Intraocular Pressure Considerations

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What Is Spaceflight-Associated Neuro-ocular Syndrome (SANS)?

The ability to see well is critical to the performance of all astronauts during spaceflight. The phenomenon of transient or persistent vision impairment in astronauts during space flight or following return to Earth has been recognized as a health risk that needs close attention [1]. This condition, coined as spaceflight-associated neuro-ocular syndrome (SANS) [2], consists of a cluster of pathological findings on eye examination including optic disc edema, retinal thickening around the optic disc, choroidal folds, retinal folds, and cotton wool spots [3]. A hyperopic shift is also observed [3]. To understand SANS, research programs have recently engaged in systematic ocular imaging studies to characterize and quantify changes in the eyes of astronauts. Optical coherence tomography (OCT) images show significant peripapillary retinal thickness increase and optic disc changes after spaceflight [4]. Recent studies reveal that retinal and choroidal changes in the eye occur early during spaceflight, persist throughout the mission, and require 45–90 days after returning to Earth to recover to preflight levels [5]. Furthermore, post-mission reductions in axial length of the eye and decreased anterior chamber depth have been noted and are likely to be associated with the observed hyperopic shift [5].

Fluid Shifts and SANS

Although the exact etiology of SANS is not yet known, microgravity-associated headward shift of intra- and extravascular fluids are implicated in this condition [6]. Optic disc edema is likely due to excessive interstitial fluid accumulation in the optic nerve head. Possible sources of this excess fluid include leaking capillaries of the optic nerve head [7, 8], and the peripapillary choroid [9] as they lack an effective blood–tissue barrier. Additional possible sources of fluid entry into the optic nerve head may be cerebrospinal fluid entry via optic nerve perivascular glymphatics [10]. The spread of excessive water from the optic disc into the surrounding retina may contribute to an increase in peripapillary retina thickness (Fig. 7.1). Other possible origins of excessive water entry into the peripapillary retina include the blood circulation via altered blood–retina barrier integrity [11], the vitreous via Muller cell aquaporin-4 [12], and the peripapillary choroid. The intraocular pressure (IOP) and the cerebrospinal fluid pressure (CSFp) would both be expected to influence the inner nerve fiber layer, the prelaminar and laminar parts of the optic nerve. We believe that fluid drained from the aqueous humor (AH) across neighboring vitreous [9, 13], and exiting across the retinal pigment epithelium [14, 15] to the richly vascularized choroid, may contribute to the retinal and choroidal

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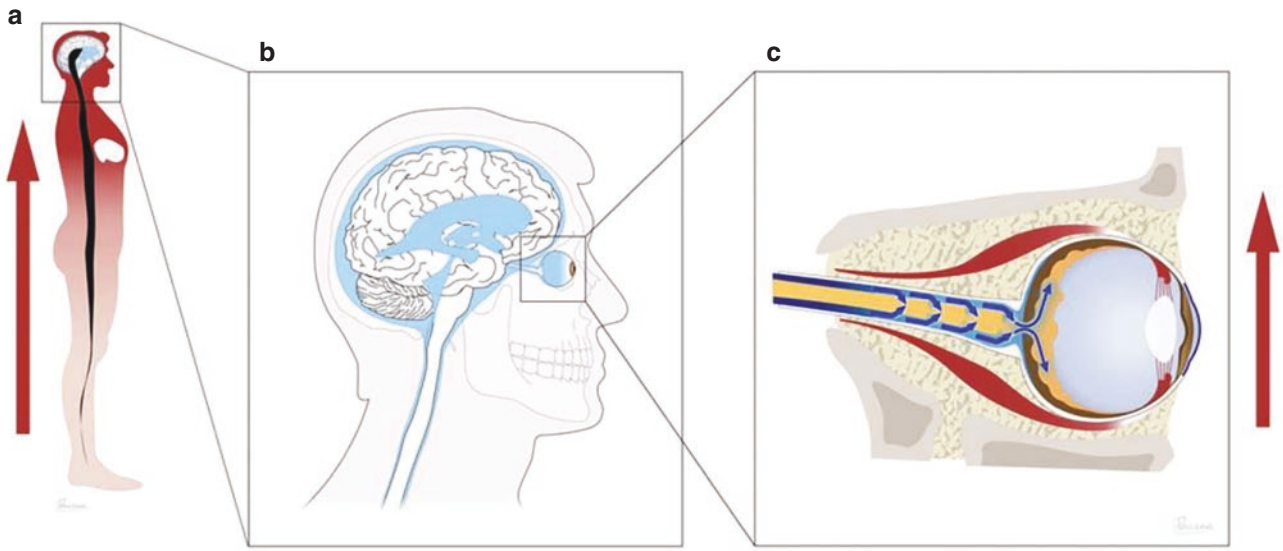

Fig. 7.1 The headward shift of fluid under microgravity conditions (**a**) moves cerebrospinal fluid (**b**) (blue) from the subarachnoid space around the optic nerve into the optic nerve head and retina (orange) and choroid (brown) via the glymphatic pathway (**c**) (blue arrows). The red arrows indicate the headward shift of fluid

changes. In addition to local hydrostatic pressure changes, this flow of fluid entry from the vitreous to the retina may be facilitated by a rise in oncotic pressure induced by plasma volume drops of 10%–15% while in flight [16].

Intraocular Pressure and SANS

Intraocular pressure (IOP) is a critical parameter to ocular function in health and disease states. It is a major risk factor for glaucoma, the leading cause of preventable irreversible vision loss projected to affect 111.8 million people by 2040 [17]. All treatments aim to lower IOP using a variety of pharmacological agents. The Ocular Hypertension Treatment Study showed that the incidence of glaucomatous damage increases with IOP [18]. Age greater than 40 years is also a risk factor for the development of both ocular hypertension and primary open-angle glaucoma, along with others such as myopia, ethnicity, and family history. Like any adult, it is recommended that all astronauts have regular eye examinations including IOP measurements and optic disc examination during and between spaceflights and post-retirement. Spaceflight-associated conditions including cardiovascular changes due to microgravity, hypercapnia, and low-grade radiation may be associated with IOP and glaucoma-like changes, and they should be taken into account with the above-listed risk factors. A critical review of the evidence regarding the role of IOP in the development of SANS is timely as private space companies (e.g., SpaceX, Blue Origin) aim to increase accessibility to spaceflight for civilian populations [19–21] with demographic and health characteristics that are different from those of astronauts.

