measured from fundus photographs by using a semi-automated computer-assisted program and summarized as CRAE and CRVE.

Results: Mean CRAE and CRVE were significantly lower in patients with left ventricular hypertrophy (left ventricular mass ≥ 110 g/m² for women, 125 g/m² for men) than in those with normal left ventricular (CRAE: 129.4 ± 3.7 vs 138.2 ± 2.3 μ m; $P=.04$; CRVE: 195.6 ± 4.4 vs 209.8 ± 2.7 μ m; $P=.008$). CRAE and CRVE were negatively correlated with urinary albumin excretion ($\beta \pm SE = -15.4 \pm 3.2$, $P<.0001$ and $\beta \pm SE = -11.9 \pm 4.4$, $P=.001$, respectively) but were not correlated with estimated glomerular filtration rate ($P=.21$ and $P=.75$, respectively), carotid-to-femoral pulse wave velocity ($P=.24$ and $P=.14$), or carotid augmentation index ($P=.43$ and $P=.16$).

Conclusion: In never-treated HT patients, reduced CRAE and CRVE were associated with cardiac and renal preclinical damage, ie, left ventricular hypertrophy and albuminuria, but not estimated glomerular filtration rate or vascular stiffness.

KEYWORDS

hypertension, microcirculation, retinal vessels, target organ damages

1 | INTRODUCTION

CV risk in HT patients is strongly associated with the presence of early changes in organ systems in the body, grouped under the term TOD, such as LVH,^{1,2} albuminuria,³⁻⁵ decreased GFR,⁶⁻⁸ retinopathy,⁹⁻¹² vascular stiffening,^{13,14} or cerebral white matter lesions.^{15,16}

Abbreviations: Alx, augmentation index; AP, augmented pressure; ARIC, atherosclerosis risk in communities; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; CV, cardiovascular; GFR, glomerular filtration rate; HT, hypertensive; LVH, left ventricular hypertrophy; LV, left ventricular; LVM, left ventricular mass; MESA, multiethnic study of atherosclerosis; PWT, posterior wall thickness; RWT, relative wall thickness; TOD, target organ damage.

Meta-analyses of epidemiological studies revealed wide retinal venules and narrow arterioles associated with increased risk of coronary heart disease in women and increased risk of global CV mortality;¹⁷ wide retinal venular caliber predicted stroke.¹⁷⁻¹⁹ In HT, both LVH and renal function are excellent independent CV event predictors.²⁰ Assessment of retinal microcirculation may help with investigating CV and renal damage.

Generalized and focal retinal arteriolar narrowing is associated with LVH.²¹ The MESA found LVH and LV concentric remodeling associated with narrow retinal arterioles and retinopathy in men and women.²²

In patients with renal failure, retinal arteriolar and venular caliber progressively decrease with increasing stage of CKD. In patients with

CKD stage 2-4, presence of small retinal arterioles and increased micro-albuminuria was correlated with decreased rate GFR.^{23,24} In healthy subjects, narrow arterioles and veins were associated with decreased GFR and small arteriolar diameter with increased albuminuria.²⁵

Fundus photography provides a noninvasive approach to assess retinal microcirculation. Changes in caliber of retinal vessels can reflect the cumulative effects of birth weight,^{26,27} body mass index,²⁸ CV risk factors,^{29,30} renal function,²⁵ inflammation,³¹ oxidative stress,³² and genetic factors.³³

Arteriolar narrowing may be associated with other markers of TOD in uncontrolled HT.³⁴⁻³⁶ However, we lack evidence of the additional benefit of assessing retinal vascular caliber to identify TOD in patients with early HT.^{37,38} Here, we aimed to assess whether a decrease in retinal vessel caliber was associated with other preclinical TOD in never-treated HT patients.

2 | PATIENTS AND METHODS

This paper followed the STROBE checklist items for reporting cross-sectional study.³⁹

2.1 | Setting

Subjects were recruited from the outpatient clinic of the Department of Medicine of University Hospital, Montpellier, France.

2.2 | Participants

The study population consisted of 88 consecutive never-treated hypertensive subjects. The subjects presented or were referred by general practitioners for detecting or investigating CV risk factors through a local screening program for CV risk.

