1874-3641/23

Send Orders for Reprints to reprints@benthamscience.net

The Open Ophthalmology Journal

Content list available at: https://openophthalmologyjournal.com

CrossMark

RESEARCH ARTICLE

Changes in Choroidal Blood Flow by Diurnal Variation in Healthy Young Adults

Yuki Hashimoto[1,*], Yumi Ishimaru[1], Miho Chiyozono[1], Sakurako Imabayashi[1], Rino Umemoto[1], Toshitaka Yamanokuchi[2] and Takeshi Yoshitomi[1]

[1]*Department of Orthoptics, Faculty of Medicine, Fukuoka International University of Health and Welfare, Fukuoka 814-0001, Japan*
[2]*Department of Physical Therapy, Faculty of Medicine, Fukuoka International University of Health and Welfare, Fukuoka 814-0001, Japan*

Abstract:

Background:

Little is known about the diurnal variation in choroidal circulatory dynamics in healthy eyes.

Objective:

This study aimed to clarify the diurnal variation in choroidal circulatory hemodynamic changes in healthy participants using laser speckle flowgraphy.

Methods:

This prospective study included the left eye of 14 healthy young adults (21.9 ± 4.0 years). The mean blur rate, a quantitative index of the relative blood flow velocity, was measured by laser speckle flowgraphy. The macular mean blur rate of choroidal blood flow velocity, subfoveal choroidal thickness, intraocular pressure, systolic blood pressure, diastolic blood pressure, mean blood pressure, and ocular perfusion pressure were evaluated at eight points every 3 h over a 24-h period. In addition, differences in each parameter between daytime and night were also investigated.

Results:

Intraocular pressure, systolic blood pressure, diastolic blood pressure, mean blood pressure, ocular perfusion pressure, and macular mean blur rate were highest at 6 PM, and subfoveal choroidal thickness was thinnest at 6 PM. There was a significant positive correlation between mean blur rate and intraocular pressure, diastolic blood pressure, and mean blood pressure. Furthermore, intraocular pressure, systolic blood pressure, diastolic blood pressure, mean blood pressure, ocular perfusion pressure, and mean blur rate were significantly higher and choroidal thickness significantly lower during daytime than at night.

Conclusion:

These results suggest that choroidal circulation hemodynamics change with diurnal variations in systemic circulation involving the autonomic nervous system in healthy eyes.

Keywords: Diurnal variation, Laser speckle flowgraphy, Mean blur rate, Subfoveal choroidal thickness, Systemic circulation, Autonomic nervous system.

Article History	Received: September 21, 2022	Revised: January 13, 2023	Accepted: January 14, 2023

1. INTRODUCTION

Although autoregulatory function varies by vascular system, choroidal vessels are poorly autoregulated, and the choroid is mainly controlled by sympathetic innervation [1 - 3]. Cold pressor tests assess sympathetic responses in systemic circulatory dynamics [4]. Recently, the vascular perfusion density in healthy subjects after a cold pressor test decreased in the choroid but remained unchanged in the retina in a report examining the vascular reactivity of the retina and choroid using functional optical coherence tomography (OCT) [2]. The choroidal morphology of young healthy participants in the cold pressor test was quantitatively evaluated using enhanced depth imaging OCT (EDI-OCT), which showed a significant decrease in subfoveal choroidal thickness (SFCT) after the test [5]. Furthermore, in the normal menstrual cycle, the sympathetic nervous system is more hyperactive in the luteal

* Address correspondence to this author at the Department of Orthoptics, Faculty of Medicine, Fukuoka International University of Health and Welfare, Fukuoka 814-0001, Japan; Tel: +81-92-832-1200 Fax: +92-832-1167;
E-mail: yuki-h@takagigakuen.ac.jp

phase compared with the follicular phase, suggesting that choroidal blood flow velocity increases with changes in systemic circulatory dynamics [6].

Blood pressure (BP) increases during the daytime due to increased sympathetic nervous system activity and decreases at night due to increased parasympathetic nervous system activity [7]. According to previous reports of diurnal variation in choroidal morphology using swept-source OCT in normal subjects, SFCT decreases during the daytime and increases at night. Mean SFCT was thinnest at 6 PM and thickest at 3 AM [8]. In addition, there was a statistically significant negative correlation between the magnitude of diurnal change and age [9].

