Organization of Retinal Microvessels: Assessment Using Optical Coherence Tomography Angiography

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Abstract

Background: The vast majority of oxygen required for outer retinal layer, including photoreceptors is provided by choriocapillaris with a little support of deep retinal capillaris. This organization may differ between individuals depending on the variability in photoreceptor density. Based on these, we evaluated the changes and interaction between the retinal capillary networks—organization of retinal microvessels—using optical coherence tomography angiography (OCTA) considering ocular perfusion pressure (OPP) and diurnal variations.

Methods: Forty eyes of 40 healthy volunteers formed the sample for this cross-sectional study.

Mean arterial pressure (mAP), OPP, and OCTA measures were noted at two different time points on a single day.

Results: The mAP, OPP, superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillaris (CC) perfusion values showed no diurnal change ($p>0.05$). When compared the mAP and OPP with the SCP, DCP, and CC perfusion measurements, there was no significant relation between them ($p>0.05$). There was a significant moderate positive correlation between DCP and CC values in both morning and afternoon ($r=0.422$; $p=0.007$, $r=0.493$; $p=0.001$, respectively).

Conclusion: The DCP and CC perfusion values show a significant moderate positive correlation. This correlation may suggest the role of DCP in the maintenance of oxygen homeostasis in outer retinal layers.

Introduction

The metabolic substrate and oxygen needs of retina are met from two vascular systems, called retinal and choroidal circulation. The retinal circulation can be divided into two vascular complexes, each consists of two plexuses: superficial vascular complex —includes the superficial vascular plexus and radial peripapillary capillary plexus— and deep vascular complex —consists of the intermediate capillary plexus and deep capillary plexus—[1]. The outer retinal layers, including photoreceptors are avascular in human retina. Oxygen required for photoreceptors is supplied by choriocapillaris and deep capillary layer of retina[2].

The macula contains two types of photoreceptors. The foveal cone density is variable between individuals. Individual variability in photoreceptor density differs with retinal region and is similar for both cones and rods[3]. The organization of retinal microcirculation may differ between individuals depending on the individual variability in photoreceptor density. Understanding the organization of retinal microvessels — the changes and interaction between the retinal capillary network and microcirculation— may reveal the underlying pathophysiology of the retinal disorder.

Optical coherence tomography angiography (OCTA) is an innovative technology using laser light reflectance of the surface of moving red blood cells. OCTA can imagine the choroid and retinal microvasculature through different segmented areas of the eye without using intravascular dyes. In addition to qualitative data, it can also provide quantitative data about flow area and vascular density[4]. In this way, the microvascular dynamics of the retina can be clarified.

When evaluating ocular blood flow (OBF), ocular perfusion pressure (OPP) and diurnal changes should be considered. OPP driving blood through the retina is the mean ophthalmic artery pressure minus the BP in the central retinal vein which is almost equal to intraocular pressure (IOP)[5]. Because of this; it would be more accurate to consider IOP as well as systemic BP for estimation of OBF. Since systemic BP, IOP, and choroidal perfusion values may show diurnal changes, it is also important to take into account the time of day, when evaluating OCTA perfusion data and OBF[6–8].

In this study, we evaluated the organization of retinal microvascular plexuses –perfusion of superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillaris (CC) measured by OCTA and their relation to each other—considering OPP and diurnal changes in healthy individuals.

Materials And Methods

Participants and Protocol

Forty eyes of 40 healthy volunteers (14 men, 26 women) with a mean age of 30.0 ± 7.01 years (range, 21–44 years) formed the sample for this prospective, cross-sectional study. Inclusion criteria for the study consisted of healthy young volunteers with no known systemic disease (e.g., diabetes mellitus, systemic hypertension, cardiac disease or obstructive sleep apnea) or ocular diseases (e.g., previous ocular surgery, vitreoretinal disease, glaucoma, ocular inflammatory disease). This study was approved by the ethics committee of SANKO University and conducted according to the Declaration of Helsinki. The aim of the study was explained to each patient and written informed consent was obtained.

All of the participants underwent complete ophthalmological examination. OCTA, IOP, and BP were measured respectively for each session. The measurements were taken at two different time points on a single day for each subject; 9:00–10:30 AM and 15:00–16:30 PM. Only measurements of right eye were used for analysis.

Patients were kept in rest for at least 5 min before the OCTA measurement to ensure BP was normalized. All measurements were performed in dim light without pupil dilatation. The measurements were acquired using the Avanti Angiovue system (Optovue Inc., Fremont, CA, USA) by the same experienced operator and according to the manufacturer's recommendations. Quality control criteria were fulfilled in accordance with the manufacturer's recommendations. The measurements were repeated in the same session if the OCTA image was not of sufficient quality. Scans with poor quality, defined by the following criteria: (1) a signal strength index (SSI) less than 48 (1 = minimum, 100 = maximum), (2) poor clarity, (3)

residual motion artifacts visible as irregular vessel pattern on the en-face angiogram, (4) local weak signal.

