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Research Article

Accumulation of microvascular target organ damage in newly diagnosed hypertensive patients

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Abstract

Early identification of hypertensive target organ damage (TOD) emerges as important for global cardiovascular risk assessment. Retinal vascular alterations, capillary rarefaction, and microalbuminuria represent different forms of microvascular TOD. However, data regarding their concomitant presence in the early stages of hypertension, the association of the number of affected organs with cardiovascular risk, and aldosterone effect on multiple TOD are lacking. We studied naïve, never-treated patients with recent duration of hypertension and healthy volunteers. Innovative software was developed to estimate retinal vascular diameters and capillary density. Biochemical parameters including microalbuminuria and serum aldosterone were derived. Framingham Risk Score was used to determine cardiovascular risk. In total 103 subjects, 66 hypertensives and 37 normotensives, were included. Hypertensive patients exhibited a greater number of affected target organs compared with normotensives ($P = .014$), with retinopathy and capillary rarefaction (40.9%) representing the most common TOD among hypertensives. The number of affected organs was linearly correlated with increased Framingham score and serum aldosterone, analyzed with univariate ($P < .001$ and $P = .002$) and multivariate analysis ($P = .025$ and $P = .004$), respectively. Physicians dealing with hypertensive patients should be aware of the possibility of diffuse microvascular impairment and seek multiple TOD even in the early stages of hypertension. J Am Soc Hypertens 2014;8(8):542–549.

Keywords: Microcirculation; retinopathy; aldosterone; capillaroscopy.

Introduction

Hypertension represents the leading cause of morbidity and mortality worldwide, exerting its deleterious effects through its cardiovascular complications. Given that hypertension has been acknowledged as the most important reversible risk factor for cardiovascular diseases,[1] early identification of hypertensive target organ damage (TOD) and assessment of global cardiovascular risk emerge as extremely important in terms of life prolongation, quality-of-life improvement, and health-care resources sparing.

A well-promising concept for assessing global cardiovascular risk in hypertension is implementation of quantitative microcirculation measures in everyday clinical practice. Structural and functional changes in small vessels of the retina, skin, and kidney are now considered inherent to hypertension. In particular, several qualitative and quantitative alterations, including arteriolar narrowing and decrease of the arteriovenous ratio (AVR), are observed in the hypertensive

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fundus,[2] and a decreased number of capillaries per area of measurement, described as capillary rarefaction, is typically observed in the skin.[3] Both measures are used for the identification of structural changes of the microvasculature, although increased excretion of albumin in urine is traditionally used as an early and reliable index of functional microvascular kidney damage in hypertension.[4]

Despite the mutual presence of hypertension and microvascular abnormalities, the prevalence of the previously mentioned microvascular changes in the very early stages of essential hypertension is not precisely known. Given that hypertensive retinopathy, capillary rarefaction, and microalbuminuria have been identified as different forms of TOD in hypertensive patients, estimation of their prevalence compared with normotensives emerges as an unbridged gap in the relevant literature. Recently, we showed for the first time that quantitative, more accurately, measured retinal vascular alterations are present even in untreated, otherwise healthy, recently diagnosed hypertensives,[5] but whether they frequently coexist with capillary rarefaction and microalbuminuria and to what extent remains unknown.

Furthermore, although the predictive value of each microcirculation index (early-stage hypertensive retinopathy, microalbuminuria) in terms of cardiovascular morbidity and mortality has been validated in several studies,[6,7] not a single study has so far addressed the hypothesis that accumulating microvascular damage indicated by the previously mentioned measures may as well denote increasing cardiovascular risk.

In addition, there is lack of data regarding the identification of potential factors inducing accumulation of multiple microvascular organ damage. Whether activation of the renin-angiotensin-aldosterone system, which is primarily involved in the pathogenesis of hypertensive vascular disease, is associated with the development of multiple microvascular TOD, has not yet been addressed.

