Dual effect of the Valsalva maneuver on autonomic nervous system activity, intraocular pressure, Schlemm's canal, and iridocorneal angle morphology

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Abstract

Background The Valsalva maneuver (VM) is common in the daily life and has been reported to cause high intraocular pressure (IOP). This study aimed to assess changes in IOP, Schlemm's canal (SC), autonomic nervous system activity and iridocorneal angle morphology in healthy individuals during different phases of the VM. Methods The high frequency (HF) of heart rate variability (HRV), the ratio of low frequency power and high frequency power (LF/HF), heart rate (HR), IOP, systolic (SBP) and diastolic blood pressure (DBP), the area of Schlemm's canal (SCAR), pupil diameter (PD) and some iridocorneal angle parameters (AOD500, ARA750, TIA500 and TISA500) were measured in 29 young healthy individuals at baseline, phase 2 and phase 4 of the VM. SBP and DBP were measured to calculate mean arterial pressure (MAP) and mean ocular perfusion pressure (MOPP). HF and LF/HF ratio were recorded using Kubios HRV Premium software to evaluate autonomic nervous activity. The profiles of anterior chamber were captured by a Spectralis optical coherence tomography device (anterior segment module). Results Compared with baseline values, in phase 2 of the VM, HR, LF/HF, IOP (15.1 ± 2.7 vs. 18.8 ± 3.5 mmHg, $p < 0.001$), SCAR(mean) (7448.64 ± 3230.82 vs. 8851.43 ± 4231.15 μm2, $p = 0.038$) and PD increased significantly, whereas MOPP, AOD500, ARA750, TIA500 and TISA500 decreased significantly. In phase 4, HR, DBP, MAP, MOPP, AOD500, ARA750, TIA500and TISA500 were significantly lower than baseline value, while PD and HF were remarkably larger than baseline. The comparison between phase 2 and phase 4 showed that HR, IOP (19.1 ± 3.3 vs. 14.7 ± 2.9 mmHg, $p < 0.001$) and PD decreased significantly from phase 2 to phase 4, but there were no significant differences in other parameters. Conclusions The expansion and collapse of SC in different phases of the VM may be arise from the changes of autonomic nervous system activity, while its influence on IOP could be counteracted even reversed by the changes of blood flow and ocular anatomy.

Background

The original Valsalva maneuver (VM) was popularized and described in detail by Mario Antonio Valsalva (1666-1723) [1]. The maneuver consists of a voluntary forced expiration against an airway obstruction[2]. Levin (1966) standardized the research method for the VM: subjects are asked to blow into a tube and to maintain a pressure of 40mmHg for 10s [3, 4].

According to previous studies, the VM consists of 4 phases. In phase 1, increasing intrathoracic pressure caused by the initiate straining of the maneuver translates to the arterial circulation. In phase 2, strain is maintained. Increased intrathoracic pressure and decreased venous return make a decrease in blood pressure as well as a reflexive increased heart rate (HR) caused by the restraint of parasympathetic nerve and increased sympathetic outflows. In phase 3, release of strain makes a rapid drop of intrathoracic pressure leading to a transient drop of blood pressure. In phase 4, the impediment to venous return to the heart is alleviated and blood is ejected into the constricted vasculature by the heart, making the pressure overshoots. Parasympathetic activity is reflexively increased, resulting in relatively quick slowing down of the heart [5-8].

The VM, which was originally used to inflate the Eustachian tubes, is deeply rooted into the history of medicine [1, 6]. Since the maneuver can induce complex physiologic responses, such as changes of autonomic nervous system activity and cardiovascular response, it has been widely studied in the cardiovascular system and nervous system [3, 4, 7].

A rise in intraocular pressure (IOP) during the VM has been reported by many studies, but the mechanism remains unclear [4, 9-11]. The VM is common in the daily life [1, 7] and high IOP is a major risk factor for glaucoma disease [12]. We have previously shown that an IOP decrease was associated with sympathetic nerve stimulation which is caused by aerobic exercise [13] and parasympathetic nervous system stimulation caused by water-drinking test may lead to the collapse of Schlemm's canal (SC) and an IOP increase [14]. In this study, we therefore research on the possible mechanism of the IOP fluctuations in different phases of the VM.

Materials And Methods

Subjects

A total of 29 healthy individuals were recruited from students of Tongji Medical College, Huazhong University of Science and Technology. All participants signed written informed consent before entering the study, and the study was conducted in accordance with the tenets of the Declaration of Helsinki. All the subjects underwent an ophthalmic examination. Their right eyes were included in the study.

Healthy individuals were at least 18 years old with normal anterior chamber depth and open angle. Individuals with systemic diseases, IOP higher than 21mmHg, ophthalmic diseases or previous ocular surgery and those using topical or systemic medications were excluded. Every volunteer received the examination in a sitting position. All examinations were performed followed the standard operating procedures. In this study, no contact was required to avoid the influence of corneal contact on the parameters and participants' health.

The Standardized Valsalva Maneuver

According to Levin. 1966, every subject was trained to perform a standardized VM. They were asked to exhale into a mouthpiece which is connected to a mercury manometer and to maintain an expiratory pressure of 40 mmHg for about 15s to finish the images acquisition processes. After training, every individual can manage the maneuver well. Resting state before breath holding, continuous blowing state and immediately recovered normal breathing were recorded respectively as baseline, phase 2 and phase 4 of the VM. Each phase took 15s. Participants were given a short break of at least 5 min between every two VMs. An individual performed the maneuver for 7 times.

Measurements of BP, HR and ECGs

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) at baseline, phase 2 and phase 4 of the VM of individuals were measured using an automatic sphygmomanometer (OmronHEM-7201; Omron,

Dalian, Liaoning, China). The mean arterial pressure (MAP) is calculated by the equation: MAP = DBP + (SBP - DBP)/3. Electrocardiograms (ECGs) were recorded in resting state, continuous blowing state and immediately recovered normal breathing, each part took 15s. Heart rate (HR) was received by measuring R-R intervals. The heart rate variability (HRV) parameters of individuals were calculated in each state (baseline, phase2 and phase4 of VM) by using Kubios HRV Premium software (version 2.2; University of Esatern Finland).

AS-OCT Imaging

In a sitting position, all participants received anterior optical coherence tomography (AS-OCT) examination using anterior optical coherence tomography (Visante OCT; Carl Zeiss Meditec, Inc.). Rectangle AS-OCT scans of front, nasal and temporal side were collected in three phases. In scans of front, the scan angle was horizontal (nasal – temporal angles at 0°-180°) across the center of the pupil in one single image, while the subject staring at the internal fixation point. All AS-OCT tests were performed under the same photopic conditions.

