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A study to investigate the association between the severity and duration of systemic HTN and specific retinal vascular parameters in adults

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ABSTRACT

Introduction: The retina provides a unique window to the microvasculature. Systemic hypertension (HTN) is hypothesized to induce quantifiable alterations in retinal vessels, including arteriolar narrowing, increased arteriolar tortuosity, and altered venular caliber. This study aimed to investigate the association between the severity and duration of systemic HTN and specific retinal vascular parameters in adults. **Methods:** A hospital-based, cross-sectional study was conducted with 96 adults (48 hypertensive patients and 48 age- and sex-matched normotensive controls). Hypertensive participants were stratified by duration (<5 years and ≥5 years) and control status (controlled vs. uncontrolled). Retinal images were obtained via fundus photography. Central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), and arterio-venular ratio (AVR) were calculated using validated semi-automated software. Arteriolar tortuosity index (ATI) was also measured. **Results:** The mean CRAE was significantly narrower in the hypertensive group compared to controls (145.3 ± 12.1 µm vs. 162.8 ± 10.5 µm, $p<0.001$). The CRVE was wider in hypertensives, particularly in those with uncontrolled BP (242.1 ± 18.3 µm vs. 228.5 ± 15.2 µm in controls, $p<0.01$). Consequently, AVR was significantly lower in the hypertensive group (0.60 ± 0.05 vs. 0.71 ± 0.04, $p<0.001$). Arteriolar tortuosity was significantly greater in hypertensives (ATI: 1.15 ± 0.08 vs. 1.04 ± 0.05, $p<0.001$). Subgroup analysis revealed that patients with HTN duration ≥5 years and those with uncontrolled BP exhibited more pronounced vascular changes (narrower CRAE, wider CRVE, lower AVR) than those with shorter duration or controlled HTN (all $p<0.05$). **Conclusion:** Systemic hypertension is strongly associated with measurable retinal microvascular changes, including arteriolar narrowing, venular widening, and increased tortuosity. These changes are more severe with longer disease duration and poor blood pressure control. Retinal vascular imaging serves as a valuable, non-invasive tool for assessing hypertensive microvascular damage.

Keywords: Hypertension, Retinal Vessels, Retinal Imaging, Microcirculation, Arteriolar Narrowing, Arterio-Venular Ratio.

INTRODUCTION:

Systemic hypertension (HTN) is a pervasive global health challenge, serving as the primary modifiable risk factor for cardiovascular morbidity and mortality, including ischemic heart disease, heart failure, and cerebrovascular accidents[1]. Its insidious nature lies in the chronic, pressure-induced injury it inflicts on the vascular endothelium, triggering a cascade of structural and functional changes that remodel both macro- and micro-vasculature. While the consequences for large arteries, such as atherosclerosis and increased stiffness, are well-characterized, the parallel damage to the microcirculation is equally critical but less accessible for direct, in vivo assessment. This microvascular dysfunction is a fundamental contributor to end-organ damage in the brain, kidneys, and heart, underscoring the need for reliable biomarkers to detect its early presence and progression[2].

The retinal circulation, an embryological extension of the diencephalon, offers a unique and non-invasive anatomical window into the state of the systemic microvasculature[3]. It shares key physiological properties—including autoregulatory mechanisms, endothelial function, and blood-retinal barrier characteristics—with cerebral and other vital organ beds. Consequently, pathological alterations observed in the retinal vessels are believed to mirror analogous microvascular

disease processes occurring in more clinically silent, yet critically important, tissues[4]. For decades, the clinical assessment of hypertensive retinopathy relied on direct ophthalmoscopy and qualitative classification systems (e.g., Keith-Wagener-Barker grades), focusing on late-stage signs such as focal arteriolar narrowing, arteriovenous nicking, hemorrhages, and exudates. However, this approach suffers from significant inter-observer variability, limited sensitivity for detecting subclinical change, and a ceiling effect where it fails to quantify the severity of alterations beyond broad categories[5].

The paradigm shifted with the development of digital retinal imaging coupled with sophisticated, computer-based quantification software. This technological advancement enabled the precise, objective measurement of retinal vascular geometry[6]. Key parameters now include the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), which use summarized formulas to represent the calibers of the six largest arterioles and venules, respectively. The arterio-venular ratio (AVR), derived from CRAE/CRVE, serves as a composite measure, historically thought to represent generalized arteriolar narrowing[7]. Furthermore, metrics of vascular geometry such as tortuosity—the increased curvature and winding of a vessel—provide insights into the biomechanical stresses and remodeling of the vascular wall[8]. Landmark epidemiological studies, including the Atherosclerosis Risk in Communities (ARIC) Study and the Rotterdam Study, have robustly linked these quantitative traits to cardiovascular risk. Narrower CRAE, wider CRVE, and lower AVR are not only correlated with concurrent blood pressure levels but also predict the future development of hypertension, stroke, and coronary events, independent of traditional risk factors[9],[10].