We considered only HT patients without other known CV, renal, or metabolic disease and who had never received antihypertensive, antidiabetic or lipid-lowering therapy. Patients were excluded if they had clinical evidence of atherosclerosis (stroke or coronary and peripheral artery disease), heart failure, renal failure (serum creatinine level >1.2 mg/dL), diabetes mellitus (fasting blood glucose >126 mg/dL), obesity (body mass index >30 kg/m²), history of alcohol abuse (>5 drinks/day), or secondary HT.

Written informed consent was obtained from each participant in adherence to the provisions of the 1995 Declaration of Helsinki (revised in 2000). This study was approved by the University Hospital of Montpellier.

2.3 | Study design

This was a cross-sectional study of data from a prospectively designed observational study.

2.4 | Data sources/measurements and variables

All patients underwent the following procedures on the same day.

2.4.1 | Blood pressure

BP was measured every 3 min with the use of an automatic device (Model Dinamap V100; GE Healthcare, Little Chalfont, UK), and reported values are the average of at least 10 measurements following a 10-min period of rest in the supine position. Mean blood pressure was calculated as systolic BP + [2* diastolic BP] / 3. HT was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg (International Society of Hypertension Guidelines 1999).

2.4.2 | Determination of renal function

On the day of investigation, patients came to the ward with a 24-h urine collection to determine urinary albumin excretion (UAE: organ damage significance level set to ≥10 mg/24 h, a cutoff value obtained in a previous local sample of normal subjects with BP <140/90 mm Hg) and levels of creatinine, urea (index of protein intake), electrolytes, sodium (index of sodium intake), and potassium. Prior to investigations, subjects were measured for weight (Model 703; CKSeca, Hamburg, Deutschland) and height (Microtoise 04-116; Stanley Black & Decker, New Britain, CT, USA). Fasting blood samples were obtained to measure serum creatinine level (IDMS enzymatic method), glucose, electrolytes, total cholesterol, triglycerides, and lipid levels.

2.4.3 | Echocardiographic parameters

Echocardiographic assessment of LV morphology was performed by the same observer (GDC) using the SC2000 ultrasound system (Siemens, Mountain View, CA, USA) with a 2.5- or 3.5-MHz transducer. Technical details were reported elsewhere.⁴⁰

LVM was estimated from end-diastolic LV diameter, interventricular septum thickness, and PWT according to the Devereux formula, using the Penn convention.⁴¹ LVM was normalized to body surface area to obtain the LVM index (LVMI, g/m²). RWT was calculated as follows:

$$RWT = \frac{(2 \times PWT)}{LVEDD}$$

PWT: PWT at end-diastole (mm)

LVEDD: LV end-diastolic dimension (mm)

The presence of LVH was defined as LVMI ≥125 g/m² for men and 110 g/m² for women. A concentric pattern was defined as RWT ≥0.44. These cutoff values were obtained in a previous local sample of normal subjects with BP <140/90 mm Hg.

To evaluate the association between cardiorenal damage and changes in retinal vessel diameters induced by HT, we created four TOD groups as follows:

- TOD 1. Normal LVMI and UAE ≤10 mg/24 h
- TOD 2. LVH and UAE ≤10 mg/24 h
- TOD 3. Normal LVMI and UAE >10 mg/24 h
- TOD 4. LVH and UAE >10 mg/24 h

2.4.4 | Retinal vascular caliber measurements

Retinal photographs of both eyes were obtained by using a non-stereoscopic, 45° nonmydriatic fundus camera (CR5-NM45; Canon

Inc., Tokyo, and TRC, Topcon Inc., Tokyo) centered on the optical disk. Diameters of all vessels in a specified area (0.5-1 disk diameter surrounding the optic disk) were measured by using image analysis software (IVAN, Department of Ophthalmology Visual Science, University of Wisconsin, Madison, WI). The caliber of the central retinal artery and vein was estimated by using the “Big-6 formula” and summarized as CRAE and CRVE.^{42,43} The reproducibility of retinal vascular measurements was high, with intraobserver correlation coefficients of 0.97 [95% CI: 0.96-0.98] and 0.95 (95% CI: 0.94-0.96) for CRAE and CRVE, respectively. With the high inter-eye correlation reported in previous studies,⁴⁴ we analyzed only one eye per subject (the right eye, or, if unavailable or not gradable, the left eye).

