Published in final edited form as:

Aerosp Med Hum Perform. 2017 July 01; 88(7): 633–640. doi:10.3357/AMHP.4768.2017.

Ophthalmological Evaluation of Integrated Resistance and Aerobic Training During 70-Day Bed Rest

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Abstract

INTRODUCTION—We evaluated ophthalmic changes in healthy individuals who underwent integrated resistance and aerobic training (iRAT) during 70-day 6° head-down-tilt (HDT) bed rest (BR).

METHODS—Participants were selected using NASA standard screening procedures. Standardized NASA BR conditions were implemented. Subjects were randomly assigned to the iRAT protocol or no exercise during HDTBR. Weekly ophthalmic examinations were performed in the sitting (pre/post-BR only) and HDT (BR only) positions. Mixed-effects linear models compared pre and post-HDTBR intraocular pressure (IOP), Spectralis OCT circumpapillary retinal nerve fiber layer thickness (cpRNFLT) and peripapillary retinal thickness observations between groups.

RESULTS—Six controls and nine exercisers completed the study. There was an overall effect of BR on our outcomes. Except Goldmann IOP (mean pre/post difference in controls and exercisers: −0.47mmHg versus +1.14mmHg), the magnitude of changes from baseline was not significantly different between groups. There was a +1.38mmHg and a +1.63mmHg iCare IOP increase during BR in controls and exercisers, respectively. Spectralis OCT detected a +1.33μm average cpRNFLT increase in both groups, a +9.77μm and a +6.65μm peripapillary retinal thickening post-BR in controls and exercisers, respectively. Modified Amsler grid, red dot test, confrontational visual field, color vision, and stereoscopic fundus photography were unremarkable.

CONCLUSIONS—Seventy-day HDTBR induced peripapillary retinal thickening and cpRNFLT thickening without visible signs of optic disc edema. The magnitude of such changes was not different between controls and exercisers. A slight IOP increase during BR subsided post-BR. Further study should evaluate whether different physical exercise paradigms may prevent/mitigate the risk of space-related visual impairment.

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Reprints will not be available from the authors.

Keywords

head-down-tilt; intraocular pressure; microgravity; optic disc; physical exercise; Spectralis OCT

INTRODUCTION

Among the outer space environmental factors known to affect the human physiology, weightlessness is recognized as causing significant multisystemic effects.¹⁹ To preserve the health and safety of the crewmembers supporting future deep space explorations to asteroids and Mars, intense research has been focused on the development and validation of countermeasures to prevent or mitigate the detrimental effects of space. For example, head-down-tilt bed rest is used to induce gravitational unloading and simulate the effects of microgravity.²² In a recent 14-day head-down-tilt bed rest study, intensive resistive and aerobic exercise was shown to preserve muscular, cardiac and respiratory fitness.²⁴ The increased metabolic needs of the muscles under exertion are sustained by a greater supply of blood and nutrients.⁶ During physical exercise, the increased mean capillary pressure, coupled with tissue hyperosmolality, produces a localized shift of fluids from the vascular to the extravascular compartment of the active muscles,^{16, 27} leading to increased muscular cross-sectional areas.²³ These notions are corroborated by early observations from the Skylab 4 crewmembers revealing that head fullness, a symptom of cephalad fluids shift, was effectively yet temporarily relieved by steady bicycle exercise; moreover, direct in-flight measurements demonstrated increased calf circumference after treadmill exercise.¹¹ Altogether, the above findings suggest that lower body physical exercise may mitigate the upward fluids shift induced by either the head-down-tilt position or the microgravity environment. This may be relevant to other physiologic processes. In fact, cephalad shift of body fluids, possibly leading to elevated intracranial pressure (ICP), has been proposed as a pathophysiological mechanism underlying the Visual Impairment/Intracranial Pressure (VIIP) syndrome described in several astronauts involved in long-duration (> 6 months) space missions.¹⁷ Changes included optic nerve sheath distension with signs of optic disc edema, posterior globe flattening with hyperopic shift, choroidal folds, and cotton wool spots.^{13, 17}

