Effect of Gravity Acceleration on Choroidal and Retinal Nerve Fiber Layer Thickness: A Swept-Source Optical Coherence Tomography Study

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Purpose. The purpose of this study was to evaluate the effect of gravity acceleration on choroidal and retinal nerve fiber layer (RNFL) thickness using swept-source optical coherence tomography (SS-OCT).

Methods. Thirteen healthy volunteers who planned to participate in human centrifuge training as part of the flight surgeon selection process enrolled this study. During centrifuge training, gravity was gradually increased up to six times that of sea level. All subjects underwent complete ophthalmologic examination and three-dimensional wide-scanning SS-OCT imaging (DRI OCT-1 Atlantis; Topcon, Tokyo, Japan). Imaging was performed before (baseline), immediately after, and 15, 30, and 60 minutes after centrifuge training. Changes in choroidal thickness, choroidal volume, retinal thickness, and RNFL thickness after centrifuge training were analyzed.

Results. Mean choroidal thickness significantly and transiently decreased immediately (258.19 ± 73.54 μm, P < 0.001), 15 minutes (258.54 ± 75.12 μm, P = 0.001), and 30 minutes (254.31 ± 66.92, P = 0.001) after human centrifuge training, relative to baseline (273.35 ± 80.80 μm). However, the decreased choroidal thickness returned to baseline levels 1 hour after centrifuge training (270.12 ± 71.69 μm, P = 0.437). Mean retinal thickness and RNFL thickness were not significantly affected by human centrifuge training. In participants who suffered from gravity-force induced loss of consciousness (G-LOC) during training, the amount of the choroidal thickness decrease was larger than in participants who did not experience G-LOC. However, because of the small sample size, the difference, although large, was not statistically significant.

Conclusions. Choroidal thickness and volume significantly and transiently decreased after human centrifuge training, which might reflect that choroidal perfusion was transiently decreased during human centrifuge training. Considering choroidal thickness decreased after human centrifuge training, long-term exposure to a high gravity environment may lead to ischemic injury to ocular structures.

Keywords: human centrifuge training, gravity, gravity increase, choroidal thickness, swept source optical coherence tomography

The choroid is a highly vascularized tissue, and its thickness has been shown to be affected by ocular perfusion status.1–3 Volume status in the cardiovascular system affects ocular perfusion status, and changes in ocular perfusion pressure eventually affect choroidal thickness.1,2 For example, drinking water or assuming the Trendelenburg position affects cardiovascular volume status, increases ocular perfusion pressure, and eventually increases choroidal thickness.1,3 On the contrary, in subjects with unilateral ocular ischemic syndrome, affected eyes have a thinner choroid than unaffected fellow eyes.6

The effective gravity during fighter aircraft operation increases during rapid acceleration to amounts greater than the gravity a person experiences at sea level. This gravity increase can be excessive and sustained during fighter aircraft operation, moving blood away from the brain and potentially causing cerebral hypoxia. This decrease in cerebral blood flow often leads to a gravity force-induced loss of consciousness (G-LOC) during fighter aircraft operation.7 When brain perfusion decreases, ocular perfusion also decreases. As a result, people often experience visual field defects during gravity acceleration, where the peripheral vision is lost (central vision remains).8 If gravity accelerates further, a complete loss of vision, and eventually G-LOC, will occur. Considering that choroidal thickness is affected by ocular perfusion pressure, it is reasonable to suspect that choroidal thickness may also decrease during gravity acceleration or fighter aircraft operation.
Effect of Gravity Increase on Choroidal Thickness

To become familiar with a gravity acceleration environment, human centrifuge training is performed by pilots and astronauts, who are frequently exposed to high levels of gravity acceleration. The human centrifuge is an exceptionally large centrifuge in which trainees can ride. It can provide a high-gravity milieu, where participants can experience the actual flight aircraft environment.

Considering the decreased ocular perfusion that occurs during gravity acceleration, we theorized that choroidal thickness may also reduce after human centrifuge training, which could indirectly reflect ocular perfusion decreases during fighter aircraft operation. Therefore, we evaluated changes in choroidal thickness before and after human centrifuge training by assessing swept-source optical coherence tomography (SS-OCT) data with an automated segmentation program.