Of note, identification of microvascular TOD largely lies on the development of the essential technology that will allow the clinician to visualize retinal and skin vessels routinely, rapidly, and non-invasively and obtain robust microcirculation quantitative measures.

Therefore, the aim of the present study was to examine (1) the prevalence of functional and structural microcirculatory changes in early-stage hypertension compared with normotension, through the simultaneous investigation of the status of small vessels of the kidney, eye, and skin; (2) whether combined microcirculatory damage represents a predictor of increased cardiovascular risk, estimated by the Framingham Risk Score (FRS), even in these early stages and long before the development of cardiovascular complications; and (3) whether an association exists between accumulating microvascular damage and activation of the renin-angiotensin-aldosterone system, in a group of meticulously selected, naïve, never-treated, hypertensive patients and normotensive individuals, confirmed by 24-hour ambulatory blood pressure monitoring (ABPM).

Methods

Participant Characteristics

Consecutive patients attending the Hypertension Unit of the 2nd Propedeutic Department of Internal Medicine, Aristotle University, Thessaloniki, were included in the study. All subjects were Caucasian and gave written informed consent. The study was approved by the ethics committee of our University and was conducted in accordance with the principles of the Helsinki declaration. Participants had never been treated with antihypertensive agents and had no other known health problems. Only patients with recent appearance of hypertension (blood pressure [BP] measurement within normal limits during the previous year) were included. The group of normotensives was recruited from subjects admitted for regular check-up. Patients with secondary causes of hypertension and other comorbidities, such as diabetes or dyslipidemia, verified by their medical history or diagnosed through medical examination and laboratory tests, were excluded.

BP Measurements

After 10 minutes of rest, office BP (oBP) was measured using standard methodology and was determined as the mean of the second and third value of three consecutive BP recordings taken at a 2-minute interval. Hypertension was defined as oBP $>$140/90 mm Hg according to guidelines.[8,9] ABPM was then performed using a SpaceLabs 90,207 device according to a standard protocol. BP was measured at 15-minute intervals during a usual working day and 30-minute intervals during the night. Only ABPM assessments that achieved a minimum of 70% of successful readings were regarded as technically sufficient. Only patients with true hypertension (oBP$\geq$140/90 mmHg and ABPM$\geq$135/85 mmHg) or confirmed normotension (oBP$<$140/90 mmHg and ABPM$<$135/85 mmHg) participated in the protocol.[9]

Microcirculation Assessment

Retinal Photography and Analysis

All patients underwent bilateral, nonmydriatic digital fundus photography using a NIDEK AFC-230/210 camera. Two photographs were obtained from each eye, and the best one was examined by a trained grader masked to the subjects' identity and BP group assignment.

To achieve retinal vessel measurement and analysis, semiautomated computer software was developed by our hypertension unit and the Institute of Computer Science, Foundation for Research and Technology–Hellas. Retinal photographs were assessed according to a standard protocol, which has been described in detail elsewhere.[5,10,11] The measurement area was defined as the area from one

half to one disc diameter from the optic disc margin. Parr and Hubbard formulas, as modified in the Atherosclerosis Risk in Communities protocol[12] were calculated automatically to summarize indices of the average retinal arterioral and vascular diameters, referred to as the central retinal artery (CRAE) and central retinal vein equivalent, respectively,[12,13] and their ratio (AVR = CRAE/central retinal vein).

Capillaroscopy Photography and Analysis

All participants were examined with nailfold capillaroscopy (DS Medica, Milan, Italy—200× magnification). A semiautomated software, for the detection and measurement of the capillaries in each image, was developed by our hypertension unit and Foundation for Research and Technology–Hellas.[14]

The software was comprised by a measurement module and a graphical user interface module. The measurement module segments the input image and detects capillaries. The user interface provides methods for the automatic and interactive measurement of capillaries at regions of interest. In addition, it provides methods for editing the obtained capillary representation to correct segmentation errors.

