

Article

Changes in Choroidal Circulation Hemodynamics Measured Using Laser Speckle Flowgraphy after a Cold Pressor Test in Young Healthy Participants

Sakurako Imabayashi ¹, Yuki Hashimoto ^{1,*}, Yumi Ishimaru ¹, Rino Umemoto ¹, Miho Chiyozone ¹, Toshitaka Yamanokuchi ² and Takeshi Yoshitomi ¹

¹ Department of Orthoptics, Faculty of Medicine, Fukuoka International University of Health and Welfare, Momochihama 3-6-40, Sawara-ku, Fukuoka 814-0001, Japan

² Department of Physical Therapy, Faculty of Medicine, Fukuoka International University of Health and Welfare, Momochihama 3-6-40, Sawara-ku, Fukuoka 814-0001, Japan

* Correspondence: yuki-h@takagigakuen.ac.jp

Abstract: Using laser speckle flowgraphy (LSFG), we investigated the time course of changes in choroidal circulation hemodynamics after a cold pressor test in healthy eyes. This prospective study included the right eye of 19 young healthy participants. The macular mean blur rate (MBR) was measured with LSFG. The MBR, intraocular pressure (IOP), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), mean blood pressure (MBP), and ocular perfusion pressure (OPP) were evaluated at baseline; immediately after the test and 10, 20, and 30 min later. Immediately after the test (0 min), SBP, DBP, MBP, and OPP were significantly elevated compared with those at baseline. The macular MBR significantly increased by $+10.3 \pm 7.1\%$ immediately after the test. However, there was no change after 10, 20, and 30 min in the above parameter. A significant positive correlation of the macular MBR with the SBP, MBP, and OPP was observed. In young healthy individuals, increased sympathetic activity induced by a cold pressor test increases choroidal hemodynamics in the macula along with an increase in systemic circulatory dynamics, which normalizes after 10 min. Therefore, LSFG may provide a novel approach for assessing sympathetic activity and intrinsic vascular responsiveness in the eye.

Keywords: choroidal circulation hemodynamics; laser speckle flowgraphy; mean blur rate



Citation: Imabayashi, S.; Hashimoto, Y.; Ishimaru, Y.; Umemoto, R.; Chiyozone, M.; Yamanokuchi, T.; Yoshitomi, T. Changes in Choroidal Circulation Hemodynamics Measured Using Laser Speckle Flowgraphy after a Cold Pressor Test in Young Healthy Participants. *Tomography* **2023**, *9*, 790–797. <https://doi.org/10.3390/tomography9020064>

Academic Editor: Emilio Quaia

Received: 7 January 2023

Revised: 1 April 2023

Accepted: 3 April 2023

Published: 6 April 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Stress caused by cold exposure activates the sympathetic nervous system, resulting in increased blood pressure (BP) and heart rate (HR); these are known as pressor responses, and cold pressor tests are performed to assess sympathetic responses in systemic circulatory dynamics [1–5]. The cold pressor test is a common stress test for evaluating BP and HR responses to cooling and involves cooling hands, feet, or the whole body. This test is used to screen individuals for hypertension, and the cardiovascular responses may be used to predict future hypertension [1,2].

The choroidal blood supply accounts for 85% of the total ocular blood flow [6]. Autoregulation varies among vascular systems, and choroidal vessels are poorly autoregulated [7–9]. Moreover, human and animal studies have also shown some degree of autoregulation of choroidal vessels in response to changes in ocular perfusion pressure (OPP) [10,11]. In addition, the regulatory mechanisms of the choroidal circulation compensate better for increases in BP than for increases in intraocular pressure (IOP), and for the same OPP, blood flow is better regulated at lower, rather than at higher IOPs [11]. However, since the choroid is mainly controlled by sympathetic innervation [7–9], choroidal autoregulation is also affected by IOP, BP, OPP, and sympathetic input [12]. It has been reported that the choroidal morphology of healthy participants was quantitatively evaluated using

enhanced depth imaging optical coherence tomography using the cold pressor test; the results showed a significant decrease in subfoveal choroidal thickness after the test. In addition, changes in Systolic BP (SBP), diastolic BP (DBP), mean BP (MBP), HR, OPP, IOP, and choroidal morphology from pre-test to immediately post-test were reported to be not significantly different by sex [13].

