· Original article ·

Response of choroidal thickness to aerobic exercise in subjects with primary open-angle glaucoma

Wei Chen, Jing-Min Guo, Yin Zhao, Hong Zhang

Department of Ophthalmology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China

Co-first authors: Wei Chen and Jing-Min Guo

Correspondence to: Hong Zhang. Department of Ophthalmology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan 430030, Hubei Province, China. dr_zhanghong@163.vip.com

Received: 2016-06-27　　Accepted: 2017-01-18

原发性开角型青光眼患者有氧运动前后脉络膜厚度变化分析

陈　威*,郭竞敏*,赵　寅,张　虹

(作者单位:430030 湖北省武汉市华中科技大学同济医学院附属同济医院眼科)

注:* 陈威与郭竞敏对本文贡献一致。

作者简介:陈威,毕业于华中科技大学同济医学院,医学博士,主治医师,讲师,研究方向:青光眼,白内障。

通讯作者:张虹,毕业于华中科技大学同济医学院,医学博士,主任医师,教授,研究方向:青光眼,白内障. dr_zhanghong@vip.163.com.

摘要

目的:研究原发性开角型青光眼患者有氧运动前后脉络膜厚度的变化。

方法:研究选取17例正常受试者(对照组)及17例原发性开角型青光眼患者(试验组)进行有氧运动(慢跑),运动前后依次记录脉络膜厚度(ChT),眼压(IOP)及平均动脉压数值(MAP)。

结果:1)运动后对照组及试验组ChT及IOP均出现显著性降低,其中,试验组运动后ChT及IOP降低幅度更为显著。2)运动后对照组及试验组MAP均出现显著性升高,而对照组MAP升高幅度更为明显。3)受试者工作曲线分析提示:对照组与试验组运动前后ChT变化量及IOP变化量曲线下面积分别为0.75及0.281。

结论:有氧运动所诱导的交感神经活性升高可能是运动后ChT及IOP降低,MAP升高的主要原因。而POAG患者自主神经功能紊乱是导致运动后ChT,IOP及MAP与正常人存在不同反应性的主要因素。

关键词:脉络膜厚度;原发性开角型青光眼;自主神经系统

引用:陈威,郭竞敏,赵寅,张虹. 原发性开角型青光眼患者有氧运动前后脉络膜厚度变化分析. 国际眼科杂志 2017;17(4):604-609

Abstract

• AIM: To determine if aerobic exercise results in changes in choroidal thickness (ChT) responses in subjects with primary open-angle glaucoma (POAG).

• METHODS: The study included 17 normal participants and 17 POAG patients (34 eyes) and subjected them to aerobic exercise in the form of jogging. During exercise, ChT, intraocular pressure (IOP), and mean arterial pressure (MAP) were recorded sequentially.

• RESULTS: ChT and IOP significantly decreased in both groups after exercise, and the significant disparate response was found in the control and POAG group ($P<0.05$). MAP increased significantly in both groups after exercise, and the increase was more significant in the control group than that in the POAG group. The values for area under the curve (AUC) of the ChT variations and IOP were 0.75 and 0.281, respectively.

• CONCLUSION: Activation of the sympathetic nerve induced by aerobic exercise might be the underlying mechanism for the decrease in ChT and IOP and the increase in MAP in both groups. The disparate responses to jogging observed in ChT, IOP, and MAP values between the groups might be because of the autonomic nervous system dysfunction in POAG patients.

• KEYWORDS: choroidal thickness; primary open angle glaucoma; autonomic nervous system

DOI:10.3980/j.issn.1672-5123.2017.4.04

Citation: Chen W, Guo JM, Zhao Y, Zhang H. Response of choroidal thickness to aerobic exercise in subjects with primary open-angle glaucoma. *Guoji Yanke Zazhi* (*Int Eye Sci*) 2017;17(4):604-609

INTRODUCTION

The choroid is a primary vascular structure, which has many essential functions in the eye[1]. It acts as the heat sink[2] and delivers blood and nutrients to the outer retinas. Active changes in the choroidal thickness (ChT), which moves the retina forward and backward to bring the photoreceptors into the focal correct position, were observed in laboratory test conducted in chickens and mammals[3-5]. Choroid are principally under neurogenic control and are thus not autonomously regulated (unlike the retinal vascular network). The diurnal rhythm of the ChT, was also observed similar to the fluctuation pattern of IOP[6]. Following autonomic denervation, obvious rhythmic disorders were found in both the ChT and IOP[7]. The responses have been observed in the IOP measurements of normal subjects and POAG patients following exercise[8-12]. The main objective of the current work was to evaluate the possible effects of aerobic exercise on the ChT, mean arterial pressure (MAP) and ocular perfusion pressure (OPP) in normal participants and patients with POAG.

