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Systemic Hemodynamics and Optic Nerve Head Microvascular Density in Healthy Adults: An Optical Coherence Tomography Angiography Study

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Abstract

Objectives

To characterize sex- and age-related differences in optic nerve head (ONH) microvascular density measured by optical coherence tomography angiography (OCTA), and to determine whether systemic hemodynamic parameters are independently associated with ONH microvascular density in healthy adults.

Methods

In this cross-sectional study, 350 healthy adults underwent standardized peripapillary OCTA imaging and assessment of peripheral and central blood pressure, mean arterial pressure, heart rate, pulse wave velocity, augmentation index, and ejection duration. OCTA-derived all-vessel (AV) and small-vessel (SV) densities were quantified for the whole peripapillary image, hemispheres, sectors, and inside-disc region. Sex differences and age associations were assessed for both OCTA and hemodynamic measures. Partial Spearman correlations, adjusted for age and sex, evaluated associations between hemodynamic parameters and vessel density, with false discovery rate (FDR) correction for multiple comparisons.

Results

Women showed significantly higher peripapillary AV and SV densities than men across most regions (FDR-adjusted $P < 0.001$). Age was associated with variation in both ONH microvascular and hemodynamic measures. After adjustment for age and sex, no hemodynamic parameter was significantly associated with OCTA-derived vessel density following FDR correction; associations were uniformly weak (absolute partial correlations ≤ 0.14).

Conclusions

ONH microvascular density shows substantial sex-related differences and age-dependent variation in healthy adults, but systemic blood pressure, arterial stiffness, and related hemodynamic parameters show no robust independent association with it after adjustment. OCTA-derived ONH vessel density should not be interpreted as a direct surrogate of systemic hemodynamic status in healthy individuals, underscoring the need for age- and sex-specific reference frameworks in ONH OCTA interpretation.

Introduction

Cardiovascular disease remains the leading cause of death worldwide, and vascular injury may develop in the microcirculation before clinically apparent disease is detected in larger vessels (1). Because most systemic microvascular beds cannot be visualized directly and non-invasively, their assessment has

traditionally relied on indirect measures of systemic vascular status, including brachial blood pressure and other hemodynamic indices. The retina and the optic nerve head (ONH) are notable exceptions. Their microvascular network can be examined non-invasively, and the microcirculation is closely linked to the neural function of the retina and is influenced by systemic metabolic and vascular disorders (2). Consequently, retinal and ONH imaging provides an accessible model for investigating relationships between systemic vascular health and end-organ microvascular status.

Optical coherence tomography angiography (OCTA) has substantially expanded the ability to study the microcirculation. OCTA generates angiographic images from motion contrast produced principally by moving erythrocytes, without the need for intravenous dye injection(3). It provides high-resolution, depth-resolved visualization of retinal vascular networks and can distinguish vascular structures within separate retinal capillary plexuses(3, 4). Around the optic disc, this includes both the radial peripapillary capillary network surrounding the ONH and the capillary network within the disc itself; in the present study, we use the term "ONH microvascular density" to refer collectively to these peripapillary and inside-disc vessel-density measures. These features enable rapid, repeatable quantification of vessel density in predefined retinal and peripapillary regions. OCTA has consequently been applied to the assessment of retinal microvascular alterations in a range of ocular and systemic conditions, including diabetic retinopathy, hypertension, and other vascular diseases(3–5). However, interpretation of OCTA vessel density as a marker of systemic microvascular health requires careful consideration of biological and technical determinants.

Among the systemic factors that may influence retinal and ONH microvascular status, arterial stiffness and related hemodynamic indices have received particular attention. Pulse wave velocity (PWV) and augmentation index are commonly used measures of arterial stiffness and wave reflection. In a study of individuals ranging from normotension to early-stage hypertension, higher PWV was associated with narrower retinal arterioles on fundus photography, while retinal arteriolar caliber and the arteriovenous ratio were independently associated with augmentation index(6). These findings suggest that abnormalities of the macro- and microcirculation may be related to the early stages of hypertension. Other studies have reported associations between arterial stiffness, retinal vascular abnormalities, and OCTA-derived vessel-density changes in populations with diabetes, retinal vein occlusion, or established hypertension(7–9). Nevertheless, these disease-enriched cohorts are affected by potential confounding from hyperglycemia, endothelial dysfunction, chronic blood-pressure elevation, vascular remodeling, and treatment exposure. Whether central and peripheral hemodynamic parameters are independently related to ONH microvascular density in adults without overt cardiometabolic disease remains uncertain. The limited OCTA-based evidence from healthy populations is itself inconsistent: in a cohort drawn from the same source population studied here, PWV correlated with lower parafoveal deep-plexus vessel density and blood pressure correlated with lower whole-image deep-plexus density, yet neither PWV nor central aortic pressure correlated with vessel density in several other macular regions examine(10).

Interpretation is further complicated by the influence of age, sex, and image quality on OCTA vessel-density measurements. In a community-based cohort of healthy Chinese adults, vessel density in both

the superficial and deep capillary plexuses decreased with age, with the decline beginning earlier and progressing more rapidly in the deep plexus; the age-related pattern in the deep plexus also differed by sex(11). In the population-based African American Eye Disease Study, older age and male sex were associated with lower radial peripapillary capillary density after adjustment for signal strength and other systemic factors (12). However, findings are not uniform across cohorts. A study of normal eyes found higher peripapillary vessel-density measures in women but no significant association between age and vessel density, while hypertension, diabetes, and scan signal strength were associated with regional vessel-density measurements(13). These differences may reflect variation in age range, ancestry, inclusion criteria, retinal region, capillary plexus, OCTA device, segmentation, and image-quality control. Accordingly, studies of systemic hemodynamics and retinal or ONH vessel density should account explicitly for age and sex and should control for relevant acquisition-related factors.

