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ORIGINAL ARTICLE

Divergent Retinal Vascular Abnormalities in Normotensive Persons and Patients With Never-Treated, Masked, White Coat Hypertension

Areti Triantafyllou,[1] Michael Doumas,[1,2] Panagiota Anyfanti,[1] Eugenia Gkaliagkousi,[1] Xenophon Zabulis,[3] Konstantinos Petidis,[1] Eleni Gavriilaki,[1] Polykarpos Karamaounas,[3] Vasileios Gkolias,[1] Athina Pyrpasopoulou,[1] Anna- Bettina Haidich,[4] Chrysanthos Zamboulis[1] and Stella Douma[1]

BACKGROUND
Hypertensive patients with retinal arteriolar abnormalities are at increased risk for cardiovascular events. However, the extent of retinal microvascular changes in naïve, never-treated patients with hypertension of short duration has not been established. In addition to this, the lack of relevant data about other phenotypes of hypertension (masked and white-coat hypertension) determined by ambulatory blood-pressure measurement (ABPM) is notable, despite their relationship to increased cardiovascular risk mediated by underlying target-organ and vascular damage.

METHODS
We conducted a study in which nonmydriatic retinal photography was used to assess central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) diameters and the retinal arteriovenus ratio (AVR) in a group of 103 individuals with never-treated hypertension of recent (< 1 year) appearance, 28 individuals with masked and 20 with white-coat hypertension, and 50 normotensive individuals, as appropriately classified by ABPM.

RESULTS
Patients with sustained and masked hypertension had narrower values of CRAE than did normotensive individuals (86.7 ± 10.1 and 87.6 ± 9.2 vs. 94.8 ± 10.6, $P < 0.001$ and $P = 0.02$, respectively). The AVR was lower in patients with sustained hypertension (0.736 ± 0.102), masked hypertension (0.716 ± 0.123), and white-coat hypertension (0.739 ± 0.127) than in normotensive subjects (0.820 ± 0.095), $P < 0.001$, $P < 0.001$, and $P = 0.03$, respectively. Both AVR and CRAE were negatively associated with mean systolic and diastolic daytime, nighttime, and 24-hour blood pressures, even after adjustment for other factors.

CONCLUSIONS
Subtle retinal microvascular signs of pathology are observed in hypertensive patients at early stages of hypertension and in patients with both masked and white coat hypertension. These changes may be indicative or may mediate the differences in cardiovascular mortality in persons with masked and white-coat hypertension, and relevant information about this can be easily accessed with retinal photography.

Keywords: hypertension, ambulatory blood pressure monitoring, microcirculation, vessels, retinopathy, masked hypertension, white-coat hypertension

The combination of two unique characteristics makes the retina a unique site for the *in vivo* study of systemic microvascular disorders induced by hypertension and cardiovascular disease. The first of these characteristics is that the retinal vasculature bears a substantial resemblance to the cerebral and coronary microcirculation in terms of anatomy and physiology. The second characteristic is the role of the retina as a window through which the human vasculature can be assessed easily, directly, noninvasively, and repeatedly.[1]

Recent advances in imaging techniques have led to the development of several computerized and semiautomated systems for processing digital retinal photography, which have permitted the evaluation of subtle retinal vascular changes in large populations and provided valuable

Correspondence: Stella Douma, (sdouma@med.auth.gr)

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[1]2nd Propedeutic Department of Internal Medicine, Hippokration General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; [2]Veteran Affairs Medical Center, George Washington University, Washington, DC; [3]Institute of Computer Science, Foundation for Research and Technology – Hellas, Heraklion, Crete, Greece; [4]Department of Hygiene and Epidemiology, Medical School of Aristotle University of Thessaloniki, Thessaloniki, Greece