METHODS

This prospective, observational study evaluated choroidal thickness changes before and after human centrifuge training. The institutional review board of the Aerospace Medical Center (Cheongju, Korea) approved this study. All study conduct adhered to the tenets of the Declaration of Helsinki, and all subjects provided written informed consent to participate in this study.

The primary objective of this study was to evaluate changes in choroidal thickness and volume after human centrifuge training using SS-OCT. The secondary objectives were to evaluate changes in choroidal thickness according to the occurrence of G-LOC during centrifuge training, as well as changes in retinal thickness and retinal nerve fiber layer (RNFL) thickness after centrifuge training.

Study Subjects

All participants were flight surgeon candidates who planned to complete human centrifuge training and agreed to participate in this study. All participants underwent a complete bilateral ophthalmic examination, including Snellen best-corrected visual acuity (BCVA) measurements, slit lamp examination, fundus examination, refractive error measurement, axial length (AL) measurement (AL scan, NIDEK, Japan), and OCT (DRI OCT-1 Atlantis; Topcon, Tokyo, Japan) examination. Participants who had any ocular disease were excluded from this study.

OCT and Choroidal Thickness Measurement

SS-OCT was used to obtain choroidal images and was performed before (baseline), immediately after, and 15, 30, and 60 minutes after human centrifuge training. A three-dimensional imaging data set was obtained using a 12×9-mm raster scan that was centered on the macular area. Each OCT scan was centered using internal fixation, which was monitored using the instrument’s built-in fundus camera.

The SS-OCT software automatically segmented each retinal layer and the choroidoscleral junction to measure the thickness of each layer in an automated manner. Reliability and repeatability of choroidal thickness measurement by SS-OCT were found to be good in previous studies. The results of auto-segmentation were evaluated by a retinal specialist (J.Y.K.) blinded to participant data. If there were segmentation errors, manual adjustments were made. Thickness data included mean subfoveal choroidal thickness, mean choroidal volume, mean retinal thickness, and mean central RNFL thickness (within 1000 μm of the foveola). The mean thickness of each region on the Early Treatment Diabetic Retinopathy Study (ETDRS) grid was also calculated (Supplementary Fig. S1).

Human Centrifuge Training

Human centrifuge training sessions were conducted at the Aerospace Medical Center (Cheongju, Korea) using the Human Performance Centrifuge (G-LAB, G-4006; E.T.C., Southampton, United Kingdom). The human centrifuge is an exceptionally large centrifuge in which trainees can ride. It can provide a high-gravity environment, where participants can experience up to nine times the gravity present at sea level. In the current study, centrifuge acceleration gradually increased until subjects were exposed to six times the gravity present at sea level. The centrifuge then maintained that speed for 30 seconds or until G-LOC occurred. During training, participants attempted to use antigravity strain maneuvers (AGSMs) to prevent G-LOC. Specific method of AGSMs included increasing chest pressure by closing the glottis (forcing blood from the heart to the brain), similar to the Valsalva maneuver, and contracting skeletal muscles in the arms, legs, chest, and abdomen (increasing muscle tension to prevent blood from moving away from the brain).

Statistical Analyses

Data are presented as mean ± SD where applicable. A generalized linear model for repeated-measures ANOVA was used to evaluate changes in choroidal, retinal, and RNFL thickness measurements obtained before and after human centrifuge training. This statistical test was also used to evaluate how changes in choroidal thickness were related to the development of G-LOC. All statistical analyses were performed using SPSS statistical software (version 21.0; SPSS, Inc., Chicago, IL, USA), and statistical significance was defined as P < 0.05.

RESULTS

A total of 26 eyes from 13 healthy participants were included in this study. The Table summarizes subject characteristics at baseline. Mean subject age was 30.7 ± 4.10 years. All ophthalmologic examinations were normal, average BCVA was approximately 20/20, and AL was 25.30 ± 1.17 mm.