Laser speckle flowgraphy (LSFG) measures the ocular blood flow noninvasively and can quantitatively evaluate circulatory hemodynamics using the mean blur rate (MBR), which is a relative value of the blood flow velocity [6, 10 - 13]. The wavelength of the measurement light is 830 nm. The macular MBR reflects choroidal blood flow due to the absence of the inner retinal layer at the fovea [14]. The macular MBR of the choroidal circulatory dynamic was found to be most elevated at 6 PM, and the macular MBR was significantly positively correlated with diastolic BP (DBP), mean BP (MBP), and ocular perfusion pressure (OPP), but no data were measured at 3 AM [15].

In the present study, we investigated the diurnal variation in the choroidal blood flow velocity at eight points every 3 h in a 24-h period in healthy young adults using LSFG.

2. MATERIALS AND METHODS

2.1. Study Design

This was a prospective study. This study was approved by the Ethics Committee of the Fukuoka International University of Health and Welfare (approval ID: 20-fiuhw-021) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after the nature and possible consequences of the study were explained to them.

2.2. Participants

The present study included the left eye of 14 healthy volunteers (five men and nine women) with no ophthalmic, cardiovascular, or systemic diseases. The mean age was 21.9 ± 4.0 (range, 20–36) years. All participants had best-corrected visual acuity (BCVA) ≥ 20/20. Each participant underwent ophthalmic examination, including BCVA; fundus photography; refractive error, axial length, and intraocular pressure (IOP), EDI-OCT, and LSFG. SBP and DBP were also measured.

LSFG, EDI-OCT, IOP, and BP were measured at eight points every 3 h over a 24-h period from 12:00 PM the following day. The use of alcohol [16, 17], caffeine [18 - 21], and nicotine [22, 23] was prohibited from the previous day because of their effects on ocular and systemic hemodynamics. The participants were restricted from eating for 2 h before the test. Each participant rested for 10–15 min in a quiet room before the test [15]. All examinations were performed in the seated position, and each session was completed within 20 min. The examinations were conducted at room temperature (24°C ± 1°C), with a humidity of (47% ± 3%).

2.3. Choroidal Thickness Measurements

EDI-OCT (RS-3000 Advance 2; NIDEK, Gamagori, Japan) measurements were obtained every 3 h over a 24-h period. Using a horizontal scan through the fovea (scan length, 12.0 mm), the SFCT was determined by manually measuring the distance at the fovea from the outer border of the hyperreflective line, corresponding to the retinal pigment epithelium to the outer border of the choroid [5]. Two authors (Y.H. and M.C.), who were blinded to the subjects' information, independently examined EDI-OCT images.

2.4. Choroidal Circulation Measurements

LSFG measurements using LSFG-NAVI (Softcare Ltd., Fukuoka, Japan) were performed to quantitatively examine the choroidal blood flow velocity. The macular MBR is derived from the choroidal blood flow velocity as there is no inner retinal layer at the fovea; that is, it lacks retinal vessels. LSFG was examined thrice at each time point in all eyes. The positioning of the circles for analysis was determined manually by comparing fundus photographs and LSFG color map images at baseline. For followed up after baseline, each circle was automatically set using the LSFG Analyzer software (v 3.7.0.4; Softcare Ltd., Fukuoka, Japan) at the same site where the circle was set at baseline. To evaluate the changes in the mean MBR, we utilized the rates of change in the mean MBR against the initial baseline values (defined as 100%) [6, 10 - 13].

2.5. Hemodynamics

BP and IOP were measured at each time point for all participants. OPP was calculated from IOP and BP. The MBP was calculated from SBP and DBP using the following equation:

MBP = DBP + 1/3 (SBP - DBP)

OPP was calculated as follows:

OPP = 2/3MBP - IOP

2.6. Statistical Analyses

All results are expressed as mean ± standard deviation. The Wilcoxon signed-rank test was used to examine the differences in IOP, SBP, DBP, MBP, OPP, SFCT, and MBR during the daytime from 12:00 PM to 9:00 PM and at night from 12:00 AM to 9:00 AM. Spearman's rank correlation test was used to determine the relationships between the MBR and other factors. *P*-values less than 0.05 were considered statistically significant for all tests.