information about the association of retinopathy with hypertension. A wealth of epidemiological data now consistently demonstrates a strong, graded association of high blood pressure (BP) with a wide spectrum of both qualitative and quantitative retinal vascular signs of physiological status, such as vascular branching, fractal dimension, vascular tortuosity, arterial and venular caliber, and the vascular wall-to-lumen ratio.[2,3] Prospective studies have shown that subjects with such retinal microvascular abnormalities such as narrowed retinal arterioles are more likely to develop hypertension and incident severe hypertension within the ensuing 3–10 years,[4] independently of other cardiovascular risk factors. The presence of generalized or focal arteriolar narrowing is predictive of an almost threefold greater risk of coronary heart disease (CHD), death from coronary vascular disease, or myocardial infarction (MI) in men at high-risk for these conditions,[5] and a decreased arteriovenous ratio (AVR) in women has similarly been found to predict an increased risk of any CHD event or death.[6,7] In addition to this, a significant association between retinopathy and incident congestive heart failure has been observed in the general population.[8] It is noteworthy that the prognostic value of mild (grade I and II) retinopathy for cardiovascular mortality among hypertensive individuals has been demonstrated,[9] whereas the predictive value of these lesions in normotensive individuals is equivocal.[10] Findings such as these suggest that microvascular abnormalities may serve as a valuable, early marker of future cardiovascular risk. Nevertheless, current guidelines for the diagnosis and management of hypertension do not refer to the clinical significance of grade I and II retinopathy, which are the most commonly encountered types of retinopathy, and assessment of the retinal vasculature has not yet been recommended as a standard approach to predicting the risk of CHD or CHD-related death for hypertensive individuals.[11,12]

Despite the abundance of large epidemiological studies overtly demonstrating the relationship of arterial narrowing and AVR to hypertension, naïve, never-treated patients without other comorbidities were not used as a pool for evaluating the association. Such patients are disproportionately encountered in the general population, and difficult to gather into a study population. In addition, previous studies have consistently assessed BP through office measurements,[2,3] even though recordings made through ambulatory blood-pressure monitoring (ABPM) show a better correlation with target-organ damage (TOD) and better predictive value for cardiovascular events than do office measurements, and provide further significant information about masked hypertension (MHT), white-coat hypertension (WCH) and dipping patterns.[13] The exacerbating effect of MHT on TOD and cardiovascular events has been repeatedly demonstrated, and there are indications that WCH may be associated with the long-term risk of stroke.[14] We therefore sought to assess potential differences in retinal microvascular changes in never-treated, otherwise healthy patients with hypertension of recent appearance, in individuals with MHT, and in individuals with WCH in comparison with retinal findings in normotensive individuals, and to evaluate their relationship with BP parameters.

METHODS

Consecutive patients attending the Hypertension Unit of the 2nd Propedeutic Department of Internal Medicine of Aristotle University over a 2-year period were included in the study. All of the subjects were Caucasian and gave written informed consent to participating in the study. The study was approved by the Ethics Committee of Aristotle University and was conducted in accordance with the principles of the Helsinki declaration. None of the participants had ever been treated with antihypertensive agents, nor had other known health problems. Only patients with hypertension of recent appearance and who had home BP measurements within normal limits during the previous year were included in the study. The groups of normotensive individuals and of individuals with MHT were recruited from among subjects admitted for regular medical assessment. Secondary causes of hypertension and other comorbities were excluded through medical examination and laboratory tests.

After 10 minutes of rest, the office BP of each subject was measured with a mercury sphygmomanometer using standard methodology, and was determined as the mean of the second and third values of three consecutive BP readings taken at 2-minute intervals. Hypertension was defined as a BP ≥ 140/90 mm Hg according to guidelines of the Seventh Report of the Joint National Committee[11] and the European Society of Hypertension(ESH)–European Society of Cardiology (ESC).[12] The mean arterial blood pressure (MABP) was calculated as:

$$(2 \times DBP + SBP)/3$$

where:

DBP = diastolic blood pressure, and
SBP = systolic blood pressure

Ambulatory BP was then monitored with a SpaceLabs Model 90207 Ambulatory Blood Pressure Monitor (SpaceLabs, Issaquah, WA) according to the following protocol: BP was measured at 15-minute intervals during a usual working day and at 30-minute intervals during the night following that day. Only ABPM assessments in which a minimum of 70% of readings were successful were regarded as technically sufficient.[12] A dipping pattern was defined as a difference of ≥10% in daytime and nighttime values of mean BP.[12]