Since prolonged head-down-tilt bed rest is used as a microgravity analog, ophthalmic testing has been implemented to monitor the subjects' ocular health during NASA bed rest campaigns. Little is known about the ability of prolonged bed rest to reproduce the VIIP signs and their severity. However, previous research has shown peripapillary retinal thickening and increased circumpapillary retinal nerve fiber layer (cpRNFL) thickness in healthy individuals who spent 70 consecutive days in the 6° head-down-tilt position.²⁹ It is conceivable that interventions with the potential to mitigate the cephalad fluids shift, such as lower body physical exercise, may also attenuate the magnitude of posture-induced ocular changes. Therefore, the purpose of the present investigation was to evaluate the ophthalmological effects of integrated resistance and aerobic training (iRAT) during 70 days of bed rest. We hypothesized that the degree of changes in the optic disc region induced by bed rest, such as peripapillary retinal thickening and cpRNFL thickening, would be attenuated in subjects undergoing the iRAT protocol. With regard to intraocular pressure

(IOP), available studies suggest opposite effects of aerobic and anaerobic exercise on IOP (i.e., a transitory reduction in IOP after aerobic training, such as jogging, versus a transient IOP increase following anaerobic exercise, such as weightlifting).^{5, 26} Since the iRAT protocol combined aerobic and anaerobic training, we hypothesized that IOP changes from baseline would not be different between subjects who did and who did not engage in exercise.

METHODS

Subjects

This multidisciplinary 70-day bed rest study was conducted at the NASA Flight Analogs Research Unit (FARU), located at The University of Texas Medical Branch at Galveston (UTMB), Galveston, Texas. The study protocol was approved in advance by the NASA Johnson Space Center and the UTMB Institutional Review Boards, and all methods adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA). Each subject provided written informed consent before participating.

Subject qualification criteria and bed rest conditions are detailed elsewhere.¹⁸ In brief, to qualify for participation, subjects passed extensive physical and psychological exams. Selection of these subjects included a rigorous fitness evaluation of muscle strength and aerobic capacity. Subjects were randomly assigned to either an exercising group or a non-exercising control group. Data from control subjects were presented elsewhere.²⁹

A standardized diet, based on the NASA space flight nutritional requirements, was provided throughout the study. To ensure nutritional intake, subjects were required to consume all food served to them. In addition, they adhered to a strict sleep/wake schedule and did not nap during the day, with lights turned on at 6:00 am and turned off at 10:00 pm. Subject health was monitored by the attending physician and nursing staff 24-hours per day for the entire duration of the study.

To become acclimated to the FARU, control and exercise subjects spent 13 and 21 days in the pre bed rest phase, respectively. Exercising subjects had a longer pre-bed rest phase to provide more time to learn the exercise activities. In this phase, subjects were ambulatory and underwent baseline assessment of their nutritional, cardiovascular, neurological and fitness status. The in-bed phase consisted of 70 consecutive days of bed rest at 6° head-down-tilt, the NASA standardized position for bed rest studies. All daily activities, including showering and toileting, were performed in this position.¹⁸ Finally, subjects were ambulatory and remained at the FARU for 14 more days post bed rest to collect post study measures and receive rehabilitation to compensate for the deconditioning that occurs after prolonged bed rest.

Equipment

Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Precision Vision, La Salle, IL) were used to assess monocular best-corrected visual acuity (BCVA). As part of a standardized protocol that included manifest refraction, subjects were required to

consecutively identify the optotypes of the ETDRS charts, starting from the top line. There were no termination criteria; rather, the total number of optotypes correctly identified was converted to logMAR units.