The shape of the outer corneal-scleral shell is maintained by IOP which is finely regulated to prevent ocular hypertension and hypotony and vision-threatening conditions that arise due to swings in eye pressure. The light path to the retina depends upon optical characteristics of the cornea, AH, pupil, lens, and vitreous, all of which are also highly dependent on the IOP. The light-sensitive retina sits on the choroid, a pigmented and highly vascularized layer, supported by the underlying sclera which is an opaque and fibrous outer layer. Their shape and integrity also depend upon IOP. Various parameters such as the axial length between the cornea and retina, in addition to anterior chamber depth, can be altered during disturbances of globe shape. As IOP depends on both ocular hydrodynamics and hemodynamics, its measurements can inform us about both of these highly regulated systems. Although changes in IOP are not included in the definition of SANS, IOP and its hydro- and hemodynamics-determinants are fundamentally relevant to our understanding and prevention of this sight-threatening condition. Here we will review and tie together observations of IOP changes during and after spaceflight, discuss methods to measure IOP, and re-iterate the role of IOP as a physiological parameter that should be monitored as part of eye changes in SANS. This approach will guide studies on the efficacy and safety of SANS countermeasures.

IOP Conceptual Model: Ocular Pressure–Volume

Several conceptual models can contribute to our understanding of IOP. In the ocular pressure–volume model, IOP is an exponential function of the total ocular volume (Vt) and the elasticity (*E*) of the corneal-scleral shell (IOP = (Vt, *E*))—the theoretical basis for indentation tonometry and tonography [22]. Another model treats steady-state IOP as a function of aqueous flow (*F*), outflow conductance (*C*), or "facility" and episcleral vein pressure (EVP) [23]. This model (IOP = *F*/*C* + EVP) is the theoretical basis for understanding ocular hypertension and hypotony as well as current medical and surgical treatment to lower IOP to treat glaucoma. Both models provide insight into IOP physiology [24].

Aqueous humor and vitreous fluid, and uveal blood, especially choroidal blood are the main compartments generating IOP in "normal gravity" or 1g conditions (Fig. 7.2).

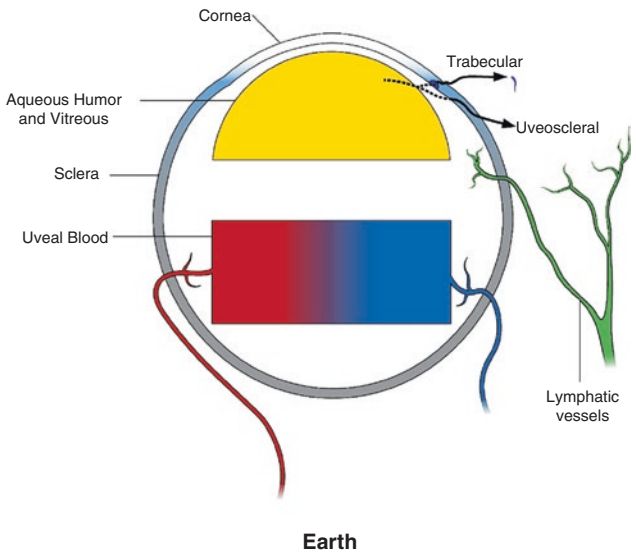

Fig. 7.2 Schematic of ocular hemodynamic and aqueous humor and vitreous fluid compartments generating IOP. Extraocular and intraocular arteries are represented in red, with extraocular and intraocular veins in blue. The uveal (ciliary body and choroid) blood compartment is represented by a red/blue rectangle. The combined aqueous humor and vitreous fluid compartment is represented in yellow. Trabecular and uveoscleral outflow pathways from the anterior chamber are indicated by black arrows. Trabecular outflow drains into episcleral veins (small blue). Lymphatic vessels in green drain fluid from the intraocular and extraocular interstitial tissue (white background). Figure adapted from Kiel et al. (2010) [24] and Watenpaugh and Hargens (1996) [25]

Aqueous Humor Dynamics and Regulation of IOP (Fig. 7.2)

AH hydrodynamics determine the quality of AH, its chemical composition, electrolyte balance, and pH. Circulating AH supplies oxygen and nutrients to the avascular tissues of the anterior segment such as the cornea, trabecular meshwork, and lens and subsequently removes metabolic waste products. Although difficult to measure with currently available techniques, some AH drains into the vitreous cavity [26] and provides regular water content to the vitreous. Compared to the plasma, the aqueous has a low protein level (about 0.02 g/ml compared to 7 g/ml) [27]. Briefly, AH secreted by the ciliary epithelium into the posterior chamber (also called AH inflow), passes between the anterior surface of the lens and posterior surface of the iris into the anterior chamber. The AH drains from the anterior chamber through several routes (also called AH outflow) [26, 28]. AH flows out of the eye either through the trabecular meshwork, eventually reaching the systemic blood circulation via the episcleral veins [29–31], or through the ciliary body into suprachoroidal spaces, and sclera via the uveoscleral route [32]. A growing body of evidence shows drainage of AH from the eye also via lymphatics [33, 34], with lymphatic channels in the human ciliary body identified using molecular markers [33]. Methods to measure the AH dynamics parameters including aqueous production, trabecular outflow, EVP, uveoscleral outflow [26], and lymphatic drainage [34] are available. The development of novel dynamic non-invasive techniques to assess specific outflow pathways to determine the drivers of intraocular pressure and their relative contributions will guide individualized care.

All currently used IOP-lowering glaucoma eye drops target aqueous inflow and/or outflow pathways. Common IOP-lowering pharmacological agents either reduce aqueous inflow by action on beta-adrenergic receptors and carbonic anhydrase inhibitors or increase outflow via their action on α_2-adrenergic receptors of the autonomic sympathetic system, prostaglandin $F_{2\alpha}$ receptors, and inhibition of Rho kinase [35].

Some aqueous outflow structures such as the trabecular meshwork, canal of Schlemm and episcleral vein; in addition to playing a filtering role, participate in cardiac-induced pulsatile aqueous outflow mechanisms with systolic expansion of the choroid [31]. Thickening of the choroid during spaceflight may cause reduced cardiac pulsatility-induced AH outflow, in addition to IOP increase due to increased volume effect.

Unlike increased IOP, low pressure in the eye known as ocular hypotony, especially after long-term or multiple missions has often been overlooked as a potential risk factor. Although the clinical signs and symptoms of ocular hypotony are usually reversible in acute and transient stages, chronically decreased IOP can have deleterious effects on intraocular tissue morphology and function [36–38]. An imbalance of aqueous production and outflow (trabecular, uveoscleral) after return to Earth after a long-duration mission may contribute to alterations of aqueous flow dynamics. These may be associated with compromised oxygen supply, nutrition, and metabolic exchange within the anterior chamber, and water content to vitreous, leading to ocular hypotony with complications of retinal [39] and choroidal folds, detachment [37, 40–42], and posterior pole and scleral flattening [43]. Close follow-up of IOP is required after landing to rule out prolonged ocular hypotension. Unfortunately, treatment options to manage ocular hypotony are limited.