When the office and ABPM readings were combined, participants were classified to four groups: (i) hypertensives (OfBP ≥ 140/90 mm Hg and daytime ABPM ≥ 135/85 mm Hg; (ii) MHT (OfBP < 140/90 mm Hg and daytime ABPM ≥135/85 mmHg); (iii) WCH (ofBP ≥ 140/90 mm Hg and daytime ABPM < 135/85 mm Hg and (iv) normotensives (ofBP < 140/90 mm Hg and daytime ABPM < 135/85 mm Hg). Alcohol intake was measured in alcohol units, with 1 unit = 12 mg of alcohol.

Retinal photography. All patients underwent bilateral, nonmydriatic digital fundus photography with a NIDEK AFC-230/210 nonmydriatic digital fundus camera (NIDEK, Fremont, CA). Two photographs were obtained

from each eye and examined by two staff members of the Hypertension Unit of the 2nd Propedeutic Department of Internal Medicine, of Hippokration GH, Aristotle University of Thessaloniki, Greece, trained in grading funduscopic findings who were masked to the subjects' identity and BP group assignment. The highest quality picture was chosen for analysis. A semiautomated computer program for assessing retinal photographs according to a standard protocol was developed by the Hypertension Unit of the 2nd Propedeutic Department of Internal Medicine, of Hippokration GH, Aristotle University of Thessaloniki, Greece, and the Institute of Computer Science, Foundation for Research and Technology–Hellas.[15,16] The software consisted of a measurement module that estimates vessel diameter in the input images and a graphical user interface module that facilitates user intervention at points of interest. Image processing methods are used to segment retinal vessels and estimate the distances of the vessel boundaries from the medial axes of the vessels at any given point.

After estimating the mean diameter of each vessel, the software allows editing of the representation of the vessel to correct errors in segmentation. The measurement area of an image was defined as the area from one-half to one whole disc diameter from the margin of the optic disc. Parr–Hubbard formula, as modified in the Atherosclerosis Risk in Communities (ARIC) protocol,[17] was calculated automatically to summarize indices of the average retinal arteriolar and venular diameters, referred to as the central retinal artery (CRAE) and central retinal vein (CRVE) equivalents, respectively.[17,18] The AVR was calculated as the ratio CRAE/CRVE. The accuracy (0.937–0.932), sensitivity (0.741–0.712), and specificity (0.967–0.966) of this method are very satisfactory and have been previously described in detail.[16] The intra- and interrater variabilities for the analysis of 20 retinal photographs were 0.823 and 0.798, respectively.

Statistical analysis. Statistical analyses of the study data were done with the SPSS software (SPSS, Chicago, IL).[16] An analysis of variance (ANOVA) with Student's *t*-test was used to estimate intergroup differences in mean values. A Bonferroni correction was used in making all eligible pairwise comparisons, and generalized linear models were used to control for age, sex, body mass index (BMI), and smoking.

Analysis of qualitative variables was done with the chi-squared test. To explore the relationships of retinal vascular calibers to the different components of BP readings while controlling for other covariates, we used partial correlation and multivariate linear regression analysis, in which, because of the high collinearity of different BP components, we used the best representative of office and ambulatory BP according to its correlation coefficient. Intra- and interrater probability was calculated with intraclass correlation coefficient. A value of $P \leq 0.05$ was considered statistically significant.