Goldmann applanation tonometry (GAT) was performed pre and post bed rest by two operators in a masked, standardized fashion: the dial was covered to eliminate potential bias from knowing prior IOP values; the IOP was recorded and the dial reset by the second operator. For reproducible measurements, contact between the inner edges of the fluorescein bands was achieved at the systolic peak of the cardiac cycle. To account for inter-operator differences, the mean of the two operators' IOP was considered in each eye.

Handheld tonometry was performed using iCare (Icare Finland Oy, Espoo, Finland). The mean of four consecutive measurements collected on the same visit was considered in each eye. In-bed IOP was obtained with subjects maintaining a 6° head-down-tilt while assuming a right and left lateral decubitus for measuring the left and the right eye IOP, respectively. To account for IOP changes possibly induced by transitioning from supine to lateral decubitus, a minimum 5-minute interval was given prior to starting the IOP measurements. At baseline, iCare was not available for the first control and the first two exercisers. Therefore, in these subjects handheld IOP was obtained at all time points using Tonopen (Reichert Inc., Depew, NY). Tonopen and iCare were not considered interchangeable for the purpose of the analysis.

Spectralis OCT (Heidelberg Engineering, GmbH, Heidelberg, Germany; software version 5.1.3.0) was used to obtain Spectral-domain OCT (SD-OCT) scans in Automatic Real-Time mode (ART = 9). The Volume Scan acquisition protocol (512 A-scans $\times$ 19 B-scans) analyzed a 20° $\times$ 15° area (5.9 mm $\times$ 4.4 mm) centered to the optic disc. After scan acquisition, an ETDRS grid was automatically placed in the center of the fundus image for evaluation of the retinal thickness. As the external sectors of the ETDRS grid exceeded the scan area, only the retinal thickness measures from the inner sectors were considered, consistently with previous bed rest studies.^{28–30} The Circle Scan protocol was used to obtain average cpRNFL thickness measures. In each scanning protocol, follow-up scans were obtained using the AutoRescan™ feature, which ensured automatic placement of the follow-up scans in the same location as baseline. The accuracy of the automated retinal segmentation was verified in each B-scan, and manual correction was performed by one experienced operator, as needed. All Spectralis OCT images were evenly illuminated with signal-to-noise ratio >15 dB, according to the minimum quality score per manufacturer's recommendation.

Procedure

Integrated Resistance and Aerobic Training—Subjects were randomly assigned to the iRAT protocol or no exercise during bed rest. The iRAT protocol is schematically represented in Fig. 1, and details can be found elsewhere.²⁴ In brief, training was performed 6 days per week. In each week, days of high-intensity interval aerobic exercise were alternated with days of continuous aerobic exercise coupled with lower body resistance training (i.e., supine squat, supine leg press, supine heel raise, and prone leg curl). A vertical

treadmill and a supine cycle ergometer were used to perform the aerobic exercise sessions, while resistance training was completed on a horizontal squat device.

Ocular Examinations—Subjects were evaluated on a weekly basis throughout the duration of the study. Pre and post bed rest ocular examinations were conducted in the sitting position at the UTMB University Eye Center. Weekly in-bed ocular examinations were performed in the 6° head-down-tilt position at the FARU. All ocular examinations followed the same sequence of testing and preceded all applicable iRAT training sessions. Efforts were made to schedule the ocular examinations of each subject at the same time in the morning to account for the potential effects of circadian variations on our outcomes, particularly IOP. Ocular testing included BCVA, modified Amsler grid test, red dot test, confrontational visual field, color vision using Hardy-Rand-Rittler plates, tonometry, and cycloplegic autorefraction (Retinomax K-plus 3; Right Mfg. Co., Ltd., Tokyo, Japan). Pre and post bed rest visits comprised also stereoscopic color fundus photography and SD-OCT scans.

Statistical Analysis

All statistical analyses were conducted using Stata (StataCorp LP, College Station, TX; software version 14.0).

