© Journal for Modeling in Ophthalmology 2020; 4:55-66
Original article

Effects of the hand-grip test on retinal vascular and structural parameters measured by optical coherence tomography in healthy subjects

Carlo Alberto Cutolo[1,2], Lorenzo Ferro Desideri[1,2], Chiara Bonzano[1,2], Felice Cardillo Piccolino[3], Alice Chandra Verticchio Vercellin[4,5,6], Carlo Enrico Traverso[1,2], Massimo Nicolò[1,2,3]

[1]Clinica Oculistica, DiNOGMI, University of Genoa, Italy; [2]Ospedale Policlinico San Martino, Genoa, Italy; [3]Fondazione per la Macula Onlus, Clinica Oculistica, DiNOGMI, University of Genoa, Italy; [4]Department of Ophthalmology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA; [5]University of Pavia, Pavia, Italy; [6]IRCCS – Fondazione Bietti, Rome, Italy

Abstract

Purpose: To examine the relationship between the cardiovascular status and variations in optical coherence tomography (OCT)-derived parameters of the peripapillary and macular tissues, and macular vascular flow area measured by optical coherence tomography angiography (OCTA) in healthy subjects.
Design: Prospective, open-label, non-randomized clinical study.
Methods: Twenty one eyes of 21 healthy subjects were analyzed using a swept-source device, including OCT and OCTA acquisitions. Cardiovascular changes were investigated by performing a practical hand-grip test (HGT). Blood pressure, heart rate, OCT and OCTA structural and vascular changes were measured and analyzed before and after the HGT-induced exercise.
Results: The mean patient age was 34.0 (± 15.2) years. While both diastolic and systolic blood pressures increased significantly after exercise ($p < 0.001$ and $p = 0.003$, respectively), the heart rate did not show a significant increment

Correspondence: Carlo Alberto Cutolo, Clinica Oculistica, Viale Benedetto XV 5, 16132, Genova (GE), Italy.
E-mail: cacutolo@gmail.com

(*p* = 0.182). OCT structural parameters of the optic nerve did not change significantly. Instead, a significant redistribution of choroidal thickness (CT) was observed in the macular region, with a significant reduction (-6.5%, *p* = 0.001) in the outer-nasal macular sector after exercise. OCTA acquisitions did not show changes in the vascular density of both the superficial retinal layer and deep retinal layer.
Conclusions: We demonstrated that HGT-induced exercise can moderately elevate blood pressure without detectable effects on OCTA-derived parameters in healthy young subjects. Moreover, it produced a significant redistribution of CT. Further studies are needed to better explain the possible role of HGT in the characterization of the pathophysiology of ocular diseases associated with abnormalities of the vascular function such as glaucoma, age-related macular degeneration, and diabetic retinopathy.

Keywords: choroidal thickness, exercise, hand-grip test, ocular blood flow, optical coherence tomography, retinal vessels

1. Introduction

The retina represents one of the most metabolically active tissues in the body, since it receives a double blood supply deriving from both the retinal and choroidal circulations.[1] The growing interest in studying the retinal and choroidal structure and blood flow relies on the possibility of further understanding the pathophysiology of potentially blinding disorders such as age-related macular degeneration, glaucoma, and diabetic retinopathy. Nowadays, optical coherence tomography (OCT) represents a widely used non-invasive imaging technique to assess changes in the structure of the different anatomical regions of the retina caused by pathologic processes. Several imaging methods are also available to assess the retinal and choroidal blood flow; however, to date, none has been recognized as gold standard.[2-4] Laser Doppler flowmetry (LDF) is a non-invasive technique that measures the Doppler shift caused by the movement of erythrocytes.[5] Several studies analyzed the different factors influencing choroidal blood flow measured by LDF during isometric exercise, showing the complex regulatory mechanisms associated with variations in mean arterial pressure (MAP), intraocular pressure (IOP), and ocular perfusion pressure (OPP).[6,7] Furthermore, laser speckle flowgraphy is another novel non-invasive technique based on the interference phenomenon, and it has shown reproducible data and a good reliability profile with LDF in the study of choroidal blood flow.[8] Doppler optical coherence tomography (Doppler-OCT) is another diagnostic tool studied for the retinal and choroidal analysis; however, further *in vivo* studies are needed in order to better clarify its clinical reliability.[9]