The best two microscopic images were chosen and examined by a grader masked to the subjects' identity and BP group assignment. At least two measurements from each participant were analyzed semiautomatically by a trained operator. Intraclass correlation coefficient for a set of 20 patients was 0.951 (with 95% confidence intervals, 0.859–0.983).

Biochemical Measurements

The determination of microalbuminuria was made by immunoturbidimetric method in samples of 24-hour urine collection, which is considered the most reliable method of microalbuminuria estimation.[15] Microalbuminuria was defined as an albumin excretion rate between 30–300 mg/24 h.

Plasma renin activity (PRA; ng/mL/h) and serum aldosterone (ng/dL) levels were estimated with radioimmunoassay. Patients rested in the supine position for 2 hours before blood sampling, which was performed in the morning between 8 and 10 AM.

Framingham Risk Score

FRS was calculated using the Wisconsin calculator based on age, sex, smoking, diabetes, BP, and cholesterol level.[16] Information was applicable only for the ages 30–74.

Statistical Analysis

Analysis was performed using the Statistical Package for Social Sciences (SPSS) 19. Student t or Mann–Whitney test was used to estimate differences between mean values between two groups and analysis of variance (ANOVA), with Bonferroni multiple comparisons test, between more than two groups. Analysis of qualitative variables was made by chi-square or Kendall's τ b test when the categories were more than two. Correlation coefficients were calculated with Pearson and Spearman rank tests. To explore the relationship between the number of microcirculation TOD forms and aldosterone, while controlling for other covariates, we applied multivariate linear regression analysis. For retinal and capillary parameters, the lower tertile of a population consisting of 250 otherwise healthy, except for the high BP (data not yet published), individuals were considered as normal values. Intrarater probability was calculated with intraclass correlation coefficient. Where needed to transform a non-to-normal distribution, we used the logarithmic mean of the parameter. A probability value of $P \leq .05$ was considered statistically significant.

Results

In total, 103 subjects with a mean age of 41.8 ± 11.2 years were included in the study. According to their office and ABPM, 66 participants were classified as hypertensives and 37 comprised the normotensive–control group. Baseline demographic and clinical characteristics of the study population are depicted in Table 1.

Prevalence of Different Microcirculation TOD in Hypertensive and Normotensive Individuals

Prevalence of TOD per BP status is depicted in Figures 1 and 2. Hypertensive patients exhibited a significantly greater number of affected organs compared with normotensives ($P = .014$). Only 27.3% of hypertensive patients were free from any form of microvascular organ damage, compared with 48.6% of normotensives (Figure 1). Compared with normotensives, hypertensive patients exhibited higher rates of early-stage hypertensive retinopathy (40.9% vs. 10.8%; $P = .001$), capillary rarefaction (40.9% vs. 27%; $P = .05$), and microalbuminuria (28.0% vs. 19.5%; $P = .685$). It should be noted that none of our patients exhibited progressive (stage III & IV) retinopathy signs (retinal hemorrhages, cotton wool spots etc). Presence of multiple (at least two different of the previously mentioned forms) microvascular damage was observed in 30.3% of hypertensive patients, compared with only 5% of normotensives individuals ($P = .003$).

Association Between the Number of Affected Target Organs and Cardiovascular Risk Estimated by the FRS

Increase in the number of microcirculatory TOD was linearly correlated with increased Framingham score (Spearman