Measurements of SC and Pupil Diameter

SC was defined as observable when a thin, black, lucent space was detected in images (Fig. 1). The area of Schlemm's canal (SCAR, μm^2) in the same location of nasal and temporal sides were measured using Image J software (version 1.45S; National Institutes of Health, Bethesda, MD, USA). The SCAR (mean) is calculated as the average of the SCAR of nasal and temporal. The distance from one side of the pupillary tip of the iris to the opposite side on images acquired by anterior optical coherence tomography was measured as the pupil diameter (PD).

Measurement of IOP

The IOP at baseline, phase 2 and phase 4 of the VM were measured using an iCare rebound tonometer (i-Care, Finland Oy, Vantaa, Finland). For every individual, three measurements (three readings per measurement) were obtained. The average value was calculated as the result of this IOP measurement in case the difference value between two readings for one measurement was within ± 1 mmHg. Mean ocular perfusion pressure (MOPP) is calculated as: MOPP = 2/3MAP – IOP.

Statistical Analysis

All statistical analyses were performed using the SPSS software package version 22.0 (Inc., Chicago, IL, USA) and plotted by GraphPad Prism7.0 (USA, GraphPad Software). All applicable data were presented as the mean ± SDs. Paired t-test were used to detect the difference of data between every two different phases. All tests were two-tailed, and statistical significance was defined as a P value less than 0.05.

Results

Twenty-nine individuals were enrolled in this study. A total of 29 right eyes (13 males; 16 females) were included in the analyses. The mean patient age was 23.83 ± 3.81 years.

In comparison with baseline value, significant change was observed in the BP during the phase 4 of the VM, including DBP (77.50 ± 9.56 vs. 72.63 ± 8.99 mmHg, p =0.001) and MAP (91.15 ± 10.36 vs. 87.51 ± 7.32, p = 0.009). Other BP values did not have significant difference among different states. HR increased from 83 ± 11.73 beats/min (bpm) at baseline to 92 ± 14.28 bpm at phase 2 (p < 0.001), and at phase 4 of the VM, HR decreased to 80 ± 10.15 bpm, significantly lower than the baseline (p = 0.030) and phase 2 (p < 0.001) (Fig. 2). As for HRV, high frequency (HF) indices of the phase4 is significantly higher than baseline (2546.08 ± 1837.11 vs. 1206.04 ± 1206.07 mm^2, p = 0.04). And the ratio of low frequency power and high frequency power (LF/HF) indices increased from base stste (1.44 ± 1.64) to phase2 (7.48 ± 11.61), p = 0.024.

We observed a significant increase in IOP from baseline to phase 2 (15.1 ± 2.7 vs. 18.8 ± 3.5 mmHg, p < 0.001) and a significant decrease from phase 2 to phase 4 (19.1 ± 3.3 vs. 14.7 ± 2.9 mmHg, p < 0.001). However, there was no significant difference between the IOP in baseline and phase 4 (15.2 ± 2.7 vs. 14.7 ± 2.9 mmHg, p = 0.112). (Fig. 3)

During phase 2 of the VM, the MOPP showed a statistically significant decrease from 46.06 ± 6.61 mmHg of baseline to 41.23 ± 7.49 mmHg (p = 0.002). And the increase from phase 2 to phase 4 is not significant (41.23 ± 7.49 vs. 44.53 ± 6.15 mmHg, p = 0.104). Between the baseline and the phase 4, significant difference was observed (46.06 ± 6.61 vs. 44.53 ± 6.15 mmHg, p = 0.017). (Fig. 4)

Images of one eye was excluded because of low image quality. As for the average of two regions, the SCAR (mean) increased significantly from baseline to phase 2 (7448.64 ± 3230.82 vs. 8851.43 ± 4231.15 μm^2, p = 0.038), as shown in Table 1. The differences among other states was not significant (Fig. 5, Fig. 6).

Compared to baseline, there was a significant increase of 12.1% in pupil diameter in the phase 2 of the VM, from a resting value of 4.23 ± 0.82 to 4.74 ± 0.74 mm during the phase 2 (p < 0.001). And a significant decrease in the mean value of pupil diameter was observed from the phase 2 to the phase 4 (4.67 ± 0.82 vs. 4.47 ± 0.73 mm, p = 0.001). We also found that the difference between baseline and the phase 4 is statistically significant (4.22 ± 0.82 vs. 4.53 ± 0.68 mm, p < 0.001). (Fig. 7, Fig. 8)

Angle opening distance at 500 μm from the scleral spur (AOD500), angle recess area at 750 μm from the scleral spur (ARA750), trabecular iris angle at 500 μm from the scleral spur (TIA500) and trabecular-iris space area at 500 μm from the scleral spur (TISA500) of horizontal scan of AS-OCT were found changed significantly in this study. From baseline to phase 2, these parameters showed a significant reduction: AOD500 (0.72 ± 0.17 vs. 0.63 ± 0.17 mm, p = 0.003), ARA750 (0.50 ± 0.12 vs. 0.44 ± 0.12 mm^2, p = 0.021), TIA500 (57.54 ± 8.46 vs. 51.84 ± 7.50 °, p < 0.001) and TISA500 (0.26 ± 0.07 vs. 0.23 ± 0.07 mm2, p = 0.016). And in phase 4, these parameters were still significantly lower than baseline: AOD500(0.73 ±

0.17 vs. 0.65 ± 0.18 mm, p < 0.001), ARA750 (0.50 ± 0.12 vs. 0.46 ± 0.12 mm^2, p = 0.005), TIA500 (58.23 ± 8.77 vs. 53.60 ± 9.72°, p = 0.001) and TISA500(0.26 ± 0.07 vs. 0.23 ± 0.07 mm^2, p = 0.016).(Fig. 9 A-D)