In this study, we sought to comprehensively characterize age- and sex-related differences in OCTA-derived ONH microvascular density and systemic hemodynamic parameters and to examine whether peripheral and central hemodynamic measures were independently associated with ONH microvascular density in healthy adults. We evaluated a broad panel of hemodynamic parameters, including peripheral and central blood pressure, mean arterial pressure, heart rate, ejection duration, augmentation index, and PWV, in relation to vessel-density measurements across predefined peripapillary and inside-disc regions. Associations were assessed after adjustment for age and sex, with false-discovery-rate correction applied to account for multiple comparisons. Given the exploratory nature of the study, no specific directional hypothesis was prespecified.

Method

Study participants

This cross-sectional study included healthy adults enrolled in the PERSIAN Organizational Cohort Study of Mashhad (POCM) at Mashhad University of Medical Sciences. Participants were excluded if they had a chronic systemic disease, were pregnant or breastfeeding, or had glaucoma, clinically apparent retinal disease, or a history of refractive or intraocular surgery, as well as for spherical refractive error greater than ± 5.00 diopters, cylindrical myopic refractive error greater than 6.00 diopters, or hyperopic refractive error greater than 4.00 diopters. Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee[IR.MUMS.MEDICAL.REC.1401.676].

OCTA acquisition and analysis

OCTA imaging was performed with the AngioVue system (RTVue XR Avanti; software version 2018.0.0.14; Optovue Inc., Fremont, CA, USA), operating at an A-scan rate of 70,000 scans/s, with repeated B-scans used to evaluate image decorrelation. Optic disc cubes were acquired using the

AngioDisc 4.5 × 4.5-mm HD scan protocol (400 lines × 400 A-scans) in horizontal and vertical orthogonal directions, centered on the optic disc, with automated default segmentation applied to the radial peripapillary capillary (RPC) network and three-dimensional projection-artifact removal. Both eyes were imaged, but the right eye was prespecified as the analysis eye for each participant; right-eye images were required to meet a scan-quality index of 7–10, and images with artifact or inadequate segmentation accuracy were independently reviewed by two authors (MA, RD) and excluded or reacquired as needed. Full acquisition parameters and image-quality criteria have been described in detail previously by our group(14).

Peripapillary vessel density was quantified as all-vessel density (AV VD, encompassing both large vessels and capillaries) and small-vessel density (SV VD, isolating the capillary-level signal after removal of larger vessels), consistent with standard AngioVue RPC output. These were computed for the whole image and whole peripapillary annulus, the superior and inferior hemispheric halves, eight peripapillary sectors (nasal-superior, nasal-inferior, inferior-nasal, inferior-temporal, superior-temporal, superior-nasal, temporal-inferior, temporal-superior), the standard grid-based regions (superotemporal, temporal, inferotemporal, inferior, superior, central, nasal, inferonasal, superonasal), and the inside-disc region.

Hemodynamic assessment

Peripheral and central hemodynamic parameters were measured using the SphygmoCor XCEL system (AtCor Medical, Itasca, IL, USA). Participants fasted ≥ 6 h and abstained from smoking, alcohol, and caffeine for ≥ 12 h before assessment; measurements were obtained after 10–15 min of supine rest, following the manufacturer's standardized protocol. Carotid–femoral pulse wave velocity (cfPWV) was determined by applanation tonometry at the carotid artery combined with a femoral cuff, and augmentation index (AIx) was derived from the central pressure waveform; heart rate, ejection duration, and mean arterial pressure were recorded simultaneously. Only recordings meeting the manufacturer's quality-control criteria were retained; participants with unreliable or incomplete recordings were excluded from the corresponding analyses. This protocol and its validation in the present cohort have been reported in detail elsewhere (10).

Statistical analysis

Statistical analyses were performed using R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 2024.12.1. A complete-case analysis was performed. The distribution of continuous variables was assessed using the Shapiro–Wilk test, and continuous variables are presented as mean ± standard deviation (SD).

Sex differences in hemodynamic and OCTA-derived vessel-density parameters were assessed using the independent-samples *t*-test for approximately normally distributed variables and the Wilcoxon rank-sum test otherwise. For each set of sex-based comparisons, *P*-values were adjusted for multiple testing using the Benjamini–Hochberg false discovery rate (FDR) procedure.

Associations between age and hemodynamic parameters, including peripheral and central blood pressure, mean arterial pressure, heart rate, ejection duration, augmentation index, and pulse wave velocity (PWV), were evaluated using Spearman rank correlation. *P*-values from these age–hemodynamic correlations were also adjusted using the Benjamini–Hochberg FDR procedure.

The primary analysis evaluated associations between hemodynamic parameters and OCTA-derived vessel-density measures using partial Spearman correlation, adjusting for age and sex. Partial correlations were estimated using the ppcor package in R. To account for multiple testing, FDR adjustment was performed separately within each hemodynamic parameter, across all corresponding OCTA-derived vessel-density measures. Thus, each hemodynamic parameter constituted a separate multiple-testing family for the partial correlation analysis.

An FDR-adjusted $P < 0.05$ was considered statistically significant. Associations with nominal $P < 0.05$ that did not remain significant after FDR correction were considered nominal findings and were not interpreted as statistically significant.

Result

A total of 350 healthy adults were included, comprising 210 men (60.0%) and 140 women (40.0%). The mean age was 40.90 ± 7.19 years. Women were significantly younger than men (39.64 ± 6.87 vs. 41.74 ± 7.28 years, P = 0.007).

