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# Intraocular Pressure during Spaceflight and Risk of Glaucomatous Damage in Prolonged Microgravity

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**Definition:** Microgravity introduces diverse pathological and various physiological changes to the human body, including intraocular pressure. Astronauts may develop a constellation of symptoms and signs including optic disc edema, choroidal folds, and a hyperopic shift from the flattening of the globe. These ocular findings have been collectively termed spaceflight-associated neuro-ocular syndrome (SANS). SANS is a condition that is unique to long-duration spaceflight. The precise pathogenesis of SANS remains ill-defined, but several hypotheses have been proposed that may be influenced by intraocular pressure. Countermeasures for SANS research also include techniques that impact intraocular pressure. In this article, we discuss intraocular pressure during spaceflight, the translaminar pressure gradient, SANS and potential SANS countermeasures, and the potential for glaucomatous damage during spaceflight.

**Keywords:** intraocular pressure; glaucoma; microgravity; space medicine



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## 1. Introduction

Astronauts during space flight and microgravity face a range of physiological and pathological challenges that include variations in intraocular pressure (IOP). Prior research has documented an initial elevation in IOP during space travel and thus it is a theoretic risk factor for the development of or progression of glaucoma [1]. Glaucoma is a very common terrestrial ocular disease defined by a degeneration of retinal ganglion cells, structural optic nerve damage, and subsequent functional reduction in the visual field [2]. In addition, astronauts after long-duration spaceflight may develop optic disc edema, choroidal folds, and a hyperopic shift from the flattening of the globe. These findings have collectively been termed SANS. The precise etiology of SANS is not completely understood; however, several proposed hypotheses include orbital and cephalad fluid shifts during microgravity. These potential mechanisms have implications for the possible role of IOP in the pathogenesis of SANS. The objective of this article is to investigate the relationship among alterations in IOP during space travel, the significance of the trans-laminar pressure gradient, the risk for development of or progression of glaucoma, and potential countermeasures.

## 2. Spaceflight-Associated Neuro-Ocular Syndrome

SANS is a unique constellation of neuro-ophthalmic findings observed in astronauts during and after long-duration space missions. SANS was first described by Mader et al. in 2011 [1,3], but extensive research since then has been conducted by the National Aeronautics and Space Administration (NASA) on SANS [4,5]. The exact cause of SANS remains ill-defined [6]; however, a growing body of evidence suggests multiple potential risk factors. Some proposed mechanisms underlying SANS include cephalad and orbital fluid shifts; increased intracranial pressure; venous and lymphatic stasis; genetic, inflammatory, and metabolic processes; axoplasmic stasis; and exposure to space radiation [3].

Crew members of NASA space shuttle missions revealed that IOP measurements were initially elevated during spaceflight, regardless of whether individuals had pre-flight glaucoma, ocular hypertension (OHT), or normal IOP [7,8]. These findings indicate that exposure to microgravity affects IOP regulation [7,8].

Existing data suggests that exposure to weightlessness leads to an immediate rise in IOP. However, following a few days of being in space, this increase eventually reverts to levels similar to those encountered on Earth. Astronauts engaged in extended ISS missions do not demonstrate a persistent elevation of IOP. However, it appears that a normalization of IOP occurs during spaceflight, despite the continued headwards displacement of venous fluid. A momentary state of weightlessness experienced during parabolic flight induces a brief period of approximately 20–30 s, during which there is an observed increase of approximately 7 mmHg in IOP [9]. In a comparable manner, following a period of 16 min of microgravity during the 8-day manned German Spacelab Mission, a significant increase of 92% in the IOP (4–7 mmHg) was found when compared to the baseline data on Earth [10]. The IOP readings conducted 15 min after the launch in the German MIR 10-day Spacelab D2 mission revealed an increase in IOP levels from the initial values of 10 mmHg (OD) and 10 mmHg (OS) to 23 mmHg (OD) and 22 mmHg (OS) within the first 24 h of the mission [11].