3. RESULTS

3.1. Ocular and Systemic Factors

Table **1** shows the clinical characteristics of the healthy participants included in this study. The changes in the diurnal variations of the ocular and systemic factors are shown in

Table **2**, and the daytime and night results are shown in Table **3**. IOP, SBP, DBP, MBP, and OPP values had the highest values at 6 PM during the course of this study. In addition, each factor was significantly higher during the daytime than that at night (*P* < 0.001, *P* < 0.001, *P* = 0.003, *P* < 0.001, and *P* = 0.008, respectively).

Table 1. Demographic characteristics for each participant.

Case	Age (years)	RE (D)	AL (mm)	Total mean IOP (mmHg)	Total mean SBP (mmHg)	Total mean DBP (mmHg)	Total mean MBP (mmHg)	Total mean OPP (mmHg)	Total mean SFCT(µm)	Total mean macular MBR	Macular MBR Max/min/max-min
1	21	+0.1	23.4	11.7±1.2	105.1±9.4	69.8±5.8	81.5±6.4	42.7±3.9	212.1±5.9	16.7±1.3	19.4/14.9/4.5
2	21	-2.6	24.9	10.8±1.0	94.0±5.0	53.6±4.2	67.1±3.7	34.0±2.4	205.3±6.6	7.3±0.6	8.0/5.9/2.1
3	20	-11.6	26.9	11.2±1.4	96.8±5.6	60.3±6.4	72.4±5.6	37.1±2.8	168.9±5.2	8.1±0.9	9.3/6.6/2.7
4	21	-5.1	24.9	12.0±1.4	100.5±6.1	61.9±5.0	74.8±4.8	37.8±3.4	269.5±8.7	21.4±1.9	24.4/18.3/6.1
5	21	-9.0	26.5	10.8±0.5	102.9±6.7	66.8±4.5	78.8±4.9	41.8±3.5	149.5±3.7	19.8±1.9	22.7/17.3/5.4
6	36	-1.0	24.4	13.4±2.0	121.3±4.1	77.0±6.1	91.8±5.1	47.8±3.0	483.9±11.3	8.7±0.5	9.3/8.0/1.3
7	20	+0.1	24.7	8.6±0.9	114.8±3.7	66.3±4.1	82.4±2.8	46.3±1.8	283.0±6.7	11.6±0.6	12.4/10.7/1.7
8	21	-1.8	24.1	11.3±0.8	119.6±7.9	70.4±6.9	86.8±6.6	46.5±3.8	383.5±6.4	15.7±1.1	17.6/13.7/3.9
9	21	-2.3	25.2	10.8±0.9	121.4±6.5	71.8±5.4	88.3±5.5	48.1±3.0	372.8±10.3	11.4±0.5	12.0/10.2/1.8
10	21	-2.8	25.9	10.7±1.1	105.5±5.0	61.1±4.3	75.9±2.7	39.9±1.5	159.5±4.0	10.8±0.7	12.1/10.1/2.0
11	21	+0.1	23.8	10.0±0.8	99.6±8.7	61.8±4.0	74.4±5.2	39.6±3.3	267.8±10.4	6.4±0.4	7.0/5.7/1.3
12	21	-0.7	23.1	9.7±1.0	102.9±3.1	62.8±3.4	76.1±3.0	41.1±1.8	316.0±6.3	5.3±0.5	5.8/4.4/1.4
13	21	-1.3	24.3	10.7±0.9	111.8±5.7	72.1±4.9	85.3±4.6	46.2±3.2	361.3±9.0	7.3±0.4	8.2/6.8/1.4
14	21	-3.6	23.9	11.6±1.9	105.3±4.9	63.1±2.3	77.2±2.6	39.9±2.9	334.9±10.5	12.8±0.6	13.6/11.8/1.8
Mean ± SD	21.9 ± 4.0	-2.9 ± 3.4	24.7 ± 1.1	10.9 ± 1.1	107.2 ± 9.0	65.6 ± 6.1	79.5 ± 6.9	42.1 ± 4.4	283.4 ± 98.4	11.7 ± 5.0	12.3/ 11.0/ 1.3

Abbreviations:SD, standard deviation; RE, refractive error; D, diopter; AL, axial length; IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; OPP, ocular perfusion pressure; SFCT, subfoveal choroidal thickness; MBR, mean blur rate OPP was calculated as:

Table 2. Diurnal changes in ocular and systemic factors.