Table 1
Baseline characteristics of the study population

Characteristic	Overall (n = 118)	Hypertensives (n = 77)	Normotensives (n = 41)	*P* Value
Age, years	42.9 ± 11.6	43.3 ± 11.4	42.4 ± 11.9	.434
BMI, Kg/m^2	27.2 ± 4.3	27.7 ± 4.1	26.1 ± 4.7	.112
Smoking (% yes)	39.5	41.6	35.1	.511
SBP, mm Hg	138.8 ± 19.4	149.9 ± 13.8	118.1 ± 9.4	<.001
DBP, mm Hg	88.0 ± 13.7	94.8 ± 10.8	75.4 ± 8.8	<.001
24h SBP, mm Hg	131.2 ± 14.9	139.7 ± 10.3	115.5 ± 7.7	<.001
24h DBP, mm Hg	83.0 ± 11.1	88.5 ± 9.3	72.8 ± 5.3	<.001
Day SBP, mm Hg	136.7 ± 15.5	145.6 ± 10.4	120.2 ± 7.7	<.001
Day DBP, mm Hg	87.4 ± 11.1	92.9 ± 9.3	77.2 ± 5.4	<.001
Night SBP, mm Hg	118.8 ± 15.6	126.8 ± 12.6	104.3 ± 8.5	<.001
Night DBP, mm Hg	73.2 ± 11.8	78.2 ± 11.1*	64.6 ± 6.5	<.001
Total cholesterol (mg/dL)	186.1 ± 28.8	200.9 ± 39.1	187.9 ± 32.9	.396
LDL (mg/dL)	114.7 ± 28.6	128.7 ± 32.2	111.2 ± 40.2	.228
Plasma renin activity (ng/mL/h)	0.51 (0.01–4.96)	0.93 (0.01–4.96)	0.82 (0.01–2.90)	.661
Aldosterone (ng/dL)	10.4 (2–34)	12.5 (2–34)	7.5 (2.2–27.4)	.004

BMI, body mass index; DBP, diastolic blood pressure; LDL, low density lipoprotein; SBP, systolic blood pressure.

test; $r = 0.358$, $P < .001$), and individuals with multiple TOD exhibited higher FRS (ANOVA test; $P < .001$), as depicted in Figure 3. Moreover, both early-stage hypertensive retinopathy (estimated by CRAE) and capillary rarefaction (estimated by the mean density of capillaries) were negatively correlated with Framingham score ($r = -0.295$, $P = .002$ and $r = -0.204$, $P = .038$, respectively), whereas the same correlation was not observed with microalbuminuria ($r = 0.078$, $P = .435$).

In the multiple linear regression model, Framingham score was associated with the number of affected organs independently of other variables including age, smoking, body mass index, office and ambulatory BP, and aldosterone levels ($P = .025$).

Interaction Between Microcirculatory Damage and the Renin Angiotensin Aldosterone System

Aldosterone levels were increasing (Figure 4) and linearly correlated ($r = 0.358$, $P < .001$) in accordance with the number of microcirculatory TOD. On the contrary, PRA was not significantly associated with the number of affected organs in our population ($r = –0.032$, $P = .785$; ANOVA $P = .949$). Likewise, PRA-to-aldosterone ratio did not differ significantly according to the microcirculatory organ damage ($r = 0.187$, $P = .107$; ANOVA $P = .702$).

Multiple linear regression analysis revealed that aldosterone remained a significant predictive factor of the number