Optical coherence tomography angiography (OCTA) is a novel, non-dye-based imaging technique for visualization and assessment of the retinal vasculature.[10-12] Alnawaiseh *et al.* were the first to use OCTA to evaluate the variations induced by exercise in the retinal vascularization of healthy subjects. The authors found a significant change in flow densities associated with systemic cardiovascular modifications (blood pressure [BP]).[13] Understanding the relationship between the patient's cardiovascular status and OCT/OCTA measurements is meaningful to the clinician because altered cardiovascular status may affect the measurements of the exam, potentially leading to misinterpretation of the results. Moreover, a hand-grip exercise that dynamically changes the results of OCT/OCTA could help to elucidate the pathophysiology of ocular diseases as recently showed for central serous chorioretinopathy, where an impairment of retinal vessel autoregulation was reported.[14]

In this study, we investigated the changes induced by a practical hand-grip test (HGT) on the OCT-derived parameters of the peripapillary and macular tissues and on the macular vasculature measured by OCTA in healthy subjects.

2. Methods

2.1. Baseline visit

This study enrolled healthy volunteers of both sexes all with ages above 18 years and without any systemic or ocular disease. The research was conducted at Clinica Oculistica, Ospedale Policlinico San Martino - IRCCS, Italy from January to March 2018. All procedures followed the tenets of the Declaration of Helsinki and informed consent was obtained from all the subjects. All the subjects completed a full ophthalmological examination, including best-corrected visual acuity (BCVA), slit-lamp examination, IOP measurement with Goldmann applanation tonometry. Optical biometry by Lenstar LS 900 (Haag-Streit AG, Köniz, Switzerland) was used to measure the axial length and central corneal thickness. Pupil dilation was obtained with tropicamide 1% eye drop (Visumidriatic, Visufarma Spa, Italy) and fundoscopy was performed using a 90-diopter hand-held lens. Eyes with a history of previous intraocular surgery as well as subjects affected by any systemic disease, diabetes, hypertension and other ocular or systemic disorders known to impair the diagnostic procedures were excluded. Eyes were also excluded if they had BCVA worse than 0.10 LogMAR and a refractive error outside the range −6.00 to +3.00 D. Each subject was asked to refrain from smoking and caffeine intake for at least 60 minutes before any examination to minimize the influence of these substances on the cardiovascular parameters.[15] Blood pressure (BP) and heart rate (HR) were measured using an automated sphygmomanometer (HEM-907, Omron Europe B.V, The Netherlands) with subjects in a seated position, after at least a five-minute resting period. The resting BP value was considered as the average of two readings taken at least five minutes apart in the same arm. The arm selected for the measurements was the non-dominant and the sphygmomanometer wrist was set at the level of the heart. One qualified eye was randomly selected as the study eye, and underwent OCT and OCTA assessment (details below).

2.2. OCT

A single, wide-field, swept-source OCT scan (DRI OCT-1 Atlantis, Topcon, Inc., Tokyo, Japan) was completed. The wide-field SS-OCT scan consists of a 9 x 12 mm rectangle that covered both the macular and disc regions and is formed by 256 b-scans, each with 512 a-scans. Only scans with an image quality index above 40 were considered for analysis. All images were reviewed for segmentation errors. Circumpapillary retinal nerve fiber layer (cpRNFL) and choroid thickness were extracted using the OCT instrument's software in the following quadrants and sectors: temporal, temporal-superior, temporal-inferior, nasal, nasal-superior, and nasal-inferior. Retinal and choroidal thicknesses were analyzed accordingly with the nine macular sectors defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) (center, inner-temporal, inner-superior, inner-nasal, inner-inferior, outer-temporal, outer-superior, outer-nasal, and outer-inferior).