IOP in Relation to Ocular Volume

If corneal-scleral elasticity is constant, acute changes in IOP must involve changes in ocular volume. AH and ocular blood volume changes are the most labile and are responsible for the greater part of IOP variation (Fig. 7.3). Uveal blood, especially choroidal blood and aqueous humor and vitreous fluid are the main compartments generating IOP in 1 G conditions (Fig. 7.3a). In this model, we have combined aqueous humor with vitreous given that the AH provides water content to the vitreous body [26]. In early microgravity, due to a headward shift of fluid, the volume of intraocular blood increases, leading to IOP elevation (Fig. 7.3b). During adaptation to microgravity, aqueous humor volume decreases with normalization of IOP (Fig. 7.3c).

During early space flight under microgravity conditions, there is an increase in uveal volume (ciliary and choroid) induced by congested blood vessels (Fig. 7.3b). There is also increased aqueous production and decreased trabecular outflow due to elevated EVP. Reduced uveoscleral outflow and lymphatic drainage would contribute to elevated IOP. Aqueous volume changes may occur with transient imbalances in aqueous production and outflow. Similarly, ocular blood volume changes may occur with blood flow imbalance into and out of the eye, especially at the level of the choroid [44], as evidenced by increased choroidal thickness observed in astronauts during spaceflight [5].

A decrease in aqueous production, with simultaneous increases in trabecular, uveoscleral and lymphatic drainage, would reduce aqueous and vitreous volume allowing a return to baseline IOP.

In early landing, uveal blood (Fig. 7.4a) volume decreases compared to adapted microgravity (Fig. 7.4b) with an IOP decrease. In late landing, the aqueous humor/vitreous volume is restituted with normalization of IOP (Fig. 7.4c). In landing, a decrease in volume of the uvea (ciliary and choroid), relative increase in trabecular outflow due to decreased EPV, and increased uveoscleral outflow with lymphatic flow would contribute to IOP lowering. A delayed increase in aqueous production with decreases in trabecular outflow, uveoscleral outflow and lymphatic flow would contribute to a return to baseline IOP. For individualized countermeasures and treatment, it would be critical to monitor specific components of AH dynamics and ocular hemodynamics.

Neurohumoral and local control mechanisms involved in the regulation of the resistance at the level of ciliary and choroidal vasculature are not fully understood. Autoregulatory myogenic [45] and autonomic neural mechanisms [46, 47] regulate ocular blood volume during changes in arterial pres-

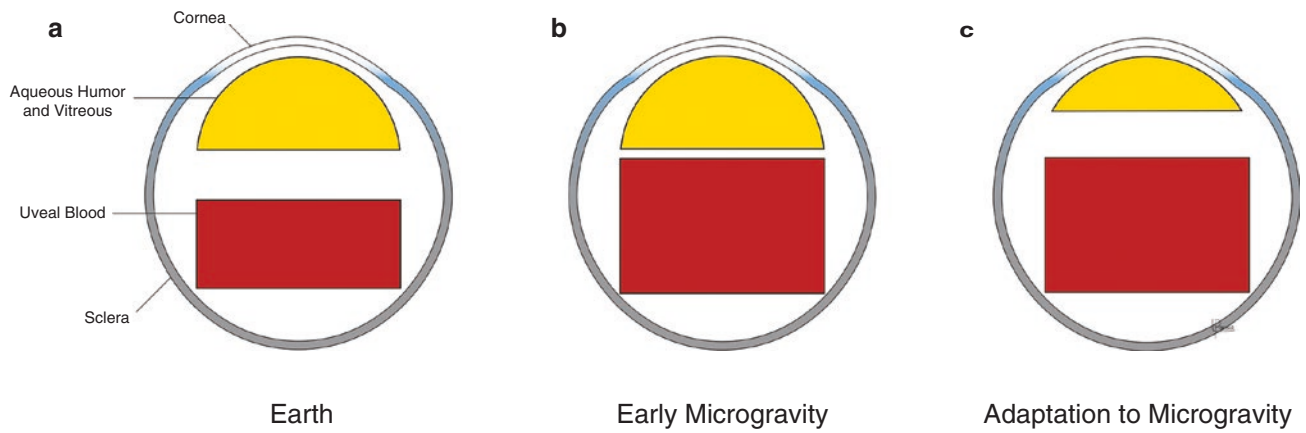

Fig. 7.3 Schematic of main ocular compartments generating IOP in Earth, Early in Space, and Adaptation in Space. Uveal blood, especially uveal blood (red), and aqueous humor and vitreous fluid (yellow) of the eye in 1g conditions. During early spaceflight under microgravity conditions, the volume of uveal blood increases due to a headward fluid shift. While in space, adaptation involves a decrease in aqueous humor/vitreous volume

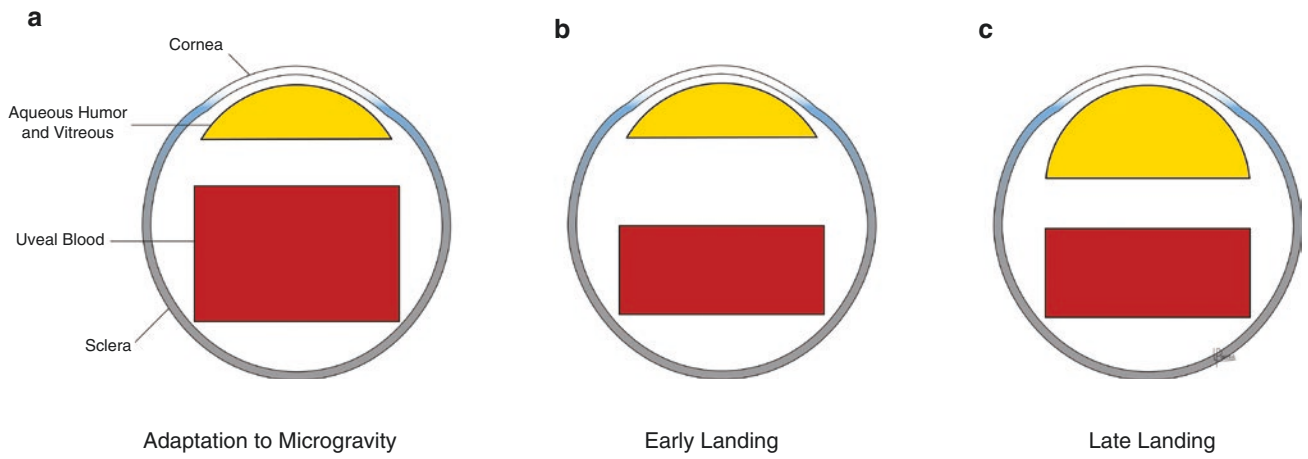

Fig. 7.4 Ocular compartments in transition to landing: Uveal blood (red), and aqueous humor and vitreous fluid (yellow) of the eye in adapted in space. In early landing the uveal blood component volume decreases. In late landing, the aqueous humor/vitreous volume increases