Sex-related differences were observed in several OCTA-derived vessel density parameters (Table 1). Women had significantly higher vessel density than men for both all-vessel (AV VD) and small-vessel (SV VD) measurements in the whole image and whole peripapillary region (all FDR-adjusted P < 0.001). Similarly, AV VD was significantly higher in women in both the superior and inferior peripapillary halves (both FDR-adjusted P < 0.001), and SV VD was also higher in women in both hemispheric regions (both FDR-adjusted P < 0.001).

Table 1
Sex differences in optical coherence tomography angiography (OCTA)–derived ONH microvascular density in healthy adults.

OCTA Parameter	Total (Mean ± SD)	Male (Mean ± SD)	Female (Mean ± SD)	Raw p	FDR-adjusted p
Whole Image – AV VD	56.49 ± 2.30	56.04 ± 2.29	57.15 ± 2.15	0.000	**0.000**
Whole Image – SV VD	50.17 ± 2.26	49.77 ± 2.29	50.78 ± 2.09	0.000	**0.000**
Inside Disc – AV VD	56.22 ± 4.11	55.92 ± 4.05	56.67 ± 4.17	0.097	0.109
Inside Disc – SV VD	46.05 ± 4.49	45.68 ± 4.39	46.61 ± 4.59	0.060	0.070
Whole Peripapillary – AV VD	59.36 ± 2.56	58.85 ± 2.59	60.12 ± 2.32	0.000	**0.000**
Whole Peripapillary – SV VD	53.22 ± 2.65	52.73 ± 2.68	53.97 ± 2.43	0.000	**0.000**
Peripapillary Superior Half – AV VD	59.95 ± 2.61	59.47 ± 2.56	60.67 ± 2.52	0.000	**0.000**
Peripapillary Inferior Half – AV VD	58.72 ± 2.79	58.19 ± 2.85	59.51 ± 2.50	0.000	**0.000**
Peripapillary Superior Hemi – SV VD	53.71 ± 2.74	53.22 ± 2.68	54.45 ± 2.68	0.000	**0.000**
Peripapillary Inferior Hemi – SV VD	52.69 ± 2.91	52.20 ± 2.96	53.43 ± 2.69	0.000	**0.000**
Peripapillary Nasal Superior – SV VD	50.68 ± 3.87	50.22 ± 3.58	51.38 ± 4.20	0.002	**0.002**
Peripapillary Nasal Inferior – SV VD	47.60 ± 4.45	47.04 ± 4.53	48.44 ± 4.21	0.003	**0.004**
Peripapillary Inferior Nasal – SV VD	52.50 ± 4.72	51.62 ± 4.73	53.83 ± 4.39	0.000	**0.000**
Peripapillary Inferior Temporal – SV VD	59.75 ± 3.48	59.22 ± 3.45	60.56 ± 3.37	0.000	**0.000**
Peripapillary Temporal Inferior – SV VD	52.90 ± 3.98	52.92 ± 3.91	52.87 ± 4.09	0.755	0.784
Peripapillary Temporal Superior – SV VD	56.33 ± 3.26	56.31 ± 3.17	56.34 ± 3.41	0.961	0.961
Peripapillary Superior Temporal – SV VD	57.12 ± 3.81	56.26 ± 3.95	58.40 ± 3.19	0.000	**0.000**
Peripapillary Superior Nasal – SV VD	51.96 ± 4.39	51.17 ± 4.30	53.15 ± 4.26	0.000	**0.000**

OCTA Parameter	Total (Mean ± SD)	Male (Mean ± SD)	Female (Mean ± SD)	Raw p	FDR-adjusted p
Grid Based AV VD – Superotemporal	53.22 ± 4.08	52.74 ± 3.92	53.94 ± 4.24	0.001	**0.002**
Grid Based AV VD – Temporal	60.35 ± 3.50	59.77 ± 3.60	61.21 ± 3.17	0.000	**0.000**
Grid Based AV VD – Inferotemporal	58.29 ± 3.22	57.57 ± 3.10	59.37 ± 3.10	0.000	**0.000**
Grid Based AV VD – Superior	52.54 ± 3.89	52.13 ± 3.84	53.14 ± 3.89	0.014	**0.019**
Grid Based AV VD – Central	57.58 ± 3.83	57.15 ± 3.89	58.23 ± 3.66	0.018	**0.023**
Grid Based AV VD – Inferior	55.52 ± 2.98	55.46 ± 2.96	55.62 ± 3.01	0.645	0.696
Grid Based AV VD – Superonasal	49.68 ± 4.23	49.39 ± 4.26	50.12 ± 4.15	0.050	0.062
Grid Based AV VD – Nasal	63.00 ± 3.63	62.48 ± 3.80	63.80 ± 3.22	0.001	**0.001**
Grid Based AV VD – Inferonasal	58.30 ± 3.34	57.80 ± 3.36	59.04 ± 3.20	0.000	**0.000**

Among the sectoral SV VD measurements, women demonstrated higher values in the nasal-superior, nasal-inferior, inferior-nasal, inferior-temporal, superior-temporal, and superior-nasal regions, with all differences remaining statistically significant after false discovery rate correction (FDR-adjusted $P \leq 0.004$). In contrast, no significant sex differences were observed for temporal-inferior or temporal-superior SV VD (FDR-adjusted $P = 0.784$ and 0.961, respectively). For the grid-based AV VD measurements, women had significantly higher values in the superotemporal, temporal, inferotemporal, superior, central, nasal, and inferonasal regions (FDR-adjusted P ranging from 0.002 to < 0.001). The inferior and superonasal grid regions did not differ significantly between sexes after FDR correction (FDR-adjusted $P = 0.696$ and 0.062, respectively). Inside-disc AV VD and SV VD also showed no statistically significant sex differences (FDR-adjusted $P = 0.109$ and 0.070, respectively).