2.3. OCTA

OCTA scans were acquired immediately after structural OCT, with the same instrument. The scans were taken from a 4.5 x 4.5 cube, with each cube consisting of 320 clusters of four repeated b-scans centered on the fovea. The automated layer segmentation performed by the OCT instrument software (IMAGEnet 6, Topcon) displayed *en-face* images of the microvasculature of the superficial retinal layer (SRL) and deep retinal layer (DRL) in the central region and four quadrants (superior, inferior, nasal, and temporal). The instrument's segmentation software defines the *en-face* slab for the SRL from 2.6 µm beneath the internal limiting membrane to 15.6 µm beneath the interface of the inner plexiform layer and inner nuclear layer (IPL/INL). The DRL slab was considered from 15.6 µm beneath the IPL/INL to 70.2 µm beneath the IPL/INL. All images were reviewed for segmentation errors for the SRL and DRL. Vascular densities of the SRL (vd-SRL) and DRL (vd-DRL) were calculated using the instrument's software.

2.4. Hand-grip exercise and OCT measurements

The experimental protocol was adapted from the work of Cardillo Piccolino *et al.*[14] After cardiovascular and OCT measurements at rest, the HGT was then performed on the dominant side by using a Jamar hand dynamometer (Lafayette Instruments, Lafayette, IN, USA). The subject was asked to squeeze the handle three times with their maximum hand strength, and 30% of the mean of the measurements was recorded. Then, the subject was asked to perform the hand-grip exercise maintaining 30% of their maximum hand strength for 3 to 5 minutes. OCT and OCTA scans were performed in the same eye of the resting measurements after two minutes from the start of the isometric effort. BP and HR were also measured.

2.5. Statistical analysis

In descriptive statistics, variables were summarized as means and standard deviation. Comparisons between resting and exercise values for each parameter were performed with the Wilcoxon signed-rank test. *P* values less than 0.05 are considered statistically significant. Because multiple tests were performed of the same dataset, the Benjamini-Hochberg procedure was used to correct for the false discovery rate to avoid that *p* values less than 0.05 were purely by chance. Computerized statistical analyses were performed with STATA software (version 15.1, STATACorp, TX, USA).

3. Results

We analyzed the data of 21 eyes of 21 subjects. All the OCT and OCTA scans had an adequate quality (image quality index > 40), and no segmentation errors were detected. Table 1 summarizes the demographics and ocular characteristics of the enrolled healthy subjects. The mean (± standard deviation) age was 34.0 (± 15.2) years and 66.7% were women. The dominant hand, which performed the HGT, was the right for 18 (85.7%) subjects. Hence, only 3 (14.3%) subjects had BP assessment in the right arm. Table 2 shows the changes in the cardiovascular parameters before and during HGT. Both diastolic and systolic BP significantly increased, whereas the

Table 1. Demographics and ocular characteristics of the study subjects

	N = 21 eyes
Age, years	34.0 (±15.2)
Gender, female	14 (66.7%)
Eye, right	12 (57.1%)
IOP, mmHg	13.6 (± 2.5)
CCT, µm	545 (± 30)
Axial length, mm	23.6 (± 0.8)
Sphere equivalent, D	-0.85 (± 2.13)
Visual acuity, LogMAR	0.00
Hand-grip maximal voluntary contraction, kg-force	33.7 (± 8.6)
Dominant hand, right	18 (85.7%)

CCT: central corneal thickness; IOP: intraocular pressure; N: number of eyes
Data are number (%) or mean (± SD).

