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Alterations in capillary morphology are found in mild blood pressure elevation

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Abstract

Objectives—Remodeling of small resistance arteries is an early sign of target organ damage in hypertension. Peripheral capillary morphology abnormalities in hypertension are not well-studied. The study objective was to determine if altered capillary morphology is associated with systolic and/or diastolic blood pressure (SBP/DBP) in subjects without and with mild blood pressure elevation (SBP=130–160 mm Hg). Another objective was to determine whether capillary morphology is associated with minimum forearm vascular resistance (MFVR), a measure of altered resistance artery structure.

Methods—Participants included 115 nonpregnant, nondiabetic subjects 23–55 years of age. A five-component morphology score (distribution, tone, configuration, hypertrophy, extravasates) was developed to describe fingernail bed capillaries visualized using venous congestion in digital photomicrographs. Multiple linear regression models adjusted for age, gender, race, tobacco use, hyperglycemia, dyslipidemia, and renal function were used to analyze the relationship between SBP, DBP, and MFVR with the morphology score.

Results—The total morphology score was significantly associated with SBP and DBP as well as MFVR ($p<0.005$ for all). Among the five individual morphology score components, Hypertrophy was significantly associated with SBP and DBP ($p=0.002$ and 0.001 respectively), while Extravasates were significantly associated with SBP only ($p=0.002$).

Conclusions—A five-component capillary morphology score is associated with SBP, DBP, and altered resistance artery structure in subjects with and without mild blood pressure elevation. These observations suggest that target organ damage at the level of the microcirculation can be detected using capillary morphology.

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Keywords

capillary; microvessels; blood vessels; hypertension; essential; microcirculation; microvascular structure; target organ damage

INTRODUCTION

Target organ damage (TOD), including left ventricular hypertrophy, microalbuminuria, and carotid artery thickening, refers to asymptomatic functional and structural abnormalities preceding the occurrence of major cardiovascular events due to hypertension and other risk factors [1,2]. TOD is a strong independent predictor of adverse outcomes [1]. While somewhat controversial, TOD assessment is recommended in some guidelines for further risk stratification in hypertensive patients, whereby patients with TOD should be treated more aggressively to achieve lower blood pressure targets.[3] Microcirculatory dysfunction precedes and contributes to the development of TOD by influencing pressure and flow in the macrocirculation [4].

Microvascular pathology is a well-known consequence of hypertension. One of the earliest signs of vascular pathology in hypertension is remodeling of small resistance arteries [5]. While changes in media thickness and lumen diameter have been documented in biopsied peripheral resistance arteries of patients with established hypertension [5–7], capillary abnormalities are less well-studied. Disruption of capillary integrity could potentially result in interstitial edema, extravasation of plasma proteins and blood cells, and inflammation triggered by activation of the microvascular endothelium [8]. However, there is limited information on capillary morphology in patients with mild hypertension.

The purpose of this study was to determine whether altered capillary morphology, visualized directly and non-invasively using capillary microscopy, is detectable in subjects with mild blood pressure elevation (untreated systolic blood pressure (SBP) = 130–160 mm Hg). For this purpose, we created a quantifiable score of capillary morphology, and analyzed the association of morphology score with blood pressure and vascular resistance measured indirectly in the forearm. Young and middle-aged adults without severe hypertension were specifically studied in order to determine if variations in capillary morphology are detectable in an early phase of blood pressure elevation, prior to the development of severe established hypertension. If detectable in beginning stages of hypertension, morphologic changes in peripheral capillaries could possibly serve as an early indicator of target organ damage.

RESEARCH METHODS AND PROCEDURES

Subjects

The study protocol was approved by the Thomas Jefferson University Institutional Review Board and written informed consent was obtained from all subjects. Subjects were part of a cohort of volunteers in ongoing investigations of capillary density and function [9,10], and were recruited from a large urban academic family medicine outpatient practice serving 40,000 individuals in Philadelphia, Pennsylvania, and from a cohort of 500 young adult African-American men and women enrolled in investigations of cardiovascular risk. Men and women 18–55 years of age with SBP lower than 160 mm Hg were eligible for enrollment in this study. Exclusion criteria were diabetes, pregnancy, secondary hypertension, coronary or cerebrovascular disease, collagen vascular disease, and organ failure (heart, kidney, liver). To avoid confounding effects from medication use, only never-treated hypertensive individuals were included in this study.