Laser speckle flowgraphy (LSFG) can be used to noninvasively measure choroidal blood flow and has the advantage of providing reproducible data throughout retinochoroidal diseases [14–18]. The mean blur rate (MBR) is a quantitative index of relative blood flow velocity. It has been reported that sex-related differences are not present in choroidal blood flow in healthy subjects using LSFG [19]. Acute central serous chorioretinopathy (CSC) is a common ocular disease caused by increased sympathetic nerve activity and/or a stress-prone personality. A previous study on acute CSC demonstrated an increased macular MBR at the acute stage, validating choroidal blood flow elevation as a factor in the pathogenesis of acute CSC [15,16]. Furthermore, a recent study reported that the macular MBR increases in the acute phase of hypertensive chorioretinopathy, caused by choroidal hyperperfusion [17].

Additionally, previous reports of a significant increase in choroidal blood flow velocity with increasing IOP, BP, and OPP after isometric exercise in healthy individuals indicate that choroidal circulatory dynamics are dependent on systemic circulatory dynamics [9,11,20].

Therefore, it is hypothesized that the choroidal circulations will also increase in conjunction with the increase in systemic circulations by the cold pressor test. This may lead to the prediction and early detection of retinochoroidal diseases and the classification of their severity. However, changes in choroidal blood flow with LSFG after an increase in sympathetic activity induced by a cold pressor test have not yet been assessed. In this study, we investigated the time course of changes in the MBR after a cold pressor test using LSFG.

2. Materials and Methods

2.1. Participants

This study was approved by the ethics committee of Fukuoka International University of Health and Welfare (approval ID: 20-fiuhw-022) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

This prospective study included the right eyes of 19 young healthy volunteers (4 males, 15 females) with no ophthalmic or cardiovascular diseases (Table S1). All participants were recruited using the voluntary response type of non-probability sampling.

Each participant underwent examinations, including best-corrected visual acuity, fundus photography, IOP, and LSFG. SBP, DBP, and HR were also measured.

2.2. Cold Pressor Test

The examinations were carried out in a quiet examination room at room temperature (24 ± 1 °C), and humidity was maintained at $47 \pm 3\%$. During the cold pressor test, the right hand was immersed up to the wrist in ice water at approximately 1 °C for 30 s [5,13]. LSFG, IOP, BP, and HR measurements were assessed at baseline, immediately after the test (0 min), and 10, 20, and 30 min later. At all measurement points, BP and HR were measured first; LSFG was performed second, followed by IOP testing. All examinations were performed in the sitting position, and each experimental session (each measurement time of 90 s for BP and HR, 12 s for LSFG, and 15 s for IOP) was completed within 3 min. Additionally, the participants were asked not to smoke or exercise for at least 2 h before the examinations and were allowed to rest for 10 min in a quiet room.

2.3. LSFG Measurement

LSFG targets moving red blood cells in the deep choroidal vessels using an 830 nm diode laser to illuminate the ocular fundus. The laser speckle method is advantageous because it is quantitative and replicable, and its application to measure ocular blood velocity has been previously reported to yield reproducible results [14,21,22]. LSFG-NAVI (Softcare

Ltd., Fukuoka, Japan) was used to measure the hemodynamics of the posterior fundus. The pupils of each participant were dilated with 0.4% tropicamide, 20 min before LSFG testing. Each LSFG examination lasts 4 s, and measurements were obtained in triplicates for each of the evaluation points at baseline, immediately after the test (0 min), and 10, 20, and 30 min later. Large retinal vessels were excluded while evaluating changes in choroidal blood flow velocity at the macula (Figure 1). When participants were followed up, each region of interest (ROI) was automatically set using the LSFG Analyzer software (v 3.0.47; Softcare Ltd., Fukuoka, Japan) at the same site where the ROI was set at baseline. The size of the ROI in the measurement area was standardized for all eyes. To evaluate changes in the average MBR, we used the rate of change of the average MBR against the initial baseline values (defined as 100%) [15–17,23].