Discussion

Forced expiration against an airway obstruction was originally presented by Antonio Maria Valsalva (1666 – 1723) as a method to inflate the Eustachain tubes [1, 5, 6]. The VM, which is now used as a procedure to investigate the function of autonomic system, can be divided into four physiological phases [4, 7]. Physiological variations in phase 2 and phase 4 of the VM are accompanied by the change of both autonomic excitability and hemodynamics. The increased intrathoracic pressure causes an obstruction of venous reflux in phase 2, stimulating the sympathetic increased excitability. And in phase 4, parasympathetic activity is increased, resulting in relatively quick slowing down of the heart. Therefore, baseline, phase 2 and phase 4 were selected in this study, to detect the dual effect of the VM on parameters in individuals at different phases [5-7, 10]. Compared with baseline (83 ± 11.73 bpm), we found a significantly increased HR in phase 2 (92 ± 14.28 bpm, p < 0.001) and a significantly decreased HR in phase 4 (80 ± 10.15 bpm, p = 0.030). Also, HR in phase 4 is significantly lower than it in phase 2 (p < 0.001). These results were consistent in numerous previous studies [5-7]. HRV is a simple, noninvasive method to evaluate the autonomic nervous system regulation and has been used in a variety of clinical situations. It is the variation in the time interval between each heartbeat which is recorded as R – R intervals [15]. Traditional HRV assessment methods include time domain, frequency domain and nonlinear analysis. LF (0.04 – 0.15 Hz) and HF (0.15 – 0.4 Hz) are two of basic components of frequency domains. A higher HF specifically shows that parasympathetic activation is increased, while the attribution of LF is widely debated and generally considered to be the combined sympathetic and parasympathetic influence [16, 17]. In recent studies, the LF/HF ratio is used as a measure of the global sympatho-vagal balance and can be used to indicate the amount of sympatho-vagal modulation of the instantaneous heart rate. An increasing LF/HF represents that sympathetic activation is predominant [18]. Compared to baseline, we found a significantly LF/HF ratio in phase 2(1.44 ± 1.64 vs. 7.48 ± 11.61, p = 0.024) that reflected an increased sympathetic activity, and a significantly increased HF indices in phase 4 (2546.08 ± 1837.11 vs. 1206.04 ± 1206.07 mm2, p = 0.04) reflecting a hyperfunction of parasympathetic nerve.

The elevation of IOP in healthy individuals during the continued strain of the VM has been reported in numerous studies [4, 9, 10, 19]. It has been speculated that IOP elevation in phase 2 of the VM is mainly caused by raised episcleral pressure reducing aqueous outflow. The anterior engorged choroidal vessels may make a small increase of the total ocular volume resulting in an elevation of IOP, because the wall of the eye has certain rigidity [20]. We also observed that, relative to baseline, phase 2 of the VM in young healthy adults led to an elevation in IOP (15.1 ± 2.7 vs. 18.8 ± 3.5 mmHg, p < 0.001). A study by Li et al. showed that the anterior choroid and the ciliary body but not posterior choroid were thickened during forced exhalation against a closed airway in phase 2 [21]. Significantly decreased AOD500, ARA750, TIA500 and TISA500 during the VM may be another reason for elevated IOP, because a narrowed anterior

chamber could lead to higher outflow resistance of aqueous humor [22]. In our study, IOP returned to baseline in phase 4 rapidly, since this phase is the normal process of physiological indexes with the resistance to blood flowing disappear. In addition, autonomic activity frequently influences IOP. Increased HR and LF/HF ratio found in phase 2 implied a sympathetic activation, while significantly increased HF and remarkably decreased HR in phase 4 showed a parasympathetic excitation. These results contrast with previous studies that suggested an active sympathetic nervous system may lead to a decrease in IOP, while overactivation of parasympathetic nerve can produce an elevation of IOP [13, 23, 24]. Therefore, we speculate that the IOP fluctuation arise from the changes of blood flow and ocular anatomy may counteracted and reversed the influences of autonomic activity.

SC is the vein at the chamber angle, which is first discovered by Friedrich Schlemm in 1830, that collects aqueous humor from anterior chamber and delivers it into the bloodstream [25]. In previous study, Chen et al. found that the collapse may be one of the reason of the IOP peak after the water-drinking test [14]. And numerous studies have reported that an IOP of 30 to 50 mmHg can make trabecular sheets distended into SC and reduce the SC lumen [26, 27]. However, in this study, the increase in SCAR from baseline to phase 2 (7448.64±3230.82 vs. 8851.43±4231.15 μm2, p = 0.038) , while IOP is significantly increased, is less easily explained. The SC might have autonomic regulation functions [13, 28, 29]. Therefore, the expansion and collapse may not be completely dependent on the IOP. The expansion of SC is possible to be caused by sympathetic nerve stimulation in phase 2 of the VM. Although the average of SCAR in phase 4 become lesser than it in baseline and phase2, there was no significant differences. It has been indicated that activation of parasympathetic nerves might be involved in the collapse of SC in previous study, and parasympathetic system was found excited in phase 4 in this study [13, 14]. But there were only 13 individuals showed a smaller SCAR in phase 4 than SCAR in baseline. We speculated that this result might relates to individual diversities in the rate of autonomic regulation, because only 15s after subjects recovered normal breath was took into account and this time may be too short for some individuals to finish the regulation.

According to previous studies, elevation and fluctuation of IOP are associated with the development and progression of glaucoma [30]. In this study, we found that breath holding in phase 2 has an additive effect on IOP, which is consistent with previous studies. It has been reported that the VM can make the IOP of patients higher than normal, in whom the IOP is near to the 20mmHg border [31]. MOPP represents the gradient of efficient perfusion for all intraocular structures, including the optic nerve head and the retina.[32] The remarkably elevated IOP we found in phase 2 resulted in a reduction in MOPP (46.06 ± 6.61 vs. 41.23 ± 7.49 mmHg, p = 0.002). Although the MOPP started raising in phase 4, a short time is difficult to recovery, as the MOPP in phase 4 was still significantly lower than it in baseline (46.06 ± 6.61 vs.44.53 ± 6.15 mmHg, p = 0.017). There was an associated possibility of mechanical and ischemic damage to the optic nerve head, leading to glaucoma process [30, 32].

Pupil diameter, which is controlled by the sphincter pupillae and the dilator pupillae, is the reflection of iris size. The sphincter pupillae is primarily controlled by the parasympathetic nervous system, and the dilator pupilae is primarily controlled by sympathetic nervous system [33]. The pupil diameter (PD) were found to

be dilated in phase 2 (4.23 ± 0.82 vs. 4.74 ± 0.74 mm, p<0.001), and the PD in phase 4 (4.47 ± 0.73 mm) declined markedly in comparison with the pupil diameter in phase 2 (p = 0.001), and meanwhile still obviously greater than it in baseline (p<0.001). It indicates that the activation of sympathetic nervous system caused by the VM was sufficient to invoke pupil dilation, and it took some time to be back to normal. A prolonged pupil dilation might be a precipitating risk factor of PACG patients in routine life [34, 35].

The VM is very common in our daily life, and is done automatically and briefly, in vomiting and coughing and sneezing, and for longer periods in bodily functions like parturition and defecation; more deliberately, in heavy lifting; in various sports; in the blowing of wind instruments, and even in singing and laughing [1]. Changes caused by the VM in healthy young individuals may carry no clinical significance, but for patients with high risk factors of glaucoma, we suggest that it may be good to avoid repeating VMs in daily life.