SUBJECTS AND METHODS

Subjects A total of 34 participants (normal subjects and patients with POAG, 17 in each group) were enrolled in this study from July 2012 to December 2014. All the participants had undergone ophthalmic examinations including best-corrected visual acuity (BCVA), refractive error (RE, dioptometry), axial length (AL, A-scan), anterior segment examination (slit lamp microscopy and gonioscopy), ocular fundus examination (direct and indirect ophthalmoscopes), IOP (Goldmann applanation tonometer), central corneal thickness (CCT, Cirrus FD-OCT, Zeiss Meditec, Dublin, CA, USA), visual field test (Humphrey Visual Field Analyzer, Swedish Interactive Thresholding Algorithm standard 24-2, Carl Zeiss Inc., Dublin, CA, USA), and retinal nerve fiber layer thickness assessment (RNFLT, Cirrus FD-OCT, Zeiss Meditec, Dublin, CA, USA) at the Tongji Hospital, Wuhan, Hubei Province, China. For the participants, either one of the eyes was selected randomly.

The subjects with POAG were included if they had an established diagnosis made by a glaucoma specialist based on glaucomatous optic disc damage and an abnormal visual field (VF) test result consisting of a pattern SD <5%, glaucoma hemifield test results outside normal limits, or both. At least two consecutive abnormal VF examinations were required, with the most recent test having been performed within 12mo of the enrollment. The subjects with POAG were not prevented from using anti-glaucoma drops prior to the study exercises because of medical and ethical principles.

The normal subjects enrolled in this study had an IOP <21 mmHg and normal ophthalmoscopic appearance of the optic nerve (cup-to-disc ratio <0.5 in both eyes, cup-to-disc ratio asymmetry <0.2, absence of hemorrhage, and localized or diffuse rim thinning).

Other inclusion criteria for all the subjects included: 1) over 18y old; 2) there aren't received any medication that affects the circulatory system for at least one month before the study commenced; 3) no caffeine intake.

The following conditions were the study exclusion criteria: 1) BCVA <20/40 (to ensure that the subjects had good central fixation); 2) RE <-6.0 D (high myopia level); 3) serious cataract and other ocular diseases that would make the test difficult; 4) other eye diseases such as age-related macular degeneration, retinal detachment, or had undergone any previous eye operations; 5) other ocular diseases or systemic diseases such as hypertension, diabetes, or a family history of these conditions.

The study protocol was reviewed by the local Ethical Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (IRBID: 20120703) and was registered in the Clinical Trial Registry (registration number: ChiCTR-ONRC-11001673). Written inform consents were obtained from all the participants, and the Declaration of Helsinki was strictly followed throughout the study.

Study Design The exercises were performed during the same period of the day (10 a.m.-12 p.m.) and after fasting for a minimum of 4h.

The systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured using an electronic sphygmomanometer. The ocular axial length (AL, IOL-Master, Carl *Zeiss* Meditec, Inc., German), CCT, IOP, RE (Refractometer, Topcon, Medical System, Inc., Japan), oxygen saturation (pulse oximeter), and ChT (optic coherence tomography, OCT, Spectralis, Heidelberg, German) were measured after the participants had filled out the International Physical Activity Questionnaire (IPAQ) while sitting down 5min (calm time).

During the 20min jogging exercise on the treadmill, the subjects were instructed to keep a steady pace at a 60-70% HR_{max}% in a thermoneutral environment. The HR and oxygen saturation were repeatedly measured every 4min using a pulse oximeter to ensure sufficient oxygen supply and evaluate the workload of the physical exercise.