The macula was imaged with a 3x3 mm scan. The SCP, DCP, and CC perfusion values were obtained automatically by the device. CC flow area was noted in a 3,144 mm² central circular area. IOP was measured using Goldmann applanation tonometer shortly after OCTA imaging.

Systemic BP composed of systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured on the upper right arm by using an electronic cuff (Omron, Bannockburn, IL, USA). The patient was asked to remain calm in a sitting position for at least 5 minutes. Patients were instructed to avoid caffeine intake, smoking, and exercise for 3 hours prior to the study visit. The patient's arm was kept at heart level during the measurement. The mean arterial pressure (mAP) and OPP were calculated for each time point, using Equation: [5]

$$\text{mAP} = \text{DBP} + 1/3(\text{SBP}-\text{DBP})$$

$$\text{OPP} = 2/3 \times \text{mAP} - \text{IOP}$$

*The factor 2/3 is due to the drop in BP between the heart and ophthalmic artery

Statistical Analysis

Descriptive statistics were given as mean and standard deviation values. Paired-samples t-test was used to evaluate the difference between the morning and afternoon values of the variables. The relation between variables was evaluated with the Pearson correlation coefficient. $p < 0.05$ was considered statistically significant.

Results

Table 1 shows the mAP and OPP measurements in two time points. Both mAP and OPP values did not show significant difference ($p > 0.05$). The SCP, DCP, and CC perfusion values also showed no diurnal change ($p > 0.05$) (Table 2).

Table 1
Diurnal changes in mean arterial pressure and ocular perfusion pressure.

	Mean ± SD	<i>p</i> value
mAP-m	86.68 ± 9.52	0.696
mAP-a	87.08 ± 8.11	
OPP -m	41.23 ± 5.85	0.087
OPP -a	42.33 ± 5.62	
mAP-m; mean arterial pressure in the morning, mAP-a; mean arterial pressure in the afternoon, OPP-m; ocular perfusion pressure in the morning, OPP-a; ocular perfusion pressure in the afternoon, SD; standard deviation		

Table 2
Diurnal changes in superficial capillary plexus, deep capillary plexus, and choriocapillaris perfusion values.

	Mean ± SD	<i>p</i> value
SCP-m	47.93 ± 1.83	0.855
SCP-a	47.88 ± 1.95	
DCP-m	52.74 ± 2.71	0.367
DCP-a	53.09 ± 2.98	
CC-m	2.15 ± 0.09	0.320
CC-a	2.14 ± 0.10	
SCP-m; superficial capillary plexus perfusion in the morning, SCP-a; superficial capillary plexus perfusion in the afternoon, DCP-m; deep capillary plexus perfusion in the morning, DCP-a; deep capillary plexus perfusion in the afternoon, CC-m; choriocapillaris perfusion in the morning, CC-a; choriocapillaris perfusion in the afternoon SD; standard deviation,		

When compared the mAP and OPP with the SCP, DCP, and CC perfusion measurements in two different time points, there was no significant relation between them ($p > 0.05$) (Table 3).

Table 3

The correlation of mean arterial pressure and ocular perfusion pressure with superficial capillary plexus, deep capillary plexus, and choriocapillaris perfusion values in two time points.

		SCP-m	DCP-m	CC-m
mAP-m	r	0.011	- 0.007	- 0.205
	p	0.946	0.968	0.203
OPP -m	r	0.052	- 0.069	- 0.254
	p	0.749	0.672	0.114
		SCP-a	DCP-a	CC-a
mAP-a	r	-0.003	- 0.046	- 0.109
	p	0.983	0.780	0.505
OPP -a	r	0.052	- 0.078	- 0.086
	p	0.748	0.634	0.596
mAP-m; mean arterial pressure in the morning, mAP-a; mean arterial pressure in the afternoon, OPP-m; ocular perfusion pressure in the morning, OPP-a; ocular perfusion pressure in the afternoon, SCP-m; superficial capillary plexus perfusion in the morning, SCP-a; superficial capillary plexus perfusion in the afternoon, DCP-m; deep capillary plexus perfusion in the morning, DCP-a; deep capillary plexus perfusion in the afternoon, CC-m; choriocapillaris perfusion in the morning, CC-a; choriocapillaris perfusion in the afternoon <i>r</i> ; pearson correlation coefficient, <i>p</i> ; statistical significance (2-tailed).				