This study had limitations. First, only 15 seconds after subjects recovered normal breath were observed in this study. It may be too short for physiological indicators of all individuals to return normal. Next, it is unclear whether similar effects of VMs would be observed in elderly subjects or patients with glaucoma, for all of our individuals were young and healthy. Lastly, the thickness of anterior choroid in AS-OCT images we gained in this study. It is necessary to acquire a more detailed data set in a future study.

In conclusion, the expansion and collapse of SC in different phases of the VM may cause by changes of autonomic nervous system activity, while its influence on IOP could be counteracted even reversed by the changes of blood flow and ocular anatomy.

Abbreviations

IOP: intraocular pressure; SC: Schlemm's canal; VM: Valsalva maneuver; HF: High frequency; HRV: heart rate variability; LF/HF: the ratio of low frequency power and high frequency power; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SCAR: SC area; PD: Pupil diameter; MAP: Mean arterial pressure; MOPP: Mean ocular perfusion pressure; ECGs: Electrocardiograms; AS-OCT: Anterior optical coherence tomography; AOD500: Angle opening distance at 500 μm from the scleral spur; ARA750: angle recess area at 750 μm from the scleral spur; TIA500: trabecular iris angle at 500 μm from the scleral spur; TISA500: trabecular-iris space area at 500 μm from the scleral spur

Declarations

Ethics approval and consent to participate

This observational study was approved by the ethics committee of Tongji Hospital (Registration Number: ChiCTR-OON-16007850, Date: 01.28.2016) and adhered to the tenets of the Declaration of Helsinki. All subjects provided written informed consent prior to study participation.

Consent for publication

Not applicable.

Availability of data and materials

The datasets and figures generated and analysed during the current study are not publicly available due concerns regarding privacy but are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZH and WJ designed the study. SL and CW performed examinations of individuals. SL prepared the carried out the analysis, interpreted and discussed the results, and wrote the first version of the manuscript. SL and CW were involved in drafting and revising the manuscript. All authors read and approved the final manuscript.

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Figure Legends

Figure 1. Image showing SC. The red curve indicates the SC.

Figure 2. Changes in HR. HR varied significantly in phase2 and phase4 of VM compared with baseline.

Figure 3. Changes in IOP. Changes in IOP in different phases during the VM.

Figure 4. Changes in MOPP. Changes in MOPP in different phases during the VM.

Figure 5. Morphology of SC (circled by red line). Baseline (A), phase 2 (B) and phase 4 (C) of the VM.

Figure 6. Changes in SCAR. Changes in SCAR(mean) at different phases of VM.

Figure 7. Measurement of PD (red line). Baseline (A), phase 2 (B) and phase 4 (C) of the VM.

Figure 8. Changes in PD. Changes in PD at different phases of VM.

Figure 9. Changes in iridocorneal angle parameters. (A-D) Changes in AOD500, ARA750, TIA500, and TISA500 at different phases in VM.

Table

Due to technical limitations, table 1 is only available as a download in the supplemental files section.

Figures

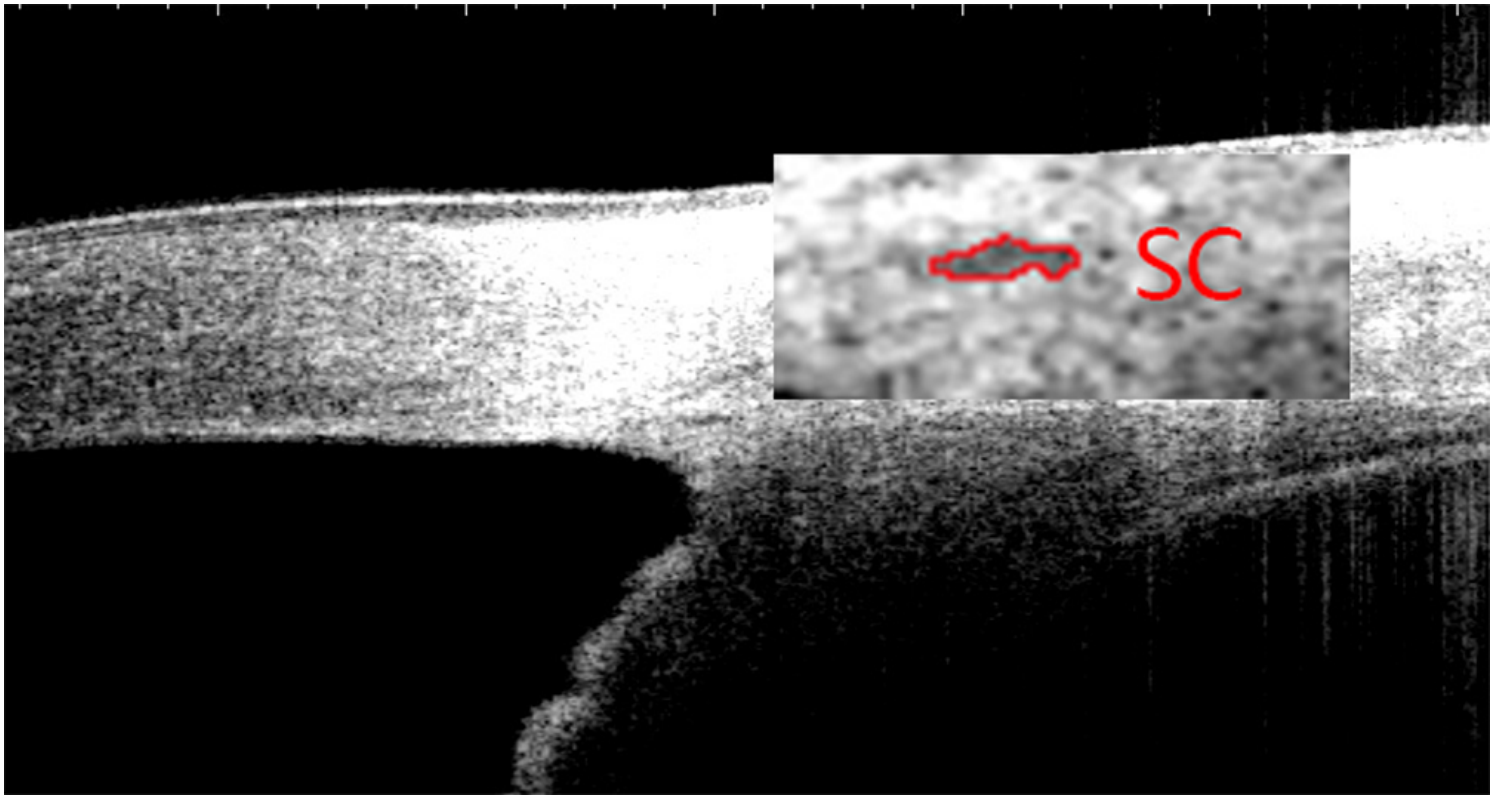

Figure 1

Image showing SC. The red curve indicates the SC.