Marked sex differences were also observed across the hemodynamic parameters (Table 2). Men had higher peripheral systolic and diastolic blood pressure, mean arterial pressure, central systolic and diastolic blood pressure, and pulse wave velocity than women (all FDR-adjusted $P < 0.001$). Conversely, women had higher heart rate and ejection duration than men (FDR-adjusted $P < 0.001$ and $P = 0.011$, respectively). Augmentation index was also significantly higher in women (FDR-adjusted $P < 0.001$).

Table 2
Sex differences in peripheral and central hemodynamic parameters in healthy adults

Hemodynamic Parameter	Total (Mean ± SD)	Male (Mean ± SD)	Female (Mean ± SD)	Raw p	FDR-adjusted p
Peripheral systolic BP	114.97 ± 10.58	118.02 ± 10.52	110.40 ± 8.90	< 0.001	**< 0.001**
Peripheral diastolic BP	71.31 ± 8.33	73.08 ± 8.73	68.66 ± 6.92	< 0.001	**< 0.001**
Mean arterial pressure	85.89 ± 8.64	88.08 ± 8.83	82.60 ± 7.22	< 0.001	**< 0.001**
Heart rate	66.46 ± 9.59	64.79 ± 9.70	68.97 ± 8.89	< 0.001	**< 0.001**
Ejection duration	335.01 ± 19.06	332.54 ± 18.68	338.73 ± 19.08	0.011	**0.011**
Pulse wave velocity	6.16 ± 1.46	6.44 ± 1.65	5.75 ± 1.00	< 0.001	**< 0.001**
Central systolic BP	119.71 ± 13.60	123.65 ± 13.44	113.80 ± 11.58	< 0.001	**< 0.001**
Central diastolic BP	78.29 ± 11.31	81.38 ± 11.30	73.66 ± 9.66	< 0.001	**< 0.001**
Augmentation index	127.08 ± 9.89	124.50 ± 9.24	130.95 ± 9.59	< 0.001	**< 0.001**

Age was positively correlated with several hemodynamic parameters (Table 3). Significant positive correlations were observed for peripheral systolic blood pressure (Spearman's ρ = 0.219, FDR-adjusted P = 0.0002), peripheral diastolic blood pressure (ρ = 0.198, P = 0.0003), and mean arterial pressure (ρ = 0.214, P = 0.0002). Pulse wave velocity was also positively correlated with age (ρ = 0.205, P = 0.0003). Among central hemodynamic measures, central systolic blood pressure showed a significant positive correlation with age (ρ = 0.192, P = 0.0005), whereas central diastolic blood pressure was not significantly associated with age (ρ = 0.063, P = 0.2384).

Table 3
Correlations between age and peripheral and central hemodynamic parameters in healthy adults

Peripheral and Central Hemodynamic Variables	Spearman_rho	Raw p	FDR-adjusted p
Peripheral systolic BP	0.219	< 0.001	0.0002
Peripheral diastolic BP	0.198	0.0002	0.0003
Central systolic BP	0.214	0.0001	0.0002
Central diastolic BP	-0.088	0.1003	0.1128
Mean arterial pressure	0.095	0.0754	0.0970
Heart Rate	0.205	0.0001	0.0003
Ejection Duration	0.192	0.0003	0.0005
Augmentation index	0.063	0.2384	0.2384
Pulse wave velocity	0.348	< 0.001	**< 0.001**

The strongest age-related association was observed for PWV (ρ = 0.348, FDR-adjusted P < 0.001). In contrast, no significant correlations were found between age and heart rate (ρ = −0.088, P = 0.1128) or ejection duration (ρ = 0.095, P = 0.0970) after FDR correction.

After adjustment for age and sex, none of the examined hemodynamic parameters showed a statistically significant association with OCTA-derived vessel density measures after false discovery rate (FDR) correction (Table 4). Overall, the observed partial correlations were small in magnitude, indicating limited evidence of an independent relationship between hemodynamic status and ONH microvascular density in this cohort.

Table 4
Partial correlations between hemodynamic parameters and OCTA-derived ONH microvascular density, adjusted for age and sex

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Whole Image – AV VD	-0.064	0.233	0.704
Whole Image – SV VD	0.011	0.834	0.900
Inside Disc – AV VD	-0.117	0.029	0.386
Inside Disc – SV VD	-0.062	0.245	0.704
Whole Peripapillary – AV VD	0.013	0.806	0.900
Whole Peripapillary – SV VD	0.081	0.131	0.684
Peripapillary Superior Half – AV VD	0.018	0.732	0.898
Peripapillary Inferior Half – AV VD	0.001	0.979	0.979
Peripapillary Superior Hemi – SV VD	0.077	0.154	0.684
Peripapillary Inferior Hemi – SV VD	0.072	0.177	0.684
Peripapillary Nasal Superior – SV VD	0.089	0.098	0.665
Peripapillary Nasal Inferior – SV VD	0.047	0.386	0.745
Peripapillary Inferior Nasal – SV VD	0.060	0.261	0.704
Peripapillary Inferior Temporal – SV VD	0.043	0.425	0.764
Peripapillary Temporal Inferior – SV VD	0.029	0.591	0.818
Peripapillary Temporal Superior – SV VD	0.003	0.956	0.979
Peripapillary Superior Temporal – SV VD	0.028	0.606	0.818
Peripapillary Superior Nasal – SV VD	0.052	0.335	0.745
Grid Based AV VD – Superotemporal	-0.144	0.007	0.191
Grid Based AV VD – Temporal	-0.030	0.576	0.818
Grid Based AV VD – Inferotemporal	-0.015	0.785	0.900
Grid Based AV VD – Superior	0.048	0.374	0.745
Grid Based AV VD – Central	-0.107	0.047	0.424
Grid Based AV VD – Inferior	0.040	0.455	0.768
Grid Based AV VD – Superonasal	-0.048	0.367	0.745

