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ORIGINAL ARTICLE – OPEN ACCESS

Relationship of Retinal Vessel Caliber to Arterial Stiffness Parameters and Nocturnal Blood Pressure Dipping Status in Essential Hypertension

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ABSTRACT

Objective: The primary aim of this study was to compare the retinal vessel caliber (RVC) with both arterial stiffness (AS) parameters and nocturnal blood pressure dipping status (DS) in essential hypertension (EH).

Materials and Methods: The retinal vessel diameter of 101 patients with EH and 31 sex- and age-matched healthy controls was measured using retinal fundus photography. Venous blood samples were obtained for biochemical tests and anthropometric measurements were also recorded. The AS parameters of carotid-femoral pulse wave velocity (cfPWV), augmentation index (AIx), and central aortic pressure (CAP) were assessed using a non-invasive TensioClinic arteriographic system (TensioMed Kft., Budapest, Hungary). DS was evaluated using 24-hour ambulatory blood pressure measurements. The baseline characteristics, AS parameters, and the nocturnal DS of hypertensive patients were statistically compared with those of healthy individuals according to RVC values.

Results: The hypertensive group had significantly higher heart rates (p=0.023); AS parameters (PWV [p<0.001], CAP [p<0.001]); and fasting glucose (p=0.028), creatinine (p=0.046), triglyceride (p=0.045), uric acid (p=0.014) and microalbuminuria (p=0.004) values than the healthy controls. Although there was a significant positive linear correlation between the duration of hypertension and PWV (p=0.024), AIx (aortic) (p=0.005) and AIx (brachial) (p=0.013), no significant difference between the EH patients and the control subjects was observed in the AS parameters and nocturnal DS values according to the RVC value.

Conclusion: The results of this study did not demonstrate a significant correlation between the RVC and the AS parameters and nocturnal DS in EH. Additional prospective studies are warranted to reach a consensus on the clinical significance of RVC measurements in EH.

Keywords: Arterial stiffness, blood pressure, essential hypertension, nocturnal dipping, retinal vessel caliber

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INTRODUCTION

Systemic hypertension (HT) is linked to structural and physiological alterations at the micro- and macro-vasculature levels (1). Retinal HT-related microvasculature alterations can be visualized directly, which offers a noninvasive opportunity to assess broad aspects of microcirculation (2). Advances in microvascular retinal caliber measurements using retinal photography provide a valuable means to achieve earlier recognition of clinically significant vascular adaptations to systemic HT.

High blood pressure (BP) and arterial stiffness (AS) have been associated with retinal microvascular caliber alterations (2–8). The vascular rigidity and decreased elasticity of the artery that defines AS has been increasingly linked to cardiovascular (CV) risk and all-cause mortality (9). There are noninvasive, reproducible, and relatively inexpensive techniques to measure AS. Carotid-femoral pulse wave velocity (PWV; cfPWV) is considered to be the gold-standard method (10). The brachial (b) or aortic (a)augmentation index (AIx), and the central aortic pressure (CAP) are additional validated AS parameters (11).

Nocturnal dipping status (DS), and particularly the lack of a drop in nocturnal BP, is a well-known CV risk factor associated with notable HT-related target organ damage (12, 13). Reports in the literature offer conflicting results about the association between a non-dipping BP profile and retinal vessel calibers (RVC) (14, 15).

This study was designed to investigate possible associations between the RVC and the AS and nocturnal DS parameters in EH patients in comparison with healthy controls using retinal fundus photography (FP).

MATERIALS and METHODS

Gülhane Faculty of Medicine Clinical Research Ethics Committee approved this study (05.04.2016, number: 5/226). Written informed consent was obtained from all of the participants. The study was conducted between May and October 2019 at the Medical School, departments of internal medicine and ophthalmology, [Ankara], Turkey.