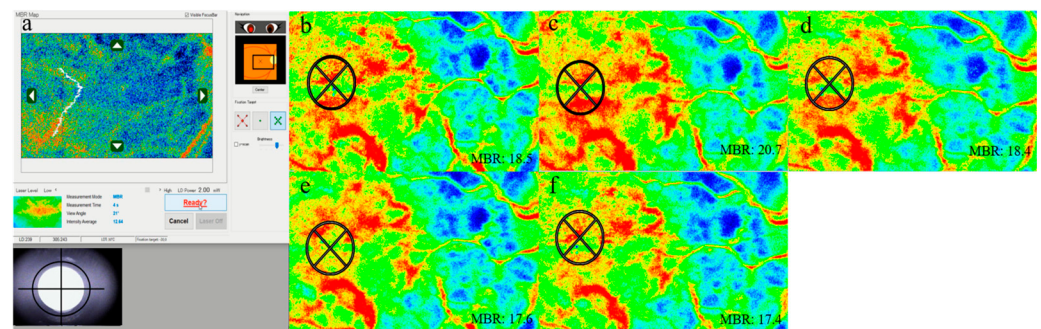


Figure 1. Laser speckle flowgraphy (LSFG) measurement screen (a) and the composite color map image of mean blur rate (MBR) at baseline (b), immediately after the test (c), and at 10 (d), 20 (e), and 30 (f) minutes later in a participant.

The measurement screen of LSFG (a). The MBR within the region of interest immediately after the cold pressor test (c) increased by 11.1% compared with that at baseline (b). However, after 10, 20, and 30 min of testing, the results were similar to those at baseline at −1.5% (d), −1.5% (e), and +0.8% (f), respectively.

2.4. Hemodynamics and IOP

For all participants, BP and IOP were measured at baseline, immediately after the cold pressor test (0 min), and 10, 20, and 30 min later. The IOP measurement was performed with a noncontact tonometer (NT-530, NIDEK, Gamagori, Japan). Hemodynamics in the eye depend on BP and IOP and are measured using an indicator called OPP, which reflects systemic circulatory dynamics. The OPP was calculated from the IOP and BP values [9]. MBP was calculated from SBP and DBP according to the following equation:

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

OPP was calculated as:

$$\text{OPP} = 2/3\text{MBP} - \text{IOP} \quad (2)$$

2.5. Statistics

All results are expressed as the mean $\pm$ standard deviation. The Friedman test and Scheffe's paired comparison test were used to examine sequential changes in IOP, SBP, DBP, MBP, HR, OPP, and the MBR. Spearman's rank correlation test was used to determine the relationships between the rate of change in MBR and other studied factors, including IOP, SBP, DBP, MBP, HR, and OPP. For all tests, p values < 0.05 indicated statistical significance.

3. Results

The mean age was 22.3 ± 3.3 years (range, 21 to 36 years). All participants had a best-corrected visual acuity score $\geq 20/20$.

3.1. IOP and Systemic Factors

Changes in the values of IOP and other systemic factors are summarized in Tables 1 and S1. The IOP and HR did not change throughout the study (Table 1 and Figure 2a,e). While SBP, DBP, and MBP significantly increased immediately after the cold pressor test (0 min) compared with those at baseline, they showed no changes after 10, 20, and 30 min (Table 1 and Figure 2b–d).

Table 1. Changes in ocular biometric parameters and systemic factors at baseline and after the cold pressor tests.