Examination	Noon	3 PM	6 PM	9 PM	Midnight	3 AM	6 AM	9 AM
IOP (mmHg)	11.9±1.9	11.2±1.2	11.9±1.6	10.4±1.5	10.0±1.2	10.5±1.6	11.1±1.3	10.6±1.4
SBP (mmHg)	110.0±9.8	107.3±12.0	113.1±10.8	109.1±8.8	106.1±11.3	103.9±9.4	103.6±10.7	104.7±9.6
DBP (mmHg)	68.0±7.6	65.7±6.7	69.4±8.4	65.0±8.2	63.9±7.0	65.1±7.1	64.5±8.0	63.2±7.0
MBP (mmHg)	82.0±7.8	79.6±8.1	83.9±8.6	79.7±7.9	78.0±7.7	78.1±7.1	77.5±8.4	77.0±7.5
OPP (mmHg)	42.8±5.3	41.9±5.3	44.1±5.3	42.7±5.4	42.1±5.2	41.6±4.0	40.6±5.5	40.8±4.9
SFCT (µm)	281.9±98.0	281.8±98.0	276.1±96.6	278.6±98.9	283.5±96.7	290.4±101.9	288.6±100.0	286.4±98.8
Macular MBR	12.0±5.5	12.0±5.3	12.3±5.5	11.5±4.6	11.3±4.5	11.6±5.4	11.7±5.5	11.0±4.6

Abbreviations:(Mean±SD)
SD, standard deviation; IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; OPP, ocular perfusion pressure; SFCT, subfoveal choroidal thickness; MBR, mean blur rate

Table 3. Comparison of daytime and night for each factor.

-	Daytime	Night	*P* value
IOP (mmHg)	11.3±1.6	10.5±1.3	<0.001
SBP (mmHg)	109.9±10.3	104.6±10.0	<0.001
DBP (mmHg)	67.0±7.7	64.2±7.1	0.003
MBP (mmHg)	81.3±8.0	77.7±7.5	<0.001
OPP (mmHg)	42.9±5.2	41.2±4.8	0.008
SFCT (µm)	279.6±95.1	287.2±96.6	<0.001
Macular MBR	12.0±5.1	11.4±4.8	0.001

Abbreviations:(Mean±SD)
SD, standard deviation; IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ocular perfusion pressure; SFCT, subfoveal choroidal thickness; MBR, mean blur rate

Table 4. Relationship between MBR and other factors.

-	Macular MBR	
	Coefficient	***P* value**
IOP	0.325	<0.001
SBP	0.164	0.083
DBP	0.199	0.035
MBP	0.202	0.032
OPP	0.122	0.199
SFCT	-0.142	0.134

Abbreviations: MBR, mean blur rate; IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; OPP, ocular perfusion pressure; SFCT, subfoveal choroidal thickness.

3.2. Choroidal Thickness Changes

SFCT changes in the participants are shown in Table **2**, and the daytime and night results are shown in Table **3**. The mean SFCT values during the course of this study were 281.9 ± 98.0, 281.8 ± 98.0, 276.1 ± 96.6, 278.6 ± 98.9, 283.5 ± 96.7, 290.4 ± 101.9, 288.6 ± 100.0, and 286.4 ± 98.8 μm in the healthy eyes. The SFCT values were most reduced at 6 PM and most elevated at 3 AM. In addition, SFCT was significantly lower during the daytime than at night ($P < 0.001$).

3.3. Macular MBR Changes

MBR changes in the participants are shown in Table **2**, and the daytime and night results are shown in Table **3**. The mean macular MBR values during the course of this study were 12.0 ± 5.5, 12.0 ± 5.3, 12.3 ± 5.5, 11.5 ± 4.6, 11.3 ± 4.5, 11.6 ± 5.4, 11.7 ± 5.5, and 11.0 ± 4.6 in the healthy eyes. The MBR values were highest at 6 PM and lowest at 9 AM. MBR was significantly higher during the daytime than at night (P = 0.001).