Our primary outcomes included GAT and iCare IOP, and Spectralis OCT peripapillary retinal thickness and average cpRNFL thickness, all of which are continuously scaled and assumed to follow a normal distribution in the population. The main outcome measures were collected in the two eyes of each subject, pre and post bed rest, and in the two groups, resulting in a $2 \times 2 \times 2$ mixed factorial experimental design. These outcomes were fit to separate mixed-effects linear models using Stata's *mixed* command syntax, with fixed parameters evaluating the pre versus post bed rest main effect, the control versus exercise group main effect, and the interaction effect that evaluated whether the control group pre/post delta differed significantly from the exercise group pre/post delta. Each model included random intercept terms for subject and eye to accommodate our repeated observations within person (left/right eye) and over time (pre/post bed rest).

RESULTS

Six control subjects (1 woman; mean [SD] age = 39.3 [7.6] years; weight = 76.2 [9.2] Kg; height = 171.3 [5.9] cm; body mass index = 25.9 [2.0] Kg/m²) and 9 men exercisers (mean [SD] age = 34.1 [5.1] years; weight = 77.0 [9.1] Kg; height = 181.7 [6.0] cm; body mass index = 23.3 [2.7] Kg/m²) participated in this study. Mean pre and post bed rest ophthalmological data are presented in Table I.

In both groups, measures of modified Amsler grid test, red dot test, confrontational visual field and color vision were within normal limits in the two eyes of each subject at all time points. No qualitative changes from baseline were detected on stereoscopic color fundus photography.

Intravital GAT and iCare IOP repeated measurements were highly reproducible in both groups. For iCare IOP, the intraclass correlation coefficient (ICC), a variability measure, was 0.97 ICC 0.99 in controls and 0.89 ICC 0.97 in exercisers, while for GAT IOP, 0.82 ICC 0.97 in controls and 0.92 ICC 0.98 in exercisers.

Analysis of GAT IOP revealed a significant interaction effect on the third day post bed rest (mean pre/post delta in controls and exercisers: -0.47 mmHg and $+1.14$ mmHg, respectively; $P = 0.03$), indicating that the magnitude of change in GAT IOP post bed rest was greater in the exercise group (Table I). On the ninth day post bed rest, instead, analysis of GAT IOP failed to reveal a significant interaction effect (mean pre/post delta in controls and exercisers: -0.67 mmHg and $+0.09$ mmHg, respectively; $P = 0.32$).

Fig. 2 shows mean iCare IOP measures for the two groups. There was an overall increase in iCare IOP during bed rest ($+1.38$ mmHg, $P = 0.03$), but no differences from baseline were observed post bed rest ($P = 0.69$). We did not find differences between controls and exercisers overall (main effect $P = 0.73$), nor did we uncover interaction effects, suggesting that the magnitude of the increase in iCare IOP during bed rest was not different between controls and exercisers ($+1.38$ mmHg and $+1.63$ mmHg, respectively; $P = 0.76$).

Spectralis OCT peripapillary retinal thickness

In all sectors, analysis revealed an overall increase in peripapillary retinal thickness post bed rest ($+4.67$ μm mean delta $+12.17$ μm , P s < 0.01), but the group (0.12 P s 0.98) and interaction effects (0.06 P s 0.76) were not significant, indicating that the magnitude of peripapillary retinal thickening post bed rest was not different between controls and exercisers.

Spectralis OCT average cpRNFL thickness

Overall, average cpRNFL thickness increased from baseline ($+1.33$ μm , $P = 0.02$). We did not find differences between controls and exercisers overall (main effect $P = 0.40$), nor did we uncover interaction effects ($P = 1.00$), suggesting that the magnitude of changes post bed rest was not different between the two groups.

DISCUSSION

This study evaluated the ophthalmic effects of integrated resistance and aerobic training during 70-day bed rest. Overall, there was a significant effect of bed rest, although the changes from baseline were not different between groups for all our outcomes except GAT IOP, whose changes were only slightly, yet significantly higher in exercisers relative to control subjects early after bed rest.