The changes in IOP during spaceflight are believed to result from various underlying mechanisms. In microgravity conditions, the normal hydrostatic pressure gradients in the body are altered and fluid distribution in the body changes [12]. Normal body fluid tends to redistribute towards the upper body and head during spaceflight and is commonly known as a 'cephalic' fluid shift [12]. This cephalad (and orbital) fluid redistribution can affect the IOP, and the cephalad fluid induces an elevation in both blood volume and intracranial pressure. The cephalad and orbital fluid shift is believed to be the cause of the radiographic and ultrasonographic findings of optic-nerve sheath distension and the flattening of the globe as well as the clinical and optical coherence tomography (OCT) findings of optic disc edema and choroidal folds [13,14]. Increased vascular pressure has been proposed as the cause for an initially increased IOP during spaceflight.

Furthermore, the altered fluid distribution can affect the fluid dynamics within the eye itself. The aqueous humor—a clear fluid that fills the anterior chamber (front part of the eye)—plays a crucial role in maintaining normal IOP [15,16]. The changes in fluid distribution may potentially disrupt the physiologic flow and drainage of the aqueous humor, which could lead to increased resistance to its outflow and a subsequent elevation of IOP [15,16]. The exact mechanisms by which fluid redistribution affects the aqueous humor dynamics and drainage pathways during spaceflight, however, are still under investigation.

The impact of an acute upward shift of fluid in the head on IOP has been extensively studied and demonstrated on Earth, with consistent findings [17–21]. Assuming a supine or head-down tilt (HDT) body position on Earth induces a cephalad fluid shift. Consequently, this fluid redistribution leads to an elevation in IOP [8]. Furthermore, there is a widespread view that the abrupt alteration in posture leads to a rise in episcleral venous pressure (EVP)—a phenomenon that has been quantified while in the supine position [22]. The increase in IOP can be significant, reaching approximately 40 mmHg in vertical head-down suspension, as reported in previous studies [23].

It is critical to note that the potential impact of fluid shifts on IOP is just one aspect of the ophthalmic changes observed in astronauts during long-duration space missions. Other key ocular findings among astronauts post-LDSF, such as globe flattening, choroidal folding, optic disc edema, and optic nerve kinking, have been reported that are unlikely to be related to IOP alone [1].

Greenwald et al. reported on the effects of lower-body negative pressure (LBNP) on IOP and choroidal thickness in crewmembers of the International Space Station (ISS). In this study, IOP was measured before and after LBNP during spaceflight. There was a reduction in IOP (compared to pre-flight measurements) when the individual was in a seated posture. The authors concluded that venous fluid redistribution by LBNP can influence IOP during spaceflight [24].

Elwy et al. conducted a comparable study investigating alterations in intracranial pressure (ICP) during spaceflight and simulated microgravity. Their findings suggest that exposure to microgravity induces an elevation in ICP, which may potentially contribute to ocular changes in SANS [25]. This study suggested that there was an increase in ICP that coincided with an elevation in IOP [25].

## 3. The Translaminar Pressure Gradient

The balance between IOP and ICP at the optic nerve head is known as the translaminar pressure gradient (TLPG). This TLPG may play a crucial role in the development of terrestrial glaucoma [26]. The optic nerve is encased by an optic nerve sheath, which contains cerebrospinal fluid within the subarachnoid space. The lamina cribosa is thus subject to both IOP and ICP [26]. Studies have highlighted the potential importance of TLPG in the pathophysiology of glaucoma, including NTG [26]. The TLPG represents the pressure difference between IOP and ICP, and it influences the pressure experienced by the retrolaminar tissues of the optic nerve [26]. The optic nerve head, particularly the lamina cribrosa, is a critical site of vulnerability in glaucoma [27]. The TLPG influences the biomechanical stresses on the lamina cribrosa and can affect its structural integrity [27].