Table 2. Cardiovascular changes of the study subjects

	Baseline	Exercise	Difference	p-value
Diastolic BP, mmHg	76.3 (± 8.6)	88.9 (± 11.7)	+ 12.6 (± 10.5)	< 0.001
Systolic BP, mmHg	123.2 (± 15.3)	135.2 (± 19.0)	+ 12.0 (± 16.3)	0.003
Hearth rate, bpm	84.3 (± 19.2)	89.1 (± 20.8)	+ 4.8 (± 13.6)	0.182

BP: blood pressure; bpm: beats per minute

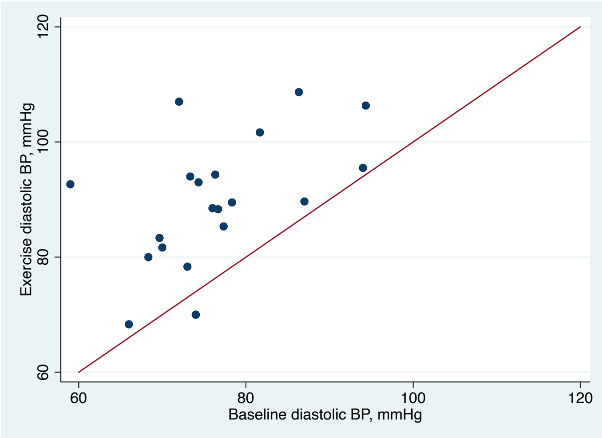

Fig. 1. The effect of exercise on diastolic blood pressure.

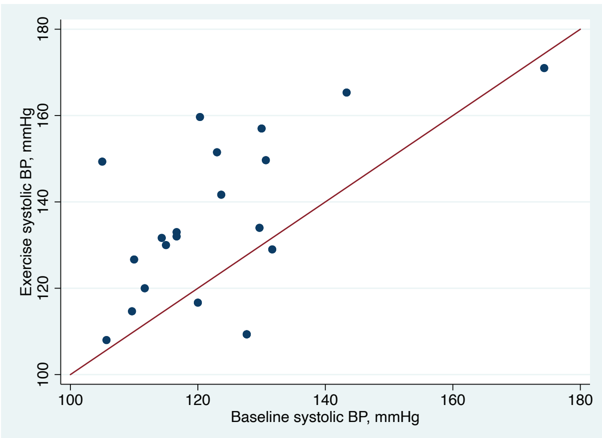

Fig. 2. The effect of exercise on systolic blood pressure.

HR increment was not statistically significant. Figures 1 and 2 show the effect of exercise on diastolic and systolic BP. The majority of subjects were located above the 'no effect' line. One and four subjects were located below the 'no effect' line for the diastolic and systolic parameter, respectively. Mean percentage changes during exercise were +16.5% and +9.7% for diastolic and systolic BP, respectively. Table 3 shows the structural changes in the cpRNFL and choroidal thickness (CT) assessed via OCT. After correction for the false discovery rate, none of the structural OCT parameters of the optic nerve changed significantly. When analyzing the structural changes of the retinal and choroidal tissues in the macular region (Table 4), we observed a statistically significant redistribution of CT. Namely, the outer-nasal sector showed a mean reduction of -6.5% (p = 0.001) during the isometric exercise. As shown in Table 5, no significant vessel density changes in the SRL and DRL were measured by OCTA.

Table 3. Circumpapillary retinal nerve fiber layer and choroidal thickness assessed by optical coherence tomography