2.4.5 | Vascular stiffness variables

Pulse wave velocity

Femoral, carotid, and radial pressure waveforms were recorded by applanation tonometry by using the SphygmoCor system (AtCor Medical, Sidney, Australia). From carotid and femoral waveforms, wave transit time was calculated with the R wave of a simultaneously recorded electrocardiogram used as a reference frame and the foot of the waves determined with an intersecting tangent algorithm. Distances from the suprasternal notch to carotid and femoral sites were measured, and transit distance was calculated by subtracting the two distances, thus allowing for correction of parallel transmission. Carotid-to-femoral pulse wave velocity (PWV) was then calculated as transit distance divided by transit time.⁴⁵

Pulse wave analysis

Carotid pressure waveform was used to estimate central aortic waveform without the use of a transfer function. Carotid pressure waveform was calibrated by using mean and diastolic pressure values of the radial pressure waveform, which was itself calibrated with cuff-measured systolic and diastolic brachial BP. AP was determined as the pressure difference between the first and second peaks of carotid waveform. The carotid Alx was calculated as AP/central pulse pressure.⁴⁶ As evaluated by Wilkinson et al.⁴⁷ and with Bland-Altman plots, within-observer variability is 0.07±1.17 m/sec for carotid-to-femoral PWV and 0.49±5.37% for Alx.

2.5 | Statistical analysis

SAS v9.4 (SAS Inst., Cary, NC, USA) was used for data analysis. Because of their skewed distribution, urinary albumin values were log-transformed before analysis. The relationship between retinal variables and age, gender, mean BP, and BMI was first tested by linear univariate analysis and then by multivariate linear regression to detect the independent relationship between retinal, vascular, and renal variables. Analysis of covariance (ANCOVA) was used to determine the association of retinal vascular caliber and cardiac patterns and TOD adjusted for age, sex, BP and BMI, smoking status, total cholesterol, triglyceride levels, and fasting blood glucose.

Post hoc pairwise comparisons were corrected for multiple testing by using the Tukey-Kramer method.

Unless otherwise stated, results are expressed as mean ± SD or median (interquartile range) for descriptive statistics and mean ± SE for results of multivariate analysis. Significance was set at *P*<.05.

3 | RESULTS

3.1 | Population characteristics

The study population consisted of 88 never-treated hypertensive subjects (38 women, mean ± SD age 54±11 years; range 32-83 years) (Table 1). Mean systolic BP was 155±15 mm Hg and diastolic BP 89±10 mm Hg. Mean RWT was 0.46 and LVMI 115±24 g/m². Average eGFR was 97.6±22.4 mL/min/1.73 m², serum creatinine level 98±22 μm/L, and median (interquartile range) UAE (5.35 [3.47-9.56] μg/min). Mean CRAE was 136±18 μm and CRVE 205±21 μm. Mean PWV was 9.9±2.5 m/sec and carotid Alx 32±10%. In this population of hypertensive subjects, 23 (26.1%) had LVH (LVMI ≥125 g/m² for men and 110 g/m² for women) and 18 (20.5%) had UAE ≥10 mg/24 h.

TABLE 1 Characteristics of 88 patients with never-treated hypertension

Age (year)	54±11
Male (%)	56.8
Current smoker (%)	18.5
BMI (kg/m ²)	26.49±4.66
Systolic BP (mm Hg)	155±15
Diastolic BP (mm Hg)	89±10
Mean BP (mm Hg)	111±10
Fasting blood glucose (mmol/L)	5.02±0.6
Hba1c (%)	5.56±0.45
Total cholesterol (mmol/L)	2.20±0.35
HDL cholesterol (mmol/L)	0.6±0.2
Calculated LDL cholesterol (mmol/L)	1.31±0.3
Triglycerides (mmol/L)	1.2±0.7
eGFR (mL/min/1.73 m ²)	97.6±22.4
Serum creatinine level (μmol/L)	98±22
Urinary albumin excretion (mg/min)	5.35 (3.47-9.56)
LVMI (g/m ²)	115±24
RWT	0.46±0.1
Femoral PWV (m/s)	9.9±2.5
Carotid Alx	32±10
CRAE (μm)	136±17.7
CRVE (μm)	205.6±20.8