sure [45]. While increases in arterial pressure produce initial increases in IOP (Fig. 7.3b), this IOP elevation is not sustained. Instead, early elevated IOP increases the pressure gradient for aqueous outflow, causing a compensatory decrease of aqueous and vitreous volume so that IOP gradually returns to baseline (Fig. 7.3c) [45]. If the increase in blood volume is small, the compensation is relatively quick, whereas compensation for a larger increase in blood volume, takes longer. IOP falls below baseline when arterial pressure-induced distention of the vasculature is abruptly ended in early landing (Fig. 7.4b). This reflects a compensatory loss of aqueous and vitreous volume, which is gradually restored by continued aqueous production, until a return to baseline IOP (Fig. 7.4c). Raising arterial pressure elicits a modest increase in IOP under control conditions. A much larger increase is elicited when choroidal blood volume regulation is impaired by systemic vasodilation by pharmacological tools [45], by altered autoregulatory myogenic [45], autonomic neural mechanisms [46, 47], and neuro- and cardioendocrine mechanisms. Thus, ocular blood volume changes are strong influencers of IOP. Ocular blood volume changes are compensated by corresponding changes in AH and vitreous volumes which contribute to the IOP regulation.

IOP and Postural Changes

Postural changes are known to affect IOP with significant increases in IOP from the upright or sitting position to the supine position [48–50]. IOP has been shown to increase by 3–4 mmHg in normal subjects when lying supine, regardless of the time of the day [51, 52]. EVP is the only component of AH dynamics that is affected by body position, increasing by 3.6 mmHg from the seated to supine position. Mean IOP and mean EVP increase significantly from the sitting to the inclined position [53]. In contrast, the rate of AH formation is stable while subjects are alternated between an upright and inverted body position [54]. No changes to outflow facility are noted between sitting and supine positions [55].

IOP and Ocular Perfusion Pressure

Ocular perfusion pressure (OPP), calculated by the mean arterial pressure (MAP) minus the IOP [56], is an important parameter to assess tissue perfusion. To avoid the collapse of intraocular veins, IOP should remain below venous pressure within the eye. If IOP is higher than MAP, the perfusion of tissues fed by intraocular arteries will be reduced. Blood flow to the inner retina and optic nerve head by branches of the central retinal artery is mainly modulated by local autoregulation according to local metabolic demands as in other parts of the central nervous system. The outer and avascular portions of the retina receive nutrients and oxygen via diffusion from the choroidal blood vessels that do not receive feedback signals from the retina. The sympathetic and parasympathetic components of the autonomic nervous system substantially influence numerous ocular functions including ocular blood flow [47]. As postural IOP changes are larger in patients with autonomic failure compared with normal subjects [57], suggesting that the autonomic nervous system plays an important role in regulating IOP during postural changes. Continuous and simultaneous measurements of IOP and local mean arterial pressure (MAP) would be opti-

mal to monitor OPP during postural changes over time, during day and night cycles, and in microgravity conditions.

IOP, CSFp, and Translaminar Pressure Difference (TLPD)

Under normal physiologic conditions, the TLPD, the difference between IOP and the retrolaminar CSF, generates both a net posterior force on the surface of the LC and a hydrostatic pressure gradient within the prelaminar and laminar optic nerve. In glaucoma, pathology occurs at the level of the LC [58], and the TLPD has been proposed to be involved in its pathogenesis [59]. In addition, TLPD may be involved in conditions in which edema of the optic disc is prominent as in idiopathic intracranial hypertension, and obstructive hydrocephalus [60]. In vivo measurement of pressure directly around the LC is currently not feasible, proxies of the pressure in regions anterior and posterior to the LC, are IOP measured at the cornea and CSFp measured by lumbar puncture (LP), respectively. A limitation of these proxies to calculate TLPD is the difference in body position at which the measurements are taken. For example, Goldmann applanation tonometry is commonly carried out in the seated position while LP is performed in the lateral decubitus position. As both IOP and CSFp change with posture, measuring them in different conditions to calculate TLPD is problematic. TLPD in healthy controls is 1.4 mmHg when measuring IOP in the sitting position and the CSFp via LP in the lateral decubitus position [61]. However, a recent study in healthy subjects demonstrates that both CSFp and IOP change during postural changes. TLPD differences of 19.8 mmHg while seated, 12.3 mmHg while supine, and 6.6 mmHg while in the 9° head-down tilt position have been shown [62]. A limitation of this estimation is the assumption that CSFp at the lumbar level is similar to CSFp at the perioptic subarachnoid space. In addition, TLPD depends on LC thickness and its reduction in highly myopic eyes may be the histologic correlate of increased susceptibility to pressure-induced injury [63].

Continuous, simultaneous, and direct measurements of IOP and CSFp in nonhuman primates have shown that TLPD changes significantly and instantaneously from the supine to seated (+14 mmHg), supine to standing (+13 mmHg), and supine to inverted (−12 mmHg) positions. No significant TLPD change from the supine to prone positions is noted. CSFp showed greater relative change than IOP [64]. The 56% increase in TLPD during waking hours in nonhuman primates [65] was reported to match the increase in TLPD due to postural change from supine to upright in humans [62].

Orbital Pressure and IOP

The orbital soft tissue surrounding the globe is confined by the bony orbital socket and semi-rigid fascia-like tissue of the eyelid anteriorly. Most orbital blood vessels are tributaries of intracranial blood vessels, and are in direct contact with ocular blood vessels, and share similar autonomic control [66, 67]. They are also connected to extracranial blood vessels via anastomoses [68].