RESULTS

In total, the study involved 201 subjects with a mean age of 44.0 ± 11.5 years, of whom 128 (63.7%) were male, with a mean (± SD) age of 42.4 ± 11.8 years, and 73 (36.3%) were female, with a mean age of 46.9 ± 10.3 years. On the basis of their office and ABPM readings, 103 participants were classified as having hypertension, 20 as having WCH, 28 as having MHT, and the remaining 50 as constituting a normotensive control group. Baseline demographic and clinical characteristics of the study population are shown in Table 1. All of the study participants reported an alcohol intake of < 5 units/week. Comparisons of retinal vascular diameters and AVRs in the study groups are shown in Figures 1–3. Hypertensive patients had smaller CRAE diameters than did normotensive subjects (86.7 ± 10.1 μm vs. 94.8 ± 10.6 μm, respectively, $P < 0.001$). Likewise, patients with MHT had smaller CRAE diameters than did normotensive individuals (87.6 ± 9.2 μm vs. 94.8 ± 10.6 μm, respectively, $P = 0.02$). However, the CRVE in the study groups did not differ significantly. Hypertensive individuals had significantly lower AVRs than did normotensive subjects (0.736 ± 0.102 vs. 0.820 ± 0.095, respectively, $P < 0.001$). Likewise, the AVR in the MHT and WCH groups was significantly lower than that in the normotensive group (0.716 ± 0.123 and 0.739 ± 0.127 vs. 0.820 ± 0.095, respectively, $P < 0.001$ and $P = 0.03$, respectively). A significant negative correlation was found between office SBP and both CRAE and AVR. Similarly, CRAE and AVR were negatively associated with office DBP; however, CRVE was not significantly associated with office BP (Table 2). The correlation of CRAE and AVR with office BP remained significant even after adjustment (partial correlation) for age, sex, BMI, and smoking (Table 2).

Table 2 summarizes the associations of quantitative vascular changes with mean ABPM recordings in the study population. Both AVR and CRAE were negatively associated with mean systolic and diastolic daytime, nighttime, and 24-hour BPs even after adjustment (partial correlation) for age, sex, BMI, and smoking. By contrast, CRVE was not significantly associated with any of these BP values. Moreover, linear regression analyses revealed that ambulatory BP was significantly associated with both AVR and CRAE independently of office BP (Table 3).

The dipping profile (after adjustment with partial correlation for age, sex, BMI and smoking) did not correlate significantly with CRAE (r = 0.07, $P = 0.35$), CRVE (r = 0.07, $P = 0.38$), or AVR (r = 0.01, $P = 0.97$). Additionally, the CRAE values of dippers and nondippers did not differ significantly from one another (89.3 ± 10.3 vs. 87.6 ± 10.6, respectively, $P = 0.29$), and the same was observed for CRVE (120.1 ± 15.1 vs. 116.6 ± 15.1. respectively, $P = 0.08$) and AVR (0.749 ± 0.113 vs. 0.758 ± 0.114, respectively, $P = 0.49$). Age, sex, BMI, and smoking did not differ significantly according to the retinal vascular changes observed in the study.

DISCUSSION

To our knowledge, this is the first study to evaluate the association of quantitatively measured retinal vascular characteristics with 24-hour ABPM-derived parameters in a series of patients with untreated, recently diagnosed WCH, MHT, and sustained hypertension as compared with normotensive individuals. The study clearly demonstrates that

Table 1. Baseline characteristics of study population

	Overall population (*n* = 201)	Hypertension (*n* = 103)	Masked hypertension (*n* = 28)	White coat hypertension (*n* = 20)	Normotension (*n* = 50)	*P* value
Age, years	44.0 ± 11.4	44.1 ± 10.7	43.1 ± 11.7	49.2 ± 12.3	41.8 ± 11.9	0.051
BMI, kg/m^2	27.2 ± 4.3	27.6 ± 4.3	27.2 ± 4.2	28.1 ± 4.2	25.8 ± 4.4	0.07
Male, %	64.6	71.8$^{\#}$	59.3	65.0	52.1	0.11
Smokers, %	35.5	42.7	33.3	15	29.8	0.08
SBP, mm Hg	139 ± 18	150 ± 15*	129 ± 7**	145 ± 12*	119 ± 10	< 0.001
DBP, mm Hg	88 ± 12	95 ± 10*	82 ± 6$^{\#}$	91 ± 7*	76 ± 9	< 0.001
24-hour SBP, mm Hg	132 ± 14	141 ± 11*	132 ± 6*	122 ± 6	116 ± 8	< 0.001
24-hour DBP, mm Hg	84 ± 10	89 ± 8*	85 ± 5	76 ± 5*	73 ± 6	< 0.001
24-hour MBP, mm Hg	100 ± 11	107 ± 8*	101 ± 4*	91 ± 4	88 ± 6	< 0.001
Daytime SBP, mm Hg	137 ± 14	147 ± 11*	138 ± 6*	127 ± 7	121 ± 8	< 0.001
Daytime DBP, mm Hg	88 ± 10	94 ± 8*	90 ± 5*	81 ± 4	77 ± 6	< 0.001
Daytime MBP, mm Hg	104 ± 11	111 ± 8*	106 ± 4*	96 ± 3	92 ± 6	< 0.001
Nighttime SBP, mm Hg	120 ± 15	129 ± 14*	117 ± 10*	111 ± 8	105 ± 9	< 0.001
Nighttime DBP, mm Hg	74 ± 11	80 ± 10*	73 ± 8**	68 ± 8	65 ± 7	< 0.001
Nighttime MBP, mm Hg	89 ± 12	96 ± 11*	88 ± 8*	82 ± 7	78 ± 7	< 0.001
Nondipper (%)	33.5	39.0	18.5	30.0	31.8	0.24

