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Ocular Biomechanical Responses to Long-Duration Spaceflight

MARISSÉ MASÍS SOLANO [1,2], REMY DUMAS [1], MARK R LESK [1,2], AND SANTIAGO COSTANTINO [1,2]

[1]Maisonneuve-Rosemont Hospital Research Center, Montreal, QC H1T 2M4, Canada
[2]University of Montreal, Montreal, QC H3T 1J4, Canada

CORRESPONDING AUTHOR: SANTIAGO COSTANTINO (e-mail: santiago.costantino@umontreal.ca).

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ABSTRACT *Objective:* To assess the impact of microgravity exposure on ocular rigidity (OR), intraocular pressure (IOP), and ocular pulse amplitude (OPA) following long-term space missions. OR was evaluated using optical coherence tomography (OCT) and deep learning-based choroid segmentation. IOP and OPA were measured with the PASCAL Dynamic Contour Tonometer (DCT). *Results:* The study included 26 eyes from 13 crew members who spent 157 to 186 days on the International Space Station. Post-mission results showed a 25% decrease in OPA ($p < 0.005$), an 11% decrease in IOP from 16.0 mmHg to 14.2 mmHg ($p = 0.04$), and a 33% reduction in OR ($p = 0.04$). No significant differences were observed between novice and experienced astronauts. *Conclusions:* These findings reveal previously unknown effects of microgravity on the eye's mechanical properties, contributing to a deeper understanding of Spaceflight-Associated Neuro-ocular Syndrome (SANS). Long-term space missions significantly alter ocular biomechanics and have the potential to become biomarkers of disease progression.

INDEX TERMS Microgravity, spaceflight, ocular rigidity, space biomechanics.

IMPACT STATEMENT Long-term space missions significantly reduce ocular rigidity and ocular pulse amplitude, revealing microgravity-induced changes in eye mechanics and advancing understanding of Spaceflight-Associated Neuro-ocular Syndrome (SANS).

I. INTRODUCTION

The reduction of health risks and the development of countermeasures is critical to the advancement of space exploration. Alterations to vision are among the most immediate physiological changes that astronauts experience in space. Although the pathological conditions associated with spaceflight-associated neuro-ocular syndrome (SANS) have been reported for over a decade, highlighting the importance of addressing this concern, neither its pathophysiology nor treatment options have been completely elucidated. [1] Several theories have been suggested such as hemodynamic fluid shift, exposure to CO2 and exercise in microgravity conditions [2]. Several theories have been suggested such as hemodynamic fluid shift, exposure to CO2 and exercise in microgravity conditions.

Long-duration space travel has been found to induce a range of ocular changes. These changes encompass unilateral or bilateral optic disc edema, globe flattening, choroidal and retinal folds, hyperopic refractive error shifts, and focal areas of retinal ischemia, also known as cotton wool spots [1]. These ocular alterations are components of SANS, which has been reported in 40–70% of crew members following their stay aboard the International Space Station (ISS). [1], [3].

Ocular tissues are constantly subject to various mechanical forces, such as intraocular pressure fluctuation and variations in ocular perfusion. In microgravity the tissue is challenged and acute and chronic adaption achieve a new balance between these forces [4]. Changes in intracranial pressure, intraocular pressure, and tissue hemodynamics have been reported to impact tissue remodeling as a chronic adaptation to