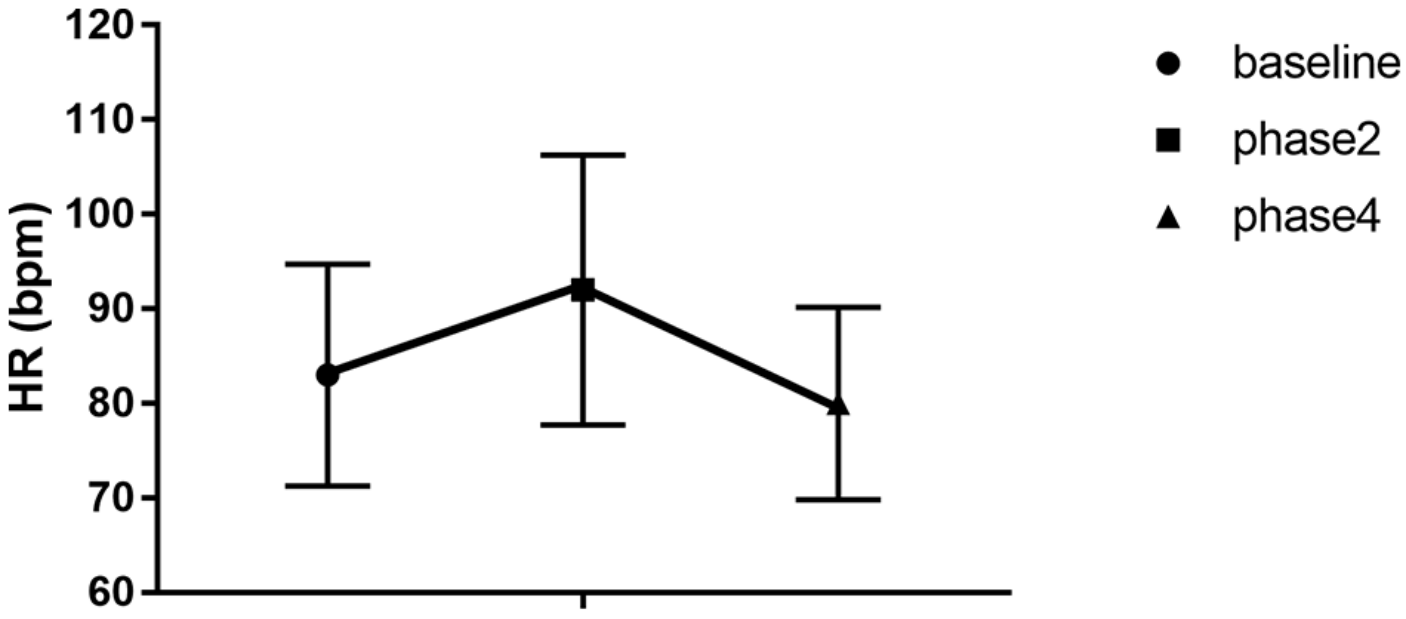

Figure 2

Changes in HR. HR varied significantly in phase2 and phase4 of VM compared with baseline.

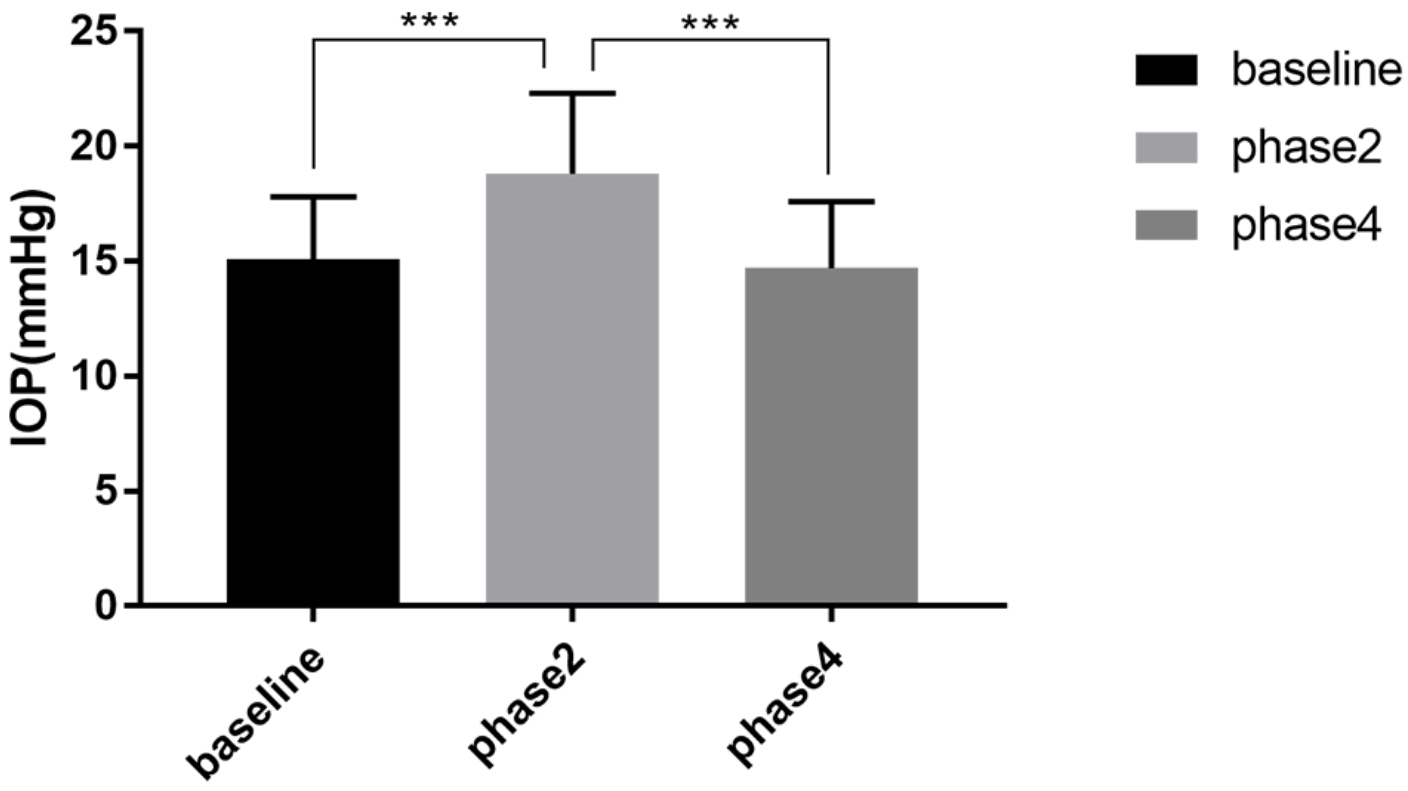

Figure 3

Changes in IOP. Changes in IOP in different phases during the VM.

