Differences in Blood Flow Between Superior and Inferior Retinal Hemispheres

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Purpose. To determine whether the blood flow in the superior retina is significantly different from that in the inferior retina, and to determine whether the posture affects the blood flow in the superior and inferior retina.

Methods. The blood flow in the vessels around the optic nerve head was measured by laser speckle flowgraphy in the sitting position in 68 healthy subjects. The blood flow in the superior peripapillary retina was compared with that in the inferior peripapillary retina. The measurements of the blood flow were performed in the sitting position, and the effect of switching to a supine position was determined at 2, 4, 6, 8, 10, and 30 minutes after the switch.

Results. The total relative flow volume (RFV)-all, RFV-artery, and RFV-vein were significantly greater in the superior retina than in the inferior retina (all $P < 0.001$). The mean diameter-all and mean diameter-artery in the superior retina were significantly larger than that in the inferior retina (all $P < 0.05$). The mean blur rate (MBR)-all, MBR-artery, and MBR-vein in the superior retina were also greater than that in the inferior retina ($P < 0.001$, $P < 0.01$, and $P < 0.001$, respectively). Although the ocular perfusion pressure was significantly changed with the postural alteration, the total RFV-all remained greater in the superior retina than in the inferior retina after the postural change.

Conclusions. Clinicians need to be aware of the differences in the blood flow between the superior and inferior retinal peripapillary area when considering the mechanisms of retinochoroidal diseases.

Keywords: blood flow, retina, superior, inferior, laser speckle flowgraphy

Evaluating the ocular blood flow is an important factor in determining the physiological dynamics of the eye, and the pathogenesis and treatment of various ocular diseases, including diabetic retinopathy,[1,2] glaucoma,[3,4] retinal detachment,[5,6] branch retinal vein occlusion (BRVO),[7,8] and central serous chorioretinopathy (CSC).[9,10] Hayreh and Zimmerman[11] reported that the retinal sector most affected by a major BRVO was the superior temporal quadrant at 65%, and the inferior temporal quadrant at 31% of the eyes. For eyes with a macular BRVO, the superior quadrant was involved in 81% of the eyes, and the inferior quadrant in 19% of the eyes.[11] Recently, Kishi et al.[12] found an asymmetry in the blood flow in the upper and lower vortex veins in eyes with a CSC. These results suggested that differences in the blood flow between the superior and inferior retina may be involved in the development and progression of retinochoroidal diseases.

There have been several reports on the functional and structural asymmetries in the superior and inferior retina. Silva et al.[13] reported that the contrast sensitivity of the intermediate spatial frequencies was significantly better in the superior retina than in the inferior retina. Curcio and Allen[14] reported that the ganglion cell density in the peripheral retina was higher in the superior retina than in the inferior retina, and the rod density in the superior retina was higher than that in the inferior retina.[15] More recently, Huynh et al.[16] reported that the superior macula was thicker than the inferior macula as determined by optical coherence tomography (OCT). In addition, Huang et al.[17] reported that the superior retina tended to be thicker than the inferior retina using Fourier-domain OCT. These findings suggested that there may also be asymmetries in the ocular blood flow, and if present, the asymmetries may be associated with the development and progression of retinochoroidal disease. Thus it is important to investigate whether there are asymmetries in the ocular blood flow in different regions of the retina in healthy eyes.

Various methods have been used to measure the ocular blood flow, for example, fluorescein fundus angiography,[18] radioactive microspheres,[19] hydrogen clearance,[20] and laser Doppler velocimetry.[21] However, the devices used to make these measurements have their limitations, for example, invasiveness, simplicity, and time intensiveness. These properties make it difficult to determine whether asymmetrical

ocular blood flow is present. This may explain why there have not been any studies to determine whether the blood flow in the superior retina is significantly different from that of the inferior retina in healthy eyes.

Laser speckle flowgraphy (LSFG; Softcare Co., Ltd., Fukutsu, Japan) is a noninvasive, real-time method to measure the blood flow velocity, which is designated as the mean blur rate (MBR). The MBR of the optic nerve head (ONH), retina, and choroid can be determined by LSFG without an intravenous injection of any contrast agents.[22–26] The recordings that can be used to determine the relative flow volume (RFV) takes only 4 seconds to acquire, and the values have been shown to reflect the volume of retinal blood flow. The RFV is calculated from the vascular diameter and the retinal flow velocity in all of the major retinal arteries and veins surrounding the ONH after subtracting the background choroidal blood flow from the overall blood flow volume in the region of interest centered on a retinal vessel.[27,28] Thus it is possible to compare the RFV between the superior and inferior retina.

In general, the ocular blood flow is measured with the LSFG in the sitting position as with most of the measurement devices. However, it is known that the posture of the examinee might affect the ocular blood flow in the superior and inferior retina. It has been shown that the ocular perfusion pressure (OPP) varies depending on the sitting and supine positions.[29,30] However, several studies have shown that the retinal blood flow is autoregulated,[29–32] and the autoregulation can maintain the blood flow constant despite changes in the OPP induced by the postural changes. Thus it is important to determine whether the blood flow rate measured by LSFG is affected by the posture.

The purpose of this study was to determine whether the retinal blood flow in the superior hemiretina is significantly different from that of the inferior hemiretina, and also to determine whether changes in the OPP induced by postural changes will alter the retinal blood flow. To accomplish these goals, we measured retinal blood flow by LSFG and observed changes in the blood flow in the sitting and supine positions.

Methods

Ethics Statement

The ethics committee of Nagoya University Hospital approved the procedures used in this prospective study. The procedures conformed to the tenets of the Declaration of Helsinki. An informed consent was obtained from all subjects after the nature and possible complications that can arise from the procedures used in this study were explained.