From a pathophysiological perspective, hypertensive retinal changes are a manifestation of adaptive and eventually maladaptive microvascular remodeling[11]. Chronic elevated pressure induces arteriolar vasoconstriction (via the myogenic response) and, over time, structural changes including medial hypertrophy, hyalinization, and endothelial dysfunction—collectively manifesting as narrowed CRAE[12]. Venular widening (increased CRVE) is a less understood but consistent finding, potentially linked to systemic inflammation, endothelial activation, and impaired nitric oxide bioavailability[13]. Increased tortuosity may reflect altered shear stress, vascular wall stiffness, and compensatory lengthening in response to local tissue factors[14]. Crucially, emerging evidence suggests that some of these early changes, particularly in caliber, may be dynamic and partially reversible with effective antihypertensive treatment, highlighting their potential utility as biomarkers of therapeutic efficacy[15].

Despite this compelling evidence base, a focused clinical gap remains. Many large studies are population-based, encompassing a wide spectrum of health states and comorbidities. There is a need for targeted clinical studies that examine how specific, clinically relevant characteristics of a diagnosed hypertensive cohort—namely, the duration of the disease and the achievement of blood pressure control—correlate with the degree of quantitative microvascular alteration[16]. Understanding whether a longer burden of hypertension leads to cumulatively worse microvascular damage, and whether stringent control can mitigate or normalize these changes, has direct implications for patient risk stratification and the emphasis placed on aggressive, long-term management[17].

Therefore, this study aims to conduct a detailed, quantitative investigation into the association between systemic hypertension and retinal microvascular parameters within a controlled clinical setting. Utilizing a cross-sectional design with a sample of 96 age- and sex-matched adults, we will rigorously compare CRAE, CRVE, AVR, and arteriolar tortuosity between normotensive controls and patients with essential hypertension. Furthermore, we will stratify the hypertensive group by disease duration (<5 years vs. ≥5 years) and by blood pressure control status (controlled vs. uncontrolled) to dissect the influence of these specific clinical factors. We hypothesize that: (1) Hypertension is associated with significantly narrower CRAE, wider CRVE, lower AVR, and greater arteriolar tortuosity compared to normotension; and (2) These microvascular alterations will be more pronounced in individuals with longer-standing hypertension and in those with uncontrolled blood pressure, providing tangible evidence of a dose-response relationship between clinical hypertension severity and end-organ microvascular damage.

MATERIALS & METHODS:

A hospital-based, cross-sectional, analytical study design was employed. The study was conducted at the outpatient departments of Ophthalmology at Saraswathi Institute of Medical Sciences, Hapur, a tertiary care teaching hospital. The target population consisted of adults aged 40-65 years. The source population for the hypertensive group was patients with a confirmed diagnosis of essential hypertension attending the cardiology and medicine outpatient departments. The source population for the normotensive control group was drawn from accompanying relatives of patients and non-medical hospital staff who presented for routine health checks, ensuring a sample from a similar socio-environmental background.

Inclusion Criteria for the Hypertensive Group:

- Adults aged 40-65 years.
- Diagnosis of essential hypertension according to JNC-7 criteria (systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg on at least two occasions, or current use of antihypertensive medication).
- Willingness to provide informed consent.

Inclusion Criteria for the Normotensive Control Group:

- Adults aged 40-65 years, matched to hypertensive participants by age (±3 years) and sex.
- Blood pressure <140/90 mmHg with no history of hypertension or antihypertensive drug use.
- Willingness to provide informed consent.

Exclusion Criteria (for both groups):

- Diagnosis of diabetes mellitus (type 1 or type 2).
- History or evidence of retinal vascular disease (e.g., retinal vein/artery occlusion, diabetic retinopathy).
- Significant ocular media opacity (e.g., advanced cataract) or refractive error > ±6 diopters preventing clear fundus photography.
- History of intraocular surgery or major ocular disease (e.g., glaucoma, uveitis).
- Pregnancy.
- Severe systemic illness (e.g., liver cirrhosis, renal failure on dialysis, active malignancy) that could independently affect vascular health.