Orbital conditions including vascular malformation such as Sturge-Weber syndrome, orbital tumors, and endocrine orbitopathy can cause congestion of the orbital veins and a subsequent rise in EPV [69]. Large vessel venous obstruction (superior vena cava syndrome), cavernous sinus thrombosis, and carotid cavernous sinus fistulas can cause an increase in superior ophthalmic vein pressure and a rise in EVP [70]. Sturge–Weber syndrome in older children and young adults with port-wine stains (hemangiomas) on the face near the eye can include intrascleral or episcleral anastomoses that increase EVP [71] and in turn, IOP [72, 73]. Some of these conditions may also be associated with increased choroidal thickness [74–76]. Further volumetric imaging studies of the orbital tissue components, intra- and extravascular fluids in and around the globe, and CNS, are needed to understand changes in SANS [77]. Lymphatics in the orbit [78] are implicated in the drainage of fluid from the orbit and contribute to lymphatic drainage from the eye [35] and perioptic subarachnoid space [79] (Fig. 7.5).

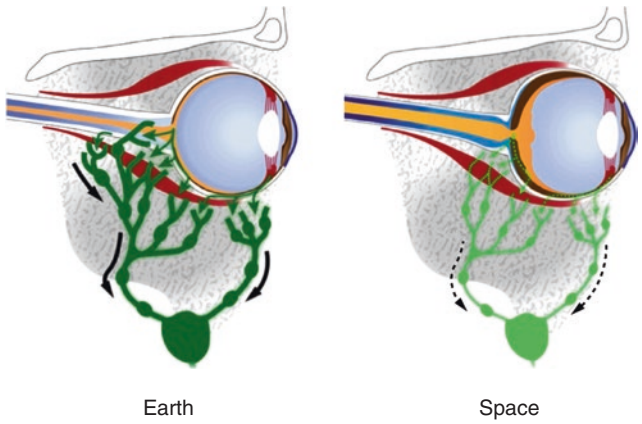

Fig. 7.5 Schematic of the globe and orbit with lymphatics draining excess fluid into regional lymph nodes (green) on Earth (left) and in space (right). Under microgravity conditions in space, lymphatic drainage from the optic nerve and the eye is reduced with fluid accumulation in the optic nerve and retina (orange), and choroid (brown). Extraocular muscles and orbital soft tissue are presented in red and gray, respectively. Black arrows represent lymphatic flow. The black arrow with dotted line represents decreased lymphatic flow in microgravity. The orbital bony socket is represented in white superiorly

Autonomic and Central Regulation of IOP

The autonomic nervous system (ANS) serves as an important interface between body, central nervous system (CNS), and external stimuli [80–82]. The ANS sympathetic noradrenergic system (SNS), parasympathetic cholinergic system (PCS), and sympathetic adrenergic system (SAS) together control visceral functions to maintain homeostasis. The SNS and PCS play key roles in regulating optimal cardiovascular function to maintain the physiological state of astronauts despite the stressors of spaceflight [83]. The role of the autonomic system in the regulation of IOP is complex, acting on both AH dynamics and ocular hemodynamics. Evidence for autonomic sympathetic and parasympathetic innervation of the anterior episcleral circulation comes from histological studies in primates [84] of trabecular meshwork and scleral spur [85]. In rodents, electrical stimulation of the superior salivatory nucleus elicits an increase in IOP and EVP [86] and choroidal vasodilation [87]. Changes in choroidal thickness due to vascular congestion during the flight [5] may contribute to altered thermal environment in the central retina [88, 89], especially when central body temperature is increased during spaceflight [90]. The action of topical adrenaline or epinephrine on the IOP, aqueous humor dynamics and ocular hemodynamics has been studied [91–94], however the role of adrenaline as a neurohormone of the sympathetic adrenergic system on the eye's physiology is not well elucidated.

Both sympathetic and parasympathetic systems are involved in the regulation of the systemic lymphatic system [95], implicating them in lymphatic drainage from the eye, orbit, and cerebrospinal fluid.

Mechanisms of central regulation of AH dynamics are underexplored. Early experiments in primates show that intracranial hypertension induced by inflation of an epidural balloon leads to an increase in IOP [96]. A recent study in rats demonstrated that a neural feedback mechanism driven by ICP regulates conventional outflow facility that leads to IOP increase [97]. Experimental studies have demonstrated the impact of the hypothalamo-pituitary-suprarenal system in the regulation of IOP [98–100]. Delivery of hypo-osmotic agents into the third ventricle resulted in IOP elevation, while the delivery of hyperosmotic agents lowered IOP [101]. Third ventricle injection of substance P [102], thyrotropin-releasing hormone (TRH) [103], or arginine vasopressin [103] also elevated IOP. Injection of a GABA(A) receptor antagonist bicuculline into the dorsomedial and perifornical hypothalamus in rats increased IOP [100].

Circadian Changes

In the general population, IOP ranges between 10 and 20 mmHg with an average of 15.5 mmHg. IOP is a dynamic parameter with distinct circadian rhythms and spontaneous variations [104]. Diurnal variation for normal eyes is between 3 and 6 mmHg. IOP undergoes nocturnal elevation due to circadian rhythm, independent of posture changes [50, 105–107] and variations of 24-h IOP in the right and left eyes are similar [108].

AH flow also demonstrates a circadian rhythm with a peak in the morning and at night [109, 110]. The role of the central circadian clock via melatonin and the possible role of the ocular circadian clock are active areas of research [111]. Recent studies in mice suggest that IOP rhythm entrainment is mediated by a systemic rather than local signal [112] and that intact adrenal function [113], glucocorticoids, and the sympathetic system [114] are required for manifest circadian rhythms of IOP. At this time, it is unknown whether circadian rhythm changes observed in spaceflight [115, 116] contribute to IOP changes.

IOP Changes in Space

Given the immediate increase in IOP noted upon entering weightlessness, studies of IOP are of great interest. The first inflight IOP readings performed during a D1 Spacelab mission showed a rise of 20–25% in IOP 44 min after entry to microgravity conditions [117]. A subsequent study documented a 92% increase in IOP after 16 min entry in microgravity (German–Russian MIR mission) [118]. A 114% increase in IOP was reported during a D2 Spacelab mission [119]. Furthermore, data acquired on the first day of six different space shuttle missions for 11 subjects revealed an increase of 4–7 mmHg [120]. While IOP has been reported to return to baseline values within the first week of microgravity exposure [118–120], a mean IOP rise of 26.3% in a woman astronaut was still present at day 8 during spaceflight [121]. Thus, currently published data suggest that IOP increases upon entering weightlessness [118, 119]. Chronically elevated IOP has not been observed in astronauts during long-duration ISS missions. Tonometry data from the Lifetime Surveillance of Astronaut Health study of 15 subjects suggested no change in IOP on day 30 in flight, and 30 days prior to return to Earth compared to pre- or postflight. The IOP among subjects with optic disc edema on fundoscopy upon

return to Earth did not differ from remaining crew members [121]. After return from long-duration spaceflight, IOP values were similar to preflight measures (10–14 mmHg vs. 10–16 mmHg, respectively) [3]. IOP measured after landing on Earth may be lower than preflight levels as suggested by postflight decrease of IOP compared with preflight measurements observed in Apollo astronauts [123].