Blood pressure

Subjects were interviewed regarding health status and current health behaviors. Height and weight were measured. Body mass index (BMI) was calculated according to the standard formula, weight (in kg) divided by height (in m) squared. Blood pressure was measured with a Dinamap ProCare 100 automatic blood pressure monitor (GE Healthcare, Piscataway, NJ) with the appropriate size cuff on the left arm for all subjects. Two successive blood pressure readings were taken and then averaged. Readings were obtained about one minute apart, with the subject in seated position, following 10 minutes of rest.

Prehypertension is defined in JNC VII as SBP between 120 and 139 mm Hg, or diastolic blood pressure (DBP) between 80 and 89 mm Hg [11]. SBP in prehypertension was previously subdivided in JNC VI [12] as normal (SBP<130 mm Hg) and high normal (SBP=130–139 mm Hg). Since there is a stepwise increase in cardiovascular mortality found across these categories [13,14], 130 mm Hg SBP was selected as the cut-point between normal and high blood pressure. Therefore, in this study, subjects with SBP 130–159 mm Hg were considered having high blood pressure (HBP), while those with SBP lower than 130 mm Hg were considered having normal blood pressure (NBP).

Capillary microscopy

The capillaroscopy technique was adapted from Serne et al [15]. Following a minimum 10-hour overnight fast and 20 minutes of seated rest, microvascular measurements were conducted for one hour between 7 and 11 AM in a quiet, temperature-controlled room (maintained between 21.5 and 22.5 °C), with the subject in the seated position and the left hand at heart level. Nailfold capillaries in the dorsal skin of the third finger were visualized using a stereo microscope (Olympus; Center Valley, PA), linked to a 4 megapixel SPOT Insight monochrome digital camera (IN-1400; Diagnostic Instruments; Sterling Heights, MI) and a laptop computer (Dell Latitude D820; Dell; Austin, TX). Nailbed illumination was achieved with a 250W halogen fiber optic lamp (KL 2500 LCD; Schott-Fostec; Elmsford, NY). Additional illumination from a supplemental 150W fiber optic halogen light source (B&B Microscopes, Ltd; Warrendale, PA) was used for darkly pigmented individuals. To visualize the capillaries, the 3.2× objective (Olympus 3.2/0.07) was used, with a total system magnification of 38.4×. To maximize visibility of the capillaries in all subjects, photomicrographs were taken using venous occlusion achieved by inflating the upper arm cuff to 50 mm Hg for 60 seconds, passively forcing blood into all patent capillaries present. Additionally, light/dark contrast in the capillary photographs was enhanced using the standard function (stretching of bright and dark levels) of the SPOT imaging software provided with the camera. Accordingly, the assessment of morphology was not influenced by skin colour, as the background pigmentation in African American (darker pigmented) subjects was lightened using our imaging software.

Capillary morphology evaluation—Using morphologic descriptors previously used to describe capillary changes in collagen vascular disease in a clinical capillaroscopy textbook [16], we developed a five-component capillary morphology score, shown in Figure 1.

Distribution (scores 0–6) describes the regular arrangement of capillaries in rows; **Tone**

(scores 0–6) describes the tone (sharply defined outline) of individual capillaries;

Configuration (scores 0–6) describes capillary shape (normal hairpin vs. abnormally coiled);

Hypertrophy (scores 0–6) describes thickening of the capillary walls; and **Extravasates**

(scores 0–2) describe blood extruded due to elevated pressure through the capillary walls into the surrounding tissue. Figure 2 shows sample photomicrographs from NBP and HBP subjects.