Sample Size Calculation

The sample size was calculated using the formula for comparing two means. Based on a previous study by Wong et al. (Hypertension, 2004), a mean difference in Arterio-Venular Ratio (AVR) of 0.05 with a standard deviation of 0.06 was anticipated. To achieve 90% power at a 5% significance level (α=0.05, two-tailed), a minimum of 43 participants per group was required. To account for potential data loss or unusable images, the sample size was rounded up to 48 per group, yielding a total sample of 96 participants.

Procedure for Data Collection

Data collection occurred over a 12-month period. Eligible participants were identified and recruited consecutively. The procedure followed a standardized protocol:

1. **Informed Consent:** Written informed consent was obtained from all participants after a detailed explanation of the study.
2. **Clinical Assessment:** A structured proforma was used to record demographic data, medical history, duration of hypertension, and current medications. Blood pressure was measured using a calibrated mercury sphygmomanometer with the participant seated after a 10-minute rest. Two readings were taken five minutes apart, and the average was recorded.
3. **Ophthalmic Examination and Imaging:** All participants underwent a basic ophthalmic examination including visual acuity testing. Pupils were dilated with tropicamide 0.5% eye drops. Digital retinal photographs (45-degree field, centered on the optic disc) of both eyes were obtained by a trained technician using a Canon CR-2 Plus AF retinal camera. The image from the eye with better quality (or the right eye if both were equal) was selected for analysis.
4. **Retinal Vessel Analysis:** The selected digital images were analyzed using semi-automated software (IVAN, University of Wisconsin) by a single trained grader who was masked to the clinical status of the participant. The grader identified and measured the six largest arterioles and venules passing through a zone 0.5 to 1.0 disc diameter from the optic disc margin. The software automatically calculated the CRAE, CRVE, and AVR using the revised Knudtson-Parr-Hubbard formulas. Arteriolar tortuosity was measured for the same vessel segments, and the ATI was calculated as the ratio of the actual vessel path length to the straight-line distance between its endpoints, averaged for all measured arterioles.

Data Analysis

All data were entered into a secure, password-protected Microsoft Excel spreadsheet. Data entry was performed twice by independent personnel to ensure accuracy and validate the dataset. The final data was then imported into SPSS software (Version 25.0, IBM Corp.) for statistical analysis.

RESULTS:

The study sample consisted of 96 participants, comprising 48 patients with essential hypertension and 48 age- and sex-matched normotensive controls. All recruited participants underwent full clinical and retinal imaging assessment. The key findings are presented in the following tables.

Table 1: Baseline Characteristics of the Study Population (n=96)

Characteristic	Hypertensive Group (n=48)	Normotensive Group (n=48)	p-value
Age (years), Mean ± SD	52.9 ± 6.5	51.9 ± 7.1	0.455
Sex, n (%)			1.000
Male	28 (58.3%)	28 (58.3%)	
Female	20 (41.7%)	20 (41.7%)	

Characteristic	Hypertensive Group (n=48)	Normotensive Group (n=48)	p-value
Smoking Status, n (%)			0.683
Current Smoker	12 (25.0%)	10 (20.8%)	
Non-Smoker	36 (75.0%)	38 (79.2%)	
BMI (kg/m²), Mean ± SD	26.8 ± 3.1	25.2 ± 2.8	**0.008**
SBP (mmHg), Mean ± SD	152.4 ± 14.7	122.6 ± 9.4	**<0.001**
DBP (mmHg), Mean ± SD	94.1 ± 8.9	78.3 ± 6.2	**<0.001**

The baseline characteristics of the study population are presented in Table 1. The hypertensive and normotensive groups were well-matched for age and sex (p=0.455 and p=1.000, respectively), with no significant difference in smoking status (p=0.683). As expected, the hypertensive group had a significantly higher mean body mass index (BMI) (26.8 ± 3.1 kg/m² vs. 25.2 ± 2.8 kg/m², p=0.008). The mean systolic and diastolic blood pressures (SBP, DBP) were markedly higher in the hypertensive group (152.4/94.1 mmHg) compared to the normotensive controls (122.6/78.3 mmHg, both p<0.001), confirming the effective group stratification.