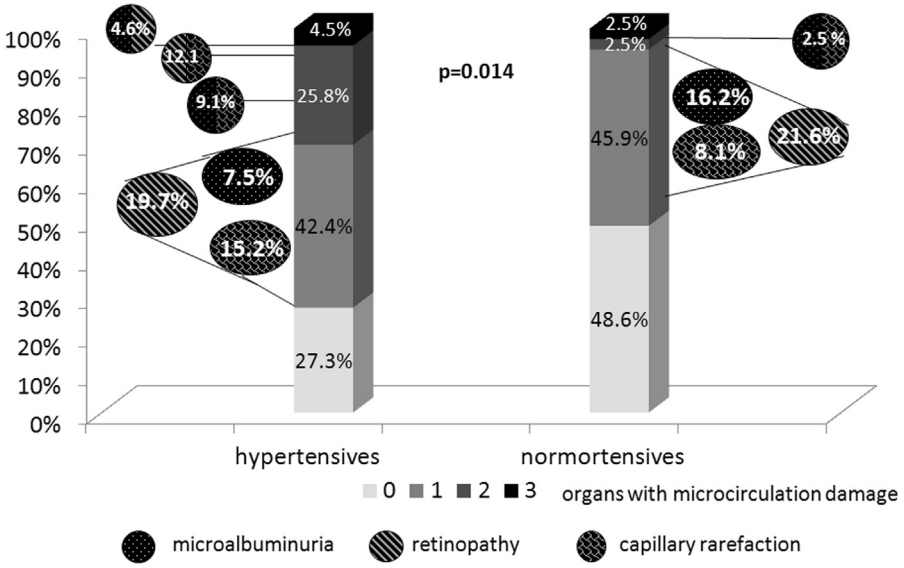

Figure 1. Concomitant presence of different forms of target organ damage per hypertension status. Microalbuminuria is defined as 24 h urinary albumin excretion ≥30 mg/dL, retinopathy is defined as the smallest tertile of central retinal arterial equivalent, and capillary rarefaction is defined as the smallest tertile of capillary number per visual field. On the side of the columns the percentages of the specific type of damage according to the number of affected organs are depicted. The test of statistical significance was made by chi-square test.

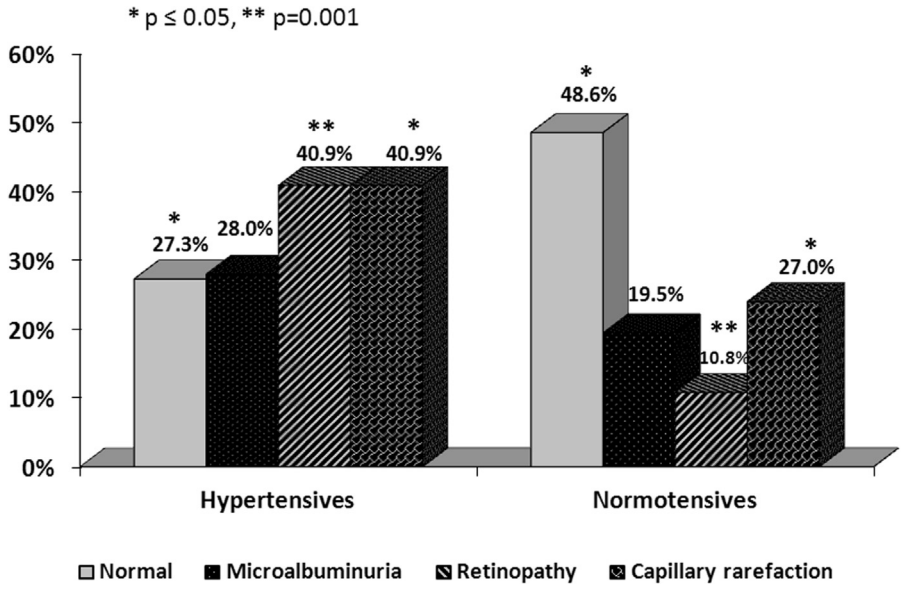

Figure 2. Prevalence of different forms of microcirculation target organ damage in hypertensive and normotensives participants. Microalbuminuria is defined as 24 h urinary albumin excretion ≥30 mg/dL, retinopathy is defined as the smallest tertile of central retinal arterial equivalent, and capillary rarefaction is defined as the smallest tertile of capillary number per visual field.

of microcirculatory TOD after adjustment for other variables ($P = .004$; Table 2).

Discussion

To our knowledge, this is the first study investigating the concomitant presence of different forms of microvascular TOD, both structural (capillary rarefaction, impaired retinal diameter calibers) and functional (microalbuminuria), in a series of ''naïve'', never-treated, true, hypertensive patients with only recently established hypertension, compared with their normotensive healthy individuals. This was achieved using easily applicable in the everyday clinical setting methods and specifically developed technology that allows rapid, noninvasive visualization of retinal and skin vessels. We thus managed to show that even in the very early stages of arterial hypertension (within just 1 year of elevated BP), the majority of hypertensive patients (72.7%) already exhibit one or more forms of the examined microvascular organ damage.