After 20min of aerobic exercise, the ChT (in 30s), IOP, HR, BP were measured in sequence. The data recorded were stored for later statistical analysis.

Measurement Indicators

IPAQ score The IPAQ was used to assess the physical activity performed under a comprehensive set of conditions that simulated daily living including the following: 1) leisure time physical activity; 2) domestic and gardening (yard) activities; 3) work-related physical activity; 4) transportation-related physical activity. The specific types of activity that were assessed included walking, moderate-intensity, and vigorous-intensity activities[13].

Maximum HR_{max}%

$$HR_{max}\% = 100\times(HR_{during\ exercise}-HR_{rest})/(HR_{max}-HR_{rest}) \quad (1)$$

$$HR_{max} = 220 - age \quad (2)$$

$HR_{during\ exercise}$ is defined as the maximum HR value during exercise.

MAP and OPP The ocular blood flow mainly depends on the OPP[14-15]. The calculation of MAP and OPP were performed as follows:

$$OPP=\frac{2}{3}MAP-IAP \quad (3)$$

$$MAP=DPP+\frac{1}{3}(SBP-DBP) \quad (4)$$

Examination Techniques

Enhanced depth imaging (EDI)-OCT The enhanced depth imaging (EDI)-OCT was used, and this was performed at 870 nm wavelength, 7 um axial resolution, and 40000 A-scans/s high-speed Fourier frequency.

In the darkroom, the participants who did not have pupillary dilation fixed their heads stably on the holder and an inverted image representation of the fundus was acquired to bring the choroidal layer approximate to the zero-delay line, by moving the device close enough to the eye.

The images were stacked at 100 frames for the B-scan using the automatic real-time and eye tracking features. The score used for the quality bar was >25 for the imageacquisition.

The selections were made 1° apart in the same direction between the twelve 30°-spaced lines radiating from the fovea, and the 30° region of the fovea was set as the center (parafoveal region, Figure 1).

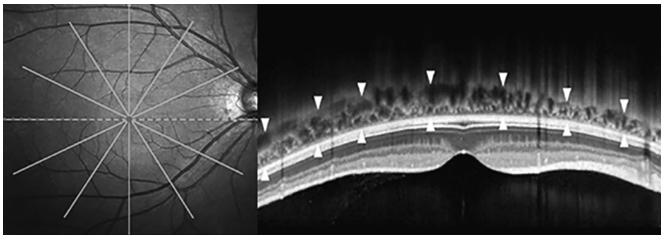

Figure 1　Image of choroid profile captured using spectral domain-optic coherence tomography.

Table 1　Difference in choroidal thickness between groups pre- and post-exercise

Parameters	Control group	POAG group	^aP
ChT (pre-exercise)	218.39 ± 68.67	231.44 ± 62.40	0.578
ChT (post-exercise)	210.84 ± 68.72	228.32 ± 63.33	0.460
^bP	<0.001	0.02	

^{a}Independent sample t-test. ^{b}Paired t-test. $P<0.05$ were significant differences. POAG: Primary open angle glaucoma.

Image J software

For the analysis, the choroid was defined as the layer extending from the retinal pigment epithelium (RPE) to the choroid-sclera hyper-reflective borderline in the profile of the image acquired.

The distortion in the image due to the different curvatures in myopic eyes may produce a systematic error during the statistical analysis. Therefore, the ChT (in the fovea and parafoveal regions), which was perpendicular to the RPE was calculated manually in that plane using the Image J software version 1.45S (National Institutes of Health, NIH, Bethesda, MD, USA) as previously mentioned[16].

Statistical Analysis

The statistical program for the social sciences (SPSS) software package version 16.0 (SPSS Inc., Chicago, IL, USA) was used for the analyses. The K-S test for normality evaluation and Levene's test for the equality variances were adopted. After the data had satisfied the above criteria, the paired t-test was used to assess the intra-group differences in the assessed parameters including ChT, IOP, MAP and OPP before and after aerobic exercise. The analysis of variance (ANOVA) test was adopted to compare the inter-group differences of these assessed parameters while the boxplot was adopted to observe their variations after the exercise. The receiver operator characteristic (ROC) curve was generated to evaluate the predictor variables of the ChT and IOP. $P<0.05$ was considered statistically significant.