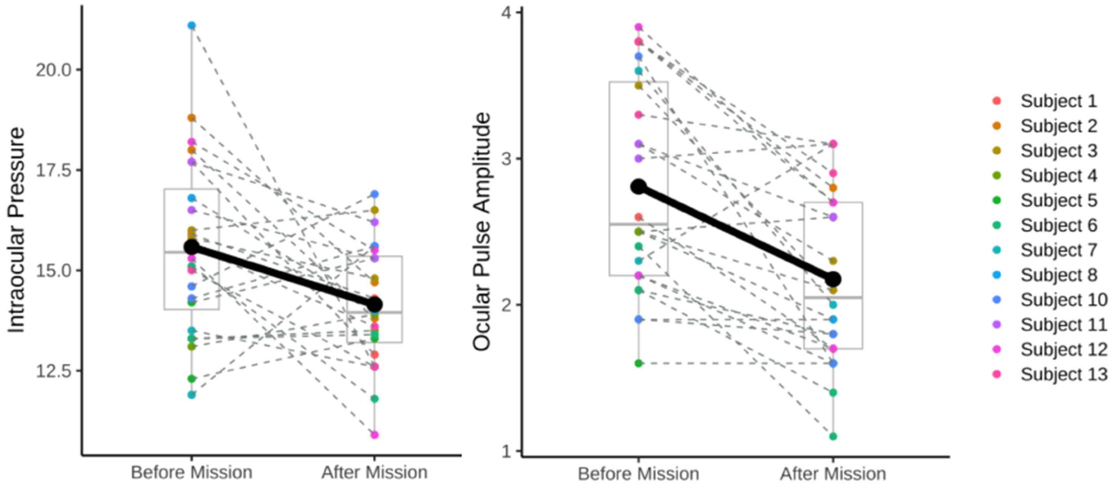

FIGURE 1. **Changes in intraocular pressure (IOP) and ocular pulse amplitude (OPA) in mmHg before and after long-term spaceflight.**

change [4], [5], [6]. Biomechanical acute adaptations are more challenging to determine.

Globe flattening (GF) in astronauts can be identified at the optic nerve head (ONH) and the macula. The initial descriptions of GF as well as subsequent studies, were based on observations of the eye's shape at the ONH as seen in ocular magnetic resonance imaging (MRI) scans [1], [7], [8]. This change may be related to tissue properties, as the rigidity of the eye is highly dependent on the scleral shell.

Ocular rigidity (OR) has emerged as a valuable biomarker for investigating terrestrial ocular pathology [9], [10], [11]. OR describes the change in IOP produced by a modification in ocular volume and is an indirect way to assess the stiffness of the outer coats of the eye.

The concept of OR was originally developed by Friedenwald, experimentally assessed ex vivo by injecting liquid inside the eyeball and described empirically with a simple (1). Today, optical coherence tomography (OCT) provides a non-invasive method to measure OR: the pulsatile change in choroidal thickness is extracted from OCT movies and used to estimate variations in ocular volume at the cardiac frequency, while IOP changes are quantified with a Pascal dynamic contour tonometer. These values are combined using Friedenwald's equation [12], [13].

$$\ln\left(\frac{IOP}{IOP_0}\right) = OR\,(V - V_0)\,. \tag{1}$$

Where both IOP and volume (V) are measured at two different timepoints, typically at diastole and systole to maximize their difference. The change in IOP between diastole and systole is known as the ocular pulse amplitude (OPA).

Exposure to microgravity can cause a headward shift of bodily fluids, potentially impacting various ocular fluid compartments [14]. This could lead to increased cerebrospinal fluid (CSF) pressure extending along the optic nerve to the optic nerve head (ONH), result in CSF accumulation or interstitial edema at the ONH, or disrupt the ocular perfusion [2], [15], [16], [17]. The change in perfusion and pressure balance in the orbit, secondary to microgravity, provides a unique environment to study the biomechanical adaptations of healthy ocular tissue. Scleral compliance would be expected to play a role in the observed variability of axial length changes, which are responsible for refractive problems, as well as in the development of retinal and choroidal folds, and globe flattening [4].

TABLE 1. **Demographic Characteristics of the Participants**

Parameter	Value
Age, mean(SD)	49(10)
Female, No(%)	5(38)
Mission Duration Days (min-max)	170-371
Novice, No(%)	8(38.4)

Understanding the changes in the mechanical properties of ocular tissue could not only shed new light into the disease's pathophysiology but potentially assist in both the identification of individuals at a higher risk of developing irreversible eye damage and in the development of countermeasures against SANS.

II. RESULTS

A total of 26 eyes from 13 crew members, with an average age of 48±9 years and 31% females, were included in the study. All subjects participated in long-duration space missions aboard the ISS. Eight of the participants (38.4%) were novices, i.e., it was their first mission. A summary of the demographic characteristics is shown in Table 1.

Post-flight measurements were taken within 1-30 days after landing. The mean IOP before and after the flight was 16.0±2 mmHg and 14.2±2 mmHg, respectively ($p = 0.04$), indicating an 11% decrease following exposure to microgravity (Fig. 1, Panel A). Furthermore, there was a decrease in OPA, measured with a Pascal dynamic tonometer, representing a 25 % reduction ($p < 0.005$) (Fig. 1, Panel B). A mixed