Subjects

Healthy Japanese volunteers without any ophthalmic or systemic diseases were studied. Both eyes were measured in Experiment 1, and one eye was measured in Experiment 2. Slit-lamp examinations, indirect ophthalmoscopy, and spectral domain (SD)-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) were used to examine the anterior and posterior segments of the eye. Subjects with a best-corrected visual acuity of 20/20 or better and with no ocular and systemic diseases were studied. Subjects with any medical conditions that could affect the ocular hemodynamics, such as diabetes, hypertension, arrhythmias, and vascular diseases, were excluded. Subjects with a history

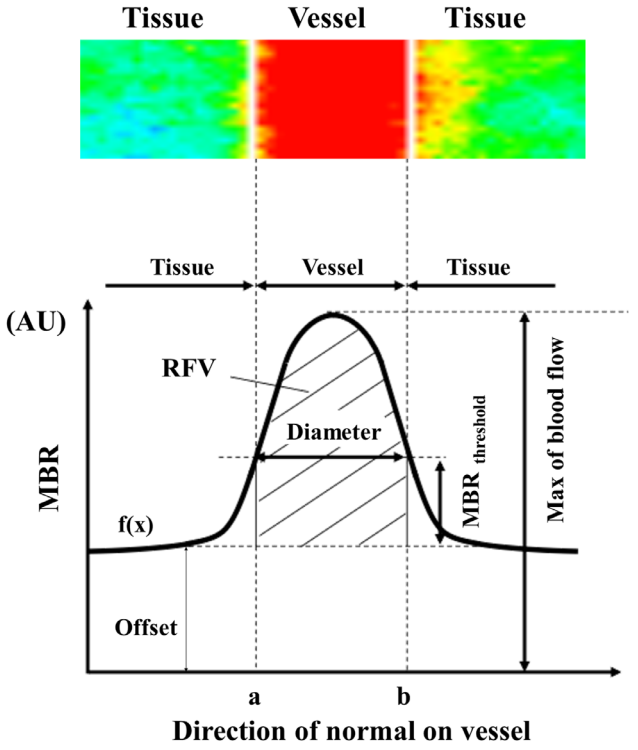

Figure 1. Calculation of the RFV. The $MBR_{threshold}$ is the threshold difference between the MBR values in the retinal vessels and the background choroid. f(x) is the distribution function of the MBR in a cross-sectional area of the retinal vessels. The diameter of the function at $MBR_{threshold}$ is represented by a and b. The RFV in the retinal vessel was calculated by subtracting choroidal MBR from overall MBR. RFV = retinal flow volume.

of ophthalmic or systemic disorders, incisional surgery, or ocular laser treatment in the experimental eye, use of topical or systemic medications, systolic blood pressure (SBP) >140 mm Hg, diastolic blood pressure (DBP) >90 mm Hg, and axial length (AL) >27.0 mm were also excluded.

All participants were asked to abstain from caffeinated and alcoholic beverages on the day of the examination.[33,34] The pupils were not dilated in Experiment 1, but were dilated with 0.4% tropicamide/phenylephrine (Mydrin P; Santen Pharmaceutical Co., Ltd., Osaka, Japan) 30 minutes before the examinations in Experiment 2. The subjects rested for approximately 15 minutes in a quiet dark room before the measurements. The ALs were measured by partial optical coherence interferometry (IOLMaster; Carl Zeiss Meditec, La Jolla, CA, USA), and the intraocular pressure (IOP) was measured with Icare (Tiolat Oy, Helsinki, Finland) in Experiment 1, and TONO-PEN AVIA (Reichert Technologies, Depew, NY, USA) in Experiment 2. The SBP and DBP were measured with an automatic sphygmomanometer (CH-483C; Citizen, Tokyo, Japan). The blood mean arterial pressures (MAP) were calculated by the following formula:

$$\mathrm{MAP} = \mathrm{DBP} + 1/3\,(\mathrm{SBP} - \mathrm{DBP})\,.$$

The mean OPP in the sitting and supine positions was calculated using the following formula[35–37]:

$$\text{Sitting position : mean OPP} = (95/140 \times \mathrm{MAP}) - \mathrm{IOP},$$

$$\text{Supine position : mean OPP} = (115/130 \times \mathrm{MAP}) - \mathrm{IOP}.$$

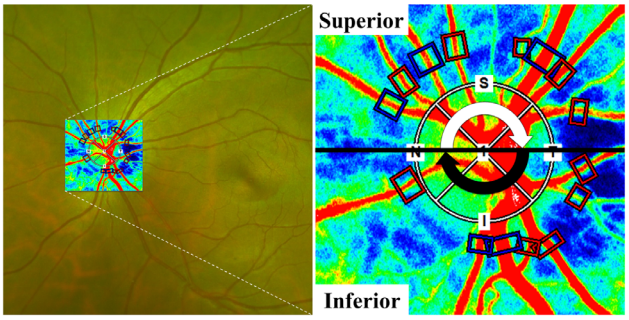

FIGURE 2. Representative composite color map recorded by LSFG. The retina was divided into two halves, the superior and inferior retina, by a horizontal line passing through the center of the ONH. Then the sum of retinal flow volume on all of the measurable arterial and venous vessels around the ONH was calculated for the superior and inferior retina.

Laser Speckle Flowgraphy

The principles of LSFG have been described in detail.[23,38–40] The LSFG images were acquired at a rate of 30 frames/s over a 4-second period, and 3 images were obtained at each time point in all eyes. The MBR was determined by the embedded software, and the MBR is a measure of the blood flow velocity. To evaluate the blood flow on the ONH, a circular band was set around the ONH image.

The calculation of the RFV has been reported in detail (Fig. 1).[28] In brief, a rectangular band was placed across all peripapillary retinal vessels recognized in the LSFG image (Fig. 2). The system can differentiate the arteries from the veins. The MBR in each of the retinal vessels is automatically corrected for the background choroidal signal derived from the underlying choroid. The vessel diameter was determined by LSFG and expressed in pixels, and the diameter was used for the calculation of the RFV.[41] The total retinal artery and vein analyses were determined semiautomatically for the total RFV index of the retinal vessels around the ONH recognized by LSFG. The software of the LSFG can also determine the total retinal artery and total vein blood flow separately.[27] The diameter of retinal blood vessels with a thickness <60 µm were not recognized semiautomatically as vessels by LSFG.

The superior and inferior hemispheres were determined by a horizontal line passing through the center of the optic disc, and the values of the parameters in the superior hemisphere were compared with the values in the inferior hemisphere (Fig. 2). In comparing the blood flow values of the superior and inferior retina, the blood flow was measured for all of the vessels around the ONH recognized by the LSFG, for example, those in which diameter was >60 µm.

The total arterial and venous RFV (total RFV-all), the total arterial RFV (total RFV-A), and total venous RFV (total RFV-V) were determined by the sum of the RFVs of all vessels in each area. The mean RFV was calculated by dividing the RFV by the number of vessels. The mean diameter and MBR are designated as the mean RFV-all, the mean RFV-A, the mean RFV-V, the mean diameter-all, the mean diameter-A, and the mean diameter-V, the MBR-all, the MBR-A, and the MBR-V.

Retinal Thickness Measurements

Vertical and horizontal cross-sectional images were obtained by the SD-OCT instrument. One vertical or horizontal OCT image centered on the fovea, which consisted of 100 B-scans, was obtained using the eye-tracking system. The central retinal thickness was defined as the average of the thickness measured at the center of the fovea in the vertical and horizontal images. The retinal thickness and the ganglion cell complex (GCC) thickness were measured at 2 mm perpendicularly above and below to the center of the fovea, and the ratio of the thicknesses were compared with the blood flow values (Fig. 3).