Table 1. Baseline characteristics of the study population (n=132)

	Patients (n=101)	Control group (n=31)	p#
Age (years)	48.99±13.54	46.35±8.29	0.193
BMI (kg/ml)	28.64±4.09	27.03±4.01	0.056
Waist circumference (cm)	98.49±9.44	94.71±11.16	0.065
Heart rate (/min)	76 (51–121)	71 (53–102)	0.023*
Blood pressure (systolic/diastolic, mm Hg)	139.43±19.75/83.21±9.63	113.39±12.08/66.48±9.15	<0.001
PWV (m/s)	10.37±2.30	7.55±0.91	<0.001
AIxa (%)	29.79±17.63	25.03±17.46	0.191
AIxb (-%)	-14.05±35.49	-24.59±34.37	0.147
CAP (mm Hg)	134.51±22.76	108.56±14.37	<0.001
Fasting glucose (mg/dL)	91 (77–99)	90 (75–97)	0.028*
Creatinine (mg/dL)	0.82±0.16	0.75±0.16	0.046
LDL (mg/dL)	118.78±25.67	118.71±26.59	0.989
HDL (mg/dL)	49.74±13.07	51.42±12.56	0.530
Total cholesterol (mg/dL)	194.90±28.90	192.94±31.98	0.747
Triglyceride (mg/dL)	121 (34–302)	102 (43–334)	0.045*
Uric acid (mg/dL)	5.26±1.11	4.67±1.25	0.014
Microalbuminuria (mg/day)	8.26 (1.28–306)	5.30 (0.32–63.60)	0.004*

#: Student's t-test; *: Mann-Whitney U test; AIxa: Augmentation index, aortic; AIxb: Augmentation index, brachial; BMI; Body mass index; CAP: Central aortic pressure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; PWV: Pulse wave velocity

The analysis included 101 patients with essential hypertension (EH) and 31 healthy controls. The inclusion criteria were age between 20–80 years and a diagnosis of EH. Exclusion criteria for the study were (1) age over 80, (2) secondary HT, (3) malignancy, (4) diabetes mellitus, (5) acute or chronic renal disease, (6) heart failure, (7) positive history or clinical signs of coronary artery disease, (8) valvular heart disease, (9) atrial or ventricular conduction disturbances, (10) peripheric vascular disease, (11) positive history or clinical signs of cerebrovascular disease, (12) dyslipidemia, (13) thyroidal disease, (14) anemia, (15) active infection, (16) positive history of retinal vein or artery occlusion, (17) glaucoma, (18) macular degeneration, or (19) a history of ocular surgery.

General Examination and Laboratory Tests

The clinical BP was calculated using the mean of 3 consecutive measurements obtained at 2-minute intervals with a sphygmomanometer on the dominant arm in the seated position after a 20-minute rest period. EH was diagnosed according to the 2018 European Society of Hypertension/European Society of Cardiology guidelines (16). Use of vasoactive drugs, caffeinated drinks, and nicotine was not permitted for at least 12 hours prior to evaluation to minimize the possible impact on RVC and BP. Anthropometric measurements of all of the participants were recorded: the body mass index (BMI) was calculated using the formula of BMI (kg/m^2)=weight (kg)/height^2 (m). Venous blood samples were obtained after 12 hours of overnight fasting from each participant for routine biochemical tests, including measurement of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) cholesterol, according to standard methods. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

Ophthalmic Examination

FP of both eyes was performed using a 45° digital nonmydriatic camera (CR-1 Mark II; Canon Inc., Tokyo, Japan) at a 5° angle from the nasal side of the macula. The FP values of the right eye used for the analysis of RVC measurements were a x2 magnification image of retinal vessels (both arteriole and venule) of the upper temporal quadrant. In this study, RVC was measured manually in an area 1 optic disc diameter from the optic disc temporal margin using the length tool of New Vision Fundus v3.0 DICOM software (Suzhou New Vision Meditec Co., Ltd., Suzhou, Jiangsu, China). At least 3 RVC measurements were taken of each eye. The repeatability of the measurements was also assessed before the statistical analysis and all of the RVC measurements showed excellent repeatability (>0.9). The mean of the measurements was used in the analysis.