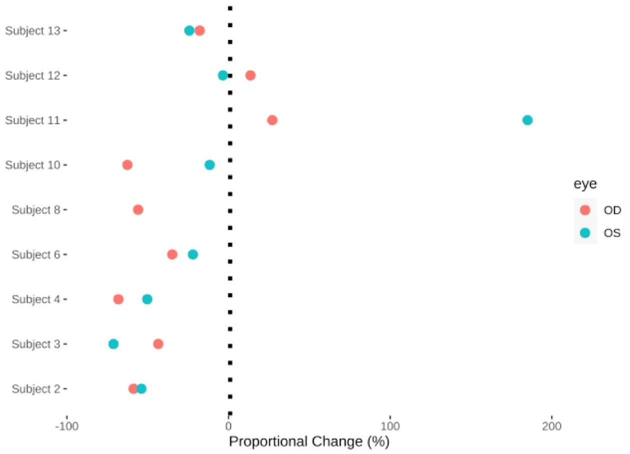

FIGURE 2. **Ocular rigidity percentage change compared to baseline in subjects with high-quality segmentation.**

effects regression was performed to correct for the use of 2 eyes per subjects and assess the significance of the change.

The analysis of OR, which included 17 eyes from 9 astronauts with satisfactory segmentation, yielded a significant mean reduction of 33% post-flight compared to baseline (p = 0.04) (see Fig. 2). However, due to large choroid thickness in some subjects, for which the Choroid-Scleral Interface (CSI) was not visible in the OCT B-Scans, 4 astronauts were excluded from the OR calculation. In addition, a partially complete dataset does not allow absolute values for OR on all subjects, and only change can be computed throughout the cohort. For these subset of subjects the measurements were taken within 1-7 days after landing(Fig. 2).

Multivariate analysis was performed to explore the effect of sex, age, experience (novice vs senior) and mission duration on ocular rigidity and IOP however, no significant correlation was found between the outcome variables and demographic characteristics in this cohort. There was also no significant difference between the days after landing (1-30 days).

The baseline choroidal thickness for the population was $<$400 mm in 8 subjects. Out of the 5 subjects with choroid thickness above 400 mm, their difference in choroid thickness was not correlated with demographic characteristics of previous exposure to microgravity. Four subjects had non-visible interface between the choroid and the sclera, therefore those subjects were excluded. One eye of one of the subjects (Subject 8) was excluded due to low quality of the scan.

III. DISCUSSION

Biomechanical responses to microgravity in humans have been extensively documented in bone, muscle and central nervous tissue [18]. In our cohort, we observed a significant decrease in OR, an important biomechanical property of the eye, as well as in OPA and IOP. While the implications for health and their correlation with the development of SANS remain to be fully understood, changes in mechanical properties of the optic nerve head have previously been associated with optic nerve damage in other ophthalmic pathologies [19], [20], [21].

Changes in the scleral wall (related to ocular rigidity) have been reported in physiological changes related to age [22] and pathological conditions such as glaucoma, pathological myopia, pachychoroid syndrome, and keratoconus [4], [9], [12], [23].

Biomechanical properties of the wall of the eye are also thought to contribute to the development of hypotony maculopathy (which shares some clinical features with SANS). Furthermore, transient exposure to micrograyity has recently been reported to cause similar changes in OR and OPA [24].

In our study, the main finding is the decrease in OR (33%) accompanied by a reduction in OPA (25%) and IOP (11%).

The IOP demonstrates a general trend of rise in the majority of the subjects. However, effect size in those that demonstrate a reduction is greater than the observed elevation of IOP in those that demonstrate an elevation of IOP.

These changes were observed during recovery from microgravity, several days to 4 weeks post-flight. They could be indicative of what occurs during microgravity, but they could also be part of the of the post-flight recovery/adaptation to regular gravitational conditions. We surmise that the decreased is OPA may be in part secondary to the reduced scleral stiffness. Lower ocular rigidity suggests that smaller stress forces could result in more deformation of the eye in microgravity conditions [25].

Even if all measures were taken between 8:00 h and 15:30, and circadian changes are expected to be in early morning and during the night in healthy subjects [26], [27] it is important to consider that postural changes and the circadian cycle could have an influence on the results.

Reduced OPA in the presence of lower OR has been observed previously and is explained by the fact that during the pulse, if the scleral wall is less stiff, the globe will expand more in response to the increased blood volume, and consequently the IOP will rise less.

