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Investigating the retinal deep capillary plexus in hypertensive patients and ischemic stroke and healthy people

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Abstract

Introduction: Microvascular damage is one of the major complications of hypertension. Capillary rarefaction is a well-known complication of hypertension end-organ damage. It causes a higher risk for systemic diseases such as stroke and cardiovascular accidents. The present study investigates the retinal deep capillary plexus in hypertensive patients and ischemic stroke and healthy people.

Materials and Methods: In this study, the patients who suffered from vascular accidents in ischemic stroke patients and were identified by a neurologist (people over 50 years old and had an ischemic stroke in the past 6 months and had an examination and imaging and confirmed by a neurologist), and the hypertensive patients (blood pressure of 140 on 90 mm Hg or a history of using hypertensive drugs) who were identified and referred by internal specialists or cardiologists, and a group of healthy people in the same age group were included into the study. For further investigation and evaluation, OCTA and enface OCT were performed with an Optoview device.

Results: According to the results, no significant relationship was observed between the three groups regarding gender. However, a significant relationship was reported between them regarding age. In addition, there was a statistically significant relationship between three groups of hypertensive patients and ischemic stroke and healthy people only in visual acuity parameters including BCVA2 and LogmAR1. However, no statistically significant relationship was observed between BCVA1 and LogmAR2, and central retinal thickness. No significant difference was observed among the three groups in the capillary plexus density.

Conclusion: The results indicated that hypertension and stroke diseases cause changes in a limited number of visual parameters of the retinal deep capillary plexus measured by OCTA.

Keywords: retinal deep capillary plexus, hypertension, ischemic stroke

Introduction

Paracentral acute medullary maculopathy (PAMM) is an OCT finding seen in patients with retinal capillary ischemia and persistent non-specific scotomas. PAMM is a separate phenomenon or a complex feature and is the primary cause of retinal vasculopathy or systemic disease (1). PAMM is a descriptive diagnosis indicating a spectrum of possible ischemic maculopathies characterized by hyperreflectivity of the inner layers of the retina. PAMM was first described by Sarraf et al. in 2013 in a small case of patients with acute scotoma, parafoveal gray-white lesions, and the location of these lesions in the middle layer of the retina in SD-OCT. These three features are still the characteristics of the condition (2).

Patients with PAMM mostly face a sudden onset of central or paracentral scotoma, which may not be resolved. These may decrease with mild to moderate vision. There are mostly minimal other ocular signs and symptoms. Funduscopic examination may show parafoveal areas of gray-white retinal discoloration, although some cases lack any fundus abnormalities (3) PAMM may also be observed in cases of retinal vascular occlusion with embolism along retinal arterial branches (3). PAMM has been described in patients with systemic cardiovascular risk factors or associated with other retinal pathologies, including retinal vascular occlusion, diabetic retinopathy, retinal vasculitis, and sickle cell retinopathy. Hypercoagulability and hypertension are also risk factors. However, some cases without identifiable underlying vascular disease have also been described (4).

Several studies have indicated that areas of PAMM-like inner retinal atrophy are commonly seen even in healthy patients, hypertensive patients, or retinal vein occlusion in the contralateral eye (2, 5). There is currently no cure for PAMM. Symptomatic scotoma may fade but is mostly persistent. Since these lesions are often associated with other vasculopathy diseases, it is crucial to screen patients presenting with PAMM for local and systemic diseases, including retinal vessel occlusion, carotid artery disease, diabetes, hypertension, and GCA or other vasculitides. Management should focus on identifying and minimizing vascular risk factors. Careful monitoring at follow-up is also vital since diffuse PAMM lesions can hide more vision-threatening occult retinal occlusions (6).

Optical coherence angiography (OCTA) is a non-invasive imaging technique known as optical coherence tomography (OCT) used to visualize vascular plexus in the human retina (7), (8), and (9) and skin choroid (10) (11). It is hoped that it will be useful in the future for diagnosing diabetic retinopathy with more work (12). Recent advances in OCT speed have enabled the sampling density required to achieve enough resolution for OCTA (13) (14). This has caused OCTA to be used clinically in diagnosing various ophthalmic diseases, including age-related macular degeneration (AMD), diabetic retinopathy, arteriovenous occlusion, and glaucoma. Recent studies have indicated that changes in retinal capillary levels occur in people with hypertension and ischemic stroke (15)