Evaluation of Arterial Stiffness

AS was assessed by measuring the cfPWV, AIx, and CAP using the noninvasive TensioClinic arteriographic system (TensioMed Kft., Budapest, Hungary). TensioClinic arteriography uses a cuff-mediated device that determines the early and late systolic and diastolic waves as well as the onset and peaks (17). The right upper arm was used for measurements in the supine position after 10 minutes of rest. First, a routine BP measurement was obtained. For oscillometric PWV and AIx measurements, the cuff automatically inflates to 35 mmHg above the systolic pressure. The AIx value is the percentage difference between the first and second systolic peak of pulse pressure. The AIx values were automatically computed and normalized to a standard heart rate (80/min). The PWV was computed using the distance between the jugulum and the symphysis (17). A single investigator evaluated all of the study patients. The AS measurements were performed 3 times at 5-minute intervals. The mean value was used for analysis.

Table 2. Retinal vessel diameter comparison

	Comparison of retinal vessel diameters between groups (n=132)		
	Patients (n=101)	Control group (n=31)	p#
RAD (μm)	137.18±19.80	135.90±17.64	0.753
RVD (μm)	176.18±25.07	170.32±19.38	0.244
AVR	0.77 (0.53–1.18)	0.76 (0.65–1.05)	0.514*

	Comparison of retinal vessel diameter in hypertensive subjects according to arterial stiffness parameters (n=101)					
	RAD		RVD		AVR	
	r†	p	R	p	r	p
PWV	-0.100	0.320	-0.052	0.620	-0.126	0.223
CAP	-0.125	0.212	0.059	0.572	-0.087	0.403
AIxa	-0.072	0.472	-0.026	0.806	-0.049	0.635
AIxb	-0.074	0.460	-0.060	0.566	-0.025	0.812
Female patients (n=54)						
PWV	-0.118	0.396	-0.125	0.369	-0.081	0.559
CAP	-0.075	0.588	0.097	0.486	-0.026	0.853
AIxa	-0.060	0.668	-0.018	0.897	-0.078	0.576
AIxb	-0.060	0.664	-0.018	0.897	-0.078	0.575
Male patients (n=47)						
PWV	-0.033	0.826	0.057	0.723	-0.197	0.217
CAP	-0.176	0.238	0.022	0.893	-0.175	0.275
AIxa	-0.038	0.799	-0.011	0.944	0.018	0.911
AIxb	-0.045	0.764	-0.081	0.616	0.067	0.677

#: Student's t-test; *: Mann-Whitney U test; r: Pearson correlation coefficient; †: Spearman's rho; AIxa: Augmentation index, aortic; AIxb: Augmentation index, brachial; AVR: Arterio-venous ratio; CAP: Central aortic pressure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; PWV: Pulse wave velocity; RAD: Retinal arteriole diameter; RVD: Retinal venular diameter

Ambulatory Blood Pressure Monitoring

Schiller BR-102 Plus (Schiller AG, Baar, Switzerland) devices were worn by the hypertensive patients for 24 hours to obtain ambulatory blood pressure monitoring (ABPM) findings. ABPM was measured at 30-minute intervals during the day (9:00 am–11:00 pm) and hourly at night (11:00 pm–9:00 am). Nocturnal DS was calculated according to the night-to-day BP ratio: 0.8–0.9 was defined as normal nocturnal BP dipping, <0.8 as extreme dipping, 0.9–1.0 as mild dipping, and >1 as non-dipping (16). All of the HT patients took their antihypertensive medications at the same time in the morning (8:00 am) to avoid any effect of medication on DS.

Statistical Analysis

The mean and SD, median (min–max), percentage, or frequency values were presented as descriptive statistics according to the normality of distribution. The Kolmogorov-Smirnov test was used to determine normality. An independent t-test or one-way analysis of variance was performed to compare normally distributed continuous variables between groups. The Mann-Whitney U test or the Kruskal-Wallis test was used for nonnormally distributed variables. Levene's test was used to examine the homogeneity of variance. A chi-squared or the Fischer exact test was used for categorical variables. Pearson coefficients were used to determine correlation. IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis and p≤0.05 was accepted as significant.