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Grid Based AV VD – Nasal	-0.025	0.647	0.832
Grid Based AV VD – Inferonasal	0.036	0.509	0.808
Peripheral diastolic BP			
Whole Image – AV VD	-0.066	0.222	0.931
Whole Image – SV VD	0.005	0.931	0.931
Inside Disc – AV VD	-0.073	0.173	0.931
Inside Disc – SV VD	-0.006	0.915	0.931
Whole Peripapillary – AV VD	-0.026	0.631	0.931
Whole Peripapillary – SV VD	0.038	0.481	0.931
Peripapillary Superior Half – AV VD	-0.017	0.753	0.931
Peripapillary Inferior Half – AV VD	-0.034	0.524	0.931
Peripapillary Superior Hemi – SV VD	0.037	0.488	0.931
Peripapillary Inferior Hemi – SV VD	0.039	0.469	0.931
Peripapillary Nasal Superior – SV VD	0.042	0.437	0.931
Peripapillary Nasal Inferior – SV VD	-0.005	0.930	0.931
Peripapillary Inferior Nasal – SV VD	0.087	0.107	0.852
Peripapillary Inferior Temporal – SV VD	0.044	0.415	0.931
Peripapillary Temporal Inferior – SV VD	-0.010	0.852	0.931
Peripapillary Temporal Superior – SV VD	0.012	0.821	0.931
Peripapillary Superior Temporal – SV VD	-0.007	0.895	0.931
Peripapillary Superior Nasal – SV VD	0.027	0.617	0.931
Grid Based AV VD – Superotemporal	-0.118	0.028	0.766
Grid Based AV VD – Temporal	0.007	0.902	0.931
Grid Based AV VD – Inferotemporal	-0.091	0.092	0.852
Grid Based AV VD – Superior	0.023	0.672	0.931
Grid Based AV VD – Central	-0.082	0.126	0.852
Grid Based AV VD – Inferior	0.026	0.633	0.931

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Grid Based AV VD – Superonasal	-0.047	0.378	0.931
Grid Based AV VD – Nasal	0.016	0.768	0.931
Grid Based AV VD – Inferonasal	-0.028	0.608	0.931
Mean arterial pressure			
Whole Image – AV VD	-0.068	0.208	0.822
Whole Image – SV VD	0.009	0.870	0.990
Inside Disc – AV VD	-0.104	0.053	0.538
Inside Disc – SV VD	-0.038	0.476	0.858
Whole Peripapillary – AV VD	-0.008	0.875	0.990
Whole Peripapillary – SV VD	0.060	0.265	0.822
Peripapillary Superior Half – AV VD	0.001	0.982	0.990
Peripapillary Inferior Half – AV VD	-0.021	0.702	0.990
Peripapillary Superior Hemi – SV VD	0.059	0.275	0.822
Peripapillary Inferior Hemi – SV VD	0.055	0.304	0.822
Peripapillary Nasal Superior – SV VD	0.069	0.196	0.822
Peripapillary Nasal Inferior – SV VD	0.021	0.691	0.990
Peripapillary Inferior Nasal – SV VD	0.080	0.134	0.822
Peripapillary Inferior Temporal – SV VD	0.049	0.362	0.846
Peripapillary Temporal Inferior – SV VD	0.003	0.953	0.990
Peripapillary Temporal Superior – SV VD	0.015	0.782	0.990
Peripapillary Superior Temporal – SV VD	0.006	0.908	0.990
Peripapillary Superior Nasal – SV VD	0.039	0.467	0.858
Grid Based AV VD – Superotemporal	-0.137	0.010	0.277
Grid Based AV VD – Temporal	-0.006	0.908	0.990
Grid Based AV VD – Inferotemporal	-0.061	0.256	0.822
Grid Based AV VD – Superior	0.041	0.446	0.858
Grid Based AV VD – Central	-0.101	0.060	0.538

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Grid Based AV VD – Inferior	0.031	0.560	0.946
Grid Based AV VD – Superonasal	-0.048	0.376	0.846
Grid Based AV VD – Nasal	0.002	0.978	0.990
Grid Based AV VD – Inferonasal	-0.001	0.990	0.990
Heart rate			
Whole Image – AV VD	-0.112	0.037	0.175
Whole Image – SV VD	-0.109	0.043	0.175
Inside Disc – AV VD	-0.033	0.540	0.730
Inside Disc – SV VD	-0.021	0.701	0.822
Whole Peripapillary – AV VD	-0.105	0.051	0.175
Whole Peripapillary – SV VD	-0.095	0.075	0.205
Peripapillary Superior Half – AV VD	-0.087	0.105	0.231
Peripapillary Inferior Half – AV VD	-0.118	0.028	0.175
Peripapillary Superior Hemi – SV VD	-0.086	0.111	0.231
Peripapillary Inferior Hemi – SV VD	-0.093	0.084	0.205
Peripapillary Nasal Superior – SV VD	-0.081	0.131	0.253
Peripapillary Nasal Inferior – SV VD	-0.104	0.052	0.175
Peripapillary Inferior Nasal – SV VD	-0.074	0.171	0.306
Peripapillary Inferior Temporal – SV VD	-0.030	0.576	0.740
Peripapillary Temporal Inferior – SV VD	-0.026	0.633	0.777
Peripapillary Temporal Superior – SV VD	-0.002	0.974	0.974
Peripapillary Superior Temporal – SV VD	-0.041	0.451	0.641
Peripapillary Superior Nasal – SV VD	-0.105	0.050	0.175
Grid Based AV VD – Superotemporal	-0.117	0.029	0.175
Grid Based AV VD – Temporal	-0.054	0.319	0.478
Grid Based AV VD – Inferotemporal	-0.072	0.181	0.306
Grid Based AV VD – Superior	-0.067	0.213	0.338