OCTA allows noninvasive imaging of retinal capillaries in multiple layers not visible on fundus images assuming that the retinal vasculature mirrors the cerebral vasculature. Based on fundus photographs, retinal abnormalities, including arteriovenous tearing, and generalized and localized arteriovenous thinning, lower arterial/venous diameter ratio, and geometric parameters are significantly associated with stroke (16). In addition, poorly controlled BP, high ambulatory BP, and estimated glomerular filtration rate or eGFR are associated with reduced DVP capillary density, indicating that systemic risk factors can lead to retinal microcirculatory changes in the capillary plexus of hypertensive patients. This is consistent with what has been previously published for the larger retinal vasculature that indicates an association between retinal arterial narrowing and elevated BP levels (17–18) and renal dysfunction (19, 20). In addition, people with primary diabetes have shown capillary rarefaction compared to healthy people (21). The mechanism of association between retinal capillary density and systemic hypertension is unclear based on the current data. However, people with chronic hypertension may develop atherosclerosis over time, where the vessels narrow with age, leading to increased resistance to blood flow and loss of retinal vascular autoregulation (22). This study investigates vascular diseases that have not been examined so far. In light of conducting this study, we can gain more knowledge about other vascular accidents in people with ischemic stroke and hypertension and its effects on the retinal deep capillary plexus.

Based on the results of the study, we can know if it can be used as a prognostic factor or an exacerbating factor in vascular diseases, and even if it can be used to slow down or prevent progression or not. Since studies have been conducted on retinal vascular diseases and their findings in OCTA, we addressed this issue on blood pressure and ischemic stroke and its findings to see if there is an association between the defects of the retinal deep capillary plexus and blood pressure and ischemic stroke. We also find if it can be used as a prognostic factor to follow up patients for the treatment and progress of their disease. In summary, in light of conducting this study and investigating the effects of blood pressure on the retinal deep capillary plexus, it is possible to achieve prognostic and descriptive findings by performing non-invasive OCTA and enface OCT tests (23).

Materials and Methods

In this study, the patients who suffered from vascular accidents in ischemic stroke patients and were identified by a neurologist (people over 50 years of age, had an ischemic stroke in the past 6 months, had an examination and imaging, and confirmed by a neurologist) and the hypertensive patients (blood pressure of 140/90 mmHg or a history of using blood pressure medications) who were identified and referred by internal specialists or cardiologists, and a group of healthy people in the same age group were included. The patients were examined and visited by an ophthalmologist before imaging for appropriate screening and removing the confounding factors. They were examined by taking a complete medical history and a questionnaire, including demographic information and the history of underlying diseases such as hypertension, diabetes, high cholesterol, heart ischemic condition, history of surgeries, especially eye surgeries, smoking status, history of drug use, and laboratory tests. They were also examined with a slit lamp in the anterior segment and with a lens 90 in the posterior segment with dilated pupils. In these examinations, people who have a history of retinal surgery, including vitrectomy, and those who have diabetic retinopathy, a history of retinal and vitreous bleeding, and a history of arterial and venous blockages, including ocular, macular scar, and macular hole, and a history of glaucoma or a high cup-to-disc ratio, or under the age of 50 or did not have the physical and mental tolerance to perform the examinations were excluded from the study. Based on these criteria, the selected subjects were selected for further examination and evaluation of OCTA and enface OCT cross-sectional using the Optoview device. They were examined to know whether there is an association between retinal capillary plexus defects and ischemic stroke and blood pressure. To compare the three groups in the quantitative variable, a one-way analysis of variance was used, to compare the qualitative B-rank variables, Kruskal-Wallis was used, and for the nominal qualitative variables, chi-square was used. All of the analyses were performed in SPSS-25 software. The significance level was considered to be 5%. Permission was obtained from the Research Deputy and Ethical Committee of Jundishapur University of Medical Sciences, Ahvaz.

Results

Table (1) shows the frequency and percentage of the gender variable in the three studied groups. The relationship between the three groups was evaluated using the chi-square method. As seen, the three investigated groups are homogeneous regarding the gender variable. There is a significant difference between the three groups regarding the age.