Data are mean ± standard deviation or median (interquartile range). BP, blood pressure; eGFR, estimated glomerular filtration rate; LV, left ventricular; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PWV, pulse wave velocity; Alx, augmentation index; LVMI, left ventricular mass index; RWT, relative wall thickness; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; AVR, retinal artery/vein ratio.

TABLE 2 Association of retinal caliber with cardiac morphology patterns (LV hypertrophy, concentric pattern)

		CRAE (μm)		CRVE (μm)	
		Crude	Adjusted ^a	Crude	Adjusted ^a
		P	P	P	P
LV hypertrophy	Increased LVMI ^b	129.6±3.5	.03	129.4±3.7	.04
	Normal LVMI	138.4±2.2		208.9±2.5	
LV concentric pattern	RWT ≥0.44	135.4±2.8	.87	205.6±3.3	.91
	RWT <0.44	136.4±2.6		205.5±3	

Data are mean ± standard error. LV, left ventricle; LVMI, left ventricular mass index; RWT, relative wall thickness; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; AVR, retinal artery/vein ratio.

^aAdjusted on age, sex, body mass index, mean blood pressure, smoking status, total cholesterol (mmol/L), Triglycerides (mmol/L), and Fasting blood glucose (mmol/L)

^b≥125 g/m² in men and ≥110 g/m² in women.

3.2 | Association of retinal caliber and LV geometry patterns

Mean CRAE was significantly lower in patients with LVH than in those with normal LVMI (mean ± SE 129.6±3.5 vs 138.4±2.2 g/m²; *P*=.03) and remained significant after adjustment on age, sex, BMI, mean BP smoking status, total cholesterol, triglyceride levels, and fasting blood glucose (129.4±3.7 vs 138.2±2.3 g/m²; *P*=.04, Table 2). The same association was found for CRVE (196.5±4.1 vs 208.9±2.5 μm; *P*=.01) even after adjustment (195.6±4.4 vs 209.8±2.7 μm; *P*=.008).

3.3 | Association of renal function and retinal microvasculature

After adjustment on age, sex, BMI, mean BP smoking status, total cholesterol, triglyceride levels, and fasting blood glucose, CRAE and CRVE were negatively correlated with UAE (β±SE=-15.4±3.2; *P*<.001; β±SE=-11.9±4.4; *P*>.001, respectively, Table 3). eGFR was not correlated with retinal vessel variables.

3.4 | Association of retinal caliber and vascular stiffness

CRAE and CRVE were negatively correlated with carotid-to-femoral PWV (β±SE=-1.52±0.75, *P*=.04, and β±SE=-1.81±0.88, *P*=.04, respectively) but not after adjustment on age, sex, BMI, mean BP smoking status, total cholesterol, triglyceride levels, and fasting blood glucose (β±SE=-1.10±0.8 *P*=.24, and β±SE-1.68±1.09, *P*=.14, respectively, Table 4).

3.5 | Association of retinal caliber and combined cardiorenal damage

About retinal caliber, adjusted CRAE was lower for TOD group 4 (LVH and high UAE), 3 (normal LVMI but high UAE), and 2 (LVH and normal UAE) than group 1 (normal LVMI and UAE) (114.5±6.3, 127.3±5.1, and 134.2±4.2 vs 140.7±2.4 μm, respectively; *P* trend=.003) (Figure 1).

Similar results were observed for adjusted CRVE (181.5±8.4, 202.2±6.3, and 199.8±4.8 vs 211.3±2.9 μm, respectively; *P* trend=.03).

4 | DISCUSSION

In the present study of 88 never-treated HT subjects, reduced arteriolar and venular retinal caliber were associated with LVH and increased albuminuria but not concentric pattern of LV, eGFR or aortic stiffness, independent of mean BP, BMI, age, and sex.