$^{*}P < 0.001$, $^{**}P < 0.01$, $^{\#}P < 0.05$ for differences between normotension and phenotypes of hypertension.

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BMI, body mass index. Comparisons among qualitative variables were made by chi-squared analysis and among quantitative variables with analysis of variance (ANOVA) with Bonferroni adjustment for multiple comparisons.

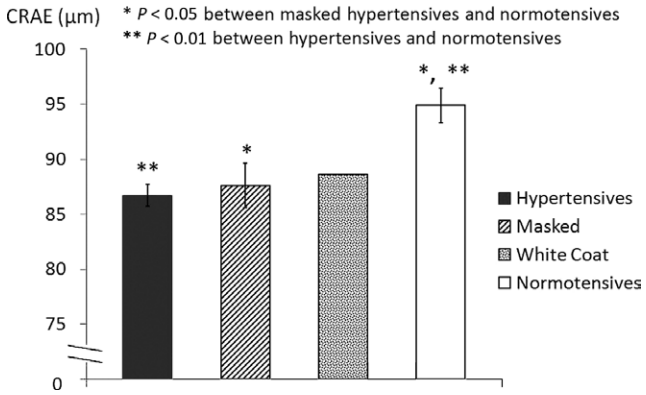

Figure 1. Comparison of the central retinal artery equivalent (CRAE) of subjects with hypertension of different phenotypes and individuals with normotension. Intergroup comparisons were made with analysis of variance (ANOVA) with Bonferroni correction, after adjustment for age, sex, body mass index (BMI) and smoking status, using generalized linear models (univariate analysis). Only differences that were statistically significant are shown in the figure.

a narrower retinal arteriolar diameter and smaller AVR were associated with all of the measured components of 24-hour BP readings in the study population. Furthermore, the AVR decreased and retinal arterioles became more narrow with increasing office BP, which accords with the outcomes of consecutive large, population-based observational studies.[2,3] However, the meticulous selection of our study population (naïve, never-treated, otherwise healthy patients with a confirmed diagnosis based on ABPM recordings and hypertension of recent appearance) heightens the significance of our findings, even though the accuracy of the participants' past BP measurements cannot be verified. We were therefore able to show that even with hypertension of short duration, CRAE and AVR differ significantly from these values in normotensive individuals. Whether these vascular changes result from increased BP or reflect systemic vasoconstriction that precedes the development of hypertension cannot be concluded from our study. The nonsignificant association of office BP or ABPM with CRVE in our sample of untreated, relatively young, and otherwise healthy subjects is in accord

