Ocular Outcomes in Healthy Subjects Undergoing a Short-Term Head-Down Tilt Test

Bahadır Özelbaykal; Gökhan Öğretmenoğlu; İ. Hakkı Tunçez

PURPOSE: This study aimed to examine the effect of head-down tilt (HDT) on vascular autoregulation in different age groups and determine its effects on intraocular pressure (IOP) and central corneal thickness (CCT).

METHODS: Included were 43 eyes of 23 men. The optic nerve head and parafoveal vascular densities were measured by optical coherence tomography angiography before and after 20 min 10° HDT. Also, the study comprised an examination of the IOP and CCT in a subset of 8 participants (14 eyes) in the sitting position and during 15 min of 10° HDT.

RESULTS: Grid-based inside disc all-vessel density (GBID) was statistically significantly lower after the HDT test in subjects under 30 yr (−1.26%). Whole image and peripapillary capillary vessel density (WICVD, PCVD), and whole image and peripapillary all-vessel density (WIAVD, PAVD) were significantly higher after the HDT test in subjects ages 30–39 yr (+1.34%, +2.16%, +1.05%, +1.72%, respectively). Inside disc capillary, all-vessel density (IDCVD, IDAVD) and GBID were significantly higher after HDT in subjects over 40 yr (+2.48%, +2.15%, +1.52%, respectively). In a subset of eight participants, IOP was significantly higher (+3.7 mmHg) and CCT was unchanged after 15 min of HDT.

CONCLUSION: Our study showed that simulated microgravity induced optic nerve head vessel density at the inside disc area, especially in persons over 40 years. In addition, IOP was increased by HDT, although no change in CCT was observed.

KEYWORDS: simulated microgravity, retinovascular autoregulation, intraocular pressure, central corneal thickness.

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Retinal vascular autoregulation keeps the bloodstream stable via myogenic and metabolic factors in case of any changes in blood pressure.[22] However, optic nerve head (ONH) and retinal vascular autoregulation may be disrupted by diseases, such as hypertensive retinopathy, diabetic retinopathy, glaucoma, purtscher retinopathy, and nonarteritic ischemic optic neuropathy, as well as by the aging process.[5–7] Microgravity leads to a fluid shift toward the upper part of the body. This rapid fluid shift due to the microgravity environment may initiate the retinovascular autoregulation mechanisms. This cephalad fluid shift can be simulated with several techniques, including Einstein's Elevator,[16] parabolic flights,[28] the Valsalva maneuver,[29] dry immersion,[13] and head-down tilt bed rest (HDT).[19,21] Although there are studies on the effects of simulated and real microgravity environments on cerebrovascular autoregulation,[1,11,30] there are few studies on the effect on the optic nerve and retinal vascular autoregulation.[17,26] The purpose of this study was to determine the effects of simulated microgravity on optic nerve head and retinal vascular autoregulation responses and how autoregulation, if observed, depends on age.

METHODS

Subjects

This prospective study was approved by the Institutional Ethics Committee of the University of Health Sciences, Adana City Training and Research Hospital (19.06.2019, 36, 478), and was

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performed under the ethical standards contained in the Declaration of Helsinki. Written informed consent for the research and the publication of this study and any accompanying images was obtained from all participants. This study comprised 43 eyes of 23 participants. The persons were recruited to consist of at least five persons in each of the three decades. All subjects were approved to participate in the optical coherence tomography angiography (OCTA) examination. Only a subset of 8 subjects (14 eyes) were approved to participate in the measurement of intraocular pressure (IOP) and corneal thickness (CCT).