Koren et al. observed that age and LVM were better predictors of CV morbidity/mortality than BP. In a 10-year follow-up study of 280 patients with uncomplicated HT, those with normal LV geometry had fewer CV outcomes than those with concentric hypertrophy.² Retinal vascular caliber has been associated with risk of CV mortality.¹⁷ Therefore, the relationship between retinal and cardiac modification in HT patients is of particular interest.

In the MESA study of 4593 patients from the general population, LVM (measured by MRI) was associated with narrow arterioles and retinopathy in both men and women. The relation between LVH and reduced vein diameter was significant only in women.²² In a subpopulation of 2622 African Americans from the ARIC study, LVM and CRAE were correlated: Increased LVM was associated with generalized and focal arteriolar narrowing but not retinopathy or arteriovenous crossing.²¹

In the present study, retinal arteriolar and venular caliber were significantly lower in subjects with LVH than in those with normal LV mass. However, in accordance with Cuspidi et al.,⁴⁸ we found no difference in retinal changes between subjects with normal LV pattern and those with LV concentric pattern.

The association between GFR or albuminuria and retinal vessel caliber is still unclear. In the ARIC study of a general population of 10 056 people, serum creatinine level was not associated with retinal vascular diameter, but 6-year increase in serum creatinine level was correlated with decrease in CRAE and CRVE.⁴⁹ In the Cardiovascular Health Study, the presence of retinopathy was associated with deteriorating renal function but not arteriolar diameter.⁵⁰ However, in a cross-sectional study of 126 patients with incipient to severe CKD,

TABLE 3 Multivariate analysis of renal outcome predictors of retinal vascular caliber

		CRAE				CRVE			
		$\beta \pm SE$	P	r ²	P	$\beta \pm SE$	P	r ²	P
UAE ($\mu\text{g}/\text{min}$, Log)	Crude	-14.7 $\pm$ 3.3	<.0001			-9.6 $\pm$ 3.7	.02		
	Adjusted ^a	-15.4 $\pm$ 3.2	<.0001	.29	<.0001	-11.9 $\pm$ 4.4	.001	.11	.04
eGFR ($\mu\text{mol}/\text{L}$)	Crude	0.07 $\pm$ 0.08	.42			0.08 $\pm$ 0.1	.43		
	Adjusted ^a	0.06 $\pm$ 0.09	.57	.06	.21	0.05 $\pm$ 0.1	.68	.02	.75

Data are mean $\pm$ standard error. UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; CRAE: central retinal artery equivalent; CRVE, central retinal vein equivalent; AVR, retinal artery/vein ratio.

^aAdjusted on age, sex, body mass index, mean blood pressure, smoking status, total cholesterol (mmol/L), Triglycerides (mmol/L), and Fasting blood glucose (mmol/L)

TABLE 4 Multivariate analysis of vascular predictors of retinal vascular caliber

		CRAE		CRVE	
		$\beta \pm SE$	P	$\beta \pm SE$	P
Carotid-to-femoral PWV	Crude	-1.52 $\pm$ 0.75	.04	-1.81 $\pm$ 0.88	.04
	Adjusted ^a	-1.10 $\pm$ 0.8	.24	-1.68 $\pm$ 1.09	.14
Central Alx (AP/PP)	Crude	-0.04 $\pm$ 0.19	.84	0.18 $\pm$ 0.22	.43
	Adjusted ^a	0.19 $\pm$ 0.20	.43	0.33 $\pm$ 0.24	.16

PWV, pulse wave velocity; AP, arterial pressure; PP, pulse pressure.

^aAdjusted on age, sex, body mass index, mean blood pressure, smoking status, total cholesterol (mmol/L), Triglycerides (mmol/L), and Fasting blood glucose (mmol/L).