Testing Protocol

Experiment 1 was performed to compare the blood flow parameters between the superior and inferior retinal hemispheres. All of the examinations were performed in the sitting position. The total RFV, the mean RFV, the mean

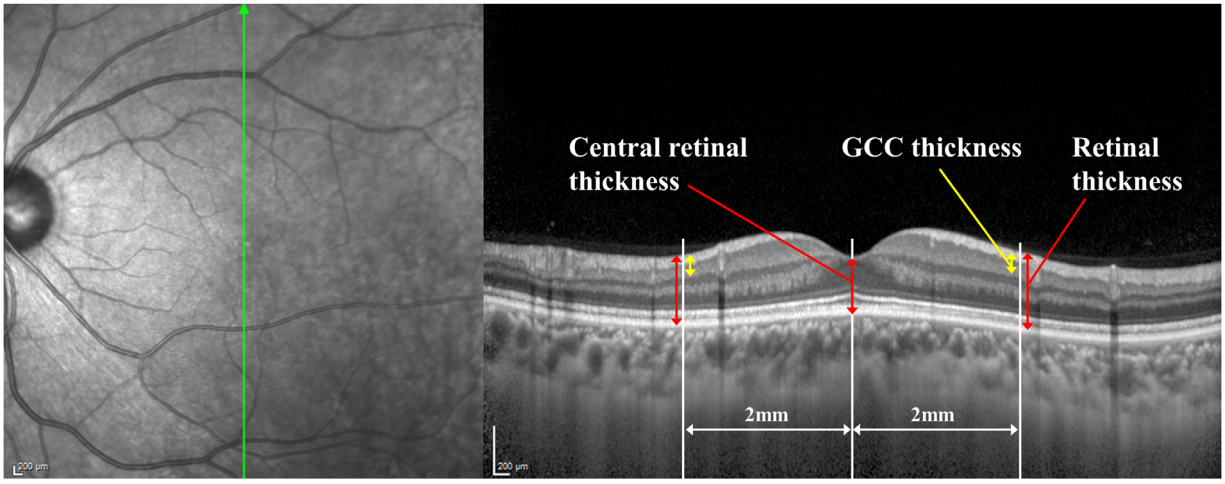

FIGURE 3. Representative vertical SD-OCT image taken by a Spectralis instrument. The retinal thickness and the GCC thickness were defined as the distance from the inner limiting membrane to the outer border of the retinal pigment epithelium, and to the outer inner plexiform layers, respectively. Those thicknesses were measured at 2 mm perpendicularly above and below to the center of the fovea. The central retinal thickness was defined as the average of the retinal thickness at the central fovea in the vertical and horizontal images.

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diameters, and the MBR of all vessels around the ONH in the superior and inferior retina were compared.

Experiment 2 was performed to evaluate the effects of the postural position on the blood flow parameters. The values of the LSFG, IOP, SBP, DBP, and heart rate were first determined in the sitting position, and then measured in a supine position at 2, 4, 6, 8, 10, and 30 minutes after the postural change. Finally, the posture was returned to the sitting position, and the measurements were repeated after 10 minutes (Fig. 4). The changes in the OPP, MBR on the ONH, total RFV-all, vessel diameter, and MBR on the vessels were determined at the same times.

Statistical Analyses

The values are presented as the means ± standard deviations (SDs). Linear mixed models were used to determine the significance of differences between the superior and inferior retina and the appropriate covariates between repeated-measured values over time. The Bonferroni correction was used to adjust for the multiple comparisons. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26 (IBM Corp., Armonk, NY, USA). The significance level was set at $P < 0.05$.

Results

The demographic data of the subjects in Experiment 1 are shown in Table 1, and that for Experiment 2 in Table 2. There were 68 volunteers for Experiment 1, and 17 volunteers for Experiment 2.

The mean ± SDs of the total RFV whole retina was 3518.0 ± 621.5 arbitrary units (AU). The total RFV of the whole retina was significantly and negatively correlated with the AL ($r = -0.307$, $P < 0.001$), the central retinal thickness ($r = -0.242$, $P = 0.004$), and age ($r = -0.221$, $P = 0.010$; Table 3). Multiple regression analysis showed that the total RFV of the whole retina was significantly related to the AL ($\beta = -0.320$, $P < 0.001$) and age ($\beta = -0.198$, $P = 0.016$; Table 4).

Determination of Blood Flow Parameters of Superior and Inferior Peripapillary Retina (Experiment 1)

The average number of retinal vessels studied in Experiment 1 was 15.6 ± 2.2/eye of which 8.0 ± 1.6 were arteries and 7.6 ± 1.5 were veins. The number of measured vessels in the superior peripapillary retina was 80 ± 1.6, which was significantly higher than that in the inferior retina at 7.6 ± 1.4 ($P = 0.011$; Table 5). The number of the arteries in the superior retina was 4.1 ± 1.1, and in the inferior was 3.9 ± 1.0. The number of the veins in the superior was 3.9 ± 1.2, and in the inferior was 3.7 ± 1.0.

Table 1. Baseline Characteristics of Subjects (Experiment 1)

Characteristic	Mean ± SDs
n (eyes)	136
Age (y)	29.3 ± 8.7
Sex (male/female)	23/45
AL (mm)	24.8 ± 1.1
IOP (mm Hg)	13.7 ± 2.5
SBP (mm Hg)	112.8 ± 13.8
DBP (mm Hg)	68.9 ± 8.5
MAP (mm Hg)	83.5 ± 9.9
Mean OPP (mm Hg)	42.0 ± 6.8
Heart rate (bpm)	72.4 ± 9.0
Central retinal thickness (µm)	225.3 ± 14.5

Table 2. Baseline Characteristics of Subjects (Experiment 2)

Characteristic	Mean ± SDs
n (eyes)	17
Age (y)	28.4 ± 2.1
Sex (male/female)	9/8
AL (mm)	25.0 ± 1.1
IOP (mmHg)	12.7 ± 2.4
SBP (mmHg)	113.9 ± 13.3
DBP (mmHg)	70.5 ± 9.3
MAP (mmHg)	88.7 ± 10.0
Mean OPP (mmHg)	46.4 ± 6.8
Heart rate (bpm)	72.4 ± 8.6

Table 3. Results of Spearman Rank Correlation Coefficient Between the Total Retinal Flow Volume and Clinical Parameters (Experiment 1)