	Baseline	**Exercise**	**Difference**	***p*-value**
cpRNFL, temporal, µm	132 (± 19)	134 (± 21)	+ 2 (± 25)	0.766
cpRNFL, temporal-superior, µm	122 (± 27)	116 (± 26)	- 7 (± 14)	0.048
cpRNFL, nasal-superior, µm	89 (± 16)	84 (± 14)	- 5 (± 16)	0.1499
cpRNFL, nasal, µm	134 (± 28)	127 (± 25)	- 7 (± 19)	0.1243
cpRNFL, nasal-inferior, µm	147 (± 19)	147 (± 32)	0 (± 27)	0.9609
cpRNFL, temporal-inferior, µm	149 (± 10)	148 (± 10)	- 1 (± 5)	0.1647
cpChoroid, temporal, µm	144 (± 69)	149 (± 75)	+ 5 (± 31)	0.4538
cpChoroid, temporal-superior, µm	138 (± 69)	143 (± 71)	+ 4 (± 19)	0.3179
cpChoroid, nasal-superior, µm	129 (± 57)	133 (± 55)	+ 4 (± 19)	0.3321
cpChoroid, nasal, µm	109 (± 60)	117 (± 66)	+ 8 (± 24)	0.1436
cpChoroid, nasal-inferior, µm	108 (± 64)	115 (± 74)	+ 7 (± 42)	0.4803
cpChoroid, temporal-inferior, µm	47 (± 6)	46 (± 4)	0 (± 4)	0.6498

cpRNFL: circumpapillary retinal nerve fiber layer thickness; cpChoroid: circumpapillary choroid
Data are mean (SD).

Table 4. Retinal and choroidal thicknesses in the macular region assessed by OCT

	Baseline	**Exercise**	**Difference**	***p*-value**
Retina, center, µm	305 (± 15)	305 (± 5)	+ 1 (± 3)	0.1128
Retina, inner-temporal, µm	308 (± 38)	316 (± 12)	+ 8 (± 38)	0.3153
Retina, inner-superior, µm	316 (± 14)	317 (± 11)	+ 2 (± 9)	0.3473
Retina, inner-nasal, v	305 (± 41)	314 (± 13)	+ 9 (± 42)	0.3378
Retina, inner-inferior, µm	264 (± 13)	263 (± 11)	- 1 (± 7)	0.7182
Retina, outer-temporal, µm	268 (± 26)	274 (± 8)	+ 6 (± 25)	0.2788
Retina, outer-superior, µm	292 (± 10)	290 (± 10)	- 2 (± 8)	0.3756
Retina, outer-nasal, µm	262 (± 27)	269 (± 10)	+ 8 (± 26)	0.1849
Retina, outer-inferior, µm	279 (± 15)	280 (± 9)	+ 1 (± 14)	0.7045
Choroid, center, µm	280 (± 66)	278 (± 65)	- 2 (± 7)	0.2259
Choroid, inner-temporal, µm	265 (± 67)	264 (± 70)	- 1 (± 14)	0.7124
Choroid, inner-superior, µm	244 (± 71)	243 (± 71)	+ 1 (± 9)	0.5662
Choroid, inner-nasal, µm	277 (± 66)	278 (± 65)	+ 1 (± 11)	0.6760
Choroid, inner-inferior, µm	265 (± 52)	264 (± 52)	- 2 (± 7)	0.2812
Choroid, outer-temporal, µm	254 (± 69)	253 (± 68)	- 2 (± 9)	0.4247
Choroid, outer-superior, µm	188 (± 74)	189 (± 73)	+ 1 (± 5)	0.4138
Choroid, outer-nasal, µm	263 (± 65)	246 (±58)	- 16 (± 20)	0.0014*
Choroid, outer-inferior, µm	106 (± 9)	103 (± 11)	- 3 (± 8)	0.1277

*P-value remained statistically significant after correction for the false discovery rate. Data are mean (SD).

