Title: Changes in optic nerve head and retinal morphology during spaceflight and acute fluid shift reversal

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KEY POINTS

Question: How do optic nerve head and retinal morphology change during spaceflight and during brief inflight exposure to lower body negative pressure (LBNP)?

Findings: Neuroretinal rim and peripapillary retinal thickness increased, optic cup volume and macular thickness decreased, and Bruch's membrane opening moved posteriorly during spaceflight. A 10-20-minute exposure to LBNP during spaceflight did not affect ocular structures.

Meaning: These findings suggest peripapillary and macular retinal thickness are affected differently by spaceflight and do not respond rapidly to acute fluid shift reversal with LBNP. Longer-duration exposure to countermeasures may be necessary to mitigate the effects of spaceflight associated neuro-ocular syndrome.

ABSTRACT

Importance: Countermeasures that reverse the headward fluid shift experienced in weightlessness have the potential to mitigate spaceflight associated neuro-ocular syndrome. This study investigated the effects of the countermeasure lower body negative pressure on ocular structures during spaceflight.

Objective: To determine whether changes to the optic nerve head and retina during spaceflight can be mitigated by brief inflight application of 25 mmHg lower body negative pressure.

Design: In NASA's "Fluid Shifts Study," a prospective cohort study, optical coherence tomography scans of the optic nerve head and macula were obtained preflight, inflight, and up to 180 days after return to Earth. Inflight scans were obtained both under normal weightless conditions and 10-20 minutes into lower body negative pressure exposure. Preflight and postflight data were collected in seated, supine, and head-down tilt postures.

Setting: Before, during, and after long-duration missions on the International Space Station.

Participants: Fourteen U.S. and international crewmembers completing 6-12 month missions.

Intervention(s) or Exposure(s): Spaceflight and lower body negative pressure

Main Outcomes and Measures: Changes in minimum rim width, optic cup volume, Bruch's membrane opening height, peripapillary total retinal thickness, and macular thickness.

Results: Mean flight duration for the 14 crewmembers (age 45 ± 6 years, 3 female) was 214 ± 72 days. Ocular changes on flight day 150, as compared to preflight seated, included an increase in minimum rim width (33.8 µm; 95% CI, 27.9 – 39.7 µm; *P* < .001), decrease in cup volume (.038 mm^3; 95% CI, .030 – .046 mm^3; *P* < .001), posterior displacement of Bruch's membrane opening (-9.0 µm; 95% CI, -15.7 – -2.2 µm; *P* = .009), and decrease in macular thickness (fovea to 500 µm: 5.1 µm; 95% CI, 3.5 – 6.8 µm; *P* < .001). Brief exposure to lower body negative pressure did not affect these parameters.

Conclusions and Relevance: Peripapillary tissue thickening, decreased cup volume, and mild central macular thinning occur during long-duration spaceflight. Acute exposure to 25 mmHg lower body

negative pressure does not alter optic nerve head or retinal morphology, suggesting that longer durations of a fluid shift reversal may be needed to mitigate spaceflight-induced changes and/or other factors are involved.

INTRODUCTION

Approximately two-thirds of crewmembers on long-duration missions to the International Space Station (ISS) develop spaceflight associated neuro-ocular syndrome (SANS).[1,2] This condition has important implications for future space travel, as mission durations are expected to increase and chronic optic disc edema (ODE), a hallmark SANS finding, could potentially lead to irreversible vision loss.

Although the etiology of SANS is not well-established, the chronic cephalad fluid shift that occurs during weightlessness is considered the primary initiating factor. Despite overlapping signs with idiopathic intracranial hypertension (IIH), recent studies suggest that intracranial pressure (ICP) is not pathologically elevated in weightlessness but may instead be slightly less than that experienced in a supine posture on Earth.[3] On Earth, humans spend ~two-thirds of the day in an upright posture, in which the hydrostatic pressure gradient shifts fluid footward. The inability to “stand up” during spaceflight and shift fluid away from the head has been proposed to result in a mean 24-hour ICP value greater than that habitually experienced on Earth, which may contribute to ODE development.[4]

Lower body negative pressure (LBNP) is a potential SANS countermeasure that aims to reverse the headward fluid shift by redistributing fluid from the upper body to the legs and abdomen. Studies on Earth that used head-down tilt (HDT) or supine postures to simulate spaceflight found that LBNP reduced the headward fluid shift, as evidenced by significant reductions in invasive and non-invasive surrogate measures of ICP.[5–9] Invasive ICP measures have not been reported during spaceflight; however, investigating changes in optic nerve head (ONH) and retinal morphology could provide insight regarding the pathophysiology of ODE in SANS, as well as relative changes in fluid shifts under normal weightless conditions and during LBNP application.