Parameters		*r*	*P* Value
Total retinal flow volume of retina	AL	−0.307	<0.001
	Central retinal thickness	−0.242	0.004
	Age	−0.221	0.010
	Sex	0.181	0.035
	Mean OPP	−0.81	0.348

Table 4. Results of Multiple Stepwise Regression Analysis for Independence of Factors Contributing to Total Retinal Flow Volume (Experiment 1)

Variable			
Dependent	Independent	β	*P* Value
Total retinal flow volume	AL	−0.320	<0.001
	Age	−0.198	0.016
	Central retinal thickness	−0.138	0.096
	Sex	0.088	0.298
	Mean OPP	0.017	0.840

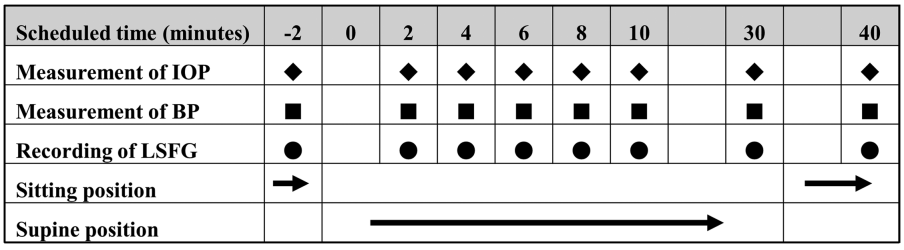

Figure 4. Time course of Experiment 2. BP, blood pressure.

Table 5. Differences in Parameters of Retinal Thickness and Retinal Vessels Between the Superior and Inferior Retina (Experiment 1)

Parameters of OCT		Superior	Inferior	*P* Value
Retinal thickness 2 mm away from the fovea (μm)		312.8 ± 16.4	303.0 ± 15.3	<0.001
GCC thickness 2 mm away from the fovea (μm)		110.8 ± 11.3	107.0 ± 9.8	<0.001
Parameters of LSFG	**Types of blood vessels**	**Superior**	**Inferior**	***P* Value**
Total number of the vessels	Artery and vein	8.0 ± 1.6	7.6 ± 1.4	0.011
	Artery	4.1 ± 1.1	3.9 ± 1.0	0.072
	Vein	3.9 ± 1.2	3.7 ± 1.0	0.097
Total retinal flow volume (AU)	Artery and vein	1878.0 ± 378.2	1640.0 ± 325.9	<0.001
	Artery	834.1 ± 202.2	721.5 ± 166.5	<0.001
	Vein	1044.0 ± 228.4	918.4 ± 210.7	<0.001
Mean retinal flow volume (AU)	Artery and vein	241.6 ± 63.0	220.9 ± 51.2	<0.001
	Artery	212.7 ± 66.9	197.1 ± 69.4	0.034
	Vein	290.8 ± 105.8	260.6 ± 71.5	0.002
Mean vessel diameter (AU)	Artery and vein	11.7 ± 1.0	11.4 ± 1.2	0.011
	Artery	10.8 ± 1.3	10.5 ± 1.4	0.031
	Vein	12.8 ± 1.5	12.6 ± 1.6	0.081
MBR (AU)	Artery and vein	29.0 ± 5.9	26.2 ± 4.4	<0.001
	Artery	27.6 ± 6.2	26.1 ± 5.6	0.005
	Vein	31.4 ± 7.5	27.3 ± 5.3	<0.001

The differences in the values of the blood flow parameters determined by LSFG in the superior and inferior retina are shown in Table 5 and Figure 5. The total RFV-all, RFV-A, and RFV-V in the superior retina were significantly larger than in the inferior retina (all $P < 0.001$). The mean RFV-all, RFV-A, and RFV-V in the superior retina were also significantly larger than that in the inferior retina ($P < 0.001$, $P = 0.034$, and $P = 0.002$, respectively). The mean diameter-all and mean diameter-A in the superior retina were significantly larger than that in the inferior retina (all P <0.05). The MBR-all, MBR-A, and MBR-V in the superior retina were also greater than that in the inferior retina ($P < 0.001$, $P = 0.005$, and $P < 0.001$, respectively).

In the vertical OCT images, the retinal thickness and GCC thickness measured at 2 mm above and below the fovea were 312.8 ± 16.4 and 110.8 ± 11.3 μm in the superior, and 303.0 ± 15.3 and 107.0 ± 9.8 μm in the inferior retina, respectively (both $P < 0.001$).

The ratio of the total RFV of the superior and inferior retina in each eye was significantly correlated with the ratio of the number of vessels of the superior and inferior retina ($r = 0.389$, $P < 0.001$) and the ratio of the MBR ($r = 0.240$, $P = 0.005$; Table 6). Multiple regression analysis showed that the ratio of the total RFV of the superior and inferior retina was significantly related to the ratio of the number of vessels of the superior to inferior retina ($\beta = 0.705$, $P < 0.001$) and the ratio of MBR ($\beta = 0.614$, $P < 0.001$; Table 7).

In comparing the parameters of the retinal vessels with the highest RFV between the superior and inferior retina, there was no significant differences in the RFV between the superior and inferior. The diameter of vein with the highest RFV was greater in the inferior than that in the superior although the MBR of the artery and vein in retinal vessel with the highest RFV was higher in superior than that in the inferior retina (Table 8).

Changes in Values of Blood Flow Parameters with Postural Alterations (Experiment 2)

The changes in the values of the blood flow parameters in Experiment 2 are shown in Table 9 and Figure 6. The OPP was significantly changed with the postural alterations, for example, it was 46.4 ± 6.8 mm Hg in the sitting position, 58.8 ± 6.3 mm Hg at 10 minutes, and 60.2 ± 9.1 mm Hg at 30 minutes after assuming the supine position (Fig. 7). After returning to the sitting position, the OPP was 49.0 ± 7.1 mm Hg at 10 minutes.

The total RFV-all was 3113.9 ± 489.8 AU in the sitting position, 3082.9 ± 597.3 AU at 10 minutes, and 3152.8 ± 630.3 AU at 30 minutes after assuming the supine position, and the total RFV was 3080.8 ± 652.2 AU at 10 minutes after returning to the sitting position. There were no significant differences in the values of all of the blood flow parameters throughout Experiment 2.

There were significant differences in the total RFV-all between the superior and inferior retina during Experiment 2, except at 4 and 8 minutes after the first postural change (Fig. 8). The ratio of the superior to the inferior in the RFV-all remained >1.0 and did not significantly change throughout Experiment 2.

Discussion

The total RFV, the mean vessel diameter, and the MBR determined by LSFG were significantly larger in the superior retina than in the inferior retina. In addition, these values for both the arteries and veins were significantly larger in the superior retina than in the inferior retina. These differences were maintained despite the change in the postural position, even though the OPP was changed.