Our analysis revealed an overall increase in iCare IOP during bed rest, consistently with previous studies evaluating posture-induced IOP changes.^{25, 29} Proposed mechanisms to explain the IOP elevation during head-down-tilt include increased episcleral venous pressure and choroidal engorgement with expansion against the sclera, respectively.^{4, 15} In our study, we found no differences in iCare IOP elevation between controls and exercisers ($+1.38$ mmHg and $+1.63$ mmHg increase from baseline, respectively). In fact, Fig. 2 reveals a

similar IOP pattern in the two groups, consisting in an acute increase in iCare IOP as subjects assumed the head-down-tilt posture, followed by stabilization during bed rest and decrease towards baseline levels post bed rest. The return to baseline IOP values was confirmed by GAT analysis, showing an early interaction effect that did not persist at day-9 post bed rest.

Overall, our IOP data from this set of healthy individuals suggest that compensatory mechanisms may have effectively stabilized the IOP throughout the 70-day bed rest duration. It is possible that decreased aqueous humor production, coupled with increased outflow mediated by the trabecular meshwork cells, prevented a progressive rise in IOP from known stressors, such as the head-down-tilt position or anaerobic exercise.

The acute effects of physical exercise on IOP have long been investigated. Studies have shown that aerobic training is responsible for a transitory IOP-lowering effect, while anaerobic exercise, such as weightlifting, may transiently elevate the IOP.^{5, 26} However, little is known about the long-term effects of sustained physical activity on IOP. Similarly to the astronauts on the International Space Station,¹⁴ our exercise subjects completed a combined aerobic and anaerobic training program designed to preserve the musculoskeletal function and minimize the cardiovascular deconditioning induced by 70-day bed rest. Overall, the IOP-lowering effect possibly associated with the aerobic training may have been counterbalanced by the IOP elevation likely induced by the resistance anaerobic training, resulting in a similar IOP pattern to the control group. Further research is needed to confirm this hypothesis, as IOP measures could not be obtained immediately before and after exercise due to rigid protocol constraints.

Spectralis OCT detected peripapillary retinal thickening post bed rest in all sectors analyzed, without differences between controls and exercisers. In general, the amount of peripapillary retinal thickening tended to be greater nasally, superiorly and inferiorly than in the temporal sector (Table I), consistently with the topographical sequence of changes characterizing the optic disc swelling process. We could not determine whether subtle changes in the caliber of the retinal vessels (e.g., venous dilation) from prolonged head-down-tilt may have also contributed to the observed retinal thickening, as a reliable measurement method of the retinal vessels diameter was not available. However, macroscopic assessment of the color fundus photographs did not reveal any dilated or tortuous retinal vessels. Spectralis OCT findings are exemplified by the two cases presented in Fig. 3, showing post bed rest optic disc changes in a sample eye from each group. In both cases, Spectralis OCT identified structural changes that would have remained undetected by conventional stereoscopic color fundus photography assessment. In particular, post bed rest peripapillary retinal thickening is best noticeable on each retinal thickness map as a widening of the white and the warm-colored areas. Furthermore, in each case of Fig. 3, the retinal thickness profile of a cross-sectional Spectralis OCT scan illustrates that the increase in retinal thickness from baseline was more pronounced on and in close proximity to the optic disc, and decreased progressively as the distance from the optic disc margins increased. This may also explain why our analysis detected only a minimal yet significant increase in average cpRNFL thickness post bed rest (+1.33 μm in both groups), as determined along a circle of 3.4 mm diameter placed around the optic disc. Mixed-effect restricted maximum likelihood

regression models have recently shown the importance of the time spent in head-down-tilt on the magnitude of peripapillary thickness changes induced by bed rest.²⁹ Thus, it is expected that longer bed rest durations would result in greater cpRNFL thickening.