The goal of this study was to determine how ocular morphology changes during spaceflight and during acute fluid shift reversal with inflight LBNP. Although changes in tissue thickness at the ONH have been described during long-duration spaceflight,[1,10–12] inflight changes in optic cup size, ONH anterior-posterior position, and macular thickness have not been established. We hypothesized that the spaceflight-induced chronic headward fluid shift results in structural changes at the ONH but not at the macula and that acute application of LBNP partially reverses these structural changes.

METHODS

Subjects

Fourteen crewmembers (age 45 ± 6 [mean ± SD] years; 3 female), including astronauts and cosmonauts, completed long-duration ISS missions in NASA's "Fluid Shifts Study." Mean flight duration was 214 ± 72 days, and six individuals had prior spaceflight experience. Additional details and outcome variables for this cohort have been reported.[13–15] This study was approved by the NASA Johnson Space Center Institutional Review Board and the Human Research Multilateral Review Board, and it adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from all crewmembers, and crewmembers were not offered compensation or incentives to participate. STROBE reporting guidelines were followed, with a few exceptions (see Supplement).

Study Design

Pre- and postflight optical coherence tomography (OCT) was performed in the Cardiovascular and Vision Laboratory at NASA's Johnson Space Center. During spaceflight, scans were acquired both under normal weightless conditions and ~10-20 minutes into a session of 25 mmHg LBNP application with the Russian Chibis-M system[16] on approximately flight day (FD) 50 and FD150. The magnitude and duration of LBNP were chosen due to logistical constraints and to maximize the potential stimulus, while limiting the possibility of syncope. Four crewmembers were also imaged on ~FD250 (range 223 – 293 days).

Postflight scans were acquired ~10 days (range 8 – 13 days; R+10), ~30 days (range 27 – 50 days; R+30), and ~180 days (range 167 – 216 days; R+180) after return to Earth. For preflight and R+10 timepoints, subjects were imaged in seated, supine, and 15° HDT postures after resting in each position for ~10-15 minutes.

Optical Coherence Tomography

The Spectralis OCT1 and OCT2 systems (Heidelberg Engineering, Heidelberg, Germany) were used to acquire images from the left eye of each subject, including a 24-line (20°) radial scan centered on the ONH and a 12-line (20°) radial scan centered on the macula (**Fig 1**). The AutoRescan feature aligned all images to the preflight seated baseline scan. All scans were inspected by two readers, who corrected segmentation errors and manually selected Bruch's membrane (BM) opening (BMO). Data were exported, and calculations were performed using MATLAB (MathWorks, Natick, MA). Each measurement represents the average of the two readers' results.

The neuroretinal rim minimum rim width (MRW), the minimum distance from each BMO point to the internal limiting membrane (ILM), was constrained to the region between BMO points. The anterior-posterior BMO position (BMO height) was quantified as the minimum distance from each BMO point to a 4-mm BM reference line centered on the ONH.[10] A line parallel and 200 µm anterior to a reference line connecting the BMO points defined the anterior boundary of the optic cup; cup volume was quantified as the region contained within this boundary and the ILM, linearly interpolated between B-scans in three-dimensional space. Peripapillary total retinal thickness (TRT) was calculated in four annular regions: BMO to 250 µm (TRT250), 250 to 500 µm (TRT500), 500 to 1000 µm (TRT1000), and 1000 to 1500 µm (TRT1500) (**Fig 1A&B**).[1,10] Macular thickness (MT) was quantified within a 500 µm radius of the fovea (MT500) and in annuli extending from 500 to 1500 µm (MT1500) and 1500 to 2500 µm (MT2500) (**Fig 1C&D**).