In terrestrial glaucoma patients, it has been observed that the TLPG is higher compared to healthy subjects, and it is associated with structural glaucomatous changes of the optic disc [28]. These findings suggest that an imbalance in the TLPG can lead to increased stress on the optic nerve and the progression of glaucoma [28,29]. The relationship between ICP and retrolaminar tissue pressure, which affects the TLPG, is complex and can be influenced by various factors [30,31]. The size of the optic canal and the thickness of the lamina cribrosa are anatomical factors that can affect this TLPG relationship [32]. Additionally, diurnal and positional variations in TLPG, the effects of glaucoma medications, lymphatic outflow, and the role of ICP in maintaining cerebrospinal fluid flow in the optic nerve to prevent glaucomatous damage are additional potential important considerations:

1. Relationship between ICP and retrolaminar tissue pressure: Extensive research has been conducted on the correlation between ICP and glaucoma [30]. Low ICP has been found to be associated with glaucoma, but the relationship between ICP and retrolaminar tissue pressure is complex [30]. Factors such as the size of the optic canal, thickness of the lamina cribrosa (a sieve-like structure in the optic nerve), and lymphatic outflow from the optic nerve can affect this relationship [30]. The lymphatic system also plays a crucial role in fluid drainage and maintaining tissue homeostasis. Alterations in lymphatic outflow from the optic nerve can affect the distribution of fluids and pressure within the retrolaminar region, potentially influencing the optic nerve's health [30].
2. Diurnal and positional variation on TLPG: The TLPG can vary throughout the day and in different body positions. Changes in posture and intra-abdominal pressure can influence ICP and, consequently, the TLPG [33]. It is important to consider these variations in TLPG when studying the potential impact of long-duration spaceflight on glaucoma development or progression. The precise impact of the circadian rhythm of IOP on the progression of glaucoma is yet to be definitively established.

However, theories suggest the modulation of the TLPG as a contributing factor. Investigating the intricate interplay between circadian rhythms, fluctuations in IOP, and variations in TLPG holds the potential for gaining valuable insights into the development of preventive strategies aimed at preserving the optic nerve from progressive glaucomatous damage.

## 4. Increasing IOP as a Potential Mitigation Strategy for SANS

Goldmann applanation tonometry (GAT), which gently presses a small, flat-tipped cone against the cornea to measure the pressure required to flatten a corneal section, is how IOP is typically measured [34]. GAT is regarded as the norm and is renowned for its accuracy and reproducibility [34]. Non-contact tonometry and the use of a handheld tonometer are examples of alternative methods [35].

The use of eye goggles that can increase IOP been proposed as a potential mitigation strategy for SANS [36]. As there is a suspected decrease in the TLPG due to a mismatch between a larger increase in ICP than IOP, and goggles have been proposed to modulate and reverse this TLPG by increasing IOP. Scott et al. conducted a study that utilized swimming goggles to increase IOP in patients in a SANS analog. Terrestrial analogs are platforms that help to mimic certain physiological states on Earth for increased research accessibility [37,38]. The authors found that there was an increase in IOP and the TLPG with goggles during this SANS analog. The mean increase in IOP in those who wore goggles was 2.9 mmHg [39]. The authors suggested that the utilization of this IOP-increasing countermeasure may be an effective SANS countermeasure, although future research is necessary. As noted previously, the initial small increase in IOP could theoretically lead to the compression of the lamina cribrosa and potential retinal ganglion-cell axon damage, like glaucoma, in susceptible populations, but this theory remains unproven [39].

There are risks to increasing IOP however as a countermeasure for SANS. External compression by goggles could lead to damage at the lamina cribrosa (similar to terrestrial glaucoma). The application of external compression has the potential to hinder the circulation of blood and alter the biomechanical characteristics of the optic nerve head [40].