The subjects underwent a complete ophthalmic examination, including medical history, best-corrected visual acuity using the Snellen visual acuity test, slit-lamp biomicroscopy, refractive error with autorefractor keratometer (Canon Inc., Tokyo, Japan), IOP with Tono-pen AVIA (Reichert Inc, Depew, NY, USA), and CCT measurement (Pocket 2, Quantel Medical, Bozeman, MT, USA). OCTA scans were performed with a spectral-domain system (RTVue-XR Avanti; Optovue, Fremont, CA, USA; software version 2017.1.0.151) by the same person. The IOP and CCT examinations consisted of three averaged measurements with the calibrated contact tonometer and five averaged measurements with the calibrated ultrasound pachymeter. Subjects were asked to abstain from consuming caffeinated and alcoholic beverages for at least 12 h before the tests, and all tests were performed in an environmentally controlled room with an ambient temperature of 24–25°C. Light intensity at the eye level was kept constant to minimize the effects on retinal blood flow.

The subjects were selected according to their age and gender. Only the subjects with a best-corrected visual acuity of at least 16/20 and no history of elevated intraocular pressure (IOP < 21 mmHg) were included in the study. Subjects with any history of systemic diseases such as hypertension, diabetes mellitus, cardiopulmonary insufficiency, or orthostatic intolerance; the use of any systemic or topical medication; refractive disorders greater than ± 3.0 diopters; a history of any intraocular disease, ocular surgery, or trauma; clinically relevant media opacities; a measurement quality lower than 8/10; and/or an inability to correctly perform the tests were excluded.

Procedure

To examine the ocular effects of a more extreme HDT, subjects were positioned in a whole-body 10° HDT; angle and duration were adjusted according to previous studies.[24,25] Baseline OCTA (N = 23), IOP (N = 8), and CCT (N = 8) measurements were obtained immediately prior to the HDT test in the sitting position. Then the subjects were positioned in the whole-body 10° head-down supine position. After that, the IOP and CCT measurements of both of eight participants' eyes were acquired at 7 min and 15 min of the HDT test in the same position. Finally, after remaining in the supine position with 10° HDT for 20 min, OCTA images of both of all participants' (N = 23) eyes were acquired within 1 min in the sitting position. The experimental protocol is summarized in **Fig. 1**.

The OCTA scans were obtained with a spectral-domain system with an A-scan rate of 70,000 scans per second, a light source centered at a wavelength of 840 nm, and a bandwidth of 45 nm; the scan uses the SSADA algorithm to obtain angiographic information. After the head was stabilized with chin and forehead rests, the subjects were asked to fixate on a flashing internal target light. Macular and ONH data were acquired over a 3 × 3 mm and 4.5 × 4.5 mm area. The software automatically calculated the perfused vessel density in the following: parafovea (the annulus with an outer diameter of 3 mm and an inner diameter of 1 mm); optic disc (the inside disc is a 2-mm diameter circle centered on the disc center; the peripapillary region is defined by two rings of 2 mm and 4 mm centered on the disc center; the whole image is 4.5 × 4.5 mm of AngioDisc scan and 3 × 3 quadrants in a 9-sector grid); and the foveal avascular zone area. Both small vessels and large vessels were used to calculate the regional density in various disc sectors (based on Garway-Heath sectors). Only capillary vessel density, without the large vessels, is termed "capillary." If annotated with "All," the density is listed for all vessels, including the larger ones (retinal arteries and retinal veins). One of our subjects' OCTA images, before and after the HDT test, are shown in **Fig 2**.

Peripapillary capillary vessel density was calculated in the radial peripapillary capillary (RPC) layer, which is a unique vascular plexus in the retinal nerve fiber layer (RNFL). The