Statistical Analysis

Statistical analyses were performed using Stata software (v17.0, StataCorp, College Station, TX), with an emphasis on characterizing the observed effects with modeled means and 95% confidence intervals, though two-tailed *P* values are also reported. All model assumptions were evaluated prior to reporting effects, resulting in the elimination of a few overly influential observations where necessary to meet model requirements. Although there were some missing data, full information maximum likelihood (FIML) mixed modeling maximized the number of observations informing each model and reduced bias associated with listwise elimination.

Each continuously scaled outcome was submitted to separate statistical mixed-models with *a-priori* fixed effects parameters. All models included random Y-intercepts to accommodate the nesting of observations within subjects and FIML estimations utilizing ANOVA-based degrees of freedom with small-*n* adjustments. Longitudinal changes in outcomes collected inflight and postflight were evaluated relative to preflight (seated position). Another set of models addressed the potential effects of LBNP on ocular structure by comparing observations collected with versus without LBNP within timepoints; comparisons were also made between inflight timepoints without LBNP. Finally, models evaluating the effects of posture and spaceflight included fully factorialized coefficients for posture (supine, HDT, relative to seated), day (preflight vs. postflight), and the posture-by-day simple interaction effects (relative to preflight seated).

RESULTS

Spaceflight results in peripapillary tissue thickening and central macular thinning

ODE, defined as an increase in TRT250 exceeding 19.4 µm,[17] occurred in 4/14 (29%) subjects by FD50 and 9/13 (69%) subjects by FD150. However, only one subject developed Frisén grade 1 edema,[18] as determined by NASA's Flight Medicine Clinic. Mean values for all parameters before, during, and after spaceflight are listed in **Table 1** (exact *P* values in **eTable 1**).

The greatest effects of spaceflight occurred at the ONH. MRW increased by 20.6 µm (95% CI, 15.0 – 26.3 µm, *P* < .001) on FD50 and 33.8 µm (95% CI, 27.9 – 39.7 µm, *P* < .001) on FD150 (**Fig 2A**). These changes were accompanied by corresponding decreases in cup volume of .028 mm^3 (95% CI, .020 – .036 mm^3, *P* < .001) on FD50 and .038 mm^3 (95% CI, .030 – .046 mm^3, *P* < .001) on FD150 (**Fig 2B**). The individual who developed grade 1 edema did not have a quantifiable optic cup at any timepoint and was excluded from cup volume analyses. After return to Earth, changes in MRW and cup volume persisted through R+30 (*P* < .008); however, by R+180, neither measure differed from baseline (*P* > .45). BMO height tended to be lower than baseline (i.e., shifted posteriorly) on FD50 (*P* = .06) and was then significantly lower on FD150 (-9.0 µm, 95% CI, -15.7 – -2.2 µm, *P* = .009) (**Fig 2C**). The subject with grade 1 edema exhibited the greatest change in BMO height (-53.3 µm).

Peripapillary TRT followed a similar pattern as MRW, although the magnitude of change was smaller and decreased with distance from the ONH (**Fig 3**). On FD50, TRT250 and TRT500 increased by 12.0 µm (95% CI, 7.6 – 16.4 µm, *P* < .001) and 6.2 µm (95% CI, 3.5 – 9.0 µm, *P* < .001), respectively. By FD150, TRT1000 also increased; respective changes in TRT250, TRT500, and TRT1000 were 23.1 µm (95% CI, 18.6 – 27.6 µm, *P* < .001), 12.3 µm (95% CI, 9.4 – 15.1 µm, *P* < .001), and 2.0 µm (95% CI, .3 – 3.7 µm, *P* = .02). TRT1000 recovered by R+10 (*P* = .27), whereas changes in TRT250 and TRT500 persisted through R+30 (*P* < .003) but recovered by R+180 (*P* > .23). Despite no changes in TRT1500 during spaceflight, both TRT1000 and TRT1500 values were slightly less than preflight values on R+180, decreasing 2.0 µm (95% CI, .3 – 3.6 µm, *P* = .02) and 1.9 µm (95% CI, .5 – 3.3 µm, *P* = .007), respectively.