FIGURE 1 Comparison of CRAE and CRVE (μm) among four TOD groups, adjusted on age, sex, body mass index, mean blood pressure, smoking status, total cholesterol, triglyceride levels, and fasting blood glucose. Results are expressed as mean and 95% confidence interval

CRAE progressively decreased with increasing renal disease stage, and Sabanayagam et al. found CRAE independently related to decreased eGFR $<60 \text{ mL}/\text{min}/1.73 \text{ m}^2$ ($P=.02$) and increased albuminuria ($P=.01$) in HT patients.^{23,51} Among healthy subjects, CRAE was related to measured GFR (urinary clearance of 99mTc-DTPA) and albuminuria.²⁵

In this study of HT patients, we found a close association between CRAE, CRVE, and UAE, considered as a marker of early kidney dysfunction, which may emphasize the role of the microvasculature in the pathogenesis of renal disease progression and the two vascular factors in predicting CKD and general CV events. However, a role for renal

perfusion pressure and more specifically intraglomerular pressure on albuminuria cannot be excluded. In the present study, BP was negatively correlated with retinal arteriolar and venular size. The possibility exists that the response of arteriolar vessels represents an autoregulation process similar to that encountered in glomerular vessels of the kidney, aiming at protecting the kidney against the deleterious effects of intraglomerular hypertension. Other mechanisms can be raised in order to explain the relationship between GFR or albuminuria and retinal vascular calibers. Although microalbuminuria was proposed as a marker of insipient nephropathy in insulin-dependant diabetes, it was later associated with cardiovascular events reflecting systemic endothelial capillary damage with increased permeability.³

Hypertensive subjects show a progressive stiffening of the aorta that may occur in parallel with retinal vascular changes. Previous studies have found an association between reduced carotid-to-femoral PWV, a sign of aortic stiffening, and hypertensive retinopathy.⁵² In 2169 subjects from a general population, elevated brachial-ankle PWV was associated with narrow CRAE but not after adjustment.⁵³ Recently, a comparison of 137 never-treated hypertensive patients and 83 healthy subjects revealed a significant inverse association between PWV and Alx with CRAE but not CRVE after adjustment on confounding factors.⁵⁴ Our findings were consistent with the existing literature because we found a possible association between CRAE and PWV but not after adjustment on age, sex, BMI, and mean BP, which are strong confounding factors of vascular stiffness.

In the present study, retinal arterial and venular caliber were significantly reduced in patients with increased UAE or LVH and even more in patients with the presence of both TOD. Of note, UAE seemed

to be more involved than LVH in arteriolar narrowing, whereas LVH was predominant on venular modifications.

The strengths of this study include the precise measurement of vascular caliber in never-treated HT subjects with no other known cardiovascular condition, thus avoiding the potential effect of anti-hypertensive drugs on renal,⁵⁵ cardiac, vascular, and retinal microcirculation.⁵⁶ Many studies point to the poor inter- and intraobserver reproducibility in grading retinopathy from direct fundoscopy or photography between Keith and Wagener grade I and II (about 80% patients).⁵⁷ However, our analysis of retinal vascular caliber was based on measurements showing high reproducibility.

The main limitation of this study was its cross-sectional nature that did not allow us to propose causal inferences such as the temporal sequence between altered retinal microcirculation and TOD. Also, the population size was small (n=88). The results of the present study may be specific to the undiagnosed hypertensive population and cannot be generalized a priori to patients with treated hypertension. Change in retinal arteriolar and venular calibers has been related to different pathophysiological processes for reasons that remain sometime unexplained. The present findings should be further validated by reference to cellular and molecular biological investigations providing further information on changes in human microcirculation. Further longitudinal analyses are needed to assess the determinants of microvascular remodeling evaluated by retinal vessels.

5 | CONCLUSION

In never-treated HT patients, reduced CRAE and CRVE were associated with cardiac and renal preclinical damage: LVH and albuminuria. Retinal vascular caliber measured by an accessible, cost-effective, noninvasive, nonmydriatic, fast semi-automated procedure could be useful in the early detection of high-risk HT. Retinal, cardiac, and kidney features could share similar determinants of early damage. The natural history of microvascular remodeling and its pathophysiological determinants remains to be investigated in larger longitudinal studies.

PERSPECTIVE

In the present study among hypertensive never treated subject, reduced arteriolar and venular retinal caliber was associated with left ventricular hypertrophy and increased albuminuria. Retinal vascular caliber measured by noninvasive fast semi-automated procedure could be useful in the early detection of high-risk hypertensive patients.

CONFLICT OF INTEREST

There are no conflicts of interest.

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