RESULTS

A total of 132 subjects were included in the study, of whom 70 (53%) were women and 62 (47%) were men. No significant differences were found in BMI, waist circumference, AIxa, AIxb, LDL, HDL, or TC values between groups. The hypertensive group had significantly higher heart rate (p=0.023), PWV (p<0.001), CAP (p<0.001), fasting glucose (p=0.028), creatinine (p=0.046), triglyceride (p=0.045), uric acid (p=0.014), and microalbuminuria (p=0.004) values than the healthy controls. A summary of baseline characteristics of the participants is shown in Table 1.

The hypertensive patients had similar retinal arteriole diameter (RAD) (p=0.753), retinal venular diameter (RVD) (p=0.244), and arterio-venous ratio (AVR) (p=0.514) values in to those of the controls. None of the AS parameters was significantly correlated with RVD measurements. The AS parameters and the RVC did not differ significantly between groups according to sex among the HT patients (Table 2).

Table 3. Dipping status of patients and comparison of dipping status with retinal vessel diameter and baseline characteristics (n=92)

Dipping status	Total		Female		Male		p[a]
	n	%	n	%	n	%	
Reverse	15	16.3	9	18	6	14.3	0. 680
Mild	48	52.2	24	48	24	57.1	
Dipping	29	31.5	17	34	12	28.6	
Extreme	0	0	0	0	0	0	

Baseline characteristics	Dipping status			
	Reverse dipping	Mild dipping	Dipping	p[#]
RAD (µm)	152.64 (109.65–188.21)	134.48 (106.06–188.21)	136.01 (82.76–201.12)	0.101*
RVD (µm)	182.62±23.86	176.41±25.55	174.47±24.93	0.593
AVR	0.82±0.16	0.78±0.12	0.77±0.12	0.469
Age (years)	57.47±10.90	49.42±12.81	45.07±13.83	0.013
BMI (kg/ml)	30.54±3.87	28.16±4.15	28.58±4.35	0.158
Waist circumference (cm)	104 (89–123)	96.50 (77–116)	100 (80–120)	0.035*
Heart rate (/min)	74.13±11.31	78.65±12.89	75.24±11.57	0.326
PWV (m/s)	10.64±2.40	10.21±2.05	10.21±2.72	0.805
AIxa (%)	33.97±17.91	26.89±17.38	30.35±17.64	0.361
AIxb (-%)	-7.25±35.38	-18.16±36.20	-14.40±34.81	0.581
CAP (mm Hg)	130.40±15.24	135.06±24.42	131.64±22.93	0.711
Fasting glucose (mg/dL)	91 (78–98)	92.50 (77–99)	90 (79–99)	0.533*
Creatinine (mg/dL)	0.80±0.17	0.83±0.17	0.82±0.15	0.773
LDL (mg/dL)	114.87±29.03	121.40±23.87	119.86±26.55	0.691
HDL (mg/dL)	46 (26–74)	48 (28–99)	49 (29–73)	0.885*
Total cholesterol (mg/dL)	191.33±30.46	197.67±27.10	195.38±29.86	0.750
Triglyceride (mg/dL)	110 (44–287)	112.50 (41–302)	131 (34–295)	0.585*
Uric acid (mg/dL)	5.44±0.90	5.34±1.14	4.99±1.20	0.324
Microalbuminuria (mg/day)	6.67 (2.74–36.17)	6.69 (1.28–217)	10 (2.13–306)	0.651*

a: Chi-squared test; #: Analysis of variance; *: Kruskall-Wallis test; AIxa: Augmentation index, aortic; AIxb: Augmentation index, brachial; AVR: Arterio-venous ratio; BMI: Body mass index; CAP: Central aortic pressure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; PWV: Pulse wave velocity; RAD: Retinal arteriole diameter; RVD: Retinal venular diameter

ABPM was successfully measured in 92 of the 101 HT patients. The results indicated that most of the patients demonstrated mild dipping (52.2%) or dipping (31.5%). The results of 15 (16.3%) indicated reverse dipping. No patient had an extreme dipping pattern. The dipping pattern did not significantly differ in terms of sex (p=0.680), BMI (p=0.158), heart rate (p=0.326), PWV (p=0.805), AIxa (p=0.361), AIxb (p=0.581), CAP (p=0.711), fasting glucose (p=0.533), creatinine (p=0.773), LDL (p=0.691), HDL (p=0.885), TC (p=0.750), TG (p=0.585), uric acid (p=0.324), or microalbuminuria (p=0.651) among the patients. The dipping patients were significantly younger than the reverse dipping patients (p=0.013). The reverse dippers had a significantly greater waist circumference than the mild dippers (p=0.035). The RAD (p=0.101), RVD (p=0.593), or RAV (p=0.469) was not significantly different between dipping categories (Table 3).