There have been several reports on the differences in the ocular blood flow between the superior and inferior retina that were determined by Doppler flowmeter.[42–46] For example, Garhofer et al.[42] measured four to eight venules/eye by laser Doppler velocimetry in 64 eyes of 64 healthy volunteers, and they reported that the retinal blood flow in the inferior retina was significantly higher than that in the superior retina. This was supported by Garcia et al.[43] who also used laser Doppler flowmeter to study five healthy young individuals, and they reported that the blood flow velocity in an inferior retinal vein was higher than that in a superior retinal vein, although the difference was not significant. Feke

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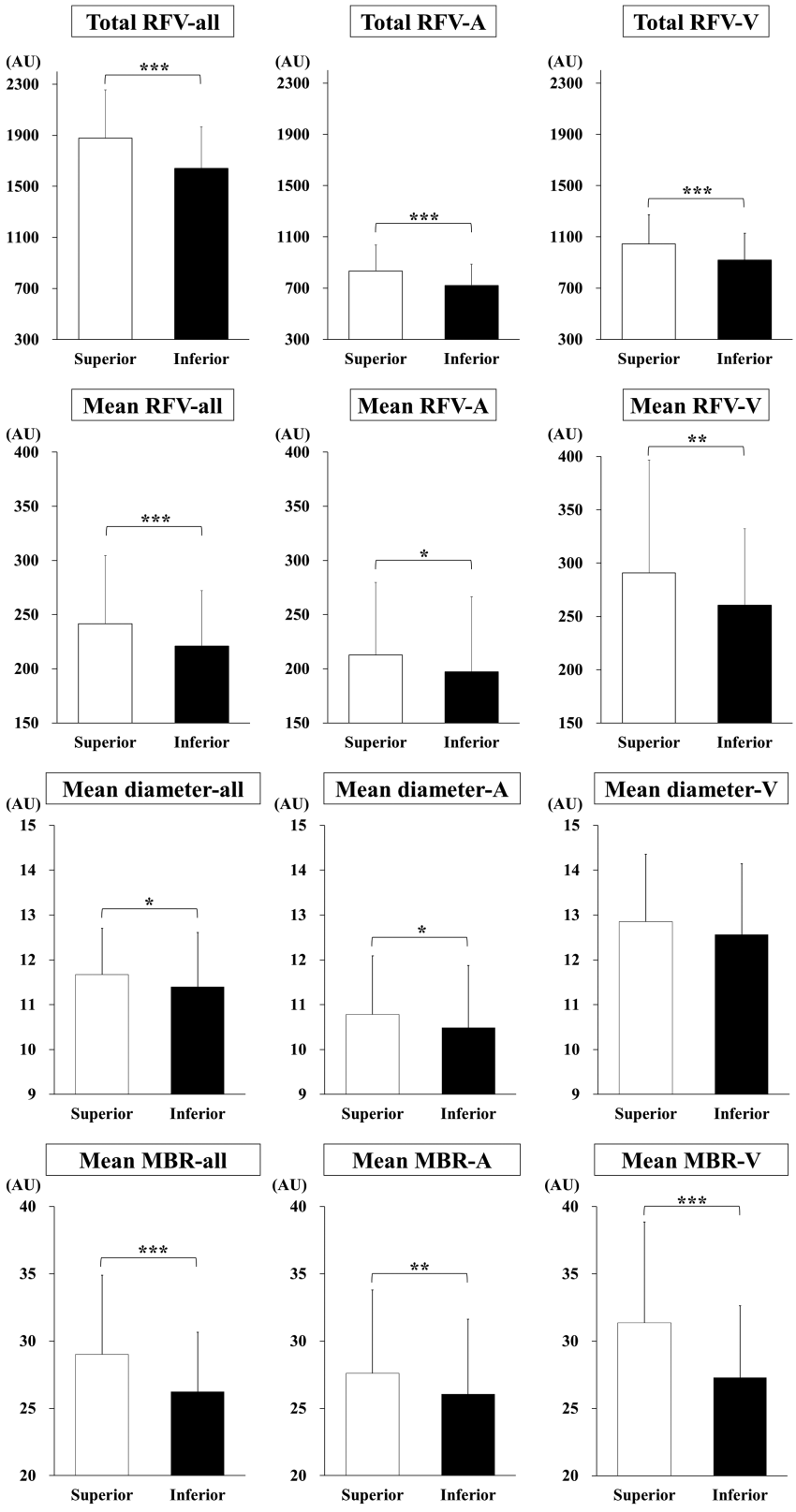

Figure 5. Differences in the values of the blood flow parameters determined by LSFG in the superior and inferior retina. The total RFV, the mean RFV, the mean diameter, and the MBR of the artery and vein, artery alone, and vein alone in the superior retina were significantly higher than that in the inferior retina. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

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Table 6. Results of Spearman Rank Correlation Coefficient Between the Ratio of Retinal Flow Volume of the Superior Retina to the Inferior Retina (Experiment 1)

Parameters		*r*	*P* Value
The ratio of retinal flow volume of the superior retina to the inferior retina	The ratio of the number of vessels in superior retina to inferior retina	0.389	<0.001
	The ratio of MBR of superior retina to inferior retina	0.240	0.005
	Sex	−0.141	0.102
	The ratio of mean vessel diameter of superior retina to inferior retina	−0.132	0.125
	Age	0.099	0.251
	AL	−0.088	0.310
	The ratio of GCC thickness of the superior retina to the inferior retina	−0.074	0.392
	The ratio of retinal thickness of superior retina to inferior retina	−0.046	0.598
	Mean OPP	0.031	0.722
	Central retinal thickness	0.013	0.882

Table 7. Results of Multiple Stepwise Regression Analysis for Independence of Factors Contributing to the Ratio of Retinal Flow Volume of the Superior Retina to the Inferior Retina (Experiment 1)

	Variable		
Dependent	**Independent**	β	***P* Value**
The ratio of retinal flow volume of the superior retina to the inferior retina	The ratio of the number of vessels in superior retina to inferior retina	0.705	<0.001
	The ratio of MBR of superior retina to inferior retina	0.614	<0.001
	Age	0.076	0.257
	Central retinal thickness	0.066	0.327
	Mean OPP	0.059	0.381
	Sex	−0.045	0.510
	The ratio of mean vessel diameter of superior retina to inferior retina	−0.046	0.578
	AL	−0.017	0.803
	The ratio of GCC thickness of the superior retina to the inferior retina	0.003	0.970

et al.[44] reported that the total retinal blood flow rate in the inferior retina of five healthy eyes was 6% greater than that in the superior retina, but the difference was not significant. Wang et al.[45] measured the blood flow in the veins around the ONH of eight healthy subjects using Doppler Fourier-domain OCT, and they reported that there was no significant difference in the retinal blood flow between the superior and inferior retina. Our results showed that there was no significant differences in the RFV between the superior and inferior retina when only the vessels with the highest RFV of each area were compared. This was found despite the fact that the diameter of vein was thicker in the inferior than that in the superior retina. These results may be partially consistent with the previous reports[42–46] when comparing the blood flow using a relatively small number of retinal vessels.