In contrast to the increase in TRT adjacent to the ONH, central MT decreased during spaceflight. MT500 decreased by 3.7 µm (95% CI, 2.1 – 5.3 µm, *P* < .001) on FD50 and 5.1 µm (95% CI, 3.5 – 6.8 µm, *P* < .001) on FD150 (**Fig 4A**). The magnitude of thinning decreased with distance from the fovea; MT1500 decreased by 2.6 µm (95% CI, 1.2 – 3.0 µm, *P* < .001) on FD50 and by 3.6 µm (95% CI, 2.2 – 5.0 µm, *P* < .001) on FD150 (**Fig 4B**), and there were no changes in MT2500 during or after spaceflight (*P* > .05) (**Fig 4C**). MT1500 recovered by R+30 (*P* = .38), whereas MT500 did not recover until R+180 (*P* = .07).

Brief LBNP exposure during spaceflight has minimal effects on ocular morphology

Changes in ocular structure were not identified during LBNP (**eTables 2&3**). Values under normal weightless conditions differed between FD50 and FD150 for MRW, cup volume, TRT250, TRT500, TRT1000, and MT500 (*P* < .05), suggesting that the magnitudes of ODE and central macular thinning increase with flight duration. Although posterior BMO displacement only became significant on FD150, there was no difference in BMO height between FD50 and FD150 (*P* = .31).

The effects of acute posture changes on Earth were investigated to provide context for measures obtained during LBNP. Supine and 15° HDT postures cause headward fluid shifts that are similar to and exceed that of spaceflight, respectively.[14] There was no significant posture-by-day interaction for any parameter (*P* > .58). MRW and TRT250 were the only parameters to demonstrate a simple main effect of posture, with MRW being 4.1 µm greater in HDT than when seated (95% CI, 1.1 – 7.1 µm, *P* = .007) and TRT250 being 2.5 µm thinner supine than when seated (95% CI, .1 – 4.9 µm, *P* = .04, **eTable 4**).

DISCUSSION

Although the increase in peripapillary tissue thickness and decrease in optic cup size that occur during long-duration spaceflight are consistent with ODE, the posterior BMO displacement and reversible macular thinning observed in this study suggest differences between SANS and IIH. Inflight fluid shift reversal via 10-20 minutes of 25 mmHg LBNP does not reverse ocular structural changes associated with spaceflight, possibly because a longer duration of exposure is required and/or other mechanisms are involved.

The increases in MRW (33.8 µm) and TRT (23.1 µm) observed on FD150 in the present study were similar in magnitude to those previously described in 11 astronauts completing 6-month missions,[1] and both studies demonstrated that peripapillary retinal thickening increases in magnitude and expands radially with flight duration. Furthermore, MRW and TRT measures closest to the ONH recovered between R+30 and R+180, similar to previous reports of recovery at R+90.[1] The comparable findings between studies highlights the mild nature of the edema during ~6 months of spaceflight. The individual who developed Frisén grade 1 ODE was the only subject with a nonexistent preflight optic cup. Future investigations will determine whether crowded ONH morphology is related to the development of ODE during spaceflight.

ODE in SANS is hypothesized to result from the chronic headward fluid shift that occurs in weightlessness. Current evidence from parabolic flight suggests that ICP in acute weightlessness is not elevated to pathological levels (i.e., >25 cm H_2O)[19,20] but is slightly less than that in a supine posture on Earth.[3] However, it is unknown if ICP measured during brief periods of weightlessness in individuals who previously received central nervous system chemotherapy due to hematological malignancy[3] reflects ICP levels during long-duration spaceflight. The influence that an absence of diurnal change in ICP has on the development of ODE is also unknown. It is possible that a chronic, unremitting ICP elevation, regardless of magnitude, may be sufficient to persistently decrease the translaminar pressure difference (TLPD, intraocular pressure [IOP] minus ICP) and disrupt axoplasmic flow, leading to axonal swelling and ODE which manifests as an increase in ONH tissue thickness and decrease in cup volume.