3.4. Correlation between MBR and other Factors

The correlation between the differences in the macular MBR and other factors is shown in Table **4**. The MBR value showed a statistically significant positive correlation for IOP, DBP, and MBP (R = 0.325, $P < 0.001$; R = 0.199, P = 0.035; and R = 0.202, P = 0.032, respectively). In contrast, there was no significant correlation between MBR and SBP, OPP, or SFCT (R = 0.164, P = 0.083; R = 0.122, P = 0.199; and R = –0.142, P = 0.134, respectively).

4. DISCUSSION

To the best of our knowledge, this is the first study to examine the diurnal variation of the macular MBR in healthy young adults at eight points every 3 h using LSFG. In the present study, IOP, SBP, DBP, MBP, and OPP were highest at 6 PM. Macular MBR was most increased at 6 PM and most decreased at 9 AM. In contrast, the SFCT was thinnest at 6 PM and thickest at 3 AM. There was a significant positive correlation between the MBR and IOP, DBP, or MBP. Furthermore, IOP, SBP, DBP, MBP, OPP, and macular MBR were significantly higher during the daytime compared with at night; however, it was significantly decreased for SFCT.

Cold pressor tests assess sympathetic responses in systemic circulatory dynamics [4]. SBP, DBP, MBP, and OPP increased significantly, but SFCT decreased significantly after the cold pressor test in young healthy participants [5]. BP increases during the daytime due to increased sympathetic nervous system activity and decreases at night due to increased parasympathetic nervous system activity [7]. Previous reports of diurnal variations in choroidal morphology in healthy subjects have shown that BP increases and SFCT decreases during the daytime when the sympathetic nervous system is active. In contrast, BP decreases and SFCT increases at night when the parasympathetic nervous system is active [8, 15]. The SFCT was thickest between 3 AM and 9 AM and thinnest between 3 PM and 9 PM [8].

The diurnal variations of the macular MBR had significant diurnal variations with a peak at 6 PM, and macular MBR was significantly positively correlated with DBP, MBP, and OPP [15]. In addition, previous studies showing a significant increase in choroidal blood flow velocity with increasing IOP, BP, and OPP after isometric exercise in healthy individuals have indicated that choroidal circulatory dynamics are dependent on systemic circulatory dynamics [3, 24, 25]. Recently, in a report examining the vascular reactivity of the retina and choroid using functional OCT, the vascular perfusion density in healthy subjects after a cold pressor test decreased in the choroid but remained unchanged in the retina. Furthermore, the choroidal vascular perfusion density has a strong inverse correlation with the integrated muscle sympathetic nerve activity [2]. In young healthy women with normal menstrual cycles, the sympathetic nervous system is more active during the luteal phase compared with during the follicular phase, suggesting that choroidal blood flow velocity increases in response to increased systemic hemodynamics, and the MBR exhibited a significant positive correlation with changes in DBP and MBP [6].

In this study, IOP, SBP, MBP, OPP, and macular MBR were highest at 6 PM. These values were also significantly higher during the daytime, when the sympathetic nervous system was dominant than at night when the parasympathetic nervous system was dominant. In contrast, the SFCT showed the most decrease at 6 PM, which was significantly lower during daytime than at night. Notably, there was a significant positive correlation between macular MBR and IOP, DBP, and MBP. In contrast, MBR and SFCT did not show a significant correlation, but the results of this study support previous reports that have found no significant correlation between SFCT and choroidal blood flow or velocity [15, 26]. Thus, it is suggested that a variety of factors are associated with choroidal changes. In addition, since it has been reported that the diurnal variation in SFCT is negatively correlated with age [9], the diurnal variation in choroidal circulatory dynamics should also be examined in a larger number of participants with a wider age range in the future.

CONCLUSION

In conclusion, these results suggest that choroidal circulatory dynamics change with diurnal changes in systemic circulation in healthy eyes. Therefore, when taking these measurements in clinical practice, it may be necessary to consider the interpretation of the data depending on the time of the measurement.

LIST OF ABBREVIATIONS

BCVA	=	Best-corrected Visual Acuity
BP	=	Blood Pressure
EDI-OCT	=	Enhanced Depth Imaging Optical Coherence Tomography
DBP	=	Diastolic Blood Pressure
IOP	=	Intraocular Pressure
LSFG	=	Laser Speckle Flowgraphy
MBP	=	Mean Blood Pressure
MBR	=	Mean Blur Rate
OPP	=	Ocular Perfusion Pressure
SBP	=	Systolic Blood Pressure
SFCT	=	Subfoveal Choroid Thickness

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Fukuoka International University of Health and Welfare (approval ID: 20-fiuhw-021).