Of the examined target organs, the skin and the retina appear to be mostly affected by high BP even in the very early stages of essential hypertension. The deleterious effects of hypertension on retinal microcirculation are overt in 40.9% of hypertensive population compared with only

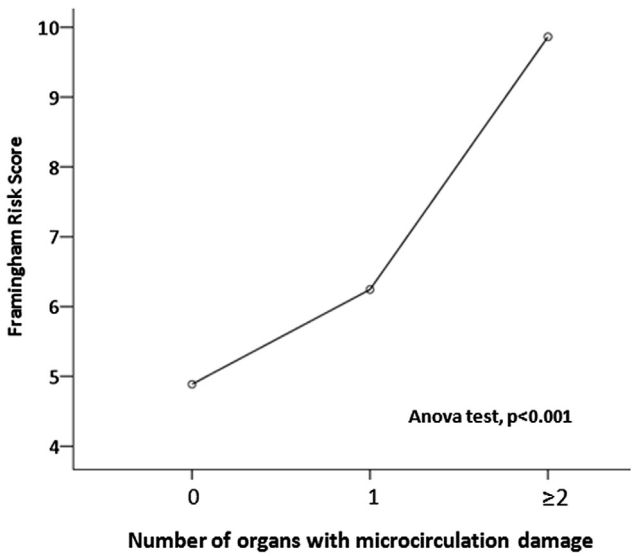

Figure 3. Cardiovascular risk score according to microcirculation TOD.

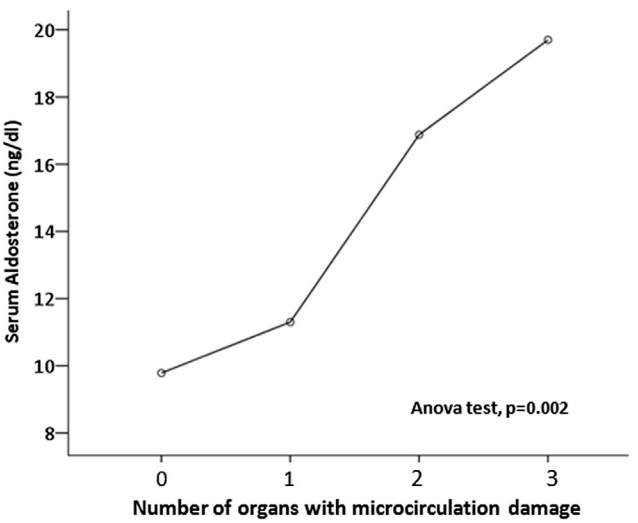

Figure 4. Aldosterone levels according to microcirculation TOD.

Table 2
Multiple linear regression models of microcirculation TOD

Number of Microcirculatory TOD-Adjusted R Square = 0.204, R Square = 0.254, $P < .001$				
	Stand. C	LB (95% CI)	UB (95% CI)	P Value
Age (years)	−0.117	−0.023	0.008	.340
Smoking	−0.060	−0.360	0.180	.511
BMI (Kg/m^2)	0.095	−0.015	0.047	.309
Office BP (DBP; mm Hg)	0.00	−0.012	0.010	.851
Ambulatory BP (night SBP; mm Hg)	0.150	−0.003	0.017	.151
Framingham Risk Score	0.287	0.005	0.076	.025
Aldosterone (ng/dL)	0.273	0.012	0.061	.004

BMI, body mass index; BP, blood pressure; CI, confidence intervals; DBP, diastolic BP; LB, lower bound; SBP, systolic BP; Stand. C, standardized coefficient; TOD, target organ damage; UB, upper bound.