RESULTS

Descriptive Analysis　A total of 34 participants (controls and patients with POAG, 17 each) were enrolled in this study. There was no statistically significant difference in age, RE, AL, IPAQ score, and between the two groups ($P>0.05$). All the ChT, IOP, and OPP data obeyed the Gaussian distribution and homogeneity of variances. (The results of the K-S and Levene's tests were not shown).

ChT Analysis Showed Differences between Both Groups during Aerobic Exercise　Table 1 shows that there was no significant difference in the ChT between the two groups pre- or post-exercise; however, an immediate decrease was observed in both groups during the exercise session (paired t-test, $P<0.05$). The ANOVA showed that the variation in the ChT during the exercise was more considerable in the control than it was in the POAG group ($F=6.071$, $P=0.02$). The boxplot of the variations of the ChT is shown in Figure 2A.

IOP, MAP, and OPP Analysis Showed Differences between Both Groups after Aerobic Exercise　Figure 3 shows that the IOP, MAP, and OPP changed significantly in both groups after the aerobic exercise. The ANOVA showed that the decrease in the IOP after exercise was more significant in the POAG than it was in the control group ($F=7.127$, $P=0.012$). The MAP increased more significantly in the control than it did in the POAG group after exercise ($F=7.776$, $P=0.009$). There was no significant difference in the OPP increase observed after the aerobic exercise between both groups ($F=1.295$, $P=0.264$). The boxplot of the IOP, MAP, and OPP are shown in Figure 2B, 2D.

Correlation Analysis of ChT and IOP in Control Group before and after Exercise　There was no significant correlation between the ChT and IOP of the control group either pre- or post-exercise ($r=0.034$, $P>0.05$).

ROC Curve Analysis of ChT and IOP in Both Groups after Aerobic Exercise　Figure 4 shows that the variation in the area under the curve (AUC) values of the ChT and IOP after exercise was 0.75 and 0.281, respectively for the subjects with POAG.

DISCUSSION

The IPAQ score and $HR_{max}\%$ were adopted as critical parameters to be determined because the exercise intensity and physical activity[8,11] are significant factors that influence the IOP response to exercise. For instance, athletes show a lower baseline IOP than the sedentary subjects and a greater decrease occurs in the IOP during running than that during walking and jogging. The oxygen saturation was also measured during the jogging exercise to ensure that the aerobic exercise was performed correctly during the entire process.

The result showed a significant decrease in the ChT after aerobic exercise for normal group and this change is likely accompanied by choroidal blood flow regulation[17]. The choroid is simultaneously innervated by the sympathetic and parasympathetic nerve[18]. The nonvascular contractive cell of choroid is innervated by the sympathetic nerve that arises from the superior cervical ganglion. This nonvascular contractile cell participates in the regulation of the IOP or the intermediate-term regulation of ChT[19]. The study also found that the sympathetic out flow was augmented during dynamic exercise even when the exercise intensity was low to moderate[20-21]. In our study, the exercise intensity we adopted was moderate for all participant (mean 63%). Therefore, activation of the sympathetic nerve may have contributed to the decrease in the ChT following the aerobic exercise.

The underlying mechanism of IOP reduction following aerobic exercise is still uncertain[13]. Similar to the results of Natsis