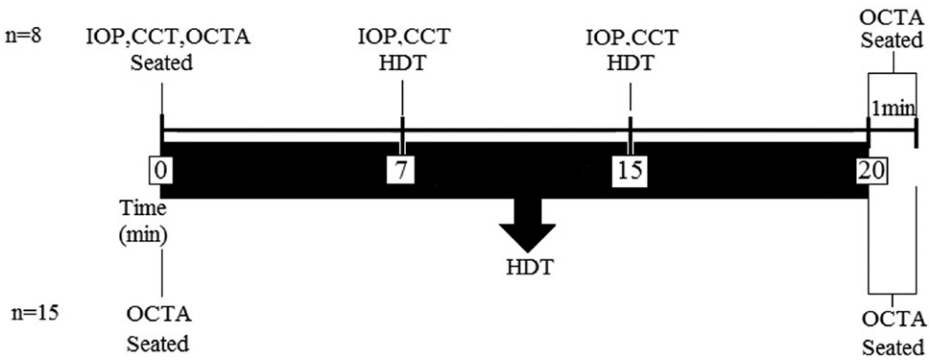

Fig. 1. Schematic of experimental protocol depicting the timeline and order in which measurements were obtained during each condition and the seated, HDT conditions. IOP, intraocular pressure; OCTA, optical coherence tomography angiography.