Table 1: Frequency and frequency percentage of gender and age variables in the three studied groups

Classification	Stroke		Hypertension		Healthy		P-value
	Frequency	frequency percentage	Frequency	frequency percentage	Frequency	frequency percentage	
Female	10	35.7	16	57.1	20	71.4	0.06
Male	18	64.3	12	42.9	8	28.6	
Age	59.67	7.98	57.71	5.80	53.50	4.04	0.01

Table 2- The frequency and frequency percentage of BCVA1 in the three groups

BCVA 1	Stroke		Hypertension		Healthy		P-value
	Frequency	frequency percentage	Frequency	frequency percentage	Frequency	frequency percentage	
20.20	14	50.0%	16	57.1%	14	50.0%	0.07
20.25	4	14.3%	9	32.1%	11	39.3%	
20.30	4	14.3%	3	10.7%	3	10.7%	
20.40	1	3.6%	0	0	0	0	
20.50	4	14.3%	0	0	0	0	
20.60	1	3.6%	0	0	0	0	

Table 2 shows the frequency and frequency percentage of the BCVA1 variable in the three studied groups. The relationship between the three groups was evaluated using Fisher's test. As seen, there is no significant relationship between the three studied groups regarding the BCVA1 variable.

Table 3: Frequency and frequency percentage of BCVA2 in the three studied groups

P-value	Healthy		Hypertension		Stroke		BCVA 2
	frequency percentage	Frequency	frequency percentage	Frequency	frequency percentage	Frequency	
0.02	0	0	0	0	7.1%	2	20.20
	60.7%	17	57.1%	16	50.0%	14	25.20
	28.6%	8	32.1%	9	7.1%	2	20.30
	10.7%	3	10.7%	3	10.7%	3	40.20
	0	0	0	0	10.7%	3	50.20
	0	0	0	0	10.7%	3	60.20

Table 3 shows the frequency and frequency percentage of the BCVA2 variable in the three studied groups. The relationship between the three groups was evaluated using the chi-square method. As seen, there is a significant relationship between the three studied groups in the BCVA2 variable.

Table 4: The mean and SD of LogmAR1 in three groups

Variable	LogmAR1		P-value
	Mean	SD	
Stroke	0.12	0.16	0.002
Hypertension	0.02	0.04	
Healthy	05	0.06	

Table (4) shows the mean and SD of LogmAR1 in three groups using a one-way analysis of variance. As seen, there is a significant difference between age and the three groups.

Table 5: Pairwise comparisons between the studied groups regarding LogmAR1

	Group	LogmAR1		P-value
		Mean difference	SD	
Stroke	Hypertension	.10071*	.02769	.000
	Healthy	.06643*	.02769	.019
Hypertension	Stroke	-.10071*	.02769	.000
	Healthy	-.03429	.02769	.219
Healthy	Stroke	-.06643*	.02769	.019
	Hypertension	.03429	.02769	.219

Table 5 shows the pairwise comparisons of stroke, hypertension, and healthy groups regarding LogmAR1 using LSD test.

Table 6: Correlation mean and SD of LogmAR2 in three groups

P-value	LogmAR2		Variable
	SD	Mean	
0.40	.21664	.1529	Stroke
	3.38891	.7100	Hypertension
	.06471	.0479	Healthy

Table 6 presents the mean and SD of LogmAR2 in three groups using a one-way analysis of variance. As seen, there is no significant difference between the three groups regarding LogmAR2.

Table 7- The mean and SD of central retinal thickness 1 in three groups

P-value	central retinal thickness		Variable	
	SD	Mean		
0.18	16.23	249.71	Stroke	central retinal thickness 1
	21.19	247.75	Hypertension	
	15.55	241.25	Healthy	
0.22	30.82	252.71	Stroke	Central retinal thickness 2
	24.75	246.85	Hypertension	
	15.41	241.35	Healthy	

As shown in Table 7, a one-way analysis of variance was used to examine the central retinal thickness in three groups. As seen, there is no significant difference between the three groups regarding the central retinal thickness 1. As shown in Table 9-4, One-way analysis of variance was used to examine the central retinal thickness 2 in three groups. As seen, there is no significant difference between the three groups regarding the central retinal thickness 2.

Table 8: Investigating the density thickness of capillary plexus 1 and capillary plexus 2 in three groups

	Variable	capillary plexus density 1		P-value
		Mean	SD	
density thickness of capillary plexus 1	Stroke	49.4436	4.34332	0.64
	Hypertension	50.2036	4.58596	
	Healthy	49.0693	4.79534	
density thickness of capillary plexus 2	Stroke	49.7796	4.09506	0.54
	Hypertension	49.3496	4.17447	
	Healthy	48.6318	3.40739	

As shown in Table 8, a one-way analysis of variance was used to investigate the capillary plexus density in three groups. As seen, there is no significant difference between the three groups regarding capillary plexus density. As shown in 11-4, a one-way analysis of variance was used to investigate the capillary plexus density in three groups. As seen, there is no significant difference between the three groups regarding the capillary plexus density.