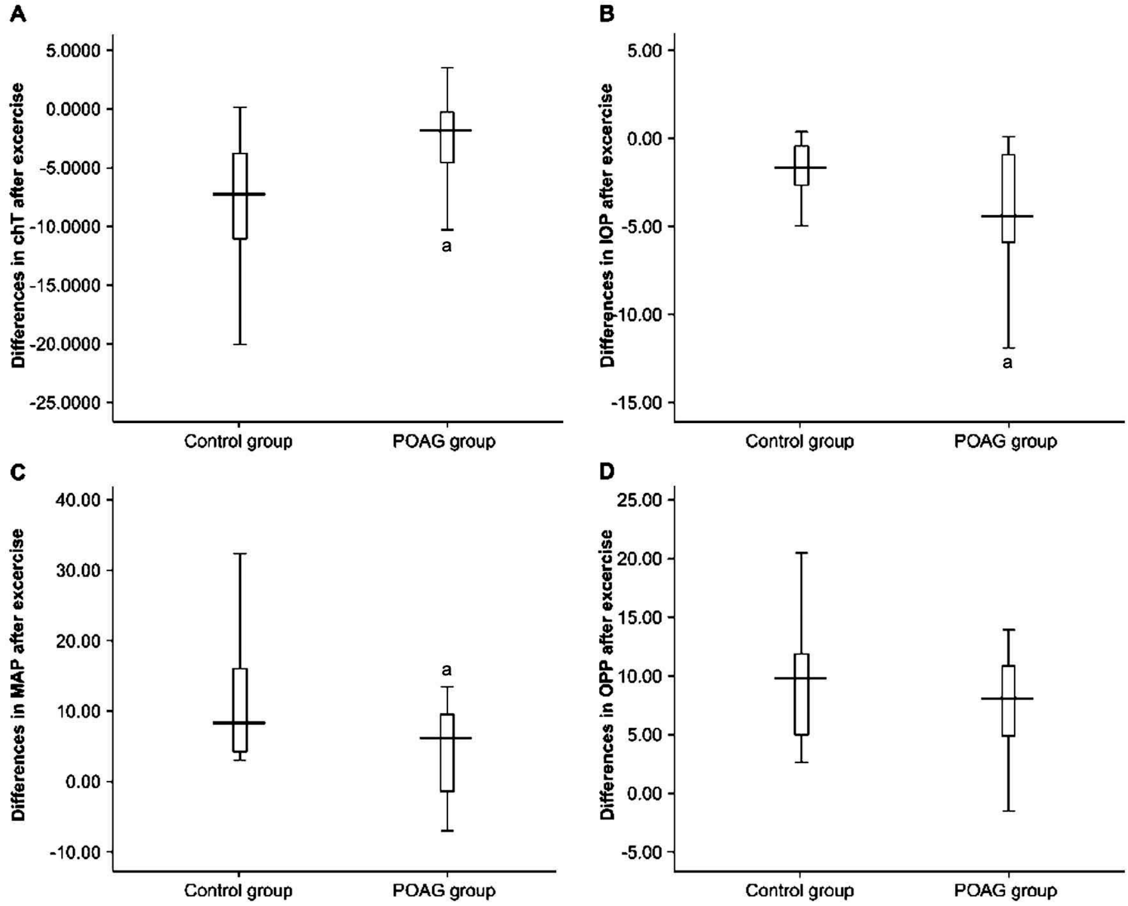

Figure 2 Disparate response of ChT, IOP, MAP after exercise in both groups [a]$P<0.05$, ANOVA. A: Choroidal thickness (ChT) was decreased after exercise more obviously in the control than in the POAG group; B: Intraocular pressure (IOP) was decreased more significantly after exercise in the POAG than in the control group; C: Mean arterial pressure (MAP) increased more significantly in the control than in the POAG group after exercise; D: Ocular perfusion pressure (OPP) did not differ significantly between both groups after aerobic exercise.

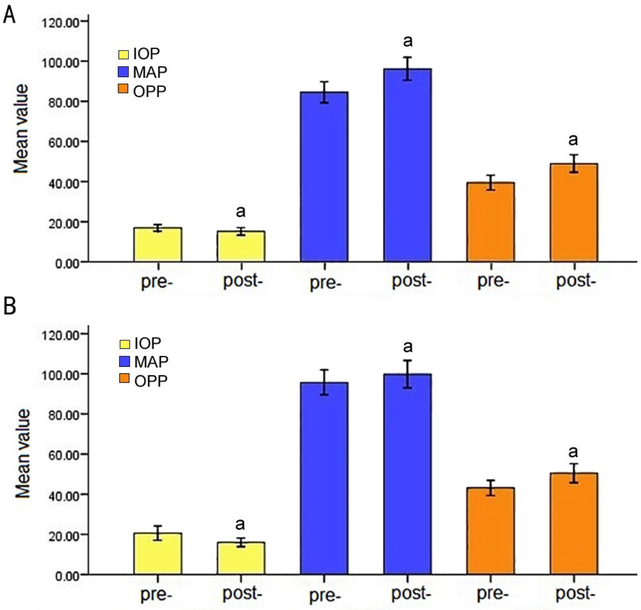

Figure 3 Intraocular pressure (IOP), mean arterial pressure (MAP) and ocular perfusion pressure (OPP) changed significantly in both groups after aerobic exercise A: Control group; B: POAG group. [a]$P<0.05$, paired t-test.