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the humans were used in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants after the nature and possible consequences of the study were explained to them.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article and its supplementary information files. The authors confirm that the data supporting the findings of this study is available upon reasonable request from the corresponding author [Y.H].

FUNDING

This work was financially supported by the JSPS KAKENHI (Funder ID: 90849689. Grant Number: JP20K19698).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Delaey C, van de Voorde J. Regulatory mechanisms in the retinal and choroidal circulation. Ophthalmic Res 2000; 32(6): 249-56. [http://dx.doi.org/10.1159/000055622] [PMID: 11015035]

[2] Jendzjowsky NG, Steinback CD, Herman RJ, Tsai WH, Costello FE, Wilson RJA. Functional-optical coherence tomography: A non-invasive approach to assess the sympathetic nervous system and intrinsic vascular regulation. Front Physiol 2019; 10: 1146. [http://dx.doi.org/10.3389/fphys.2019.01146] [PMID: 31572206]

[3] Okuno T, Sugiyama T, Kohyama M, Kojima S, Oku H, Ikeda T. Ocular blood flow changes after dynamic exercise in humans. Eye 2006; 20(7): 796-800. [http://dx.doi.org/10.1038/sj.eye.6702004] [PMID: 16021186]

[4] Budidha K, Kyriacou PA. Photoplethysmography for quantitative assessment of sympathetic nerve activity (SNA) during cold stress. Front Physiol 2019; 9: 1863. [http://dx.doi.org/10.3389/fphys.2018.01863] [PMID: 30687108]

[5] Umemoto R, Hashimoto Y, Imabayashi S, Yoshitomi T. Changes in choroidal thickness in healthy participants after induction of sympathetic hyperactivity using the cold pressor test. Graefes Arch Clin Exp Ophthalmol 2022; 261(2): 585-7. [http://dx.doi.org/10.1007/s00417-022-05820-5] [PMID: 36053330]

[6] Haneda M, Hashimoto Y, Mishima A, Saito D, Yoshitomi T. Changes in choroidal circulation hemodynamics during the menstrual cycle in young, healthy women. PLoS One 2022; 17(6): e0270501. [http://dx.doi.org/10.1371/journal.pone.0270501] [PMID: 35759478]

[7] Deryagina GP, Kraevskii YM. Circadian rhythm of body temperature, blood pressure, and heart rate. Hum Physiol 1983; 9(2): 133-40. [PMID: 6671656]

[8] Usui S, Ikuno Y, Akiba M, *et al.* Circadian changes in subfoveal choroidal thickness and the relationship with circulatory factors in healthy subjects. Invest Ophthalmol Vis Sci 2012; 53(4): 2300-7. [http://dx.doi.org/10.1167/iovs.11-8383] [PMID: 22427554]

[9] Osmanbasoglu OA, Alkin Z, Ozkaya A, Ozpınar Y, Yazici AT, Demirok A. Diurnal choroidal thickness changes in normal eyes of Turkish people measured by spectral domain optical coherence tomography. J Ophthalmol 2013; 2013: 1-6. [http://dx.doi.org/10.1155/2013/687165] [PMID: 23589769]

[10] Saito M, Saito W, Hashimoto Y, *et al.* Macular choroidal blood flow velocity decreases with regression of acute central serous chorioretinopathy. Br J Ophthalmol 2013; 97(6): 775-80. [http://dx.doi.org/10.1136/bjophthalmol-2012-302349] [PMID: 23532615]

[11] Hashimoto Y, Saito W, Saito M, *et al.* Decreased choroidal blood flow velocity in the pathogenesis of multiple evanescent white dot syndrome. Graefes Arch Clin Exp Ophthalmol 2015; 253(9): 1457-64. [http://dx.doi.org/10.1007/s00417-014-2831-z] [PMID: 25341956]

[12] Hirooka K, Saito W, Namba K, *et al.* Relationship between choroidal blood flow velocity and choroidal thickness during systemic corticosteroid therapy for Vogt–Koyanagi–Harada disease. Graefes Arch Clin Exp Ophthalmol 2015; 253(4): 609-17. [http://dx.doi.org/10.1007/s00417-014-2927-5] [PMID: 25619665]