The impact of external compression on the optic nerve and its adjacent structures has been an area of concern. Prior to implementing interventions as countermeasures for SANS, it is imperative to thoroughly assess the potential risks and carefully evaluate the safety and efficacy of these interventions. Additional research and studies are required in order to gain a comprehensive understanding of the consequences of elevating IOP through external compression, as well as to formulate effective strategies for managing the potential risks associated with this method.

Paula et al. investigated the impact of wearing swimming goggles on IOP, ocular perfusion pressure (OPP), and ocular pulse amplitude (OPP), and found that swimming goggles resulted in a notable increase in IOP following a 2 minute duration and caused a disruption in the OPP and ocular hemodynamics, suggesting the need for extra caution when being applied for glaucoma patients [41]. Other studies also demonstrated an acute rise in IOP after wearing swimming goggles [42,43]. A Paula et al. investigation using swimming goggles (SG) found that IOP significantly increased after 2 min of use from 13.34 $\pm$ 2.67 to 23.46 $\pm$ 7.20 mm Hg [41]. Following removal, there was a notable decrease in IOP: 10.20 $\pm$ 5.85 mm Hg [41]. A similar investigation found IOP measurements, recorded prior to, during, and following the use of SG, of 11.88 +/$-$ 2.82 mmHg, 14.20 +/$-$ 2.81 mmHg, and 11.78 +/$-$ 2.89 mmHg, respectively [42], which is similar to an average of a 4.5 mmHg rise in IOP reported [44].

On Earth, negative-pressure goggles have been studied for their potential to regulate IOP and its impact on the optic nerve and retinal structures [36]. Negative-pressure goggles create a slight vacuum around the eyes, which can help reduce IOP [36]. Negative-pressure goggles (like lower-body negative-pressure devices) can counteract the potential increase in IOP when transitioning from microgravity to Earth's gravity (g) [36]. This g-transition can cause fluid redistribution in the body, including the eyes, and result in elevated IOP [36].

Samuelson et al. reported on 10 individuals with open-angle glaucoma who wore negative-pressure goggles (NPGs). This study showed that NPGs were safe, could deliver treatment over an extended period of time, and were well-tolerated [45]. A pressure of −10 mm Hg was administered to one eye, while the contralateral eye was subjected to surrounding atmospheric pressure, over a duration of 8 h [45]. The mean tolerability score was $1.8 \pm 0.4$ on a scale where 1 and 10 represent the best and worst results, respectively [45]. Additionally, there was a positive interest response with a mean score of $1.8 \pm 0.5$ on the same scale [45]. The utilization of multi-pressure dial (MPD) goggles to apply negative pressure to the periorbital region has been observed to lead to a decrease in IOP in another investigation [46]. The IOP-lowering effect is mediated by alterations in globe volume, blood volume within the eye, and a reduction in episcleral venous pressure [46]. The collective impacts described above have the potential to be therapeutically significant in the management of glaucoma and in space medicine; however, further studies are required [46].

The difference between changes in translaminar pressure gradient caused by swimming goggles and the impact of microgravity experienced during spaceflight is apparent. The use of swimming goggles has been found to cause a brief rise in intraocular pressure and translaminar pressure gradient as a result of the pressure exerted on the eyes [39]. Similarly, exposure to microgravity during spaceflight has been observed to induce alterations in the eye–brain axis and intracranial pressure [33,47,48]. Both situations present ocular concerns, as increased intraocular pressure may potentially increase the risk of glaucoma in both swimming goggles and microgravity environments [38,47]. The mechanisms and long-term effects, nevertheless, reveal variations as a consequence of unique physiological conditions [12,38].