Table 8. Differences in Parameters of Retinal Vessels with the Highest RFV in Each of the Superior and Inferior Retina (Experiment 1)

Parameters	Types of Blood Vessels	Superior	Inferior	*P* Value
Retinal flow volume (AU)	Artery	346.6 ± 104.6	340.1 ± 93.6	0.527
	Vein	515.7 ± 139.9	513.4 ± 134.8	0.872
Vessel diameter (AU)	Artery	12.8 ± 1.9	12.9 ± 1.9	0.609
	Vein	16.4 ± 1.9	17.2 ± 1.8	<0.001
MBR (AU)	Artery	38.0 ± 10.4	34.8 ± 8.3	<0.001
	Vein	42.0 ± 9.6	38.1 ± 7.7	<0.001

Table 9. Changes in Ocular Blood Flow Parameters with Posture Change (Experiment 2)

		Supine							
Parameters	**Sitting Baseline**	**2 Minutes**	**4 Minutes**	**6 Minutes**	**8 Minutes**	**10 Minutes**	**30 Minutes**	**Sitting 40 Minutes**	***P* Value**
OPP (mm Hg)	46.4 ± 6.8	59.6 ± 7.5	59.1 ± 7.8	60.3 ± 7.0	58.6 ± 8.4	58.8 ± 6.3	60.2 ± 9.1	49.0 ± 7.1	<0.001
ONH MBR (AU)	46.4 ± 5.1	47.2 ± 5.9	47.6 ± 6.6	46.3 ± 6.4	47.0 ± 6.6	47.4 ± 7.1	47.4 ± 7.0	46.1 ± 6.3	0.672
Total retinal flow volume (AU)	3113.9 ± 489.8	3044.7 ± 618.1	3079.1 ± 607.3	3025.1 ± 597.3	3051.5 ± 593.8	3082.9 ± 597.3	3152.8 ± 630.3	3080.8 ± 652.2	0.616
Mean vessel diameter (AU)	12.5 ± 1.1	12.6 ± 1.2	12.6 ± 1.2	12.7 ± 1.1	12.8 ± 1.1	12.7 ± 1.3	12.5 ± 1.1	12.3 ± 1.0	0.062
MBR (AU)	27.5 ± 3.4	27.0 ± 3.9	27.3 ± 4.2	26.9 ± 3.9	27.0 ± 3.8	27.3 ± 4.4	27.9 ± 3.8	26.9 ± 4.2	0.519

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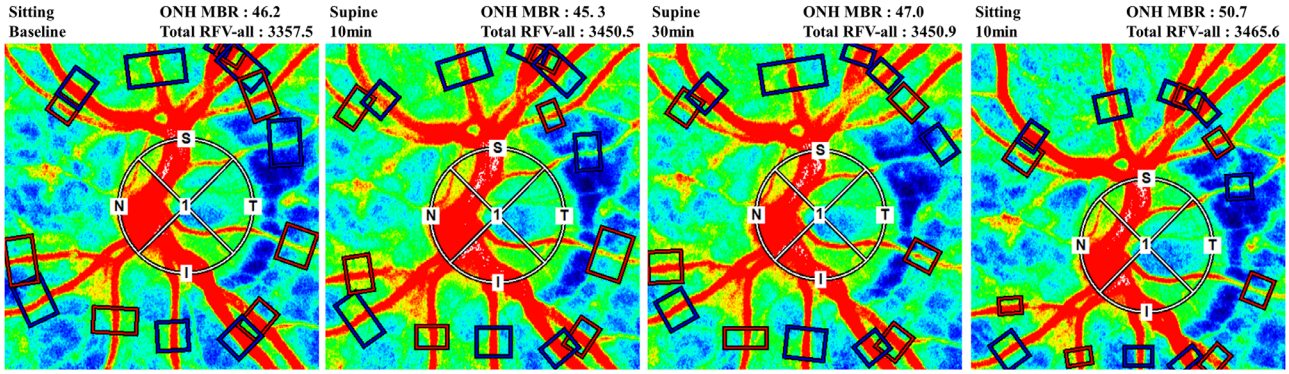

Figure 6. Composite color map and changes in the MBR of the ONH and the total RFV-all. The composite color map in the sitting position, in the supine position 10 minutes after changing posture to the supine position, 30 minutes after changing posture, and in the sitting position 10 minutes after changing posture to the sitting position. There were no significant changes in the ONH MBR and the total RFV-all.