The observed posterior BMO displacement is inconsistent with a decreased TLPD. IIH patients often exhibit anterior BMO displacement, thought to be a mechanical deformation caused by elevated ICP exerting a force at the ONH;[21–23] therefore, we hypothesized that any sustained ICP stimulus at the posterior pole during spaceflight would also result in anterior BMO displacement. Instead, BMO height was posteriorly displaced by -9.0 µm, similar to a previous study that measured BMO height within ~1 week postflight (-9.9 µm),[10] and the individual with grade 1 ODE demonstrated the greatest posterior displacement. Either a relative reduction in ICP or increase in IOP would be consistent with posterior BMO displacement. IOP only increased by ~1 mmHg during spaceflight in the present subjects,[13] suggesting that ICP would need to remain low or decrease during spaceflight if these were the only factors contributing to the displacement. A notable difference between IIH and SANS is that the latter often presents with choroidal thickening.[1,13] An increase in choroid thickness could anteriorly displace the BM reference used to calculate BMO height, causing an apparent relative posterior displacement of the BMO. While use of a choroid/sclera reference could circumvent this issue, the sclera is also not a stationary landmark, as globe flattening at the ONH is common in SANS.[1,2,24] Further work is needed to better understand factors that influence BMO position during spaceflight and to characterize differences in peripapillary shape deformations between SANS and IIH. Although changes in the position of the lamina cribrosa could provide insight regarding changes in the TLPD, laminar position was not assessed in this study due to unreliable visibility.

We hypothesized that spaceflight-induced changes in retinal thickness would be isolated to the peripapillary region. Although no retinal thickening was detectable past TRT1000, retinal thinning occurred in the central macula. The mild decrease in MT (~5 µm) was consistent across timepoints, exceeded the mean posture-induced changes, and returned to preflight levels after spaceflight. This thinning presumably cannot be attributed to a loss of retinal ganglion cells or their axons, as thinning recovered after return to Earth and was greatest at the fovea where inner retinal structures are laterally displaced.[25] Anatomical differences at the fovea may make it particularly susceptible to mechanical deformations. For example, the foveal avascular zone (~200 to 1100 µm diameter)[26] is hypothesized to be more deformable than vascularized retinal regions and therefore more vulnerable to the effects of IOP.[27,28] Additionally, the foveola does not contain rods, astrocytes, or microglia,[25] which may influence tissue properties. Muller cells in the central fovea also express increased glial fibrillary acidic protein, which may indicate increased susceptibility to mechanical stress.[25] It is possible that the chronic, albeit mild,[13] increase in IOP that occurs during spaceflight exerts a compressive force at the macula, as has been observed following cataract surgery.[29] The spaceflight-induced choroidal thickening reported for this cohort[13] may also contribute an opposing compressive force at the macula.

Brief application of 25 mmHg LBNP during spaceflight reduced both internal jugular vein pressure and IOP in the present subjects,[13,14] suggesting that this magnitude of negative pressure is sufficient to reverse the fluid shift at the head and eye. However, this LBNP exposure did not affect choroid thickness[13] and did not significantly alter ONH or retinal morphology presented here. Similarly, a previous study on Earth determined that brief LBNP application did not reverse mild choroidal thickening in a supine posture.[5] To our knowledge, the effects of LBNP on ONH morphology have not previously been studied. Given that ~10-15 minutes of exposure to 15° HDT had no effect, the lack of a response to a similar duration of LBNP during spaceflight may be a result of insufficient exposure duration rather than the magnitude of the fluid shift. Evidence that changes in MRW and TRT occur over hours in response to pressure and posture changes[31,32] suggests that it may be possible for longer-duration LBNP application to reverse spaceflight-induced ocular changes.

There are a few study limitations. Due to crew scheduling constraints, obtaining OCT scans without and with LBNP on the same day and testing subjects at the exact same time of day were not possible. However, efforts were made to minimize the days between the inflight conditions, and all testing occurred during the first half of the day. The study also had a limited sample size and did not have a control group that was not exposed to spaceflight, as is common in spaceflight research. Therefore, cause and effect relationships for spaceflight could not be confirmed.