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Grid Based AV VD – Central	-0.016	0.767	0.829
Grid Based AV VD – Inferior	0.013	0.810	0.841
Grid Based AV VD – Superonasal	-0.095	0.077	0.205
Grid Based AV VD – Nasal	-0.115	0.032	0.175
Grid Based AV VD – Inferonasal	-0.019	0.731	0.822
Ejection duration			
Whole Image – AV VD	0.071	0.188	0.797
Whole Image – SV VD	0.060	0.266	0.797
Inside Disc – AV VD	-0.022	0.682	0.830
Inside Disc – SV VD	-0.025	0.648	0.830
Whole Peripapillary – AV VD	0.062	0.249	0.797
Whole Peripapillary – SV VD	0.040	0.455	0.830
Peripapillary Superior Half – AV VD	0.043	0.426	0.830
Peripapillary Inferior Half – AV VD	0.074	0.168	0.797
Peripapillary Superior Hemi – SV VD	0.006	0.908	0.908
Peripapillary Inferior Hemi – SV VD	0.062	0.252	0.797
Peripapillary Nasal Superior – SV VD	0.030	0.583	0.830
Peripapillary Nasal Inferior – SV VD	0.022	0.678	0.830
Peripapillary Inferior Nasal – SV VD	0.102	0.057	0.797
Peripapillary Inferior Temporal – SV VD	0.045	0.400	0.830
Peripapillary Temporal Inferior – SV VD	0.019	0.725	0.830
Peripapillary Temporal Superior – SV VD	-0.013	0.812	0.843
Peripapillary Superior Temporal – SV VD	-0.017	0.746	0.830
Peripapillary Superior Nasal – SV VD	0.016	0.766	0.830
Grid Based AV VD – Superotemporal	0.098	0.069	0.797
Grid Based AV VD – Temporal	0.051	0.347	0.830
Grid Based AV VD – Inferotemporal	0.039	0.468	0.830

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Grid Based AV VD – Superior	0.030	0.582	0.830
Grid Based AV VD – Central	-0.022	0.680	0.830
Grid Based AV VD – Inferior	-0.034	0.526	0.830
Grid Based AV VD – Superonasal	0.083	0.122	0.797
Grid Based AV VD – Nasal	0.083	0.121	0.797
Grid Based AV VD – Inferonasal	-0.016	0.768	0.830
Pulse wave velocity			
Whole Image – AV VD	-0.040	0.456	0.919
Whole Image – SV VD	0.003	0.949	0.985
Inside Disc – AV VD	0.039	0.472	0.919
Inside Disc – SV VD	0.031	0.570	0.919
Whole Peripapillary – AV VD	0.001	0.992	0.992
Whole Peripapillary – SV VD	0.058	0.277	0.919
Peripapillary Superior Half – AV VD	0.022	0.686	0.919
Peripapillary Inferior Half – AV VD	-0.015	0.775	0.919
Peripapillary Superior Hemi – SV VD	0.074	0.166	0.919
Peripapillary Inferior Hemi – SV VD	0.040	0.458	0.919
Peripapillary Nasal Superior – SV VD	0.022	0.681	0.919
Peripapillary Nasal Inferior – SV VD	0.042	0.440	0.919
Peripapillary Inferior Nasal – SV VD	-0.009	0.872	0.941
Peripapillary Inferior Temporal – SV VD	0.038	0.475	0.919
Peripapillary Temporal Inferior – SV VD	0.074	0.168	0.919
Peripapillary Temporal Superior – SV VD	0.095	0.076	0.919
Peripapillary Superior Temporal – SV VD	0.035	0.516	0.919
Peripapillary Superior Nasal – SV VD	0.052	0.335	0.919
Grid Based AV VD – Superotemporal	-0.124	0.021	0.564
Grid Based AV VD – Temporal	-0.065	0.223	0.919

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Grid Based AV VD – Inferotemporal	-0.010	0.852	0.941
Grid Based AV VD – Superior	0.023	0.665	0.919
Grid Based AV VD – Central	0.015	0.783	0.919
Grid Based AV VD – Inferior	0.045	0.404	0.919
Grid Based AV VD – Superonasal	-0.015	0.779	0.919
Grid Based AV VD – Nasal	-0.020	0.713	0.919
Grid Based AV VD – Inferonasal	0.033	0.541	0.919
Central systolic BP			
Whole Image – AV VD	0.023	0.663	0.746
Whole Image – SV VD	0.081	0.133	0.476
Inside Disc – AV VD	-0.014	0.796	0.827
Inside Disc – SV VD	0.029	0.587	0.721
Whole Peripapillary – AV VD	0.058	0.278	0.496
Whole Peripapillary – SV VD	0.108	0.045	0.476
Peripapillary Superior Half – AV VD	0.065	0.227	0.496
Peripapillary Inferior Half – AV VD	0.040	0.458	0.681
Peripapillary Superior Hemi – SV VD	0.099	0.064	0.476
Peripapillary Inferior Hemi – SV VD	0.095	0.075	0.476
Peripapillary Nasal Superior – SV VD	0.063	0.243	0.496
Peripapillary Nasal Inferior – SV VD	0.035	0.513	0.693
Peripapillary Inferior Nasal – SV VD	0.076	0.159	0.476
Peripapillary Inferior Temporal – SV VD	0.097	0.069	0.476
Peripapillary Temporal Inferior – SV VD	0.038	0.479	0.681
Peripapillary Temporal Superior – SV VD	0.059	0.273	0.496
Peripapillary Superior Temporal – SV VD	0.078	0.145	0.476
Peripapillary Superior Nasal – SV VD	0.059	0.276	0.496
Grid Based AV VD – Superotemporal	-0.077	0.154	0.476