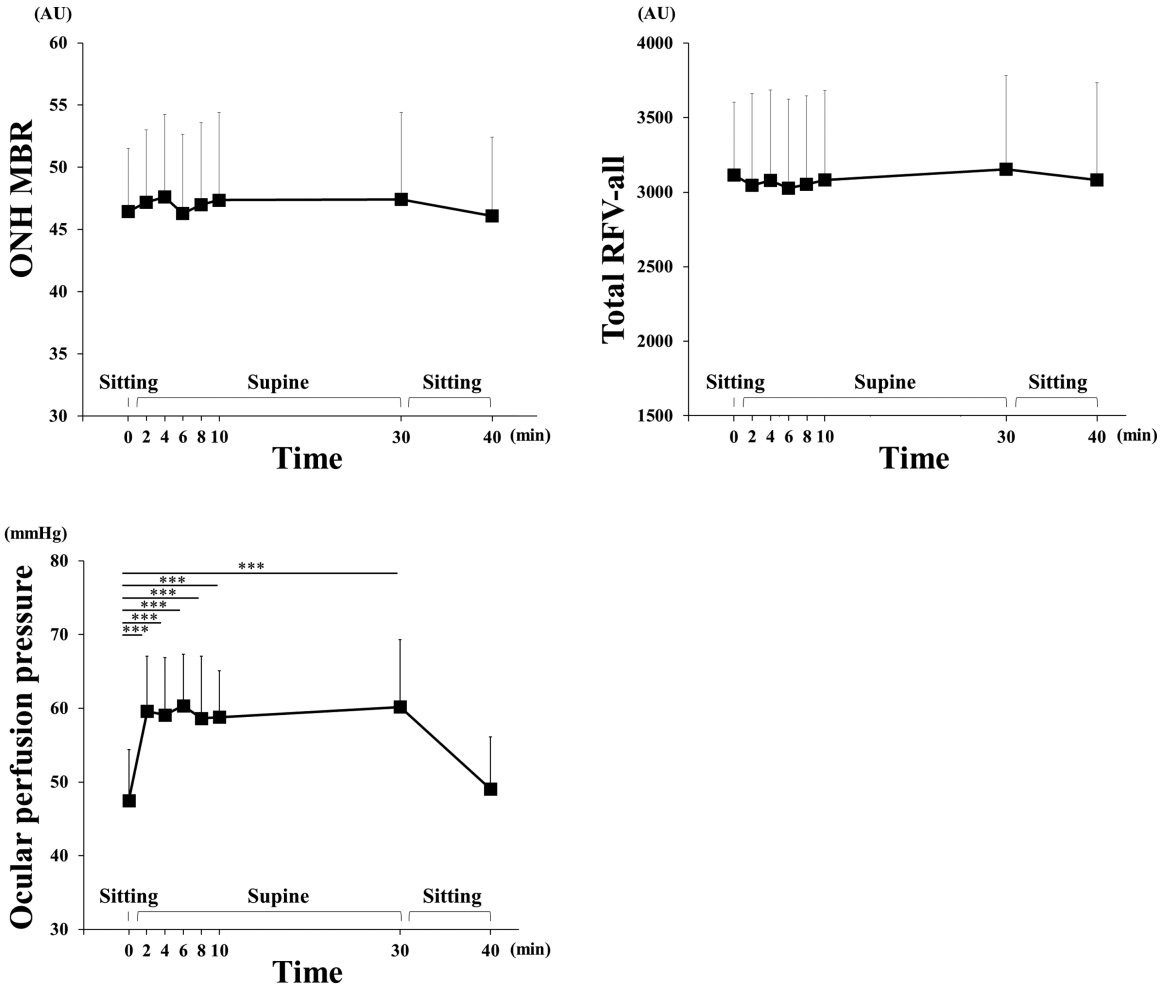

Figure 7. Changes in the ocular blood flow parameters in Experiment 2. The mean OPP was significantly increased after changing posture to the supine position, but the other parameters did not significantly change before and after changing posture. ***P <0.001.

In evaluating the blood flow for all of the measurable vessels determined by LSFG, the mean number of vessels was 15.6 ± 2.2 per eye, which was much higher than that reported for earlier studies.[42–46] Interestingly, the results in such situations of evaluating all of the measurable vessels were not similar to that in evaluating a small number of vessels in our study. The total retinal blood flow volume, the mean retinal flow volume per vessel, the MBR, and the mean vessel diameter in the superior retina were greater than that in the inferior retina in evaluating all of the measurable vessels. In addition, the ratio of the total RFV of the superior to the inferior retina in each eye was significantly correlated

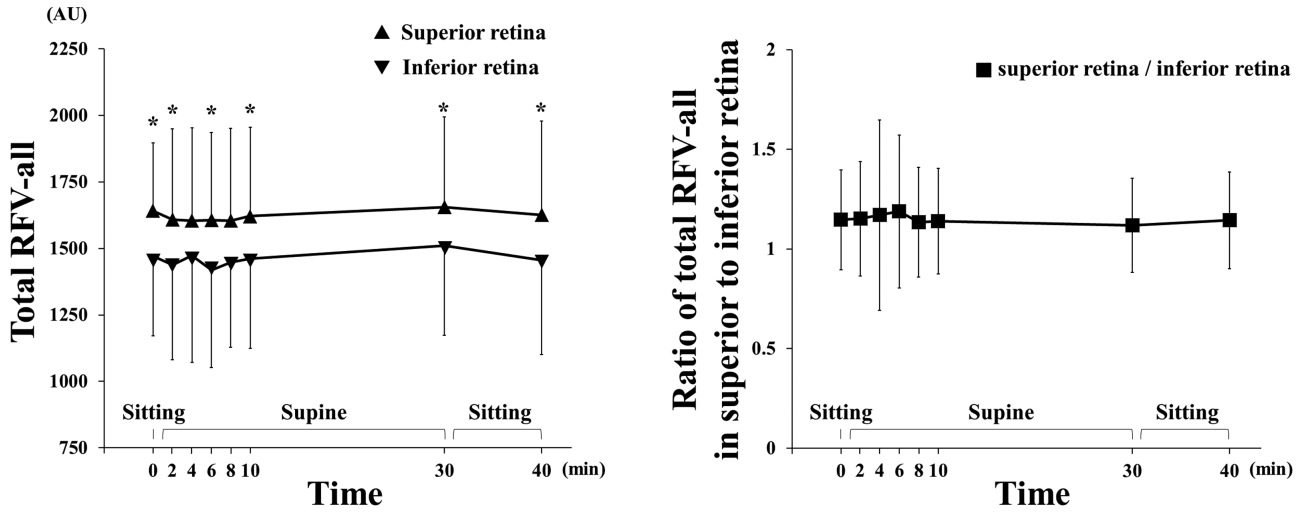

Figure 8. Differences in the total RFV-all between the superior and inferior retina in Experiment 2. There were significant differences in the total RFV-all between the superior and inferior hemispheres throughout Experiment 2, except for 4 and 8 minutes after first posture change. *$P < 0.05$.

with the ratio of the number of retinal vessels and the ratio of the MBRs. These findings indicate that the number of vessels measured in addition to the MBR altered the differences in the blood flow between the superior and inferior retina. Therefore one of the differences of the results between previous reports[42–46] and our study could be because of the number of vessels analyzed.

When evaluating the blood flow for all of the measurable vessels, the results should be more precise in comparing blood flow between the superior and inferior retinas. Thus the blood flow in the superior retina is greater than in the inferior retina. Yaoeda et al.[47] examined the blood flow in the neuroretinal rim of the ONH by LSFG, and they reported that the blood flow velocity in the superior rim was higher than that in the inferior rim in 60 normal volunteers. These observations are in keeping with our results. However, there is still the possibility that there are differences in the measurement properties of LSFG and laser Doppler flowmetry.

In addition, it may not be possible to compare these findings accurately because the positional relationship between the fovea and the optic disc is slanted. Further, when examining the relationship with the difference of the whole of the retinal blood flow between the superior and inferior retina, it may not be enough to measure only parts of the macula. In the future, the development of a device that can measure the retinal status of a wider area may provide evidence for these retinal blood flow differences.