	Baseline	Post				Friedman Test (<i>p</i> Value)	Scheffe's Paired Comparison (<i>p</i> Value)			
		0 min	10 min	20 min	30 min		0 min	10 min	20 min	30 min
IOP (mmHg)	13.3 ± 2.2	13.2 ± 2.2	12.7 ± 2.3	12.7 ± 2.4	12.6 ± 2.3	0.232	0.991	0.783	0.613	0.374
SBP (mmHg)	101.2 ± 8.3	109.3 ± 8.2 ***	102.6 ± 7.3	103.2 ± 8.6	102.4 ± 8.6	<0.001	<0.001	0.443	0.533	0.623
DBP (mmHg)	66.8 ± 7.0	70.2 ± 8.4 *	66.6 ± 7.0	66.2 ± 8.0	66.5 ± 7.9	<0.001	0.025	0.982	0.982	0.996
MBP (mmHg)	78.3 ± 7.1	83.2 ± 7.5 **	78.6 ± 6.8	78.5 ± 7.9	78.4 ± 7.6	<0.001	0.005	0.983	0.994	0.998
HR (bpm)	78.8 ± 9.6	79.1 ± 9.8	77.3 ± 8.5	77.0 ± 8.6	76.9 ± 8.7	0.565	0.999	0.970	0.815	0.951
OPP (mmHg)	38.9 ± 5.0	42.3 ± 5.6 **	39.7 ± 4.2	39.7 ± 5.4	39.7 ± 4.8	0.001	0.004	0.776	0.901	0.931
MBR	12.9 ± 6.2	14.2 ± 7.0 ***	13.1 ± 6.2	12.5 ± 5.5	13.2 ± 6.5	<0.001	<0.001	0.894	0.969	0.987
MBR (%)	100.0 ± 0.0	110.3 ± 7.1 ***	101.6 ± 3.8	100.2 ± 13.4	102.3 ± 6.6	<0.001	<0.001	0.894	0.969	0.987

IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; bpm, beats per minute; OPP, ocular perfusion pressure; MBR, mean blur rate; min, minutes. Results are expressed as the mean ± standard deviation. Scheffe's paired comparison, * $p < 0.05$, ** $p < 0.01$ *** $p < 0.001$.

The mean IOP and HR did not change throughout the study (Friedman test = 0.232, 0.565, respectively) (Figure 2a,e). The mean SBP (Figure 2b), DBP (Figure 2c), MBP (Figure 2d), ocular perfusion pressure (OPP) (Figure 2f), MBR, (Figure 2g), and MBR (%) (Figure 2h) significantly increased immediately after the cold pressor test (0 min) compared with those at baseline ($p < 0.001$, $p = 0.025$, $p = 0.005$, $p = 0.004$, $p < 0.001$, $p < 0.001$); they showed no changes after 10, 20, and 30 min.

3.2. OPP Data

The changes in the OPP are presented in Table 1 and Table S1. The mean OPP was 38.9 ± 5.0 mmHg at baseline, 42.3 ± 5.6 mmHg at 0 min, 39.7 ± 4.2 mmHg at 10 min, 39.7 ± 5.4 mmHg at 20 min, and 39.7 ± 4.8 mmHg at 30 min after the cold pressor test. The mean OPP value at 0 min was significantly higher than the baseline value; however, there was no significant difference at 10, 20, and 30 min relative to the baseline data (Table 1 and Figure 2f).