The total morphology score is computed by adding the scores on all 5 components (range = 0–26), with higher scores indicating more abnormal morphology. Morphology was assessed by investigators blinded to the identity and blood pressure status of the subjects. For each

subject, the investigators examined 4 different photomicrographs, all taken at the same magnification, using the capillary morphology scoring system. The inter-observer reproducibility of the morphology scoring procedure was verified with four observers independently evaluating photographs of 11 different subjects. Following training, the intraclass correlation coefficient (ICC) among the four raters was 0.85, indicating a high level of inter-observer agreement [17]. Intra-observer reproducibility of the total and component scores was also assessed by the PI, who performed blinded morphology evaluations on 20 subjects twice, with a 3 day interval in between ratings. The intraclass correlation coefficient (ICC) for the total morphology score was 0.99. Test-retest agreement for the 5 score components ranged from 90% to 100%, and kappa statistics ranged from 0.94 to 1.00, both indicative of a high level of short-term reproducibility.

Plethysmography/peripheral vascular resistance

Minimum forearm vascular resistance (MFVR) at maximal vasodilatation is considered an integrated measure of vascular resistance in the forearm [18,19]. MFVR was assessed non-invasively using plethysmography measurements obtained during postocclusive reactive hyperemia, according to the method of Sivertsson [20]. With the subject in the seated position following 10 minutes of rest, a mercury-in-rubber strain gauge stretched to 10% beyond its resting length was looped around the subject's forearm 5 cm below the antecubital fossa. The strain-gauge was connected to a plethysmograph (EC-4: DE Hokanson, Inc; Bellevue, WA) connected to a Doppler recorder (CW-1: DE Hokanson, Inc; Bellevue, WA). SBP, DBP, and heart rate were obtained with a Dinamap cuff placed on the opposite arm. A pediatric cuff around the wrist was inflated to 200 mm Hg to occlude flow to the hand. An occlusion cuff on the upper arm cuff was inflated to 50 mm Hg, deflated for 1.5 seconds, and then re-inflated rapidly prior to each forearm blood flow measurement, obtained through expansion of the forearm strain gauge. Four consecutive FBF curves were obtained at baseline within 30 seconds (FBF_{base}). The upper arm occlusion cuff was then inflated to 40 mm Hg above SBP for 10 minutes. Following release of arterial occlusion (postocclusive reactive hyperemia), four consecutive FBF curves were obtained within the first 30 seconds of flow (FBF_{max}). Minimum forearm vascular resistance (FVR) is calculated by dividing mean arterial pressure (MAP) by the mean FBF_{max} .

Statistical analysis

The main objective of this study was to determine if there is an association between capillary morphology and hemodynamic measures: blood pressure (SBP, DBP) and MFVR. The main analysis was based on multiple linear regression models adjusted for age, gender, and race, tobacco use, hyperglycemia (prediabetic/non-prediabetic classification, with prediabetes =fasting plasma glucose 100–125 mg/dL[21]), dyslipidemia (LDL > 100 mg/dL, HDL < 40 mg/dL, and/or TG > 150 mg/dL)[22], and renal function (presence of microalbuminuria defined as albumin (μ g/creatinine (mg) ratio (ACR) > 30)[23]. Since MFVR has a skewed distribution, logMFVR was used in the linear regression model, and the corresponding geometric mean ratios are reported. The total morphology score was compared in subjects without and with HTN using Wilcoxon's rank sum test; comparison for the five score components was carried out using Fisher's exact test. Analyses were performed using SAS 9.1 (SAS Institute; Cary, NC).

RESULTS

Data were obtained on 115 subjects, including 91 subjects with NBP and 24 with HBP. Patients were between 18 and 55 years of age, and included both blacks and non-blacks. Table 1 summarizes the characteristics of the enrolled subjects.

Figure 3 shows the distribution of the total morphology score for subjects without (NBP) and with (HBP) mild blood pressure elevation. The total score ranged from 2–15 for normotensive subjects, and 5–16 for subjects with mild blood pressure elevation (median=7 vs. 12 respectively, $p<0.001$). Table 2 shows the distribution of the five components of the morphology score (distribution, tone, configuration, hypertrophy, extravasates) for subjects without (NBP) and with (HBP) mild blood pressure elevation. Like the total morphology score, four of the five components were significantly lower in subjects without mild blood pressure elevation ($p<0.001$ for distribution, configuration, hypertrophy and extravasates; $p=0.063$ for tone).