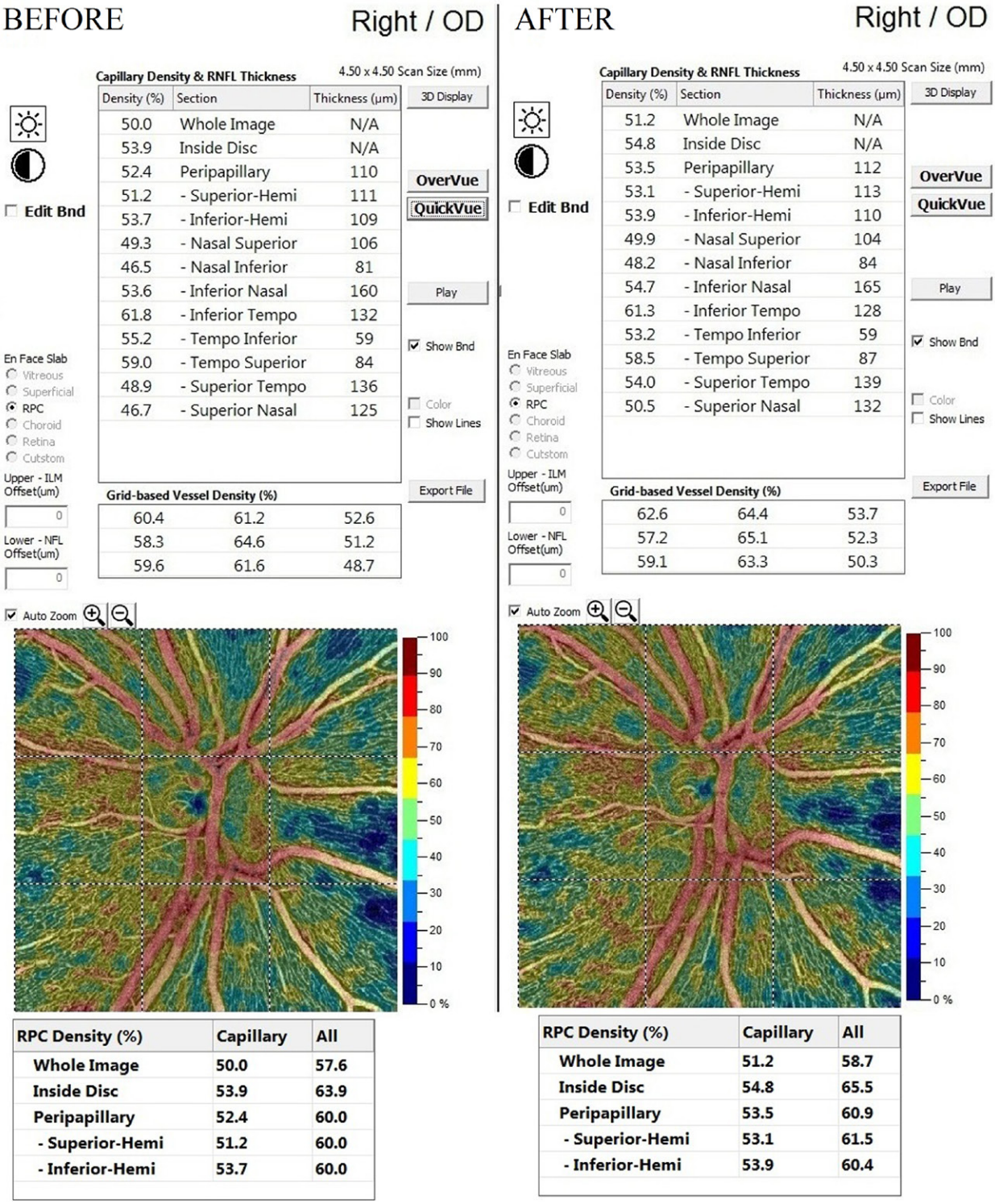

Fig. 2. One of our patient's optic nerve head OCTA images before and after 20 min HDT exposure. In this case, IOP increased during 15 min of HDT (+1.4 mmHg).

inside disc capillary vessel density was calculated in the RPC and peripapillary choriocapillaris. Image quality was assessed for all OCTA scans. Poor quality images (quality index lower than 8/10) or images with motion artifacts or segmentation errors were excluded from the analysis.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics for Windows (SPSS 23.0; IBM Inc., Chicago, IL, USA). Descriptive statistics are presented as mean (SD) with differences presented as means (95% CI). The normality analysis of the data was

analyzed with the Kolmogorov-Smirnov test. Foveal avascular zone (FAZ), ONH, and retinal perfused vessel density before and after HDT exposure were compared using paired sample *t*-tests. The assessment of variability resulting from changes in IOP and CCT within each eye among all the subjects was performed using the Bonferroni corrected one-way ANOVA analysis. Correlations were examined with Pearson correlation analysis.

RESULTS

In this study, 43 eyes of 23 men were examined. The mean age was 35.23 ± 8.99 yr. Whole image capillary vessel density (WICVD) and peripapillary capillary vessel density (PCVD) were significantly higher in the post-HDT test (95% CI, df = 40, 50.16 ± 2.05 to 50.93 ± 1.60, $t = -2.892$, $P = 0.006$, and 52.22 ± 2.57 to 53.16 ± 1.99, $t = -2.555$, $P = 0.015$, respectively). Whole image all vessel density (WIAVD) and peripapillary all vessel density (PAVD) were higher in the post-HDT test (95% CI, 57.40 ± 1.98 to 58.07 ± 1.67, $t = -2.658$, $P = 0.011$, and 59.27 ± 2.37 to 60.13 ± 1.91, $t = -2.763$, $P = 0.009$, respectively). Pearson correlation analyses revealed a positive correlation between age and inside disc capillary vessel density (IDCVD) changes (R^2=0.386, 95% CI, $P = 0.013$), and changes in inside disc all vessel density (IDAVD) correlated with age ($R^2 = 0.376$, 95% CI, $P = 0.014$) (**Fig. 3**).

The FAZ area detectable with OCTA decreased (0.254 ± 0.113 to 0.252 ± 0.113) significantly after the HDT test (95% CI, df = 42, $t = 2.201$, $P = 0.033$). Deep whole image vessel density (55.98 ± 2.89 to 57.01 ± 2.37) and deep parafovea vessel density (57.60 ± 3.01 to 58.60 ± 2.40) increased post-HDT (95% CI, df = 42, $t = -3.066$, $P = 0.004$, and $t = -3.040$, $P = 0.004$, respectively) (**Fig. 4**, **Table I**).