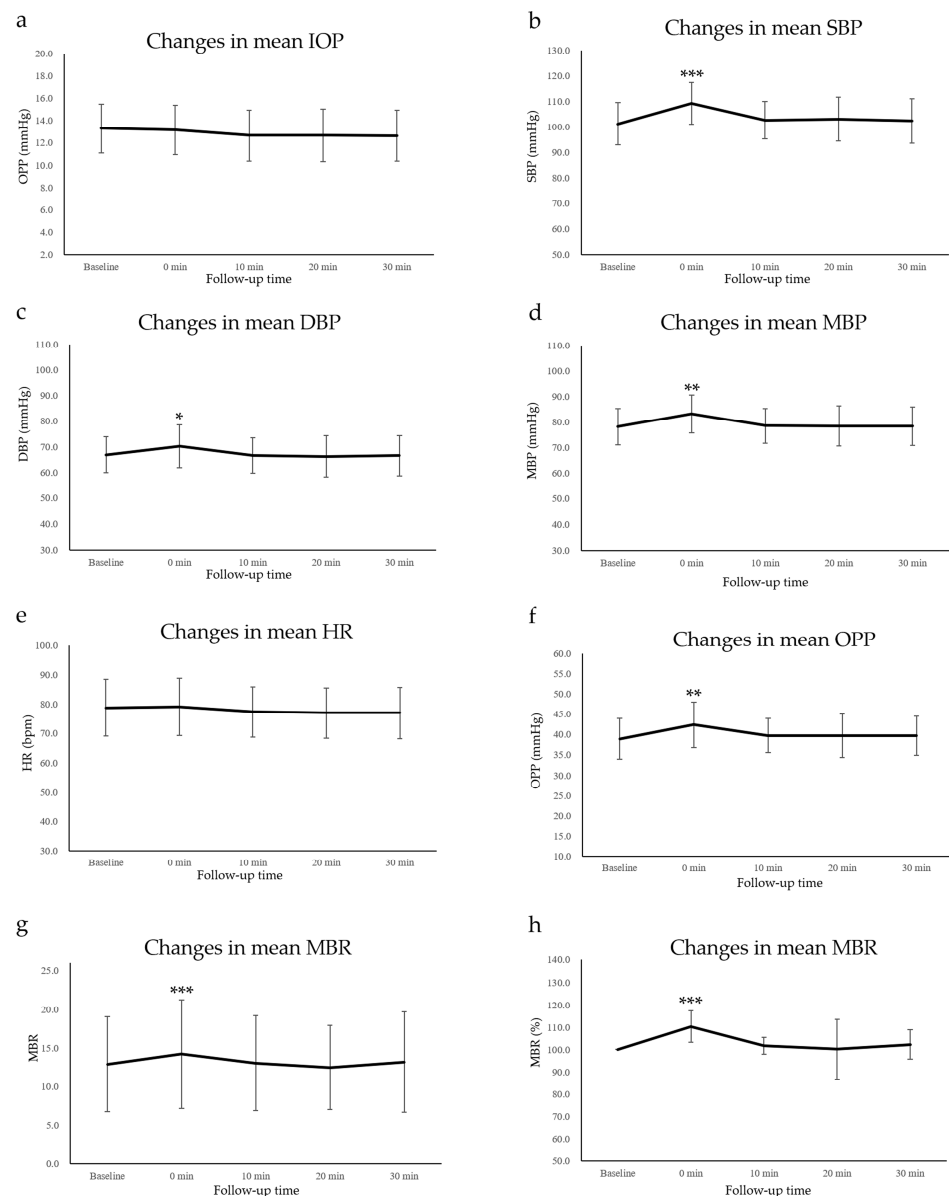


Figure 2. Changes in intraocular pressure (IOP) (a), systolic blood pressure (SBP) (b), diastolic blood pressure (DBP) (c), mean blood pressure (MBP) (d), heart rate (HR) (e), ocular perfusion pressure (OPP) (f), MBR (g), and MBR (%) (h) at baseline and after the cold pressor tests (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

3.3. LSFG Data

MBR changes are presented in Table 1 and Table S1. The average macular MBR values at baseline, immediately after the cold pressor test (0 min), and 10, 20, and 30 min later, respectively, were 12.9 ± 6.2 , 14.2 ± 7.0 , 13.1 ± 6.2 , 12.5 ± 5.5 , and 13.2 ± 6.5 . The macular MBR values significantly increased by $+10.3 \pm 7.1\%$ immediately after the test, but there was no significant difference at 10, 20, and 30 min relative to the baseline data (Table 1 and Figure 2g,h).