Despite the sustained headward fluid shift and cardiovascular changes during the first few days of spaceflight, the immediate IOP increase followed by a return to baseline within the first week suggests compensatory mechanisms that are not yet fully elucidated. If we assume this early IOP increase is due to headward fluid shift and cardiovascular adaptation leading to an increased in intravascular volume, especially in the uvea, the compensatory mechanisms may relate to aqueous inflow and outflow changes that decrease AH volume. Understanding these compensatory mechanisms are important to understanding the long-term effect of these changes.

During long-duration missions, cardiovascular changes of decreased mean arterial pressure (MAP) and increased cardiac output (CO), indicate a lower systemic vascular resistance (MAP/CO) [124]. These changes alter ocular blood volume and exert influence on IOP. Neurohormonal changes implicated in the cardiovascular adaptative process may also influence both ocular hemodynamics and hydrodynamics. Thus, IOP changes are an integral part of the development and progression of ocular changes during flight, and recovery after landing. While determinants of IOP such as ocular hydro- and hemodynamics in the development and progression of SANS remain relatively unexplored, IOP is an important parameter to include in future studies to understand, prevent and treat SANS.

IOP decrease below baseline after landing may also be explained by a decrease in choroidal vascular congestion and delayed recovery of decreased aqueous volume by changes in aqueous inflow and outflow. Measurements of episcleral pressure changes, and outflow facility performed after landing can help to understand these compensatory changes.

IOP is a dynamic parameter with many influences, with distinct circadian rhythms, and spontaneous variations [104]. Its measurement depends on the devices used to evaluate IOP before, during, and after flight. In addition, the training of operator with the device, time of the day, body position, are critical to insights into IOP elevation. In most IOP studies in astronauts, details regarding IOP measurement methodology are lacking. Future studies should disclose this important information per subject rather than reporting only group differences. Long-term spaceflight-induced IOP changes may be in the order of a few mmHg, so more sensitive IOP measuring devices can better assess IOP changes.

Elevated CSFp was previously believed to be related to SANS given the swollen optic disc appearance of papill-edema and optic nerve edema observed [125, 126]. The observation that CSFp does not go up under microgravity conditions has questioned the role of high CSFp in astronauts [127]. There is no evidence of sustained IOP increase [3, 117, 128] or decreased CSFp. Carefully designed studies with simultaneous IOP and CSFp measurements will allow correlation of their changes with retinal, optic nerve, and choroidal changes observed by ocular imaging during and after flight.

In addition to microgravity, other extreme conditions such as hypercapnia [129, 130] and various type of exercise regimes [131–144] likely contribute to IOP changes during flight and to SANS development. Whether chronic low-dose radiation exposure is associated with IOP changes and SANS also need to be studied.

Countermeasures such as exercise with or without the Advanced Resistive Exercise Device (ARED) and Lower Body Negative Pressure (LBNP) suit are used to mitigate microgravity-induced bone loss, muscle atrophy, and cardiac deconditioning [145].

The effects countermeasures on IOP and SANS are not yet known. Studies in experimental models and on-ground analogs that mimic microgravity conditions will help to unravel the relationship involved in changes of IOP to SANS and the efficacy and safety of countermeasures.

IOP in Microgravity Models

Ground-Based Analogs

As space missions are costly and low in number, human studies in ground analogs are good alternatives for gravitational research that can complement and inform research studies in space [146]. The main ground-based analogs are head-down tilt bed rest and dry immersion.

Head-Down Tilt (HDT) Bed Rest

HDT bed rest is the most common ground-based model used to study the physiological effects of microgravity on the cardiovascular and musculoskeletal systems [147]. The HDT bed rest mimics cephalic fluid shift, immobilization, confinement, and inactivity. The subject remains in the supine position at −6 degrees HDT bed rest for either short periods (from 1 week to 1 month) or sometimes longer periods (>1 month). HDT bed rest may be used to understand eye changes during headward fluid shift. Subjects who underwent 70-day −6° HDT bed rest showed an increase in OCT peripapillary retinal nerve thickening [148], unlike subjects who underwent 4.5-h-HDT at −6°,−12°, and −18° tilt angles or 14-day exposure to −6° HDT bed rest [149]. Healthy subjects undergoing strict HDT bed rest showed a larger increase in peripapillary total retinal thickness compared to 20 astronauts during ~30 days in spaceflight [150]. Interestingly, choroid thickness shows a larger increase in astronauts compared to the strict HDT bed rest subjects.

−6° HDT bed rest studies have shown inconsistent findings regarding IOP. Early studies showed normalization or lower IOP within 5–6 days [151], while more recently, an increase of 2 mmHg after 10 days has been reported [149]. One −6° HDT study of 14- and 70-days observed an increase in IOP with +1.42 and +1.79 mmHg from baseline, respectively. Systematic comparisons of spaceflight IOP data and HDT bed rest studies with close attention to IOP measuring device, body position and time of the day, are needed. The sympathetic system is decreased in HDT bed rest and not in spaceflight [152], suggesting differences that should also be considered.

HDT bed rest studies may also help to study possible risk factors for SANS such as myopia [153], and its effect on the water content in the vitreous using MRI [154].

Dry Immersion

In the dry immersion model of microgravity, the subject remains immersed in thermoneutral water covered with an elastic waterproof fabric, isolating the subject from the water. Thus, the subject floats freely while remaining dry. One of the main features of dry immersion is that it imitates the absence of any supporting structure for the body, centralization of body fluids, immobilization, and hypokinesia observed during spaceflight [155]. Dry immersion rapidly induces a wide range of physiological effects of weightlessness including cardiovascular alterations [156] associated with sympathoexcitation [157] and possible effect on intracranial pressure (ICP) effects [158]. During 5-day dry immersion experiments, although IOP did not differ from baseline in the healthy eye, intraocular fluid production rate (F) was decreased in 60% of cases by day 1 [159].

Ground-based analogs such as HDT bed rest and dry immersion represent an opportunity to better understand IOP with rigourous IOP measurement technologies.

Countermeasures

Exercise

To mitigate muscle atrophy due to microgravity, astronauts undergo 2.5 h of intensive resistance and aerobic exercise nearly every day onboard the ISS [160].