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Grid Based AV VD – Temporal	0.047	0.381	0.604
Grid Based AV VD – Inferotemporal	0.057	0.293	0.496
Grid Based AV VD – Superior	0.015	0.779	0.827
Grid Based AV VD – Central	0.000	0.996	0.996
Grid Based AV VD – Inferior	0.082	0.125	0.476
Grid Based AV VD – Superonasal	-0.025	0.636	0.746
Grid Based AV VD – Nasal	0.033	0.545	0.701
Grid Based AV VD – Inferonasal	0.056	0.294	0.496
Central diastolic BP			
Whole Image – AV VD	-0.021	0.691	0.918
Whole Image – SV VD	0.040	0.453	0.918
Inside Disc – AV VD	-0.026	0.623	0.918
Inside Disc – SV VD	0.019	0.729	0.918
Whole Peripapillary – AV VD	0.014	0.801	0.918
Whole Peripapillary – SV VD	0.068	0.204	0.868
Peripapillary Superior Half – AV VD	0.028	0.608	0.918
Peripapillary Inferior Half – AV VD	-0.008	0.880	0.931
Peripapillary Superior Hemi – SV VD	0.066	0.220	0.868
Peripapillary Inferior Hemi – SV VD	0.061	0.257	0.868
Peripapillary Nasal Superior – SV VD	0.036	0.507	0.918
Peripapillary Nasal Inferior – SV VD	0.006	0.911	0.931
Peripapillary Inferior Nasal – SV VD	0.050	0.350	0.918
Peripapillary Inferior Temporal – SV VD	0.083	0.124	0.868
Peripapillary Temporal Inferior – SV VD	0.016	0.772	0.918
Peripapillary Temporal Superior – SV VD	0.064	0.234	0.868
Peripapillary Superior Temporal – SV VD	0.024	0.657	0.918
Peripapillary Superior Nasal – SV VD	0.034	0.530	0.918

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Grid Based AV VD – Superotemporal	-0.104	0.053	0.868
Grid Based AV VD – Temporal	-0.013	0.816	0.918
Grid Based AV VD – Inferotemporal	0.022	0.682	0.918
Grid Based AV VD – Superior	-0.025	0.639	0.918
Grid Based AV VD – Central	-0.015	0.773	0.918
Grid Based AV VD – Inferior	0.084	0.119	0.868
Grid Based AV VD – Superonasal	-0.073	0.173	0.868
Grid Based AV VD – Nasal	0.005	0.931	0.931
Grid Based AV VD – Inferonasal	0.045	0.403	0.918
Augmentation index			
Whole Image – AV VD	0.025	0.642	0.964
Whole Image – SV VD	0.026	0.626	0.964
Inside Disc – AV VD	0.069	0.200	0.964
Inside Disc – SV VD	0.039	0.472	0.964
Whole Peripapillary – AV VD	0.001	0.982	0.982
Whole Peripapillary – SV VD	-0.011	0.837	0.964
Peripapillary Superior Half – AV VD	-0.024	0.656	0.964
Peripapillary Inferior Half – AV VD	0.026	0.625	0.964
Peripapillary Superior Hemi – SV VD	-0.037	0.492	0.964
Peripapillary Inferior Hemi – SV VD	0.005	0.928	0.964
Peripapillary Nasal Superior – SV VD	0.008	0.889	0.964
Peripapillary Nasal Inferior – SV VD	0.034	0.521	0.964
Peripapillary Inferior Nasal – SV VD	0.008	0.880	0.964
Peripapillary Inferior Temporal – SV VD	-0.014	0.795	0.964
Peripapillary Temporal Inferior – SV VD	-0.082	0.128	0.964
Peripapillary Temporal Superior – SV VD	-0.128	0.017	0.466
Peripapillary Superior Temporal – SV VD	-0.057	0.290	0.964

	Partial ρ	Raw P	FDR-adjusted P
Peripheral systolic BP			
Peripapillary Superior Nasal – SV VD	0.014	0.792	0.964
Grid Based AV VD – Superotemporal	0.062	0.249	0.964
Grid Based AV VD – Temporal	0.006	0.913	0.964
Grid Based AV VD – Inferotemporal	-0.027	0.616	0.964
Grid Based AV VD – Superior	0.012	0.821	0.964
Grid Based AV VD – Central	0.041	0.449	0.964
Grid Based AV VD – Inferior	-0.047	0.383	0.964
Grid Based AV VD – Superonasal	0.061	0.257	0.964
Grid Based AV VD – Nasal	0.034	0.525	0.964
Grid Based AV VD – Inferonasal	-0.079	0.143	0.964

For peripheral systolic blood pressure, the strongest associations were observed with Inside Disc–AV VD (partial ρ = −0.117, FDR-adjusted P = 0.386) and Grid Based AV VD–Superotemporal (partial ρ = −0.144, FDR-adjusted P = 0.191); neither remained significant after FDR correction. Similarly, no significant associations were observed for peripheral diastolic blood pressure or mean arterial pressure across the examined OCTA parameters.

Heart rate showed generally weak inverse correlations with several OCTA measures, including Whole Image–AV VD (partial ρ = −0.112) and Peripapillary Inferior Half–AV VD (partial ρ = −0.118), but these associations did not remain significant after FDR correction (both FDR-adjusted P = 0.175). Ejection duration was not significantly associated with any OCTA-derived vessel-density parameter.

Pulse wave velocity likewise showed no significant associations with ONH microvascular density after FDR correction, with partial correlations generally close to zero. Central systolic and central diastolic blood pressure also showed no significant associations with any OCTA parameter after correction. Finally, augmentation index was not significantly related to OCTA-derived vessel density; although a nominal association was observed with Peripapillary Temporal Superior–SV VD (partial ρ = −0.128, raw P = 0.017), this did not remain significant after FDR correction (FDR-adjusted P = 0.466).