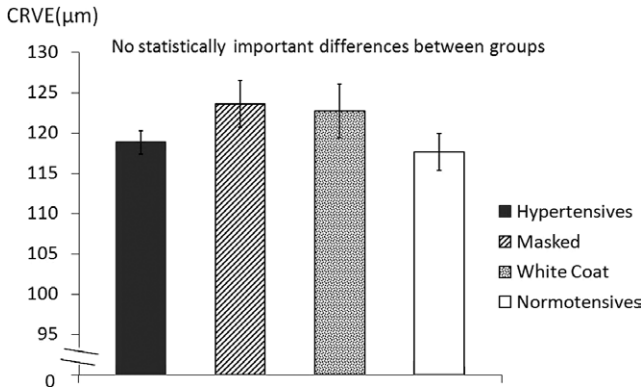

Figure 2. Comparison of the central retinal vein equivalent (CRVE) in subjects with hypertension of different phenotypes and individuals with normotension. Intergroup comparisons were made with analysis of variance ANOVA with Bonferroni correction after adjustment for age, sex, body mass index (BMI), and smoking status, using generalized linear models (univariate analysis). No statistically significant differences were found between the groups shown in the figure.

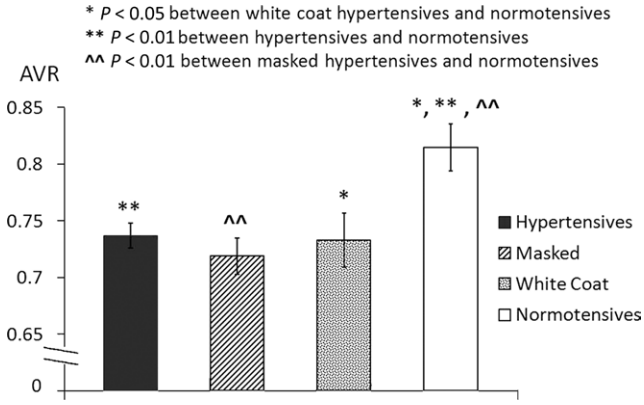

Figure 3. Comparison of the arteriovenous ratio (AVR) in subjects with hypertension of different phenotypes and individuals with normotension. Intergroup comparisons were made with analysis of variance ANOVA with Bonferroni correction after adjustment for age, sex, body mass index (BMI), and smoking status, using generalized linear models (univariate analysis). Only the statistically significant differences are shown in the figure.

with evidence that arteriolar narrowing, rather than venular widening, reflects increased peripheral resistance and represents the initial process in the series of pathophysiological changes preceding or following the development of hypertension,[19] although further clarification of possible confounding factors is necessary.

Our study also provides insight into the clinical significance of retinal vascular changes in the specific population with WCH and MHT. These patients represent a significant portion of the total hypertensive population and may even account for the misclassification of as many as one-third of patients attending a hypertension clinic,[20] yet retinal vascular abnormalities in these groups have not been addressed in previous reports. With the present study we show for the first time that retinal CRAE and AVR in MHT are not only significantly decreased as compared with these measures in normotensive subjects, but are also similar to the values of these measures in individuals with sustained hypertension. This finding is in accordance with the findings in previous studies of TOD in the form of left-ventricular hypertrophy, increased intimal-medial thickness of the carotid artery, and microalbuminuria in subjects with MHT.[21] Notably, mild (grade I and II) retinopathy was not found to predict cardiovascular mortality among normotensive individuals,[10] but was predictive of the incidence of hypertension.[4] The design of previous studies in terms of assessments of BP that misclassified individuals with MHT as normotensive may have contributed to this finding. On the other hand, there is still no definite association of WCH with TOD.[22–24] In our study, the AVR of the population with WCH differed significantly from that of normotensive subjects and resembled that in the hypertensive retina, thus providing evidence that whether or not it progresses to sustained hypertension, WCH is associated with retinopathy, a marker of TOD.