10.8% of normotensives ($P = .001$), whereas capillary rarefaction affects 40.9% of hypertensives and represents the most frequently encountered form of microvascular impairment in normotensive individuals (27%). The increased frequency of capillary rarefaction in hypertensive patients may be at least partially explained by the fact that capillary rarefaction often precedes the development of hypertension[17,18] as also implied by the increased portion of normotensives exhibiting this particular TOD (Figure 2). Microalbuminuria followed the same pattern of increased prevalence among hypertensives (28.0% vs. 19.5%), although it did not reach statistical significance, possibly due to sample size. In addition, prevalence of multiple organ damage (at least two of the previously mentioned forms) was observed in 30.3% of hypertensive patients, compared with a minimum of 5.0% of normotensive individuals ($P = .003$).

We attempted to approach the microvasculature in essential hypertension because the biological basis of hypertension-induced TOD lies on both functional and structural alterations in the small arteries, arterioles, and capillaries. Abnormal regulation of vasomotor tone, resulting in increased vasoconstriction or impaired vasodilation, may underlie microvascular changes in the background of hypertension. Structural alterations have also been found to contribute to hypertension-related TOD, both in precapillary resistance vessels resulting in increase in wall-to-lumen ratio and subsequent arteriolar lumen narrowing (which may be quantitatively measured with CRAE and AVR), and at the level of capillary network, through a reduction of their density within a given vascular bed (rarefaction).[19] The latter may be quantitatively assessed with nailfold capillaroscopy in the skin in the dorsum of the fingers, where it is mainly perceived as a result of anatomic rather than functional rarefaction.[3] On the other hand, microalbuminuria is considered an index of functional microvascular injury, with several mechanisms (including endothelial dysfunction and impaired metabolic profile) implicated in its development.[20]

Through the previously mentioned microvascular abnormalities, microcirculation represents a major player in the dynamic process of vascular resistance control. Evidence suggests that microcirculatory changes may initiate, maintain, or amplify high BP through increase of peripheral vascular resistance, although the pathogenic sequence is traditionally considered reverse.[21] Other than affecting resistance, the cellular delivery of nutrients and oxygen may be impaired by microvasculature abnormalities, thus contributing to hypertensive end-organ damage. This may explain why the previously described microvascular lesions (retinal arteriolar narrowing, capillary rarefaction in the skin, microalbuminuria) may be observed in normotensive individuals as well, often preceding hypertension. Overall, it seems that microvascular abnormalities are both a cause and consequence of high BP.[22] Either way, the great challenge lies on understanding the clinical significance of microcirculatory abnormalities, which are easily detectable and quantified even at early stages by use of appropriate tools, rather than identification of the direction of the previously mentioned association.

Although further research is warranted toward this direction, the clinical interpretation of the findings of the present study could be of critical importance. The predictive value of mild hypertensive retinopathy and microalbuminuria in terms of cardiovascular morbidity and mortality has been verified in several studies.[6,23,24] Of equal or even greater significance, we showed that the concomitant presence of mild retinopathy, and/or microalbuminuria, and/or capillary rarefaction, reflected by the number of the affected organs, is linearly correlated with increased FRS (Figure 3) and aggravates a subject's cardiovascular risk profile, even after adjustment for other parameters (Table 2). Therefore, identification of multiple TOD with intelligent software may denote higher risk for subsequent development of cardiovascular disease. Identification of either hypertensive retinopathy or capillary rarefaction was significantly associated with increased FRS ($P = .002$ and $P = .038$, respectively), while the same correlation was not observed with microalbuminuria. Because microalbuminuria was the less frequently encountered form of microvascular organ damage in our population, it could be assumed that microalbuminuria develops in the progression of hypertension,

suggesting that mild hypertensive retinopathy and capillary rarefaction might represent earlier markers (within only one year of hypertension duration) of TOD and subsequent cardiovascular risk stratification. Either way, clinicians should be alert for the possibility of patients with multiple TOD, who might represent a significant portion even in the newly diagnosed hypertensive population (30.3% in our study), to decelerate its progression and identify those with a worse cardiovascular risk profile. Whether aggressive treatment of hypertension aiming at the reversal of the examined microvascular damage would lead to cardiovascular risk reduction, remains to be investigated in future studies.