Short-term exercise overall has an IOP-lowering effect [161]. Dynamic exercise has a greater IOP-lowering effect than isometric exercise [133], and the IOP-lowering effect of exercise increases with its intensity [134, 135]. Anaerobic exercise also seems to decrease IOP [136, 137]. With strenuous exercise, it appears that IOP is inversely related to plasma osmolarity during and after strenuous exercise [137]. Dehydration during strenuous exercise and elevated colloid osmotic pressure significantly reduced IOP compared with hydrated subjects with normal colloid osmotic pressure [162].

Although choroidal blood flow increases somewhat in the immediate post-exercise period [163], it is not yet known whether exercise-induced choroidal changes contribute to IOP changes during and after exercise.

Certain types of exercises such as weightlifting or exercise at maximal exertion can increase IOP. One study compared weightlifting with and without subjects holding their breath and found that IOP increased more prominently when the subject hold their breath [142]. Another study concluded that elevated ICP reduces ocular venous outflow in weightlifting subjects who are essentially performing a Valsalva maneuver, contributing to raise in IOP [143]. During maximal exertion, subjects are essentially performing a Valsalva maneuver known to increase IOP in the absence of other factors [144].

NASA's integrated resistance and aerobic training during a 70-day non-hypercapnia strict −6° HDT bed rest protocol was not associated with a significant difference in retinal thickening or signs of optic disc edema compared to a con-

trol HDT bed rest group though IOP was slightly higher in the exercise group [164]. Interestingly, −15° HBT bed rest for less than an hour was associated with a decrease in IOP in subjects undergoing either moderate-intensity aerobic, resistance or high-intensity interval aerobic exercise [165]. These differences highlight the impact of countermeasures that depends on duration and tilt angle of HDT bed rest. Integrating results from different HDT bed rest models is needed to better understand the short- and long-term effects of countermeasures.

Astronauts follow a rigorous exercise regime [160], so it is important to consider the effect of exercise in subjects who undergo regular exercise programs. A regular exercise program lowers baseline IOP, and diminishes acute decreases in IOP in the post-exercise period [140, 141, 166]. Exercise regimes may differ in type and intensity which may alter baseline IOP and their relative risk profile. IOP measurement before, during, and after spaceflight should consider time of the day in relation to exercise and should report individual data rather than strictly between groups, compared to the age-matched general population.

Lower Body Negative Pressure (LBNP)

LBNP using the Chibis Suit is commonly used by cosmonauts to counteract cephalic fluid shifts [167]. This countermeasure mitigates headward fluid shift, attenuating ocular changes (choroidal engorgement) associated with cephalad fluid shifts seen in HDT bed rest [168–170]. 15° head-down tilt increases IOP, while application of LBNP significantly reduces IOP [52]. The effect of LBNP on IOP during-6° HDT bed rest for longer periods is not yet known.

Artificial Gravity

Exposure to artificial gravity (AG) either continuously or intermittently simulates gravitational states on board the spacecraft. Enhancing adaptation during the mission to Mars gravity and re-adaptation to Earth [171], AG offers a countermeasure with the potential to address bone loss, cardiovascular deconditioning, and muscle weakening [172, 173]. AG is considered an integrated countermeasure because it addresses all of these systems [174] and can be combined with other countermeasures [172]. AG has been proposed as a potential countermeasure for SANS [171]. IOP increases observed in the supine position remained elevated under AG conditions in healthy volunteers [175].

Animal Models

Experimental animal studies both in space and on the ground may help us to better understand the role of IOP and the determinants of AH dynamics and ocular hemodynamics.

Animal Experiments in Space

Recent studies in mice on ISS at the Japan Aerospace Exploration Agency's mouse housing unit [176] demonstrated molecules involved in the regulation of intraocular fluids and of the blood–retina barrier. Immunohistochemical analysis of the retina revealed increased expression of aquaporin-4, a water channel mainly seen in the CNS, as a strong indication of altered blood–retina barrier integrity after spaceflight compared to controls. There was also a significant increase in the expression of platelet endothelial cell adhesion molecule-1 (PECAM-1) and a decrease in the expression of the BRB-related tight junction protein and Zonula occludens-1 (ZO-1) after spaceflight [11]. It is interesting to note that aquaporin-4 is implicated in the outflow of water from the vitreous into the retina [12].

Animal Ground Models

Nonhuman primates have been used in spaceflight to understand microgravity effects [177], and are also used in biomedical research to study IOP and AH dynamics-related h, based on their similarities with humans [178–181]. The nonhuman primate model has been used for continuous monitoring of IOP and ICP to evaluate posture-related IOP changes [64, 65]. Head-out water immersion experiments in primates show some similarities to cardiovascular deconditioning [182]. Similarities to man regarding CNS and CSF dynamics, eye and brain anatomy and physiology [179–181] make the nonhuman primate model may also be adaptable to study SANS with capacity to develop and validate of new non-invasive IOP measuring technology that can be used during spaceflight.

An experimental ground model of hindlimb unloading in rodents that mimics microgravity conditions has been developed by NASA to study bone loss, muscle atrophy, and cardiovascular changes observed in astronauts [183, 184]. Changes in gravitational forces and central venous pressure likely alter passive lymphatic flow [185, 186], and there is evidence that the active pump of cervical lymphatic vessels is inhibited [185]. The mouse model shows similar AH dynamics to men [187] and its small size has multiple advantages for biomedical science [188]. The mouse hindlimb

unloading model may be adapted to study eye changes induced by headward fluid shift and to study the interplay between the eye, cardiovascular system, and central nervous system. Recent studies show CSF entry into the optic nerve along small perforating pial vessels through sleeve-like paravascular spaces between vessel walls and aquaporin-4-positive astrocytic endfeet [10]. AH drains into cervical lymph nodes [35, 189], and these coincide with those into which CSF is also drained [190, 191]. Non-invasive in vivo quantitative techniques in mice [192, 193] and studies of these elusive fluid pathways in hindlimb unloading experiments may help to inform otherwise more expensive studies on Earth and in space.

Non-invasive IOP Measurement and Devices

Tonometry is used to measure IOP based on the relationship between the IOP and the force necessary to deform the cornea by a given amount. Several types of tonometers are used during spaceflight and in-ground analog experiments. Some are slit-lamp mounted devices, while others are portable. While a comprehensive review of tonometers is beyond the scope of this chapter, the main instruments been used on astronauts are highlighted below.