In group 1 ($N = 14$ eyes, 20–29 yr), no significant difference was found in WICVD (50.25 ± 1.34 to 50.51 ± 1.33), PCVD (51.72 ± 1.86 to 52.25 ± 1.84), WIAVD (57.35 ± 1.64 to 57.57 ± 1.540), or PAVD (58.85 ± 1.99 to 59.31 ± 1.88) (95% CI, df = 13, $t = -0.554$, $P = 0.589$; $t = -0.889$, $P = 0.390$; $t = -0.483$, $P = 0.637$; and $t = -0.835$, $P = 0.419$, respectively). IDCVD (54.77 ± 3.28 to 53.44 ± 3.87) and IDAVD (64.38 ± 2.98 to 63.32 ± 3.14) were lower post-HDT than pre-HDT, but this was not statistically significant (95% CI, df = 13, $t = 1.667$, $P = 0.119$; $t = 1.853$, $P = 0.087$, respectively). Grid-based inside disc all vessel density (GBID) was statistically significantly lower post-HDT than pre-HDT (64.42 ± 2.70 to 63.16 ± 2.76, 95% CI, df = 13, $t = 2.769$, $P = 0.016$).

In group 2 ($N = 12$ eyes, 30–39 yr), WICVD (49.46 ± 3 to 50.80 ± 1.70), PCVD (52.03 ± 3.79 to 54.19 ± 2.21), WIAVD (57.13 ± 2.64 to 58.18 ± 1.71), and PAVD (59.34 ± 3.12 to 61.06 ± 1.85) were significantly higher post-HDT than pre-HDT (95% CI, df = 11, $t = -2.660$, $P = 0.022$; $t = -2.920$, $P = 0.014$; $t = -2.217$, $P = 0.047$; and $t = -3.138$, $P = 0.009$, respectively). IDCVD (51.72 ± 5.83 to 52.75 ± 6.35), IDAVD (61.66 ± 4 to 62.73 ± 4.90), and GBID (63.16 ± 2.40 to 64.46 ± 3.43) were slightly higher post-HDT than pre-HDT, but not statistically significant (95% CI, $t = -1.080$, $P = 0.303$; $t = -1.158$, $P = 0.270$; and $t = -2.011$, $P = 0.067$, respectively).

In group 3 ($N = 15$, ≥ 40 yr), WICVD (50.64 ± 1.63 to 51.44 ± 1.71), PCVD (52.84 ± 1.93 to 53.19 ± 1.60), WIAVD (57.68 ± 1.69 to 58.46 ± 1.73), and PAVD (59.61 ± 2.05 to 60.08 ± 1.72) were higher post-HDT than pre-HDT, but this was not statistically significant (95% CI, df = 14, $t = -1.915$, $P = 0.076$; $t = -0.651$, $P = 0.526$; $t = -1.946$, $P = 0.072$; and $t = -0.983$, $P = 0.343$, respectively). IDCVD (51.52 ± 3.94 to 54 ± 2.85), IDAVD (61.7 ± 2.59 to 63.85 ± 2.42), and GBID (62.30 ± 2.46 to 63.82 ± 2.49) were higher post-HDT than pre-HDT (95% CI, df = 14, $t = -3.415$, $P = 0.004$; $t = -3.833$, $P = 0.002$; and $t = -2.622$, $P = 0.02$, respectively) (**Table II**).