It has been suggested that certain optic nerve conditions, such as glaucoma or optic disc edema, may result from a pressure imbalance between the IOP and the ICP across the two sides of the lamina cribrosa.¹² If that is the case, in this study prolonged head-down-tilt, alone or in combination to repeated Valsalva maneuvers during resistance training causing marked increase of the systolic blood pressure and concomitant ICP elevation to stabilize the cerebrovascular transmural pressure,^{8, 20, 32} may have raised the ICP more than IOP. This may have impaired the regular axoplasmic flow and caused retinal nerve fibers swelling,⁹ which was captured by Spectralis OCT post bed rest. Unfortunately, we are unable to confirm this hypothesis, as direct or indirect ICP estimates could not be obtained in our study.

In general, the results did not provide evidence of a significant effect of physical exercise on our ocular outcomes. However, it should be emphasized that absence of evidence does not correspond to evidence of absence.^{1, 7} That is, our analysis cannot prove that physical exercise had no ophthalmic effects. For example, as noted above, both the aerobic and anaerobic iRAT training sessions may have transiently affected the IOP. Furthermore, recent evidence suggests a positive role of physical exercise on the retinal physiology.^{21, 31} In this study, the lack of significant ocular structural differences between the two groups may be related to experimental factors. For example, although our subjects exercised six days per week, the duration of each training session may have not been long enough to effectively counteract the cephalad fluids shift induced by head-down-tilt and to reduce the amount of peripapillary retinal thickening post bed rest. The relatively small number of participants may have also contributed to the lack of differences between groups, although the analysis was able to detect a significant effect of bed rest on our main outcomes and a small but significant interaction effect on GAT IOP in the early post-bed rest phase. Nevertheless, we encourage further investigations aimed at evaluating the ophthalmic effects of physical exercise, particularly when performed in a supine or tilted position. Common examples range from the yoga head-down poses to decline bench exercises. In the United States, the estimated prevalence of yoga and muscle-strengthening physical activity is 9.5% (> 20 million) and 29.3%, respectively.^{2, 3} Current knowledge derives mainly from case reports/case series in yoga practitioners and/or from studies characterized by short follow-up.^{10, 25} Therefore, it would be important to evaluate and quantify the long-term ophthalmic risks associated with routine performance of such posture-related practices in larger samples of individuals with and without underlying ocular conditions like glaucoma or ocular hypertension. Additional study should also elucidate the role of other important factors, such as gender, fitness status and anthropometric characteristics (e.g., height, weight) in determining the ocular responses to physical exercise. In fact, the rigid inclusion and exclusion criteria of this study aimed at recruiting a cohort of healthy individuals that closely resembled the astronaut corps.

Our research has limitations. First, only weekly assessments were performed. Therefore, the acute ocular responses to physical exercise (e.g., immediately before and after each training

session), as well as the acute effects of postural changes (e.g., immediately after head-down-tilt placement and immediately after reassuming the upright position post bed rest), could not be fully characterized. Unfortunately, the multidisciplinary study design composed of parallel investigations significantly restricted the subjects' availability for ocular testing. However, this study systematically evaluated ocular structural and functional effects of physical exercise during bed rest over an extended, 70-day period.

Second, our findings may not apply to different training regimens. The iRAT protocol combined aerobic and anaerobic exercise 6 days per week. Further research is needed to determine whether training protocols integrating different types of exercise and/or durations may lead to ophthalmic changes of a different magnitude. However, the present investigation was conducted in a tightly controlled research environment that ensured maximal compliance with the assigned training regimen while adopting standardized setting (e.g., temperature, humidity) and training (e.g., type, intensity and duration of exercise) conditions.

In conclusion, 70-day bed rest induced peripapillary retinal thickening and a small amount of cpRNFL thickening, as detected by Spectralis OCT, without any visible signs of optic disc edema. Such changes may have resulted from cephalad shifts of body fluids induced by the 6° head-down-tilt position. There was a small, non-progressive IOP elevation during 70-day bed rest that subsided post bed rest. This study found no evidence that an integrated aerobic and resistance training protocol during 70-day bed rest mitigated the amount of bed rest-induced ophthalmic changes. Further research should evaluate whether different paradigms of type, intensity and/or duration of exercise, alone or combined with lower body negative pressure, may effectively counteract the cephalad fluids shift and prevent/mitigate the risk of space-related visual impairment.