Swimming goggles, negative-pressure goggles, and multi-pressure dial goggles exhibit unique mechanisms of action. Swimming goggles create an impermeable barrier around the ocular region, effectively inhibiting the entry of water and minimizing any potential discomfort. There is evidence indicating that swimming goggles may cause a brief spike in IOP, which is of importance for individuals who suffer from glaucoma [44]. negative-pressure goggles (NPGs) employ negative periocular pressure as a means of reducing IOP in a non-pharmacological and non-invasive manner [46]. NPGs are designed to generate a mild vacuum in the surrounding area of the ocular region, with the objective of reducing IOP which is significant for managing glaucoma [46]. Multi-pressure dial goggles are equipped with a pressure-modulating mechanism that is incorporated into their design [45]. The administration of negative periocular pressure (NPP) in conjunction with the reduction in IOP has the potential to control IOP and glaucoma [45].

The majority of physical activities, including yoga and various other forms of exercise, provide a multitude of health benefits encompassing enhanced muscular strength, endurance, mental well-being, and the regulation of blood pressure [49]. Physical activities with dynamic movements, such as weightlifting, vigorous cardio exercises, and high-impact activities, have the potential to cause elevated IOP and ICP as a result of the exertion and stress imposed on the body [50]. For example, studies have demonstrated that handgrip exercises can increase IOP [51]. The increase in pressure might result in implications for individuals with glaucoma and other neurological disorders. On the other hand, other investigations carried out demonstrated an acute drop in IOP among healthy and glaucoma patients following exercise [52,53]. Furthermore, a recent study conducted by Scott et al. revealed that engaging in physical exercise resulted in reductions in both IOP and the estimated translaminar pressure gradient [39]. This implies that engaging in physical activity may play a role in preserving optimal ocular parameters under challenging conditions such as microgravity [39].

Exercise offers a multitude of health advantages; however, it is crucial to acknowledge its potential influence on pressure-related ocular diseases, particularly for individuals with pre-existing ocular or neurological conditions. In the context of spaceflight, the impact of exercise on IOP and ICP in microgravity is currently being investigated. The effects

of exercise on these pressures and their corresponding health implications are yet to be fully elucidated.

Achieving an optimal balance between maximizing the health benefits of physical activity and protecting one's general well-being and safety is of paramount significance, especially in spaceflight conditions where diagnostic and therapeutic resources tend to be more limited.

## 5. Potential Development of Glaucoma in Astronauts during Spaceflight

As noted previously, the initial elevation of IOP during spaceflight raised concerns about the development of glaucoma among astronauts. Terrestrial glaucoma is a multifactorial disease, and elevated IOP is a well-established risk factor [2]. Potential mechanisms contributing to elevated IOP in space include headward fluid shift, choroidal volume expansion, increased ciliary body perfusion, and increased episcleral venous pressure [54,55]. The utilization of the head-down tilt position serves as an analogous model for spaceflight, as it effectively replicates the physiological impacts of microgravity on the human body [37,56]. The technique of extended head-down tilt bed rest (HDBR) exposes participants to headward fluid shifts, which are comparable to the fluid shifts experienced in space [37,56]. This exposure results in changes in fluid distribution, alterations in cardiovascular function, and an increased risk of physiological alterations, and thus, HDBR enables researchers to explore potential health conditions that may occur during space travel, such as SANS [57,58]. Furthermore, investigations leveraging the head-down tilt model provide valuable insights into ocular changes, blood vessel responses, and general adaptations, hence augmenting our comprehension of the effects of space travel on human health [17,57].

Wei Chen et al. measured alterations in IOP during terrestrial head-down tilt testing [32]. In this study, 21 participants had a statistically significant rise in IOP after assuming a head-down position of 20 degrees, as well as a reduction in the cross-sectional area of Schlemm's canal after a 15 min head-down tilt (HDT) test [32]. The investigation also documented alterations in heart rate variability, indicating autonomic nervous system (ANS) stimulation during head-down tilt [32]. These findings suggest that the increase in IOP and ANS stimulation during HDT may contribute to structural changes in the Schlemm's canal lumen [32].