Although hypertensive vascular disease has been traditionally conceived as a result of altered hemodynamics, several factors are now implicated in the development of adverse structural and functional changes within the vessel wall under the continuous effect of high BP. Of them, aldosterone has been shown to exert a direct effect on the cardiovascular system, mediating myocardial fibrosis and the accumulation of collagen fibers and growth factors in the arterial wall, eventually leading to remodeling of hypertensive vessels, vascular injury, and TOD.[23] We showed for the first time that aldosterone levels significantly and linearly correlate with the number of the affected organs. In addition, aldosterone was identified as a significant predictor of the number of affected organs even after adjustment for other factors. Our results suggest that aldosterone-mediated effects may play a prime role in the development of multiple TOD in the early stages of essential hypertension.

There are significant strengths in the present study. First, the meticulous selection of our study population (naïve, otherwise healthy, never-treated hypertensive patients with hypertension onset within a year confirmed by 24-hour ABPM, and healthy volunteers) allows the assessment of net BP effect on target organs, independently of other cardiovascular risk factors and diseases. Most importantly, innovative software for microcirculation assessment was developed and applied. Easy and prompt applicability of such noninvasive methods in everyday clinical practice is a prerequisite for the conduction of large studies investigating the impact of microvascular alterations on the cardiovascular system and their subsequent wide use within the clinical setting. Available data regarding the prevalence of early-stage hypertensive retinopathy and capillary rarefaction in newly diagnosed hypertensives are scarce or even nonexistent, although we found those to be the most prevalent forms of microvascular organ damage among hypertensive patients, associated with a worse cardiovascular profile.

A limitation of our study is that the prevalence of any TOD was influenced by the cutoff values used to define TOD in a categorical way. Because the software used to quantitatively assess retinal and capillary vasculature varies in different studies and no large population databases have been studied with the purpose of determining cutoff limits, there is no consensus regarding normal values of nailfold capillaries per visual field or retinal caliber diameters. We therefore used a population consisting of 250 hypertensive and normotensive, otherwise healthy individuals, to define the lower tertile for retinal and capillary parameters as normal values. Using the previously mentioned cutoff values, we did find a relatively increased prevalence of hypertensive retinopathy (10.8%) and capillary rarefaction (27%).

Although available data regarding precise prevalence of the previously mentioned microvascular organ damage in healthy, normotensive individuals are extremely scarce, our findings are in accordance with other studies showing that microvascular organ damage[24–26] may be present in a nonnegligible portion of normotensive groups as well. Future, large-scale studies are warranted to determine normal values for the addressed parameters per age, sex, and BP status. Presence of such microvascular abnormalities in normotensive individuals might imply a predisposition to hypertension, as has already been suggested in previous studies.[25,27] Identifying the hypertension-prone individuals from the normotensive pool using their baseline microvasculature status would be of paramount clinical significance, but requires a prospective design and was beyond the scope of our study.

Conclusions

We showed that newly diagnosed patients with recent onset of hypertension exhibit a significantly greater number of affected target organs compared with normotensives, with early-stage hypertensive retinopathy and capillary rarefaction being the most common forms of TOD among hypertensives compared with their normotensive counterparts. Accumulation of multiple microvascular TOD was associated with an aggravated cardiovascular risk profile, underlining the significance of quantifying and revealing TOD (by fundoscopy and capillaroscopy), even at the very time of the establishment of hypertension diagnosis. Aldosterone levels correlated with and significantly predicted the number of microcirculation TOD even after adjustment for other variables, highlighting its detrimental effects on the arterial wall. Physicians dealing with the hypertensive patient should be aware of the possibility of diffuse microvascular impairment and seek multiple TOD even in the early stages of hypertension, to apply appropriate treatment and decelerate its progression toward cardiovascular disease.

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