Normal choroidal thickness in healthy subjects has been reported between 250–400 μm depending on the population, age, sex and diurnal variation [28], [29], [30]. In this cohort 5 subjects (38%) present thick choroids. This finding was not correlated to gender age or previous space flights. Further research is needed to explain this finding,

It is repeatedly reported that there are major cephalad venous blood volume shifts during microgravity [24], [31], [32]. As a consequence, venous volume in the eye may increase, particularly in the choroid, and evidence is emerging in support of this. We speculate that choroidal expansion during weightlessness, when present, may lead to stretching of the scleral collagen. Upon return to gravity the choroidal volume returns towards normal, but the scleral mechanical properties remain altered, resulting in lower OR. It is well known that scleral collagen fibres do not necessarily recover their former mechanical properties following stretching [33].

An association between intracranial venous congestion and SANS has also been reported. Abnormal blood flow dynamics during spaceflight, leading to increased venous compliance, may raise the risk of developing SANS. A recent study suggested that vascular tissue rigidity in the central nervous system may also predispose individuals to pathological responses to microgravity [34]. Likewise, it is conceivable that the mechanical properties of ocular veins might contribute to ocular congestion and the development of SANS.

Pulsatile changes during microgravity conditions could also have a role in SANS physiopathology. In the SPACECOT Study, participants underwent head-down tilt tests to examine how fluid redistribution could mimic the effects of microgravity. The researchers propose that prolonged exposure to the rhythmic impact of pulsations, akin to a water hammer phenomenon, might lead to long-term remodeling in adjacent tissues, similar to what has been observed in studies of arterial pulsatility. [31], [35] It is possible that a similar water hammer effect could also lead to tissue remodelling in the eye, effecting scleral stiffness.

This data should be interpreted with consideration to the small sample size, which is inevitable with this type of very unique cohort. However, it is remarkable that almost every astronaut showed reduced OR following return to earth. A more extended follow-up and correlation with additional clinical characteristics of SANS, when available, could yield valuable insights into the persistent effects and possible biomechanical adaptations of the eye during and after prolonged space missions.

This study was conducted in collaboration with external organizations, which imposes certain limitations on our follow-up time and methods. Consequently, we have restricted access to additional data at this time, and we lack axial length measurements and specific imaging timepoints for some individuals. Despite these constraints, our conclusions remain relevant and possibly represent an advancement in the field.

IV. CONCLUSION

The findings from this study describe the impact of long-term space missions on the mechanical properties of ocular tissues. The reduction in OR highlights a decrease in scleral stiffness, which may be influenced by fluid shifts and changes in intracranial and ocular pressure during spaceflight. The decrease in OPA suggests alterations in ocular hemodynamics, which could be secondary to reduced scleral stiffness. These results suggest that microgravity induces notable biomechanical changes in the eye, potentially contributing to the pathophysiology of Spaceflight-Associated Neuro-ocular Syndrome (SANS).

V. MATERIALS AND METHODS

This prospective cohort study was designed with the objective of assessing ocular rigidity in a cohort of 13 crew members from 4 different missions.

Optical Coherence Tomography (OCT) images were obtained using a Heidelberg Spectralis OCT2 (Heidelberg Engineering, Heidelberg, Germany) with a customized video module allowing acquisitions at up to 85 Hz using Enhanced Depth Imaging Mode (EDI), and cardiac frequency was measured simultaneously.

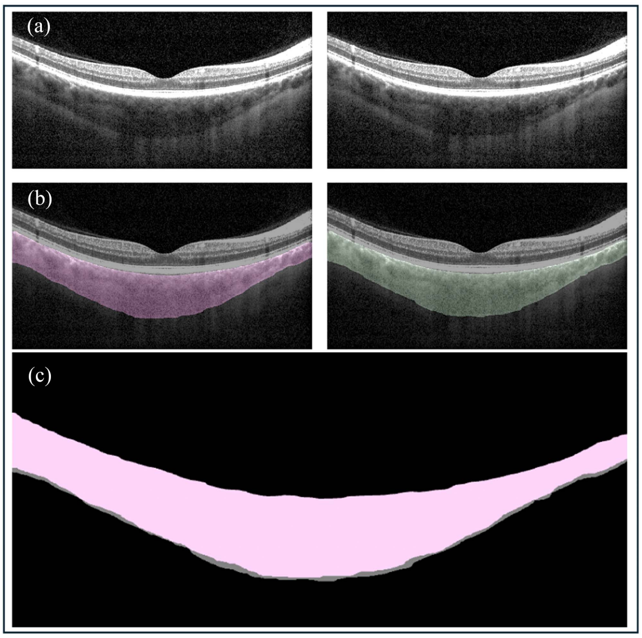

FIGURE 3. Choroidal thickness segmentation is computed in each one of the frames of the movie. The thickness variations are calculated to extract temporal differences in choroidal thickness. (a) Example of B-Scan in 2 different timepoints. (b) Automated choroidal segmentation. (c) Example of differences in choroidal thickness between two overlapping choroidal masks. The gray area corresponds the choroidal thickness difference between these 2 scans.