	Group	capillary plexus density 1		P-value
		Mean difference	SD	
Stroke	Hypertension	-.76000	1.22368	.536
	Healthy	.37429	1.22368	.760
Hypertension	Stroke	.76000	1.22368	.536
	Healthy	1.13429	1.22368	.357
Healthy	Stroke	-.37429	1.22368	.760
	Hypertension	-1.13429	1.22368	.357

	Group	capillary plexus density 1		P-value
		Mean difference	SD	
Stroke	Hypertension	.43000	1.04433	.682
	Healthy	1.14786	1.04433	.275
Hypertension	Stroke	-.43000	1.04433	.682
	Healthy	.71786	1.04433	.494
Healthy	Stroke	-1.14786	1.04433	.275
	Hypertension	-.71786	1.04433	.494

Discussion

The results revealed a statistically significant relationship between three groups of hypertensive patients and ischemic stroke and healthy people only in terms of visual acuity parameters, including BCVA2 and LogmAR1. However, no statistically significant relationship was observed between BCVA1 and LogmAR2, and central retinal thickness. Other results of the present study revealed no significant difference between the three groups in capillary plexus density. The study by Liu et al. (2021) investigated the retinal microvascular characteristics of 189 stroke patients and 195 controls in a hospital in China. The macular vascular density (VD) in the superficial capillary plexus (SCP), deep capillary plexus (DCP), foveal avascular zone (FAZ) criteria, and optic disc VD were measured by OCTA. Their results indicated that after adjusting for gender, visual acuity, systolic and diastolic blood pressure, history of smoking, hemoglobin (HbA1c), cholesterol, and high-density lipoprotein (HDL), macular VD from SCP and DCP decreased in all parts (24). Past studies have reported an association between stroke and retinal microvascular lesions such as narrower arterial caliber, arteriovenous perforation, and wider venous caliber (25). These studies indicated that retinal vascular abnormalities in stroke patients may be associated with systemic risk factors such as hypertension. Past studies also reported hypertensive-induced cerebral vascular remodeling leading to hypoperfusion and exacerbation of brain ischemia (26). In the retina, similar pathological changes may also be present in hypertensive patients. It has been shown that retinal vascular morphology is altered in hypertension since it has been observed that retinal VD decreases in hypertensive patients.

Zhang et al. (2020) investigated vascular unit disorders in patients with large artery atherosclerosis (LAA) or small artery occlusion (SAA) and control subjects in twenty-eight LAA patients, forty-one SAA patients, and sixty and five control groups who were of the same age and gender. The results showed that the thickness of the upper peripapillary retinal nerve fiber layer (pRNFL) was different among the three groups and the LAA group had the thinnest thickness. Compared to the control group, the density of retinal deep capillary vessels in the other two stroke subgroups was significantly reduced in all parts except the lower parts. Compared with the superficial microvascular plexus, the deep capillary plexus is more sensitive to ischemic stroke. Differences in upper quadrant pRNFL thickness between stroke subtypes may indicate that changes in the retinal nerve fiber layer are more sensitive to subtype identification than changes in retinal microvascular structure (28).

A high prevalence of vision problems in stroke patients has been reported (29). Vision problems include reduced central visual acuity, reduced visual field, eye movement disorders, visual perception disorders, etc., leading to ischemic and hypoxic damage to the brain tissue. In addition, retinal hypoperfusion, especially in the DCP layer, can reduce BCVA. The retinal deep capillary plexus is predominantly lined by pericytes that are sensitive to hypoxia secondary to hypoperfusion (30). In addition, DCP capillaries are vital for feeding and supporting oxygen to the inner nuclear layer (INL) and outer plexiform layer (OPL), where photoreceptor axon terminals form ribbon synapses with bipolar cells and horizontal cells (31). The retina is a very metabolically active tissue. It is one of the tissues that consumes the most oxygen in our body. Thus, the retina is very sensitive to hypoperfusion and hypoxia. It has been found that Retinal VD is reduced in hypertension, coronary heart disease, and congenital heart disease (32).

Recent studies have indicated that the integration of all OCTA parameters and important stroke risk factors can provide a good identification of stroke. A recent study showed that OCTA parameters in the stroke group are not related to the time interval between stroke attacks (first and last attacks), and OCTA examination. OCTA parameters were also not significantly different between stroke patients with a shorter time interval and patients with a longer time interval (24). HTNR is one of the markers of target organ damage in the initial evaluation of HTN patients, and the degree of HTNR is associated with mortality. Thus, it is clinically vital to evaluate retinal changes in HTN patients.