Table 3 shows results of multiple linear regression modeling SBP and DBP as a function of the total morphology score in one analysis, and the five components of the scoring system in a second analysis. The total morphology score was a significant predictor of both SBP and DBP ($p<0.001$). Among the five individual components of the capillary morphology score, hypertrophy was a significant predictor of SBP and DBP ($p=0.002$ and 0.001 , respectively), and extravasates were a significant predictor for SBP only ($p=0.002$).

Table 3 also shows the results of multiple linear regression modeling logMFVR as a function of the total morphology score in one analysis, and the five components of the scoring system in a second analysis. The total morphology score was significantly associated with MFVR ($p=0.003$). The association between extravasates and MFVR was borderline significant ($p=0.09$).

DISCUSSION

In this study, direct visualization of finger nailfold capillaries identified alterations in capillary morphology in subjects with mild blood pressure elevation (prehypertension and stage 1 hypertension) compared with normotensive subjects. The degree of capillary morphology alteration assessed with the summed total morphology score was significantly associated with both SBP and DBP, as well as MFVR, an indirect estimate of resistance artery hypertrophy.

This study was not designed to test the reproducibility of our new scoring system. The number of subjects required to do so was beyond the scope of this initial study, although we need to and will be able to report reproducibility in future studies involving more patients. We have however analyzed and reported the high reliability of the scoring system among different users (intra-class correlation coefficient = 0.85).

Among the individual score components, capillary distribution, tone, and configuration were less well associated with SBP and DBP, compared to capillary hypertrophy and exudates. Based on our study findings, we conclude that the distribution, tone and configuration of capillaries are not greatly disordered in mild hypertension. While the presence of reduced capillary **density** (termed capillary rarefaction) has been well documented in hypertension [9,10,24,25], capillary **distribution** is the regularity of the arrangement of the capillaries, which is different from capillary density.

In scoring systems, individual score components are often more variable and exhibit lower reliabilities than a global score. In fact, items with modest individual reliability are often summed to yield scales with much higher reliability, and this is standard practice in educational, psychological, and other standardized instruments [26,27]. Future study of the score components may confirm that one or more of these elements provide less information than the others and may therefore be removed from the morphology scoring system we have developed.

Normal capillaries are homogeneous in size and morphology, arranged uniformly in rows of hairpin loops. A contrasting disorganized pattern in the nailfold has been observed consistently

in various collagen vascular diseases [28] [29]. However, directly visualized capillary morphology in human hypertension has not been extensively studied. Both Landau [30] and Duprez [31] described capillary thinning, but no other changes in morphology, in patients with hypertension.

The purpose of this study was not to directly compare our new scoring system with previous scoring systems—the number of subjects required to do so was beyond the scope of this initial study, although we plan to perform a direct comparison in future studies. Furthermore, initial capillary morphology classification systems were largely qualitative (Rouen[32], Norris[33]). For example, Rouen et al described capillaries as “within normal limits”, “tortuous”, “meandering”, “generally enlarged” and “giant”. Other researchers later developed semiquantitative scores. Efforts to standardize terminology and quantify capillary loop patterns were described by Houtman et al [34]. They identified hairpin, tortuous, bushy and coiled loops. Capillaries with diameters $> 38.5 \mu\text{m}$ were described as enlarged, and capillaries with diameters $> 76 \mu\text{m}$ were described as giant. Kabasakal et al [29] also described normal and connective tissue diseases patterns qualitatively. This group quantified capillary loop length, and classified open loops longer than $300 \mu\text{m}$ as elongated. A computer program was developed by Jones et al [35]. Based on the quantitative measurement of capillary width and length, capillary morphology was stratified into one of 17 descriptive classes.. However, the complexity of this computer based image analysis system may limit its ease of use for widespread use in research and clinical applications. In a study on patients with Familial Mediterranean fever, Dinc et al [36] developed a nonparametric 4-item capillary morphology score, with subcategories rated from 0–2. This score is slightly less descriptive compared to our 5-item score, with each category is rated on a six-point scale.