Each of the movie frames consisted of a B-scan centered at the macula with a 30-degree inclination to avoid including the optic nerve in the scan. The built in eye-tracking feature was used to ensure the same area is scanned in each frame as well as before and after the mission. During acquisitions, video recordings are automatically halted when the machine detects a change of the scanned area and resumes after repositioning.

Ocular pulse amplitude (OPA) (the variation of IOP between diastole and systole) and intraocular pressure (IOP) were obtained with a Pascal Dynamic Contour Tonometer (Ziemer, Switzerland).

A. OCULAR RIGIDITY CALCULATION

The estimation of OR assumes that pulsatile ocular volume changes are due mostly to variations of choroidal thickness. Thus, the choroid is segmented from each one of the 400 frames of an OCT time series acquired at 20 Hz, and the average distance between the retinal pigment epithelium (RPE) and the choroidal scleral interface (CSI) is computed per image for all the B-scan, over the entire scan width of 8.4 mm. The amplitude of temporal variations of choroidal thickness (CT) is measured (Fig. 3).

The quality of the segmentation was thoroughly evaluated by different metrics. Initially a manual segmentation was performed for 10 frames for each one of the movies. Afterwards, the absolute difference between manual and automated segmentation and the Dice and Jaccard similarity coefficients were computed. Similarity metrics showing a difference of 20% of above between manual and automated segmentation were defined as inaccurate.

Besides the described methods, given the small sample size of the data the quality of the segmentation was also visually assessed for each one of the subjects.

A model that considers the choroid volume within the ocular anatomy is used to estimate choroidal volume from single B-Scans at the macula. [12]

$$\Delta V \cong \frac{\pi}{2}(AL + CT)^2 \Delta CT \tag{2}$$

Where ΔV is the change in volume, AL is axial length, and ΔCT is the choroidal thickness change.

Pre- and post-flight OR changes are expressed as:

$$\frac{\Delta OR}{OR} = \frac{OR^{(\text{post })} - OR^{(pre)}}{OR^{(pre)}} \tag{3}$$

B. IMAGE PREPROCESSING

Automated choroid segmentation was achieved using convolutional neural network-based (CNN) models previously trained on a dataset composed of 42145 B-Scans from 151 movies. We used ResNet-101, U-Net encoder decoder combination where speckle noise was added to 30% of the image dataset for data augmentation. Both architectures were pretrained on the ImageNet database using mini-batch gradient descent, learning rate of 0.001, a batch size of 8 and cross entropy as the loss function. The model operates on 512x768 pixel images, and smaller images where linearly interpolated to match this size.

The Spectralis OCT data acquisition software assigns a quality metric value to each B-scan image. For analysis, all B-scans with a quality metric value beneath a threshold of 18 dB were discarded. Inference was performed iteratively on all remaining B-scans of every movie, yielding a two-classes probability map for each B-scan binarized using an argmax function.

For postprocessing, binary images were subject to morphological opening operations to minimize undesirable false positive regions. The identification of anterior and posterior choroid boundaries follows a series of steps when the segmentation leads to more than one object. Upper and lower boundaries are treated independently and in the same way: individual segments are connected to their closest neighbor with straight lines, the leftmost and rightmost pixel of its segment is connected horizontally with the edge of the image, and the shortest path is chosen as the final trace.

ETHICS STATEMENT

The Institutional Review Boards at NASA Johnson Space Center, the Canadian Space Agency (CSA), and the Maisonneuve Rosemont Hospital Research Center approved the protocol in accordance with the ethical requirements of the Declaration of Helsinki, and all participants provided written informed consent.

CONFLICT OF INTEREST

The authors have no conflict of interests related to this publication.

AUTHOR'S CONTRIBUTION

S.C and M.R.L achieved conceptualization, S.C, M.R.L and M.M.S methodology, R.D software, M.M.S experiment performance, S.C, M.R.L and M.M.S analysis and manuscript writing, S.C and M.R.L manuscript supervision, S.C and M.R.L resources. All authors reviewed and approved the content of the manuscript.

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