Correlation analysis revealed insignificant associations between the duration of HT and RAD (p=0.562), RVD (p=0.768), and RAV (p=0.817). The results remained similar when male and female subgroups were considered. In contrast, there were significantly positive linear correlations between the duration of HT and PWV (p=0.024), AIxa (p=0.005), and AIxb (p=0.013). The duration of HT did not demonstrate a significant correlation with CAP (p=0.513) or microalbuminuria (p=0.419) (Table 4).

DISCUSSION

The current study used retinal FP to visualize the microvasculature in EH patients and compared the findings with the AS parameters. We found no significant associations. Furthermore, the RVC results did not reveal a significant change between dipping subgroups in our study. An insignificant result remained when the analysis

Table 4. Correlation between duration of HT and retinal vessel diameter, arterial stiffness parameters, and microalbuminuria (n=101)

	Duration of HT	
	r	**p**
RAD	-0.078†	0.562
RVD	-0.031	0.768
AVR	-0.024	0.817
PWV	0.224	0.024
AIxa	0.279	0.005
AIxb	0.246	0.013
CAP	0.066	0.513
Microalbuminuria	-0.081	0.419

r: Pearson correlation coefficient; †: Spearman's rho; AIxa: Augmentation index, aortic; AIxb: Augmentation index, brachial; AVR: Arterio-venous ratio; CAP: Central aortic pressure; HT: Hypertension; PWV: Pulse wave velocity; RAD: Retinal arteriole diameter; RVD: Retinal venular diameter

was performed separately in women and men. Only the PWV, AIxa, and AIxb were significantly correlated with the duration of HT. The negative results of this study could be attributed to controlled and uncontrolled HT in the study population.

Although our data showed significant differences in PWV and CAP values when compared with normotensive subjects, the groups had a similar RVD. This finding indicates that macrocirculation alterations started before microcirculation changes in our cohort of EH patients. This results of our study were not consistent with some previous studies (4–6, 18, 19). Liao et al. (18) reported that carotid AS measured with ultrasonic echo tracking was associated with increased retinal arteriolar narrowing, independent of the presence of HT. A limitation of that study was that the carotid arterial elasticity assessment used was performed 3–6 years before the retinal photography. Also, their study population was healthy middle-aged individuals, rather than HT patients. Paini et al. (5) found that carotid PWV was independently associated with the retinal wall to lumen (W/L) ratio in primary HT patients. Those findings were different from those of the current study; however, we only analyzed the RVC and did not measure the retinal W/L ratio. In another study analyzing associations between RVC and AS in early-stage HT individuals, the investigators demonstrated that there was a significant inverse association between the PWV and AIx and the retinal arteriole calibers and AVR (4). Similarly, Kumagai et al. (6) reported substantial associations between the baPWV and RAD but not retinal venules in a middle-aged study group. The authors noted that this association was not present when adjusted for covariates. In a multicenter study conducted using the United Kingdom Biobank, significant associations were found between retinal vessel morphometry and BP and AS parameters (19). Contrary to other reports, Pressler et al. (20) reported that there were no associations between the peripheral wave reflection and the dilatation of retinal vessels in marathon-runner study subjects, which was similar to our findings. In that study, the AIx was used for AS assessment. Another recent report observed no statistically significant associations between RVD and central hemodynamic measures, with the exception of central diastolic pressure, as in the current study (21).