Table 5. Macular vessel density assessed by OCTA

	Baseline	Exercise	Difference	p-value
Vd-SRL, central	47.3 (± 4.1)	47.2 (± 5.3)	- 0.1 (± 6.5)	0.9428
Vd-SRL, superior	16.5 (± 3.5)	16.9 (± 4.3)	+ 0.4 (± 2.3)	0.4324
Vd-SRL, inferior	42.9 (± 3.3)	45.1(± 2.5)	+ 2.3 (± 2.7)	0.0127
Vd-SRL, nasal	46.5 (± 2.7)	46.8 (± 2.6)	+ 0.3 (± 2.6)	0.6206
Vd-SRL, temporal	40.0 (± 2.6)	40.5 (± 2.1)	+ 0.5 (± 2.5)	0.3847
Vd-DRL, central	52.4 (± 8.0)	51.6 (± 2.4)	- 0.8 (± 8.2)	0.6636
Vd-DRL, superior	15.3 (± 4.4)	16.2 (± 4.3)	+ 0.9 (± 3.7)	0.2656
Vd-DRL, inferior	50.4 (± 4.9)	49.7 (± 3.6)	- 0.7 (± 3.5)	0.5506
Vd-DRL, nasal	49.0 (± 2.6)	49.0 (± 2.6)	0.0 (± 3.3)	0.9847
Vd-DRL, temporal	43.6 (± 2.0)	43.1 (± 1.9)	- 0.4 (± 2.5)	0.4429

vd-DRL: vessel density of the deep retinal layer, %; vd-SRL: vessel density of the superficial retinal layer, % Data are mean (SD).

4. Discussion

In the present study, we tested the hypothesis that perturbation of the cardiovascular status caused by an isometric exercise significantly affects the structural and vascular OCT measurements. We found that only slight changes in the CT in the macular region occurred during the exercise.

Recently, Cardillo Piccolino *et al.* applied a similar methodology to demonstrate an increase of retinal blood flow in central serous chorioretinopathy patients. They also found no significant changes in the control group of age-matched healthy subjects using 85-kHz spectral-domain OCT with a wavelength of 870 nm.[14] Conversely to the Cardillo Piccolino's study, we used 100-kHz swept-source OCT with a wavelength of 1050 nm, allowing better penetration of light into the choroidal tissue and thus, better delineation of the sclero-choroidal junction and reliable CT measurements.[16] Swept-source OCT allows automatic analysis of CT in the peripapillary and macular area, which seems to be related to choroidal blood flow.[17] After the isometric exercise, the redistribution of choroidal blood flow appears to cause the reduction of the CT detected by swept-source OCT.

In healthy eyes, retinal blood flow is highly autoregulated by an intrinsic mechanism that changes the myogenic tone accordingly to the perfusion pressure, whereas choroidal circulation is mainly controlled by the extrinsic autonomic innervation.[18-20] Namely, the reduction in choroidal blood flow is driven by the sympathetic nervous system, while the increases are driven by the parasympathetic nervous system.[21] The HGT can cause a reduction of the parasympathetic nervous system, followed by an increase of sympathetic stimulation.[22] As shown in Figures 1 and 2, the HTG elicited an increase in diastolic and systolic BP in the vast majority of subjects. However, even for subjects whose BP does not increase, the HTG can cause changes in the autonomic nervous system which can affect the ocular blood flow. Changes in the autonomic innervation of the choroid elicited by the HGT may explain the slight but significant reduction in CT observed in the present study. Using LDF, Bata *et al.* also found a reduction of choroidal blood flow during HGT in a limited number of individuals of a cohort of healthy subjects and glaucoma patients.[23]

In a cohort of 40 healthy subjects, Kim *et al.* demonstrated a reduction of the vd-DRL after 20 minutes of maximal physical exercise consisting of riding a training bike reaching 85% of maximum theoretical HR.[24] The strength of this work is that Kim *et al.* obtained changes detectable by OCTA. However, this exercise could be impractical in the clinical setting compared to the HGT, which is relatively easy to perform and has been validated in many clinical studies.[14,23,25–27] Alnawaiseh *et al.* also showed a reduction of the peripapillary and parafoveal flow density immediately after a specific training program that included sit-ups, push-ups, squats, lunges, and rope skipping.[13] Both the intensive program and the training bike exercise reported in the previously cited studies have caused a greater elevation of BP compared to our study (after exercise systolic pressure, mmHg: 141.8 ± 10.1[13]; 167.8 ± 13.8[24] *vs* 135.2 ± 19.0, respectively).