3.4. Correlation between MBR and the Other Studied Factors

The correlation between the rate of change in MBR and changes in other studied factors from baseline to a point immediately after the cold pressor test (0 min) was examined. MBR showed a statistically significant positive correlation with SBP, MBP, and OPP (Table 2). However, MBR showed no significant correlation with IOP, DBP, and HR (Table 2).

Table 2. Relationship between MBR and other studied factors.

	Macular MBR	
	Coefficient	<i>p</i> Value
IOP	−0.196	0.421
SBP	0.732	<0.001
DBP	0.196	0.420
MBP	0.545	0.015
HR	−0.009	0.704
OPP	0.495	0.030

MBR, mean blur rate; IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; OPP, ocular perfusion pressures.

4. Discussion

In this study, SBP, DBP, MBP, OPP, and MBR increased significantly after the cold pressor test but did not vary further after 10 or more minutes. In addition, there was a statistically significant positive correlation of the macular MBR with SBP, MBP, and OPP. These results indicate that an increase in sympathetic activity induced by cold stimulation also increases the choroidal circulation hemodynamics, depending on systemic circulatory hemodynamics, and that these values normalize after 10 min.

Previous reports have shown that both SBP and DBP increase owing to vasoconstriction caused by sympathetic hyperactivity in the cold pressor test [1–5]. Recently, in a report examining the vascular reactivity of the retina and choroid using functional optical coherence tomography, the vascular perfusion density of healthy participants after a cold pressor test decreased in the choroid but remained unchanged in the retina. Furthermore, choroidal vascular perfusion density had a strong, inverse correlation with integrated muscle sympathetic nerve activity [8].

It has been reported that choroidal blood flow velocity increases during the acute phase in sympathetic hyperactivity etiologies such as CSC. There are two possible causes of increased choroidal blood flow in eyes with acute CSC. Firstly, the activation of sympathetic α -adrenergic receptors causes vasoconstriction of the choroidal arteries and secondary overflow into the choroidal vasculature. Secondly, the cardiac output is increased owing to the activation of sympathetic β -adrenergic receptors, which increases blood flow in the choroid [15,16]. Furthermore, the MBR changes in hypertensive chorioretinopathy, where severe hypertension is an etiologic factor, are similar to those observed in CSC [17]. In the present study, choroidal blood flow velocity increased immediately after the cold pressor test, when the activity of the sympathetic nervous system was high, and accordingly, BP and OPP increased. Our LSFG results after the cold pressor test in healthy eyes are comparable to previous observations in CSC and may be described as a “non-inflammatory (sympathetic)” pattern in the choroid [15,16].

Additionally, previous studies showing a significant increase in choroidal blood flow velocity with increasing IOP, BP, and OPP after isometric exercise in healthy individuals indicate that choroidal circulatory dynamics are dependent on systemic circulatory dynamics [9,11,20]. Although IOP, BP, OPP, and neural input need to be considered with regard to choroidal autoregulation [11,12], a particularly pertinent point is that choroidal vessels are predominantly controlled by sympathetic innervation [7–9]. The cold pressor test performed in this study can evaluate sympathetic responses in systemic circulatory dynamics [1–5]. Therefore, our data suggest that an increase in sympathetic activity during cold stimulation increases systemic circulatory dynamics and choroidal blood flow velocity.

The primary limitations of this study were as follows: first, the relatively small sample size and the difference in sex ratio and, second, the absence of other choroidal circulatory examinations. To further investigate choroidal changes in healthy participants, the relationship between choroidal function and morphology should be assessed in large and equally sexed samples using both LSFG and optical coherence tomography angiography. Future

studies should compare the MBR of CSC eyes and healthy eyes using the cold pressor test to determine the relationship between the severity of CSC and the prediction of future onset.