Previous studies addressing the association of initial retinal changes in hypertension with 24-hour ABPM-derived parameters are few, and have evaluated hypertensive retinopathy only qualitatively, by identifying various stages of hypertensive retinopathy.[25] Likewise, very few studies have focused on evaluating retinopathy as a form of TOD in untreated hypertensive patients with a nondipping profile,[26,27] on the basis of a nondipping pattern being possibly indicative of a higher prevalence of TOD.[28] However, in our study, a dipping profile was not associated with any of the retinal vascular parameters examined quantitatively. Despite methodological differences in the assessment of retinopathy,

Table 2. Correlation of retinal measurements with office blood pressure and 24-hour blood pressure components adjusted for age, sex, body mass index, and smoking

		Central retinal arteriolar equivalent μm	Central retinal vein equivalent μm	Retinal arteriovenous ratio
		Partial r[a]		
Office	SBP	–0.17*	–0.06	–0.13*
	DBP	–0.22**	–0.04	–0.16*
Daytime	SBP	–0.30***	–0.04	–0.19*
	DBP	–0.27***	0.02	–0.24**
	MBP	–0.30***	–0.01	–0.24**
Nighttime	SBP	–0.29***	–0.08	–0.15*
	DBP	–0.27***	–0.02	–0.21**
	MBP	–0.28***	–0.05	–0.19*
24-Hour	SBP	–0.30***	–0.06	–0.19*
	DBP	–0.27***	0.01	–0.24**
	MBP	–0.30***	–0.02	–0.23**

*$P < 0.05$, ** $P < 0.01$,*** $P < 0.001$

[a]r adjusted for age, sex, body mass index (BMI), and smoking

BP, blood pressure (mm Hg); SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BMI, body mass index (kg/m^2)

Table 3. Multiple linear regression models of retinal vascular calibers

	CRAE (adjusted $R^2 = 0.08$, $R^2 = 0.110$, $P < 0.01$)				CRVE (adjusted $R^2 = –0.01$, $R^2 = 0.037$, $P = 0.43$)				AVR (adjusted $R^2 = 0.01$, $R^2 = 0.040$, $P = 0.02$)			
			CI 95%				CI 95%				CI 95%	
	Unst. C.	P	LB	UB	Unst. C.	P	LB	UB	Unst. C.	P	LB	UB
Age	–0.08	0.27	–0.207	0.057	–0.18	0.07	–0.373	0.013	<0.01	0.39	0.000	0.002
Sex	1.16	0.47	–2.024	4.340	–1.41	0.55	–6.075	3.265	0.01	0.50	–0.022	0.046
BMI	0.33	0.07	–0.029	0.686	0.46	0.08	–0.063	0.982	<0.001	0.84	–0.003	0.004
Smoking	0.17	0.92	–3.326	2.988	0.31	0.89	–4.280	4.901	–0.01	0.67	–0.041	0.026
Office BP	–0.07	0.36	–0.234	0.085	–0.04	0.72	–0.171	0.247	<0.001	0.56	–0.002	0.001
Ambulatory BP	–0.26	<0.01	–0.439	–0.076	–0.09	0.31	–0.250	0.080	<-0.01	0.02	–0.004	0.000

CRAE, central retinal arteriolar equivalent (μm); CRVE, central retinal vein equivalent (μm); AVR, arteriovenus ratio; BP, blood pressure (mm Hg); Unst. C., unstandardized coefficient; CI, confidence intervals; LB, lower boundary; UB, upper boundary; BMI, body mass index (kg/m^2).

Because of the high collinearity of different BP components, the best representative of office and ambulatory BP was used, according to its correlation coefficient. DBP was used as Office BP. As ambulatory blood pressure, 24hour SBP, Night-time SBP and 24hour MBP were used for the model of CRAE, CRVE and AVR respectively.

our findings appear to accord with those in previous studies showing a similar prevalence of stage I and II retinopathy in groups with a nondipping and with a dipping profile.[26] A study of 67 untreated patients with newly diagnosed hypertension showed a higher prevalence of hypertensive retinopathy in nondippers than in dippers, but that study included indices of all stages of hypertensive retinopathy according to the Keith–Wagener classification.[25] Because nighttime mean BP has been found to predict the severity of retinopathy ≥ stage II[27], it might be assumed that subtle changes (stage I) in the retinal vasculature are not significantly affected by a dipping profile. Hypertensive retinopathy is currently defined as a form of TOD by guidelines for the management of hypertension, but there is still no consensus about the prognostic value of early retinal microvascular abnormalities (e.g., focal or generalized arterioral narrowing, low AVR). Although all stages of hypertensive retinopathy are designated as target organ injury by the JNC report[11] and in the recently published NICE guidelines,[29] the more recent European ESH/ESC 2007 guidelines address the more advanced changes found in retinopathy of stages III and IV as TOD, and recommend examination of the retina only in persons with severe hypertension, while casting doubt on the prognostic value of retinopathy of stages I and II.[12] The rationale for this recommendation is based on three relatively old studies that claim a limited applicability