Table 4 shows the relation of SCP, DCP, and CC perfusion values with each other. There was a significant moderate positive correlation between DCP and CC values in both morning and afternoon measurements ($r = 0.422$; $p = 0.007$ and $r = 0.493$; $p = 0.001$, respectively).

Table 4

The relation of superficial capillary plexus, deep capillary plexus, and choriocapillaris perfusion with each other

	<i>r</i>	<i>p</i>
SCP-m <i>vs</i> DCP-m	0.280	0.080
SCP-m <i>vs</i> CC-m	0.074	0.651
DCP-m <i>vs</i> CC-m	0.422	0.007
SCP-a <i>vs</i> DCP-a	0.082	0.615
SCP-a <i>vs</i> CC-a	- 0.101	0.535
DCP-a <i>vs</i> CC-a	0.493	0.001
SCP-m; superficial capillary plexus perfusion in the morning, SCP-a; superficial capillary plexus perfusion in the afternoon, DCP-m; deep capillary plexus perfusion in the morning, DCP-a; deep capillary plexus perfusion in the afternoon, CC-m; choriocapillaris perfusion in the morning, CC-a; choriocapillaris perfusion in the afternoon, <i>r</i> ; pearson correlation coefficient, <i>p</i> ; statistical significance (2-tailed).		

Discussion

The regulation of RBF is carried out through a local autoregulatory increase in vascular resistance, since the retinal vessels are independent of the influence of autonomic nerve terminals[5, 9]. Thanks to the autoregulatory mechanisms of the retina, the blood flow remains largely unaffected by moderate changes in OPP. The RBF is unchanging until the mean OPP is elevated by an average of 34–60% above baseline values[10–12]. Similarly, low perfusion pressure is compensated by low resistivity to flow through autoregulatory mechanisms. Ischemic damage may occur if low perfusion pressure is combined with abnormal or insufficient autoregulation[13].

There are a few studies in the literature evaluating the systemic BP and OCTA measurements together[7, 14, 15]. In a study with healthy subjects, no significant correlation was detected between mAP or IOP and retinal perfusion values[7]. Differently from the mentioned literature, we evaluated OPP in addition to systemic BP. We found that, both the mAP and OPP did not show any significant correlation with choroid and retinal microcirculation as expected due to the autoregulatory mechanisms of the retina.

The time of day in which measurements are taken should be considered for evaluating OBF, as some ocular parameters associated with OBF may show diurnal changes. Studies of diurnal variations in measurements have variously reported. Rommel *et al.* showed diurnal variation in mAP, increasing from morning to afternoon[7]. The authors also reported no significant fluctuation in the perfusion of SCP and DCP. On the contrary, in studying the diurnal variation of the OPP, Kanadani *et al.* found lower values afternoon in volunteered individuals[13]. In our study, the measurements were taken at two different time points on a single day for each subject. We detected no significant diurnal change in mAP, OPP, SCP, DCP,

and CC perfusion values. Our findings are different from the previous reports in terms of diurnal change in mAP and OPP.

The choroidal vascular system provides oxygen mainly to the outer retina, and the retinal vasculature nourishes the inner retinal layers[16]. In the avascular outer retina, the inner segments of photoreceptors are the dominant oxygen consuming layer, as they contain large numbers of mitochondria[17–19]. In an attempt to maintain sufficient tissue oxygenation, the outer retina may increase oxygen use from the deep retinal capillary plexus. Yu and Cringle reported intraretinal oxygen distribution in the rat, under light and dark conditions[2]. The authors reported that the vast majority of oxygen required for outer retinal layer is provided by choriocapillaris with a little support of deep retinal capillaris under light conditions. Additionally, they observed increased oxygen delivery from both capillary plexuses under dark conditions. This suggests a dynamic regulation of the oxygen supply to the photoreceptors as discussed[16].

In our study, we found a significant moderate positive correlation between DCP and CC values in both time points. This organization may be related with the individual variability in photoreceptor density and oxygen demand in participants. In other words, this correlation may suggest the role of DCP in the compensation of oxygen consumption in outer retinal layers, including photoreceptors in accordance with the literature[2, 16]. Our findings also showed no correlation between SCP and DCP perfusion values. This situation might be explained by the different structural properties of the vessels[18,20.] In an OCTA-based study with healthy subjects, Bonnin *et al.* reported different topographic organizations in SCP and DCP and speculated that the different structural patterns of these two capillary plexuses may explain the differences in their flow resistance and perfusion[20].

As a result, DCP density shows a positive moderate correlation with CC density. This organization may suggest the role of DCP in the maintenance of oxygen homeostasis in outer retinal layer.

Declarations

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