CONCLUSIONS

The increased peripapillary TRT and decreased optic cup size that occur during spaceflight are consistent with mild ODE. However, inflight posterior ONH displacement and thinning of the central macula suggest that ICP alone cannot explain the ocular findings associated with long-duration spaceflight. Brief inflight application of 25 mmHg LBNP did not influence ONH or retinal morphology, suggesting that longer-duration exposure to headward fluid shift countermeasures may be required to prevent or reverse ocular changes associated with spaceflight, or that other factors contribute to SANS.

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FIGURES & LEGENDS

Figure 1. Optic nerve head and retinal optical coherence tomography parameters. A) 30-degree infrared image showing a radial scan pattern (green) centered on the ONH, best-fit BMO ellipse (orange), and concentric ellipses forming the boundaries for TRT measurement (white). B) Radial B-scan illustrating ONH parameters and relevant landmarks, including Bruch's membrane opening (orange dots), MRW (solid green lines), BM reference (red dashed line), BMO height (solid red lines), BMO reference (orange dashed line), cup reference (cyan dashed line), optic cup (shaded region), and the boundaries for TRT measurement (labeled white dashed lines). C) 30-degree infrared image illustrating a radial scan pattern (green) centered on the macula and boundaries for macular thickness measurements (white). D) Radial B-scan showing the boundaries for macular thickness measurement (labeled white dashed lines) and fovea (yellow arrow). ONH, optic nerve head; BMO, Bruch's membrane opening; MRW, minimum rim width; BM, Bruch's membrane. Scale bars = 200 μm.

Figure 2. Changes in optic nerve head morphology during spaceflight. (A) MRW increased on FD50 and FD150 and gradually recovered after return to Earth, with no difference from the preflight baseline by R+180. (B) Cup volume followed a similar timeline as MRW, initially decreasing on FD50 and returning to baseline by R+180. (C) BMO height was significantly reduced (i.e., posteriorly displaced) on FD150 but did not differ from baseline at any other timepoint. Circles show all individual subject data representing data obtained on Earth (white), data obtained during spaceflight (gray), and the subject with Frisén grade 1 disc edema (black); this individual did not have a detectable optic cup and was therefore excluded from the cup volume analysis. Horizontal bars represent the estimated marginal mean values across subjects, and error bars represent the 95% CI. *P*-values for the change relative to the preflight seated baseline value are provided in eTable 1 of the Supplement. Statistics were not performed on

FD250 data due to the small sample size (n = 4). MRW, minimum rim width; BMO, Bruch's membrane opening; FD, flight day; R+, days after return to Earth.

Figure 3. Changes in peripapillary total retinal thickness during spaceflight are greatest adjacent to the optic nerve head. (A) TRT250 and (B) TRT500 increased on FD50 and FD150 and did not return to preflight baseline values until R+180. (C) TRT1000 was only significantly increased on FD150 and was slightly reduced relative to the preflight seated baseline on R+180. (D) TRT1500 did not increase during spaceflight and was also slightly reduced relative baseline on R+180. Circles show all individual subject data representing data obtained on Earth (white), data obtained during spaceflight (gray), and the subject with Frisén grade 1 disc edema (black). Horizontal bars represent the estimated marginal mean values across subjects, and error bars represent the 95% CI. The shaded area in (A) represents the pre-defined range of normal day-to-day variation in TRT250 (± 19.4 µm).[17] *P*-values for the change relative to the preflight seated baseline value are provided in eTable 1 of the Supplement. Statistics were not performed on FD250 data due to the small sample size (n = 4). TRT, total retinal thickness; BMO, Bruch's membrane opening; TRT250, TRT from the BMO to 250 µm; TRT500, TRT from 250 to 500 µm; TRT1000, TRT from 500 to 1000 µm; TRT1500, TRT from 1000 to 1500 µm; FD, flight day; R+, days after return to Earth.

Figure 4. Central macular thinning occurs during spaceflight. (A) MT500 decreased on FD50 and FD150, and it did not return to preflight baseline values until R+180. (B) MT1500 also decreased on FD50 and FD150 but returned to baseline by R+30. (C) There were no significant changes in MT2500 during or after spaceflight. Circles show all individual subject data representing data obtained on Earth (white), data obtained during spaceflight (gray), and the subject with Frisén grade 1 disc edema (black). Horizontal bars represent the estimated marginal mean values across subjects, and error bars represent

the 95% CI. *P*-values for the change relative to the preflight seated baseline value are provided in eTable 1 of the Supplement. Statistics were not performed on FD250 data due to the small sample size (n = 4). MT, macular thickness; MT500, MT from the fovea to 500 µm; MT1500, MT from 500 to 1500 µm; MT2500, MT from 1500 to 2500 µm; FD, flight day; R+, days after return to Earth.