5. Conclusions

In conclusion, to the best of our knowledge, this is the first study to report changes in the MBR after a cold pressor test. Our data suggested that in young healthy individuals, as we hypothesized, an increase in sympathetic activity induced by a cold pressor test increases choroidal hemodynamics in the macula along with an increase in systemic circulatory dynamics, which normalizes after 10 min. These novel findings suggest that LSFG may provide a novel approach for assessing sympathetic activity and intrinsic vascular responsiveness in the eye. In addition, a comparison of the choroidal circulation in CSC eyes and healthy eyes using the cold pressor test may reveal the relationship between the severity of CSC and the prediction of future development.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/tomography9020064/s1>, Table S1: Changes in ocular biometric parameters and Table S2: Changes in systemic factors.

Author Contributions: Conceptualization, S.I. and Y.H.; methodology, Y.H.; validation, Y.H. and T.Y. (Takeshi Yoshitomi); formal analysis, Y.H. and T.Y. (Toshitaka Yamanokuchi); investigation, S.I., Y.I., R.U. and M.C.; resources, S.I.; data curation, S.I. and Y.H.; writing—original draft preparation, S.I. and Y.H.; writing—review and editing, T.Y. (Takeshi Yoshitomi); visualization, S.I. and Y.H.; supervision, T.Y. (Takeshi Yoshitomi); project administration, Y.H.; funding acquisition, Y.H. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by JSPS KAKENHI Grant Number JP20K19698.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of FUKUOKA INTERNATIONAL UNIVERSITY OF HEALTH AND WELFARE (approval ID: 20-fiuhw-022; Date of approval: 25 July 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hines, E.A.; Brown, G.E. The cold pressor test for measuring the reactivity of the blood pressure: Data concerning 571 normal and hypertensive subjects. *Am. Heart J.* **1936**, *11*, 1–9. [\[CrossRef\]](#)
2. Reiser, M.F.; Ferris, E.B., Jr. The nature of the cold pressor test and its significance in relation to neurogenic and humoral mechanisms in hypertension. *J. Clin. Investig.* **1948**, *27*, 156–163. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Korhonen, I. Blood pressure and heart rate responses in men exposed to arm and leg cold pressor tests and whole-body cold exposure. *Int. J. Circumpolar Health* **2006**, *65*, 178–184. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Velasco, M.; Gómez, J.; Blanco, M.; Rodríguez, I. The cold pressor test: Pharmacological and therapeutic aspects. *Am. J. Ther.* **1997**, *4*, 34–38. [\[CrossRef\]](#)
5. Budidha, K.; Kyriacou, P.A. Photoplethysmography for quantitative assessment of sympathetic nerve activity (SNA) during cold stress. *Front. Physiol.* **2018**, *9*, 1863. [\[CrossRef\]](#)
6. Flügel-Koch, C.; May, C.A.; Lütjen-Drecoll, E. Presence of a contractile cell network in the human choroid. *Ophthalmologica* **1996**, *210*, 296–302. [\[CrossRef\]](#)
7. Delaey, C.; Van De Voorde, J. Regulatory mechanisms in the retinal and choroidal circulation. *Ophthalmic Res.* **2000**, *32*, 249–256. [\[CrossRef\]](#)
8. Jendzjowsky, N.G.; Steinback, C.D.; Herman, R.J.; Tsai, W.H.; Costello, F.E.; Wilson, R.J.A. Functional-optical coherence tomography: A non-invasive approach to assess the sympathetic nervous system and intrinsic vascular regulation. *Front. Physiol.* **2019**, *10*, 1146. [\[CrossRef\]](#)
9. Okuno, T.; Sugiyama, T.; Kohyama, M.; Kojima, S.; Oku, H.; Ikeda, T. Ocular blood flow changes after dynamic exercise in humans. *Eye* **2006**, *20*, 796–800. [\[CrossRef\]](#)
10. Kiel, J.W.; Shepherd, A.P. Autoregulation of choroidal blood flow in the rabbit. *Investig. Ophthalmol. Vis. Sci.* **1992**, *8*, 2399–2410.