Though there are some significant correlations between AS and RVC, there have been conflicting findings. Moreover, there is no standard methodology for assessing AS or RVC. Different measurements have been used to measure AS (PWV, either aortic or brachial and/or AIx, either aortic or brachial). Additionally, various measurement devices and methods, including ultrasonic echo (5, 18), the SphygmoCor system (AtCor Medical, Sydney, Australia) (4, 20), the cuff-oscillometric method (6), and the VaSera 1500 (Fukuda Denshi, Tokyo, Japan) arteriograph, make it difficult to compare reports.

In our study, the PWV and CAP values of EH patients were significantly different from those of the control group, while the AIxa and AIxb values were similar. Though the AIx parameters were not significant, a positive linear significant correlation between the AIx and HT duration was observed. Therefore, AIx parameters may be useful alternative in the assessment of EH patient follow-up.

Additionally, the computer-assisted formulas used in some studies to measure RVC have some weaknesses. These formulas are dependent on the number of retinal vessels measured (22). Secondly, revised formulas use branch arteriolar coefficients, which may not be constant (23). In addition, there may be a lack of normative data for the reference levels for comparison (24). Although we used specific software to measure the RVC, we think manual intervention for the assessment of the RVC may lead to different results.

Furthermore, age, glucose levels, cigarette smoking, posture, inflammation, dyslipidemia, instant BP level, cardiac cycle, and autonomic nervous system activity may have a significant impact on RVC size (24, 25). Therefore, a single, static retinal FP image may not reflect all of the dynamic physiological alterations. It should also be noted that publication bias may be an issue in reporting insignificant associations.

We observed significantly higher heart rates in EH subjects. Increased sympathetic system activity and dihydropyridine-type calcium channel blockers (CCB) rather than non-dihydropyridine CCB and beta-blockers may cause this result. Interestingly, though the RVC difference was insignificant between groups, the microalbuminuria and creatinine levels were significantly higher in the EH patients than in the healthy controls, suggesting that HT nephropathy may start before retinopathy in EH.

Sleep disturbance, obstructive sleep apnea, obesity, high salt intake in salt-sensitive subjects, orthostatic hypotension, autonomic dysfunction, chronic kidney disease, diabetic neuropathy, and older age have been reported to be likely causes for a lack of dipping. Although dipping groups were similar according to sex and age distribution, AS parameters, and RVC in our study, we think the statistically significant difference of a greater waist circumference between dipping groups was noteworthy. Waist circumference may be an additional variable for assessing DS in EH. In a recent study, non-dipping BP was associated with a larger RVD in a subgroup of Black men, while this association was not evident in a white male subgroup (14). As in our study, Triantafyllou et al. (15) did not find any significant correlation between RVC and nocturnal BP profile. Disruption of the nocturnal BP profile has been associated with target organ damage (lower glomerular filtration rate with higher left ventricular mass index and higher serum creatinine level) in masked HT patients compared with normotensive individuals (26). This finding might indicate that renal end-organ damage may begin before the development of retinal vessel findings. Similarly, Çoner et al. (27) reported that a higher albumin-to-creatinine ratio and a high-sensitive C-reactive protein level were significantly linked to a reverse dipping BP pattern in normotensive study participants.

The results of this cross-sectional study conducted at a single tertiary referral center may not represent all EH patients. Although we used software to measure RVC, manual measurement errors may have had an adverse effect on our results. We did not evaluate the retinopathy grading severity on the retinal photography in our study, which could provide a helpful comparison with AS parameters in addition to RVC. Moreover, due to inward remodeling in EH corresponding to a greater media thickness and a reduced lumen with an increased media-to-lumen ratio, without any significant change of the total caliber, the use of only a retinal caliber measurement in our study may have caused difficulty in detecting structural alterations. A further study using a recently validated deep-learning system for RVC evaluation would be valuable (28).

Nonetheless, this study had specific strengths. To the best of our knowledge, this is the first report to provide comparisons of RVC with both AS parameters and DS in EH. Given the scarcity of studies and contrasting results on the topic in the literature, we think our report may be a valuable reference study.

In conclusion, additional prospective randomized studies are needed to guide clinicians in the management of EH. Retinal vessel assessment in EH may become a significant objective tool for clinicians in routine applications.

Ethics Committee Approval: The Gülhane University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 05.04.2016, number: 1491/325).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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