The assessment of glaucoma risk in relation to the fluctuation of IOP during spaceflight and subsequent return to baseline involves a comprehensive evaluation that considers both the temporary alterations in IOP and the individual's pre-existing risk factors for the development of glaucoma [31]. Initially, it is imperative to evaluate the patient's baseline IOP, optic nerve head morphology, visual field condition, and other pertinent risk factors, including familial medical history, age, and systemic health conditions.

Frequent monitoring of IOP is of utmost importance. It is vital to carefully monitor not only the IOP level alone but also its historical variations. Research findings suggest that the long-term fluctuation of IOP may pose a potential risk for the progression of glaucoma. In addition, regular examination of the optic nerve head and RNFL using techniques such as OCT is vital to monitor the progression of glaucoma.

### *5.1. Mechanical and Structural Findings in SANS*

Mechanical Factors

In microgravity, the normal pressure gradients within the eye are disrupted, leading to alterations in fluid dynamics and drainage. The absence of g-induced fluid movement could hinder the effective circulation of aqueous humor, potentially leading to elevated IOP [12]. Additionally, changes in the shape and volume of the eye, such as globe flattening and optic disc edema, have been observed in astronauts, which may contribute to the development of glaucoma [12]. On Earth, low (rather than high) IOP can result in hypotony-induced choroidal folds and optic disc edema.

### *5.2. Vascular Factors*

Microgravity can affect vascular regulation and blood flow within the eye. Disruption of blood flow to the optic nerve and retina may lead to ischemic damage and contribute to the pathogenesis of glaucoma [8]. The potential role of vascular congestion in the choroid with secondary choroidal and retinal folds as well as focal areas of the retinal ischemia (cotton wool patch) in astronauts [8,59] remains unproven.

The distinct circumstances of microgravity have a disruptive effect on the regular regulation of IOP and ocular blood flow, which may result in an elevated susceptibility to glaucoma. Ongoing research to investigate various areas of how microgravity affects the ophthalmic system will hopefully elucidate the underlying mechanisms for SANS in space [60,61].

## 6. Conclusions

In conclusion, the relationship between IOP and the development and progression of glaucoma, specifically in the context of space travel and microgravity, is complex and multifaceted. Existing research suggests that exposure to microgravity results in an initial increase in IOP, which subsequently returns to normal levels over the course of long-duration space missions. The deep comprehension of the specific mechanisms responsible for the alterations in IOP during space travel remains incomplete.

The TLPG is a significant factor in the pathogenesis of glaucoma. An elevated IOP is linked to the presence of structural glaucomatous alterations in the optic disc among individuals diagnosed with terrestrial glaucoma. The TLPG has an impact on the biomechanical strains experienced by the lamina cribrosa, which is a crucial area of susceptibility in individuals with glaucoma. Additional factors to consider in comprehending TLPG include diurnal and positional variations, the impact of glaucoma medications, lymphatic outflow, and the role of ICP in sustaining cerebrospinal fluid flow within the optic nerve.

There is growing concern regarding the potential occurrence of glaucoma among astronauts during space missions. Although an association between elevated IOP and glaucoma on Earth has been firmly established, there is still uncertainty regarding whether the initial increase in IOP experienced during space travel contributes to an increased risk of glaucoma development among astronauts. The potential development of glaucoma may be influenced by various mechanical and vascular factors in microgravity, such as changes in fluid dynamics, blood flow, and modifications in the shape and volume of the eye.

One proposed mitigation strategy for SANS involves the utilization of eye goggles to elevate IOP. Nevertheless, the elevation of IOP carries inherent hazards, such as the possibility of detrimental effects on the optic nerve and retinal structures. Therefore, additional investigation is required to examine the efficacy and safety of these countermeasures.

Additional research is required to provide a comprehensive understanding of the fundamental mechanisms involved, devise efficacious strategies to mitigate the effects, and investigate alternative methodologies for promoting neuroprotection and neuroregeneration in individuals affected by glaucoma. These technological advancements will not only yield benefits for astronauts but also make significant contributions to the comprehension and management of glaucoma within terrestrial and microgravity contexts.

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