Goldman applanation tonometry (GAT) has been the standard in clinical practice for the measurement of IOP. It is, however, largely influenced by ocular properties and variations in corneal biomechanics [194]; it is subjective and prone to learning; its use outside clinical settings is limited by the need for topical anesthetic, fluorescein, and a slit-lamp microscope to perform measurements. The portable version of this is the Perkins tonometer. A portable applanation self-tonometer specifically designed for spaceflight used by Draeger and coworkers is based on an automatic measuring procedure and an optical sensor that replaces the eye of an examiner [128].

The Tono-pen is a handheld portable tonometer that determines IOP by making contact with the cornea by way of a probe tip, causing applanation/indentation of a small area. Topical anesthesia eye drops are used. After four valid readings are obtained, the average measurement is given together with the standard error. Some studies have reported that the Tono-Pen underestimates postural IOP responses [51, 195–197], while other studies do not during spaceflight [121].

Rebound tonometry (RT) (iCare, Tiolat, Helsinki, Finland) is portable and easy to use. Although it is a contact tonometer, topical anesthesia drops are not required and the tonometer has a disposable tip to minimize cross-infection. The device processes the rebound movement of a rod probe resulting from its interaction with the eye; rebound increases (shorter duration of impact) as the IOP increases. Six measurements are taken and their average is displayed. RT shows high reproducibility and less dependency on ocular characteristics [198–200]. RT has been used in a 7-day-HDT best rest study [151].

The TON-1 compact eye tonometer-tonograph in an impression tonometric method. The device is designed for easy and rapid measurements of true IOP, and quantitative monitoring of intraocular fluid and blood in the eye, and calculates tonometric, tonographic, and sphygmographic characteristics [201]. The TON-1 was used in a 5-day dry immersion experiment [159].

A pressure phosphene tonometer that is applied to the eye with closed eyelids has also been used during spaceflight [122]. It was reported that phosphene tonometer measurements may be influenced by eyelid skin edema due to fluid shifts [122].

Dynamic contour tonometry (DCT, or Pascal) is a slit-lamp mounted and contact IOP measurement device that may present some advantages. It contains a sensor tip with concave surface contour and a miniaturized pressure sensor. The results and quality score measures are provided digitally. DCT is considered an accurate technique [202], and is less influenced by central corneal thickness compared with GAT [203–205]. Additionally, it measures the ocular pulse amplitude which is the difference between the mean systolic and diastolic IOP. These characteristics may present some advantages for ground analog experiments.

Tonometry data is collected as part of medical testing requirements for astronauts, GAT mounted on a slit-lamp, measures pre- and postflight on subjects while seated, and the handheld Tono-pen is used by crew members on each other during spaceflight [121]. Understanding the principles, advantages, and limitations of various IOP measuring devices and effects of different contexts before, during, and after flight or in ground analog experiments is an important area of future research. Low-mass, low-volume devices that can be used during flight requiring to allow self-IOP assessment, or use by another astronaut, are important considerations.

IOP measurements during space flight are based on the assumption that the compliance of the cornea and sclera remain unchanged. However, it is not yet known whether biomechanical properties of cornea and sclera may also change. Rich in glycosaminoglycans [206–208], the corneal stroma may be altered in microgravity and this in turn, may affect corneal tissue elasticity, corneal thickness, and its deformation during IOP measurement. Variations after corneal refractive surgery are known to limit interpretability of tonometric readings [209, 210].

A single IOP measurement cannot accurately assess IOP, as measurements vary depending on the conditions under which they are taken (e.g., supine vs. erect, resting vs. exercise, on Earth vs. microgravity) as well as the state of the patient (e.g., underlying disease state, hydration status, medications, comorbidities, and stress).

Current IOP measuring devices used in clinical settings provide measurements at a single timepoint and are not able to represent the range of spontaneous IOP variations during a 24-h cycle or daily activities in an ambulatory setting [211, 212]. This is a limitation that prevents the ability to distinguish between spontaneous IOP changes and the effects of experimental or therapeutic interventions or of extreme physiological conditions such as microgravity. Contact lens sensors [104, 213–219] and implantable intraocular IOP sensors [220, 221] that can be used by telemetry to monitor IOP continuously represent an active area of research and development.

IOP measurements should ideally be performed with the same device with adequate calibration before, during, and after spaceflight, and by the same operator. Difference between operators depending on their level of training may be associated with significant disagreement [222]. Devices that are portable, user-friendly, sensitive to monitor minor IOP changes continuously without being affected by corneal conditions are needed. The development of a reliable and sensitive IOP measuring or surrogate measuring device with [223] or without a contact lens adapted to spaceflight would offer considerable information regarding important eye changes. Grounds analog experiments should be leveraged for the development and validation of new IOP measuring technologies. The advancements are highly relevant to understanding SANS and io developing countermeasures.

Future Directions for In-Flight Studies and Ground studies

The ambitious plans for future missions to MARS will present new eye health challenges in healthy and productive astronauts and need careful consideration. Long-duration spaceflights will introduce increased ocular risks that include IOP changes.

In preparation for these missions, space agencies must accomplish the following:

1. Assess IOP-associated risk for the eye health during their active life and after retirement of astronauts.
   1a. Improve IOP measurements in spaceflight: The design and the development of a compact and sensitive IOP measuring device and techniques adapted to IOP changes during spaceflight should be a high priority as current devices do not respond to these requirements.
   1b. Design and develop a wearable device to monitor IOP and other IOP-related parameters in an ambulatory setting that allows simultaneous and continuous measurements of other physiological parameters such as blood pressure.
   1c. Develop novel non-invasive devices to assess specific AH dynamics components including blood flow in and around the eye underlying IOP changes to guide personalized countermeasures.
   1d. Leverage ground analog experiments to study and assess IOP-related risk, assess potential sex-differences, and develop and validate IOP and related parameters as biomarkers of SANS with an interdisciplinary approach.
   1e. Develop individualized analysis methods to assess the relationship between IOP changes over time and other eye changes dependent on systemic, CNS and ANS physiology under varying doses and duration of microgravity conditions.
2. Develop or adapt rodent and nonhuman primate models to study SANS in relation to determinants of IOP regulation: ocular blood flow, fluid homeostasis in ocular and orbital tissues, lymphatic drainage, and their modulation by autonomic nervous system and hormones. The nonhuman primate model can help to validate new miniaturized IOP measurement devices under non-invasive conditions and in a continuous manner.
3. Develop and/or adapt pharmacological and other countermeasures to prevent eye changes in SANS including IOP-related risk, and evaluate the efficacy and safety of countermeasures.
4. Evaluate the efficacy and safety of multisystem countermeasures such as exercise regimes and LBNP or their combinations to prevent IOP changes and the development of SANS.

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