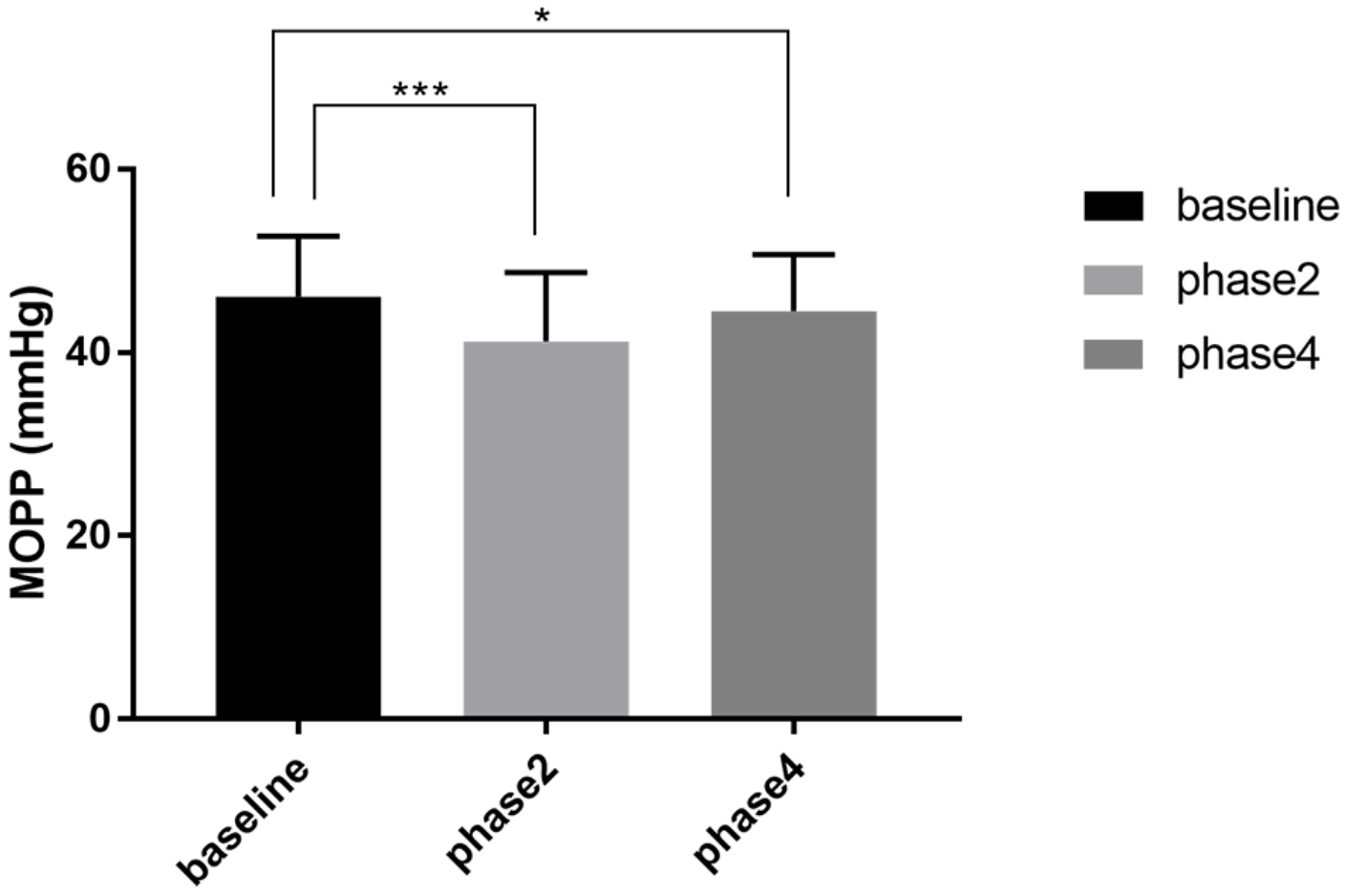

Figure 4

Changes in MOPP. Changes in MOPP in different phases during the VM.

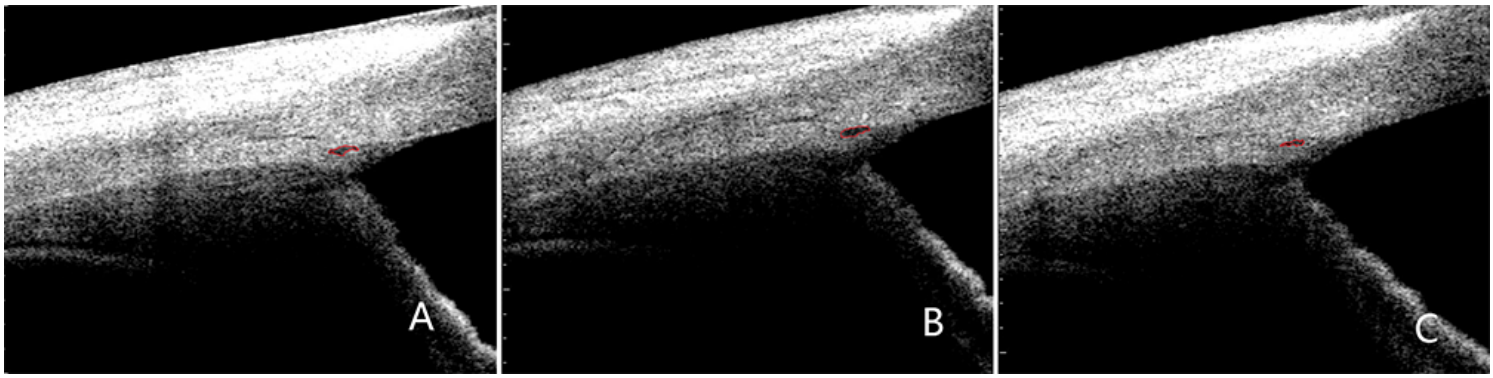

Figure 5

Morphology of SC (circled by red line). Baseline (A), phase 2 (B) and phase 4 (C) of the VM.