Recent reports suggest that alterations in small resistance artery morphology may represent the earliest form of target organ damage in essential hypertension [5]. Structural alterations in the microcirculation may represent an important phase in development of target organ damage associated with hypertension and may have prognostic significance. Rizzoni et al found that changes in small artery structure strongly predicted cardiovascular events [37]. It has also been suggested that microvascular structural changes could be considered, in the future, as an intermediate end point for the evaluations of the benefits of antihypertensive therapy [38]. However, structural evaluation of small resistance arteries is performed invasively using microscopic evaluation of surgical tissue biopsies. Other studies have reported retinal (central) arteriolar narrowing as a predictor of future development of hypertension[39], atherosclerosis [40], coronary and cerebrovascular events [40] [41]. However, there is no accepted standardized classification of retinal vascular changes, and also a lack of age-, sex-, body size- and blood pressure-specific reference data, currently limiting clinical usefulness of retinal vascular changes. The peripheral capillaroscopy technique for fingernail beds utilized in this investigation is an easily learned, alternative noninvasive method for visualizing the microvasculature directly using relatively inexpensive equipment [16].

Studies in recent years suggest that investigation of the cutaneous circulation is both accessible and representative of generalized microcirculatory function [42]. Capillary rarefaction (reduced capillary density) has previously been described in patients with hypertension [9, 10,24,25]. An earlier report described an elevation in capillary pressure determined by micropuncture measurements in a small sample of patients with hypertension [43]. However, associations of changes in capillary morphology with elevated blood pressure have not been reported.

A few studies in rats [44] and humans [45,46] have shown that changes in the peripheral microcirculation reflect concurrent alterations in coronary vessels, and that the peripheral microcirculation may therefore possess clinical predictive value for coronary artery disease.

However, no data are currently available about the prognostic significance of morphologic changes in peripheral capillaries as an indicator of TOD. Early forms of target organ damage associated with hypertension include retinal arteriolar vasculature, small artery resistance, mild hypertrophy or remodeling of the heart, diastolic dysfunction (stiffness of the ventricle, deficient filling), arterial stiffness and microalbuminuria [3,4]. While these data, and specifically serum creatinine and estimated GFR data, were not available on our study subjects, we controlled for the presence of microalbuminuria in our analysis defined as albumin ($\mu\text{g}/\text{creatinine (mg)}$ ratio (ACR) > 30 : see Methods p. 9). Also, we specifically enrolled younger subjects without severe hypertension for this study in order to decrease the likelihood of including subjects with these other forms of TOD.

CONCLUSIONS

A five-component capillary morphology scoring system correlates with SBP, DBP, and forearm vascular resistance in a cohort of subjects with and without mild blood pressure elevation. These observations suggest that alterations in capillary morphology could represent evidence of early target organ damage at the level of the microcirculation. However, since the design of this study was cross-sectional, future longitudinal study is needed to determine whether alterations in capillary structure and morphology are cause or consequence of elevated blood pressure.

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Figure 1. Capillary morphology scoring system

Shown is the two-page capillary morphology scoring system developed by Cheng et al. Capillary drawings and images used with permission from *Clinical Capillaroscopy: A Guide to Its Use in Clinical Research and Practice* by Bollinger and Fagrell, ISBN 0-88937-048-6, ISBN 3-456-81924-2, 1990, pp. 6–7.

A. NBP, 2 different subjects **A1** **A2****B. HBP, 2 different subjects** **B1** **B2****Figure 2. Sample photomicrographs from NBP and HBP subjects**

Black dots representing extravasates can be seen in photomicrographs of HBP subjects in Figure 2B. In the photomicrograph of the HBP subject shown in B1, there is an extravasate in the center of the upper left quadrant. In the photomicrograph of the HBP subject shown in B2, there are several extravasates scattered from left to right across the top of the picture.