Discussion

In this cross-sectional study of healthy adults, ONH microvascular density showed clear sex-related differences, whereas systemic hemodynamic parameters were not independently associated with ONH vessel density after adjustment for age and sex and correction for multiple comparisons. Women

generally had higher vessel density across most peripapillary regions, while men had higher peripheral and central blood pressure and PWV. Age was positively associated with several hemodynamic measures, most strongly with PWV. Together, these findings suggest that demographic characteristics may contribute more consistently to physiological variation in ONH microvascular density than resting systemic hemodynamic status in healthy adults.

Women demonstrated higher all-vessel and small-vessel density across most peripapillary regions, consistent with previous OCTA studies reporting sex-related differences in retinal and peripapillary vascular measurements(11–13). Sex-related vascular and hormonal mechanisms may contribute to this pattern, as estrogen has been associated with vasodilatory effects and modulation of ocular vascular resistance(15–18). However, because hormonal status was not assessed in the present study, this mechanism remains speculative. The regional variability in sex differences further suggests that these effects may not be spatially uniform across the ONH microvasculature.

The observed sex-related differences in systemic hemodynamics were broadly consistent with established cardiovascular physiology. Men had higher peripheral and central blood pressure and PWV, whereas women had higher heart rate, ejection duration, and augmentation index. The higher augmentation index in women is consistent with previous reports and may partly reflect differences in body size and pulse-wave reflection rather than greater arterial stiffness per se(18, 19). Age was positively associated with peripheral systolic and diastolic BP, central systolic BP, heart rate, ejection duration, and PWV, with the strongest association observed for PWV ($\rho = 0.348$, FDR-adjusted $P < 0.001$), consistent with age-related increases in arterial stiffness.

Age was positively associated with peripheral systolic and diastolic blood pressure, central systolic blood pressure, heart rate, ejection duration, and PWV after FDR correction. The strongest association was observed between age and PWV ($\rho = 0.348$, FDR-adjusted $P < 0.001$), consistent with the progressive increase in arterial stiffness that accompanies vascular aging. The positive associations of age with peripheral and central systolic blood pressure and with PWV further demonstrate the expected age-related changes in systemic vascular properties in our cohort. In contrast, central diastolic blood pressure, mean arterial pressure, and augmentation index were not significantly associated with age after FDR correction. These findings highlight that different hemodynamic indices capture distinct components of vascular physiology and do not necessarily exhibit identical age-related trajectories.

The principal finding was the absence of robust independent associations between systemic hemodynamic parameters and ONH vessel density after adjustment for age and sex. One possible explanation is the autoregulatory capacity of the retinal and ONH circulation, in which local myogenic, metabolic, and endothelial mechanisms help maintain vascular perfusion despite physiological changes in systemic pressure(20–22). Such autoregulatory buffering could attenuate the relationship between resting systemic hemodynamic variation and OCTA-derived vessel density in individuals without overt vascular disease. Importantly, our findings do not establish the absence of such a relationship, but

indicate that no robust association was detectable within the physiological range represented in this healthy cohort.

These findings also provide context for previous studies reporting associations between arterial stiffness, blood pressure, and retinal vascular parameters in populations with diabetes, hypertension, or retinal vascular disease (7–9). Disease-related endothelial dysfunction, vascular remodeling, and impaired autoregulation may increase the coupling between systemic vascular abnormalities and ocular microvascular changes. Conversely, findings from our group's previous macular OCTA study in the same source population showed associations between selected hemodynamic parameters and specific macular vessel-density measures, but not consistently across all regions(14). Together, these observations raise the possibility that systemic hemodynamic influences on the ocular microcirculation are both disease- and region-dependent.

From a clinical and research perspective, these findings suggest that age and sex should be carefully considered when interpreting ONH vessel-density measurements in healthy populations. In contrast, resting blood pressure, PWV, and related hemodynamic measures did not demonstrate consistent independent associations with ONH vessel density in this cohort. Thus, ONH OCTA measurements should not be assumed to represent direct surrogates of systemic hemodynamic status in healthy adults.

This study has several strengths, including comprehensive assessment of ONH vessel density across multiple anatomical regions, simultaneous evaluation of peripheral and central hemodynamic parameters, adjustment for age and sex, and systematic FDR correction for multiple comparisons. Limitations include the cross-sectional design, single-time-point hemodynamic measurements, and recruitment from a single population. Hormonal status was not assessed, limiting interpretation of the observed sex differences, and subclinical vascular abnormalities cannot be completely excluded despite the healthy study population.

In conclusion, sex and age were important sources of variation in ONH microvascular density and systemic hemodynamic characteristics, whereas no robust independent association between systemic hemodynamics and ONH vessel density was detected in healthy adults after adjustment for age, sex, and multiple comparisons. These findings highlight the importance of demographic normalization of ONH OCTA measurements and suggest that the relationship between systemic hemodynamics and ocular microvascular density may become more evident in the presence of vascular disease or impaired autoregulation.

Declarations

Competing interests:

The authors declare that they have no competing interests.

Consent for publication:

Consent for publication was obtained from patients.

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Author Contribution

M.A., S.M.H. conceptualized and designed the study. M.A., S.M.H., G.Z., Z.M., M.Ab., and M.M.S. were responsible for data acquisition and clinical assessments. N.A.S, M.T.S. and N.Sa. performed the statistical analysis and contributed to data interpretation. M.R.H. and M.Ak. contributed to data curation and quality control. S.E. contributed to study methodology, data interpretation, and critical revision of the manuscript. N.A.S., M.A., and M.M.S. wrote the main manuscript text. All authors reviewed and approved the final manuscript.

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Data Availability

The datasets used during the current study are available from the corresponding author upon reasonable request.

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