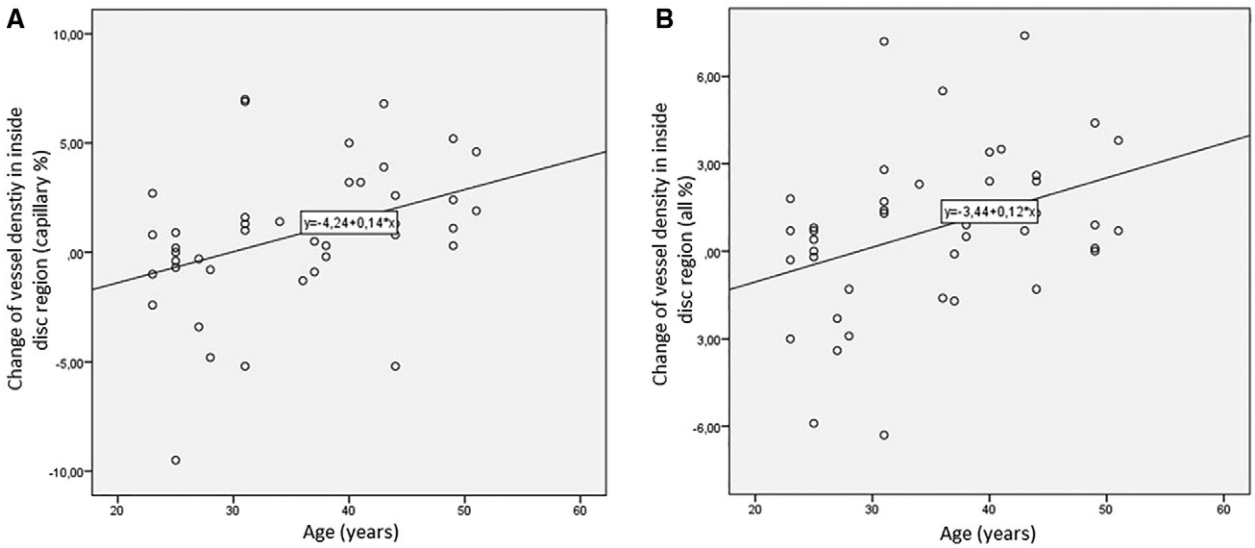

Fig. 3. Correlations between age and 10° HDT induced response of retina perfused vessel density in the inside disc area. A) Capillary vessels. B) All vessels.

Fig. 4. One of our patient's foveal avascular zone area (FAZ) measurements before and after 20 min HDT.

In a subset of 8 participants (14 eyes, 33.86 ± 7.49 yr), changes in the IOP and CCT were investigated with the subjects in a sitting position and during 15 min of 10° HDT position (in-bed phase). IOP was increased by HDT from 15.31 ± 0.92 mmHg in the sitting position to 19.01 ± 3.27 mmHg with 15-min HDT (95% CI, F = 9.301, P = 0.001). However, no change in CCT was observed (544.93 ± 31.34 µm in the sitting position, and 544.93 ± 34.25 µm with 15-min HDT) (95% CI, F = 0.002, P = 0.998) (**Table III**).

DISCUSSION

This study was designed to simulate the effects of microgravity-based cephalad fluid shifts on ONH and retinovascular autoregulation. Parazynski et al.[20] were first to quantify all four types of Starling-Landis pressures during HDT. In that study, upper body capillary and interstitial fluid pressure, as well as plasma and tissue oncotic pressure, were measured in seven men. It was found that capillary fluid pressure increased from 27.7 ± 1.5 mmHg to 33.9 ± 1.7 mmHg by the end of the bed rest, while interstitial fluid pressure did not change significantly. Therefore, we examined the reaction of the autoregulation system to the increase of pressure in the retina vessels related to the HDT test.

Table I. Additional Pre 10° HDT and Post 10° HDT Test Values.

OUTCOME	PRE-HDT	POST HDT	*P*
FAZ (mm^2) (N = 43)	0.254 ± 0.113	0.252 ± 0.113	0.033*
FT (µm) (N = 43)	225.07 ± 16.19	224.86 ± 16.15	0.277
SWI (%) (N = 43)	48.90 ± 2.37	49.04 ± 2.13	0.482
DWI (%) (N = 43)	55.98 ± 2.89	57.01 ± 2.37	0.004*
Sparafovea (%) (N = 43)	51.91 ± 2.54	52.05 ± 2.21	0.498
Dparafovea (%) (N = 43)	57.60 ± 3.01	58.60 ± 2.40	0.004*
SFovea (%) (N = 43)	18.55 ± 6.69	18.49 ± 7.02	0.750
Dfovea (%) (N = 43)	36.08 ± 7.50	36.32 ± 7.89	0.373

FAZ: foveal avascular zone; FA: flow area; FD: flow density; FT: foveal thickness; SWI: superficial whole image; DWI: deep whole image; S: superfical; D: deep.
All values given as mean (SD).
*P < 0.05.