Table 1. Estimated marginal mean *(95% CI)* for each parameter before, during, and after spaceflight.

	Preflight Seated	**FD50**	**FD150**	**R+10**	**R+30**	**R+180**
MRW (µm)	361.1 *(330.4 – 391.8)*	381.7 *(351.0 – 412.4)*	394.9 *(364.1 – 425.4)*	378.3 *(347.4 – 409.2)*	369.0 *(338.3 – 399.7)*	358.9 *(328.2 – 389.6)*
Cup volume (mm^3)	.193 *(.103 – .283)*	.167 *(.077 – .258)*	.158 *(.068 – .248)*	.163 *(.072 – .253)*	.177 *(.087 – .268)*	.193 *(.103 – .284)*
BMO height (µm)	-118.3 *(-147.1 – -89.4)*	-124.7 *(-153.5 – -95.8)*	-127.2 *(-156.1 – -98.3)*	-117.2 *(-146.4 – -88.0)*	-118.4 *(-147.3 – -89.5)*	-122.3 *(-151.2 – -93.4)*
TRT250 (µm)	395.8 *(376.4 – 415.1)*	407.8 *(388.4 – 427.1)*	418.9 *(399.5 – 438.2)*	411.7 *(392.1 – 431.2)*	403.0 *(383.7 – 422.4)*	393.7 *(374.4 – 413.1)*
TRT500 (µm)	371.8 *(359.1 – 384.5)*	378.0 *(365.3 – 390.7)*	384.0 *(371.3 – 396.8)*	381.3 *(368.5 – 394.1)*	376.2 *(363.5 – 388.9)*	370.1 *(357.4 – 382.8)*
TRT1000 (µm)	338.0 *(328.1 – 347.9)*	338.3 *(328.4 – 348.2)*	340.0 *(330.1 – 349.9)*	339.1 *(329.1 – 349.1)*	339.3 *(329.4 – 349.2)*	336.0 *(326.1 – 346.0)*
TRT1500 (µm)	302.5 *(294.2 – 310.9)*	303.2 *(294.8 – 311.5)*	302.7 *(294.4 – 311.1)*	301.9 *(293.5 – 310.3)*	302.6 *(294.2 – 310.9)*	300.6 *(292.3 – 309.0)*
MT500 (µm)	272.4 *(262.6 – 282.1)*	268.7 *(258.9 – 278.4)*	267.2 *(257.5 – 277.0)*	267.2 *(257.4 – 277.0)*	269.9 *(260.1 – 279.6)*	270.9 *(260.1 – 279.6)*
MT1500 (µm)	348.1 *(339.4 – 356.8)*	345.5 *(336.8 – 354.2)*	344.5 *(335.8 – 353.2)*	344.7 *(336.0 – 353.5)*	347.4 *(338.7 – 356.1)*	347.0 *(338.3 – 355.7)*
MT2500 (µm)	315.7 *(308.1 – 323.4)*	314.8 *(307.1 – 322.4)*	314.7 *(307.0 – 322.4)*	314.3 *(306.6 – 322.0)*	316.1 *(308.5 – 323.8)*	315.2 *(307.6 – 322.9)*

MRW, minimum rim width; BMO, Bruch’s membrane opening; TRT, total retinal thickness; TRT250, TRT from BMO to 250 µm; TRT500, TRT from 250 to 500 µm; TRT1000, TRT from 500 to 1000 µm; TRT1500, TRT from 1000 to 1500 µm; MT, macular thickness; MT500, MT from the fovea to 500 µm; MT1500, MT from 500 to 1500 µm; MT2500, MT from 1500 to 2500 µm; FD, flight day; R+, days after return to Earth.

The R+10 time point includes only 8 subjects, as several international crewmembers did not return directly to Houston