This study is not without limitations. One limitation was the lack of IOP measurement during the exercise since IOP is affected by physical exercise.[28] However, a 3-to-5 minute HGT seems unlikely to cause a considerable change in IOP, and accordingly, in OPP. Additionally, it is important to highlight that the mean age of our study population was 34 years (± 15.2). The results of our study cannot therefore be generalized to older subjects, since changes in the physiologic cardiovascular response to exercise occur with the aging process. The effect of aging on the relationship between exercise, cardiovascular system, and ocular OCT-derived parameters need therefore to be further investigated. Further studies are also needed to investigate the role of gender. Another limitation is the study's small sample size. Finally, studies are needed to compare the effect of exercise on OCT- and OCTA-derived parameters not only in healthy subjects, but also in patients affected by different ocular diseases.

In conclusion, our study showed that the hand-grip exercise is able to moderately elevate BP without detectable effects on OCTA-derived parameters in healthy subjects. We also showed that an easy to perform hand-grip exercise is able to produce small but significant effects on CT. In healthy subjects, a moderate elevation of BP seems unlikely to affect OCTA measurements, whereas it can affect CT. In subsequent studies, the HGT could be used to better define the pathophysiology of ocular diseases considered to be associated with impaired vascular function such as glaucoma, age-related macular degeneration, and diabetic retinopathy.

Acknowledgements

The contribution of Dr. Alice C. Verticchio Vercellin was supported by Fondazione Roma and the Italian Ministry of Health.

References

1. Funk RH. Blood supply of the retina. Ophthalmic Res. 1997;29(5):320–325.
2. Causin P, Guidoboni G, Malgaroli F, Sacco R, Harris A. Blood flow mechanics and oxygen transport and delivery in the retinal microcirculation: multiscale mathematical modeling and numerical simulation. Biomech Model Mechanobiol. 2016;15(3):525–542.
3. Wei X, Balne PK, Meissner KE, Barathi VA, Schmetterer L, Agrawal R. Assessment of flow dynamics in retinal and choroidal microcirculation. Surv Ophthalmol. 2018;63(5):646–664.
4. Verticchio Vercellin AC, Cutolo CA, Dellafiore C, Lava M, Tinelli C, De Silvestri A, et al. Inter-device reproducibility of retrobulbar blood flow velocity measurements in healthy subjects using color Doppler imaging. J Ultrasound. 2016;1–6.
5. Kouadio AA, Jordana F, Koffi NJ, Le Bars P, Soueidan A. The use of laser Doppler flowmetry to evaluate oral soft tissue blood flow in humans: A review. Arch Oral Biol. 2018;86:58–71.
6. Popa-Cherecheanu A, Schmidl D, Werkmeister RM, Chua J, Garhöfer G, Schmetterer L. Regulation of Choroidal Blood Flow During Isometric Exercise at Different Levels of Intraocular Pressure. Invest Ophthalmol Vis Sci. 2019;60(1):176–182.
7. Schmidl D, Schmetterer L, Witkowska KJ, et al. Factors Associated With Choroidal Blood Flow Regulation in Healthy Young Subjects. Invest Ophthalmol Vis Sci. 2016;57(13):5705–5713.
8. Calzetti G, Fondi K, Bata AM, et al. Assessment of choroidal blood flow using laser speckle flowgraphy. Br J Ophthalmol. 2018;102(12):1679–1683.
9. Leitgeb RA, Werkmeister RM, Blatter C, Schmetterer L. Doppler Optical Coherence Tomography. Prog Retin Eye Res. 2014;41:26–43.
10. Kashani AH, Chen C-L, Gahm JK, Zheng F, et al. Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. Prog Retin Eye Res. 2017;60:66–100.
11. Koustenis A, Harris A, Gross J, Januleviciene I, Shah A, Siesky B. Optical coherence tomography angiography: an overview of the technology and an assessment of applications for clinical research. Br J Ophthalmol. 2017;101(1):16–20.
12. Rodríguez FJ, Staurenghi G, Gale R, Vision Academy Steering Committee. The role of OCT-A in retinal disease management. Graefes Arch Clin Exp Ophthalmol. 2018;256(11):2019–2026.
13. Alnawaiseh M, Lahme L, Treder M, Rosentreter A, Eter N. Short-term effects of exercise on optic nerve and macular perfusion measured by optical coherence tomography angiography. Retina. 2017;37(9):1642.
14. Cardillo Piccolino F, Lupidi M, Cagini C, et al. Retinal Vascular Reactivity in Central Serous Chorioretinopathy. Invest Ophthalmol Vis Sci. 2018;59(11):4425–4433.