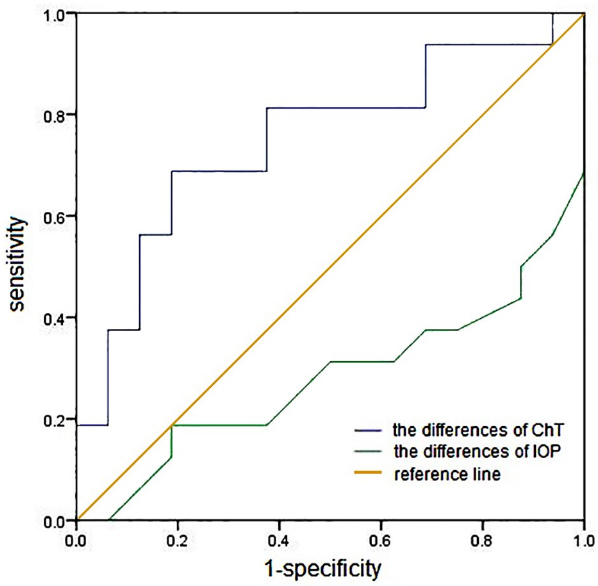

Figure 4 Area under the curve (AUC) of choroidal thickness (ChT) and intraocular pressure (IOP) showed variations of 0.75 and 0.281, respectively for subjects with primary open-angle glaucoma (POAG).

et al[11], we also observed a decrease in the IOP for both the control and POAG groups following the jogging exercise in our study. The dynamic equilibrium of the IOP depends on a sufficient outflow of aqueous humor through the uvea-scleral pathway. This process can be simulated by adrenergic receptor agonist (α-2 receptor), which achieve reasonably good results for IOP decrease[22]. There is evidence showing that the increase in the IOP is accompanied by an intensive decrease in the norepinephrine nerve fiber activity in uvea-sclera tissues[23]. Therefore, from the results of our study, activation of the sympathetic nerve may also be the mechanism responsible for the decrease in the IOP following aerobic exercise.

The ANOVA test showed that a greater decrease of ChT in the control than in the POAG group (F=6.071, P=0.02) after aerobic exercise. But a more significant decrease in the IOP was observed in the POAG than in the control group after the exercise. The increase in the OPP after the jogging exercise was not significantly different in both groups. As mentioned above, the normal task performed by the ChT, IOP, and MAP were greatly dependent on the regulation of the autonomic nervous system[24-28]. In 2009, the dysfunction of the autonomic nervous system in patients with POAG was reported by Clark and Mapstone[29]. In that study, parasympathetic and sympathetic neuropathies were observed in 37.3% of subjects and 6% of patients, respectively. Since then, the dysfunction of the autonomic nervous system has been investigated by numerous researchers. Based on our results, we postulated that the differences in the fluctuation of the ChT, IOP, and MAP in the subjects with POAG after the exercise might be because of the autonomic nervous system dysfunction.

However, this result was inconsistent with previous studies, which showed that the submacular ChT did not change significantly following cardiac exercise stress testing[30]. The distinct measuring range of the ChT and the different mode of exercise adopted in this study may explain this discrepancy.

In our study, the AUC of the ChT was 0.75, which was significantly higher than that of the IOP (0.281) in predicting the POAG disease status during the performance of the aerobic exercise. We propose that the decreased value in IOP may have resulted from the administration of the anti-glaucoma drops before the exercise in the patients with POAG. The variation of the ChT could be adopted as a marker for anticipating the aggravation of POAG disease after a moderate jogging exercise.