[13] Yamashita Y, Hashimoto Y, Namba K, Mizuuchi K, Ishida S. Optic nerve head microcirculation in eyes with Vogt-Koyanagi-Harada disease, accompanied by anterior ischemic optic neuropathy. Case Rep Ophthalmol 2021; 12(3): 899-908. [http://dx.doi.org/10.1159/000520036] [PMID: 34950018]

[14] Isono H, Kishi S, Kimura Y, Hagiwara N, Konishi N, Fujii H. Observation of choroidal circulation using index of erythrocytic

velocity. Arch Ophthalmol 2003; 121(2): 225-31.
[http://dx.doi.org/10.1001/archopht.121.2.225] [PMID: 12583789]

[15] Iwase T, Yamamoto K, Ra E, Murotani K, Matsui S, Terasaki H. Diurnal variations in blood flow at optic nerve head and choroid in healthy eyes: diurnal variations in blood flow. Medicine 2015; 94(6): e519.
[http://dx.doi.org/10.1097/MD.0000000000000519] [PMID: 25674750]

[16] Klatsky AL, Friedman GD, Siegelaub AB, Gérard MJ. Alcohol consumption and blood pressure. kaiser-permanente multiphasic health examination data. N Engl J Med 1977; 296(21): 1194-200.
[http://dx.doi.org/10.1056/NEJM197705262962103] [PMID: 854058]

[17] MacMahon S. Alcohol consumption and hypertension. Hypertension 1987; 9(2): 111-21.
[http://dx.doi.org/10.1161/01.HYP.9.2.111] [PMID: 3546118]

[18] Nurminen M-L, Niittynen L, Korpela R, Vapaatalo H. Coffee, caffeine and blood pressure: A critical review. Eur J Clin Nutr 1999; 53(11): 831-9.
[http://dx.doi.org/10.1038/sj.ejcn.1600899] [PMID: 10556993]

[19] Mahmud A, Feely J. Acute effect of caffeine on arterial stiffness and aortic pressure waveform. Hypertension 2001; 38(2): 227-31.
[http://dx.doi.org/10.1161/01.HYP.38.2.227] [PMID: 11509481]

[20] Worthley MI, Prabhu A, De Sciscio P, Schultz C, Sanders P, Willoughby SR. Detrimental effects of energy drink consumption on platelet and endothelial function. Am J Med 2010; 123(2): 184-7.
[http://dx.doi.org/10.1016/j.amjmed.2009.09.013] [PMID: 20103032]

[21] Freestone S, Ramsay LE. Effect of coffee and cigarette smoking on the blood pressure of untreated and diuretic-treated hypertensive patients. Am J Med 1982; 73(3): 348-53.
[http://dx.doi.org/10.1016/0002-9343(82)90725-2] [PMID: 7124761]

[22] Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med 1976; 295(11): 573-7.
[http://dx.doi.org/10.1056/NEJM197609092951101] [PMID: 950972]

[23] Tachmes L, Fernandez RJ, Sackner MA. Hemodynamic effects of smoking cigarettes of high and low nicotine content. Chest 1978; 74(3): 243-6.
[http://dx.doi.org/10.1378/chest.74.3.243] [PMID: 688779]

[24] Polska E, Simader C, Weigert G, *et al.* Regulation of choroidal blood flow during combined changes in intraocular pressure and arterial blood pressure. Invest Ophthalmol Vis Sci 2007; 48(8): 3768-74.
[http://dx.doi.org/10.1167/iovs.07-0307] [PMID: 17652750]

[25] Riva CE, Titze P, Hero M, Movaffaghy A, Petrig BL. Choroidal blood flow during isometric exercises. Invest Ophthalmol Vis Sci 1997; 38(11): 2338-43.
[PMID: 9344357]

[26] Sogawa K, Nagaoka T, Takahashi A, *et al.* Relationship between choroidal thickness and choroidal circulation in healthy young subjects. Am J Ophthalmol 2012; 153(6): 1129-1132.e1.
[http://dx.doi.org/10.1016/j.ajo.2011.11.005] [PMID: 22310083]