In humans, the blood vessels on the ONH have the autoregulatory ability during experimental increases in retinal artery blood pressure.[29] In this study, no significant differences in the vessel densities before and after the test were found among the subjects under 30 yr of age. Furthermore, we found that vessel densities were decreased in the inside disc area, both in capillary and all vessel measurements, including central retinal artery and central retinal vein. A previous study of Jeppesen et al.[10] may explain this decrease in vessel densities of vascular beds. In that study, they concluded that a change in blood pressure is transmitted directly to all parts of the arteriole, and the contraction occurring along the whole length of the vessel can be explained as the sum of the local diameter responses in all vascular segments.

The measurements of subjects in group 2 (30-39 yr) showed an increase in PAVD. In group 3 (over 40 yr), there was a considerable increase in the IDAVD. These increases may be a result of impaired autoregulation of the vascular bed. In normal retinal circulation, autoregulation keeps the blood flow relatively constant by constriction of the resistance vessels until mean arterial pressure is raised to 40% above baseline.[23] Also, the increase in intravascular pressure causes vasoconstriction in the retinal vessels through a myogenic response. This autoregulative response

Table II. Pre 10° HDT and Post 10° HDT Test Vessel Density Values (%) of the Optic Nerve According to Age and Image Sector.

AGE	CAPILLARY PRE HDT	CAPILLARY POST HDT	P^A	ALL PRE HDT	ALL POST HDT	P^B
Overall (*N* = 41)						
Whole image	50.16 ± 2.05	50.93 ± 1.60	0.006*	57.40 ± 1.98	58.07 ± 1.67	0.011*
Inside Disc	52.69 ± 4.54	53.44 ± 4.37	0.161	62.58 ± 3.38	63.32 ± 3.52	0.099
Peripapillary	52.22 ± 2.57	53.16 ± 1.99	0.015*	59.27 ± 2.37	60.13 ± 1.91	0.009*
GBID				63.27 ± 2.62	63.80 ± 2.87	0.169
Group 1; 20–29 (*N* = 14)						
Whole image	50.25 ± 1.34	50.51 ± 1.33	0.589	57.35 ± 1.64	57.57 ± 1.54	0.637
Inside Disc	54.77 ± 3.28	53.44 ± 3.87	0.119	64.38 ± 2.98	63.32 ± 3.14	0.087
Peripapillary	51.72 ± 1.86	52.25 ± 1.84	0.390	58.85 ± 1.99	59.31 ± 1.88	0.419
GBID				64.42 ± 2.70	63.16 ± 2.76	0.016*
Group 2; 30–39 (*N* = 12)						
Whole image	49.46 ± 3	50.80 ±1.70	0.022*	57.13 ± 2.64	58.18 ± 1.71	0.047*
Inside Disc	51.72 ± 5.83	52.75 ± 6.35	0.303	61.66 ± 4	62.73 ± 4.90	0.270
Peripapillary	52.03 ± 3.79	54.19 ± 2.21	0.014*	59.34 ± 3.12	61.06 ± 1.85	0.009*
GBID				63.16 ± 2.40	64.46 ± 3.43	0.067
Group 3; ≥40 (*N* = 15)						
Whole image	50.64 ± 1.63	51.44 ± 1.71	0.076	57.68 ± 1.69	58.46 ± 1.73	0.072
Inside Disc	51.52 ± 3.94	54 ± 2.85	0.004*	61.7 ± 2.59	63.85 ± 2.42	0.002*
Peripapillary	52.84 ± 1.93	53.19 ± 1.60	0.526	59.61 ± 2.05	60.08 ± 1.72	0.343
GBID				62.30 ± 2.46	63.82 ± 2.49	0.02*

GBID: Grid based inside disc all vessel density; HDT: 10° head down tilt test; ALL: vessel density including retinal artery and vein; P^A "capillary" vessel density; P^B "all" vessel density.
*$P < 0.05$. All values are given as mean (SD).

has been seen in previous studies of the central retinal artery and posterior ciliary arteries.[12] We thought that the myogenic autoregulation response starts breaking down after the age of 40 yr. Likewise, Jeppesen et al.[9] concluded that the autoregulative response disappears after this age. Therefore, eyes with poor autoregulation are at a much greater risk of developing ONH ischemic damage and retinovascular complications than those with sufficient autoregulation. Sosi and Anderson[27] speculated that glaucomatous optic neuropathy may be due to deficient autoregulation, perhaps acquired with age. The findings of this study support that head-down tilt induced perfused vessel density in the optic nerve head in persons older than 40 yr.