15. Kallioinen N, Hill A, Horswill MS, Ward HE, Watson MO. Sources of inaccuracy in the measurement of adult patients' resting blood pressure in clinical settings: a systematic review. J Hypertens. 2017;35(3):421–441.
16. Komma S, Chhablani J, Ali MH, Garudadri CS, Senthil S. Comparison of peripapillary and subfoveal choroidal thickness in normal versus primary open-angle glaucoma (POAG) subjects using spectral domain optical coherence tomography (SD-OCT) and swept source optical coherence tomography (SS-OCT). BMJ Open Ophthalmol. 2019;4(1):e000258.
17. Akahori T, Iwase T, Yamamoto K, Ra E, Terasaki H. Changes in Choroidal Blood Flow and Morphology in Response to Increase in Intraocular Pressure. Invest Ophthalmol Vis Sci. 2017;58(12):5076–5085.
18. Harris A, Arend O, Bohnke K, Kroepfl E, Danis R, Martin B. Retinal blood flow during dynamic exercise. Graefes Arch Clin Exp Ophthalmol. 1996;234(7):440–444.
19. Iester M, Torre PG, Bricola G, Bagnis A, Calabria G. Retinal Blood Flow Autoregulation after Dynamic Exercise in Healthy Young Subjects. Ophthalmologica. 2007;221(3):180–185.
20. Bill A, Sperber GO. Control of retinal and choroidal blood flow. Eye. 1990;4(2):319–325.
21. Kur J, Newman EA, Chan-Ling T. Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease. Prog Retin Eye Res. 2012;31(5):377–406.
22. Martin CE, Shaver JA, Leon DF, Thompson ME, Reddy PS, Leonard JJ. Autonomic Mechanisms in Hemodynamic Responses to Isometric Exercise. J Clin Invest. 1974;54(1):104–115.
23. Bata AM, Fondi K, Witkowska KJ, et al. Optic nerve head blood flow regulation during changes in arterial blood pressure in patients with primary open-angle glaucoma. Acta Ophthalmol (Copenh). 2019;97(1):e36–41.
24. Kim SV, Semoun O, Pedinielli A, Jung C, Miere A, Souied EH. Optical Coherence Tomography Angiography Quantitative Assessment of Exercise-Induced Variations in Retinal Vascular Plexa of Healthy Subjects. Invest Ophthalmol Vis Sci. 2019;60(5):1412–1419.
25. Bond V, Curry BH, Adams RG, Obisesan T, Pemminati S, Gorantla VR, et al. Cardiovascular Responses to an Isometric Handgrip Exercise in Females with Prehypertension. North Am J Med Sci. 2016;8(6):243–249.
26. Walamies M, Turjanmaa V. Assessment of the reproducibility of strength and endurance handgrip parameters using a digital analyser. Eur J Appl Physiol. 1993;67(1):83–86.
27. Khurana RK, Setty A. The value of the isometric hand-grip test-studies in various autonomic disorders. Clin Auton Res. 1996;6(4):211–218.
28. Vera J, Jiménez R, Redondo B, Torrejón A, De Moraes CG, García-Ramos A. Effect of the level of effort during resistance training on intraocular pressure. Eur J Sport Sci. 2019;19(3):394–401.