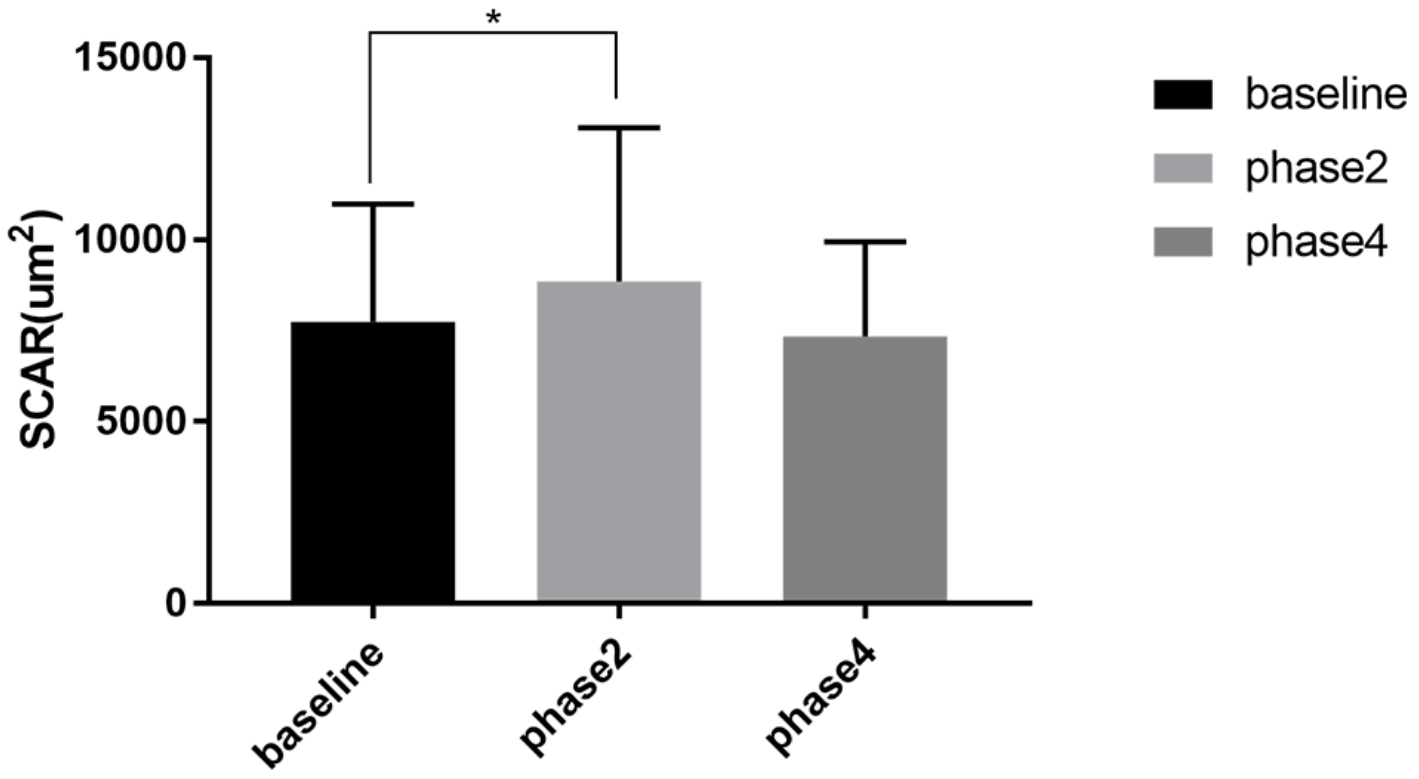

Figure 6

Changes in SCAR. Changes in SCAR(mean) at different phases of VM.

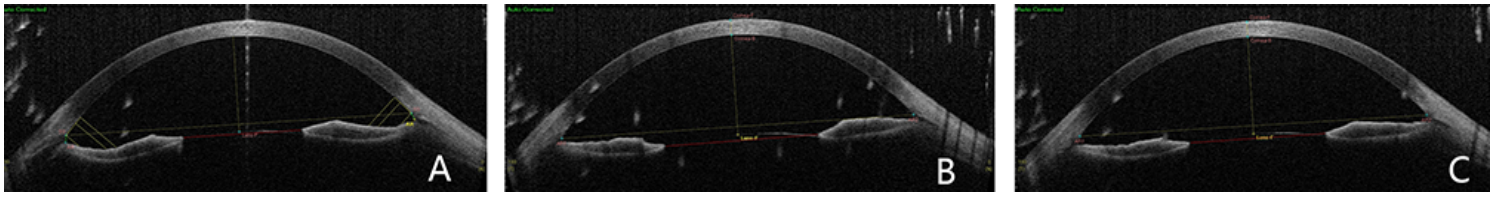

Figure 7

Measurement of PD (red line). Baseline (A), phase 2 (B) and phase 4 (C) of the VM.