In the long-term condition, a disrupted autoregulation mechanism may cause increased luminal pressures and RPC damage. This will result in the formation of cotton-wool spots (CWS) due to RNFL infarction such as hypertensive retinopathy. CWS have been documented in astronauts following long-duration spaceflight.[18] In this regard, we hypothesized that elevated luminal pressures due to disrupted retinovascular autoregulation will be an additional cause of CWS in astronauts. Further studies are needed in a microgravity environment to test this hypothesis. Other possible reasons why astronauts have CWS include local asymmetric microgravity-related changes in cerebrospinal fluid flow within the intraorbital optic nerve, radiation exposure, and solar flare activity.[15]

Table III. IOP and CCT Measured Pre −10° HDT and Post −10° HDT.

OUTCOME	SITTING POSITION	7-MIN HDT	15-MIN HDT	*P*
IOP (mmHg) (*N* = 14)	15.31 ± 0.92	18.14 ± 2.31	19.01 ± 3.27	0.001*
CCT (µm) (*N* = 14)	544.93 ± 31.34	544.21 ± 33.75	544.93 ± 34.25	0.998

IOP, intraocular pressure; CCT, central corneal thickness.
*$P < 0.05$. *P* between 0 min–15 min, Bonferroni adjusted one-way ANOVA.
All values are given as mean (SD).

On the other hand, after implementing the 10° HDT test, the FAZ area was decreased significantly. In addition, there were no significant changes in the superficial capillary plexus but some increase in the deep capillary plexus. Similarly, in an OCTA study, researchers found that FAZ shrinkage in the HDT position was partially reversed with venoconstrictive thigh cuff devices.[8] Thus, there may be a negative correlation between the density in the deep capillary plexus and FAZ areas.

Shinojima et al.[25] confirmed a 54% increase in IOP (21 mmHg) at 30 min of 10° HDT compared with IOP in a sitting position (14 mmHg). Also, Mader et al. found that the IOP was increased from 14.2 mmHg to 18.9 mmHg.[19] Draeger et al.[4] reported an initial 20–25% increase in IOP 44 min into a space shuttle flight and, in a German D2 mission, a 114% increase in IOP was noted 16 min after reaching

microgravity.[3] In agreement with these previous studies, we found 3.7 mmHg of increase in IOP at 15 min of 10° HDT compared with the sitting position. This increase may be due to the choroidal expansion, elevation in episcleral venous pressure or narrowed anterior chamber angle. In addition, we examined changes in corneal thickness during HDT. A previous study showed that the mean CCT increases from around 8 to 17 μm during bed rest (days 5 and 7, respectively), whereas the mean IOP decreases.[2] However, we found no significant difference in corneal thickness, perhaps because of the shorter duration of HDT.

Our study had several limitations. IOP and perfused vessel density could not be simultaneously monitored, and OCTA scans were not performed in the HDT position due to the lack of hand-held OCTA. HDT bed rest produces cephalad fluid shift but does not perfectly replicate microgravity. The CO_2 levels in the International Space Station environment are different from the Earth's atmosphere and, for this reason, HDT tests should be implemented in elevated ambient CO_2.[14]

In conclusion, this OCTA study suggests that head-down tilt induced optic nerve head perfused vessel density at the inside disc area, especially in persons over 40 yr. Intraocular pressure was increased during short-term whole-body 10° HDT, although central corneal thickness remained unchanged. Further studies are needed to confirm these findings in microgravity environments.

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