Acknowledgments

Supported by NASA Flight Analogs Project 516724.03.04.01; National Institutes of Health/National Center for Research Resources 1UL1RR029876-01. Supported in part by an unrestricted grant from Research to Prevent Blindness (RPB) to the University of Texas Medical Branch at Galveston, Galveston, Texas, USA.

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Fig. 1. Schematic representation of the integrated Resistance and Aerobic Training (iRAT) protocol. Single capital letters indicate the days of the week.

Fig. 2. ICare intraocular pressure plots of the 70-day bed rest control (A) and exercise (B) groups. Error bars represent the 95% confidence interval of the mean. The vertical lines identify the pre bed rest (*left*), bed rest (*middle*) and post bed rest (*right*) phases.

A) Control

B) Exercise

Fig. 3.

Spectralis OCT data and color fundus photographs of one sample eye from the control (A) and the exercise (B) groups. From left to right: pre/post bed rest peripapillary retinal thickness (*black*) and volume (*red*) measures, retinal thickness maps, cross sectional OCT tomograms passing through the optic disc with retinal thickness profile plot, and color fundus photographs. In both case examples, no changes were detectable on fundus photography after 70-day head-down-tilt bed rest. However, post bed rest peripapillary retinal thickening is best noticeable on Spectralis OCT retinal thickness map as an enlargement of the *white* and *warm-colored areas* (*arrows*), corresponding to a +18.4 μm

(+5.2 %) and a +23.6 μm (+5.34 %) mean increase in peripapillary retinal thickness from baseline in the control (A) and the exercise (B) eye, respectively.

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Table I

Pre and post bed rest ophthalmological data.

	Control		Exercise	
	Pre	Post	Pre	Post
Near BCVA, logMAR	-0.16 (-0.21, -0.11)	-0.19 (-0.23, -0.15)	-0.14 (-0.19, -0.09)	-0.19 (-0.26, -0.13)
Spherical Equivalent, D	0.77 (0.06, 1.48)	0.49 (0.03, 0.95)	-0.22 (-1.79, 1.34)	-0.40 (-1.91, 1.11)
Goldmann IOP, mmHg	15.42 (13.51, 17.32)	14.94 (12.98, 16.90)	13.89 (12.33, 15.45)	15.03 (13.47, 16.58)
iCare IOP, mmHg	12.53 (9.58, 15.47)	12.78 (9.83, 15.72)	11.84 (9.35, 14.33)	13.04 (10.55, 15.53)
Peripapillary retinal thickness - Temporal sector, μ m	307.17 (286.52, 327.81)	311.83 (291.19, 332.48)	305.17 (288.31, 322.02)	310.22 (293.37, 327.08)
Peripapillary retinal thickness - Superior sector, μ m	407.25 (379.48, 435.02)	419.42 (391.64, 447.19)	379.00 (356.32, 401.68)	387.83 (365.16, 410.51)
Peripapillary retinal thickness - Nasal sector, μ m	351.67 (322.66, 380.67)	363.33 (334.33, 392.34)	357.11 (333.43, 380.79)	364.94 (341.26, 388.63)
Peripapillary retinal thickness - Inferior sector, μ m	400.92 (366.15, 435.68)	411.50 (376.73, 446.27)	401.44 (373.06, 429.83)	406.33 (377.95, 434.72)
Average cpRNFL thickness, μ m	103.42 (96.33, 110.51)	104.75 (97.66, 111.84)	99.44 (93.66, 105.23)	100.78 (94.99, 106.57)

Data presented as marginal mean (95% Confidence Interval) estimated from mixed-effects REML regression models.

BCVA, best corrected visual acuity; IOP, intraocular pressure; cpRNFL, circumpapillary retinal nerve fiber layer.