Figure 3. Distribution of total morphology scores shows the distribution of the total morphology score for subjects without (NBP) and with (HBP) mild blood pressure elevation. The median total scores were 7 and 12 respectively for subjects without and with mild blood pressure elevation ($p < 0.001$).

Table 1

Subject demographics

	All Subjects (N=116)	NBP (N = 91)	HBP (N = 25)
Age (years), mean $\pm$ sd	38.3 $\pm$ 9.2	37.4 $\pm$ 9.1	39.4 $\pm$ 9.7
Gender , n (%)			
Female	67 (58)	55 (60)	12 (48)
Male	49 (42)	36 (40)	13 (52)
Race , n (%)			
Black	54 (47)	39 (43)	15 (60)
Non-black	62 (53)	52 (57)	10 (40)
SBP (mm Hg), mean $\pm$ sd	121 $\pm$ 13	114 $\pm$ 9	137 $\pm$ 8
DBP (mm Hg), mean $\pm$ sd	73 $\pm$ 8	70 $\pm$ 7	79 $\pm$ 10
MFVR (U), mean $\pm$ sd	4.2 $\pm$ 2.8	3.3 $\pm$ 1.6	4.9 $\pm$ 2.1

Table 2

Distribution of morphology scores for subjects with and without high blood pressure elevation.

Morphology score component	Score value	NBP (N = 91)	HBP (N = 24)
Distribution N (%)	0	9 (10)	0
	1	49 (54)	7 (29)
	2	23 (25)	2 (8)
	3	1 (1)	1 (4)
	4	8 (9)	14 (58)
	5	1 (1)	0
	6	0	0
Tone N (%)	0	16 (18)	1 (4)
	1	45 (49)	8 (33)
	2	24 (26)	12 (50)
	3	3 (3)	1 (4)
	4	3 (3)	2 (8)
	5	0	0
	6	0	0
Configuration N (%)	0	10 (11)	0
	1	29 (32)	7 (29)
	2	16 (18)	0
	3	25 (27)	5 (21)
	4	11 (12)	10 (4)
	5	0	2 (8)
	6	0	0
Hypertrophy N (%)	0	0	0
	1	65 (71)	6 (25)
	2	23 (25)	13 (54)
	3	3 (3)	4 (17)
	4	0	1 (4)
	5	0	0
	6	0	0
Extravasates N (%)	0	24 (26)	0
	1	47 (52)	11 (46)
	2	20 (22)	13 (54)

Table 3

Linear regression results for total morphology score and components as predictors of systolic and diastolic blood pressure and minimum forearm vascular resistance, adjusted for age, gender, and race, tobacco use, *hyperglycemia, *dyslipidemia, and *renal function (*See Methods for defining criteria)

	Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Minimum Forearm Vascular Resistance	
	<i>Mean Difference</i> ** (95% CI)	<i>P</i>	<i>Mean Difference</i> ** (95% CI)	<i>P</i>	<i>Geometric Mean Ratio</i> ** (95% CI)	<i>P</i>
Total morphology score	1.6 (0.84, 2.3)	<0.001	0.95 (0.44, 1.5)	<0.001	1.04 (1.01, 1.06)	0.004
Distribution	1.8 (-0.16, 3.8)	0.072	0.4 (-1.0, 1.8)	0.58	1.04 (0.98, 1.1)	0.22
Tone	-0.70 (-3.7, 2.3)	0.64	1.0 (-1.1, 3.2)	0.34	1.0 (0.92, 1.1)	0.77
Configuration	0.31 (-1.7, 2.4)	0.77	0.02 (-1.5, 1.5)	0.98	1.03 (0.97, 1.1)	0.32
Hypertrophy	5.7 (2.0, 9.3)	0.003	4.6 (2.0, 7.3)	<0.001	1.05 (0.92, 1.2)	0.46
Extravasates	5.0 (1.7, 8.0)	0.003	1.7 (-0.6, 4.0)	0.15	1.1 (0.99, 1.2)	0.07

(**) Corresponding to a 1-unit increase in the total morphology score, or in each of its individual components.