Effect of Human Centrifuge Training on Choroidal Thickness and Volume

Figure 1 shows representative SS-OCT images and the mean choroidal thickness before and after human centrifuge training, according to the occurrence of G-LOC. Human centrifuge training significantly and transiently decreased mean subfoveal choroidal thickness from baseline (273.55 ± 80.80 μm) for at least 30 minutes (immediately after: 258.19 ± 73.54 μm, P < 0.001; 15 minutes after: 258.54 ± 75.12 μm, P = 0.001; 30 minutes after 254.31 ± 66.92, P = 0.001). Even after the

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trainees that suffered G-LOC were excluded, reduction of choroidal thickness after centrifuge training was statistically significant ($P < 0.001$).

Figure 2 summarizes subfoveal choroidal thickness and volume changes induced by human centrifuge training. Time course data for individual participants are shown in Supplementary Figure S2. Choroidal thickness had increased back up to baseline levels 60 minutes after human centrifuge training (270.12 ± 71.69 μm, $P = 0.472$). A generalized linear model for repeated-measures ANOVA showed that mean choroidal thickness ($P < 0.001$) and volume ($P < 0.001$) were significantly and transiently decreased by human centrifuge training. To normalize for the different baseline choroidal thickness, we analyzed analyze percentage of choroidal thickness thinning compared with baseline. We found that percentage of choroidal thickness thinning compared with baseline also showed significantly and transiently decreased after human centrifuge training ($P = 0.009$).

Mean choroidal thickness and choroidal volume within each ETDRS grid region were also significantly and transiently decreased by human centrifuge training (all $P < 0.05$; Fig. 3). The extent of choroidal thickness decrease after human centrifuge training was not significantly different between right and left eyes (right eyes: 16.62 ± 19.93 μm; left eyes: 13.69 ± 17.97 μm; $P = 0.172$).

**Changes in Choroidal Thickness with G-LOC**

Four of 13 subjects (30.7%) experienced G-LOC during human centrifuge training. Figure 4 summarizes choroidal thickness changes following training in subjects that had G-LOC. The choroidal thickness decrease that occurred immediately after human centrifuge training in participants with and without G-LOC was 22.50 ± 18.83 and 11.88 ± 18.13 μm, respectively. However, this large difference was not statistically significant ($P = 0.285$), likely because of the relatively small number of subjects examined. The generalized linear model for repeated-measures ANOVA also showed that choroidal thickness changes were not significantly different between subjects with and without G-LOC ($P = 0.209$).

**Effect of Human Centrifuge Training on Retinal Thickness and RNFL Thickness**

Mean retinal thickness and RNFL thickness did not significantly change from baseline (247.23 ± 14.16 μm) following human centrifuge training (Fig. 5). Mean retinal thickness was 246.62 μm.
The effects of gravity increase on choroidal thickness were studied, showing significant decreases in choroidal thickness and volume after human centrifuge training. These effects were transient and returned to baseline levels within 1 hour after training. The choroidal thickness decrease was larger in subjects who experienced G-LOC during training compared to those who did not, but this difference was not statistically significant. Retinal thickness and RNFL thickness were not significantly affected by human centrifuge training.

**Discussion**

Mean choroidal thickness and volume were significantly and transiently decreased from baseline after human centrifuge training. Both parameters had returned to baseline levels 1 hour after human centrifuge training. The choroidal thickness decrease tended to be larger in subjects who experienced G-LOC during human centrifuge training than in subjects who did not, but this difference was not statistically significant. In contrast to choroidal thickness and volume, retinal thickness and RNFL thickness were not significantly affected by human centrifuge training.

Quantifying the effect of gravity acceleration on ocular perfusion is difficult because of the lack of devices that can accurately measure ocular perfusion status. However, considering that choroidal thickness reflects ocular tissue perfusion status, choroidal thickness changes likely reflect ocular perfusion status during gravity acceleration. Advances in OCT technology now allow precise choroidal images to be obtained, particularly when longer wavelength light sources are used. Furthermore, SS-OCT devices can automatically segment these images by retinal layer to produce individual layer thickness measurements.