of fundoscopic examination and disregard the prognostic value of milder forms of retinopathy.[30,31] However, one of these three studies involved only 25 hypertensive individuals[30] and another did not include patients with recently diagnosed hypertension,[31] and in all three studies the assessment of stage I and II retinopathy was done only qualitatively. Since the time of publication of the current European ESH/ESC guidelines for the management of hypertension,[12] additional large epidemiological studies have provided further insight into the clinical significance of topographical alterations of retinal architecture, using software that processes photographic digital retinal images quickly, easily, and accurately. Over a 14-year follow-up period with 4,294 nondiabetic subjects, the Beaver Dam Eye Study found a significant association between moderate retinopathy at baseline and all-cause mortality, which was even stronger for CHD mortality.[32] Furthermore, another study found that a generalized decrease in retinal arteriolar diameter was associated with a twofold risk of left-ventricular concentric remodeling, an association also found in the normotensive subgroup in this latter study, suggesting that microvascular disease may contribute to cardiac remodeling.[33]

With regard to coronary artery disease, reduced arteriolar caliber was found in another study to correlate independently with a diminished myocardial perfusion reserve in asymptomatic individuals without coronary artery calcification, supporting a role for the quantitative assessment of retinopathy as a marker of coronary microvascular disease.[34] These data appear to accord with the finding in prospective population-based studies that quantitative assessment of retinopathy is generally predictive of coronary morbidity and mortality, especially in women and persons under the age of 75 years.[6,7,35,36] In the light of accumulating data, the 2009 Reappraisal of the ESH/ESC guidelines referred to the assessment of the media/lumen ratio of small retinal arteries as a promising method for large-scale evaluation of target organ damage,[37] yet the significance of evaluating those early features of hypertensive retinopathy remains unclear.[38] For quantitative assessment of the retinal vascular network, we used a newly-developed program that allows rapid measurement of retinal vessels with great accuracy and repeatability and minimal observer bias, permitting the early detection of abnormalities in the retinal microcirculation. The combination of these characteristics warrants the use of retinal caliber measurement in large subject cohorts in both everyday clinical practice and in research. Considering the specific characteristics of our study participants, and especially the short duration of their hypertension, we found that quantitative retinal arteriolar indices, even with the limitation of our relatively small study population, differentiate well among populations with sustained hypertension, MHT, and normotension from the earliest stages of hypertension and long before the appearance of macrovascular injury. Indeed, the initial stages of hypertensive retinopathy have been proposed as an early, reliable marker of TOD in hypertension, suggesting that they have a good correlation with such other subclinical indices of cardiovascular disease as left-ventricular remodeling and aortic stiffening.[39,40] Provided that larger studies confirm our findings, we believe that quantitative assessment of the retinal vasculature with a nonmydriatic camera and sophisticated software should be recommended as a routine, noninvasive, and cost-effective procedure for the overall risk stratification of patients with newly diagnosed hypertension.

CONCLUSIONS

Detecting early retinal microvascular changes with a nonmydriatic camera may contribute significantly to the stratification of patient risk for cardiovascular disease. Retinal arteriolar narrowing and a smaller AVR are significantly associated with the findings of ABPM. Patients with MHT exhibit early retinal abnormalities similar to those of patients with sustained hypertension. Interestingly, the retinal vascular picture of patients with WCH appears comparable to those of individuals with sustained hypertension and MHT. The findings on retinal nonmydriatic photography processed with an appropriate system may be a valuable, rapid, easily accessible, reproducible, and highly effective means of detecting microvascular injury in routine clinical practice.

DISCLOSURE

The authors have no conflicts of interest to declare.

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