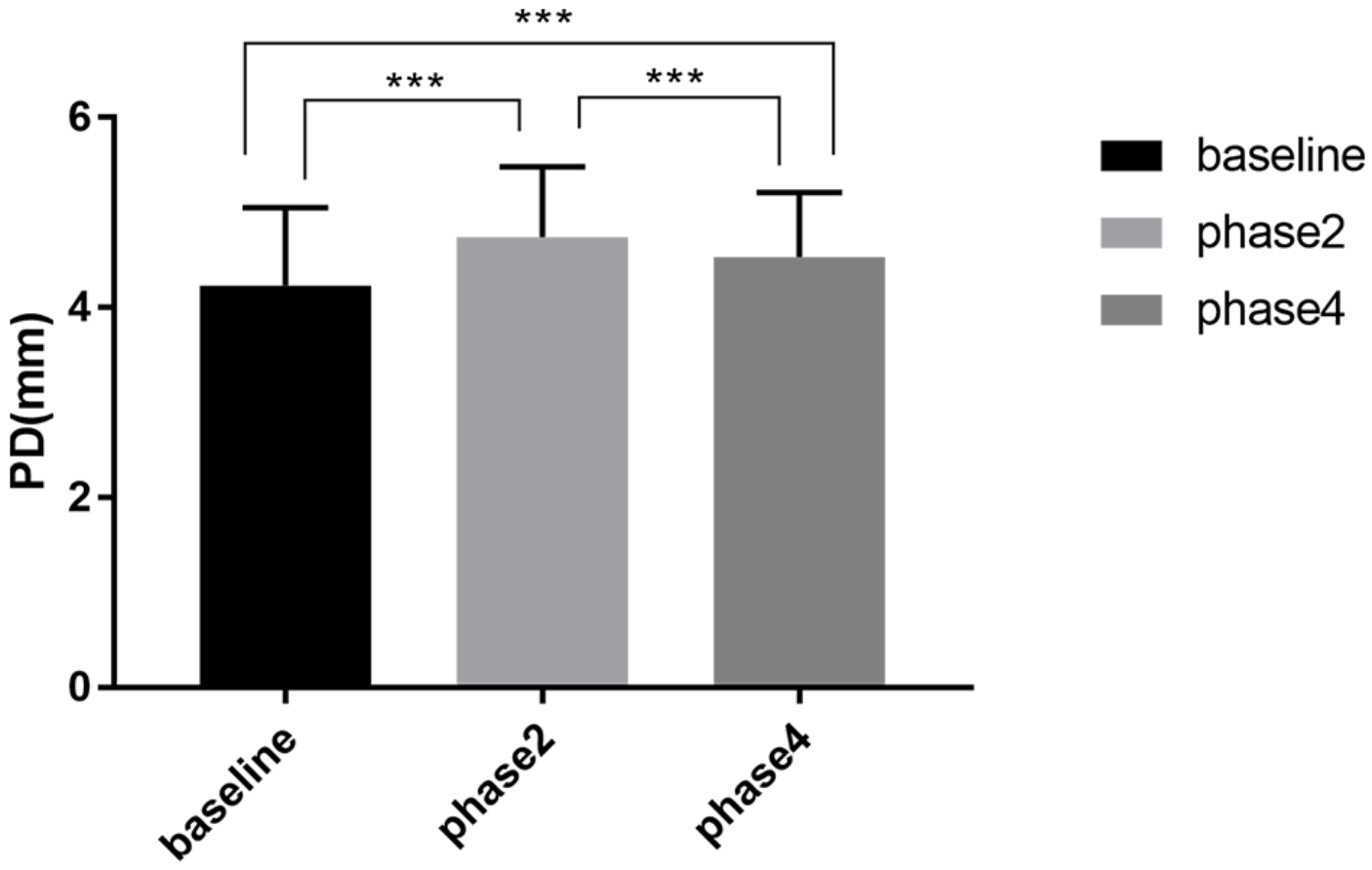

Figure 8

Changes in PD. Changes in PD at different phases of VM.

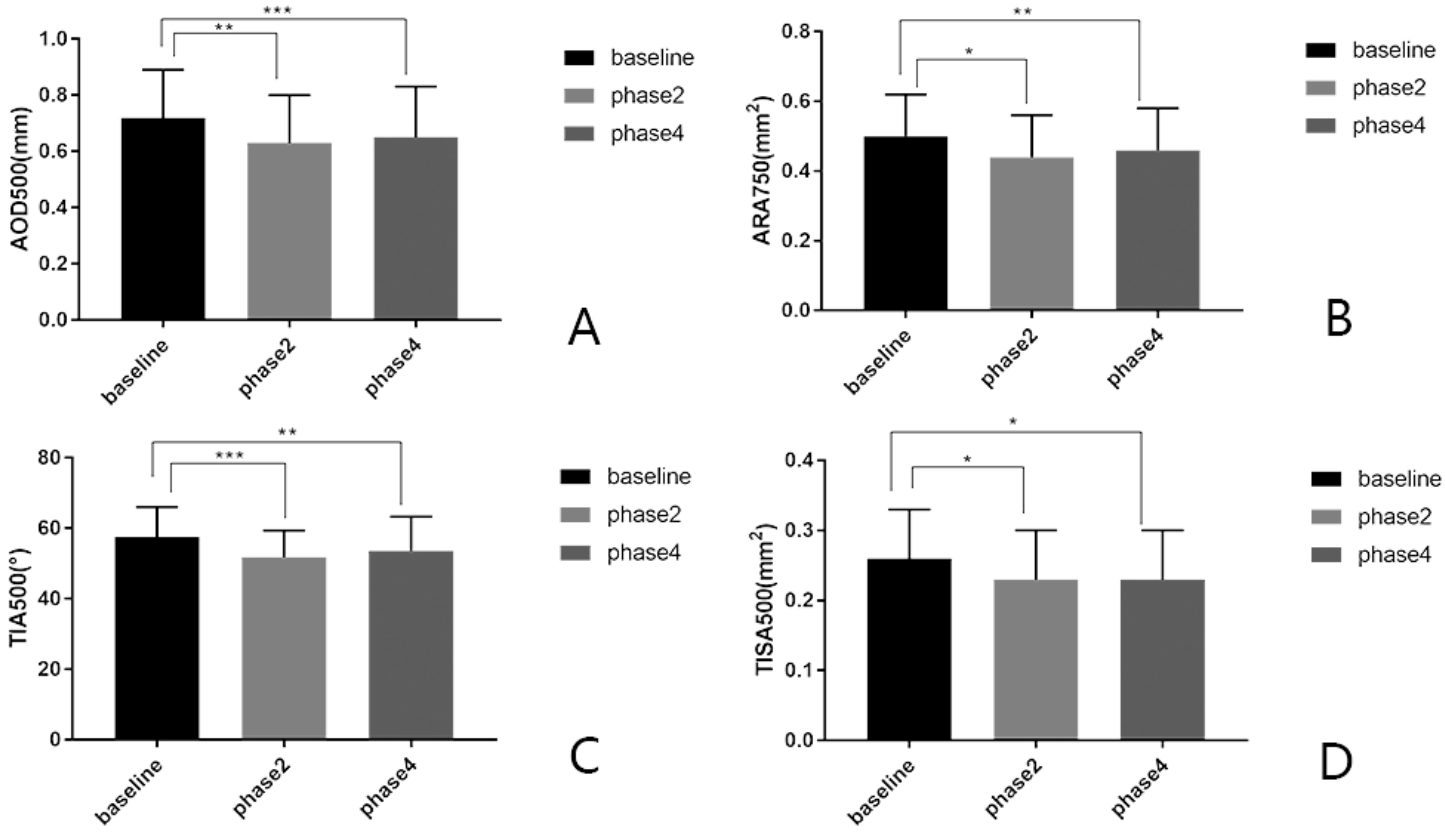

Figure 9

Changes in iridocorneal angle parameters. (A-D) Changes in AOD500, ARA750, TIA500, and TISA500 at different phases in VM.

Supplementary Files

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- supplement1.jpg