We considered that choroidal thickness decreases after acceleration of gravity might reflect that gravity acceleration actually decrease ocular perfusion pressure. Additionally, the decrease in choroidal thickness, and presumably ocular perfusion, following human centrifuge training, indicates that long-term exposure to high-gravity environments may potentially lead to ischemic injury of the ocular structures. This is particularly relevant to the optic nerve, because studies on glaucoma patients have shown that ischemic injury is involved in glaucomatous optic nerve changes. It may be that long-term exposure to high-gravity environments would result in glaucomatous-like optic nerve changes. Therefore, the long-term effects of high-gravity environments on the choroidal circulation require further evaluation.

However, choroidal thickness decrease after human centrifuge training could be caused by interstitial fluid reabsorption or intraocular pressure change, not by decreased ocular perfusion. Therefore, to prove that gravity acceleration reduces ocular perfusion pressure, blood flow measurement such as the Doppler test should be performed. However, as gravity increases, all participants involved in human centrifuge training experiences G-LOC or a sudden decrease in visual field, which were resulted by decreased perfusion to brain or ocular tissue, respectively. Given the fact that the reduction in visual field or G-LOC is prevented by AGSM, we could reasonably know that human centrifuge training has a negative impact on intraocular blood flow and the decrease in ocular perfusion.
perfusion may be seen as a decrease in choroidal thickness on SD-OCT.

All subjects included in this study were flight surgeon candidates and not professional pilots. Therefore, the quality and efficacy of AGSMs in our subjects were likely not as high as in professional pilots, who receive long-term AGSM training. Therefore, repeating this study with professional pilots is necessary and may produce different results. It is likely that professional pilots can prevent the choroidal thickness decrease following human centrifuge training observed here.

The current study provides new insight into the relationship between choroidal thickness and gravity acceleration. The observed decrease in choroidal thickness after gravity acceleration may indicate that gravity acceleration actually decreases ocular perfusion. However, our study had notable limitations. First, the sample size of this study was small, which limited the statistical power of our analyses. We calculated estimated subjects number to demonstrate a difference in the G-LOC versus no G-LOC subjects based on our study result. Approximately 120 subjects were required to demonstrate a difference in the G-LOC versus no G-LOC. Second, we did not evaluate the correlation between the amount of gravity and the magnitude of the choroidal thickness decrease. The maximum gravity level to which our subjects was exposed was six times the gravity at sea level. If we had found that the choroidal thickness decrease was larger when gravity level was further increased, the effect of gravity acceleration on ocular perfusion could be further proven. Third, the efficacy of AGSM might affect choroidal thickness changes. To increase the reliability of the study, it would be necessary to control the efficacy of AGSM. Through sufficient education and simulations of AGSM before the human centrifuge training, all participants were able to do the AGSM proficiently. However, because the effect of AGSM was determined by individual factors, such as proficiency and muscle mass, there was no way to control its effect. One of the types of human centrifuge training is a relaxed gravity-tolerance test. This training slowly increases the degree of gravity, without using AGSM. This would allow detection of choroidal thickness changes due to gravity acceleration, without the confounding effects of AGSM. We plan to study changes in choroidal thickness after a relaxed G-tolerance test, in future. Finally, all the participants were male, and thus the applicability of the results to both sexes might be limited. Many of the participants in the study had myopia. This factor is also a
consideration in interpreting the results of the study. Therefore, future studies that include 120 participants, both sexes, and professional pilots and that examine a variety of gravity levels are needed.

In conclusion, choroidal thickness and volume significantly and transiently decreased after human centrifuge training, which might reflect that choroidal perfusion was transiently decreased during human centrifuge training. Given that glaucoma could be caused by ischemic injury to the optic nerve, exposure to high gravity over a long period of time could cause glaucomatous optic nerve changes.\textsuperscript{18,19} Therefore, the long-term effects of high-gravity environments on the choroidal circulation should be further studied.

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\textbf{References}