In a case-control study by Sun et al. (2020), retinal vascular parameters were measured in all eyes using OCTA on 94 participants with systemic hypertension and 46 normal control eyes from Singaporean Chinese. The results of multivariate analysis with adjustment of confounding factors showed that compared to the control group, the eyes of hypertensive patients decreased in VD [OR 0.02; 95% CI, 0 to 0.64; P 0.027] and DCP [OR 0.03; 95% CI, 0 to 0.41; P 0.009]. The results also showed an increase in the FAZ area (33). Studies using laser Doppler flowmetry scans have indicated an increase in retinal vascular resistance and a reduction in retinal capillary density in hypertensive patients compared to people with normal blood pressure (34, 35). In a study by Dupas et al., they found that vessel density in DVP was less affected compared to SCP in patients with diabetic retinopathy and type 1 diabetes.

Several other studies have provided similar results in type 1 and 2 diabetes. Some of them also claim that ischemia at the level of the DVP leads to outer retinal and photoreceptor dysfunction (36). Burnasheva et al. (2019) investigated the changes in retinal microcirculation and the prevalence of chronic lesions of paracentral acute middle maculopathy (PAMM) in patients with mild hypertension. The results showed that the vascular density of the superficial capillary plexus or the FAZ area was no different between the hypertension group and the healthy group. Chronic PAMM lesions were observed in 24 out of 27 patients (88.9%) with hypertension and in 4 out of 24 (16.7%) healthy people. The odds ratio of the presence of chronic PAMM lesions in subjects with mild hypertension was 40.0. Chronic PAMM lesions are very common in hypertensive patients and may indicate the first changes in retinal circulation in patients with mild hypertension before the changes in OCT angiography parameters are revealed (37).

Increased vascular resistance may impair blood flow. This slow blood flow may be reflected as a lack of perfusion in OCT-A. Since OCT-A relies on the change between successive retinal scans, it detects flow only above a minimum threshold (38). Thus, areas with flow less than the slowest detectable flow are considered non-perfusion using the OCT-A imaging technique. Thus, microvascular rarefaction may be an interesting target for therapy (39). The presence of microvascular changes in the eye (retinal capillary density reduction using OCT-A) has been observed in hypertensive retinopathy in patients with kidney disease (40). The inconsistency in the results of different studies investigated the retinal vessels between hypertensive patients and patients with ischemic stroke can be related to the difference in volume, the use of different diagnostic methods other than OCT-A, differences in the clinical and vascular profiles of hypertensive patients and stroke, and lack of the control of important confounding variables.

OCTA enables a non-invasive, efficient, and increasingly available method for retinal microvascular imaging with advantages compared to conventional dye injection angiography, which is inappropriate for large cohort studies and for consecutive follow-up visits. OCT is extensively used for the diagnosis and treatment of retinal diseases and glaucoma. It can detect ten retinal layers with high resolution and has the advantage of quantitatively evaluating the thickness of each layer. In HTN patients without retinopathy or glaucoma, GC-IPL and peripapillary RNFL thinning have been reported (41). In addition, past studies reported that the inner retina is more vulnerable to hypoxia during ischemia. This reduction in inner retinal thickness may be associated with hypertensive retinal ischemia, so chronic microvascular dysfunction is associated with slow inner retinal thinning. Recent studies with OCTA have indicated a reduction in foveal microvascular parameters and an increase in foveal avascular area in patients with chronic HTN and hypertensive retinopathy (42). Due to an association between microvasculature and inner retinal layer thickness, inner retinal thinning may be related to retinal microcirculation. Additionally, patients with poorly controlled blood pressure showed a higher reduction in retinal capillary density compared to patients with well-controlled blood pressure.

Conclusion

Generally, the results revealed that hypertension and stroke patients experience changes in a limited number of visual parameters of the retinal deep capillary plexus measured by OCTA. However, more studies with a higher sample size are needed. If a relationship is found between defects in the retinal deep capillary plexus, blood pressure, and ischemic stroke can be used as a prognostic factor or a factor to follow up with the patients for the treatment and progression of the disease and even to slow down or prevent the progression of the disease. The present study has limitations such as the small sample size, the difficulty of detecting the occurrence of previous hypertension accidents, the use of antihypertensive drugs or the lack of ambulatory blood pressure measurement due to the retrospective and cross-sectional nature of the study, the lack of examination of changes in retinal vessels with other peripheral microvascular parameters, and lack of determination of sensitivity and specificity of OCTA parameters in determining the prognosis of hypotensive and stroke patients.

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