During the WDT, the expansion of the ChT was thought to be responsible for the IOP elevation[31]. The diurnal pattern was shown to exhibit turbulence in both the ChT and IOP following cervical sympathetic trunk resectioning[7]. The ChT and IOP are not closely associated in our study, which were similar to the results obtained by Hong *et al*[32]. A number of factors should be considered when attempting to interpret these findings. Firstly, a minimum ChT fluctuation requires a diurnal IOP rhythm amplitude of 12 mmHg[6], the 5 mmHg decrease observed in the IOP in our study may not be sufficient. Secondly, the 25% OPP elevation in this study may not have been sufficient to induce any significant variations in the ChT after jogging, which required at least a 67% change of OPP in the isometric exercise[33]. Finally, the patients with glaucoma in our study were administered anti-glaucoma drops (prostanoid in 10 subjects, carbonic anhydrase inhibitor in three, and alpha-2 agonist in two), and the drug-induced decrease in IOP may have also influenced the extent of its decreased following exercise. Therefore, the correlation between the ChT and IOP still needs to be clarified in future studies.

It is important to consider some of the limitations encountered in this study. Firstly, only 34 participants were enrolled and, therefore, the small sample statistical analysis tool was used (non-randomized controlled trial). The expansion of the sample size will be necessary for future studies. Secondly, the subjects with glaucoma were administered the anti-glaucoma drops during the study period, and the subsequent reduction in the IOP may have influenced the extent of IOP decrease after the exercise.

REFERENCES

1 Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res* 2010;29(2):144-168

2 Parver LM, Auker C, Carpenter DO. Choroidal blood flow as a heat dissipating mechanism in the macula. *Am J Ophthalmol* 1980;89(5):641-646

3 Saw SM, Gazzard G, Shih-Yen EC, Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt* 2005;25:381-391

4 Vongphanit J, Mitchell P, Wang JJ. Prevalence and progression of myopic retinopathy in an older population. *Ophthalmology* 2002;109(4):704-711

5 Alimanovic-Halilovic E. Correlation between refraction level and retinal breaks in myopic eye. *Bosn J Basic Med Sci* 2008;8(4):346-349

6 Kinoshita T, Mitamura Y, Shinomiya K, Egawa M, Iwata A, Fujihara A, Ogushi Y, Semba K, Akaiwa K, Uchino E, Sonoda S, Sakamoto T. Diurnal variations in luminal and stromal areas of choroid in normal eyes. *Br J Ophthalmol* 2016;0:1-5

7 Zhan GL, Lee PY, Ball DC, Mayberger CJ, Tafoya ME, Camras CB, Toris CB. Time dependent effects of sympathetic denervation on aqueous humor dynamics and choroidal blood flow in rabbits. *Curr Eye Res* 2002;25(2):99-105

8 Dane S, Koçer I, Demirel H, Ucok K, Tan U. Effect of acute submaximal exercise on intraocular pressure in athletes and sedentary subjects. *Int J Neurosci* 2006;116(10):1223-1230

9 Najmanova E, Pluhacek F, Botek M. Intraocular Pressure Response to Moderate Exercise during 30-Min Recovery. *Optom Vis Sci* 2016;93(3):281-285

10 Bakke EF, Hisdal J, Semb SO. Intraocular pressure increases in parallel with systemic blood pressure during isometric exercise. *Invest Ophthalmol Vis Sci* 2009;50(2):760-764

11 Natsis K, Asouhidou I, Nousios G, Chatzibalis T, Vlasis K, Karabatakis V. Aerobic exercise and intraocular pressure in normotensive and glaucoma patients. *BMC Ophthalmol* 2009;9:6

12 Risner D, Ehrlich R, Kheradiya NS, Siesky B, McCranor L, Harris A. Effects of exercise on intraocular pressure and ocular blood flow: a review. *J Glaucoma* 2009;18(6):429-436

13 Patterson M. Guidelines for data processing and anlyses of the International Physical Activity Questionnaire (IPAQ). 2005. Available at: https://sites.google.com/site/theipaq/scoring-protocol

14 Németh J, Knézy K, Tapasztó B, Kovács R, Harkányi Z. Different autoregulation response to dynamic exercise in ophthalmic and central retinal arteries: a color Doppler study in healthy subjects. *Graefes Arch Klin Exp Ophthalmol* 2002;240(10):835-840