Table 2: Comparison of Retinal Vascular Parameters Between Hypertensive and Normotensive Groups

Retinal Parameter	Hypertensive Group (n=48)	Normotensive Group (n=48)	p-value
CRAE (µm), Mean ± SD	145.3 ± 12.1	162.8 ± 10.5	**<0.001**
CRVE (µm), Mean ± SD	236.4 ± 20.1	228.5 ± 15.2	**0.032**
AVR, Mean ± SD	0.60 ± 0.05	0.71 ± 0.04	**<0.001**
Arteriolar Tortuosity Index (ATI), Mean ± SD	1.15 ± 0.08	1.04 ± 0.05	**<0.001**

Table 2 details the comparison of quantitative retinal vascular parameters between the two groups. The hypertensive group exhibited a significantly narrower central retinal arteriolar equivalent (CRAE) (145.3 ± 12.1 µm vs. 162.8 ± 10.5 µm, p<0.001) and a wider central retinal venular equivalent (CRVE) (236.4 ± 20.1 µm vs. 228.5 ± 15.2 µm, p=0.032). Consequently, the derived arterio-venular ratio (AVR) was substantially lower in hypertensives (0.60 ± 0.05) compared to controls (0.71 ± 0.04, p<0.001). Furthermore, arteriolar tortuosity, measured by the tortuosity index (ATI), was significantly greater in the hypertensive group (1.15 ± 0.08) than in the normotensive group (1.04 ± 0.05, p<0.001).

Table 3: Retinal Vascular Parameters Stratified by Hypertension Duration and Control Status (within the Hypertensive Group, n=48)

Parameter	HTN Duration <5 years (n=23)	HTN Duration ≥5 years (n=25)	p-value	Controlled HTN (n=25)	Uncontrolled HTN (n=23)	p-value
SBP (mmHg)	147.8 ± 12.4	156.7 ± 15.2	**0.034**	132.5 ± 5.8	173.8 ± 9.1	**<0.001**
DBP (mmHg)	92.0 ± 7.8	96.0 ± 9.5	0.105	85.4 ± 4.3	103.5 ± 6.0	**<0.001**
CRAE (µm)	149.1 ± 11.5	141.7 ± 11.8	**0.032**	148.8 ± 11.9	141.5 ± 11.2	**0.026**

Parameter	HTN Duration <5 years (n=23)	HTN Duration ≥5 years (n=25)	p-value	Controlled HTN (n=25)	Uncontrolled HTN (n=23)	p-value
CRVE (µm)	231.2 ± 17.8	241.2 ± 20.9	**0.041**	231.0 ± 18.1	242.1 ± 18.3	**0.012**
AVR	0.645 ± 0.04	0.588 ± 0.05	**<0.001**	0.644 ± 0.04	0.585 ± 0.05	**<0.001**
ATI	1.12 ± 0.07	1.18 ± 0.08	**0.008**	1.13 ± 0.07	1.17 ± 0.08	0.065

Subgroup analysis within the hypertensive cohort revealed notable variations based on disease duration and control status, as shown in Table 3. Participants with a hypertension duration of five years or more (≥5 years) had significantly narrower CRAE (141.7 ± 11.8 µm vs. 149.1 ± 11.5 µm, p=0.032), wider CRVE (241.2 ± 20.9 µm vs. 231.2 ± 17.8 µm, p=0.041), a lower AVR (0.588 ± 0.05 vs. 0.645 ± 0.04, p<0.001), and greater arteriolar tortuosity (ATI: 1.18 ± 0.08 vs. 1.12 ± 0.07, p=0.008) compared to those with a shorter disease history (<5 years). Similarly, patients with uncontrolled hypertension demonstrated more adverse retinal changes than their controlled counterparts, with a narrower CRAE (141.5 ± 11.2 µm vs. 148.8 ± 11.9 µm, p=0.026), a wider CRVE (242.1 ± 18.3 µm vs. 231.0 ± 18.1 µm, p=0.012), and a significantly lower AVR (0.585 ± 0.05 vs. 0.644 ± 0.04, p<0.001). The trend towards greater tortuosity in the uncontrolled group did not reach statistical significance (p=0.065).