In Experiment 2, we evaluated the changes in the blood flow parameters before and after a change in the posture. Although the OPP was significantly changed by the postural alteration, no significant changes were observed in the retinal blood flow parameters. These results indicate that autoregulation was functioning.

There have been several reports on the ocular blood flow changes after postural changes. Feke and Pasquale[29] studied changes in the retinal arterial diameter, blood flow velocity, and blood flow rate, which were calculated from the diameter and velocity of the arteries. The measurements were taken 30 minutes after shifting from a sitting position to a lying position in a glaucoma group and a control group.[29] They found that the change in the blood flow rate in the reclined position was not significantly different from that in the upright position in the control group, indicating an effective autoregulation in the retinal blood flow. However, the glaucoma group showed a much broader range of blood flow changes in response to the postural change compared with the baseline blood flow. Baer and Hill[48] reported that when the retinal blood vessels were photographed with a fundus camera in a 30° head-down position, the arterial diameter decreased and the vein diameter increased. Shiga et al.[30] reported that the ONH-MBR determined by LSFG increased significantly 2 and 4 minutes after a shift from a sitting to a supine position, but returned to the initial level after 6 minutes. We do not know the exact reason for the differences between the previous findings and our results, but it may be due to differences in the measurement methods. In any case, these results indicate that the significantly higher blood flow in the superior retina was not due to gravity, OPP, or intrinsic factors.

There are several possible explanations for the difference in the retinal blood flow in the superior and inferior retina. First, the superior retina may be more active functionally than the inferior retina. Miyake et al.[49] reported that the amplitudes of the a-wave, b-wave, and oscillatory potentials of the focal electroretinograms were significantly larger in the upper macular region than in the lower macular region. Nagatomo et al.[50] reported that the amplitudes of multifocal electroretinograms were larger in the superior retina than in the inferior retina, suggesting that the superior retina was more active functionally. Second, there can be anatomic differences between the superior and inferior retina.

Versaux-Botteri et al.[51] reported that the superior retina in rats had a larger number of ganglion cells than the inferior retina. Additionally, it has been reported that the partial pressure of oxygen in the superior retina in diabetic mice during carbogen breathing was significantly lower than that in normal rats but not in the inferior retina.[52–56] Luan et al.[52] suggested that the greater metabolic demand of the superior retina may make it more susceptible to a hyperglycemic state than the inferior retina. In humans, Curcio and Allen[14] reported the density of the retinal ganglion

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cells was 65% higher at 4 mm superior to the fovea than at 4 mm inferior to the fovea. In addition, the superior retina 4 mm away from the fovea to the ora serrata had an average of 60% more ganglion cells than the inferior retina in six bank donor eyes.[14] These anatomic differences may be the cause of the differences in the blood flow. The retinal thickness was measured 2 mm away from the fovea in the vertical OCT images in our study. The superior retina was thicker than the inferior, which is consistent with earlier reports.[13,16,17] However, no significant correlation was found between the ratio of the total RFV in the superior and inferior retina and the other parameters, including the ratio of the retinal thickness and GCC thickness of each area. The difference in the retinal thickness may affect the blood flow between the superior and the inferior retina, but our results did not find sufficient anatomic evidence.

Taken together, the blood flow in the superior retina is higher than that of the inferior retina independent of the posture. This difference might be associated with the development of some retinochoroidal diseases, for example, BRVO or CSC, because more occlusion sites occur in the superior retina than in the inferior retina in eyes with a BRVO.[11] In addition, asymmetrical choroidal vessel have been reported in eyes with CSC.[37] Therefore clinicians need to pay more attention to the differences in the blood flow between the superior and inferior retina when considering the mechanism of retinochoroidal diseases.

Jeppesen and Bek[57] reported that there were significant variations in the uncorrected oxygen saturation levels in the four retinal quadrants using retinal oximetry. However, the differences were not significant when a correction was made for the linear blood velocity measured by Doppler OCT.[57] Our results showed that there were differences in the retinal blood flow variables between the superior and inferior retina. However, the oxygen saturation in the retinal vessels was not measured when using LSFG, thus the blood flow variables between the superior and inferior retina might not be significantly different if the retinal blood flow is corrected with the oxygen saturation levels.

It has been reported that the autoregulation is impaired in patients with glaucoma and with type 2 diabetes.[29,58–60] In this study, the differences in retinal blood flow between the superior and inferior retina before and after the postural changes were almost constant, but it may be possible that patients with such disorders have lost or enhanced the differences. In the future, it is necessary to examine how the difference is changed or is affected by diseases, and these results are important as a basis for future retinal blood flow studies in eyes with retinochoroidal disorders. This is especially important in studies in which the eye is divided and partially compared, as is often the case with diseases, such as BRVO and glaucoma. It is necessary to do research after recognizing that there is the difference in the superior and inferior retina.

This study has several limitations. First, it is not known whether the differences in the superior and inferior retina affect the incidence or severity of retinochoroidal disorders. These vertical differences may change for retinal diseases that can lead to an impairment of blood flow, but this is not known at this time. It is necessary to clarify the relationship between the vertical difference and diseases in the future. Second, we only measured the retinal blood flow in the peripapillary vessels that could be recognized in the LSFG images. We could not measure the smaller retinal vessels, including the capillaries. Third, the retinal thickness and GCC thickness of the superior and inferior retina were measured at 2 mm perpendicularly above and below to the center of the fovea using vertical B-scan OCT image taken by a Spectralis instrument. However, it would be better to measure those thicknesses of an averaged area with volume scans using other OCT instruments for a more accurate measurement of the thicknesses. Fourth, our exclusion criteria of the AL >27.0 mm included relatively high myopic eyes. It has been reported that the AL is correlated significantly and negatively with ocular blood flow,[61] and our results showed similar significant correlations. However, our study showed that AL was not correlated with the ratio of retinal flow volume of the superior retina to the inferior retina, which suggests that the AL would not affect the differences in blood flow between the superior and inferior. Fifth, we did not consider the differences of ocular blood flow between men and women. It has been reported that there are differences in the ocular blood flow between men and women.[62] Although there were more women than men in Experiment 1, the difference in the ocular blood flow between men and women was not considered. Sixth, tropicamide and phenylephrine were used to dilate the pupils in the Experiment 2, and phenylephrine may influence the blood flow on the ONH.[63]

Conclusions

The blood flow in the superior retina is higher than that in the inferior retina, and this difference is not affected by the posture, even though there are changes in the OPP. Clinicians need to pay attention to the differences of blood flow between the superior and inferior retina when considering the mechanism of retinochoroidal diseases. The lack of change in the blood flow when the body was shifted from a sitting position to a supine position should indicate that autoregulation was active.

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