11. Polska, E.; Simader, C.; Weigert, G.; Doelemeyer, A.; Kolodjaschna, J.; Scharmann, O.; Schmetterer, L. Regulation of choroidal blood flow during combined changes in intraocular pressure and arterial blood pressure. *Investig. Ophthalmol. Vis. Sci.* **2007**, *48*, 3768–3774. [[CrossRef](#)] [[PubMed](#)]
12. Schmidl, D.; Garhofer, G.; Schmetterer, L. The complex interaction between ocular perfusion pressure and ocular blood flow—relevance for glaucoma. *Exp. Eye Res.* **2011**, *93*, 141–155. [[CrossRef](#)] [[PubMed](#)]
13. 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. *Graefe's Arch. Clin. Exp. Ophthalmol.* **2022**, *261*, 585–587. [[CrossRef](#)]
14. Aizawa, N.; Yokoyama, Y.; Chiba, N.; Omodaka, K.; Yasuda, M.; Otomo, T.; Nakamura, M.; Fuse, N.; Nakazawa, T. Reproducibility of retinal circulation measurements obtained using laser speckle flowgraphy-NAVI in patients with glaucoma. *Clin. Ophthalmol.* **2011**, *5*, 1171–1176. [[CrossRef](#)] [[PubMed](#)]
15. Saito, M.; Saito, W.; Hashimoto, Y.; Yoshizawa, C.; Fujiya, A.; Noda, K.; Ishida, S. Macular choroidal blood flow velocity decreases with regression of acute central serous chorioretinopathy. *Br. J. Ophthalmol.* **2013**, *97*, 775–780. [[CrossRef](#)]
16. Saito, M.; Saito, W.; Hirooka, K.; Hashimoto, Y.; Mori, S.; Noda, K.; Ishida, S. Pulse waveform changes in macular choroidal hemodynamics with regression of acute central serous chorioretinopathy. *Investig. Ophthalmol. Vis. Sci.* **2015**, *56*, 6515–6522. [[CrossRef](#)]
17. Saito, M.; Noda, K.; Saito, W.; Hirooka, K.; Hashimoto, Y.; Ishida, S. Increased choroidal blood flow and choroidal thickness in patients with hypertensive chorioretinopathy. *Graefe's Arch. Clin. Exp. Ophthalmol.* **2020**, *258*, 233–240. [[CrossRef](#)]
18. Iwase, T.; Ueno, Y.; Tomita, R.; Terasaki, H. Relationship between retinal microcirculation and renal function in patients with diabetes and chronic kidney disease by laser speckle flowgraphy. *Life* **2023**, *13*, 424. [[CrossRef](#)]
19. Yanagida, K.; Iwase, T.; Yamamoto, K.; Ra, E.; Kaneko, H.; Murotani, K.; Matsui, S.; Terasaki, H. Sex-related differences in ocular blood flow of healthy subjects using laser speckle flowgraphy. *Investig. Ophthalmol. Vis. Sci.* **2015**, *56*, 4880–4890. [[CrossRef](#)]
20. Riva, C.E.; Titze, P.; Hero, M.; Movaffaghy, A.; Petrig, B.L. Choroidal blood flow during isometric exercises. *Investig. Ophthalmol. Vis. Sci.* **1997**, *38*, 2338–2343.
21. Nagahara, M.; Tamaki, Y.; Tomidokoro, A.; Araie, M. In vivo measurement of blood velocity in human major retinal vessels using the laser speckle method. *Investig. Ophthalmol. Vis. Sci.* **2011**, *52*, 87–92. [[CrossRef](#)] [[PubMed](#)]
22. Tamaki, Y.; Araie, M.; Kawamoto, E.; Eguchi, S.; Fujii, H. Noncontact, two-dimensional measurement of retinal microcirculation using laser speckle phenomenon. *Investig. Ophthalmol. Vis. Sci.* **1994**, *35*, 3825–3834.
23. 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*, e0270501. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.