15 Portmann N, Gugleta K, Kochkorov A, Polunina A, Flammer J, Orgul S. Choroidal blood flow response to isometric exercise in glaucoma patients and patients with ocular hypertension. *Invest Ophthalmol Vis Sci* 2011;52(10):7068-7073

16 Chen W, Wang Z, Zhou X, Li B, Zhang H. Choroidal and

photoreceptor layer thickness in myopic population. *Eur J Ophthalmol* 2012;22(4):590-597

17 Kim DY, Silverman RH, Chan RV, Khanifar AA, Rondeau M, Lloyd H, Schlegel P, Coleman DJ. Measurement of choroidal perfusion and thickness following systemic sildenafil (Viagra(®)). *Acta Ophthalmol* 2013;91(2):183-188

18 McDougal DH, Gamlin PD. Autonomic control of the eye. *Compr Physiol* 2015;5(1):439-473

19 Lütjen-Drecoll E. Choroidal innervation in primate eyes. *Exp Eye Res* 2006;82(3):357-361

20 Tsuchimochi H, Matsukawa K, Komine H, Murata J. Direct measurement of cardiac sympathetic efferent nerve activity during dynamic exercise. *Am J Physiol Heart Circ Physiol* 2002; 283(5): H1896-H1906

21 Sone R, Tan N, Nishiyasu T, Yamazaki F. Autonomic heart rate regulation during mild dynamic exercise in humans: insights from respiratory sinus arrhythmia. *Jpn J Physiol* 2004;54(3):273-284

22Rahman MQ, Ramaesh K, Montgomery DM. Brimonidine for glaucoma. *Expert Opin Drug Saf* 2010;9(3):483-491

23Cavallotti C, Pescosolido N, Artico M, Pacella E, Cavallotti D. Occurrence of catecholaminergic nerve fibers in the human uveoscleral tissue in conditions of normal and raised intraocular pressure. *Int Ophthalmol* 2001;24(3):133-139

24 Riccadonna M, Covi G, Pancera P, Presciuttini B, Babighian S, Perfetti S, Bonomi L, Lechi A. Autonomic systemactivity and 24-hour blood pressure variations in subjects with normal- and high-tension glaucoma. *J Glaucoma* 2003;12(2):156-163

25 Delaey C, Van De Voorde J. Regulatory mechanisms in the retinal and choroidal circulation. *Ophthalmic Res* 2000;32(6):249-256

26 Trivino A, De Hoz R, Salazar JJ, Ramírez AI, Rojas B, Ramírez JM. Distribution and organization of the nerve fiber and ganglion cells of the human choroid. *Anat Embryol* 2002;205(5-6):417-430

27 May CA, Neuhuber W, Lütjen-Drecoll E. Immunohistochemical classification and functional morphology of human choroidal ganglion cells. *Invest Ophthalmol Vis Sci* 2004;45(2):361-367

28 Trivino A, de Hoz R, Rojas B, Salazar JJ, Ramirez AI, Ramirez JM. NPY and TH innervation in human choroidal whole-mounts. *Histol Histopathol* 2005;20(2):393-402

29 Clark CV, Mapstone R. Systemic autonomic neuropathy in open-angle glaucoma. *Doc Ophthalmol* 1986;64(2):179-185

30 Alwassia AA, Adhi M, Zhang JY, Regatieri CV, Al-Quthami A, Salem D, Fujimoto JG, Duker JS. Exercise-induced acute changes in systolic blood pressure do not alter choroidal thickness as measured by a portable spectral-domain optical coherence tomography device. *Retina (Philadelphia, Pa)* 2013;33(1):160-165

31 De Moraes CG, Reis AS, Cavalcante AF, Sano ME, Susanna R Jr. Choroidal expansion during the water drinking test. *Graefes Arch Klin Exp Ophthalmol* 2009;247(3):385-389

32 Hong J, Zhang H, Kuo DS, Wang H, Huo Y, Yang D, Wang N. The short-term effects of exercise on intraocular pressure, choroidal thickness and axial length. *PLoS ONE* 2014;9(8):e104294

33 Riva CE, Titze P, Hero M, Movaffaghy A, Petrig BL. Choroidal blood flow during isometric exercises. *Invest Ophthalmol Vis Sci* 1997;38(11):2338-2343