Table 4: Pearson Correlation Coefficients (r) Between Blood Pressure and Retinal Vascular Parameters in the Total Cohort (n=96)

Retinal Parameter	Systolic Blood Pressure (SBP)		Diastolic Blood Pressure (DBP)	
	r-value	p-value	r-value	p-value
CRAE (µm)	-0.72	<0.001	-0.65	<0.001
CRVE (µm)	0.41	<0.001	0.35	<0.001
AVR	-0.75	<0.001	-0.68	<0.001
ATI	0.52	<0.001	0.47	<0.001

The correlation analysis, summarized in Table 4, revealed strong and statistically significant linear relationships between blood pressure levels and retinal vascular parameters across the entire cohort. Systolic blood pressure (SBP) showed a strong negative correlation with CRAE (r = -0.72, p<0.001) and AVR (r = -0.75, p<0.001), and a moderate positive correlation with CRVE (r = 0.41, p<0.001) and ATI (r = 0.52, p<0.001). Diastolic blood pressure (DBP) followed a similar pattern, with slightly weaker but still highly significant correlation coefficients (all p<0.001).

DISCUSSION:

This cross-sectional study of 96 adults provides clear, quantitative evidence that systemic hypertension is strongly associated with distinct alterations in the retinal microvasculature. Our findings demonstrate that hypertensive individuals exhibit significant arteriolar narrowing (reduced CRAE), venular widening (increased CRVE), a decreased arterio-venular ratio, and increased arteriolar tortuosity compared to their normotensive counterparts. These results substantiate the retina's role as a reliable mirror of systemic microvascular health and validate quantitative imaging as a sensitive tool for detecting subclinical hypertensive end-organ damage.

The primary finding of generalized arteriolar narrowing aligns perfectly with the established pathophysiology of hypertension, where chronic elevated pressure induces vasoconstriction, medial hypertrophy, and vascular remodeling. The magnitude of narrowing observed in our cohort is consistent with previous large-scale epidemiological studies. For instance, the Multi-Ethnic Study of Atherosclerosis (MESA) reported that each 10-mmHg increase in systolic blood pressure was associated with a 1.53-µm decrease in CRAE, a relationship we corroborate with our strong negative correlation (r = -0.72)[18]. More specifically, our finding of a mean CRAE difference of 17.5 µm between groups is comparable to results from the Rotterdam Study, which found significant narrowing in hypertensive participants[19]. This consistency across diverse populations underscores the robustness of CRAE as a biomarker of hypertensive microvascular burden.

Perhaps more insightful are our subgroup analyses, which move beyond the mere presence of hypertension to explore the impact of disease chronicity and management. The significantly worse retinal vascular parameters—particularly the more severely reduced AVR—in patients with hypertension duration ≥5 years suggests a cumulative "dose-effect" of elevated blood pressure on the microvasculature. This temporal relationship implies progressive structural damage that may not be fully reversible, highlighting the critical importance of early intervention[20]. Furthermore, the stark contrast between controlled and uncontrolled hypertensives offers compelling clinical evidence. Patients with uncontrolled blood pressure exhibited a microvascular profile akin to longer-standing disease, with markedly narrower arterioles and lower AVR. This finding echoes the results of the Australian Heart Eye Study, which demonstrated that treated but uncontrolled hypertension was associated with retinal arteriolar caliber changes similar to those of untreated individuals[21]. Our data visually reinforce the principle that the microvascular benefit of antihypertensive therapy is contingent upon achieving actual control, not merely receiving treatment.

The observed venular widening (increased CRVE) and increased arteriolar tortuosity add further dimensions to our understanding. While arteriolar narrowing is a direct hemodynamic response, venular dilation is increasingly linked to systemic inflammation, endothelial dysfunction, and increased venous pressure[13]. The correlation between higher blood pressure and wider venules in our study supports this multifactorial pathogenesis. The increased tortuosity likely represents a biomechanical adaptation to chronic stress, vascular wall remodeling, and altered shear forces[14]. Together, these changes paint a comprehensive picture of a microvasculature under sustained duress, undergoing both constrictive and geometric remodeling.

CONCLUSION:

In conclusion, this study confirms that systemic hypertension induces quantifiable, adverse changes in the retinal microvasculature, detectable via modern imaging techniques. The severity of these changes is modulated by both the duration of hypertension and the adequacy of blood pressure control. These findings have dual implications. For clinical practice, quantitative retinal vascular assessment could serve as a valuable, non-invasive adjunct for stratifying microvascular risk in hypertensive patients, potentially identifying those who may benefit from more aggressive management. For research, our results support the use of retinal parameters as intermediate endpoints in trials evaluating the microvascular benefits of antihypertensive therapies. Ultimately, the retinal vessels offer a clear window into the systemic burden of hypertension, reminding us that effective management must aim not only to lower a number on a sphygmomanometer but to preserve the integrity of the entire vascular tree.

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Conflicts of interests: The authors declare no conflicts of interest.
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